Microwave-Promoted Solid-Acid-Catalyzed One-Pot Synthesis of Phthalazinones

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Abstract: A one-pot, solid-acid-catalyzed, microwave-assisted synthesis of phthalazinones is described. The commercially available montmorillonite K-10 effectively catalyzed the condensation and substitution reactions. The approach was based on the direct cyclization of phthalaldehydic acid and opianic acid with substituted hydrazines. The reactions provided excellent yields and high selectivities in very short time (5–35 minutes).

Key words: phthalazinones, phthalaldehydic acid, opianic acid, hydrazines, montmorillonite K-10, microwave heating

Nitrogen-containing heterocycles are important core motifs in a broad range of biologically active compounds[1] that are frequently used in pharmaceutical and drug research, agricultural science, and the dye industry. Phthalazinones, a group of condensed N-heterocycles, are particularly well known for their biological activity. They have significant potential in the treatment of a variety of disorders, such as asthma,[2] diabetes,[3] hepatitis B,[4] vascular hypertension[5] and arrhythmia,[6] and also alleviate convulsions,[7] counter multi-drug resistance in cancer patients,[6] show potent antimicrobial activity[8] and are potent inhibitors of poly(ADP-ribose) polymerase-1 (PARP-1).[9] Azelastine®, a phthalazinone derivative, is a well known anti-allergy and anti-asthmatic drug.[2,10] Phthalazinone is a crucial substructure and has been used as a starting material in the preparation of a new phosphodiesterase-4 (PDE-4) inhibitor.[2,11] A few examples of phthalazinone-based drugs and potential drug candidates are illustrated in Figure 1.

Due to the significant interest in these compounds, several methods have been developed for their synthesis. Such methods include, but are not limited to, cyclocondensation,[2,12] cycloaddition,[13] reduction,[14] or multi-step synthesis including halogenations and hydrolysis followed by cyclization.[13a] Biotechnological approaches have also been used for the synthesis of phthalazinones.[15] However, these methods usually require strong acids and bases, strong reducing agents, long reaction times, high temperatures or multiple steps. The biological importance of phthalazinones and the lack of environmentally benign methods that conform to current standards clearly indicate the need for continued efforts in this area.

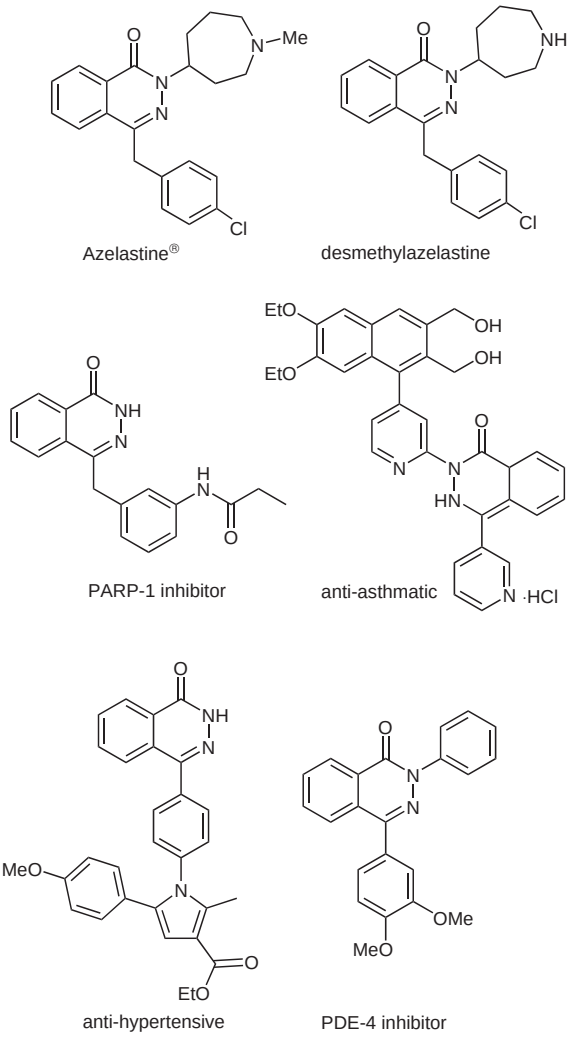

Figure 1 Examples of biologically active phthalazinones

Herein, we describe a novel method for the synthesis of phthalazinones by the condensation and substitution reactions of phthalaldehydic acid with hydrazines. The two-step, one-pot method was carried out by the combination of solid-acid catalysis and microwave energy. Previously, we illustrated the essential advantages of such systems[16] in a wide range of reactions[17–20] and, based on our experience, montmorillonite K-10 was selected as a catalyst. This clay-based solid acid is not only an effective catalyst, it is also economic, durable, and absorbs microwaves. Most importantly, it is an environmentally friendly material that does not produce any waste and is usually recy-

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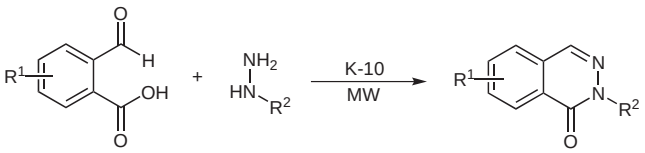
clable.[21] The schematic depiction of the process is shown in Scheme 1.



R^1 = H, 3,4-di-OMe
R^2 = H, alkyl, aryl

Scheme 1 Microwave-assisted, one-pot synthesis of phthalazinones from phthalaldehydic acid and hydrazines using montmorillonite K-10 catalyst

To verify our hypothesis and to find optimum reaction conditions, we chose the coupling of phthalaldehydic acid and hydrazine hydrochloride as a test reaction. Initially, we studied the effect of reaction temperature and time. We also compared the effect of microwave and conventional heating, and determined whether the reaction occurred without catalyst. The coupling reaction took place on the surface of the catalyst without using solvent during the reaction. Each reaction was carried out in a CEM Discover microwave reactor at constant temperature. The results are summarized in Table 1.

Table 1 Optimizing the Synthesis of 1(2*H*)-Phthalazinone from Phthalaldehydic Acid and Hydrazine Dihydrochloride on K-10 Montmorillonite[a]

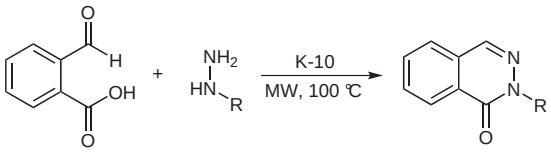
Entry	Heating method[b]	Temp (°C)	Time (min)	Yield (%)[c]
1	MW	90	15	88
2	MW	100	5	98
3[d]	MW	100	5	8
4[d]	MW	100	15	14
5	CH	100	90	79
6	CH	100	180	84

[a] 1:1 reactant ratio.
[b] Microwave heating (MW; 200 W), conventional heating (CH).
[c] GC yields, based on phthalaldehydic acid.
[d] No catalyst.

Since the initial test reaction (150 °C for 10 min with 1:1 molar ratio of the reactants) gave 100% conversion and selectivity, we then screened more benign conditions such as lower temperatures and shorter times. As shown in Table 1 (entry 2), 100 °C and five minutes reaction time appeared to be optimal. Although the starting materials were consumed quantitatively without the assistance of the catalyst, the yield of the desired product was diminished by the very low selectivity of the reactions; reactions in absence of K-10 catalyst resulted in low yields for the phthalazinone, due to high amounts of by-products (Table 1, entries 3 and 4). The conventional reaction, carried out in a closed pressure vessel in the absence of microwave irradiation, resulted in 84% product yield together with substantial amounts of by-products, in 20 times longer reaction time. Thus, the solid-acid catalyst and microwave energy are both necessary to obtain high yield and purity. In summary, 100 °C temperature, an equimolar reactant ratio and five minutes microwave irradiation, gave excellent yield and selectivity; these conditions were therefore chosen for further reactions with substituted hydrazines. In order to test the scope of the method, a variety of substituted hydrazines were selected for the reaction with phthalaldehydic acid to synthesize substituted phthalazinones (Table 2).

The results, depicted in Table 2, clearly show that the cyclization takes place effectively with all the substituted hydrazines tested. The products were obtained in good to excellent yields; six of nine reactions afforded close to quantitative product formation. The remaining three hydrazines also gave high yields (72–85%; Table 2, entries 6, 8 and 9). The reaction of 2,5-dimethylphenylhydrazine with phthalaldehydic acid required higher temperature (150 °C) and a slightly longer reaction time. Generally, the products formed in very short reaction times; even the longest reaction was complete in ten minutes. The lowest, but still good, yield of 72% was obtained with *tert*-butylhydrazine, possibly due to steric constraints (Table 2, entry 8). This reaction gave the best result at one minute reaction time; extending the time to five or ten minutes decreased the yield of phthalazinone product to 69% and 58%, respectively, due to product decomposition and the formation of a cyclic acetal by-product.

Table 2 Microwave-Assisted, One-Pot Synthesis of Phthalazinones from Phthalaldehydic Acid and Hydrazines using Montmorillonite K-10 Catalyst at 100 °C[a]



R = H, alkyl, aryl

Entry	R	Time (min)	Yield (%)[b]
1	H	5	98
2	Ph	8	98
3	3-MeC_6H_4	5	98
4	Me	5	98
5	2-MeOC_6H_4	5	98
6[c]	2,5-$(Me)_2C_6H_3$	10	85[c]
7	2-EtC_6H_4	10	98
8	*t*-Bu	1	72
9	4-MeOC_6H_4	1	83

[a] P = 200 W, 1:1 reactant ratio, 100 °C.
[b] GC yields, based on phthalaldehydic acid.
[c] Reaction temperature 150 °C.

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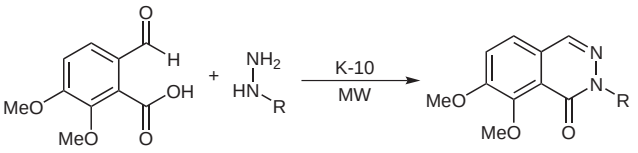
In order to extend the procedure to further applications, a substituted derivative of phthalaldehydic acid was applied. Opianic acid (2-carboxy-3,4-dimethoxybenzaldehyde) and its derivatives are well known for their biological activity.[22] The verbatim application of the above described optimized reaction conditions, however, did not appear effective with opianic acid. The reactivity of the starting material and the stability of the products under the experimental conditions required careful adjustments of the procedure to most reactions individually. The presence of the two methoxy groups in the opianic acid structure had a deactivating effect, likely due to their strong adsorption capability on K-10; this strong complex formation deactivated the reactant. Therefore, in many cases, higher reaction temperatures were necessary. The optimization of these cyclizations followed the approach already shown in Table 1. Without detailing these efforts, we have carried out the reactions of various substituted hydrazines with opianic acid. The optimized results are summarized in Table 3. These reactions were difficult to bring to completion even at higher temperatures and longer reactions times. The temperature and time range varied from as low as 60 °C to 150 °C and from 5 to 35 minutes, respectively. The products appeared sensitive to the reaction conditions, as shown by the product loss as a result of prolonged irradiation. Increasing reaction times beyond those reported in Table 3 caused product decomposition in all reactions except those with 2,5-dimethylphenylhydrazine and 2-ethylphenylhydrazine (Table 3, entries 6 and 7).

The above limitations reduced the efficiency to some extent, however, the products still formed in moderate to good yields. Supporting our earlier observations regarding substituent effects (Table 2), reactions with sterically hindered hydrazines gave moderate yields. The major by-products usually included reduced dihydro-derivatives of phthalazinones, which possibly formed via acid-catalyzed ionic hydrogenation, where cracking products with low molecular weight served as hydrogen sources.

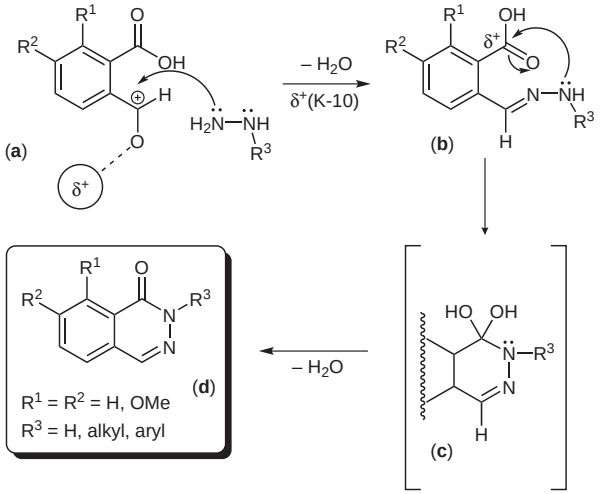
Table 3 Microwave-Assisted, One-Pot Synthesis of Phthalazinones from Opianic Acid and Hydrazines using Montmorillonite K-10 Catalyst[a]



R = H, alkyl, aryl

Entry	R	Time (min)	Temp (°C)	Yield (%)[b]
1	H·2HCl	5	90	82
2	Ph	5	150	98
3	3-MeC_6H_4	5	150	65
4	Me	5	150	73
5	2-MeOC_6H_4	5	100	60
6	2,5-$(Me)_2C_6H_3$	35	60	62
7	2-EtC_6H_4	25	80	82
8	*t*-Bu	5	100	59

[a] P = 200 W, 1:1 reactant ratio, 100 °C.
[b] GC yields, based on opianic acid.



Scheme 2 Proposed mechanism for the K-10-catalyzed synthesis of substituted phthalazinones via one-pot nucleophilic cyclocondensation reactions of 2-carboxybenzaldehydes and hydrazines.

The proposed mechanism, summarized in Scheme 2, illustrates the reactions between phthalaldehydic acid with hydrazine derivatives. The cyclization is initiated by K-10, based on its ability to form surface-bound complexes with electron-donors such as oxygen and nitrogen atoms. The first step is the activation of the carbonyl group of the phthalaldehydic acid by the Lewis acid sites of K-10, depicted as δ^+. This interaction creates a carbocation-like complex, which undergoes a nucleophilic attack by the hydrazine's primary amino group (Scheme 2a) and ultimately results in a hydrazone intermediate. A cyclization of this Schiff base occurs via a nucleophilic attack on the carboxylic acid carbon by the hydrazine's secondary NH-group (Scheme 2b) and results in a *gem*-diol intermediate (Scheme 2c). The elimination of a water molecule yields the final product, phthalazinone (Scheme 2d).

In conclusion, a simple, efficient and environmentally benign method has been developed for the synthesis of phthalazinones from readily available phthalaldehydic and opianic acids via cyclizations with hydrazine derivatives. Our one-pot, microwave-assisted, solid-acid-catalyzed method was successful in producing a broad variety of phthalazinone derivatives. The application of the solid-acid catalyst offers significant improvements in all aspects of the synthesis of these compounds compared to available conventional methods. These improvements are, in part, due to the combination of microwave irradiation with the highly efficient solid-acid catalyst (K-10). The application of the microwave dielectric heating was instrumental in reducing reaction times and increasing

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yields, while the catalyst facilitated the completion of the two-step process. The environmental compatibility of the catalyst and the ease of product isolation are further advantages that make this approach an attractive alternative for the synthesis of the target compounds.

Phthalaldehydic acid, opianic acid, hydrazines and K-10 montmorillonite were purchased from Aldrich and used without further purification. The reactions were carried out at constant temperatures in a Discover Benchmate microwave reactor, with continuous stirring. The temperature was measured and controlled by a built-in infrared detector. The ^{1}H and ^{13}C NMR spectra were obtained on a 300 MHz Varian NMR spectrometer in $CDCl_3$. Tetramethylsilane, or the residual solvent signal was used as internal reference. MS identification of the products were carried out using an Agilent 6850 GC and 5973 MS system (70 eV electron impact ionization) using a 30 m long DB-5 type column (J&W Scientific). The melting points are uncorrected and were recorded on a MEL-TEMP apparatus.

Synthesis of Substituted Phthalazinones; General Procedure

Phthalaldehydic acid (1 mmol) was dissolved in MeOH (1 mL) and CH_2Cl_2 (2 mL) in a round-bottomed flask and combined with a hydrazine derivative (1 equiv). K-10 montmorillonite was added to the solution in a 5:1 mass ratio. The mixture was stirred thoroughly and the solvent was evaporated in vacuo. The dry mixture was transferred into a reaction vial. The open vial was placed in the microwave reactor (CEM Discover Benchmate) and was irradiated at constant temperature with continuous stirring. All reactions were carried out at atmospheric pressure. Upon completion of the reactions, the products were separated from catalyst with MeOH and CH_2Cl_2 using vacuum filtration. Products were purified and isolated using column chromatography (40–140 mesh silica gel; CH_2Cl_2–MeOH). During optimization the reaction was monitored by TLC and GCMS.

1(2*H*)-Phthalazinone (Table 2, Entry 1)

Pale-yellow crystals; mp 182–184 °C (CH_2Cl_2–MeOH, 90:10).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.48 (s, 1 H, NH), 8.45–8.48 (dd, *J* = 7.5, 0.3 Hz, 1 H, Ar), 8.23 (s, 1 H, Ar), 7.73–7.89 (m, 3 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.0, 139.0, 133.7, 131.8, 130.2, 127.9, 126.4, 126.2.

MS: *m*/*z* (%) = 146 (100) [M$^+$], 118 (27), 90 (26), 89 (91), 74 (7), 63 (35), 62 (15).

2-Phenyl-1(2*H*)-phthalazinone (Table 2, Entry 2)

Pale-orange crystals; mp 104–106 °C (CH_2Cl_2–MeOH, 90:10).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.47–8.50 (m, 1 H, Ar), 8.26 (s, 1 H, Ar), 7.65–7.83 (m, 5 H, Ar), 7.45–7.51 (m, 2 H, Ar), 7.34–7.39 (m, 1 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 141.7, 138.3, 133.3, 131.8, 129.2, 128.6, 128.3, 127.6, 127.0, 126.0, 125.5.

MS: *m*/*z* (%) = 222 (92) [M$^+$], 221 (100), 193 (10), 165 (12), 91 (26), 89 (45), 77 (66).

2(3-Methylphenyl)-1(2*H*)-phthalazinone (Table 2, Entry 3)

Orange solid; mp 48–50 °C (CH_2Cl_2–MeOH, 95:5).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 7.5 Hz, 1 H, Ar), 8.27 (s, 1 H, Ar), 7.71–7.85 (m, 3 H, Ar), 7.35–7.46 (m, 3 H, Ar), 7.18–7.21 (m, 1 H, Ar), 2.42 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 141.7, 138.6, 138.2, 133.3, 131.8, 129.3, 128.5, 128.4 (2×), 127.0, 126.2, 126.0, 122.7, 21.28.

MS: *m*/*z* (%) = 236 (89) [M$^+$], 235 (100), 207 (20), 192 (12), 165 (18), 104 (37), 91 (66).

2-Methyl-1(2*H*)-phthalazinone (Table 2, Entry 4)

Pale-yellow crystals; mp 112–114 °C (CH_2Cl_2–MeOH, 90:10).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.40–8.43 (m, 1 H, Ar), 8.14 (s, 1 H, Ar), 7.67–7.82 (m, 3 H, Ar), 3.85 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4, 137.4, 132.8, 131.4, 129.6, 127.5, 126.2, 125.8, 39.2.

MS: *m*/*z* (%) = 160 (64) [M$^+$], 132 (100), 104 (31), 89 (89), 76 (18), 63 (38), 62 (14).

2-(2-Methoxyphenyl)-1(2*H*)-phthalazinone (Table 2, Entry 5)

Orange crystals; mp 98–100 °C (CH_2Cl_2–MeOH, 90:10).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.46–8.50 (m, 1 H, Ar), 8.25 (s, 1 H, Ar), 7.71–7.86 (m, 3 H, Ar), 7.35–7.44 (m, 2 H, Ar), 7.01–7.10 (m, 2 H, Ar), 3.79 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2, 154.7, 138.2, 133.3, 131.7, 130.7, 130.2, 129.8, 128.6, 128.4, 127.1, 126.1, 120.9, 112.2, 55.9.

MS: *m*/*z* (%) = 252 (22) [M$^+$], 235 (18), 221 (100), 195 (26), 120 (23), 89 (22), 76 (29).

2-(2,5-Dimethylphenyl)-1(2*H*)-phthalazinone (Table 2, Entry 6)

Colorless crystals; mp 89–91 °C (CH_2Cl_2–MeOH, 95:5).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.49–8.52 (m, 1 H, Ar), 8.28 (s, 1 H, Ar), 7.75–7.90 (m, 3 H, Ar), 7.16–7.26 (m, 3 H, Ar), 2.36 (s, 3 H, CH_3), 2.15 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 140.6, 138.2, 136.6, 133.4, 131.8, 130.8, 129.7, 128.3, 127.7, 127.0, 126.1, 125.4, 116.3, 20.8, 17.1.

MS: *m*/*z* (%) = 250 (55) [M$^+$], 233 (100), 152 (56), 130 (72), 102 (71), 91 (62), 76 (73).

2-(2-Ethylphenyl)-1(2*H*)-phthalazinone (Table 2, Entry 7)

Yellow solid; mp 50–52 °C (CH_2Cl_2–MeOH, 95:5).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.50–8.53 (d, *J* = 7.80 Hz, 1 H, Ar), 8.29 (s, 1 H, Ar), 7.76–7.90 (m, 3 H, Ar), 7.30–7.43 (m, 4 H, Ar), 2.54 (q, *J* = 7.8 Hz, 2 H, CH_2), 1.16 (t, *J* = 7.8 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3, 140.8, 140.4, 138.1, 133.5, 131.9, 129.7, 129.2 (2×), 128.3, 127.5, 127.1, 126.8, 126.2, 24.0, 14.0.

MS: *m*/*z* (%) = 250 (31) [M$^+$], 233 (100), 221 (28), 130 (25), 104 (55), 89 (55), 77 (94).

2-(*tert*-Butyl)-1(2*H*)-phthalazinone (Table 2, Entry 8)

Orange oil; (CH_2Cl_2–MeOH, 95:5).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.40–8.43 (m, 1 H, Ar), 8.12 (s, 1 H, Ar), 7.64–7.80 (m, 3 H, Ar), 1.73 (s, 9 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.2, 135.6, 132.7, 131.0, 129.4, 129.2, 126.6, 125.2, 64.2, 28.3.

MS: *m*/*z* (%) = 202 (20) [M$^+$], 187 (12), 147 (100), 146 (95), 118 (35), 89 (55), 76 (13).

2-(4-Methoxyphenyl)-1(2*H*)-phthalazinone (Table 2, Entry 9)

Brown crystals; mp 105–107 °C (CH_2Cl_2–MeOH, 95:5).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 7.2 Hz, 1 H, Ar), 8.27 (s, 1 H, Ar), 7.73–7.87 (m, 3 H, Ar), 7.56 (d, *J* = 9.0 Hz, 2 H, Ar), 7.01 (d, *J* = 9.0 Hz, 2 H, Ar), 3.85 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.1, 158.8, 138.2, 135.2, 133.3, 131.9, 129.4, 128.4, 127.1, 126.9, 126.0, 113.9, 55.5.

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MS: *m*/*z* (%) = 252 (100) [M$^+$], 237 (36), 207 (15), 130 (15), 122 (19), 121 (39), 76 (17).

7,8-Dimethoxy-1(2*H*)-phthalazinone (Table 3, Entry 1)
Yellow-orange crystals; mp 162–164 °C (CH_2Cl_2–MeOH, 95:5).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.3 (s, 1 H, NH), 8.01 (s, 1 H, Ar), 7.48 (d, *J* = 8.7 Hz, 1 H, Ar), 7.46 (d, *J* = 8.7 Hz, 1 H, Ar), 4.01 (s, 3 H, CH_3), 4.00 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.9, 155.4, 148.5, 138.6, 123.2 (2×), 122.2, 118.5, 62.1, 56.5.

MS: *m*/*z* (%) = 206 (32) [M$^+$], 191 (100), 189 (49), 177 (42), 160 (41), 146 (47), 118 (25), 63 (97).

7,8-Dimethoxy-2-phenyl-1(2*H*)-phthalazinone (Table 3, Entry 2)
Orange solid; mp 174–176 °C (CH_2Cl_2–MeOH, 95:5).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 7.8 Hz, 1 H, Ar), 8.11 (s, 1 H, Ar), 7.45–7.80 (m, 6 H, Ar), 4.01 (s, 3 H, CH_3), 3.99 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.8, 154.9, 137.9, 135.6, 132.7, 131.0, 129.3, 128.7, 126.5, 126.0, 125.2, 118.3, 61.9, 56.5.

MS: *m*/*z* (%) = 282 (48) [M$^+$], 267 (100), 253 (18), 235 (22), 149 (21), 91 (23), 77 (90).

7,8-Dimethoxy-2-(3-methylphenyl)-1(2*H*)-phthalazinone (Table 3, Entry 3)
Orange solid; mp 78–80 °C (CH_2Cl_2–MeOH, 99:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10 (s, 1 H, Ar), 7.50 (d, *J* = 8.7 Hz, 1 H, Ar), 7.45 (d, *J* = 8.7 Hz, 1 H, Ar), 7.32–7.43 (m, 3 H, Ar), 7.17 (d, *J* = 7.2 Hz, 1 H, Ar), 4.01 (s, 3 H, CH_3), 3.99 (s, 3 H, CH_3), 2.41 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.5, 155.8, 149.0, 142.0, 138.7, 137.8, 128.6, 128.5, 126.7, 124.7, 123.2, 123.1, 118.3, 116.4, 61.9, 56.5, 21.4.

MS: *m*/*z* (%) = 296 (64) [M$^+$], 281 (100), 265 (16), 249 (20), 237 (18), 207 (39), 91 (41), 77 (20).

7,8-Dimethoxy-2-methyl-1(2*H*)-phthalazinone (Table 3, Entry 4)
Yellow crystals; mp 131–133 °C (CH_2Cl_2–MeOH, 99:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97 (s, 1 H, Ar), 7.45 (d, *J* = 8.7 Hz, 1 H, Ar), 7.42 (d, *J* = 8.7 Hz, 1 H, Ar), 4.01 (s, 3 H, CH_3), 3.99 (s, 3 H, CH_3), 3.80 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.0, 155.4, 137.0, 130.9, 128.8, 125.1, 122.9, 118.0, 61.9, 56.5, 39.4.

MS: *m*/*z* (%) = 220 (55) [M$^+$], 205 (100), 191 (67), 177 (45), 160 (42), 146 (42), 119 (46), 77 (50).

7,8-Dimethoxy-2-(2-methoxyphenyl)-1(2*H*)-phthalazinone (Table 3, Entry 5)
Orange crystals; mp 140–142 °C (CH_2Cl_2–MeOH, 99:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06 (s, 1 H, Ar), 7.34–7.48 (m, 4 H, Ar), 7.00–7.07 (m, 2 H, Ar), 3.97 (s, 3 H, CH_3), 3.96 (s, 3 H, CH_3), 3.78 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.3, 155.7, 154.7, 148.9, 137.7, 131.0, 129.9, 128.8, 125.0, 123.1, 122.7, 120.8, 118.2, 112.1, 61.9, 56.5, 55.8.

MS: *m*/*z* (%) = 312 (22) [M$^+$], 297 (40), 281 (70), 265 (18), 204 (25), 174 (24), 120 (82), 78 (100).

7,8-Dimethoxy-2-(2,5-dimethylphenyl)-1(2*H*)-phthalazinone (Table 3, Entry 6)
Orange solid; mp 93–95 °C (CH_2Cl_2–MeOH, 99:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (s, 1 H, Ar), 7.48 (d, *J* = 8.7 Hz, 1 H, Ar), 7.43 (d, *J* = 8.7 Hz, 1 H, Ar), 7.08–7.21 (m, 3 H, Ar), 3.97 (s, 3 H, CH_3), 3.96 (s, 3 H, CH_3), 2.32 (s, 3 H, CH_3), 2.13 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.2, 155.7, 148.8, 140.8, 137.7, 136.5, 131.8, 130.7, 129.4, 127.8, 124.8, 123.1, 122.5, 118.3, 61.9, 56.5, 20.8, 17.1.

MS: *m*/*z* (%) = 310 (76) [M$^+$], 293 (100), 277 (25), 251 (19), 205 (37), 190 (20), 77 (73).

7,8-Dimethoxy-2-(2-ethylphenyl)-1(2*H*)-phthalazinone (Table 3, Entry 7)
Light-yellow crystals; mp 94–96 °C (CH_2Cl_2–MeOH, 99:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10 (s, 1 H, Ar), 7.52 (d, *J* = 8.7 Hz, 1 H, Ar), 7.46 (d, *J* = 8.7 Hz, 1 H, Ar), 7.31–7.40 (m, 4 H, Ar), 4.01 (s, 3 H, CH_3), 3.98 (s, 3 H, CH_3), 2.55 (q, *J* = 7.5 Hz, 2 H, CH_2), 1.16 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.5, 155.8, 149.0, 140.8, 137.6, 129.0, 128.9, 127.7, 126.8, 125.0, 123.1, 122.6, 118.4, 116.4, 62.0, 56.5, 24.0, 14.0.

MS: *m*/*z* (%) = 310 (36) [M$^+$], 295 (100), 293 (83), 281 (40), 263 (38), 190 (28), 118 (45), 104 (34).

7,8-Dimethoxy-2-(*tert*-butyl)-1(2*H*)-phthalazinone (Table 3, Entry 8)
Colorless oil; (CH_2Cl_2–MeOH, 95:5).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (s, 1 H, Ar), 7.03–7.15 (m, 2 H, Ar), 3.85 (s, 3 H, CH_3), 3.83 (s, 3 H, CH_3), 1.57 (s, 9 H, 3CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.2, 154.9, 148.1, 134.8, 129.0, 128.2, 122.0, 118.0, 61.7, 56.5, 31.6, 28.4.

MS: *m*/*z* (%) = 262 (22) [M$^+$], 207 (35), 191 (100), 177 (54), 160 (37), 149 (44), 89 (54).

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