# Green Synthesis of 3-Hydroxynaphthalene-1,4-dione Derivatives *via* Microwave-Assisted Three-Component Reactions in Neat Water

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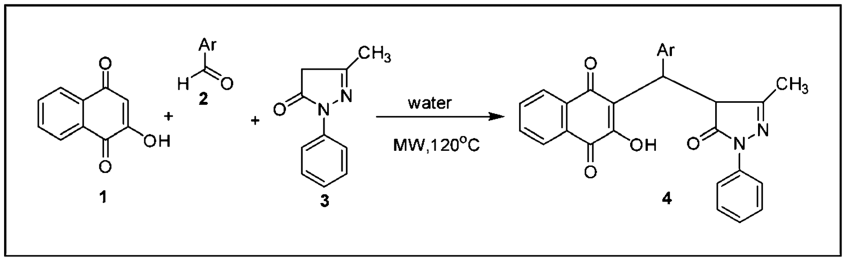


A novel and efficient access to 2-(argio(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl) methyl)-3-hydroxynaphthalene-1,4-dione derivatives from readily available substrates in neat water is described with aid of microwave irradiation. The results of our study provide a green, simple and practical one-pot approach to the synthesis of 3-hydroxynaphthalene-1,4-dione analogs in excellent yields without further purification.

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## INTRODUCTION

Naphthoquinones (NQs) are compounds present in the secondary metabolites of plants and microorganisms, which confer activity in various biological oxidative processes. Originating among native Ameridian populations, plants containing NQs have been used for the treatment of a number of diseases such as cancer [1,2]. Mass screening programs of natural products by the National Cancer Institute have identified the quinone moiety as an important pharmacophoric element for cytotoxic activity [3]. Furthermore, the NQ subunit is considered as privileged structures in medicinal chemistry [4] with numerous bioactivities [5] including antibacterial [6], fungicidal [6], antimalarial [7], trypanocidal [8], and antitumoral [9] activities.

Pyrazoles are of interest as possible antiviral agents [10] and a wide spectrum of pharmacological activities are described for them, exemplified by antimalarial [11], immunostimulatory [12], antianginal [13], and antitumor [14] properties. Based on the versatile bioactivities of pyrazoles and NQs, it is promising that the integration of these two bioactive units into an organic whole may exhibit new or improved pharmacological properties.

Recently, we have synthesized a new class of α-lapachone derivatives with diverse structures in one pot by three-component condensations [15]. However, to the best of our knowledge, the synthesis of 2-(argio(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)methyl)-3-hydroxynaphthalene-1,4-diones, imbedded with the two motifs of pyrazole and NQ, has seldom been reported. To expand the families containing NQ skeletons, the development of practically simple, economical, and environmentally friendly routes to a wide variety of 3-hydroxynaphthalene-1,4-dione derivatives is strongly desired.

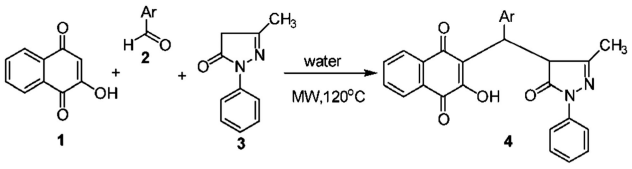
Water, a safe and environmentally benign solvent, has attracted much attention in synthetic chemistry recently [16]. The both use of water as solvent and microwave (MW) irradiation for heating make the reaction process more attractive as it combines the two prominent green chemistry principles of "safer solvents" and "energy efficiency" [17].

In view of the prominent merits of MW-assisted multicomponent reactions in water and as a continuation of our efforts on synthesizing bioactive heterocyclic compounds with green approach [18], herein, we report a green method to prepare a new class of NQ derivatives **4** integrated with pyrazole unit by MW-assisted three-component condensations of 2-hydroxynaphthalene-1,4-dione **1**, aldehyde **2**, and 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one **3** in water (Scheme 1).

## RESULTS AND DISCUSSION

To choose the most appropriate solvent, the MW-assisted reaction (Scheme 2) of 2-hydroxynaphthalene-1,4-dione (**1**, 1.0 mmol), 4-chlorobenzaldehyde (**2c**, 1.0 mmol),

**Scheme 1**




and 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**3**, 1.0 mmol) was examined using ethanol (EtOH), ethylene glycol, *N*,*N*-dimethylformamide (DMF), glacial acetic acid (HOAc), and water as the solvent (2.0 mL) at 120°C, respectively. All the reactions were carried out at the maximum power of 250 W (initial power 100 W). Reaction under EtOH and ethylene glycol, afforded the product with very low yield (less than 45%).

The use of DMF gave rise to side reactions and therefore led to low product yields (63%). As shown in Table 1, the reaction with HOAc and $H_2O$ both gave higher yields. Although the reaction in HOAc proceeded with better yield than that in $H_2O$, finally water was used as the reaction media for the following reactions, because it turned out to be the best choice in view of its relatively environmental-friendly characteristics, as a "cleaner" reaction medium compared with others (Table 1, entries 1–4).

To further optimize reaction conditions, the same reaction was performed in water and 250 W at temperatures ranging from 100 to 140°C. Initially, the product **4c** was easily obtained with yield 59% (100°C). The yield of product **4c** was increased as the temperature was increased from 100 to 120°C (Table 1, entries 5–7). However, further increase of the temperature from 130 to 140°C (Table 1, entries 9 and 10) failed to improve the yield of **4c**. Therefore, 120°C was chosen as the reaction temperature for all further MW-assisted reactions (Scheme 1).

Under the optimal conditions [$H_2O$, 120°C, 250 W (maximum power)], reactions of different aldehydes were performed and afforded various 3-hydroxynaphthalene-1,4-diones. As shown in Table 2, we made a research for the aldehyde substrate scope, and the results indicated that aromatic aldehydes bearing both electron-withdrawing (such as nitro) and electron-donating (such as alkoxy) readily provided compounds **4** in good yields (Table 2, entries 1–12). Moreover, heterocyclic aldehydes such as thiophene-2-carbaldehyde (Table 2, entry 13) still displayed a high reactivity under this standard condition. It is worth noting that this conclusion is significant since there is no literature precedent for the synthesis of 3-hydroxynaphthalene-1,4-diones.

**Scheme 2**

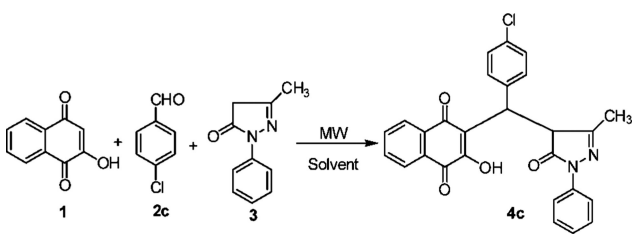



**Table 1**

Optimization for the synthesis of **4c** under microwave irradiation.

| Entry | Solvent | Temperature (°C) | Time (min) | Yield (%) |
|---|---|---|---|---|
| 1 | EtOH | 120 | 6 | 30 |
| 2 | Glycol | 120 | 6 | 45 |
| 3 | DMF | 120 | 6 | 63 |
| 4 | HOAc | 120 | 6 | 78 |
| 5 | Water | 100 | 6 | 59 |
| 6 | Water | 110 | 6 | 72 |
| 7 | Water | 120 | 6 | 88 |
| 8 | Water | 130 | 6 | 82 |
| 10 | Water | 140 | 6 | 69 |

The formation of **4** is expected to proceed *via* initial condensation of aldehydes with 2-hydroxynaphthalene-1,4-dione to afford 3-(argiomethylene)naphthalene-1,2,4(3*H*)-trione **5**, which further undergoes *in situ* Michael addition with 3-methyl-1-phenyl-1*H*-pyrazol-5-ol **6**, isomerized by 3-methyl-1-phenyl-1H-pyrazol-5(4*H*)-one **3**, to yield final product **4** (Scheme 3). In this study, all the products were characterized by IR, $^1$H-NMR, and MS. Furthermore, the structure of **4d** was established by X-ray crystallography [19]. The molecular structure of **4d** was shown in Figure 1.

In summary, we demonstrated a rapid and direct route for the one-pot green synthesis of 2-(argio(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)methyl)-3-hydroxynaphthalene-1,4-diones from easily available substrates in aqueous medium. Particularly, valuable features of this method included environmental friendliness, operational simplicity, short reaction time, high yields, and broader substrate scope.

## EXPERIMENTAL

All reactions were performed in a monomodal Emrys$^{TM}$ Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a FT-IR-tensor 27 spectrometer in KBr. $^1$H-NMR spectra were measured on a DPX 400 MHz spectrometer using TMS as an internal standard and DMSO-$d_6$ as solvent. HRMS (ESI) was determined by using the micrO-TOF-Q II HPLC/MS instrument (BRUKER). X-Ray crystallographic analysis was performed with a Siemens SMART CCD and a Semens P4 diffractometer.

**Sample experimental.** ***General procedure for the synthesis of 3-hydroxynaphthalene-1,4-dione derivatives 4 under microwave irradiation.*** In a 10-mL Emrys$^{TM}$ reaction vial, 2-hydroxynaphthalene-1,4-dione (1 mmol) with aromatic

**Table 2**

The synthesis of compounds **4**.

| Entry | Compound | Ar | Time (min) | Yield (%) | Mp (°C) |
|---|---|---|---|---|---|
| 1 | **4a** | $C_6H_5$ | 7 | 85 | 267.2–268.4 |
| 2 | **4b** | 4-$FC_6H_4$ | 6 | 79 | 257.5–259.6 |
| 3 | **4c** | 4-$ClC_6H_4$ | 6 | 88 | 262.1–264.0 |
| 4 | **4d** | 2,4-$Cl_2C_6H_4$ | 8 | 86 | 257.3–258.5 |
| 5 | **4e** | 4-$BrC_6H_4$ | 7 | 90 | 270.0–271.8 |
| 6 | **4f** | 4-$O_2NC_6H_4$ | 5 | 82 | 247.3–248.9 |
| 7 | **4g** | 3-$O_2NC_6H_4$ | 7 | 77 | 266.2–268.0 |
| 8 | **4h** | 4-$MeC_6H_4$ | 7 | 89 | 265.3–266.4 |
| 9 | **4i** | 3,4-$(MeO)_2C_6H_3$ | 9 | 77 | 235.3–237.4 |
| 10 | **4j** | 3,4-$OCH_2OC_6H_3$ | 7 | 82 | 261.7–263.2 |
| 11 | **4k** | 4-$Me_2NC_6H_4$ | 7 | 78 | 211.3–212.6 |
| 12 | **4l** | 4-Benzo[*d*]oxazol-2-yl | 9 | 84 | 257.2–259.5 |
| 13 | **4m** | Thiophen-2-yl | 8 | 72 | 238.7–239.8 |

aldehyde (1.0 mmol) and 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (1.0 mmol) and water (2.0 mL) were mixed and then capped. The mixture was irradiated by MW at 250 W and 120°C for a given time. The automatic mode stirring helped the mixing and uniform heating of the reactants. Upon completion, monitored by thin layer chromatography (TLC), the reaction mixture was cooled to room temperature and then poured into cold water, filtered to give the crude products, which were further purified by recrystallization from 95% EtOH. The reaction time and the yields are listed in Table 2. The analytical data of new products are as following.

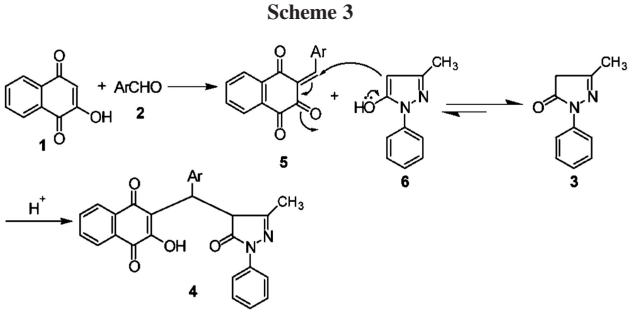
*2-Hydroxy-3-((3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)(phenyl)methyl)naphthalene-1,4-dione (**4a**).* IR (KBr): 3175, 3069, 1656, 1634, 1605, 1572, 1501, 1460, 1375, 1287, 1122, 1030, 954, 833, 728, 695, 610 $cm^{-1}$. $^1$H-NMR (400 MHz, DMSO) (δ, ppm): 8.04 (d, *J* = 6.8 Hz, 1H, ArH), 7.97 (d, *J* = 6.4 Hz, 1H, ArH), 7.84–7.77 (m, 2H, ArH), 7.69 (d, *J* = 6.4 Hz, 2H, ArH), 7.51–7.47 (m, 2H, ArH), 7.32–7.18 (m, 6H, ArH), 5.85 (s, 1H, CH), 2.27 (s, 3H, $CH_3$). HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{27}H_{20}N_2O_4$: 459.1316; found: 459.1329.

*2-((4-Fluorophenyl)(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)methyl)-3-hydroxynaphthalene-1,4-dione (**4b**).* IR (KBr): 3174, 3067, 1656, 1634, 1608, 1571, 1504, 1376, 1254, 1157, 1016, 956, 823, 729, 615 $cm^{-1}$. $^1$H-NMR (400 MHz, DMSO) (δ, ppm): 8.04 (d, *J* = 7.6 Hz, 1H, ArH), 7.97 (d, *J* = 7.2 Hz, 1H, ArH), 7.85–7.76 (m, 2H, ArH), 7.69 (d, *J* = 7.6 Hz, 2H, ArH), 7.49 (t, *J* = 8.0 Hz, 2H, ArH), 7.32–7.24 (m, 3H, ArH), 7.08 (t, *J* = 8.8 Hz, 2H, ArH), 5.81 (s, 1H, CH), 2.27 (s, 3H, $CH_3$). HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{29}H_{21}FO_4$: 477.1222; found: 477.1216.

*2-((4-Chlorophenyl)(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)methyl)-3-hydroxynaphthalene-1,4-dione (**4c**).* IR (KBr): 3155, 3058, 1659, 1633, 1605, 1572, 1500, 1488, 1376, 1287, 1094, 955, 823, 726, 612 $cm^{-1}$. $^1$H-NMR (400 MHz, DMSO) (δ, ppm): 8.03 (d, *J* = 7.6 Hz, 1H, ArH), 7.97 (d, *J* = 7.6 Hz, 1H, ArH), 7.85–7.76 (m, 2H, ArH), 7.69 (d, *J* = 8.0 Hz, 2H, ArH), 7.49 (t, *J* = 8.0 Hz, 2H, ArH), 7.32–7.24 (m, 5H, ArH), 5.81 (s, 1H, CH), 2.28 (s, 3H, $CH_3$). HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{27}H_{19}ClN_2O_4$: 493.0926; found: 493.0916.

*2-((2,4-Dichlorophenyl)(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)methyl)-3-hydroxynaphthalene-1,4-dione (**4d**).* IR (KBr): 3174, 3067, 1648, 1609, 1593, 1577, 1502, 1468, 1373, 1256, 1119, 1047, 955, 838, 753 $cm^{-1}$. $^1$H-NMR (400 MHz, DMSO) (δ, ppm): 7.99 (t, *J* = 7.8 Hz, 2H, ArH), 7.86–7.76 (m, 2H, ArH), 7.71 (d, *J* = 7.6 Hz, 2H, ArH), 7.54 (s, 1H, ArH), 7.48–7.43 (m, 3H, ArH), 7.37 (dd, $J_1$ = 8.4 Hz, $J_2$ = 2.0 Hz, 1H, ArH), 7.25 (t, *J* = 7.2 Hz, 1H, ArH), 5.76 (s, 1H, CH),

**Scheme 3**



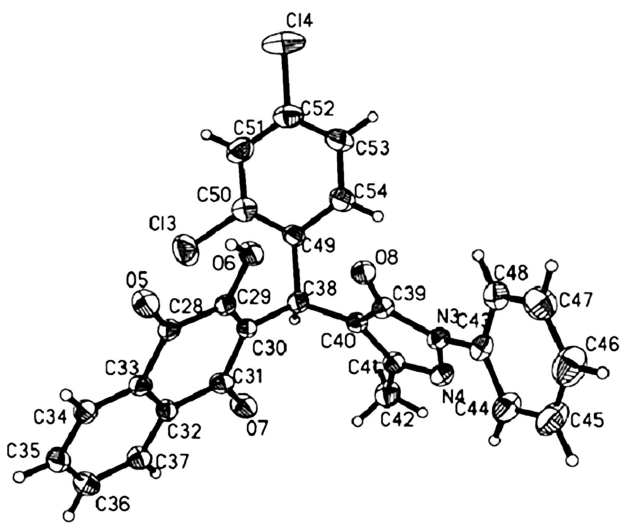




**Figure 1.** ORTEP diagram of **4d**.

2.08 (s, 3H, $CH_3$). HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{27}H_{18}C_{l2}N_2O_4$: 527.0536; found: 527.0553.

*2-((4-Bromophenyl)(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)methyl)-3-hydroxynaphthalene-1,4-dione (**4e**).* IR (KBr): 3149, 3055, 1660, 1633, 1605, 1572, 1500, 1484, 1373, 1285, 1252, 1074, 1010, 955, 821, 757 $cm^{-1}$. $^1$H-NMR (400 MHz, DMSO) (δ, ppm): 8.03 (d, *J* = 7.6 Hz, 1H, ArH), 7.97 (d, *J* = 7.6 Hz, 1H, ArH), 7.85–7.76 (m, 2H, ArH), 7.70 (d, *J* = 8.0 Hz, 2H, ArH), 7.51–7.43 (m, 4H, ArH), 7.30 (t, *J* = 7.2 Hz, 1H, ArH), 7.19 (d, *J* = 8.0 Hz, 2H, ArH), 5.79 (s, 1H, CH), 2.28 (s, 3H, $CH_3$). HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{27}H_{19}BrN_2O_4$: 537.0421; found: 537.0431.

*2-Hydroxy-3-((3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)(4-nitrophenyl)methyl)naphthalene-1,4-dione (**4f**).* IR (KBr): 3154, 3072, 2903, 1672, 1639, 1604, 1575, 1459, 1346, 1253, 954, 851, 728, 692 $cm^{-1}$. $^1$H-NMR (400 MHz, DMSO) (δ, ppm): 8.12 (d, *J* = 8.8 Hz, 2H, ArH), 8.04 (d, *J* = 7.6 Hz, 1, ArH), 7.98 (d, *J* = 7.6 Hz, 1H, ArH), 7.86–7.76 (m, 2H, ArH), 7.70 (d, *J* = 7.6 Hz, 2H, ArH), 7.50 (q, *J* = 8.0 Hz, 4H, ArH), 7.30 (t, *J* = 7.2 Hz, 1H, ArH), 5.91 (s, 1H, CH), 2.28 (s, 3H, $CH_3$). HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{27}H_{19}N_3O_6$: 504.1167; found: 504.1167.

*2-Hydroxy-3-((3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)(3-nitrophenyl)methyl)naphthalene-1,4-dione (**4g**).* IR (KBr): 3203, 3071, 3041 1666, 1639, 1608, 1524, 1500, 1460, 1347, 1254, 1123, 964, 861, 726, 687 $cm^{-1}$. $^1$H-NMR (400 MHz, DMSO) (δ, ppm): 8.09–8.07 (m, 1H, ArH), 8.05–8.03 (m, 2H, ArH), 7.98 (d, *J* = 8.0 Hz, 1H, ArH), 7.86–7.79 (m, 2H, ArH), 7.76 (d, *J* = 8.0 Hz, 1H, ArH), 7.70 (d, *J* = 7.6 Hz, 2H, ArH), 7.57 (t, *J* = 8.0 Hz, 1H, ArH), 7.50 (t, *J* = 8.0 Hz, 2H, ArH), 7.31 (t, *J* = 7.2 Hz, 1H, ArH), 5.93 (s, 1H, CH), 2.29 (s, 3H, $CH_3$). HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{27}H_{19}N_3O_6$: 504.1167; found: 504.1166.

*2-Hydroxy-3-((3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)(p-tolyl)methyl)naphthalene-1,4-dione (**4h**).* IR (KBr): 3160, 3057, 1660, 1635, 1604, 1572, 1501, 1459, 1374, 1287, 1254, 954, 814, 753, 730, 691 $cm^{-1}$. $^1$H-NMR (400 MHz, DMSO) (δ, ppm): 8.03 (d, *J* = 7.6 Hz, 1H, ArH), 7.97 (d, *J* = 7.6 Hz, 1H, ArH), 7.85–7.76 (m, 2H, ArH), 7.70 (d, *J* = 8.0 Hz, 2H, ArH), 7.49 (t, *J* = 8.0 Hz, 2H, ArH), 7.30 (t, *J* = 7.6 Hz, 1H, ArH), 7.08 (q, *J* = 8.0 Hz, 4H, ArH), 5.80 (s, 1H, CH), 2.27 (s, 3H, $CH_3$), 2.25 (s, 3H, $CH_3$). HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{28}H_{22}N_2O_4$: 473.1472; found: 473.1471.

*2-((3,4-Dimethoxyphenyl)(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)methyl)-3-hydroxynaphthalene-1,4-dione (**4i**).* IR (KBr): 3158, 3039, 2973, 2834, 1655, 1636, 1604, 1573, 1510, 1460, 1377, 1243, 1143, 1025, 956, 850, 733, 692, 634 $cm^{-1}$. $^1$H-NMR (400 MHz, DMSO) (δ, ppm): 8.03 (d, *J* = 6.8 Hz, 1H, ArH), 7.97 (d, *J* = 7.6 Hz, 1H, ArH), 7.83–7.77 (m, 2H, ArH), 7.69 (d, *J* = 7.6 Hz, 2H, ArH), 7.49 (t, *J* = 8.0 Hz, 2H, ArH), 7.29 (t, *J* = 7.2 Hz, 1H, ArH), 6.84–6.73 (m, 3H, ArH), 5.77 (s, 1H, CH), 3.71 (s, 3H, $OCH_3$), 3.62 (s, 3H, $OCH_3$), 2.24 (s, 3H, $CH_3$). HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{29}H_{24}N_2O_6$: 497.1708; found: 497.1715.

*2-(Benzo[*d*][1,3]dioxol-5-yl(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)methyl)-3-hydroxynaphthalene-1,4-dione (**4j**).* IR (KBr): 3167, 3064, 2887, 1660, 1639, 1607, 1573, 1501, 1486, 1375, 1238, 1041, 939, 813, 757, 726 $cm^{-1}$. $^1$H-NMR (400 MHz, DMSO) (δ, ppm): 8.02 (d, *J* = 7.2 Hz, 1H, ArH), 7.96 (d, *J* = 7.6 Hz, 1H, ArH), 7.84–7.75 (m, 2H, ArH), 7.69 (d, *J* = 8.0 Hz, 2H, ArH), 7.49 (t, *J* = 8.0 Hz, 2H, ArH), 7.29 (t, *J* = 7.2 Hz, 1H, ArH), 6.80–6.78 (m, 2H, ArH), 6.68 (d, *J* = 8.0 Hz, 1H, ArH), 5.96 (s, 2H, $CH_2$), 5.74 (s, 1H, CH), 2.26 (s, 3H, $CH_3$). HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{28}H_{20}N_2O_6$: 503.1214; found: 503.1203.

*2-((4-(Bimethylamino)phenyl)(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)methyl)-3-hydroxynaphthalene-1,4-dione (**4k**).* IR (KBr): 3150, 3096, 3010, 2963, 2808, 1653, 1638, 1606, 1573, 1520, 1499, 1361, 1280, 1164, 1066, 953, 812, 756, 727, 694 $cm^{-1}$. $^1$H-NMR (400 MHz, DMSO) (δ, ppm): 8.02 (d, *J* = 7.2 Hz, 1H, ArH), 7.95 (d, *J* = 7.6 Hz, 1H, ArH), 7.84–7.74 (m, 2H, ArH), 7.70 (d, *J* = 8.0 Hz, 2H, ArH), 7.48 (t, *J* = 8.0 Hz, 2H, ArH), 7.28 (t, *J* = 7.2 Hz, 1H, ArH), 7.06 (d, *J* = 8.4 Hz, 2H, ArH), 6.74–6.72 (m, 2H, ArH), 5.74 (s, 1H, CH), 2.87 (s, 6H, $2CH_3$), 2.25 (s, 3H, $CH_3$). HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{29}H_{25}N_3O_4$: 502.1738; found: 502.1715.

*2-((4-(Benzo[*d*]oxazol-2-yl)phenyl)(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)methyl)-3-hydroxynaphthalene-1,4-dione (**4l**).* IR (KBr): 3156, 3065, 2967, 1654, 1638, 1609, 1572, 1498, 1453, 1372, 1243, 1061, 953, 808, 760, 727 $cm^{-1}$. $^1$H-NMR (400 MHz, DMSO) (δ, ppm): 8.11 (d, *J* = 8.4 Hz, 2H, ArH), 8.06 (d, *J* = 7.6 Hz, 1H, ArH), 7.99 (d, *J* = 7.6 Hz, 1H, ArH), 7.85 (t, *J* = 7.2 Hz, 1H, ArH), 7.82–7.77 (m, 3H, ArH), 7.72 (d, *J* = 8.0 Hz, 2H, ArH), 7.52–7.47 (m, 4H, ArH), 7.42–7.39 (m, 2H, ArH), 7.31 (t, *J* = 7.2 Hz, 1H, ArH), 5.93 (s, 1H, CH), 2.31 (s, 3H, $CH_3$). HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{34}H_{23}N_3O_5$: 576.1530; found: 576.1523.

*2-Hydroxy-3-((3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)(thiophen-2-yl)methyl)naphthalene-1,4-dione (**4m**).* IR (KBr): 3192, 3101, 1657, 1634, 1609, 1571, 1500, 1459, 1375, 1287, 1091, 946, 828, 729, 688, 610 $cm^{-1}$. $^1$H-NMR (400 MHz, DMSO) (δ, ppm): 8.04 (d, *J* = 7.6 Hz, 1H, ArH), 7.97 (d, *J* = 7.6 Hz, 1H, ArH), 7.86–7.76 (m, 2H, ArH), 7.68 (d, *J* = 8.4 Hz, 2H, ArH), 7.50 (t, *J* = 8.0 Hz, 2H, ArH), 7.33–7.30 (m, 2H, ArH), 6.91–6.88 (m, 1H, ArH), 6.85–6.84 (m, 1H, ArH), 5.98 (s, 1H, CH), 2.31 (s, 3H, $CH_3$). HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{25}H_{18}N_2O_4S$: 465.0880; found: 465.0866.

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[19] The single-crystal growth was carried out in DMF at room temperature. X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Semens P4 diffractometer (graphite monochromator, MoKa radiation $\lambda$ = 0.71073 Å). Crystal data for **4d**: Empirical formula $C_{27}H_{17}Cl_2N_2O_4$, red crystal, crystal dimensions 0.19 mm × 0.17 mm × 0.06 mm, Monoclinic, space group *P*2(1)/*c*, *a* = 22.583(2) Å, *b* = 13.4467(15) Å, *c* = 15.7624(16) Å, $\alpha$ = 90°, $\beta$ = 97.8920(10)°, $\gamma$ = 90°, *V* = 4741.1(9) Å$^3$, Mr = 504.33, *Z* = 8, Dc = 1.413 Mg/m$^3$, $\lambda$ = 0.71073 Å, $\mu$ (MoK$\alpha$) = 0.312 mm$^{-1}$, *F*(000) = 2072, *S* = 1.050, R1 = 0.0924, wR2 = 0.1809.