A Chemoselective Microwave-Assisted One-Pot Cross-Stille Reaction of Benzylic Halides with 2(1*H*)-Pyrazinones Using Simultaneous Cooling

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Abstract: This manuscript reports the chemoselective one-pot cross-Stille coupling of benzylic halides with 3,5-dichloro-2(1*H*)-pyrazinones, which avoids the purification and handling of toxic stannylated intermediates. Significant improvements in yields were established when microwave irradiation was performed with simultaneous cooling.

Key words: microwave, 2(1*H*)-pyrazinone, Stille, cross-coupling, simultaneous cooling

In the course of the last two decades our laboratory explored 3,5-dichloro-2(1*H*)-pyrazinones as interesting starting materials for a gateway to the elaboration of different types of biologically active compounds. This valuable scaffold allows an easy introduction of a wide range of pharmacologically active groups with the ability to address the diverse set of biological targets.[1] We have previously demonstrated that the 2(1*H*)-pyrazinones, upon Diels–Alder reaction[2] with ethylene followed by suitable manipulations, could furnish the invaluable 5-aminopiperidinone-2-carboxylate (APC) unit, mimicking the β-turn[3] of the type VI with a conformationally restricted *cis*-peptide bond. This concept has since been used in the synthesis of a number of β-turn mimics with diversity at the *i*+1 and *i*+2 positions, generating pharmacologically interesting molecules such as β-turn mimics for modifying the C-terminus of substance P[4] (an undecapeptide neurotransmitter implicated in several diseases including arthritis and asthma).

According to our approach it is clear that the nature of the functional group at the C-3 position of the original 2(1*H*)-pyrazinone scaffold has a critical role for constructing the turn mimics, as the *i*+1 residue of the adapted side chain is a direct outcome of the C-3 substituent, e.g., a benzyl group at the C-3 position constitutes a Phe mimic in the APC system (Figure 1). For the purpose of biological screening, it is therefore important to elaborate an easy and flexible protocol for the incorporation of various alkyl and benzyl moieties at the C-3 position of the 2(1*H*)-pyrazinone scaffold, in view of generating APC systems incorporating unnatural amino acids at the *i*+1 position. We have recently demonstrated the use of Grignard reagents for the introduction of benzyl and alkyl groups at the C-3 position of the 2(1*H*)-pyrazinone system.[5] However, this reaction is rather harsh and known to demand sensitive conditions. Even though the Stille reaction[6] was successfully carried out on the C-3 position of the pyrazinone for this purpose,[7] this protocol was solely restricted for the introduction of (hetero)aryl moieties. Syntheses of the corresponding benzyl and alkyl stannanes are known to be cumbersome due to the toxicity of these compounds and the tedious purification procedures. During search for an easier and straightforward approach, we found that the cross-coupling can be effected by a microwave-enhanced one-pot reaction applying a dedicated monomode instrument (Scheme 1). The reactions proceed with high chemoselectivity and high yields, avoiding the process of isolation (or purification) of any stannous intermediates during the reaction. Even though transition-met-

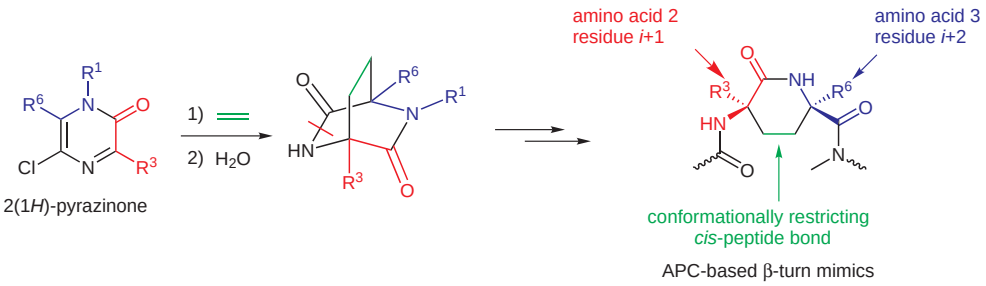

Figure 1 2(1*H*)-pyrazinone and the APC-based β-turn mimics

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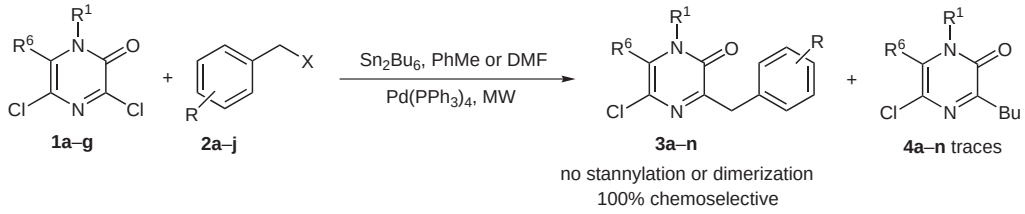
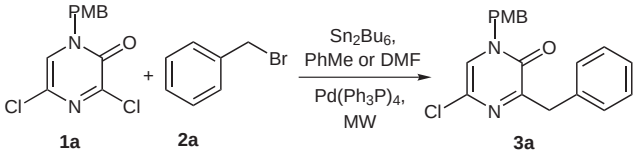


Scheme 1 The microwave-enhanced cross-Stille reaction

al-catalyzed one-pot cross-coupling reactions are known, albeit rarely, in the literature,[8] these reactions generally furnish the homocoupled products. In this contribution, we wish to delineate the outcome of our investigations.

We started our experiments by choosing the cross-coupling reaction between benzyl bromide **2a** and 3,5-dichloro-1-(4-methoxybenzyl)pyrazin-2(1*H*)-one (**1a**). Pyrazinone **1a** and bromide **2a** (1.2 equiv) were suspended in toluene (2 mL) in a 10 mL microwave vial together with hexabutyldistannane (Sn_2Bu_6, 1.1 equiv) and $Pd(PPh_3)_4$ (5 mol%). The vial was irradiated in the cavity of a monomode microwave apparatus at a preselected temperature of 150 °C for 15 minutes, using a maximum irradiation power of 200 W. After the chromatographic separation, the required target compound, 3-benzyl-5-chloro-1-(4-methoxybenzyl)pyrazin-2(1*H*)-one (**3a**), was isolated in a good yield of 71% (Table 1, entry 1). A high chemoselectivity was obtained during reaction and no traces of homodimerized or stannylated products of either the 2(1*H*)-pyrazinone or benzyl bromide (**2a**) were observed. The only by-product that was isolated during the course of the reaction was 3-butyl-5-chloro-1-(4-methoxybenzyl)pyrazin-2(1*H*)-one (**4a**), which is typical

Table 1 Optimization of the Cross-Stille Reaction under Microwave Irradiation[a]



PMB = 4-OMe-Bn

Entry	Catalyst	Solvent	Temp (°C)	Time (min)	Yield (%)
1	$Pd(Ph_3P)_4$	PhMe	150	15	71
2	$Pd(Ph_3P)_4$	PhMe	175	15	79
3	$Pd(Ph_3P)_4$	PhMe	130	15	67
4	$Pd(Ph_3P)_4$	PhMe	110	15	58
5	$Pd(Ph_3P)_4$	PhMe	175	10	79
6	$Pd(Ph_3P)_4$	PhMe	175	20	79
7	$Pd(Ph_3P)_2Cl_2$	PhMe	175	10	69
8	$Pd(dppf)Cl_2$	PhMe	175	10	55
9	$Ni(dppe)Cl_2$	PhMe	175	10	41
10	$Pd(Ph_3P)_4$	DMF	175	10	79
11	$Pd(Ph_3P)_4$	DMF	150	10	79
12	$Pd(Ph_3P)_4$	DMF	150	10	79[b]
13	$Pd(Ph_3P)_4$	DMF	150	10	79[c]
14	$Pd(Ph_3P)_4$	DMF	150	10	74[d]

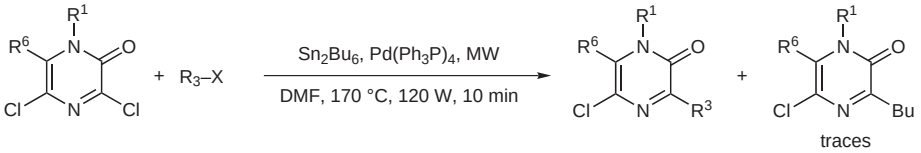
[a] All reactions were carried out on a 0.25 mmol scale with 1.2 equiv of BnBr, 1.1 equiv of Sn_2Bu_6 and 5 mol% of $Pd(Ph_3P)_4$ in 2.0 mL of solvent. Reactions were run at 200 W (toluene) and 150 W (DMF) maximum power.
[b] Reaction was performed with 1.5 equiv of Sn_2Bu_6.
[c] Reaction was performed with 2.0 equiv of Sn_2Bu_6.
[d] Reaction was performed with 1.1 equiv of BnCl.

for reactions applying Sn_2Bu_6 at high temperatures. The optimum conditions were found to be the use of $Pd(Ph_3P)_4$ as the catalyst in toluene, while the reaction was run at 175 °C for 10 minutes (Table 1, entry 5) at 200 W maximum power.

The 3-benzyl derivative **3a** was obtained in 79% yield. When the reactions were carried out at lower temperatures inferior yields were observed (Table 1, entries 1, 3, 4). Furthermore, $Pd(Ph_3P)_4$ was found to be the catalyst of choice, as the application of alternative catalysts resulted in lower yields (Table 1, entries 7–9). However, switching the solvent from toluene to DMF afforded the product in a similar yield of 79% in 10 minutes, but a lower temperature of 150 °C could be applied at 150 W maximum power (Table 1, entries 10, 11). Increasing the amount of Sn_2Bu_6 (Table 1, entries 12, 13) failed to improve the yields, and resulted in the formation of several unidentified side products. We then investigated the cross-Stille reaction of **1a** with BnCl (**2b**), being cheaper and comparatively less hazardous than its bromo counterpart. The reaction was found to proceed smoothly under the already optimized microwave-enhanced conditions in DMF and cross-coupled compound **3a** was isolated in 74% yield (Table 1, entry 14).

Thus, after optimizing the reaction conditions, we decided to investigate the scope and limitation of the cross-Stille reaction applying a number of differently substituted pyrazinones. In view of scaling up the reactions, we decided to apply a dedicated multimode microwave apparatus designed for large-scale reactions. To maintain

Table 2 Cross-Stille Reaction of Various Pyrazinones **1b–g** with Benzylic Halides **2a–j**[a]



1b–g **2a–j** **3b–n** **4b–n**

Entry	Pyrazinone	R^1	R^6	Halide	R^3	X	Product	Yield (%)
1	**1b**	$(CH_2)_3Ph$	H	**2a**	Bn	Br	**3b**	71
2	**1b**	$(CH_2)_3Ph$	H	**2b**	Bn	Cl	**3b**	68
3	**1c**	$CH_2C_6H_{11}$	H	**2a**	Bn	Br	**3c**	71
4	**1c**	$CH_2C_6H_{11}$	H	**2b**	Bn	Cl	**3c**	65
5	**1d**	C_6H_{11}	H	**2a**	Bn	Br	**3d**	74
6	**1d**	C_6H_{11}	H	**2b**	Bn	Cl	**3d**	66
7	**1e**	CH_2Ph	Me	**2a**	Bn	Br	**3e**	69
8	**1e**	CH_2Ph	Me	**2b**	Bn	Cl	**3e**	65
9	**1f**	Ph	Ph	**2a**	Bn	Br	**3f**	81
10	**1f**	Ph	Ph	**2b**	Bn	Cl	**3f**	73
11	**1g**	Ph	Ph	**2c**	(4-MeO)Bn	Br	**3g**	79
12	**1g**	Ph	Ph	**2d**	(4-MeO)Bn	Cl	**3g**	75
13	**1b**	$(CH_2)_3Ph$	H	**2d**	(4-MeO)Bn	Cl	**3h**	58
14	**1b**	$(CH_2)_3Ph$	H	**2e**	(3,4,5-MeO)Bn	Cl	**3i**	57
15	**1b**	$(CH_2)_3Ph$	H	**2f**	(2-F)Bn	Br	**3j**	72
16	**1b**	$(CH_2)_3Ph$	H	**2g**	$(2\text{-}NO_2)Bn$	Cl	**3k**	0[b]
17	**1b**	$(CH_2)_3Ph$	H	**2h**	$(4\text{-}NO_2)Bn$	Br	**3l**	0[b]
18	**1b**	$(CH_2)_3Ph$	H	**2i**	Allyl	Br	**3m**	94
19	**1b**	$(CH_2)_3Ph$	H	**2j**	Propargyl	Br	**3n**	0[b]

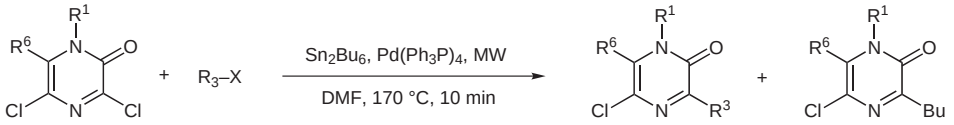
[a] All reactions were carried out on a 1.0 mmol scale with 1.2 equiv of the corresponding halide and 1.1 equiv of Sn_2Bu_6 and 5 mol% of $Pd(Ph_3P)_4$ in 12.0 mL of solvent at a preselected temperature of 170 °C for 10 min, using a maximum irradiation power of 120 W.
[b] Only starting material was recovered.

the same rates and yields of our optimized procedure, we found that the ceiling temperature of the reactions had to be raised from 150 °C to 170 °C. A variety of 2(1*H*)-pyrazinones **1b**–**f** was chosen to react with **2a** as well as **2b** according to these new conditions (Table 2, entries 1–10). The reactions were found to proceed smoothly, furnishing the required 3-benzyl analogues **3b**–**f** in 65–81% yield. Once again, optimal chemoselectivity was obtained during the reaction and no traces of dimers or stannanes were isolated as by-products, albeit with the presence of traces of butylated compounds **4b**–**f**.

Our next goal was to incorporate diversity at the C-3 position of the pyrazinone scaffold by varying the benzyl halide component. As can be viewed from Table 2, the highly electron-rich 4-methoxybenzyl bromide (**2c**) and 4-methoxybenzyl chloride (**2d**) furnished the required 3-benzyl analogues **3g**–**h** in 58–79% yields, (Table 2, entries 11–13). The *ortho*-fluorobenzyl bromide (**2f**) reacted equally well and the product **3j** was isolated in 72% yield (Table 2, entry 15). However, the *ortho*- and *para*-nitrobenzyl halides **2g**,**h** failed to promote the cross-Stille reaction, and only starting pyrazinone **1b** was isolated together with unidentified decomposition products (Table 2, entries 16, 17). Surprisingly, allylbromide **2i** underwent the coupling reaction in a remarkably cleaner fashion and the product **3m** was isolated in an excellent 94% yield (Table 2, entry 18). On the contrary, propargyl bromide **2j** failed to promote the reaction and the starting pyrazinone remained untouched (Table 2, entry 19).

Recently, it has been demonstrated that simultaneous cooling by passing a jet of air over the reaction vial during irradiation can result in higher yields and can provide novel pathways that are otherwise unattainable,[9] as it allows higher intake of microwave energy.[10] We have investigated our microwave-enhanced cross-Stille reaction under simultaneous cooling, in view of obtaining possible improvements. We expected an advantageous effect as the palladium catalyst, which is strongly absorbing the microwave energy, will be activated much stronger if a higher power could be maintained during the reaction by the air-jet cooling. The temperature of the reaction mixture was monitored using external IR as well as fiberoptic temperature measurement, as the former is known to indicate too low temperatures due to the stream of air passed over the vial. Under simultaneous cooling, the microwave energy intake of the reaction was found to increase up to

Table 3 Comparison of Experiments Performed under Simultaneous Cooling[a]



1b–f **2b–d** **3b–f,h,i** **4b–f,h,i** traces

Entry	Pyrazinone	R^1	R^6	Halide	R^3	Product[11,12]	Cooling	Power (W)[b]	Yield (%)
1	**1b**	$(CH_2)_3Ph$	H	**2b**	Bn	**3b**	No	84	68
2	**1b**	$(CH_2)_3Ph$	H	**2b**	Bn	**3b**	Yes	113 (135%)	72
3	**1c**	$CH_2C_6H_{11}$	H	**2b**	Bn	**3c**	No	86	65
4	**1c**	$CH_2C_6H_{11}$	H	**2b**	Bn	**3c**	Yes	140 (163%)	74
5	**1d**	C_6H_{11}	H	**2b**	Bn	**3d**	No	74	66
6	**1d**	C_6H_{11}	H	**2b**	Bn	**3d**	Yes	111 (150%)	74
7	**1e**	CH_2Ph	Me	**2b**	Bn	**3e**	No	65	65
8	**1e**	CH_2Ph	Me	**2b**	Bn	**3e**	Yes	127 (195%)	69
9	**1f**	Ph	Ph	**2b**	Bn	**3f**	No	77	73
10	**1f**	Ph	Ph	**2b**	Bn	**3f**	Yes	123 (160%)	75
11	**1b**	$(CH_2)_3Ph$	H	**2c**	(4-MeO)Bn	**3h**	No	75	58
12	**1b**	$(CH_2)_3Ph$	H	**2c**	(4-MeO)Bn	**3h**	Yes	120 (160%)	74
13	**1b**	$(CH_2)_3Ph$	H	**2d**	(3,4,5-MeO)Bn	**3i**	No	84	57
14	**1b**	$(CH_2)_3Ph$	H	**2d**	(3,4,5-MeO)Bn	**3i**	Yes	123 (146%)	69

[a] All reactions were carried out on a 1.0 mmol scale with 1.1 equiv of the corresponding benzyl chloride, 1.1 equiv of Sn_2Bu_6 and 5 mol% of $Pd(Ph_3P)_4$ in 3.0 mL of DMF at a preselected temperature of 170 °C for 10 min at a preselected maximum power of 350 W.
[b] The power values indicated in the table are the total power input values in each case; between brackets is given the percentage of power input compared to the experiment without simultaneous cooling.

135–195% in most cases (Table 3). As can be viewed from Table 3, the cross-Stille reactions clearly benefit from the simultaneous cooling during the microwave irradiation resulting in higher yields. The reaction of **2b** with different pyrazinones **1b**–**f** furnished slightly improved yields in the range of 2–9% (Table 3, entries 1–10).

However, important yield enhancements of 12–16% were observed when pyrazinone **1b** was cross-coupled with the electron-rich benzyl halides like **2c** and **2d** (Table 3, entries 11–14). These results indeed indicate that simultaneous cooling during microwave irradiation could be a very useful tool to obtain higher product yields in certain cases. Further experiments to extend this cross-Stille reaction to other heterocyclic systems are under current investigation.

In conclusion, we have developed a practical microwave-enhanced one-pot cross-Stille protocol for the 3-chloro-2(1*H*)-pyrazinones which avoids the purification and handling of any toxic stannylated intermediates while introducing benzyl and alkyl moieties via conventional Stille coupling. Even though one-pot Stille reactions are documented in the literature, they mostly focus on the coupling of (hetero)aromatic molecules and often tend to provide homodimerization products. A high chemoselectivity was obtained during the course of the reaction, while no stannous byproducts or homocoupling was observed. A number of otherwise difficultly obtainable 3-benzylated and allylated 2(1*H*)-pyrazinones was generated according to the protocol. The microwave-enhanced cross-Stille reactions were investigated under simultaneous cooling and improved yields were obtained during reactions.

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(11) **Representative Experimental Procedure Using a Dedicated Multimode Microwave Apparatus – Synthesis of 1,3-Dibenzyl-5-chloro-6-methylpyrazin-2 (1*H*)-one (3e).**

Pyrazinone **1e** (0.324 g, 1.0 mmol), bromide **2a** (0.205 g, 1.2 mmol, 1.2 equiv), hexabutyldistannane (0.649 g, 1.1 mmol, 1.1 equiv) and $Pd(Ph_3P)_4$ (0.058 g, 5 mol%) were suspended in DMF (12 mL) in a 50 mL glass vial equipped with a small magnetic stirring bar. The mixture was irradiated in the cavity of a Milestone-MYCROSYNTH multimode oven at a preselected maximum temperature of 170 °C for 10 min, using a maximum irradiation power of 120 W. The mixture was then cooled to r.t., poured into crushed ice, diluted with Et_2O and the contents were stirred at r.t. for 2 h. It was then extracted with Et_2O and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude residue was subjected to column chromatography (silica gel, PE–EtOAc, 3:1) as eluent to afford analytically pure product **3e** (0.224 g, 69%) as a viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17–7.35 (m, 10 H), 5.38 (s, 2 H), 4.12 (s, 2 H), 2.49 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.2, 153.3, 136.1, 134.1, 133.9, 129.2, 129.0, 128.5, 127.2, 127.0, 126.4, 123.2, 50.2, 39.1, 16.9 ppm. MS (CI): *m/z* (%) = 325 (100) [MH^+]. HRMS (EI): *m/z* calcd for $C_{19}H_{17}N_2ClO$: 324.1029; found: 324.1034.

(12) **3-Benzyl-5-chloro-1-(4-methoxybenzyl)-2(1*H*)-pyrazinone (3a).**
Mp 102–103 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.8 (s, 3 H), 4.12 (s, 2 H), 4.93 (s, 2 H), 6.9 (d, 2 H, *J* = 8.7 Hz), 7.01 (s, 1 H), 7.30–7.35 (m, 5 H), 7.44 (d, 2 H, *J* = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.8, 51.8, 55.2, 114.4, 124.3, 125.7, 125.8, 126.5, 128.3, 129.3, 130.2, 136.3, 154.4, 158.8, 159.8 ppm. MS (CI): *m/z* (%) = 341 [MH^+], 121 (100). HRMS (EI): *m/z* calcd for $C_{19}H_{17}N_2ClO_2$: 340.0978; found: 340.0972.
3-Benzyl-5-chloro-(3-phenylpropyl)-2(1*H*)-pyrazinone (3b).
Mp 98–100 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.03–2.19 (m, 2 H), 2.68 (t, *J* = 7.35 Hz, 2 H), 3.84 (t, *J* = 7.35 Hz, 2 H), 4.12 (s, 2 H), 6.92 (s, 1 H, C-6H), 7.15–7.44 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.6, 32.7, 39.9, 49.8, 125.3, 125.6, 126.3, 126.7, 128.2, 128.3, 128.4, 128.6, 136.0, 139.0, 154.5, 158.9 ppm. MS (CI): *m/z* (%) = 339 (100) [MH^+]. HRMS (EI): *m/z* calcd for $C_{20}H_{19}N_2ClO$: 338.1185; found: 338.1194.
3-Benzyl-5-chloro-1-cyclohexylmethyl-2(1*H*)-pyrazinone (3c).
Mp 107–108 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13–1.90 (m, 11 H), 3.78 (d, *J* = 7.41 Hz, 2 H), 4.10 (s, 2 H), 7.21 (s, 1 H), 7.12–7.18 (m, 3 H), 7.32 (d, *J* = 7.32 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.5, 26.1, 30.6, 36.8, 40.2, 57.4, 122.4, 126.2, 126.7, 128.4, 129.3, 136.5, 154.1, 158.7 ppm. MS (CI): *m/z* (%) = 317 (100) [MH^+]. HRMS (EI): *m/z* calcd for $C_{18}H_{21}N_2ClO$: 316.1342; found: 316.1344.
3-Benzyl-5-chloro-1-cyclohexyl-2(1*H*)-pyrazinone (3d).
Mp 139–140 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37–1.91 (m, 10 H), 4.10 (s, 2 H), 4.68–4.76 (m, 1 H), 7.12 (s, 1 H), 7.18–7.30 (m, 3 H), 7.41 (d, *J* = 7.32 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2, 25.6, 30.0, 40.3, 55.5, 121.8, 126.2, 126.7, 128.5, 129.6, 136.7, 154.2, 158.6 ppm. MS (CI): *m/z* 303 (100) [MH^+]. HRMS (EI): *m/z* calcd for $C_{17}H_{19}N_2ClO$: 302.1185; found: 302.1184.
3-Benzyl-5-chloro-1,6-diphenyl-2(1*H*)-pyrazinone (3f).
Mp 180–181 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.12 (s, 2 H), 6.96–7.84 (m, 15 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.2, 125.6, 126.87, 128.2, 128.2, 28.6, 128.7, 129.0, 129.1, 129.8, 130.0, 130.7, 131.2, 136.7, 137.2, 155.5, 158.3 ppm. MS (CI): *m/z* (%) = 373 (100) [MH^+]. HRMS (EI): *m/z* calcd for $C_{23}H_{17}N_2ClO$: 372.1029; found: 372.1020.
5-Chloro-3-(4-methoxybenzyl)-1,6-diphenyl-2(1*H*)-pyrazinone (3g).
Mp 194–195° °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3 H), 4.16 (s, 2 H,), 6.89 (d, 2 H, *J* = 8.47 Hz), 6.96–7.29 (m, 10 H), 7.49 (d, 2 H, *J* = 8.29 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.8, 55.3, 114.0, 125.6, 128.2, 128.7, 129.0, 129.2, 130.0, 130.8, 131.3, 136.4, 137.2, 155.1, 158.3, 159.5 ppm. MS (CI): *m/z* (%) = 403 (100) [MH^+]. HRMS (EI): *m/z* calcd for $C_{24}H_{19}N_2ClO_2$: 402.1135; found: 402.1142.
5-Chloro-3-(4-methoxybenzyl)-1-(3-phenylpropyl)-2(1*H*)-pyrazinone (3h).
Mp 113–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.03–2.08 (m, 2 H), 2.66 (t, *J* = 7.32 Hz, 2 H), 3.75 (s, 3 H), 3.82 (t, *J* = 7.32 Hz, 2 H), 4.03 (s, 2 H), 6.83 (d, *J* = 8.22 Hz, 2 H), 6.99 (s, 1 H), 7.14 (d, *J* = 6.39 Hz, 2 H), 7.19–7.28 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.7, 32.7, 39.1, 49.8, 55.2, 113.9, 125.2, 125.7, 126.7, 128.2, 128.5, 128.6, 130.5, 140.0, 154.6, 158.5, 159.2 ppm. MS (CI): *m/z* = 369 (100) [MH^+]. HRMS (EI): *m/z* calcd for $C_{21}H_{21}N_2ClO_2$: 368.1291; found: 368.1287.
5-Chloro-1-(3-phenylpropyl)-3-(3,4,5-trimethoxybenzyl)-2(1*H*)-pyrazinone (3i).
Mp 104–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.05–2.10 (m, 2 H), 2.67 (t, *J* = 7.44 Hz, 2 H), 3.80–3.88 (m, 11 H), 4.03 (s, 2 H), 6.67 (s, 2 H), 7.02 (s, 1 H), 7.15–7.30 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.8, 32.8, 40.1, 50.0, 56.2, 56.3, 55.4, 106.5, 125.5, 125.7, 126.5, 128.3, 128.7, 132.3, 136.8, 140.0, 153.2, 153.3, 154.7, 158.7 ppm. MS (CI): *m/z* (%) = 429 (100) [MH^+]. HRMS (EI): *m/z* calcd for $C_{23}H_{25}N_2ClO_4$: 428.1502; found: 428.1499.
5-Chloro-3-(2-fluorobenzyl)-1-(3-phenylpropyl)-2(1*H*)-pyrazinone (3j).
Mp 97–98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.03–2.13 (m, 2 H), 2.67 (t, *J* = 7.40 Hz, 2 H), 3.85 (t, *J* = 7.47 Hz, 2 H), 4.15 (s, 2 H), 7.01 (s, 1 H), 7.02–7.31 (m, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.8, 32.8, 33.2, 49.9, 115.6, 124.0, 125.5, 125.8, 126.5, 128.3, 128.5, 128.7, 131.5, 131.6, 140.1, 154.5, 158.7, 162.9 ppm. MS (CI): *m/z* (%) = 357 (100) [MH^+]. HRMS (EI): *m/z* calcd for $C_{20}H_{18}N_2FClO$: 356.1092; found: 356.1098.
3-Allyl-5-chloro-1-(3-phenylpropyl)-2(1*H*)-pyrazinone (3m).
Viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.05–2.13 (m, 2 H), 2.22 (dd, *J* = 1.83, 5.49 Hz, 2 H), 2.71 (t, *J* = 7.34 Hz, 2 H), 3.89 (t, *J* = 7.30 Hz, 2 H), 6.83 (dd, *J* = 1.88, 14.16 Hz, 2 H), 6.99 (s, 1 H), 7.17–7.33 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.1, 31.9, 33.1, 50.2, 124.6, 124.5, 125.8, 126.8, 128.6, 129.1, 139.3, 140.5, 152.3, 154.7 ppm. MS (CI): *m/z* (%) = 289 (100) [MH^+]. HRMS (EI): *m/z* calcd for $C_{16}H_{17}N_2ClO$: 288.1029; found: 288.1034. Anal. Calcd for $C_{16}H_{17}N_2ClO$: C, 66.55; H, 5.93; N, 9.70. Found: C, 66.60; H, 5.97; N, 9.68.