HETEROCYCLES, Vol. 106, No. 1, 2023, pp. 135 - 149. © 2023 The Japan Institute of Heterocyclic Chemistry
Received, 3rd November, 2022, Accepted, 28th November, 2022, Published online, 1st December, 2022
DOI: 10.3987/COM-22-14778

CATALYST-FREE GREEN SYNTHESIS OF PHTHALAZINONES AT ROOM TEMPERATURE

Kang Lv,[a] Zixi Xie,[a] Xi Chen,[b] Weiwei Yao,[a]* and Mengtao Ma[b]*

[a]College of Pharmacy, Nanjing University of Chinese Medicine, Nanjing 210023, China; E-mail: 320003@njucm.edu.cn
[b]Department of Chemistry and Material Science, College of Science, Nanjing Forestry University, Nanjing 210037, China; E-mail: mengtao@njfu.edu.cn

Abstract – An efficient catalyst-free synthesis of phthalazinones from 2-formyl/acetyl/benzoylbenzoic acids and substituted hydrazines is described. The direct cyclocondensation of a series of aryl/alkylhydrazines and various 2-formyl/acetyl/benzoylbenzoic acids was performed at room temperature to afford the corresponding phthalazinones in very high isolated yields. The gram-scale reaction and application in the biological activity phthalazinone derivative demonstrated its practical potential. The plausible reaction mechanism was proposed based on the corresponding DFT calculations.

INTRODUCTION

Heterocyclic compounds especially nitrogen-containing heterocycles widely distribute in nature. Many important natural products, biologically and pharmacologically active molecules are heterocyclic compounds such as alkaloids, antibiotics, hormones and so on.[1-8] Amongst a range of heterocycles, nitrogen-containing heterocycles are very important core motifs in various biologically active compounds that are frequently found in natural products, pharmaceutical drugs, agrochemicals, and functional materials etc.[9-13] Among the numerous nitrogen-containing heterocycles, phthalazinone is a kind of annulated six-membered N-heterocycles and has diverse biological activities.[14-18] Phthalazinone and their derivatives have been widely used in the treatment of a variety of diseases such as diabetes, hepatitis B, asthma, vascular hypertension, arrhythmia, cancers, and are as potent inhibitors of poly(ADP-ribose) polymerase-1 (PARP-1) (**Figure 1**).[19-23] For example, azelastine, a phthalazinone derivative, is a well-known antiallergic and antiasthmatic drug (sales $0.24 billion in 2008).[24] Moreover, some of phthalazinone derivatives demonstrate anti-inflammatory activity such as phosphodiesterase-4 (PDE-4) inhibitor and vascular endothelial growth factor (VEGF) inhibitor.[25]

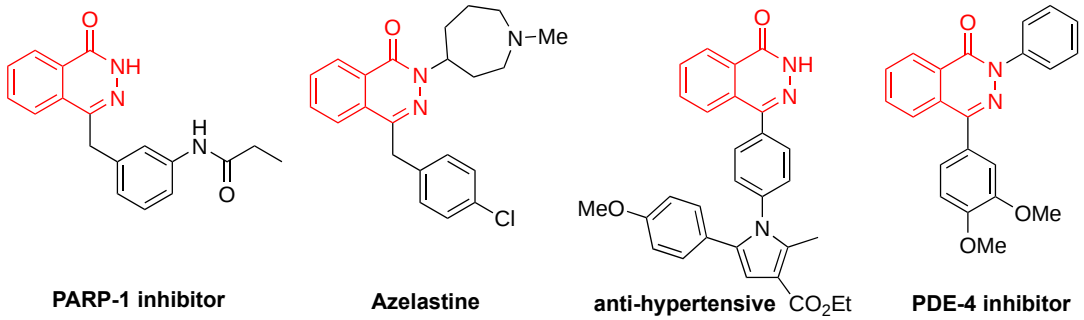
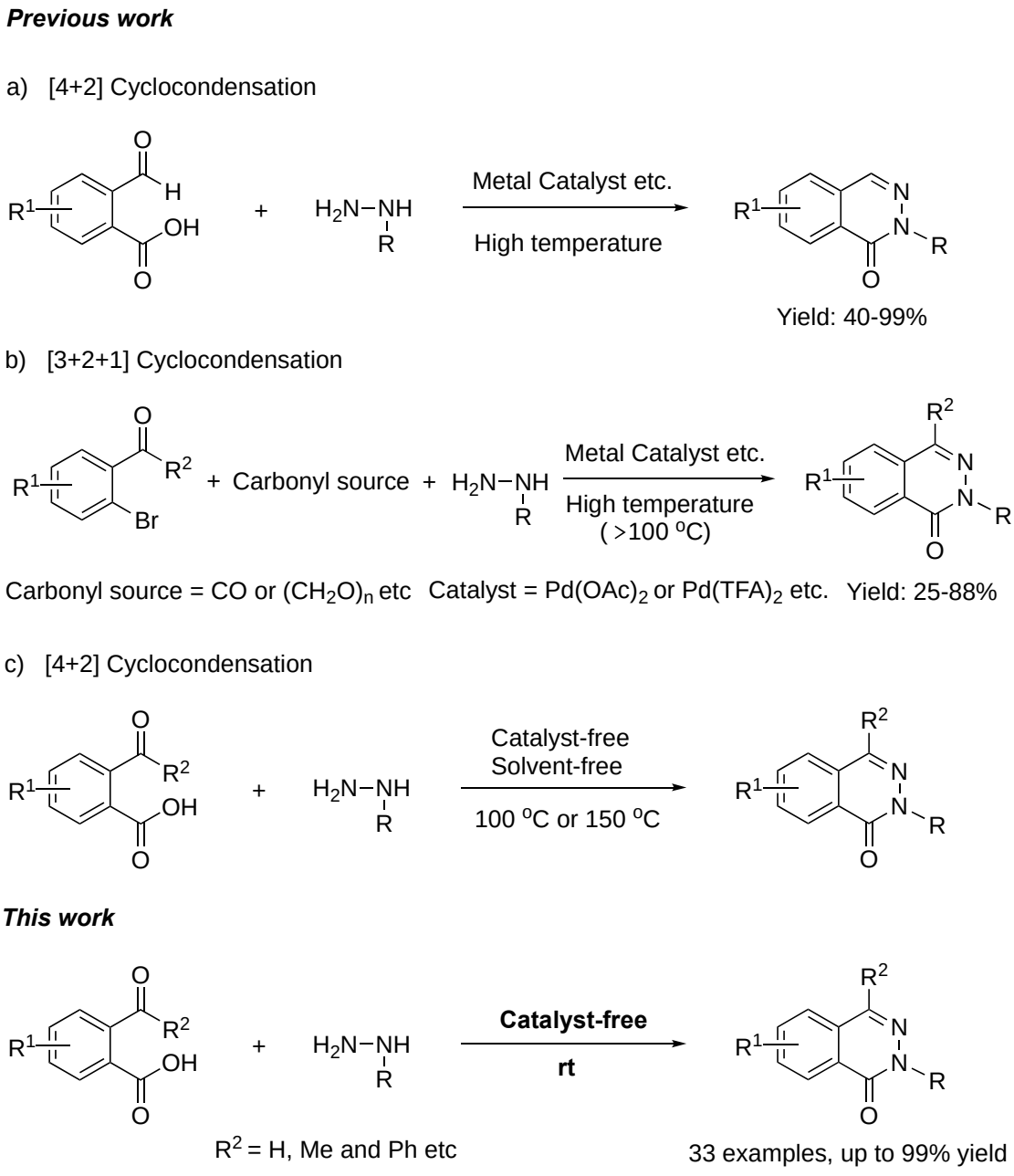


Figure 1. Selected examples of drugs containing phthalazinone

Because of the significant potential in pharmaceuticals and versatile biological activities, the preparation of phthalazinones has attracted considerable attention. In the last two decades various methods have been developed for their synthesis. In general, there are two main synthetic approaches to prepare the six-membered phthalazinone heterocycle.[19] The first efficient method is based on the two-component [4+2] cyclocondensation of the corresponding 2-carboxybenzaldehydes and substituted hydrazines with various catalysts such as Pt nanowires, $HClO_4$-SiO_2, heteropolyacids, solid acid etc (**Scheme 1a**).[26-29] For instance, in 2012, Gu and Cao et al. described the highly efficient synthesis of phthalazinones in high yields via the intramolecular amidation of 2-carboxybenzaldehyde and hydrazine or phenylhydrazine using Pt nanowires as the catalyst. However, the substrate scope is very limited and only two examples of phthalazinone were obtained.[26] Other traditional method is the three-component [3+2+1] cyclocondensation of 2-bromobenzaldehyde or 2-halomethyl benzoates, hydrazines and a carbonyl source such as CO, paraformaldehyde, molybdenum hexacarbonyl $Mo(CO)_6$ and dicobalt octacarbonyl $Co_2(CO)_8$ under the Pd-catalysis conditions (**Scheme 1b**).[30-33] For example, Wu, Beller and co-workers reported the $Pd(OAc)_2$-catalyzed synthesis of phthalazinones in moderate yields via the carbonylative couplig of 2-bromobenzaldehyde, hydrazine and CO (10 bar) at 100 °C in the presence of 2 mol% DPPF (1,1-bis(diphenylphosphino)ferrocene) ligand, one equivalent of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) base and $MgSO_4$ additive in 2012. However, dehalogenation of 2-bromobenzaldehyde side product was observed in some cases apart from the desired product.[30] Due to carbon monoxide is a very toxic gas, solid metal carbonyl complexes [$Mo(CO)_6$, $Co_2(CO)_8$] were subsequently used as the carbonyl source to replace CO in the above transformation.[31] In 2014, Deng et al. reported the $Pd(TFA)_2$-catalyzed one-pot synthesis of phthalazinones from 2-halomethyl benzoates, arylhydrazines and paraformaldehyde in the presence of K_2CO_3. Various substituted phthalazinones were selectively obtained in good yields at 160 °C in 24 h using $(CH_2O)_n$ as the cheap and relatively safe carbon source.[32] Considerable progress has been achieved in the synthesis of phthalazinones, however, the above various synthetic methods usually required precious transition metal catalysts, high temperature (>100 °C), strong acids and bases, additional additives or toxic CO gas etc. Hence, a simple, environmentally benign and efficient method

for the preparation of phthalazinones is highly desirable. In 2019, Lu reported the catalyst-free and solvent-free synthesis of phthalazinones with the broad scope and high yields, but a harsh condition such as high reaction temperature was required (**Scheme 1c**)[18] Herein, we describe a novel efficient protocol for the synthesis of phthalazinones by the condensation reaction of various 2-formyl/acetyl/benzoyl-benzoic acids and substituted hydrazines under the mild reaction conditions. The catalyst-free cyclocondensation reaction was carried out at room temperature in very high yields (**Scheme 1**).

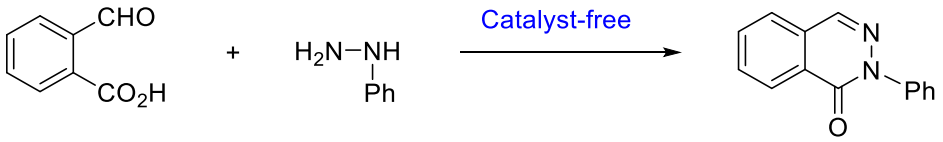


Scheme 1. Synthesis of phthalazinones

RESULTS AND DISCUSSION

At room temperature, we began our investigation by using phenylhydrazine, 2-formylbenzoic acid as model substrates and acetonitrile as the solvent. Initially, the reaction between phenylhydrazine and 2-formylbenzoic acid in equimolar ratio was performed in the absence of any catalyst and base at room temperature. The volume of solvent has a considerable effect on the yield of the desired product. When the volume amount of acetonitrile has been increased from 0.2 to 2 mL, the yield of phthalazinone was increased to 93% gradually (Table 1, entries 1-4). However, too much solvent such as 3 or 5 mL resulted in the slightly decrease of yield (Table 1, entries 5, 6). When phenylhydrazine is excessive than 2-formylbenzoic acid (1.5:1 molar ratio), there is not an improvement on the yield (Table 1, entry 7). Subsequently, different reaction time has been investigated, with the reaction time decreased from 11 h to 6 or 4 h, the yield of the desired phthalazinone product was diminished as well (Table 1, entries 8, 9). When the reaction temperature was elevated from room temperature to 40 °C, the yield was slightly increased (Table 1, entry 10). Different solvent influence has also been studied. When tetrahydrofuran (THF) or ethyl acetate was used as the solvent, the yield was sharply decreased to 10% or 40%, respectively (Table 1, entries 11, 12). The reaction used toluene as the solvent gave the same yield as acetonitrile (Table 1, entry 13). To our delight, when dichloromethane (DCM) was employed as the reaction solvent, the almost quantitative yield (97%) was observed (Table 1, entry 14). When the reaction time was shortened, the yield was reduced accordingly (Table 1, entries 15, 16). The reaction temperature was elevated to 40 °C, the yield was not improved (Table 1, entry 17).

Table 1. Optimization of the reaction conditions[a]



Entry	T (°C)	Solvent	Volume (mL)	Time (h)	Yield (%)
1	25	MeCN	0.2	11	40
2	25	MeCN	0.5	11	51
3	25	MeCN	1	11	89
4	25	MeCN	2	11	93
5	25	MeCN	3	11	92
6	25	MeCN	5	11	90
7	25	MeCN	2	11	93[b]
8	25	MeCN	2	6	88

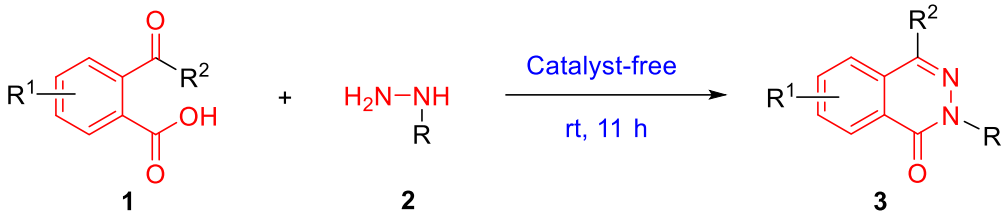
9	25	MeCN	2	4	85
10	40	MeCN	2	11	94
11	25	THF	2	11	10
12	25	EtOAc	2	11	40
13	25	toluene	2	11	93
14	25	DCM	2	11	97
15	25	DCM	2	6	91
16	25	DCM	2	4	88
17	40	DCM	2	11	95

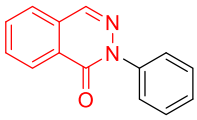
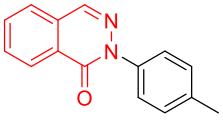
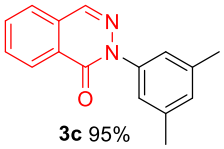
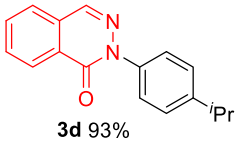
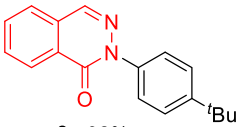
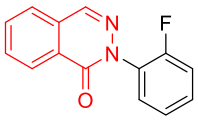
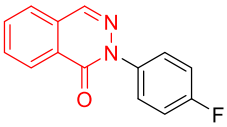
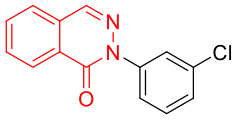
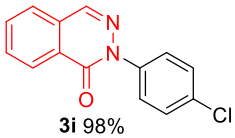
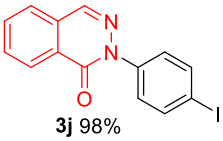
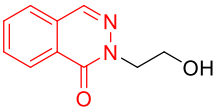
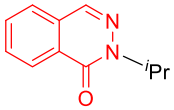
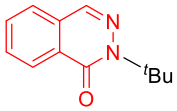
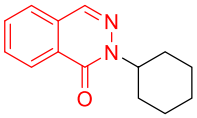
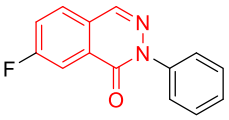
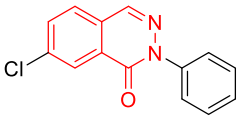
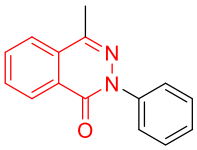
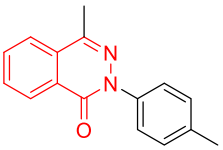
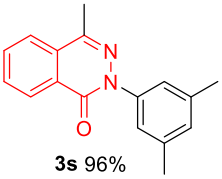
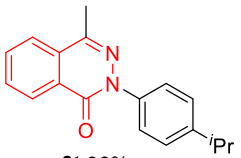
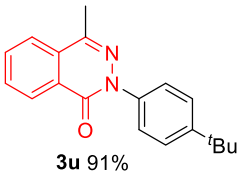
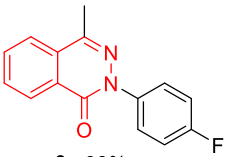
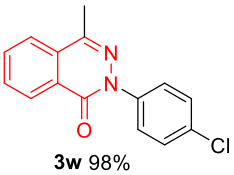
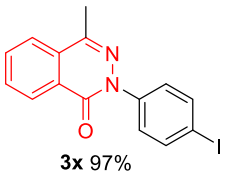
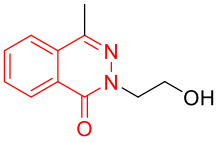
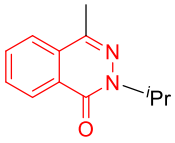
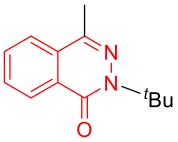
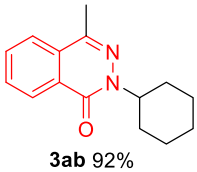
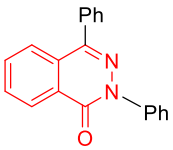
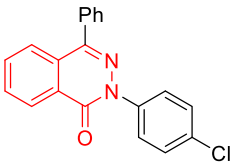
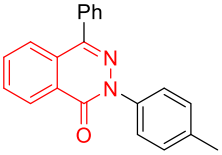
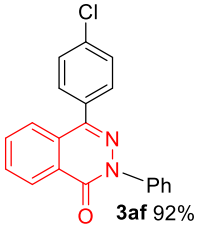
[a]Reaction conditions: phenylhydrazine (0.2 mmol), 2-formylbenzoic acid (0.2 mmol), no catalyst, air, isolated yield. [b]phenylhydrazine (0.3 mmol), 2-formylbenzoic acid (0.2 mmol).

With the optimal conditions in hand, a variety of 2-formylbenzoic acid, 2-acetylbenzoic acid or 2-benzoylbenzoic acid and various arylhydrazines or alkylhydrazines were selected to expand the scope of this [4+2] cyclocondensation reaction (**Table 2**). All cyclization reactions proceeded smoothly and resulted in very high yield without any by-products regardless of the steric and electronic nature of the substituents. When 2-formylbenzoic acid is selected as the reaction substrate, it can be reacted with various arylhydrazine and alkylhydrazine in high yields (Table 2, entries 3a−3n). Arylhydrazines bearing electron-donating group such as -Me, -*i*Pr, -*t*Bu or electron-withdrawing group such as -F, -Cl, -I all afforded the corresponding desired phthalazinone products in high isolated yields (Table 2, entries 3a−3j). A series of alkylhydrazine with -*i*Pr, -*t*Bu, -Cy substituents also provided excellent isolated yields (Table 2, entries 3k−3n). Moreover, when 5-fluoro/chloro-2-formylbenzoic acid was reacted with phenylhydrazine at room temperature respectively, high yield was obtained as well (Table 2, entries 3o-3p). Furthermore, the 2-acetylbenzoic acid was also compatible with this catalyst-free protocol. The reaction between 2-acetylbenzoic acid and various arylhydrazine and alkylhydrazine gave the corresponding cyclocondensation products in very high isolated yields (Table 2, entries 3q-3ab). In addition, the reaction of more steric bulky 2-benzoylbenzoic acid and 2-(4-chlorobenzoyl)benzoic acid proceed smoothly under the standard conditions (Table 2, entries 3ac-3af).

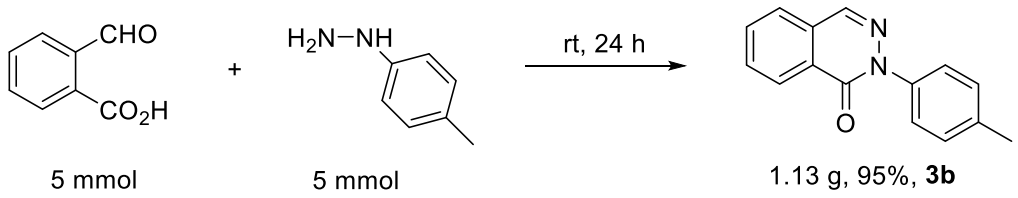
In addition, a 25-fold scale-up gram-scale reaction between 2-formylbenzoic acid and *p*-tolylhydrazine was performed under the standard conditions as described in **Scheme 2**, and the desired phthalazinone product **3b** was obtained in an isolated yield of 95% (1.13 g) after 24 h which demonstrated the practical utility in organic synthesis.

Table 2. Substrate scope for catalyst-free syntheses of phthalazinones[a]



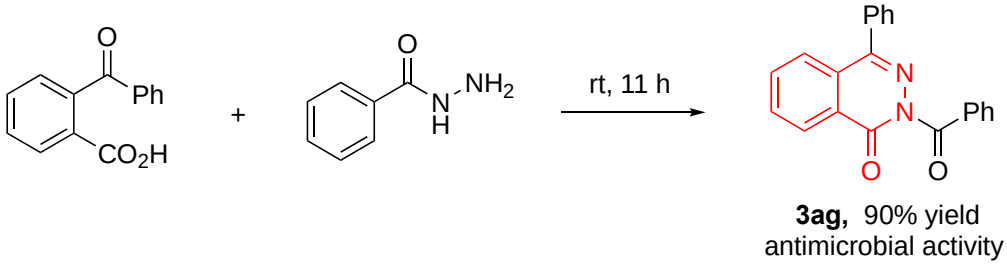
 **3a** 97%	 **3b** 99%	 **3c** 95%	 **3d** 93%
 **3e** 92%	 **3f** 91%	 **3g** 99%	 **3h** 99%
 **3i** 98%	 **3j** 98%	 **3k** 96%	 **3l** 94%
 **3m** 95%	 **3n** 92%	 **3o** 93%	 **3p** 91%
 **3q** 95%	 **3r** 99%	 **3s** 96%	 **3t** 96%
 **3u** 91%	 **3v** 93%	 **3w** 98%	 **3x** 97%
 **3y** 94%	 **3z** 98%	 **3aa** 97%	 **3ab** 92%
 **3ac** 95%	 **3ad** 91%	 **3ae** 90%	 **3af** 92%

[a]Reaction conditions: 1 (0.2 mmol), 2 (0.2 mmol), DCM (2 mL), rt, 11 h, isolated yields.

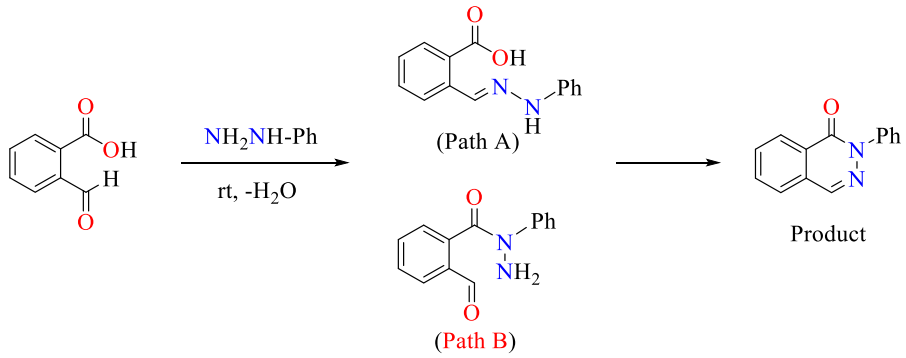


Scheme 2. Gram-scale reaction

Interestingly, this catalyst-free approach could be also applied to the synthesis of biological activity phthalazinone derivative. For example, the antimicrobial phthalazinone **3ag** could be prepared from the cyclocondensation of 2-benzoylbenzoic acid and benzohydrazide at room temperature in 90% yield (**Scheme 3**).



Scheme 3. Synthesis of bioactive compound **3ag**



Scheme 4. Proposal mechanisms

In order to gain further insight into the reaction mechanism, two possible reaction paths were investigated via the corresponding density functional theory (DFT) calculations (**Scheme 4**). In the first preferred possible path A, the primary amino group of phenylhydrazine preferred to react with the aldehyde group of 2-formylbenzoic acid and afforded the corresponding imine intermediate. Subsequently, the secondary amino group of phenylhydrazine was further reacted with carboxyl group of 2-formylbenzoic acid. Finally, the intramolecular reaction of the corresponding imine intermediate generated the desired phthalazinone product with the elimination of a water molecule. In the secondary possible reaction path B, the secondary amino group of phenylhydrazine was firstly reacted with the carboxyl group of

2-formylbenzoic acid and generated the corresponding amide intermediate. Next, the primary amino group of phenylhydrazine was further reacted with the aldehyde group of 2-formylbenzoic acid. At last, the intramolecular reaction of the corresponding amide intermediate yielded the final phthalazinone product.

In order to verify our hypothesis, a series of the corresponding DFT calculations were carried out at the level of M06-2X-D3/def2-SVP. In theoretical computational study, the aforementioned two proposed mechanisms are calculated. The Gibbs free energy profile are plotted shown in Figure 2 and all computation details can be found in the supporting information. In the beginning of the two paths, the Gibbs free energy of a-IM1 (path A, black line) is 6.09 kJ/mol lower than that of b-IM1 (path B, blue line). This indicated that 2-formylbenzoic acid molecules tended to be activated through combining a proton with the corresponding aldehyde group firstly, which was advantageous to path A. For the whole computational study, the activation energies of the first step and second step of reaction in path A are both less than those of path B (136.51 vs 147.76 kJ/mol for the first step; 140.10 vs 146.08 kJ/mol for the second step). Furthermore, it must also be mentioned that for the corresponding structure on both paths, the structures on path A have lower Gibbs free energy than the similar structures on path B. Based on the above corresponding DFT calculation results, we supposed that the path A was more possible than path B.

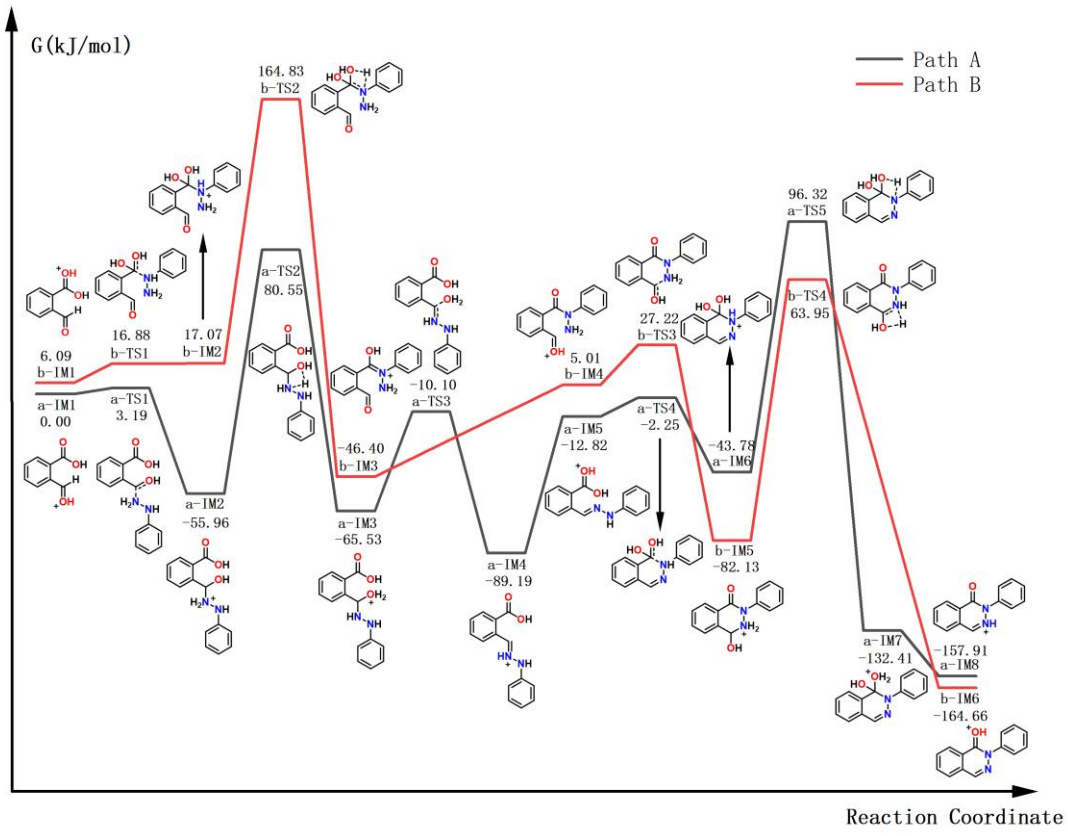


Figure 2. Gibbs free energy profile of two plausible mechanisms

In conclusion, a simple, straightforward and environmentally benign method for the synthesis of a series of functionalized phthalazinone derivatives has been developed. The cyclocondensation of various aryl/alkylhydrazines and 2-formyl/acetyl/benzoylbenzoic acids was carried out at room temperature in very high isolated yields without any catalyst. It shows a broad functional group tolerance and provides the facile access to potential biologically active phthalazinones. This new catalyst-free protocol produces no by-products, avoids heavy metal pollution from the catalyst source, and conforms to the basic concept of green chemistry.

EXPERIMENTAL SECTION

General Information. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded at 25 °C on Bruker Avance III 500 MHz spectrometer in deuterated solvents and chemical shifts were referenced to $CDCl_3$ (δ = 7.26 for ^{1}H and δ = 77.16 for $^{13}C\{^{1}H\}$ NMR) as an internal standard. All reagents were purchased from Sigma Aldrich, Alfa Aesar, Acros Organics and Energy Chemical without further purification.

General Procedure for the Synthesis of Phthalazinones 3. The mixture of 2-formyl/acetyl/benzoyl-benzoic acids (**1**, 0.2 mmol) and arylhydrazines or alkylhydrazines (**2**, 0.2 mmol) in DCM (2 mL) was stirred for 11 h at room temperature. After the solvent was removed in vacuum, the corresponding pure phthalazinone products (**3**) were obtained in high isolated yields by flash chromatography on silica gel using petroleum and EtOAc as eluent.

Gram Scale Reaction. The mixture of *p*-tolylhydrazine (5.0 mmol) and 2-formylbenzoic acid (5.0 mmol) in DCM (10 mL) was stirred for 24 h at room temperature. After the solvent was removed in vacuum, the crude product was purified by silica gel column chromatography to give **3b** as a white solid in 95% yield (1.13 g).

Spectroscopic Data for Product of 3. 2-Phenylphthalazin-1(2*H*)-one (3a).[26] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.51 (dd, J = 7.8 Hz, 0.7 Hz, 1H), 8.30 (s, 1H), 7.80-7.87 (m, 2H), 7.74-7.76 (m, 1H), 7.65-7.67 (m, 2H), 7.48-7.52 (m, 2H), 7.37-7.40 (m, 1H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 159.16, 141.86, 138.44, 133.47, 131.96, 129.48, 128.74, 128.54, 127.74, 127.24, 126.10, 125.70.

2-(*p*-Tolyl)phthalazin-1(2*H*)-one (3b).[32] White solid. $_{1}H$ NMR (500 MHz, $CDCl_3$): δ 8.50 (dd, J = 7.8 Hz, 0.7 Hz, 1H), 8.27 (s, 1H), 7.78-7.85 (m, 2H), 7.73-7.74 (m, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 2.41 (s, 3H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 159.16, 139.38, 138.25, 137.61, 133.34, 131.84, 129.47, 129.33, 128.51, 127.18, 126.03, 125.46, 21.12.

2-(3,5-Dimethylphenyl)phthalazin-1(2*H*)-one (3c).[32] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.48 (d, J = 7.6 Hz, 1H), 8.24 (s, 1H), 7.74-7.81 (m, 2H), 7.68-7.70 (m, 1H), 7.24 (s, 2H), 7.01 (s, 1H), 2.37 (s, 6H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 158.90, 141.51, 138.24, 137.97, 133.11, 131.60, 129.32, 129.19, 128.22, 126.82, 125.87, 123.28, 21.05.

2-(4-Isopropylphenyl)phthalazin-1(2*H*)-one (3d).[32] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.51 (dd, J = 7.8 Hz, 0.7 Hz, 1H), 8.27 (s, 1H), 7.78-7.85 (m, 2H), 7.73-7.74 (m, 1H), 7.56 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 2.97 (sept, J = 7.0 Hz, 1H), 1.28 (d, J = 7.0 Hz, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 159.14, 148.45, 139.56, 138.25, 133.33, 131.82, 129.45, 128.49, 127.17, 126.76, 126.02, 125.48, 33.82, 23.90.

2-(4-(*tert*-Butyl)phenyl)phthalazin-1(2*H*)-one (3e).[32] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.48 (dd, J = 7.6 Hz, 0.8 Hz, 1H), 8.24 (s, 1H), 7.73-7.80 (m, 2H), 7.68-7.69 (m, 1H), 7.59 (d, J = 8.6 Hz, 2H), 7.50 (d, J = 8.6 Hz, 2H), 1.35 (s, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 158.90, 150.39, 139.13, 138.11, 133.14, 131.62, 129.22, 128.25, 126.91, 125.88, 125.51, 124.94, 34.42, 31.12.

2-(2-Fluorophenyl)phthalazin-1(2*H*)-one (3f).[28] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.51 (d, J = 7.9 Hz, 1H), 8.29 (s, 1H), 7.82-7.90 (m, 2H), 7.76-7.78 (m, 1H), 7.50-7.53 (m, 1H), 7.42-7.46 (m, 1H), 7.28-7.31 (m, 1H), 7.24-7.26 (m, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 158.92, 158.34, 156.33, 138.92, 133.69, 132.12, 130.30, 130.24, 129.69, 129.56, 128.80, 128.18, 127.25, 126.28, 124.59, 124.56, 116.69, 116.54.

2-(4-Fluorophenyl)phthalazin-1(2*H*)-one (3g).[32] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.49 (d, J = 7.8 Hz, 1H), 8.27 (s, 1H), 7.79-7.86 (m, 2H), 7.73-7.75 (m, 1H), 7.63-7.66 (m, 2H), 7.15-7.18 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 162.56, 160.59, 159.09, 138.51, 137.83, 137.80, 133.51, 132.01, 129.38, 128.34, 127.47, 127.40, 127.14, 126.13, 115.57, 115.39.

2-(3-Chlorophenyl)phthalazin-1(2*H*)-one (3h).[32] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.49 (dd, J = 7.8 Hz, 0.8 Hz, 1H), 8.29 (s, 1H), 7.80-7.88 (m, 2H), 7.73-7.76 (m, 2H), 7.62-7.63 (m, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.34-7.36 (m, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 159.01, 142.75, 138.77, 134.20, 133.67, 132.13, 129.56 129.32, 128.36, 127.71, 127.24, 126.19, 125.91, 123.74.

2-(4-Chlorophenyl)phthalazin-1(2*H*)-one (3i).[32] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.51 (dd, J = 7.8 Hz, 0.7 Hz, 1H), 8.29 (s, 1H), 7.81-7.88 (m, 2H), 7.74-7.76 (m, 1H), 7.65 (d, J = 8.9 Hz, 2H), 7.45 (d, J = 8.9 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 159.07, 140.32, 138.71, 133.63, 133.22, 132.11, 129.39, 128.78, 128.40, 127.26, 126.87, 126.18.

2-(4-Iodophenyl)phthalazin-1(2*H*)-one (3j).[32] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.47 (d, J = 7.8 Hz, 1H), 8.26 (s, 1H), 7.77-7.84 (m, 4H), 7.71 (d, J = 7.7 Hz, 1H), 7.46 (d, J = 8.2 Hz 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 158.91, 141.51, 138.73, 137.67, 133.59, 132.06, 129.29, 128.31, 127.32, 127.19, 126.15, 92.64.

2-(2-Hydroxyethyl)phthalazin-1(2*H*)-one (3k).[18] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.40 (dd, J = 7.9 Hz, 0.7 Hz, 1H), 8.20 (s, 1H), 7.76-7.84 (m, 2H), 7.70-7.72 (m, 1H), 4.44 (t, J = 5.0 Hz, 2H), 4.07 (t, J = 5.0 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 160.42, 138.33, 133.30, 131.87, 129.50, 127.61, 126.62, 126.05, 61.67, 53.86.

2-Isopropylphthalazin-1(2*H*)-one (3l).[18] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.44 (dd, J = 7.8 Hz, 0.6 Hz, 1H), 8.22 (s, 1H), 7.73-7.81 (m, 2H), 7.68-7.69 (m, 1H), 5.45 (sept, J = 6.5 Hz, 1H), 1.41 (d, J = 6.5 Hz, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 158.89, 137.49, 132.84, 131.33, 129.29, 127.86, 126.80, 125.71, 48.40, 20.98.

2-(*tert*-Butyl)phthalazin-1(2*H*)-one (3m).[18] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.41 (d, J = 7.9 Hz, 1H), 8.11 (s, 1H), 7.70-7.77 (m, 2H), 7.64-7.66 (m, 1H), 1.72 (s, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 159.98, 135.57, 132.65, 131.00, 129.34, 129.27, 126.55, 125.19, 64.16, 28.27.

2-Cyclohexylphthalazin-1(2*H*)-one (3n).[18] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.44 (d, J = 7.8 Hz, 1H), 8.20 (s, 1H), 7.73-7.80 (m, 2H), 7.67-7.69 (m, 1H), 5.02-5.05 (m, 1H), 1.81-1.90 (m, 7H), 1.15-1.54 (m, 2H), 1.25-1.27 (m, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 158.93, 137.25, 132.80, 131.27, 129.18, 127.84, 126.83, 125.65, 55.93, 31.20, 25.63, 25.40.

6-Fluoro-2-phenylphthalazin-1(2*H*)-one (3o).[32] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (s, 1H), 8.11-8.13 (m, 1H), 7.74-7.77 (m, 1H), 7.65 (d, J = 7.8 Hz, 2H), 7.53-7.55 (m, 1H), 7.47-7.51 (m, 2H), 7.38 (t, J = 7.5 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 165.40, 163.37, 158.18, 158.16, 141.54, 137.46, 130.80, 130.73, 129.08, 129.01, 128.66, 127.76, 126.14, 126.12, 125.52, 122.22, 122.03, 112.85, 112.67.

6-Chloro-2-phenylphthalazin-1(2*H*)-one (3p).[32] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.46 (s, 1H), 8.26 (s, 1H), 7.77-7.79 (m, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.64 (d, J = 8.2 Hz, 2H), 7.50 (t, J = 7.9 Hz, 2H), 7.39 (t, J = 7.6 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 157.96, 141.57, 138.43, 137.53, 134.02, 129.73,128.76, 127.89, 127.70, 126.90, 125.55.

4-Methyl-2-phenylphthalazin-1(2*H*)-one (3q).[18] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.53 (dd, J = 7.5 Hz, 1.3 Hz, 1H), 7.77-7.86 (m, 3H), 7.66-7.67 (m, 2H), 7.47-7.50 (m, 2H), 7.35-7.38 (m, 1H), 2.64 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 159.09, 144.16, 141.91, 133.18, 131.50, 129.64, 128.68, 128.28, 127.52, 125.74, 124.82, 18.88.

4-Methyl-2-(*p*-tolyl)phthalazin-1(2*H*)-one (3r).[18] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.53 (dd, J = 7.5 Hz, 1.3 Hz, 1H), 7.81-7.85 (m, 1H), 7.76-7.79 (m, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 2.63 (s, 3H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 159.10, 143.95, 139.46, 137.39, 133.06, 131.41, 129.63, 129.29, 128.28, 127.49, 125.53, 124.77, 21.07, 18.85.

2-(3,5-Dimethylphenyl)-4-methylphthalazin-1(2*H*)-one (3s).[18] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.49 (d, J = 7.5 Hz, 1H), 7.71-7.79 (m, 3H), 7.25 (s, 2H), 6.99 (s, 1H), 2.60 (s, 3H), 2.36 (s, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 158.71, 143.54, 141.48, 138.06, 132.76, 131.07, 129.21, 129.06, 127.87, 126.99, 124.49, 123.28, 20.97, 18.51.

2-(4-Isopropylphenyl)-4-methylphthalazin-1(2*H*)-one (3t).[18] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.53 (dd, J = 7.7 Hz, 1.2 Hz, 1H), 7.76-7.85 (m, 3H), 7.56 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H),

2.96 (sept, *J* = 7.0 Hz, 1H), 2.64 (s, 3H), 1.28 (d, *J* = 7.0 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 159.07, 148.21, 143.95, 139.63, 133.05, 131.40, 129.61, 128.27, 127.48, 126.75, 125.54, 124.76, 33.81, 23.89, 18.84.

2-(4-(*tert*-Butyl)phenyl)-4-methylphthalazin-1(2*H*)-one (3u).[18] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.54 (d, *J* = 8.1 Hz, 1H), 7.77-7.86 (m, 3H), 7.57 (d, *J* = 8.7 Hz, 2H), 7.51 (d, *J* = 6.7 Hz, 2H), 2.65 (s, 3H), 1.35 (s, 9H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 159.11, 150.46, 144.02, 139.34, 133.10, 131.45, 129.67, 128.33, 127.55, 125.76, 125.20, 124.81, 53.39, 34.60, 31.29, 18.90.

2-(4-Fluorophenyl)-4-methylphthalazin-1(2*H*)-one (3v).[18] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.53 (dd, *J* = 7.1 Hz, 1.7 Hz, 1H), 7.84-7.87 (m, 1H), 7.79-7.82 (m, 2H), 7.64-7.67 (m, 2H), 7.16 (t, *J* = 8.6 Hz, 2H), 2.65 (s, 1H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 162.50, 160.53, 159.10, 144.34, 137.94, 137.91, 133.29, 131.63, 129.63, 128.19, 127.55, 127.52, 127.48, 124.89, 115.56, 115.38, 18.97.

2-(4-Chlorophenyl)-4-methylphthalazin-1(2*H*)-one (3w).[18] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.51 (dd, *J* = 8.6 Hz, 1.5 Hz, 1H), 7.83-7.87 (m, 1H), 7.78-7.81 (m, 2H), 7.66 (d, *J* = 8.9 Hz, 2H), 7.43 (d, *J* = 8.9 Hz, 2H), 2.64 (s, 3H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 158.97, 144.49, 140.37, 133.32, 132.89, 131.62, 129.54, 128.66, 127.51, 126.86, 124.88, 18.86.

2-(4-Iodophenyl)-4-methylphthalazin-1(2*H*)-one (3x).[18] White solid. 1H NMR (500 MHz, $CDCl_3$): δ 8.47 (dd, *J* = 7.3 Hz, 1.5 Hz, 1H), 7.79-7.82 (m, 1H), 7.73-7.76 (m, 4H), 7.47 (d, *J* = 8.8 Hz, 2H), 2.60 (s, 3H). 13C{1H} NMR (125 MHz, CDCl3): δ 158.58, 144.33, 141.38, 137.33, 133.13, 131.39, 129.19, 127.78, 127.19, 127.12, 124.69, 92.12, 53.33, 18.74.

2-(2-Hydroxyethyl)-4-methylphthalazin-1(2*H*)-one (3y).[18] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.45 (dd, *J* = 8.6 Hz, 2.0 Hz, 1H), 7.81-7.85 (m, 1H), 7.76-7.79 (m, 2H), 4.42 (t, *J* = 5.0 Hz, 2H), 4.06 (t, *J* = 5.0 Hz, 2H), 3.55 (s, 1H), 2.60 (s, 3H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 160.40, 144.28, 133.07, 131.51, 129.65, 127.50, 127.06, 124.79, 62.06, 53.69, 18.83.

2-Isopropyl-4-methylphthalazin-1(2*H*)-one (3z).[18] White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 7.2 Hz, 1.7 Hz, 1H), 7.61-7.64 (m, 1H), 7.56-7.59 (m, 2H), 5.30 (sept, *J* = 7.0 Hz, 1H), 2.46 (s, 3H), 1.28 (d, *J* = 7.0 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 158.42, 142.62, 132.26, 130.57, 129.02, 127.36, 126.78, 124.15, 47.80, 20.68, 18.67.

2-(*tert*-Butyl)-4-methylphthalazin-1(2*H*)-one (3aa).[18] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.29 (dd, *J* = 8.2 Hz, 1.2 Hz, 1H), 7.57-7.61 (m, 1H), 7.51-7.56 (m, 2H), 2.41 (s, 3H), 1.59 (s, 9H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 159.58, 140.60, 132.13, 130.34, 129.14, 128.92, 126.63, 123.81, 63.33, 28.12, 18.70.

2-Cyclohexyl-4-methylphthalazin-1(2*H*)-one (3ab).[18] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.46 (dd, *J* = 7.3 Hz, 1.5 Hz, 1H), 7.76-7.79 (m, 1H), 7.71-7.73 (m, 2H), 4.97-5.03 (m, 1H), 2.59 (s, 3H), 1.84-1.89 (m, 6H), 1.70-1.73 (m, 1H), 1.47-1.51 (m, 2H), 1.24-1.28 (m, 1H). $^{13}C\{^{1}H\}$ NMR (125 MHz,

$CDCl_3$): δ 158.75, 142.64, 132.45, 130.75, 129.17, 127.57, 127.10, 124.31, 55.65, 31.02, 25.57, 25.34, 18.85.

2,4-Diphenylphthalazin-1(2*H*)-one (3ac).[18] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.62 (dd, J = 7.4 Hz, 1.4 Hz, 1H), 7.78-7.81 (m, 3H), 7.72-7.74 (m, 2H), 7.63-7.64 (m, 2H), 7.47-7.51 (m, 5H), 7.35-7.38 (m, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 158.92, 147.60, 141.95, 134.99, 133.12, 131.62, 129.51, 129.20, 129.08, 128.91, 128.69, 128.60, 127.71, 127.63, 126.83, 125.81.

2-(4-Chlorophenyl)-4-phenylphthalazin-1(2*H*)-one (3ad).[18] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.58 (dd, J = 7.1 Hz, 1.5 Hz, 1H), 7.76-7.82 (m, 3H), 7.71-7.73 (m, 2H), 7.61-7.63 (m, 2H), 7.50-7.53 (m, 3H), 7.12-7.16 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 162.49, 160.52, 158.81, 147.68, 137.89, 137.87, 134.76, 133.16, 131.66, 129.38, 129.21, 128.96, 128.70, 128.56, 127.58, 127.52, 127.45, 126.83, 115.49, 115.31.

4-Phenyl-2-(*p*-tolyl)phthalazin-1(2*H*)-one (3ae).[18] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.61 (dd, J = 7.5 Hz, 1.3 Hz, 1H), 7.77-7.82 (m, 3H), 7.63-7.65 (m, 2H), 7.60 (d, J =8.4 Hz, 2H), 7.50-7.52 (m, 3H), 7.28 (d, J = 8.2 Hz, 2H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 158.93, 147.41, 139.47, 137.52, 135.03, 133.02, 131.53, 129.51, 129.29, 129.13, 129.05, 128.89, 128.55, 127.68, 126.77, 125.58, 21.12.

4-(4-Chlorophenyl)-2-phenylphthalazin-1(2*H*)-one (3af).[18] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.61 (dd, J = 7.3 Hz, 1.7 Hz, 1H), 7.78-7.84 (m, 2H), 7.70-7.74 (m, 3H), 7.59 (d, J = 8.5 Hz, 2H), 7.46-7.50 (m, 4H), 7.37 (t, J = 7.5 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 158.77, 146.37, 141.79, 135.38, 133.40, 133.25, 131.77, 130.83, 128.88, 128.86, 158.77, 128.70, 127.83, 127.70, 126.42, 125.71.

2-Benzoyl-4-phenylphthalazin-1(2*H*)-one (3ag).[18] White solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.61 (d, J = 7.4 Hz, 1H), 7.79-7.82 (m, 1H), 7.77 (d, J = 3.8 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.63-7.65 (m, 2H), 7.46-7.53 (m, 5H), 7.34-7.37 (m, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 158.85, 147.54, 141.91, 134.94, 133.09, 131.58, 129.47, 129.16, 129.02, 128.86, 128.65, 128.56, 127.65, 127.58, 126.79, 125.76.

ACKNOWLEDGEMENTS

We are thankful for financial support from the National Natural Science Foundation of China (22171137, 21772093).

REFERENCES

1. A. Borissov, Y. K. Maurya, L. Moshniaha, W. Wong, M. Żyła-Karwowska, and M. Stępień, *Chem. Rev.*, 2022, **122**, 565.
2. S. Devi, D. Wadhwa, and J. Sindhu, *Org. Biomol. Chem.*, 2022, **20**, 5163.
3. L. Yang, W. B. Xu, L. Sun, C. Zhang, and C. H. Jin, *ChemMedChem*, 2022, **17**, e202200221.

4. R. Hassan, R. Mohi-Ud-Din, M. O. Dar, A. J. Shah, P. A. Mir, M. Shaikh, and F. H. Pottoo, *Anti-Cancer Agents Med. Chem.*, 2022, **22**, 551.
5. S. F. Cai, H. R. Li, and L. N. He, *Green Chem.*, 2021, **23**, 9334.
6. H. A. Goulart, D. R. Araujo, F. Penteado, R. G. Jacob, G. Perin, and E. J. Lenardão, *Molecules*, 2021, **26**, 7523.
7. Y. Sun, M. Hu, S. Fu, and B. Liu, *Org. Biomol. Chem.*, 2020, **18**, 6443.
8. J. Feng, W. C. Geng, H. Jiang, and B. Wu, *Biotechnol. Adv.*, 2021, **54**, 107813.
9. A. Mermer, T. Keles, and Y. Sirin, *Bioorg. Chem.*, 2021, **114**, 105076.
10. F. L. Hong and L. W. Ye, *Acc. Chem. Res.*, 2020, **53**, 2003.
11. G. Grover, R. Nath, R. Bhatia, and M. J. Akhtar, *Bioorg. Med. Chem.*, 2020, **28**, 115585.
12. D. K. Lang, R. Kaur, R. Arora, B. Saini, and S. Arora, *Anti-Cancer Agents Med. Chem.*, 2020, **20**, 2150.
13. Z. Hosseinzadeh, A. Ramazani, and N. Razzaghi-Asl, *Curr. Org. Chem.*, 2018, **22**, 2256.
14. C. Sivaraj, A. Ramkumar, N. Sankaran, and T. Gandhi, *Org. Biomol. Chem.*, 2021, **19**, 8165.
15. W. Shi, P. Zhang, F. Zou, J. Zhou, Z. Yin, Z. Cai, H. Ghaleb, Y. Jiang, W. Huang, Y. Liu, Q. Qiu, and H. Qian, *Eur. J. Med. Chem.*, 2022, **233**, 114231.
16. C. Ye, R. Xu, Z. Cao, Q. Song, G. Yu, Y. Shi, Z. Liu, X. Liu, and Y. Deng, *Bioorg. Chem.*, 2021, **111**, 104895.
17. I. G. Salado, A. K. Singh, C. Moreno-Cinos, G. Sakaine, M. Siderius, P. V. Veken, A. Matheeussen, T. Meer, P. Sadek, S. Gul, L. Maes, G. Sterk, R. Leurs, D. Brown, and K. Augustyns, *J. Med. Chem.*, 2020, **63**, 3485.
18. B. Lu, Z. Xie, J. Lu, J. Liu, S. Cui, Y. Ma, X. Hu, Y. Liu, and K. Zhong, *ACS Sustainable Chem. Eng.*, 2019, **7**, 134.
19. G. R. Madhavan, R. Chakrabarti, S. K. Kumar, P. Misra, R. N. Mamidi, V. Balraju, K. Kasiram, R. K. Babu, J. Suresh, B. B. Lohray, V. B. Lohray, J. Iqbal, and R. Rajagopalan, *Eur. J. Med. Chem.*, 2001, **36**, 627.
20. (a) W. Chen, F. Liu, Q. Zhao, X. Ma, D. Lu, H. Li, Y. Zeng, X. Tong, L. Zeng, J. Liu, L. Yang, J. Zuo, and Y. Hu, *J. Med. Chem.*, 2020, **63**, 8134; (b) E. El Ashry, A. Abdel-Rahman, N. Rashed, and H. Rasheed, *Pharmazie*, 1999, **54**, 893.
21. T. Ukita, M. Sugahara, Y. Terakawa, T. Kuroda, K. Wada, A. Nakata, Y. Ohmachi, H. Kikkawa, K. Ikezawa, and K. Naito, *J. Med. Chem.*, 1999, **42**, 1088.
22. S. Demirayak, A. C. Karaburun, and R. Beis, *Eur. J. Med. Chem.*, 2004, **39**, 1089.
23. X. Cockcroft, K. J. Dillon, L. Dixon, J. Drzewiecki, F. Kerrigan, V. M. Loh Jr, N. M. Martin, K. A. Menear, and G. C. Smith, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1040.

24. M. Nakajima, K. Ohyama, S. Nakamura, N. Shimada, H. Yamazaki, and T. Yokoi, *Drug Metab. Dispos.*, 1999, **27**, 792.
25. (a) M. Van der Mey, K. M. Bommelé, H. Boss, A. Hatzelmann, M. Van Slingerland, G. J. Sterk, and H. Timmerman, *J. Med. Chem.*, 2003, **46**, 2008; (b) G. Bold, K. H. Altmann, J. Frei, M. Lang, P. W. Manley, P. Traxler, B. Wietfeld, J. Brüggen, E. Buchdunger, R. Cozens, S. Ferrari, P. Furet, F. Hofmann, G. Martiny-Baron, J. Mestan, J. Rösel, M. Sills, D. Stover, F. Acemoglu, E. Boss, R. Emmenegger, L. Lässer, E. Masso, R. Roth, C. Schlachter, W. Vetterli, D. Wyss and J. M. Wood, *J. Med. Chem.*, 2000, **43**, 2310.
26. L. Shi, L. Hu, J. Wang, X. Cao, and H. Gu, *Org. Lett.*, 2012, **14**, 1876.
27. V. M. Outerbridge, S. M. Landge, H. Tamaki, and B. Török, *Synthesis*, 2009, 1801.
28. M. M. Heravi, B. Baghernejad, and H. A. Oskooie, *J. Heterocycl. Chem.*, 2009, **46**, 351.
29. M. M. Heravi, B. Baghernejad, H. A. Oskooie, and F. F. Bamoharram, *Heterocycl. Commun.*, 2008, **14**, 375.
30. X. F. Wu, H. Neumann, S. Neumann, and M. Beller, *Chem. Eur. J.*, 2012, **18**, 8596.
31. (a) K. P. Rao, A. K. Basak, P. K. Deb, S. Sharma, and L. K. Reddy, *Tetrahedron Lett.*, 2013, **54**, 3694; (b) A. S. Suresh, P. Baburajan, and M. Ahmed, *Tetrahedron Lett.*, 2014, **55**, 3482.
32. H. Wang, J. Cai, H. Huang, and G. J. Deng, *Org. Lett.*, 2014, **16**, 5324.
33. B. Liu, C. Zhang, and X. Zhou, *Tetrahedron*, 2016, **72**, 8282.