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ORIGINAL PAPER

Synthesis, chemical properties, and antimicrobial activity of 2- and 2,3-substituted [(tetrahydro-2,4-dioxopyrimidin-1(2*H*)-yl)-phenoxy]naphthalene-1,4-diones

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Abstract Mono- and disubstituted [(tetrahydro-2,4-dioxopyrimidin-1(2*H*)-yl)phenoxy]naphthalene-1,4-diones were synthesized by the reaction of dihydro-1-(3-hydroxy- and 4-hydroxyphenyl)pyrimidine-2,4(1*H*,3*H*)-diones their 5- and 6-methyl derivatives with 2,3-dichloro-1,4-naphthoquinone. Their stability in alkaline and acidic media was investigated. Four of the compounds exhibited good antimicrobial activity against *Staphylococcus aureus*, *Mycobacterium luteum, Candida tenuis*, and *Aspergillus niger*.

Keywords Heterocycles · 1,4-Naphthoquinone derivatives · Dihydropyrimidine-2,4(1*H*,3*H*)-dione · Antibacterial activity · Fungicides

Introduction

Cyclic diketones, quinones, play an important role in our lives, and the potential of their biological functions has stimulated enormous interest in this class of compounds. Naphthoquinones, particularly 1,4-naphthoquinones, are widely distributed phenolic compounds in nature. Natural and synthetic agents containing the 1,4-naphthoquinone moiety elicit a broad spectrum of biological activities including cytotoxic [1, 2], antiviral [3, 4], anti-inflammatory [5, 6], antimalarial [7], antibacterial [8, 9], antifungal [10], and antiproliferative [11]. The pyrimidinedione moiety represents an important substructure of a wide variety of biologically active compounds [12–14].

Reactions of 2,3-dichloro-1,4-naphthoquinone with O-nucleophiles have been described [15–17]. It has been shown that depending on the reaction conditions, either 2-OR-substituted 3-chloronaphthoquinones or 2,3-$(OR)_2$-substituted naphthoquinones can be formed in the reaction of 2,3-dichloro-1,4-naphthoquinone with alkoxides and phenols [15, 16]. Often, mixtures of both reaction products are obtained. Reactions of 2,3-dichloro-1,4-naphthoquinone with phenol under various conditions using K_2CO_3, Et_3N, and $CsCO_3$ as a base are described in [17]. The authors had determined that exclusively 2-chloro-3-phenoxy-1,4-naphthoquinones were prepared when the reactions were carried out in tetrahydrofuran in the presence of $CsCO_3$. Thus, a series of 2-chloro-3-phenoxy- and 3-alkoxynaphthoquinones were synthesized.

As part of our continuing interest towards synthesis of heterocyclic compounds possessing antimicrobial activity [18], we report herein a synthesis of the title compounds containing both 1,4-naphthoquinone and dihydropyrimidine-2,4(1*H*,3*H*)-dione moieties. Their stability in alkaline and acidic media was investigated.

Results and discussion

In this work, mono- and disubstituted naphthoquinone derivatives containing substituents with dihydropyrimidinedione,

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5-methyl-, and 6-methyldihydropyrimidinedione moieties at the 2- and 3-positions were synthesized by the reactions of dihydro-1-(3-hydroxy- and 4-hydroxyphenyl)pyrimidine-2,4(1*H*,3*H*)-diones and their 5-methyl and 6-methyl analogues **2a**–**2c** and **3a**–**3c** with 2,3-dichloro-1,4-naphthoquinone. The starting compounds were synthesized from the corresponding *N*-(3-hydroxyphenyl- and 4-hydroxyphenyl)-*β*-alanines, their α- and *β*-methyl derivatives and carbamide in acidic medium [19]. These compounds are only slightly soluble in such organic solvents as aromatic hydrocarbons, alcohols, dioxane, and tetrafydrofuran, but are very soluble in dimethyl sulfoxide and dimethylformamide. 1-[3- and 4-(3-Chloro-1,4-dihydro-1,4-dioxonaphthalen-2-yloxy)phenyl]-dihydropyrimidine-2,4(1*H*,3*H*)-diones **4** and **5** were obtained by stirring the mixture of the respective dihydro-1-(3- or 4-hydroxyphenyl)-2,4-pyrimidinedione (**2** and **3**), 2,3-dichloro-1,4-naphthoquinone (**1**), and sodium carbonate as a base in dimethyl sulfoxide for 48 h at room temperature (Scheme 1). The reaction was quenched by diluting the reaction mixture with water, causing the products to precipitate.

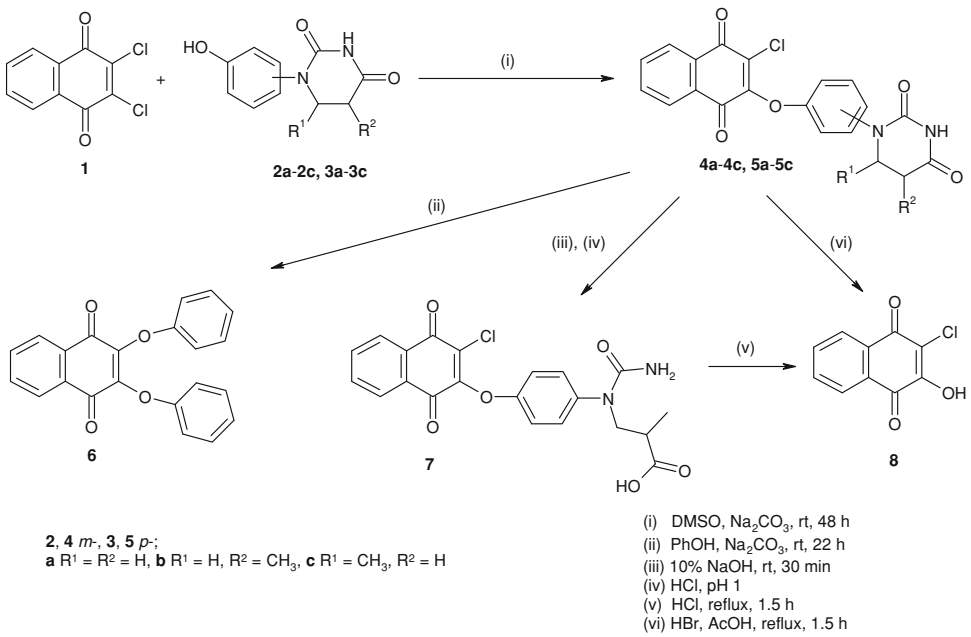
Some chemical properties of the synthesized compounds were investigated. Treatment of **5b** with phenol in dimethyl sulfoxide in the presence of Na_2CO_3 at room temperature as well as at 50 °C resulted in formation of 2,3-diphenoxynaphthoquinone (**6**), which was isolated from the reaction mixture by column chromatography. In the ^{1}H NMR spectrum of **6**, besides the proton resonances of the naphthoquinone ring in the 6.98–7.30 ppm and 7.86–8.05 ppm regions, resonances of two benzene ring protons are present, and furthermore, spectral lines characteristic of the pyrimidinedione moiety are absent. Physical properties of **6** correspond to the ones described in the literature [20].

It is known that 1-substituted dihydropyrimidine-2,4(1*H*,3*H*)-diones are unstable in alkaline medium and cleave to the corresponding ureido acids, which undergo cyclization back to the initial compounds under treatment with mineral acids [19]. In this work, when **5b** was heated in 10% aqueous NaOH solution, the pyrimidinedione ring cleaved, resulting in the formation of a corresponding salt of *N*-substituted *N*-carbamoyl-*β*-alanine. *N*-Substituted ureido acid **7** was then prepared by acidifying the cooled basic hydrolysate with dilute hydrochloric acid. However, attempts to obtain **5b** by heating ureido acid **7** in hydrochloric acid under reflux failed, and only 2-chloro-3-hydroxynaphthoquinone (**8**) was isolated from the reaction mixture. The same compound **8** was obtained when **5b** was heated under reflux with HBr in acetic acid.

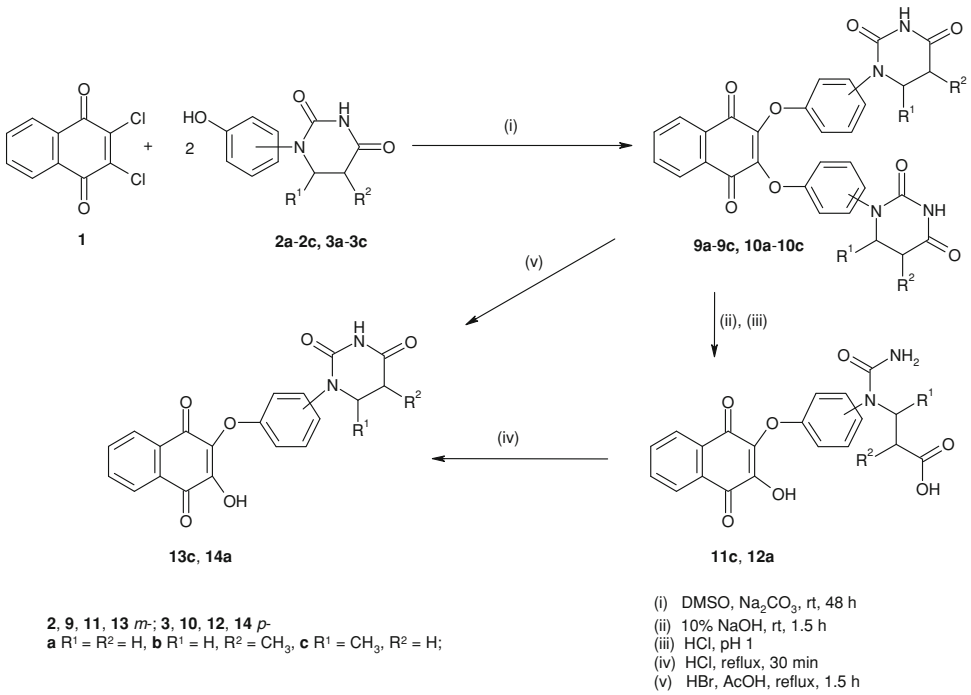
It was noticed that along with the target products **4** and **5**, small amounts of 2,3-disubstituted derivatives were formed. Therefore, the reactions of 2,3-dichloro-1,4-naphthoquinone with an excess of compounds **2** and **3** were carried out (Scheme 2) affording 2,3-bis[3-(tetrahydro-2,4-dioxopyrimidin-1(2*H*)-yl)phenoxy]naphthalene-1,4-diones **9** and **10**.

The comparison of the ^{1}H NMR spectra of **5c** and **10c** revealed that the integral intensities of the proton signals proved the formation of monosubstituted naphthoquinone in the first case and disubstituted derivative in the second one. These spectra showed the identical signals of the functional group protons; just the protons of monosubstituted derivative resonated at lower field than those of the disubstituted naphthoquinone. Proton signals of the pyrimidinedione moiety possessing a methyl group gave rise to an ABX spin system, whereas resonances of the NH

Scheme 1



Scheme 2



group protons were observed at 10.38 ppm (**5c**) and 10.35 ppm (**10c**).

In the IR spectrum of **5c**, an absorption band attributed to NH group was observed at 3,197 cm^{-1}, and three C=O group bands were identified at 1,725, 1,681, and 1,675 cm^{-1}. The IR spectrum of **10c** differed just slightly from the one of the monosubstituted derivative. The absorption band of the NH group was observed at 3,200 cm^{-1}, and C=O group bands were present in the region of 1,726–1,675 cm^{-1}.

The stability of **9c** and **10a** in alkaline medium was investigated, and it has been determined that in sodium hydroxide solution, one ether bond of these compounds cleaves, resulting in the formation of hydroxynaphthoquinone, whereas another one stays unchanged. Only the pyrimidinedione ring cleaves to form sodium salts of the corresponding ureido acids. Ureido acids **11c** and **12a** were obtained by acidifying the basic solutions of these salts with dilute hydrochloric acid. When **11c** and **12a** were heated under reflux with concentrated hydrochloric acid, they underwent cyclization to pyrimidinediones **13c** and **14a**, which were also prepared from **9** and **10**, respectively, by heating them under reflux with HBr.

The synthesized 2- and 2,3-substituted [tetrahydro-2,4-dioxopyrimidin-1(2*H*)-yl)phenoxy]naphthalene-1,4-diones **4**, **5**, **9**, and **10** were evaluated for their antibacterial and antifungal activity against strains of *Escherichia coli B-906, Staphylococcus aureus 209-P, Mycobacterium luteum B-917* (as a nonpathogenic test bacteria culture representative of genus *Mycobacterium*), *Candida tenuis VKM Y-70*, and *Aspergillus niger F-1119* by diffusion technique [21] and serial dilution technique [22] [determination of minimal bacteriostatic (MBSC) and minimal bactericidic (MBCC) concentrations, minimal fungistatic (MFSC) and minimal fungicidic (MFCC) concentrations]. Their activities were compared with those of the known antibacterial agent vancomicine and the antifungal agent nistatine.

As seen from the data presented in Tables 1, 2, and 3, the synthesized compounds are active against *S. aureus, M. luteum*, *C. tenuis*, and *A. niger*.

S. aureus and *M. luteum* were sensitive to compounds **4a**–**4c** and **5a**–**5c** among the monophenoxy-substituted naphthoquinones, for which the diameters of inhibition zones at 0.5% concentration of investigated compounds were 7–13.7 mm for *S. aureus* and 7–13.4 mm for *M. luteum*. Based on these data, the following correlation between structure and antibacterial activity in the series of monochlorosubstituted naphthoquinones was made:

for *S. aureus:*

4c > 4a > 4b > 5a > 5c > 5b

Increase of antibacterial activity

for *M. luteum:*

4c > 5a > 4a > 4b > 5c

Increase of antibacterial activity

Table 1 Bactericidal and fungicidal activities of **4**, **5**, **9**, and **10** determined by diffusion method

Comp.	Conc. (%)	Inhibition diameter of microorganism growth (mm)				
		Bactericidal activity			Fungicidal activity	
		E.coli	*S. aureus*	*M. luteum*	*C. tenuis*	*A. niger*
4a	0.5	0	13.4	10.7	19.4	20.7
	0.1	0	11.0	7.0	11.4	18.4
4b	0.5	0	12.0	10.0	13.7	20.7
	0.1	0	11.0	0	12.7	17.0
4c	0.5	0	13.7	13.4	25.4	22.7
	0.1	0	11.7	12.0	20.7	19.7
5a	0.5	0	11.0	11.4	19.3	21.7
	0.1	0	10.0	10.7	15.0	19.7
5b	0.5	0	7.0	0	10.7	7.7
	0.1	0	6.0	0	9.4	7.0
5c	0.5	0	8.0	7.0	11.0	14.0
	0.1	0	7.0	6.0	10.0	13.0
9a	0.5	0	19.0	14.4	0	0
	0.1	0	14.6	13.3	0	0
9b	0.5	0	6.7	12.0	0	0
	0.1	0	0	11.3	0	0
9c	0.5	0	18.0	6.0	0	0
	0.1	0	11.0	0	0	0
10a	0.5	0	12.4	0	0	0
	0.1	0	0	0	0	0
10b	0.5	0	7.4	0	0	0
	0.1	0	6.0	0	0	0
10c	0.5	0	15.4	13.7	0	0
	0.1	0	10.4	0	0	0
C*	0.1	14.0	15.0	18.0	19.0	20.0

* Vancomicine was used as a control in the tests of antibacterial activity of the synthesized compounds, and nistatine was used in the tests of antifungal action

Compounds **4a**–**4c** and **5a**–**5c** showed minimal bacteriostatic and minimal bactericidal action against *S. aureus* at 31.2–125 μg/cm^3, and the one against *M. luteum* was observed at 15.6–500 μg/cm^3 and 62.5–500 μg/cm^3, respectively.

S. aureus and *M. luteum* were most sensitive to diphenoxy-substituted naphthoquinones **9a**, **9c**, and **10c** for which the diameters of inhibition zones at 0.5% concentration of the investigated compounds were 15.4–19, 13.7, and 14.4 mm, respectively. Other compounds showed moderate activity against *S. aureus*. The strain *M. luteum* appeared not to be sensitive to **10a** and **10b** at investigation concentrations. **9a**, **9c**, and **10c** completely inhibited growth of *M. luteum* at 250 μg/cm^3. MBSC of **10a** towards *S. aureus* was 250 μg/cm^3.

The evaluation of antifungal activity has revealed that diphenoxy-substituted naphthoquinones have no fungicidal action against *C. tenuis* and *A. niger* at the investigated concentrations, whereas the compounds with high antifungal activity were identified among monophenoxy-substituted derivatives. *C. tenuis* and *A. niger* were sensitive to **4a**–**4c** and **5a**–**5c**. Diameters of inhibition zones for strain *C. tenuis* were 10.7–25.4 mm, and the ones for *A. niger* were from 7 to 22.7 mm. Based on these data, antifungal activity of the investigated compounds decreases in the following order:

for *C. tenuis:*

4c > 4a > 5a > 4b> 5c > 5b

← Increase of antifungal activity

for *A. niger:*

4c > 5a > 4a ~4b > 5c> 5b

← Increase of antifungal activity

Compounds **4a**–**4c** and **5a**–**5c** showed MFSC at 1.9–15.6 μg/cm^3 and MFCC at 7.8–31.2 μg/cm^3 against *C. tenuis*, and MFSC at 15.6–62.5 μg/cm^3 and MFCC at 125–500 μg/cm^3 against *A. niger*.

The antimicrobial activity of the tested compounds can be correlated with their structure. It has been observed that 3-chloro-2-phenoxynaphthoquinones containing heterocyclic substituents at *m*-position in the phenoxy moiety show more significant antibacterial and antifungal activities than the analogous compounds containing substituents at the *p*-position. Besides, among 1-[3-(3-chloro-1,4-dihydro-1,4-dioxonaphthalen-2-yloxy)phenyl]dihydropyrimidine-2,4-(1*H*,3*H*)-diones, the compound containing a methyl group at the 6-position of the heterocyclic ring was the most active, whereas the compound possessing no methyl groups in the heterocycle showed the highest activity among 1-[4-(3-chloro-1,4-dihydro-1,4-dioxonaphthalen-2-yloxy)-phenyl]dihydropyrimidine-2,4(1*H*,3*H*)-diones. In all cases, compounds containing a methyl group at the 5-position of the heterocyclic ring showed the weakest activity.

In conclusion, a convenient synthesis route of 2- and 2,3-substituted [(tetrahydro-2,4-dioxopyrimidin-1(2*H*)-yl)-phenoxy]naphthalene-1,4-diones from dihydro-1-(3-hydroxy- and 1-(4-hydroxyphenyl)pyrimidine-2,4(1*H*,3*H*)-diones and their 5- and 6-methyl derivatives and 2,3-dichloro-1,4-naphthoquinone is reported. It has been determined that the ether bond in 2-chloro-3-phenoxy-naphthoquinones is stable in alkaline medium, whereas 2,3-diphenoxy-substituted naphthoquinones cleave forming 2-hydroxy-3-phenoxynaphthoquinone derivatives. Compounds

Table 2 Bactericidal activity of **4**, **5**, **9**, and **10** determined by serial dilution method (compounds that gave positive results at least in one case are included in the table)

Comp.	*E. coli*		*S. aureus*		*M. luteum*	
	MBSC (μg/cm^3)	MBCC (μg/cm^3)	MBSC (μg/cm^3)	MBCC (μg/cm^3)	MBSC (μg/cm^3)	MBCC (μg/cm^3)
4a	+	+	31.2	31.2	62.5	250.0
4b	+	+	125.0	125.0	125.0	250.0
4c	+	+	125.0	*	500.0	500.0
5a	+	+	31.2	31.2	62.5	62.5
5b	+	+	125.0	*	+	+
5c	+	+	31.2	31.2	15.6	62.5
9a	+	+	+	+	250.0	*
9b	+	+	+	+	250.0	250.0
10a	+	+	250.0	*	+	+
10c	+	+	+	+	15.6	250.0

+: Growth of microorganisms

* In the investigated concentrations the indexes of biocidic effect were not determined

Table 3 Fungicidal activity of the synthesized compounds determined by serial dilution method (compounds that gave positive results at least in one case are included in the table)

Comp.	*C. tenuis*		*A. niger*	
	MFSC (μg/cm^3)	MFCC (μg/cm^3)	MFSC (μg/cm^3)	MFCC (μg/cm^3)
4a	3.9	7.8	62.5	125.0
4b	7.8	15.6	62.5	125.0
4c	15.6	31.2	31.2	250.0
5a	3.9	7.8	15.6	500.0
5b	1.9	3.9	62.5	*
5c	15.6	31.2	31.2	125.0

* In the investigated concentration the index of fungicidic effect was not determined

with a high antimicrobial activity against *S. aureus*, *M. luteum*, *C. tenuis*, and *A. niger* at low concentrations, **4a**–**4c** and **5a**–**5c**, were identified among the synthesized compounds, 1-[3-(3-chloro-1,4-dihydro-1,4-dioxonaphthalen-2-yloxy)phenyl]-5,6-dihydro-6-methylpirimidine-2,4-(1*H*,3*H*)-dione (**4c**) being the most promising one.

Experimental

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Inova 300 MHz spectrometer operating in Fourier transfom mode with TMS as internal standard. The IR spectra were measured on a Perkin-Elmer Spectrum BX FT-IR spectrometer. Melting points were determined on an Auto probe analyzer APA 1. Elemental analyses (C, H, N) were performed on an Elemental Analyzer CE-440, and their results were found to be in good agreement (±0.2%) with the calculated values. Silica gel plates (Merck, F_{254}) were used for analytical purposes. Silica gel 60 (Fluka, 0.04-0.063 mm, 230–400 mesh) was used for column chromatography.

*General procedure for preparation of monophenoxy-substituted naphthoquinone derivatives **4a–4c** and **5a–5c***

A mixture of 1.98 g 2,3-dichloro-1,4-naphthoquinone (**1**, 8.7 mmol), the appropriate **2a**–**2c** or **3a**–**3c** (7.2 mmol), 1.5 g Na_2CO_3, and 25 cm^3 DMSO was stirred at room temperature (20 °C) for 48 h and diluted with 150 cm^3 H_2O. The precipitate formed was filtered, washed with H_2O, and purified by recrystallization or column chromatography.

1-[3-(3-Chloro-1,4-dihydro-1,4-dioxonaphthalen-2-yloxy)-phenyl]-5,6-dihydropyrimidine-2,4(1H,3H)-dione
(**4a**, $C_{20}H_{13}ClN_2O_5$)
Yield 1.83 g (53%); m.p.: 101–102 °C (from EtOAc); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.68$ (t, $J = 6.6$ Hz, 2H, $COCH_2$), 3.76 (t, $J = 6.6$ Hz, 2H, NCH_2), 7.02–8.14 (m, 8H, H_{Ar}), 10.40 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 30.61$ (CH_2), 44.16 (CH_2), 112.77, 112.99, 119.96, 126.16, 126.28, 129.14, 130.27, 131.06, 133.44, 134.11, 134.24, 143.01, 151.65, 151.83 (C_{Ar}), 155.83, 170.59, 177.40, 177.81 (CO) ppm; IR (KBr): $\bar{\nu} = 3{,}201$ (NH), 1,708, 1,677, 1,662 (C=O) cm^{-1}; MS (APCI+, 20 eV): *m/z* (%) = 397 $[M+H]^+$ (100), 399 $[M+2+H]^+$ (40).

1-[3-(3-Chloro-1,4-dihydro-1,4-dioxonaphthalen-2-yloxy)-phenyl]-5,6-dihydro-5-methylpyrimidine-2,4(1H,3H)-dione
(**4b**, $C_{21}H_{15}ClN_2O_5$)
Yield 1.54 g (43%); m.p.: 220–222 °C (purified by column chromatography, EtOAc:hexane 1:1, $R_f = 0.31$); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.11$ (d, $J = 6.9$ Hz, 3H, CH_3), 2.78–2.95 (m, 1H, CH), 3.56–3.78 (m, 2H, CH_2),

7.02–8.18 (m, 8H, H_{Ar}), 10.40 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 12.09 (CH_3), 34.80 (CH), 50.63 (CH_2), 113.10, 113.22, 120.16, 126.46, 126.58, 129.45, 130.57, 131.34, 133.71, 134.42, 134.54, 143.24, 151.98, 152.19 (C_{Ar}), 156.13, 173.13, 177.69, 178.10 (CO) ppm; IR (KBr): $\bar{\nu}$ = 3,191 (NH), 1,730, 1,691, 1,675 (C=O) cm^{-1}; MS (APCI+, 25 eV): *m/z* (%) = 411 $[M+H]^+$ (100), 413 $[M+2+H]^+$ (40).

1-[3-(3-Chloro-1,4-dihydro-1,4-dioxonaphthalen-2-yloxy)-phenyl]-5,6-dihydro-6-methylpyrimidine-2,4(1H,3H)-dione (**4c**, $C_{21}H_{15}ClN_2O_5$)

Yield 2.29 g (63%); m.p.: 219–220 °C (from MeOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.12 (d, J = 6.6 Hz, 3H, CH_3), 2.43 (dd, J_{AB} = 16.5 Hz, J_{AX} = 3.9 Hz, $1H_A$, CH_2), 3.05 (dd, J_{AB} = 16.5 Hz, J_{BX} = 5.7 Hz, $1H_B$, CH_2), 3.96–4.09 (m, 1H, CH), 7.06–8.16 (m, 8H, H_{Ar}), 10.42 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 18.44 (CH_3), 37.70 (CH), 51.21 (CH_2), 114.35, 115.28, 122.49, 126.40, 126.54, 129.67, 130.54, 131.29, 133.58, 134.39, 134.50, 141.90, 151.29, 152.18 (C_{Ar}), 156.25, 169.85, 177.66, 178.06 (CO) ppm; IR (KBr): $\bar{\nu}$ = 3,187 (NH), 1,726, 1,670 (C=O) cm^{-1}; MS (APCI+, 25 eV): *m/z* (%) = 411 $[M+H]^+$ (100), 413 $[M+2+H]^+$ (40).

1-[4-(3-Chloro-1,4-dihydro-1,4-dioxonaphthalen-2-yloxy)-phenyl]-5,6-dihydropyrimidine-2,4(1H,3H)-dione (**5a**, $C_{20}H_{13}ClN_2O_5$)

Yield 1.28 g (37%); m.p.: 268–269 °C (purified by column chromatography, EtOAc, R_f = 0.45); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.70 (t, J = 6.7 Hz, 2H, $COCH_2$), 3.77 (t, J = 6.7 Hz, 2H, NCH_2), 7.18–8.16 (m, 8H, H_{Ar}), 10.39 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 31.00 (CH_2), 44.67 (CH_2), 116.09, 126.45, 126.57, 126.85, 130.56, 131.37, 133.79, 134.39, 134.55, 137.37, 152.21, 152.31 (C_{Ar}), 153.96, 170.59, 177.80, 178.11 (CO) ppm; IR (KBr): $\bar{\nu}$ = 3,183 (NH), 1,713, 1,677 (C=O) cm^{-1}; MS (APCI+, 25 eV): *m/z* (%) = 397 $[M+H]^+$ (100), 399 $[M+2+H]^+$ (33).

1-[4-(3-Chloro-1,4-dihydro-1,4-dioxonaphthalen-2-yloxy)-phenyl]-5,6-dihydro-5-methylpyrimidine-2,4(1H,3H)-dione (**5b**, $C_{21}H_{15}ClN_2O_5$)

Yield 2.34 g (65%); m.p.: 273 °C (decomposes, from MeOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.12 (d, J = 6.9 Hz, 3H, CH_3), 2.78–2.95 (m, 1H, CH), 3.56–3.78 (m, 2H, NCH_2), 7.17–8.20 (m, 8H, H_{Ar}), 10.36 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 12.13 (CH_3), 34.84 (CH), 50.86 (CH_2), 116.08, 126.41, 126.54, 126.74, 130.56, 131.37, 133.73, 134.36, 134.52, 137.28, 152.18, 152.29 (C_{Ar}), 153.92, 173.20, 177.77, 178.08 (CO) ppm; IR (KBr): $\bar{\nu}$ = 3,197 (NH), 1,734, 1,685, 1,666 (C=O) cm^{-1}; MS (APCI+, 25 eV): *m/z* (%) = 411 $[M+H]^+$ (100), 413 $[M+2+H]^+$ (40).

1-[4-(3-Chloro-1,4-dihydro-1,4-dioxonaphthalen-2-yloxy)-phenyl]-5,6-dihydro-6-methylpyrimidine-2,4(1H,3H)-dione (**5c**, $C_{21}H_{15}ClN_2O_5$)

Yield 2.26 g (63%); m.p.: 238–240 °C (from MeOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.13 (d, J = 6.6 Hz, 3H, CH_3), 2.43 (dd, J_{AB} = 16.5 Hz, J_{AX} = 3.6 Hz, $1H_A$, CH_2), 3.09 (dd, J_{AB} = 16.5 Hz, J_{BX} = 6.0 Hz, $1H_B$, CH_2), 3.94–4.06 (m, 1H, CH), 7.20–8.16 (m, 8H, H_{Ar}), 10.38 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 18.42 (CH_3), 37.70 (CH), 51.39 (CH_2), 116.25, 126.42, 126.54, 128.96, 130.53, 131.36, 133.87, 134.36, 134.52, 135.89, 151.49, 152.21 (C_{Ar}), 154.57, 169.98, 177.74, 178.05 (CO) ppm; IR (KBr): $\bar{\nu}$ = 3,197 (NH), 1,725, 1,682, 1,675 (C=O) cm^{-1}; MS (APCI+, 25 eV): *m/z* (%) = 411 $[M+H]^+$ (100), 413 $[M+2+H]^+$ (40).

2,3-Diphenoxynaphthoquinone (**6**)

A mixture of 1.0 g **5b** (2.4 mmol), 0.34 g phenol (3.6 mmol), 0.5 g Na_2CO_3, and 20 cm^3 DMSO was kept at room temperature (20 °C) for 22 h. Afterwards it was diluted with 50 cm^3 H_2O. The crystals formed were filtered and washed with H_2O to afford 0.42 g (50%) **6**. M.p.: 202–203 °C (purified by column chromatography, silicagel 60, EtOAc:hexane 1:5, R_f = 0.49); Ref. [20] m.p.: 202–203 °C.

3-[N-(Aminocarbonyl)-N-[4-(3-chloro-1,4-dihydro-1,4-dioxonaphthalen-2-yloxy)phenyl]amino]-2-methylpropanoic acid (**7**, $C_{21}H_{17}ClN_2O_6$)

A mixture of 1.0 g **5b** (2.4 mmol) and 10 cm^3 10% aqueous NaOH was stirred at room temperature for 30 min, then it was heated until boiling temperature, cooled, and acidified with dilute HCl (red color of the solution turned yellow) to pH 1. Crystals formed were filtered and washed with H_2O. Purification by dissolving crystals in 10% aqueous NaOH (15 cm^3), filtering, and acidifying the filtrate with dilute HCl (the procedure was repeated 2 times) afforded 0.85 g (81%) **7**. M.p.: 184–185 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.01 (d, J = 7.2 Hz, 3H, CH_3), 2.38–2.50 (m, 1H, CH), 3.53–3.78 (m, 2H, CH_2), 5.36 (br.s., 2H, NH_2), 6.69–8.09 (m, 8H, H_{Ar}) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.63 (CH_3), 38.36 (CH), 51.41 (CH_2), 116.05, 117.57, 126.14, 126.27, 129.37, 129.76, 131.47, 133.19, 133.47, 134.62, 156.27, 156.52 (C_{Ar}), 157.83, 176.07, 177.98, 179.40 (CO) ppm; IR (KBr): $\bar{\nu}$ = 3,433, 3,267 (OH, NH), 1,676, 1,661, 1,640 (C=O) cm^{-1}; MS (APCI+, 25 eV): *m/z* (%) = 428 $[M+H]^+$ (100), 429 $[M+2+H]^+$ (40).

2-Chloro-3-hydroxynaphthoquinone (**8**)

Method A. A mixture of 0.25 g **7** (5.9 mmol) and 10 cm^3 concentrated HCl was heated under reflux for 1.5 h and

then cooled. Crystals formed were filtered and washed with H_2O to afford 0.11 g (90%) **8**. M.p.: 215–216 °C; Ref. [23] m.p.: 215–216 °C.

Method B. A mixture of 2 g **5b** (4.9 mmol), 10 cm^3 AcOH, and 30 cm^3 concentrated HBr was heated under reflux for 1.5 h and then cooled. Crystals formed were filtered and washed with H_2O to afford 0.87 g (85%) **8**. Melting point and NMR spectral data of **8** synthesized by method B are the same as the ones obtained by method A.

*General procedure for preparation of diphenoxy-substituted naphthoquinone derivatives **9a–9c** and **10a–10c***

A mixture of 2.27 g **1** (10.0 mmol), the appropriate **2a–2c** or **3a–3c** (20.0 mmol), 3 g Na_2CO_3, and 25 cm^3 DMSO was stirred at room temperature for 48 h, and afterwards diluted with 75 cm^3 H_2O. The precipitate formed was filtered, washed with H_2O, and purified by recrystallization or column chromatography.

1,1'-[(1,4-Dihydro-1,4-dioxo-2,3-naphthalenediyl)bis-(oxy-3,1-phenylene)]bis(5,6-dihydropyrimidine-2,4(1H,3H)-dione) (**9a**, $C_{30}H_{22}N_4O_8$)
Yield 5.0 g (87%); m.p.: 268–269 °C (from dioxane); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.66$ (t, $J = 6.6$ Hz, 4H, $2COCH_2$), 3.68 (t, $J = 6.7$ Hz, 4H, 2 NCH_2), 6.98–8.07 (m, 12H, H_{Ar}), 10.37 (s, 2H, 2NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 30.88$ ($COCH_2$), 44.43 (NCH_2), 113.11, 113.52, 120.06, 126.04, 129.15, 130.89, 134.32, 143.01, 145.55, 151.90 (C_{Ar}), 156.43, 170.46, 179.92 (CO) ppm; IR (KBr): $\bar{\nu} = 3{,}216$ (NH), 1,736, 1,690, 1,674 (C=O) cm^{-1}; MS (APCI+, 25 eV): *m/z* (%) = 567 $[M+H]^+$ (100).

1,1'-[(1,4-Dihydro-1,4-dioxo-2,3-naphthalenediyl)bis-(oxy-3,1-phenylene)]bis(5,6-dihydro-5-methylpyrimidine-2,4(1H,3H)-dione) (**9b**, $C_{32}H_{26}N_4O_8$)
Yield 5.3 g (89%); m.p.: 248–249 °C (from dioxane); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.10$ (d, $J = 6.9$ Hz, 6H, $2CH_3$), 2.75–2.88 (m, 2H, 2CH), 3.52–3.66 (m, 4H, $2CH_2$), 6.98–8.07 (m, 12H, H_{Ar}), 10.36 (s, 2H, 2NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 12.10$ (CH_3), 34.78 ($COCH_2$), 50.63 (NCH_2), 113.15, 113.42, 119.93, 126.04, 129.15, 130.89, 134.32, 142.95, 145.53, 151.92 (C_{Ar}), 156.42, 173.11, 179.91 (CO) ppm; IR (KBr): $\bar{\nu} = 3{,}182$ (NH), 1,720, 1,692, 1,678 (C=O) cm^{-1}; MS (APCI+, 25 eV): *m/z* (%) = 595 $[M+H]^+$ (100).

1,1'-[(1,4-Dihydro-1,4-dioxo-2,3-naphthalenediyl)bis-(oxy-3,1-phenylene)]bis(5,6-dihydro-6-methylpyrimidine-2,4(1H,3H)-dione) (**9c**, $C_{32}H_{26}N_4O_8$)
Yield 5.4 g (91%); m.p.: 197–198 °C (from dioxane); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.07$ (d, $J = 6.5$ Hz, 6H, $2CH_3$), 2.41 (dd, $J_{AB} = 16.4$ Hz, $J_{AX} = 3.9$ Hz, 2H, 2(H_A, CH_2)), 3.02 (dd, $J_{AB} = 16.5$ Hz, $J_{BX} = 5.9$ Hz, 2H, 2(H_B, CH_2)), 3.88–3.98 (m, 2H, 2CH), 6.99–8.07 (m, 12H, H_{Ar}), 10.39 (s, 2H, 2NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 18.42$ (CH_3), 37.68 ($COCH_2$), 51.22 (NCH_2), 114.49, 115.27, 122.23, 126.02, 129.37, 130.91, 134.32, 141.65, 145.45, 151.27 (C_{Ar}), 156.55, 169.91, 179.90 (CO) ppm; IR (KBr): $\bar{\nu} = 3{,}188$ (NH), 1,717, 1,683, 1,671 (C=O) cm^{-1}; MS (APCI+, 25 eV): *m/z* (%) = 595 $[M+H]^+$ (100).

1,1'-[(1,4-Dihydro-1,4-dioxo-2,3-naphthalenediyl)bis-(oxy-4,1-phenylene)]bis(5,6-dihydropyrimidine-2,4(1H,3H)-dione) (**10a**, $C_{30}H_{22}N_4O_8$)
Yield 4.8 g (85%); m.p.: 262–263 °C (from dioxane); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.68$ (t, $J = 6.6$ Hz, 4H, $2COCH_2$), 3.72 (t, $J = 6.6$ Hz, 4H, $2NCH_2$), 7.16, 7.22 (2d, $J = 9.2$ Hz, 8H, H_{Ar}), 7.89–8.05 (m, 4H, H_{Ar}), 10.34 (s, 2H, 2NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 30.98$ ($COCH_2$), 44.67 (NCH_2), 116.09, 126.01, 126.63, 130.92, 134.30, 137.02, 145.99, 152.15 (C_{Ar}), 154.42, 170.57, 179.96 (CO) ppm; IR (KBr): $\bar{\nu} = 3{,}069$ (NH), 1,727, 1,693, 1,684 (C=O) cm^{-1}; MS (APCI+, 25 eV): *m/z* (%) = 567 $[M+H]^+$ (100).

1,1'-[(1,4-Dihydro-1,4-dioxo-2,3-naphthalenediyl)bis-(oxy-4,1-phenylene)]bis(5,6-dihydro-5-methylpyrimidine-2,4(1H,3H)-dione) (**10b**, $C_{32}H_{26}N_4O_8$)
Yield 4.98 g (84%); m.p.: 288–289 °C (purified by column chromatography, acetone:$CHCl_3$ 1:5, $R_f = 0.64$); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.11$ (d, $J = 6.9$ Hz, 6H, $2CH_3$), 2.80–2.88 (m, 2H, 2CH), 3.54–3.71 (m, 4H, $2CH_2$), 7.16, 7.22 (2d, $J = 9.2$ Hz, 8H, H_{Ar}), 7.89–8.05 (m, 4H, H_{Ar}), 10.32 (s, 2H, 2NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 12.14$ (CH_3), 34.83 ($COCH_2$), 50.89 (NCH_2), 116.08, 125.99, 126.54, 130.92, 134.28, 136.93, 145.99, 152.13 (C_{Ar}), 154.40, 173.20, 179.94 (CO) ppm; IR (KBr): $\bar{\nu} = 3{,}069$ (NH), 1,735, 1,685, 1,668 (C=O) cm^{-1}; MS (APCI+, 25 eV): *m/z* (%) = 595 $[M+H]^+$ (100).

1,1'-[(1,4-Dihydro-1,4-dioxo-2,3-naphthalenediyl)bis-(oxy-4,1-phenylene)]bis(5,6-dihydro-6-methylpyrimidine-2,4(1H,3H)-dione) (**10c**, $C_{32}H_{26}N_4O_8$)
Yield 4.9 g (82%); m.p.: 264–265 °C (from EtOH); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.09$ (d, $J = 6.5$ Hz, 6H, $2CH_3$), 2.42 (dd, $J_{AB} = 16.4$ Hz, $J_{AX} = 3.6$ Hz, 2H, 2(H_A, CH_2)), 3.06 (dd, $J_{AB} = 16.4$ Hz, $J_{BX} = 6.0$ Hz, 2H, 2(H_B, CH_2)), 3.89–3.98 (m, 2H, 2CH), 7.16, 7.21 (2d, $J = 9.1$ Hz, 8H, H_{Ar}), 7.89–8.06 (m, 4H, H_{Ar}), 10.35 (s, 2H, 2NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 18.38$ (CH_3), 37.70 ($COCH_2$), 51.42 (NCH_2), 116.31, 126.02, 128.73, 130.93, 134.30, 135.57, 145.79, 151.47 (C_{Ar}), 154.95, 170.02, 179.95 (CO) ppm; IR (KBr):

$\bar{\nu}$ = 3,200 (NH), 1,726–1,675 (C=O) cm^{-1}; MS (APCI+, 25 eV): *m/z* (%) = 595 $[M+H]^+$ (100).

*General procedure for preparation of naphthoquinone derivatives **11c** and **12a***

A mixture of **9c** or **10a** (1.8 mmol) and 8 cm^3 10% aqueous NaOH was stirred at room temperature (20 °C) for 1.5 h and acidified with dilute HCl to pH 1. The precipitate formed was filtered, washed with H_2O, and purified by recrystallization or by dissolving in 10% aqueous NaOH and subsequently acidifying with dilute HCl.

3-[1-[3-(1,4-Dihydro-3-hydroxy-1,4-dioxonaphthalen-2-yloxy)phenyl]ureido]butyric acid (**11c**, $C_{21}H_{18}N_2O_7$)
Yield 0.50 g (67%); m.p.: 170–171 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.99 (d, J = 6.8 Hz, 3H, CH_3), 2.11 (dd, 1H, J_{AB} = 15.1 Hz, J_{AX} = 7.9 Hz, H_A, CH_2), 2.43 (dd, 1H, J_{AB} = 15.1 Hz, J_{BX} = 6.7 Hz, H_B, CH_2), 4.69–4.81 (m, 1H, CH), 5.19 (s, 2H, NH_2), 6.71–7.93 (m, 8H, H_{Ar}), 12.17 (br.s., 1H, COOH) ppm; IR (KBr): $\bar{\nu}$ = 3,484 (NH_2), 3,375 (OH), 1,703, 1,661, 1,620, 1,590 (C=O) cm^{-1}; MS (APCI+, 25 eV): *m/z* (%) = 433 $[M+Na]^+$ (100).

3-[1-[4-(1,4-Dihydro-3-hydroxy-1,4-dioxonaphthalen-2-yloxy)phenyl]ureido]propanoic acid (**12a**, $C_{20}H_{16}N_2O_7$)
Yield 0.54 g (77%); m.p.: 198–199 °C (from acetone); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.37 (t, J = 7.4 Hz, 2H, $COCH_2$), 3.69 (t, 2H, J = 7.4 Hz, NCH_2), 5.53 (s, 2H, NH_2), 7.06–8.05 (m, 8H, H_{Ar}), 11.56 (br.s., 1H, OH), 12.21 (br.s., 1H, COOH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 33.18 (CH_2), 45.27 (CH_2), 116.07, 125.84, 129.27, 130.81, 133.46, 134.49, 135.25, 136.37, 150.84, 155.61 (C_{Ar}), 157.28, 172.72, 179.57, 181.7 (C=O) ppm; IR (KBr): $\bar{\nu}$ = 3,466 (NH_2), 3,328 (OH), 1,723, 1,674, 1,660, 1,654 (C=O) cm^{-1}; MS (APCI+, 25 eV): *m/z* (%) = 419 $[M+Na]^+$ (100).

*Preparation of naphthoquinone derivatives **13c** and **14a**, method A*

1-[3-(1,4-Dihydro-3-hydroxy-1,4-dioxonaphthalen-2-yloxy)phenyl]-5,6-dihydro-6-methylpyrimidine-2,4(1H,3H)-dione (**13c**, $C_{21}H_{16}N_2O_6$)
A mixture of 0.2 g **11c** (0.05 mmol) and 8 cm^3 concentrated HCl was heated under reflux for 1.5 h, cooled, and diluted with 20 cm^3 H_2O. Crystals formed were filtered and washed with H_2O to afford 0.12 g (63%) **13c**. M.p.: 138–139 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.11 (d, J = 6.5 Hz, 3H, CH_3), 2.41 (dd, 1H, J_{AB} = 16.4 Hz, J_{AX} = 3.8 Hz, H_A, CH_2), 3.05 (dd, 1H, J_{AB} = 16.4 Hz, J_{BX} = 5.9 Hz, H_B, CH_2), 3.94–4.03 (m, 1H, CH), 6.96–8.06 (m, 8H, H_{Ar}), 10.40 (s, 1H, NH), 11.43–11.99 (br.s., 1H, OH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 18.22 (CH_3), 37.43 (CH_2), 51.05 (CH_2), 113.31, 114.35, 121.02, 125.40, 125.59, 129.11, 129.99, 130.52, 130.62, 133.23, 134.24, 134.87, 141.46, 150.38, 151.06 (C_{Ar}), 157.02, 169.76, 179.29, 181.37 (C=O) ppm; IR (KBr): $\bar{\nu}$ = 3,320 (OH), 3,213 (NH), 1,700, 1,672, 1,655, 1,594 (C=O) cm^{-1}; MS (APCI+, 25 eV): *m/z* (%) = 415 $[M+Na]^+$ (100).

1-[4-(1,4-Dihydro-3-hydroxy-1,4-dioxonaphthalen-2-yloxy)-phenyl]-5,6-dihydropyrimidine-2,4(1H,3H)-dione (**14a**, $C_{20}H_{14}N_2O_6$)
A mixture of 0.12 g **12a** (0.3 mmol) and 8 cm^3 concentrated HCl was heated under reflux for 30 min. Crystals formed already during the reaction were filtered and washed with H_2O to afford 0.1 g (91%) **14a**. M.p.: >320 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.69 (t, J = 6.7 Hz, 2H, $COCH_2$), 3.73 (t, J = 6.7 Hz, 2H, NCH_2), 7.06–8.06 (m, 8H, H_{Ar}), 10.35 (s, 1H, NH), 11.35–12.05 (br.s., 1H, OH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 31.03 (CH_2), 44.81 (CH_2), 115.32, 125.84, 126.73, 130.26, 130.77, 133.49, 134.48, 136.22, 150.68, 152.26 (C_{Ar}), 154.96, 170.64, 179.61, 181.64 (C=O) ppm; IR (KBr): $\bar{\nu}$ = 3,344 (OH), 3,186 (NH), 1,735, 1,680, 1,663, 1,652 (C=O) cm^{-1}; MS (APCI+, 25 eV): *m/z* (%) = 401 $[M+Na]^+$ (100).

*Preparation of naphthoquinone derivatives **13c** and **14a**, method B*

A mixture of **9c** or **10a** (0.25 mmol), 3 cm^3 AcOH, and 8 cm^3 concentrated HBr was heated under reflux for 1.5 h, then cooled and diluted with 20 cm^3 H_2O. Crystals formed were filtered and washed with H_2O to afford 0.06 g (61%) **13c** or 0.07 g (78%) **14a**. Melting points and NMR spectral data of **13c** and **14a** synthesized by method B are the same as the ones of the corresponding compounds obtained by method A.

Biology

Diffusion technique
Antimicrobial activity of compounds was evaluated by diffusion in agar on solid nutrient medium (nutrient agar for bacteria; wort agar for fungi). Disks (5 mm diameter) were soaked in 0.02 mg/cm^3 of compound solutions in DMSO. Disks were put on an exponentially growing plated culture. The microbial loading was 10^9 cells/cm^3. The plates were then incubated for bacteria for 24 h at 35 °C and for fungi for 48–72 h at 28–30 °C. The results were recorded by measuring the zones surrounding the disk. A control disk contained vancomicine (for bacteria) or nistatine (for fungi) as a standard.

Serial dilution technique

Testing was performed in a flat-bottomed 96-well tissue culture plate. The tested compounds were dissolved in DMSO, and the concentration range was 500–1.9 μg/cm^3. The inoculum of bacteria and fungi was inoculated in nutrient medium (nutrient meat extract for bacteria; wort for fungi). The duration of incubation was 24–72 h at 37 °C for bacteria and 30 °C for fungi. The results were estimated according to the presence or absence of microorganism growth.

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