Synthesis and Biological Evaluation of Naphthalene-1,4-dione Derivatives as Potent Antimycobacterial Agents

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Abstract: The recent increase in the incidence of tuberculosis with the emergence of multi-drug resistant (MDR) cases has lead to the search for new drugs that are effective against MDR strains of *Mycobacterium tuberculosis* (*M. tb*) and can augment the potential of existing drugs against tuberculosis. In the present study a series of naphthalene-1,4-dione derivatives were synthesized and evaluated for their *in vitro* antimycobacterial activity against *M. tb* $H_{37}Rv$ strain. Preliminary results indicated that most of the compounds demonstrated significant antimycobacterial activities. The most effective compounds of the series **7**, **8** and **10** have MIC values of 3.13 μg/mL and growth inhibition of 99 %. Compound **7** has an IC_{50} value of 0.49 μg/mL. Compounds **1**, **3** and **18** with MIC values of 3.13 μg/mL also showed 96-98 % growth inhibition. The objective of our study is to generate new leads through different mode of action and to optimize their structure to display the potent efficacy.

Key Words: Tuberculosis, antimycobacterial activity, naphthalene-1,4-dione derivatives.

INTRODUCTION

Tuberculosis (TB) an infectious disease caused by different species of *M. tb*, is one of the leading global public health problems. Nearly one third of the world's population is infected with this disease and it is estimated that close to 5500 people died every day [1]. The first-line drugs currently used for the treatment of TB are streptomycin (SM), isoniazid (INH), ethambutol (EMB), pyrazinamide (PZA) and rifampicin (RMP) [2]. However, TB is still a challenging worldwide health problem, especially with the emergence of multidrug-resistant (MDR) strains of *M. tb*, which are insensitive to one or more of the first-line anti-TB drugs [3-5]. Because of this, there is an impetus for developing new structural classes of anti-TB drugs [6] with novel mechanisms of action [7] and improved properties such as enhanced activity against MDR strains, reduced toxicity and shortened duration of therapy.

Recent years have witnessed emergence of many new structural classes of anti-TB agents, which have exhibited promising activities against drug-sensitive and drug-resistant strains of the causative organism *M. tb* [6]. Naturally occurring compounds containing a quinone group are useful as synthetic intermediates and biologically active compounds. Naphthalene-1,4-dione derivatives Fig. (**1**), have been known to possess a wide spectrum of biological activities such as antibacterial, antifungal, antiinflammatory, anticancer, antidiabetic and antimalarial activities [8-16]. Plumbagin and juglone have strong sterilizing activity against mycobacterium, potentially with a unique mechanism of action [8]. Diospyrin and methyljuglone have been found to inhibit several antibiotic resistant as well as antibiotic susceptible strains of *M. tb* [17]. A combination treatment of diospyrin and methyljuglone, which may be more effective than a single drug treatment of the two naphthoquinones, is also being considered [13]. Novel antibacterial agents for drug-resistant bacteria and antichlamydia agents comprise highly active furanonaphthoquinone derivatives having acetyl groups as effective compounds [13].

The biological activity of naphthalene-1,4-diones is mainly due to the presence of two carbonyl groups that have the ability to accept one and/or two electrons to form the corresponding radical anion or dianion species as well as their acid–base properties [18]. The presence of electron-donating or –attracting substituents in naphthalene-1,4-diones modulates the generation of radical anion and the redox property which is further responsible for compounds to catalytically cycle and generate oxidative radicals, such as hydrogen peroxide and superoxide which damage the cells [19]. There are some papers describing about the mechanism of naphthalene-1,4-diones such as extrusion pumps, cell penetration, and redox cycling [20-22]. However, the mechanism is still under investigation. But there are no published reports examining the toxicity of quinones against the genus *Mycobacterium*.

Our research efforts towards the development of novel antituberculosis agents are in the direction of discovering new classes of compounds, which are structurally different from known anti-tuberculosis drugs [23,24]. Many amino and heterocyclic naphthalene-1,4-diones have been used for the synthesis of numerous biologically important compounds [25,26]. The interesting biological profile resulting from the presence of heteroatom, nitrogen, oxygen or sulfur in the naphthalene-1,4-diones prompted us to synthesize derivatives **1**-**22** according to Schemes **1**, **2** and **3**, possessing ni-

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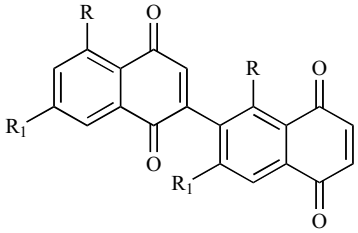
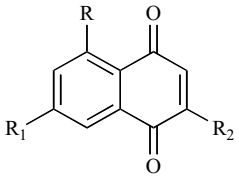
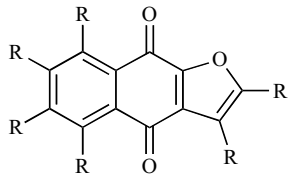


Diospyrin: R = OH, $R_1 = CH_3$



Juglone: R = OH, R_1, R_2 = H
Methyljuglone: R = OH, $R_1 = CH_3$, R_2 = H
Plumbagin: R = OH, R_1 = H, $R_2 = CH_3$



Furanonaphthoquinone
R = H, COR_1, $OCOR_1$, SR_1

Fig. (1). Structures of naphthoquinones.

trogen or sulfur atoms at 2 position inside the ring and evaluating them for their *in vitro* antimycobacterial activities.

These derivatives were synthesized following standard procedures starting from 1, 2, 3 and/or 6-substituted naphthalenes and naphthalene-1,4-dione [27-29]. The synthesis of **1, 2, 5, 6, 21** and **22** involved the oxidation of substituted naphthalenes. The oxidative coupling of naphthalene-1,4-dione with 2-substituted heterocycles in acetic acid and stoichiometric amounts of palladium acetate under reflux conditions gave the corresponding 2-heteroaryl-substituted naphthalene-1,4-diones **7-20** [27,28]. The structures of all the compounds were established on the basis of spectroscopic analysis and analytical data. It is expected that these naphthalene-1,4-diones may be effective against drug-resistant strains of *M. tb* and make them excellent leads for synthesizing derivatives for antimycobacterial activity.

RESULTS AND DISCUSSION

All the synthesized compounds were primarily screened against *M.tb* strain $H_{37}Rv$ (ATCC 27294) using the microplate alamar blue assay (MABA) [30], at the single concentration 6.25 µg/mL. Compounds were also tested in the BACTEC 460 radiometric system [31] and the activities expressed as minimum inhibitory concentration (MIC, µg/mL) are summarized in Table **1**. The MIC is defined as the lowest concentration effecting a reduction in fluorescence of ≥90 % relative to controls. Activity is designated by a '**+**' in the column labeled *Activity*. The standard antitubercular drug Rifampicin (MIC 6.25 µg/mL) was taken as positive controls. Amongst the tested compounds **7**, **8**, and **10** were found to be more active with MIC values of 3.13 µg/mL and growth inhibitory activity of 99 %. Some of the other derivatives **1**, **3** and **18** also exhibited good potency with MIC values of 3.13 µg/mL and >96 % growth inhibition, and their activities are comparable to Rifampicin (91 %) at 6.25 µg/mL. Compounds **2**, **5**, **9**, **11**, **14**, **15**, **16**, **17**, **19** and **20** also showed 47-71% inhibition. Only compounds **4, 6, 12, 13, 21** and **22** showed low or no activity (21%, 2%, 36%, and 0% growth inhibition, respectively). Derivatives containing sulphur or oxygen heterocycles **12, 13, 19** and **20** were less active, where as derivatives containing 2-substituted pyridine side-chain or substituted pyrrole heterocycle are quite potent and can be further explored for new antitubercular agents. Compounds demonstrating at least 90 % inhibition at 6.25 µg/mL in the initial screening were retested in the broth micro dilution assay at the lower concentrations to determine the actual MIC. Compound **7** was further screened by serial dilution to assess cytotoxicity to a VERO cell line, to determine the selectivity index (SI), defined as the ratio of the measured IC_{50} in VERO cells to the MIC described above. Compound **7** showed good *in vitro* profile with IC_{50} value of 0.49 µg/mL but the corresponding SI (0.16) against *M.tb* $H_{37}Rv$ strain is too low to be considered significant. The in silico predictions also indicated a strong likelihood of good oral bioavailability, through the generation of predictors based on the calculated parameters described by Lipinski [32]. The Lipinski's rule of five suggests selected parameters for estimation of solubility and permeability of new candidate compounds as barriers to absorption. The physical parameters such as polar surface area of less than <130 Å, no of rotatable bonds <10, number of hydrogen bond donors and acceptors <5 and 10, ClogP <5 and molecular weight <500 are predictive of H-bonding potential, permeability, oral activity and lipophilicity. The calculated predictors which are within these ranges are indicative of good oral bioavailability.

The present study on the synthesis and evaluation of naphthalene-1,4-dione derivatives has established the discovery of a new series of analogues with significant and promising activity against drug-sensitive *M. tb* cultures. These effective derivatives are ideally suited for further modifications to obtain more efficacious antimycobacterial compounds. For the therapeutic development of more potent and non toxic antitubercular agents, further investigations on the structural modifications are currently underway and results will be reported in due course.

EXPERIMENTAL SECTION

General Procedures

Melting points were recorded on a Buchi capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Nicolet Impact-410 FTIR spectrometer. ^1H spectra were recorded on a 300MHz Bruker FT-NMR spectrometer in $CDCl_3$ solution. The chemical shifts are reported in δ (ppm) relative to internal standard tetramethylsilane (TMS) and coupling constants J are given in Hz. Mass spectrometry was conducted using GCMS (Shimadzu QP 5000 spectrometer) auto sampler/direct injection (EI/CI) or LCMS (Finnigan Mat LCQ spectrometer) (APCI/ESI). Elemental analyses were recorded on Elementar Vario EL analyzer. All chromatographic purifications were performed with silica gel 60 (230–400 mesh), whereas all TLC devel-

Table 1. ***In Vitro*** **Antimycobacterial Activities and In Silico Parameters of naphthalene-1,4-dione Derivatives, Expressed as MIC (µg/mL)[a] Against Drug-Sensitive Strain of *M. tb* $H_{37}Rv$**

Compound	MIC[a]	GI %[b]	Activity	*C*log*P*	*C*log*D* at pH 7.4 & 6.5	No. of Rotatable Bonds	PSA (Å^2)
1	<6.25, =3.13	96	+	2.38	2.38	0	34.14
2	>6.25	48	_	2.84	2.84	0	34.14
3	<6.25, =3.13	98	+	1.82	1.62, 1.79	0	74.6
4	>6.25	21	_	1.80	1.80	2	52.6
5	>6.25	56	_	3.90	3.90	2	34.14
6	>6.25	2	_	2.91	2.91	1	34.14
7	<6.25, =3.13	99	+	2.14	2.14	2	64.1
8	<6.25, =3.13	99	+	2.37	2.37	2	64.1
9	>6.25	49	_	2.77	2.77	2	64.1
10	<6.25, =3.13	99	+	2.17	2.08, 1.72	2	66.48
11	>6.25	57	_	2.31	2.31	2	76.99
12	>6.25	36	_	3.16	3.16	2	51.21
13	>6.25	2	_	2.32	2.32	2	60.44
14	>6.25	71	_	2.65	2.65	2	63.24
15	>6.25	48	_	3.89	3.88	2	54.45
16	>6.25	47	_	3.83	3.83	2	63.24
17	>6.25	69	_	3.23	3.23	2	64.1
18	<6.25, =3.13	96	+	2.06	2.06	2	54.45
19	>6.25	53	_	3.62	3.62	2	51.21
20	>6.25	60	_	3.35	3.35	2	51.21
21	>6.25	0	_	2.97	2.97	0	34.14
22	>6.25	0	_	3.25	3.25	1	34.14

[a] MIC(µg/mL) is defined as the lowest concentration inhibiting ≥90 % of the inoculum relative to controls.

[b] Growth Inhibition of $H_{37}Rv$ strain of *M. tb*. According to the TAACF program, compounds effecting less than 90% inhibition are considered to be inactive.

opment was done on silica gel coated (Merck Kiesel 60 F254, 0.2mm thickness) plates. All chemicals were purchased from Aldrich Chemical Company (USA) and were used as received unless otherwise noted. Solvents used for the chemical synthesis were of laboratory and analytical grade, and were used without further purification unless otherwise stated.

General Method for the Synthesis of Derivatives (1), (2), (5), (6), (21) and (22) (Scheme 1)

A solution of 10 mol of chromium trioxide in glacial acetic acid was added to a solution of 1mol of 1, 2, 3 and/or 6-substituted naphthalene and heated at 50ºC for 10-12 h. The resulting mixture was poured over crushed ice with stirring. The crystals were separated by filtration and recrystallized from methanol to give naphthalene-1,4-dione derivatives **(1), (2), (5), (6), (21)** and **(22)**.

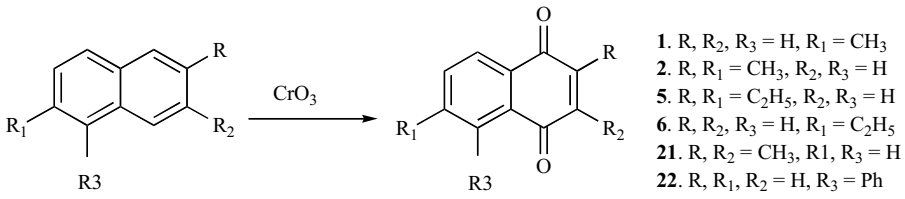
Preparation of (3) and (4) [29] (Scheme 2)

*5,8-dihydroxynaphthalene-1,4-dione (**3**)*

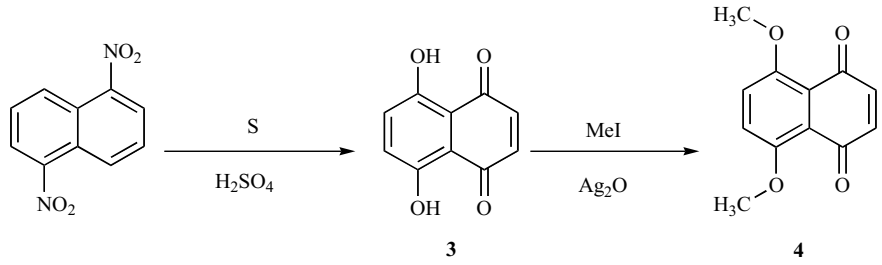
A solution of 2.5 g of sulfur in 50 mL sulfuric acid was added drop wise with stirring to a suspension of 5 g of 1,5-dinitronaphthalene in 20 mL of conc. sulfuric acid. The reaction mixture was heated at 50-60ºC for about 5 h and then poured over crushed ice. The resulting dark blue solution was filtered and heated until the filtrate became dark red and a thick mass was formed. The red solid was filtered and dried. The product **3** was obtained by repeated extraction of the red solid with hot benzene and evaporation of the solvent as red solid, yield (0.650 g, 15 %).

*5,8-dimethoxynaphthalene-1,4-dione (**4**)*

A solution containing 0.500 g of 5,8-dihydroxynaphthalene-1,4-dione **3**, 2 mL of methyl iodide, and 15 mL of chlo-



Scheme 1.



Scheme 2.

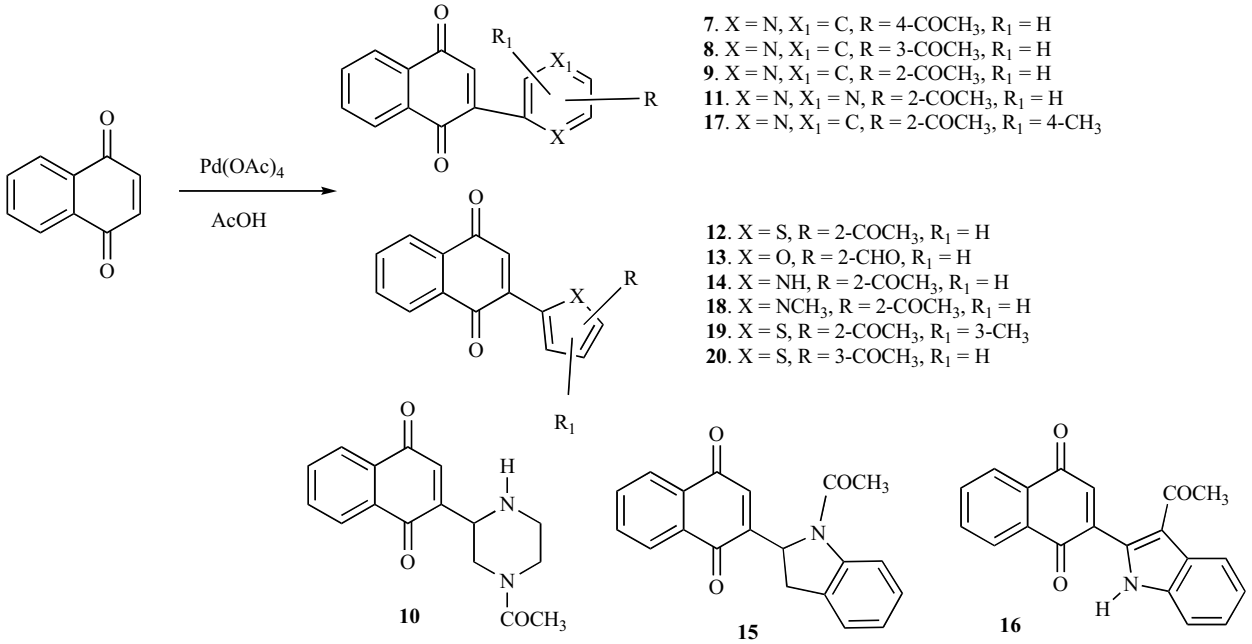
roform was refluxed with 0.5 g of silver oxide for 48 h. The reaction was heated until an aliquot from the reaction mixture failed to give a violet color with 5 % sodium hydroxide. Addition of 1ml of methyl iodide and 0.5 g of silver oxide was done after every 2, 6 and 24 h. When the reaction was completed, the silver salt was removed by filtration and the filtrate was passed through an alumina column and eluted with hexane. The product **4** was obtained as orange needles, yield (0.160 g, 29 %).

General Method for the Synthesis of Derivatives (7)-(20) (Scheme 3)

A solution of naphthalene-1,4-dione, substituted aromatic heterocyclic compounds and palladium acetate in glacial acetic acid in the 1:1:1 ratios were heated at reflux temperature under nitrogen atmosphere for 10-24 hours. The reaction mixture was evaporated to give a residue, which was then chromatographed on a silica gel column and eluted with hexane: ethyl acetate to give 2-substituted naphthoquinone derivatives **(7)- (20)**.

2-methylnaphthalene-1,4-dione (**1**) [33]. Obtained from 2-methylnaphthalene and recrystallized from methanol to give **1** as a white solid. Yield 80%; mp 105-107ºC [Lit. 104-105ºC]; IR (KBr): ν_{max} cm^{-1} 1660; ^1H NMR ($CDCl_3$): δ 8.12-8.05 (m, 2H), 7.75-7.71 (m, 2H), 6.85 (s, 1H), 2.20 (s, 3H); LRMS (ES^+): m/z 172.13 [$(M)^+$, 100%]; Anal. Calc for $C_{11}H_8O_2$ (172.18): C, 76.73; H, 4.6; found: C, 76.85; H, 4.75.

2,6-dimethylnaphthalene-1,4-dione (**2**) [34]. Obtained from 2, 6-dimethylnaphthalene and recrystallized from methanol to give **2** as a white solid. Yield 81%; mp 138-139ºC [Lit. 136-137ºC]; IR (KBr): ν_{max} cm^{-1} 1661, 1598; ^1H



Scheme 3.

NMR ($CDCl_3$): δ 8.0-7.98 (d, 1H, J = 7.45 Hz), 7.85 (s, 1H), 7.52 (d, 1H, J =7.40 Hz), 6.80 (d, 1H), 2.49 (s, 3H), 2.18 (s, 3H); LRMS (ES^+): m/z 186.09 [$(M)^+$, 100%]; Anal. Calc for $C_{12}H_{10}O_2$ (186.21): C, 77.40; H, 5.41; found: C, 77.56; H, 5.50.

5,8-dihydroxynaphthalene-1,4-dione (**3**) [29]. Yield 15%; mp 234ºC, Lit. 234ºC decomp; IR (KBr): ν_{max} cm^{-1} 1614; ^1H NMR ($CDCl_3$): δ 12.42 (s, 2H), 7.15 (s, 4H arom & quinoidal); LRMS (ES^+): m/z 190.03 [$(M)^+$, 100%]; Anal. Calc for $C_{10}H_6O_4$ (190.15): C, 63.16; H, 3.18; found: C, 63.40; H, 3.55.

5,8-dimethoxynaphthalene-1,4-dione (**4**) [29]. Yield 29%; mp 155ºC, Lit. 155ºC ; IR (KBr): ν_{max} cm^{-1} 1650, 1250; ^1H NMR ($CDCl_3$): δ 7.33 (s, 2H), 6.78 (s, 2H), 3.96 (s, 6H); LRMS (ES^+): m/z 218.10 [$(M)^+$, 100%]; Anal. Calc for $C_{12}H_{10}O_4$ (218.21): C, 66.05; H, 4.62; found: C, 66.10; H, 4.75.

2,6-diethylnaphthalene-1,4-dione (**5**). Yield 22%; viscous oil; IR (Neat): ν_{max} cm^{-1}1655, 1589; ^1H NMR ($CDCl_3$): δ 8.00-7.98 (d, 1H, J = 6.95 Hz), 7.88 (s, 1H), 7.49 (d, 1H, J = 7.20 Hz), 7.30 (d, 1H, J = 6.94 Hz), 2.55-2.40 (m, 4H), 1.25-1.00 (m, 6H); LRMS (ES^+): m/z 215.09 [$(M+H)^+$, 100%]; Anal. Calc for $C_{14}H_{14}O_2$ (214.26): C, 78.48; H, 6.59; found: C, 78.50; H, 6.96.

2-ethylnaphthalene-1,4-dione (**6**). Obtained from 2-ethylnaphthalene as a liquid. Yield 28%; IR (Neat): ν_{max} cm^{-1} 1650; ^1H NMR ($CDCl_3$): δ 7.98 (m, 2H), 7.75 (m, 2H), 6.85 (s, 1H), 2.44 (q, 2H), 1.25 (t, 3H); LRMS (ES^+): m/z 187.10 [$(M+H)^+$, 100%]; Anal. Calc for $C_{12}H_{10}O_2$ (186.21): C, 77.40; H, 5.41; found: C, 78.10; H, 6.08.

2-(4-acetylpyridin-2-yl)naphthalene-1,4-dione (**7**). Obtained by reaction of naphthalene-1,4-dione and 4-acetylpyridine to give **7** as dark yellow solid, yield 42%; mp 124ºC; IR (KBr): ν_{max} cm^{-1} 1675, 1595, 1275; ^1H NMR ($CDCl_3$): δ 8.49 (m, 1H), 8.46 (s, 1H), 7.70-7.68 (m, 3H), 7.53-7.50 (m, 3H), 2.54 (s, 3H); LRMS (ES^+): m/z 278.11 [$(M+H)^+$, 100%]; Anal. Calc for $C_{17}H_{11}NO_3$ (277.27): C, 73.64; H, 4.00; N, 5.05; found: C, 73.85; H, 4.48; N, 4.90.

2-(5-acetylpyridin-2-yl)naphthalene-1,4-dione (**8**). Obtained by reaction of naphthalene-1,4-dione and 3-acetylpyridine to give **8** as yellow solid, yield 32%; mp 94ºC; IR (KBr): ν_{max} cm^{-1} 1678, 1595, 1280; ^1H NMR ($CDCl_3$): δ 8.55-8.28 (m, 3H), 7.90-7.55 (m, 5H), 2.46 (m, 3H); LRMS (ES^+): m/z 278.09 [$(M+H)^+$, 100%]; Anal. Calc for $C_{17}H_{11}NO_3$ (277.27): C, 73.64; H, 4.00; N, 5.05; found: C, 74.80; H, 4.7; N, 5.12.

2-(6-acetylpyridin-2-yl)naphthalene-1,4-dione (**9**). Obtained by reaction of naphthalene-1,4-dione and 2-acetylpyridine to give **9** as yellow solid, yield 52%; mp 148ºC; IR (KBr): ν_{max} cm^{-1} 1670, 1595, 1280; ^1H NMR ($CDCl_3$): δ 8.42 (s, 1H), 7.78-7.66 (m, 4H), 7.52-7.49 (m, 3H), 2.14 (s, 3H); LRMS (ES^+): m/z 277.14 [$(M)^+$, 100%]; Anal. Calc for $C_{17}H_{11}NO_3$ (277.27): C, 73.64; H, 4.00; N, 5.05; found: C, 73.80; H, 4.15; N, 5.00.

2-(4-acetylpiperazin-2-yl)naphthalene-1,4-dione (**10**). Obtained by reaction of naphthalene-1,4-dione and 1-acetylpiperazine as viscous oil, yield 30%; IR (Neat): ν_{max} cm^{-1} 3400, 1650, 1597, 1250; ^1H NMR ($CDCl_3$): δ 7.78-7.56 (m, 5H), 4.00 (m, 1H), 3.56-3.30 (m, 4H), 2.75-2.52 (m, 2H), 2.20 (s, 3H); LRMS (ES^+): m/z 285.19 [$(M+H)^+$, 100%]; Anal. Calc for $C_{16}H_{16}N_2O_3$ (284.31): C, 67.59; H, 5.67; N, 9.85; found: C, 67.00; H, 5.76; N, 9.78.

2-(6-acetylpyrazin-2-yl)naphthalene-1,4-dione (**11**). Obtained by reaction of naphthalene-1,4-dione and acetylpyrazine as viscous oil, yield 32%; IR (Neat): ν_{max} cm^{-1} 1650, 1590, 1280; ^1H NMR ($CDCl_3$): δ 8.76 (s, 2H), 7.78-7.50 (m, 5H), 2.20 (m, 3H); LRMS (ES^+): m/z 278.13 [$(M)^+$, 100%]; Anal. Calc for $C_{16}H_{10}N_2O_3$ (278.26): C, 69.06; H, 3.62; N, 10.07; found: C, 70.00; H, 3.96; N, 9.78.

2-(5-acetylthiophen-2-yl)naphthalene-1,4-dione (**12**) [28]. Obtained by reaction of naphthalene-1,4-dione and 2-acetylthiophene as yellow solid. Yield 44%; mp 202-205ºC, Lit. 202-205ºC; IR (KBr): ν_{max} cm^{-1} 1645, 1595, 1250; ^1H NMR ($CDCl_3$): δ 8.39 (s, 1H), 8.07-8.20 (m, 2H), 7.81-7.71 (m, 2H), 7.61 (d, 1H, J = 4.18 Hz), 7.29 (d, 1H, J = 4.22 Hz), 2.60 (s, 3H); LRMS (ES^+): m/z 282.12 [$(M)^+$, 100%]; Anal. Calc for $C_{16}H_{10}O_3S$ (282.31): C, 68.07; H, 3.57; found: C, 67.90; H, 3.80.

5-(1,4-dioxo-1,4-dihydronaphthalen-2-yl)furan-2-carbaldehyde (**13**) [28]. Obtained by reaction of naphthalene-1,4-dione and 2-furaldehyde. Yield 50%; mp 178-180ºC, 178-80ºC; IR (KBr): ν_{max} cm^{-1} 1695, 1650, 1595; ^1H NMR ($CDCl_3$): δ 9.78 (s, 1H), 8.17-8.11 (m, 3H), 7.81-7.55 (m, 2H), 7.59 (s, 1H), 7.37 (d, 1H, J = 4.22 Hz); LRMS (ES^+): m/z 252.15 [$(M)^+$, 100%]; Anal. Calc for $C_{15}H_8O_4$ (252.22): C, 71.43; H, 3.20; found: C, 71.65; H, 4.18.

2-(5-acetyl-1*H*-pyrrol-2-yl)naphthalene-1,4-dione (**14**). Obtained by reaction of naphthalene-1,4-dione and 2-acetylpyrrole. Yield 35%; mp 104ºC; IR (KBr): ν_{max} cm^{-1} 3315, 1665, 1598, 1250; ^1H NMR ($CDCl_3$): δ 8.12 (s, 1H), 7.99-7.68 (m, 4H), 7.26 (m, 1H), 6.50 (m, 1H), 2.20 (s, 3H); LRMS (ES^+): m/z 265.05 [$(M)^+$, 100%]; Anal. Calc for $C_{16}H_{11}NO_3$ (265.26): C, 72.45; H, 4.18; N, 5.28; found: C, 73.55; H, 4.58; N, 5.00.

2-(1-acetylindolin-2-yl)naphthalene-1,4-dione (**15**). Obtained by reaction of naphthalene-1,4-dione and 1-acetylindoline. Yield 50%; mp viscous oil; IR (Neat): ν_{max} cm^{-1} 1651, 1595, 1250; ^1H NMR ($CDCl_3$): δ 7.98-7.50 (m, 5H), 7.38-7.26 (m, 4H), 4.50 (s, 1H), 2.78-2.50 (m, 2H), 2.24 (s, 3H); LRMS (ES^+): m/z 318.12 [$(M+H)^+$, 100%]; Anal. Calc for $C_{20}H_{15}NO_3$ (317.34): C, 75.70; H, 4.76; N, 4.41; found: C, 76.70; H, 4.96; N, 4.76.

2-(3-acetyl-1H-indol-2-yl)naphthalene-1,4-dione (**16**). Obtained by reaction of naphthalene-1,4-dione and 3-acetylindole as a liquid, yield 51%; IR (Neat): ν_{max} cm^{-1} 3325, 1654, 1350, 1233; ^1H NMR ($CDCl_3$): δ 8.42-8.22 (m, 2H), 7.98-7.62 (m, 4H), 7.58-6.88 (m, 3H), 2.45 (s, 3H); LRMS (ES^+): m/z 316.18 [$(M+H)^+$, 100%]; Anal. Calc for $C_{20}H_{13}NO_3$ (315.32): C, 76.18; H, 4.16; N, 4.44; found: C, 75.80; H, 4.76; N, 4.12.

2-(6-acetyl-4-methylpyridine-2-yl)naphthalene-1,4-dione (**17**). Obtained by reaction of naphthalene-1,4-dione and 2-acetyl-4-methylpyridine. Viscous liquid, yield 41%; IR (Neat): ν_{max} cm^{-1} 1655, 1590, 1245; ^1H NMR ($CDCl_3$): δ 8.12

(s, 1H), 7.89-7.60 (m, 4H), 7.32 (m, 1H), 6.52 (d, 1H), 2.40 (s, 3H), 2.24 (s, 3H); LRMS (ES^+): m/z 292.11 [$(M+H)^+$, 100%]; Anal. Calc for $C_{18}H_{13}NO_3$ (291.30): C, 74.22; H, 4.50; N, 4.81; found: C, 74.80; H, 4.76; N, 4.72.

2-(5-acetyl-1-methyl-1H-pyrrol-2-yl)naphthalene-1,4-dione (**18**). Obtained by reaction of naphthalene-1,4-dione and 2-acetyl-1-methylpyrrole as colourless liquid, yield 30%; IR (Neat): ν_{max} cm^{-1} 1655, 1586, 1238; ^1H NMR ($CDCl_3$): δ 7.74-7.52 (m, 5H), 7.28 (d, 1H, J = 7.45 Hz), 6.56 (d, 1H, J = 7.40 Hz), 3.66 (s, 3H), 2.20 (s, 3H); LRMS (ES^+): m/z 280.20 [$(M+H)^+$, 100%]; Anal. Calc for $C_{17}H_{13}NO_3$ (279.29): C, 73.11; H, 4.69; N, 5.02; found: C, 74.10; H, 4.76; N, 4.82.

2-(5-acetyl-4-methylthiophen-2-yl) naphthalene-1,4-dione (**19**). Obtained by reaction of naphthalene-1,4-dione and 2-acetyl-3-methylthiophene as colourless liquid, yield 23%; IR (Neat): ν_{max} cm^{-1} 1645, 1589, 1248; ^1H NMR ($CDCl_3$): δ 8.20 (s, 1H), 7.98-7.50 (m, 4H), 7.38 (s, 1H), 2.65 (s, 3H), 2.20 (s, 3H); LRMS (ES^+): m/z 297.23 [$(M+H)^+$, 100%]; Anal. Calc for $C_{17}H_{12}O_3S$ (296.34): C, 68.90; H, 4.08; found: C, 68.80; H, 4.76 .

2-(4-acetylthiophen-2-yl)naphthalene-1,4-dione (**20**). Obtained by reaction of naphthalene-1,4-dione and 3-acetylthiophene as a liquid, yield 22%; IR (Neat): ν_{max} cm^{-1} 1648, 1588, 1252; ^1H NMR ($CDCl_3$): δ 8.42 (d, 1H, J = 7.50 Hz), 8.00 (m, 2H), 7.84-7.54 (m, 4H), 2.44 (s, 3H); LRMS (ES^+): m/z 282.23 [$(M)^+$, 100%]; Anal. Calc for $C_{16}H_{10}O_3S$ (282.31): C, 68.07; H, 3.57; found: C, 68.80; H, 4.06.

2,3-dimethylnaphthalene-1,4-dione (**21**) [35]. Obtained by oxidation of 2,3-dimethylnaphthalene according to Scheme **1** and recrystallized from methanol. Yield 22%; mp 128-135ºC, Lit. 127ºC; IR (KBr): ν_{max} cm^{-1} 1660, 1590; ^1H NMR ($CDCl_3$): δ 8.00-7.98 (m, 2H), 7.75-7.71 (m, 2H), 2.40 (s, 6H); LRMS (ES^+): m/z 187.14 [$(M+H)^+$, 100%]; Anal. Calc for $C_{12}H_{10}O_2$ (186.21): C, 77.40; H, 5.41; found: C, 78.00; H, 5.96.

5-phenylnaphthalene-1,4-dione (**22**) [36]. Obtained by oxidation of 1-phenylnaphthalene and recrystallized from methanol to give **22** as a yellow solid, yield 24%; mp 152-155ºC, Lit. 150-152ºC; IR (KBr): ν_{max} cm^{-1} 1675; ^1H NMR ($CDCl_3$): δ 8.50 (m, 1H), 7.90-7.70 (m, 7H, aryl), 7.0-6.60 (m, 2H); LRMS (ES^+): m/z 235.10 [$(M+H)^+$, 100%]; Anal. Calc for $C_{16}H_{10}O_2$ (234.25): C, 82.04; H, 4.30; found: C, 81.24; H, 4.09.

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