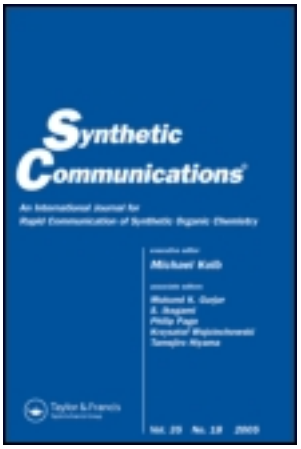

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Microwave-Promoted Synthesis of Some Novel 4-(4-Methyl-phenyl)-Substituted Phthalazin-1-one Derivatives

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MICROWAVE-PROMOTED SYNTHESIS OF SOME NOVEL 4-(4-METHYL-PHENYL)-SUBSTITUTED PHTHALAZIN-1-ONE DERIVATIVES

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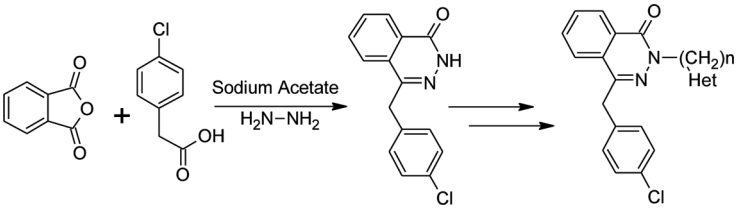
GRAPHICAL ABSTRACT



Abstract *In this study, a series of 4-(4-methyl-phenyl)-substituted phthalazin-1-one derivatives have been synthesized with the combination of rapid microwave synthesis and phase-transfer catalyst methodology, which is characterized by very short reaction times and easy workup procedures and which can be exploited to generate some novel phthalazinone heterocycles. Substituted phthalazin-1-one derivatives have been synthesized from phthalyl derivatives as starting material. The structures of these compounds were confirmed by NMR and mass spectral studies.*

Keywords Alkylation; bicyclic compounds; cyclization; heterocycles; phase-transfer catalyst

INTRODUCTION

The diverse biological activities of various functional derivatives of 4-substituted alkyl-1-(2H)-phthalazinones are well known. Some of the phthalazinone derivatives have found application in clinical medicine because of their pronounced antipyretic, analgesic, and tuberculostatic activity while others have shown interesting vasodilator[1] and antihypertensive properties. Phthalazine-1-(2H)-ones bearing a substitutent at the C-4 position represent key intermediates in the syntheses of various compounds with highly interesting pharmacological properties, such as the blood platelet aggregation inhibitor MV-5445 [1-(3-chloroanilino)-4-phenylphthalazine],[2]

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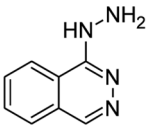
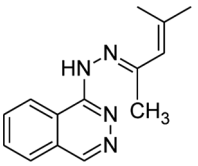
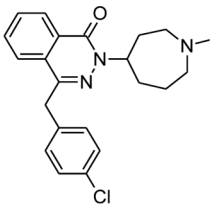
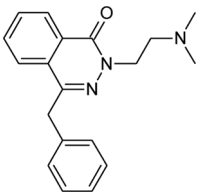
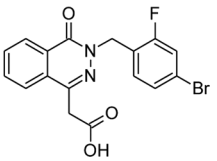
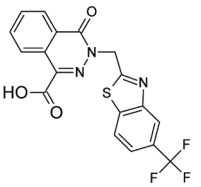
which has been found to be a selective phosphodiesterase VA inhibitor, and the thromboxane A2 syntheses inhibitor and bronchodilator 2-[2-(1-imidazolyl)ethyl]-4-[3-pyridyl]-phthalazine-1[2H]-one.[3] The phthalazinone nucleus has been proved to be a versatile system in medicinal chemistry.

A literature survey revealed that phthalazinone-based compounds have widespread applications in the field of pharmaceuticals. The heteroderivatives of phthalazinones were claimed to have antiviral, antibacterial, and antitumor activity as well as sedative and tranquilizing properties. Moreover, a number of established drug

Table 1. Some of the commercially important phthalaziones

Structure	Generic name	Brand name	Activity
	Hydralazine	Apresoline	Antihypertensive
	Budralazine	Buterazine	Antihypertensive
	Azelastine	Astelin	Histamine antagonist
	Talastine	Ahanon	Antihistamine
	Ponalrestat	Statil	Aldose reductase inhibitor
	Zopolrestat	Alond	Aldose reductase inhibitor

molecules such as hydralazine, budralazine,[4] azelastine,[5] ponalrestat,[6] and zopolrestat[7] are accessible starting from the corresponding phthalazinones. Some of the commercially important phthalaziones are described in Table 1.

The development of new and efficient methodologies for the synthesis of such potentially bioactive phthalazine derivatives was important. Despite the useful nature of phthalazinone, there are very few synthetic approaches in the literature for the formation of 4-phenyl and 4-substituted alkyl-1-(2H)-phthalazinones and their derivatives.[8–11] Therefore, functionalization of the nucleus continues to be of synthetic interest. In general, most of the structural modifications of the parent system that have been carried out to optimize the biological activity of phthalazine-derived drugs can be seen as a variation of the substitution pattern at positions 1, 2, and 4, that is, the substitution pattern of the 1,2-diazine part of the bicyclic system.

Most of the methods available for the construction of the phthalazinone nucleus suffer from one or more drawbacks, such as long reaction time or the use of expensive and hazardous reagents and solvents. Recent advances in technology have now made microwave energy a more efficient means of heating.[12] Chemical transformations that took hours or even days for completion can now be accomplished in minutes or seconds. Microwave energy offers numerous benefits for performing synthesis including enhancements in reaction rate, yield, and clean chemistry. These advantages are of the special importance in traditional organic synthesis, high-speed combinatorial and medicinal chemistry, as well as industrial-scale production.[13,14] We report synthesis of some novel phthalazinones and their derivatives with use of a highly sophisticated instrument, CEM Discover.

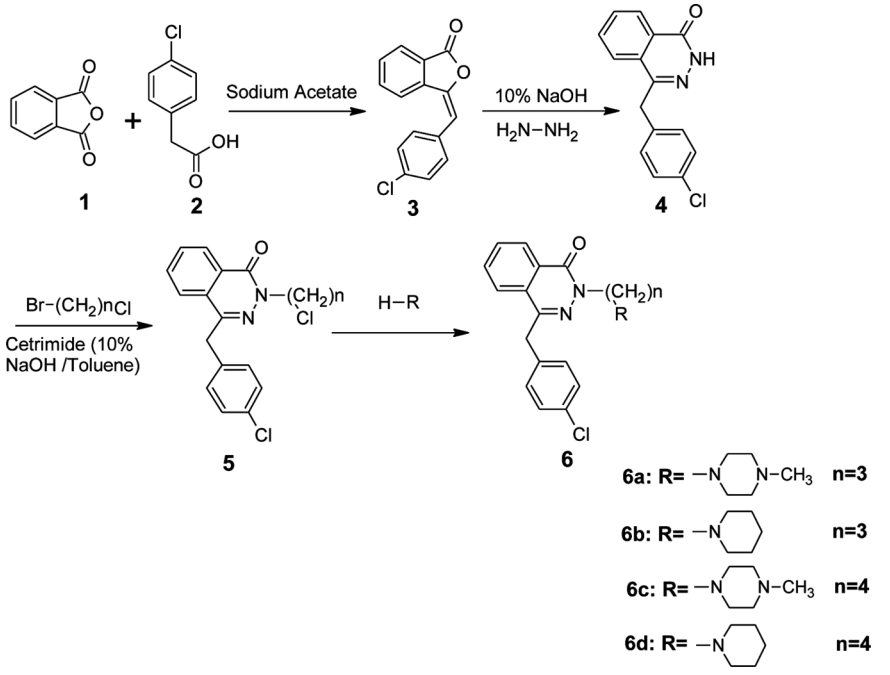
RESULTS AND DISCUSSION

In this article, we report the synthesis of novel phthalazines through microwave-assisted synthesis.

In our first approach, phthalic anhydride **1** was condensed with 4-chloro phenyl acetic acid **2** to obtain condensed product **3**. This was converted to phthalazine derivative **4** by treatment with hydrazine hydrate, which was further reacted with halogenated aliphatic molecules to obtain selective compounds **5a** and **5b** (Scheme 1). The reactions were carried out under microwave irradiation using microwave synthesizer CEM Discover.

The compounds **5a** and **5b** were synthesized using a novel green chemistry approach by condensing compound **4** with different pharmacologically active halogenated aza heterocyles. The aliphatic compound was coupled with compound **4** in biphasic condition in the presence of a phase-transfer catalyst to get product in greater yield with less reaction time.

To optimize the reaction conditions, we selected the various phase-transfer catalysts, such as tetraethyl ammonium iodide (TEAI), tetramethyl ammonium bromide (TMAB), tetrabutyl ammonium bromide (TBAB), tetraethyl ammonium bromide (TEAB), and cetrimide. It is shown that the use of a phase-transfer catalyst can significantly improve the yield in all of the cases studied, but different phase-transfer catalysts can give different results. Cetramide was the most suitable catalyst for the reaction studied. These phase-transfer catalysts under microwave irradiation afford better yields than the conventional method.



Scheme 1. Synthesis of compounds **6(a–d)**.

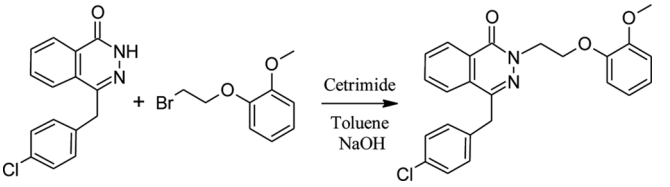
We therefore decided to investigate the reaction upon microwave irradiation with simultaneous cooling. As advocated in the literature,[15] this should allow for greater levels of microwave energy to be introduced into the reaction mixture, while maintaining the bulk of the material at a relatively low temperature by cooling the vial with a stream of compressed air or a microwave transparent cooling liquid. Using the same reagent ratios and solvent as those for the reactions run at room temperature, the reaction condition was optimized using different phase transfer condition as described in Table 2.

As illustrated in Table 2 use of cetrimide as phase-transfer catalyst in microwaves shows remarkable efficiency for the reaction.

Table 2. Comparison of microwave and conventional syntheses of compounds **5a** and **5b**

Phase-transfer catalysts	Microwave method[a]		Conventional method[b]	
	5a yield (%)	**5b** time (h)	**5a** yield (%)	**5b** time (h)
TEAI	88	0.3	37	14
TMAB	78	0.3	39	14
TBAB	90	0.3	48	14
TEAB	60	0.3	56	14
Cetrimide	92	0.3	61	14

[a]Microwave condition at 100 W for 30 min.
[b]Conventional heating at 50 °C for 14 h.



Scheme 2. Synthesis of compound **6e**.

The compounds **5a** and **5b** were condensed with various pharmacologically active halogenated aza heterocyles under microwave conditions to give products **6(a–d)** (Scheme 1). The reactions were carried out under microwave irradiation using microwave synthesizer CEM Discover.

In a second approach, compound **6e** was synthesized by condensing 1-(2-bromoethoxy)-2-methoxybenzene with compound **4** using phase-transfer catalyst cetrimide under microwave irradiation as per Scheme 2. The reaction condition was optimized based on reaction data described in Table 1.

In summary, we have developed a direct and efficient method for the synthesis of substituted phthalazine derivatives synthesized from phthalyl derivatives as starting material, with a combination of rapid microwave synthesis and phase-transfer catalyst methodology.

EXPERIMENTAL

Microwave reactions were conducted using a CEM Discover Synthesis unit (CEM Corp. Matthews, NC).[12] The machine consists of a continuous focused microwave power delivery system with operator-selectable power output from 0 to 300 W. Reactions were performed in glass vessels. The temperature of the contents of the vessel was monitored using a calibrated infrared (IR) temperature control mounted under the reaction vessel. All experiments were performed using a stirring option whereby the contents of the vessel are stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel.

Chromatographic purification was performed using instrument Combiflash Teledyne model companion with Ultraviolet–visible detector [flow rate, 25.0 ml min^{-1}; detector dual wavelength, 254 and 272 nm; chromatographic columns Redisep Silica Gel (24 gm)]. Mass spectrometer Agilent 6300 series with electrospray ionization (ESI) probe was operated in the positive ion mode.

^{1}H NMR spectra were recorded in $CDCl_3$ on a 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) relative to the appropriate standards: tetramethylsilane (TMS) as an internal standard for ^{1}H NMR. All melting points were determined in open capillary tubes and are uncorrected. Thin-layer chromatogrphic (TLC) analysis was performed with aluminum-backed plates precoated with silica gel and examined under ultraviolet (UV) fluorescence (254 nm).

Synthesis of 3-(4-Chlorobenzylidene)-2-benzofuran-1(3H)-one (3)

Phthalic anhydride **1** (14.8 g, 0.1 mol), 4-chlorophenyl acetic acid **2** (17.05 g, 0.1 mol), sodium acetate (4.2 g, 0.05 mol), and acetonitrile (10 ml) was added in

a round-bottom glass flask equipped with a magnetic stirring bar and reflux condenser. The flask was placed in a CEM Discover focused microwave synthesis system. The reaction mixture was stirred for 1 min at room temperature. The reaction mass was exposed to microwave irradiation at 85 °C at initial power 120 W for 20 min in a self-tuning single-mode CEM Discover synthesizer. The progress of reaction was monitored (using TLC) after 5-min intervals. The resulting mixture was allowed to cool to room temperature and the reaction was poured into ice water. The resulting precipitated solid was collected by vacuum filtration, washed with chilled water and dried. The crude product on recrystallization from methanol yielded 3-(4-chlorobenzylidene)-2-benzofuran-1(3H)-one **(3)**.

Yield 65%, mp 138 °C (lit.[16] 268–272 °C) MS (ESI): m/z [M + H] calcd. for $C_{15}H_9ClO_2$:256.6; found: 257.4.

Synthesis of 4-(4-Chlorobenzyl)phthalazin-1(2H)-one (4)

Compound **3** (26.0 g, 0.101 mol) was charged into a solution of 10% NaOH (10 ml) in a round-bottom glass flask equipped with a magnetic stirring bar and reflux condenser. The flask was placed in a CEM Discover focused microwave synthesis system. The reaction mixture was stirred for 1 min at room temperature. Hydrazine hydrate (1 ml) was added dropwise under stirring. The reaction mixture was exposed to microwave irradiation at initial power 80 W at 90 °C for 30 min in a self-tuning single-mode CEM Discover synthesizer. The progress of the reaction was monitored (using TLC) after 15-min intervals. The resulting mixture was allowed to cool at room temperature and the reaction was poured into ice water. The resulting precipitated solid was collected by vacuum filtration and washed with chilled water. The crude product was recrystallized in ethanol and yielded 4-(4-chlorobenzyl) phthalazin-1(2H)-one **(4)**.

Yield 70%, mp 270 °C (lit.[17] 268–272 °C). MS (EI): m/z [M + H] calcd. for $C_{15}H_{11}ClN_2O$: 270.71; found: 271.2.

4-(4-Chlorophenyl)-2-(3-chloropropyl) phthalazine-1-(2H)-one (5a)

A compound **4** (2.70 g, 0.01 mol) was suspended in toluene (10 ml) and a solution of 10% NaOH (10 ml) was added to the reaction mass. 1-Bromo-3-chloropropane (4.8 g, 0.03 mol) was added, and the reaction mixture was stirred at room temperature (around 26 °C) for 5 min. Cetrimide (1.9 g) was added to the reaction mass. The reaction mixture was exposed to microwave irradiation at initial power of 100 W and simultaneous cooling to maintain reaction temperature below 50 °C for 30 min using a self-tuning single-mode CEM Discover synthesizer. The progress of the reaction was monitored (using TLC) after 15-min intervals. After completion of the reaction, the resulting mixture was allowed to cool to room temperature. The organic layer was separated and washed with water (3 × 25 ml). The solvent was evaporated on a rotavapor under vacuum, maintaining temperature below 60 °C. The obtained solid was recrystallized by ethanol, yielding 4-(4-chlorophenyl)-2-(3-chloropropyl) phthalazine-1-(2H)-one **(5a)**.

Yield 80%, mp 205 °C. ^{1}H NMR ($CDCl_3$): δ = 2.11–2.20 (m, 2H, -CH_2), 3.51–3.53 (t, 2H, -CH_2), 4.29–4.36 (m, 4H, 2 -CH_2), 7.21–7.31 (m, 4H, Ar-H),

7.70–7.76 (m, 3H, Ar-H), 8.49–8.51 (m, 1H, Ar-H). MS (EI): m/z [M + H] calcd. for $C_{18}H_{16}Cl_2N_2O$: 347.23; found: 347.2. Anal. calcd. for $C_{18}H_{16}Cl_2N_2O$: C, 62.26%; H, 4.64; Cl, 20.42; N, 8.07. Found: C, 62.19%; H, 4.67; Cl, 20.30; N, 8.11.

4-(4-Chlorophenyl)-2-(4-chlorobutyl) phthalazin-1-(2H)-one (5b)

Compound **4** (2.70 g, 0.01 mol) was suspended in toluene (10 ml) and solution of 10% NaOH (10 ml) was added to reaction mass. 1-Bromo-3-chlorobutane (5.1 g, 0.03 mol) was added, and the reaction mixture was stirred at room temperature (around 26 °C) for 5 min. Cetrimide (1 g) was added to the reaction mass. The reaction mixture was exposed to microwave irradiation at initial power of 100 W and simultaneous cooling to maintain reaction temperature below 50 °C for 30 min in a self-tuning single-mode CEM Discover synthesizer. The progress of the reaction was monitored (using TLC) after 15-min intervals. After completion of the reaction, the resulting mixture was allowed to cool to room temperature. The organic layer was separated and washed with water (3×25 ml). The solvent was evaporated on a rotavapor under vacuum, maintaining temperature below 60 °C. The solid was recrystallized by ethanol, yielding 4-(4-chlorophenyl)-2-(4-chlorobutyl) phthalazin-1-(2H)-one **(5b)**.

Yield 60%, mp 290 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.84$–1.92 (m, 2H, -CH_2), 2.02–2.10 (m, 2H, -CH_2), 3.60–3.63 (t, 2H, -CH_2), 4.27–4.33 (m, 4H, 2-CH_2), 7.19–7.29 (m, 4H, Ar-H), 7.68–7.73 (m, 3H, Ar-H), 8.45–8.48 (m, 1H, Ar-H). MS (EI): m/z [M + H] calcd. for $C_{19}H_{18}Cl_2N_2O$: 361.26; found: 361.0. Anal. calcd. for $C_{18}H_{16}Cl_2N_2O$: C, 62.26%; H, 4.64; Cl, 20.42; N, 8.07. Found: C, 62.19%; H, 4.67; Cl, 20.30; N, 8.11.

4-(4-Chlorobenzyl)-2-(3-(4-methylpiperazin-1-yl)propyl)phthalazin-1 (2H)-one (6a)

A mixture of compound **5a** (3.8 g, 0.01 mol), N-methyl piperazine (2.0 g, 0.02 mol), and acetonitrile (5 ml) was stirred at room temperature (around 26 °C) for 5 min. The reaction mixture was exposed to microwave irradiation at initial power of 120 W at 75 °C for 20 min in a self-tuning single-mode CEM Discover synthesizer. The progress of reaction was monitored (using TLC) after 5-min intervals. The reaction mixture was allowed to cool to room temperature and poured into ice water. The precipitated solid was collected by vacuum filtration and washed with chilled water. The product was purified by flash chromatography under normal phase condition on a silica-gel column using hexane–ethyl acetate as eluent, yielding the 4-(4-chlorobenzyl)-2-(3-(4-methylpiperazin-1-yl)propyl) phthalazin-1(2H)-one **(6a)**.

Yield 70%, mp 228 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.30$–2.50 (m, 15H, -CH_2 & -CH_3), 4.26–4.32 (m, 4H, -CH_2), 7.19–7.66 (m, 4H, Ar-H), 7.67–7.72 (m, 3H, Ar-H), 8.44–8.47 (d, 1H, Ar-H). ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 25.9$ (CH_2), 38.3 (CH_3), 46.1 (CH_2), 49.4 (CH_3), 53.2 (CH_2), 55.2 (CH_2), 55.8 (-CH_2), 124.8 (ArC), 127.4 (2-ArC), 128.3 (ArC), 128.8 (ArC), 129.0 (-ArC), 129.8 (ArC), 131.2 (ArC), 132.6 (ArC), 132.8 (ArC), 136.3 (ArC), 144.5 (C=N), 159.2 (CO). MS (EI): m/z [M + H] calcd. for $C_{23}H_{27}ClN_4O$: 410.93; found: 411.42. Anal. calcd. for

$C_{23}H_{27}ClN_4O$: C, 67.22; H, 6.62; Cl, 8.63; N, 13.63. Found: C, 67.27; H, 6.66; Cl, 8.59%; N, 13.63.

4-(4-Chlorobenzyl)-2-(3-(piperidin-1-yl)propyl)phthalazin-1 (2H)-one (6b)

A mixture of compound **5a** (3.4 g, 0.01 mol), piperidine (1.7 g, 0.02 mol), and acetonitrile (5 ml) was stirred at room temperature (around 26 °C) for 5 min. The reaction mixture was exposed to microwave irradiation at initial power of 120 W at 75 °C for 20 min in a self-tuning single-mode CEM Discover synthesizer. The progress of the reaction was monitored (using TLC) after 5-min intervals. The reaction mixture was allowed to cool to room temperature and poured into ice water. The precipitated solid was collected by vacuum filtration, washed with chilled water, and dried. The product was purified by flash chromatography under normal-phase condition on a silica-gel column using hexane–ethyl acetate as a eluent, yielding 4-(4-chlorobenzyl)-2-(3-(piperidin-1-yl)propyl)phthalazin-1(2H)-one **(6b)**.

Yield 60%, mp 110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.25$–1.63 (m, 4H, -CH_2), 1.84–1.91 (m, 3H, -CH_2), 2.33–2.36 (m, 7H, -CH_2), 4.25–4.29 (m, 4H, -CH_2), 7.19–7.26 (m, 4H, Ar-H), 7.64–7.69 (m, 3H, Ar-H), 8.43–8.46 (d, 1H, Ar-H). ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 24.0$ (CH_2), 24.4 (CH_2), 25.9 (CH_2), 26.6 (CH_3), 38.2 (CH_2), 50.8 (CH_2), 54.5 (CH_2), 124.7 (ArC), 127.2 (2-ArC), 128.2 (ArC), 128.8 (ArC), 131.1 (2-ArC), 132.4 (ArC), 132.7 (ArC), 136.3 (ArC), 144.3 (C=N), 159.1 (CO). MS (EI): m/z [M + H] calcd. for $C_{23}H_{26}ClN_3O$: 395.92; found: 396.5. Anal. calcd. for $C_{23}H_{26}ClN_3O$: C, 69.77; H, 6.62; Cl, 8.95; N, 10.61. Found: C, 69.71; H, 6.59; Cl, 8.89; N, 10.64%.

4-(4-Chlorobenzyl)-2-(3-(4-methylpiperazin-1-yl)butyl)phthalazin-1 (2H)-one (6c)

A mixture of compound **5a** (3.8 g, 0.01 mol), N-methylpiperazine (0.02 mol), and acetonitrile (5 ml) was stirred at room temperature (around 26 °C) for 5 min. The reaction mixture was exposed to microwave irradiation at initial power of 120 W at 75 °C for 20 min in a self-tuning single-mode CEM Discover synthesizer. The progress of reaction was monitored (using TLC) after 5-min intervals. The reaction mixture was allowed to cool at room temperature. The reaction mixture was poured into ice water, and the precipitated solid was collected by vacuum filtration. The solid was washed with chilled water and dried. The product was purified by flash chromatography under normal phase condition on a silica-gel column using hexane–ethyl acetate as a eluent, yielding 4-(4-chlorobenzyl)-2-(3-(4-methylpiperazin-1-yl) butyl) phthalazin-1(2H)-one **(6c)**.

Yield 60%, mp 110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.18$–2.38 (m, 17H, -CH_2-& CH_3), 4.17–4.22 (m, 4H, -CH_2), 7.11–7.57 (m, 4H, Ar-H), 7.58–7.62 (m, 3H, Ar-H), 8.35–8.38 (t, 1H, Ar-H). ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 24.0$ (CH_2), 26.5 (CH_2), 29.9 (CH_2), 38.2 (CH_2), 46.1 (CH_2), 50.8 (CH_3), 53.2 (CH_2), 55.1 (2-CH_2), 58.2 (CH_2), 124.8 (ArC), 127.3 (ArC), 128.2 (ArC), 128.8 (ArC), 128.9 (ArC), 129.7 (ArC), 131.1 (ArC), 132.5 (ArC), 132.7 (ArC), 136.3 (ArC), 144.4 (C=N), 159.1 (CO). MS (EI): m/z [M + H] calcd. for $C_{24}H_{29}ClN_4O$: 424.96; found: 425.4. Anal.

calcd. for $C_{24}H_{29}ClN_4O$: C, 67.83; H, 6.88; Cl, 8.34; N, 13.18. Found: C, 67.89; H, 6.84; Cl, 8.29; N, 13.14%.

4-(4-Chlorobenzyl)-2-(4-(piperidin-1-yl)butyl)phthalazin-1 (2H)-one (6d)

A mixture of compound **6d** (3.6 g, 0.01 mol), piperidine (1.7 g, 0.02 mol), and acetonitrile (5 ml) was stirred at room temperature (around 26 °C) for 5 min. The reaction mixture was exposed to microwave irradiation at initial power of 120 W at 75 °C for 20 min in a self-tuning single-mode CEM Discover synthesizer. The progress of reaction was monitored (using TLC) after 5-min intervals. The reaction mixture was allowed to cool at room temperature and poured into ice water. Precipitated solid was collected by vacuum filtration, washed with chilled water, and dried. The product was purified by flash chromatography under normal phase condition on a silica-gel column using hexane–ethyl acetate as a eluent, yielding 4-(4-chlorobenzyl)-2-(4-(piperidin-1-yl)butyl)phthalazin-1(2H)-one **(6d)**.

Yield 60%, mp 220 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.4$–1.6 (m, 8H, -CH_2), 1.83–1.9 (m, H, -CH_2), 2.32–2.36 (m, 3H, -CH_2), 4.24–4.28 (m, 4H, -CH_2), 7.18–7.25 (m, 6H, Ar-H), 7.64–7.69 (m, 2H, Ar-H), 8.42–8.45 (d, 1H, Ar-H). ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 24.2$ (CH_2), 24.5 CH_2), 26.0 (CH_2), 26.7 (CH_2), 38.3 (CH_2), 50.9 (CH_2), 54.6 (CH_2), 59.2 (CH_2), 124.8 (ArC), 127.3 (ArC), 128.3 (ArC), 128.9 (ArC), 129.7 (ArC), 131.2 (ArC), 132.5 (ArC), 132.8 (ArC), 136.4 (ArC), 144.4 (C=N), 159.1 (CO). MS (EI): m/z [M + H] calcd. for $C_{24}H_{28}ClN_3O$: 409.95; found: 410.4. Anal. calcd. for $C_{24}H_{28}ClN_3O$: C, 70.31; H, 6.88; Cl, 8.65; N, 10.25. Found: C, 70.34; H, 6.90; Cl, 8.61; N,10.28%.

4-(4-Chlorobenzyl)-2-(2-(3-methoxyphenoxy)ethyl)phthalazin-1 (2H)-one (6e)

A mixture of compound **4** (2.7 g, 0.01 mol), 1-(2-bromoethoxy)-2-methoxybenzene (2.31 g, 0.01 mol), and toluene was stirred at room temperature (around 26 °C) for 5 min. Cetrimide (1 g) was added to the reaction mass. The reaction mixture was exposed to microwave irradiation at initial power of 100 W and simultaneous cooling maintained reaction temperature below 50 °C for 30 min in a self-tuning single-mode CEM Discover synthesizer. The progress of reaction was monitored (using TLC) after 15-min intervals. The reaction resulting mixture was allowed to cool to room temperature. The organic layer was separated and washed with water (3×25 ml). The solvent was evaporated on a rotavapor under vacuum, maintaining temperature below 60 °C. The product was purified by flash chromatography under normal phase condition on a silica-gel column using hexane–ethyl acetate as a eluent, yielding 4-(4-chlorobenzyl)-2-(2-(3-methoxyphenoxy)ethyl)phthalazin-1(2H)-one **(6e)**.

Yield 75%, mp 130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.28$–1.32 (s, 3H, -OCH3), 3.9–4.27 (m, 6H, -CH_2), 6.88–7.27 (m, 8H, Ar-H), 7.68–7.74 (m, 3H, Ar-H), 8.47–8.5 (m, 1H, Ar-H). ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 38.3$ (CH_2), 50.2 (CH_2), 55.9 (CH_2), 64.5 (CH_2), 66.5 (CH_3), 114.5 (ArC), 115.0 (ArC), 121.1 (ArC), 121.8 (ArC), 124.9 (ArC), 127.4 (ArC), 128.3 (ArC), 128.8 (ArC), 129.1 (ArC), 129.8 (ArC), 131.3 (ArC), 132.5 (ArC), 133.0 (ArC), 136.2 (ArC), 144.7

(ArC), 148.5 (ArC), 149.1 (C=N), 159.9 (CO). MS (EI): m/z [M + H] calcd. for $C_{24}H_{21}ClN_2O_3$: 420.88; found: 421.1. Anal. calcd. for $C_{24}H_{21}ClN_2O_3$: C, 68.49; H, 5.03; Cl, 8.42; N, 6.66. Found: C, 68.46; H, 5.07; Cl, 8.39; N, 6.70%.

CONCLUSION

A synergistic combination of phase-transfer catalyts and microwave techniques can be used to carry out a number of organic reactions under mild conditions. The substitution reactions under conventional heating take many hours and poor yields of desired products were obtained. Our present study demonstrated that microwave irradiation can greatly facilitate the synthesis of phthalazine moiety. Microwave irradiation is a promising method for the synthesis organic compounds. In summary, we have developed a simple procedure for the rapid synthesis of some biologically active phthalazinone analogs.

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