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First synthesis and anticancer activity of novel naphthoquinone amides

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ABSTRACT

Sixteen novel naphthoquinone aromatic amides were synthesized by a new route starting from 1-hydroxy-2-naphthoic acid in nine or ten steps with good to excellent yield. Amide formation reaction was carried out by using 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) as an efficient condensing agent leading to carboxamides in high yield. The key step for converting naphthol to 3-hydroxynaphthoquinone was the Fremy's salt oxidation followed by hydroxylation with *tert*-butyl hydroperoxide and triton B. Anticancer activity of these new naphthoquinone amides were evaluated and benzamide **22** showed potent inhibition against NCI-H187 cell lines while naphthamides **23** and **43** were the most potent inhibition against KB cells. The decatenation assay revealed that compounds **24** and **43** at 20 μM can inhibit hTopoIIα activity while three other compounds, namely compounds **22**, **23**, and **45**, exhibited hTopoIIα inhibitory activity at final concentration of 50 μM. Docking experiment revealed the same trend as the cytotoxicity and decatenation assay. Therefore, naphthamides **24** and **43** can be promising target molecules for anticancer drug development.

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1. Introduction

Rhinacanthus nasutus (Acanthaceae) is a rhinacanthin-rich medicinal plant, which is widely distributed in Southeast Asia and South China. This herb has been used for treatment of ringworm [1], skin diseases [2–4], inflammation [5,6], and cancer [7–13]. Many secondary metabolites can be isolated from this plant such as flavonoids, triterpenoids, steroids, benzenoids, lignans, glycosides, and naphthoquinones [14–18]. The major constituents in this plant are naphthoquinones which are rhinacanthone (1,2-naphthoquinone), dehydro-α-lapachone, fifteen rhinacanthins (1,4-naphthoquinone) as shown in Fig. 1. Rhinacanthone has been reported [19] to possess antitumor activity against Dalton's ascetic lymphoma (DAL) in Swiss albino mice. Rhinacanthins also showed anticancer activity against P-388, A-549, HT-29, and HL-60 cell lines [17].

In 2003, we have reported [20] the successful synthesis and anticancer evaluation of rhinacanthone, 1,2-pyrano and -furanonaphthoquinones, 1,4-pyrano and -furanonaphthoquinones (Fig. 2). In 2004 and 2010, rhinacanthins and fifty-one related 1,4-naphthoquinone aromatic esters (Fig. 3) with various C-2′ substituents were also synthesized and evaluated their anticancer activity [21,22]. Most of them exhibited significant cytotoxicities against three cancer cell lines (KB (oral cavity cancer), HeLa (cervical cancer), and $HepG_2$ (hepatocellular cancer)). We also found that the substituent at C-2′ position played a crucial role by affecting the anticancer activity. Most naphthoquinone aromatic esters with 2′,2′-dimethyl substituents exhibited the most potent cytotoxicity against KB, HeLa, and $HepG_2$ cell lines than those of one methyl substituent, no methyl substituent, and also than with more rigid cyclopentyl and cyclohexyl substituents at C-2′ position. Since our naphthoquinone esters showed very promising anticancer activity and it is well known that compounds associated with broad spectrum of biological activity are amides [23,24], therefore it is worthwhile to synthesize naphthoquinone amides related to the naphthoquinone ester analog.

Thus in this report, sixteen novel naphthoquinone aromatic amides related to our previous anticancer naphthoquinone aromatic esters were synthesized and their anticancer activity was evaluated. The decatenation assay of all sixteen compounds for human Topoisomerase IIα and molecular docking analysis of some selected novel naphthoquinone aromatic amides were also carried out.

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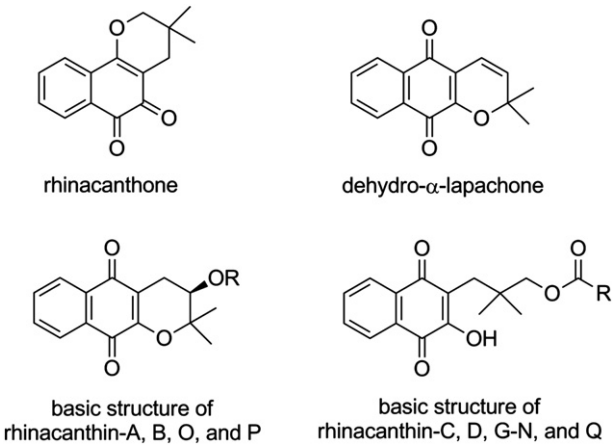


Fig. 1. Structures of the major components in *Rhinacanthus nasutus*.

2. Results and discussion

2.1. Chemistry

A new route for the synthesis of novel naphthoquinone aromatic amides **21**–**28** (Scheme 1) was accomplished in nine to ten steps with good to excellent yield (Scheme 1), starting from 1-hydroxy-2-naphthoic acid (**1**). Alkylation of the naphthyl methyl bromide **2** [20] with isobutyronitrile gave cyanide **3** which was reduced with lithium aluminum hydride to provide amine **4**. Attempts to couple amine **4** with benzoic acid (**5**) by using DCC as a condensing agent gave unsatisfactory yield of product **9**. Amide formation of amine **4** with benzoic acid (**5**) was successful by using the easily prepared 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) [25,26] as a condensing agent to give benzamide **9** with excellent yield. Treatment of **9** with boron tribromide afforded naphthol **13** followed by oxidation with Fremy's salt in the presence of 1 M sodium acetate as a buffer to prevent the decomposition of Fremy's salt in the reaction condition provided 1,4-naphthoquinone **17** in effective yield. Hydroxylation of 1,4-naphthoquinone **17** with *tert*-butyl hydroperoxide (TBHP) and triton B [27] afforded naphthoquinone **21**. Methylation of hydroxyl group of compound **21** by using dimethyl sulfate under basic condition provided methyl ether **25** in high yield. Naphthoquinone amides **22**–**24** and **26**–**28** were prepared by the same procedure but using the appropriate aromatic acid for the amide formation step (Scheme 1).

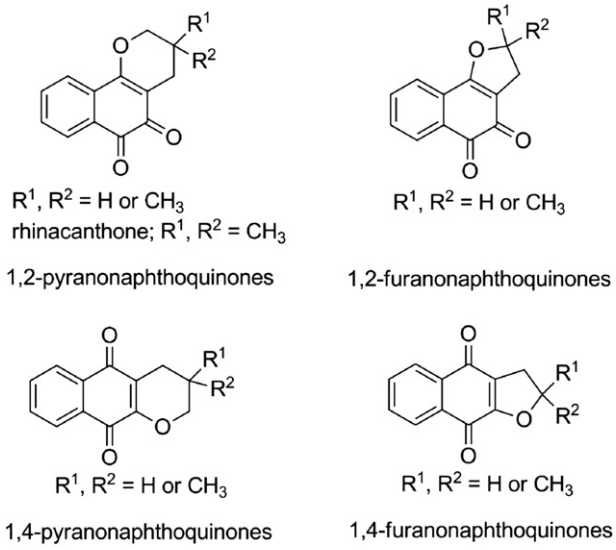


Fig. 2. Structures of rhinacanthone, 1,2-pyrano and -furanonaphthoquinones, and 1,4-pyrano and -furanonaphthoquinones.

Since naphthoquinone amides **22** and **24** contain two hydroxyl groups at C-3 of naphthoquinone nucleus and C-1 of naphthalene ring, so methylation of naphthoquinones **22** and **24** can occur at both hydroxyl groups. To prepare mono methoxy aromatic amides, methylation of the hydroxyl group of naphthoquinone amides **18** and **20** was done prior to hydroxylation to give the resultant naphthoquinone **29** and **30** and then hydroxylation at C-3 of naphthoquinone moiety to obtain methyl ether naphthoquinone aromatic amides **31** and **32**, respectively (Scheme 2).

Demethylation of the methoxyl group of amine **4** was done to give naphthol amine **33** which is not stable (Scheme 3). The crude amine product **33** was readily coupled with 2,5-dimethoxybenzoic acid (**34**) in the presence of DMTMM as a condensing agent to give naphthol **36** which was oxidized by using Fremy's salt to obtain naphthoquinone 2,5-dimethoxybenzamide **38**. Only a methoxyl group, *ortho* directed to carbonyl group was demethylated by treatment of **38** with boron tribromide at −78 °C to provide naphthoquinone **40** which was hydroxylated by using TBHP and triton B to afford naphthoquinone benzamide **42**. The trimethoxy naphthoquinone benzamide **46** could be prepared by hydroxylation of naphthoquinone **38** to give naphthoquinone benzamide **44** prior to methylation. Naphthoquinone naphthamides **41**, **43**, **45**, and **47** were prepared according to the method used to synthesize naphthoquinone 1,4-disubstituted benzamide but using 1,4-dimethoxynaphthoic acid (**35**) instead of 2,5-dimethoxybenzoic acid (**34**).

2.2. Biological activities

Sixteen new synthetic naphthoquinone aromatic amides were evaluated for their cytotoxicity against human cancer cell lines KB (oral cavity cancer), NCI-H187 (small cell lung cancer), and MCF-7 (breast cancer) by the rezasurin microplate assay (REMA) [28] and normal Vero cell lines by green fluorescent protein (GFP)-based assay [29]. The results are shown in Table 1.

The cytotoxicity results revealed that benzamide **22** showed the most potent inhibition against NCI-H187 with IC_{50} value of 8.83 ± 1.79 μM whereas naphthamides **23** and **43** exhibited potent inhibition against KB cell lines with IC_{50} values of 9.00 ± 2.17 and 8.62 ± 2.26 μM, respectively. Naphthoquinone amides **22** and **23** showed moderate inhibition against MCF-7 with IC_{50} values of 28.07 ± 7.04 and 28.18 ± 8.42 μM, respectively. Most tested compounds exhibited weak toxicity to normal Vero cell lines, being less toxic than our previous synthetic naphthoquinone esters [21].

The cytotoxic activity was also affected by benzene type and naphthalene type of amides. Naphthamide **23** which has no substituent on C-1 of naphthalene ring inhibited three cancer cell lines more efficiently than benzamide **21** which has also no substituent on C-1 of benzene ring with IC_{50} in the range of 9.00 ± 2.17 to 28.18 ± 8.42 and 15.16 ± 3.77 to 40.09 ± 7.79 μM, respectively. Both compounds were still less toxic to normal Vero cell lines (IC_{50} = 46.65 and 50.49 μM). In contrast, naphthamide **28** which possesses a methoxyl group on C-1 of naphthalene ring exhibited less cytotoxicity against three cancer cell lines than benzamide **26** with the same substituent on C-1 of benzene ring with IC_{50} values in the range of 53.24 ± 10.60 to 95.73 ± 7.98 and 33.16 ± 9.87 to 70.66 ± 10.36 μM, respectively.

The presence of hydroxyl (OH) or methoxyl (OMe) group at C-3 position on naphthoquinone backbone and at C-1 on naphthalene or benzene ring also influenced to the cytotoxicity of these

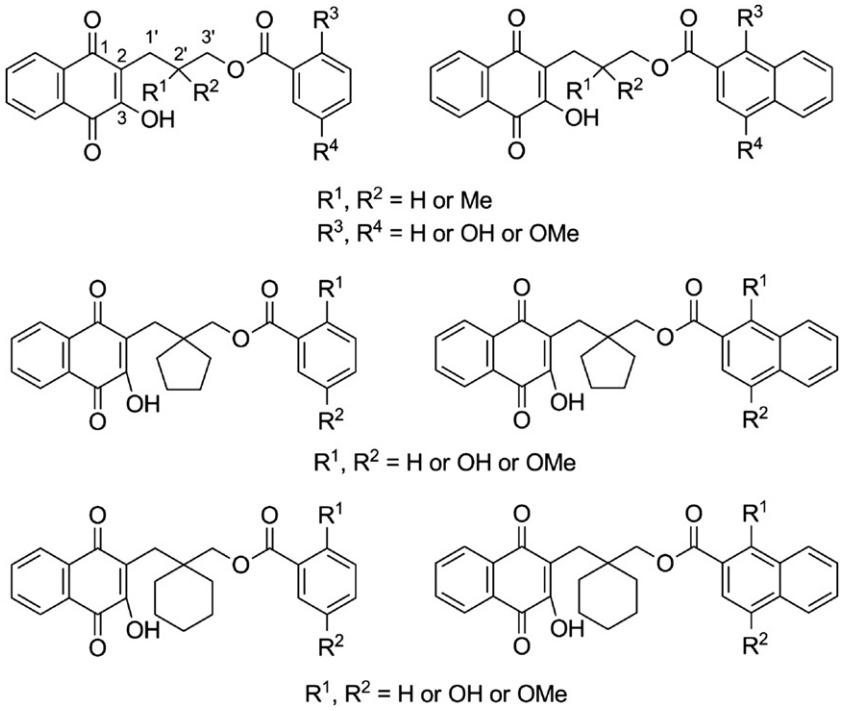
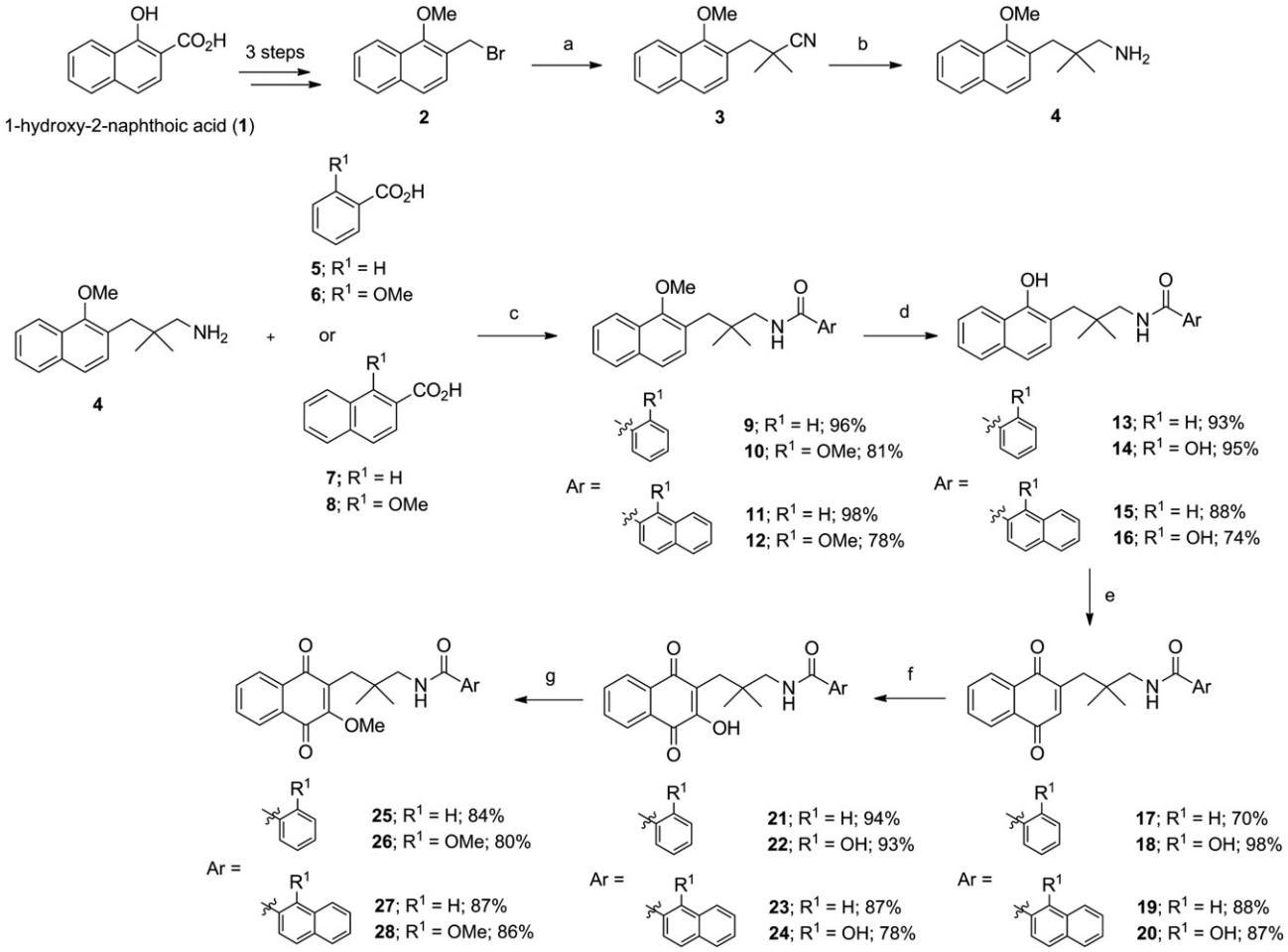
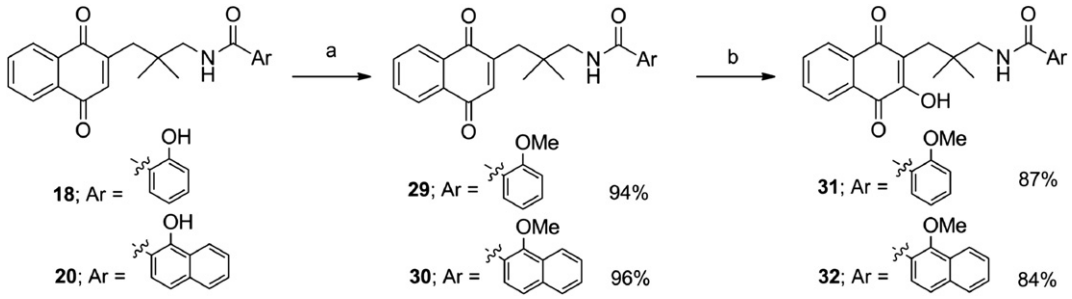


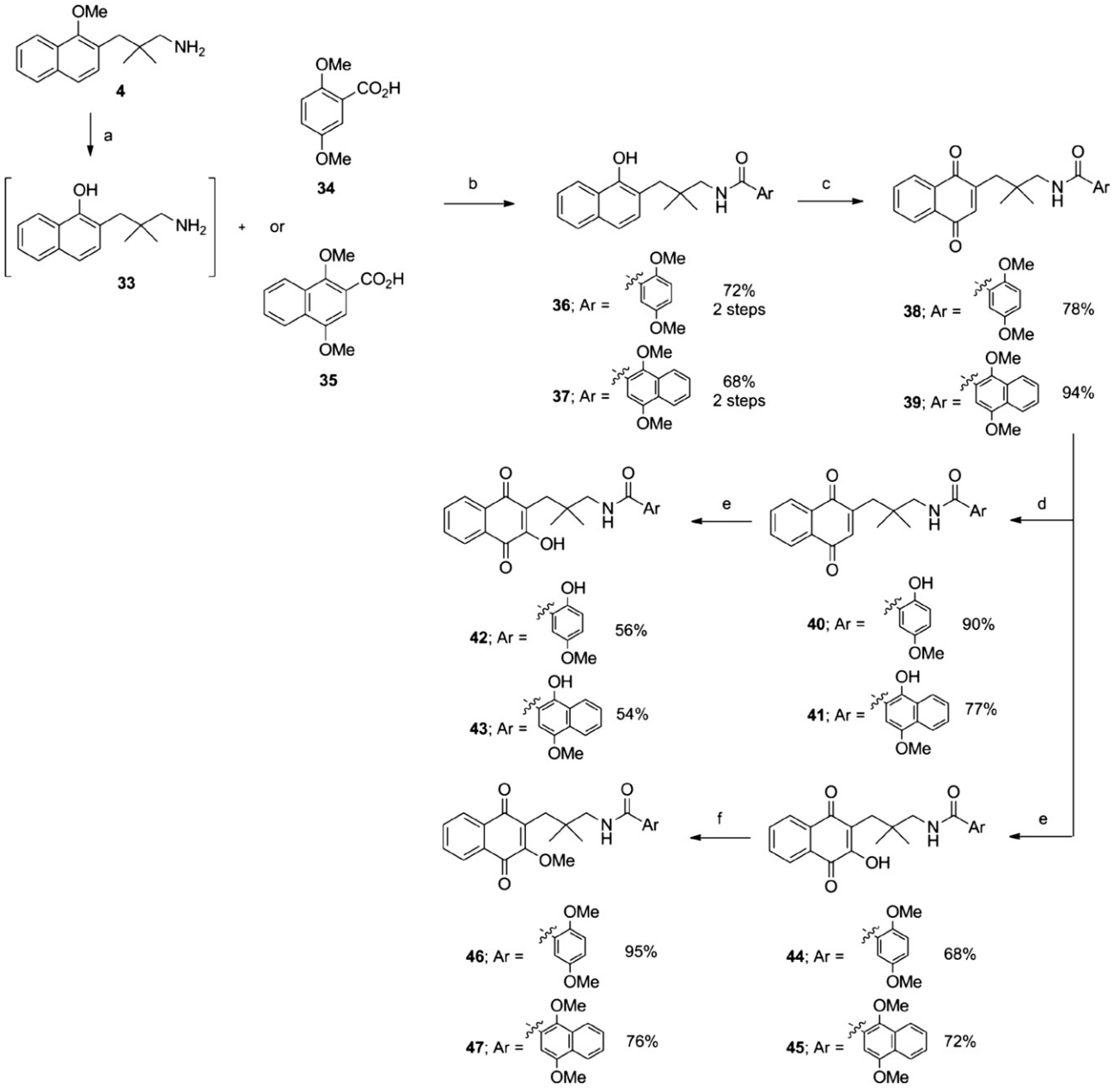
Fig. 3. Synthetic 2′-substituted naphthoquinone aromatic esters.



Scheme 1. Synthesis of naphthoquinone aromatic amides **21**–**28**: (a) 1.6 M *n*-BuLi, diisopropylamide, isobutyronitrile, HMPA, THF, −78 °C, 90%; (b) $LiAlH_4$, THF, 0 °C to rt, 92%; (c) DMTMM, MeOH, rt; (d) BBr_3, dry DCM, 0 °C to rt; (e) Fremy's salt, H_2O, 1 M NaOAc, MeOH:DMF (3:1), rt; (f) TBHP, triton B, THF, rt; (g) Me_2SO_4, K_2CO_3, acetone, rt.



Scheme 2. Synthesis of naphthoquinone aromatic amides **31** and **32**: (a) Me_2SO_4, K_2CO_3, acetone, rt; (b) TBHP, triton B, THF, rt.



Scheme 3. Synthesis of naphthoquinone 1,4-disubstituted aromatic amides **42**–**47**: (a) BBr_3, dry DCM, 0 °C to rt; (b) DMTMM, MeOH, rt; (c) Fremy's salt, H_2O, 1 M NaOAc, MeOH:DMF (3:1), rt; (d) BBr_3, dry DCM, −78 °C; (e) TBHP, triton B, THF, rt; (f) Me_2SO_4, K_2CO_3, acetone, rt.

Table 1
Cytotoxicity of naphthoquinone amides **21**–**28**, **31**, **32**, and **42**–**47** against human carcinoma cell lines (KB, NCI-H187, and MCF-7) and Vero cell lines.

Compounds	Cancer cell lines, [a] IC_{50} (μM) [b]			Vero cell lines, [a] IC_{50} (μM) [b]
	KB	NCI-H187	MCF-7	
21	15.16 ± 3.77	40.09 ± 7.79	37.07 ± 16.37	50.49
22	44.94 ± 20.08	8.83 ± 1.79	28.07 ± 7.04	32.10
23	9.00 ± 2.17	19.54 ± 2.49	28.18 ± 8.42	46.65
24	26.92 ± 12.57	14.41 ± 1.58	79.50 ± 20.35	93.65
25	117.21 ± 10.36	19.05 ± 0.64	61.76 ± 11.50	12.27
26	33.16 ± 9.87	34.70 ± 12.42	70.66 ± 10.36	27.34
27	34.06 ± 9.82	25.66 ± 7.42	52.47 ± 14.16	35.98
28	64.11 ± 11.52	53.24 ± 10.60	95.73 ± 7.98	60.63
31	26.31 ± 7.52	42.93 ± 4.40	111.23 ± 11.49	31.19
32	66.86 ± 26.95	37.02 ± 0.56	39.80 ± 1.13	47.26
42	Inactive	14.95 ± 1.59	39.57 ± 8.30	31.12
43	8.62 ± 2.26	26.01 ± 10.16	35.56 ± 13.51	15.84
44	86.60 ± 6.90	40.85 ± 13.53	99.35 ± 9.82	89.10
45	46.97 ± 10.39	19.75 ± 2.41	Inactive	17.66
46	34.31 ± 6.01	74.29 ± 4.50	57.92 ± 9.58	36.21
47	41.23 ± 15.92	19.59 ± 0.92	Inactive	30.05
Doxorubicin[c]	0.90 ± 0.31	0.16 ± 0.06	17.90 ± 2.78	28.81

[a] KB = oral cavity cancer. NCI-H187 = small cell lung cancer. MCF-7 = breast cancer. Vero cells = African green monkey kidney cells.
[b] The results are the mean of three replicate determinations ± SD.
[c] Used as reference.

naphthoquinone aromatic amides. It was found that the presence of OH group on C-3 naphthoquinone moiety enhanced the anticancer activity rather than the OMe group on the same position. For example, naphthamides **23** and **32** exhibited a better inhibition against all three cancer cell lines than naphthamides **27** and **28**, respectively. In addition disubstituted benzamide **44** and disubstituted naphthamide **45** showed more potent inhibition against NCI-H187 cell lines than benzamide **46** and naphthamide **47**, respectively. In the same manner of C-3 position, the presence of OH group at C-1 of naphthalene or benzene ring could improve the cytotoxicity against NCI-H187 cell lines rather than the OMe group; for instance, compounds **22**, **24**, and **42** with IC_{50} values of 8.83 ± 1.79, 14.41 ± 1.58, and 14.95 ± 1.59 μM, respectively, showed stronger cytotoxicity than compounds **31**, **32**, and **44** with IC_{50} values of 42.93 ± 4.40, 37.02 ± 0.56, and 40.85 ± 13.53 μM, respectively.

2.3. Human Topoisomerase IIα inhibitory activity

The decatenation assay was used to determine the inhibitory activity of novel naphthoquinone aromatic amides and human Topoisomerase IIα (hTopoIIα). The enzyme catalyzes the ATP-dependent decatenation of long-chained, catenated DNA molecules into free relaxed and supercoiled forms [30]. Fig. 4 shows hTopoIIα inhibitory activity of all sixteen compounds at final concentration of 50 μM. It can be clearly seen that compounds **22**, **23**, **24** and **43** exhibited strong hTopoIIα inhibitory activity while compound **45** can almost inhibit the enzyme activity. In comparison with the cytotoxicity test, these five compounds also exhibited potent inhibition against the cancer cell lines, indicating that both experiments are correlated. Additionally, these compounds were further used to evaluate their hTopoIIα inhibitory activity at final concentration of 10 and 20 μM as shown in Fig. 5. Only compounds **24** and **43** can still strongly inhibit hTopoIIα activity at final concentration of 20 μM; however, the selected five compounds did not show any hTopoIIα inhibitory activity at final concentration of 10 μM compared to doxorubicin at the same concentration. According to the decatenation assay, three interesting points can be concluded. First, naphthamides showed higher hTopoIIα inhibitory activity than benzamides. Second, a hydroxy substituent on C-1 position of benzene or naphthalene nucleus exhibited significant hTopoIIα inhibition. Third, all naphthoquinone amides that contain a C-3 hydroxy group on the naphthoquinone ring showed better hTopoIIα inhibitory activity than those containing a C-3 methoxy group. Thus, it is clear that compounds **24** and **43**, consisting of the naphthalene ring, C-1 hydroxy group on the naphthalene nucleus and C-3 hydroxy group on the naphthoquinone ring, display the most significant hTopoIIα inhibition.

2.4. Molecular docking

According to our previous work [21], naphthoquinone esters were found to bind at the DNA-binding domain of hTopoIIα and in order to continue the further study, the molecular docking analysis of hTopoIIα with selected novel naphthoquinone amides was carried out. The homology model of hTopoIIα was built by SWISS-MODEL. The final model consisted of 758 amino acid residues. Docking studies were carried out for compounds **21**, **23**, **25**, **27**, **43** and **45** with DNA-binding domain of hTopoIIα to where other naphthoquinone esters were reported to bind [21]. Compounds **21** and **23** were chosen as to investigate the importance of benzene type and naphthalene type of amides whereas compounds **25** and **27** were selected for the assessment of the presence of methoxyl group at C-3 position on naphthoquinone backbone with benzene type and naphthalene type of amides. Additionally, the presence of OH or OMe group at C-1 on naphthalene nucleus can be evaluated from compounds **43** and **45**. An analysis of the docked compounds to the DNA-binding domain showed that all six compounds fit into the DNA-binding site (Fig. 6). The conserved residues for hTopoIIα catalytic site, such as K798, S800, A801 and S802 are in proximity of the docked compounds. Fig. 7 shows the superposition of the docked doxorubicin (a control) and the docked naphthoquinone amides. It can be seen that the position of the naphthoquinone ring overlaps well with that of quinone ring of doxorubicin.

According to Fig. 7, two spatial arrangements of the naphthoquinone amides can be observed. The more active compounds (**23**, **27**, **43** and **45**) are positioned in the similar fashion to doxorubicin while the less active compounds (**21** and **25**) are not. Additionally, the position of naphthoquinone amides containing naphthoate group is noticeably different from that containing benzoate group (**21** and **25**) in that the former ones form a bent conformation similar to doxorubicin while the latter ones form

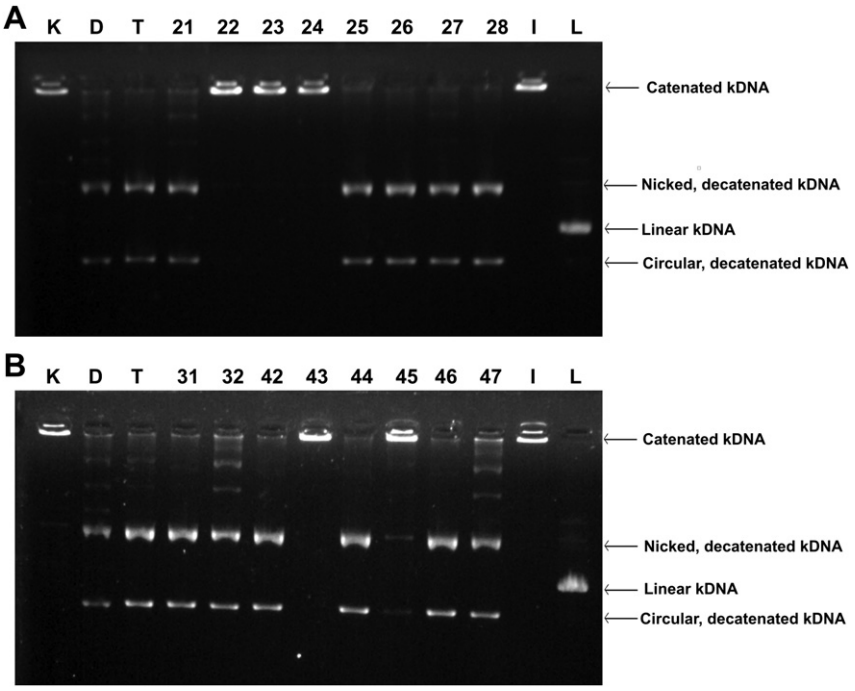


Fig. 4. Topoisomerase IIα inhibitory activity of sixteen naphthoquinone amides (**21**–**28**, **31**,**32** and **42**–**47**). The compounds were examined in final concentration of 50 μM. (A) Lanes K: kDNA only, Lane D: decatenated kDNA only, Lane T: kDNA + TopoIIα, Lane 21–28: kDNA + TopoIIα + compounds **21**–**28**, respectively, Lane I: kDNA + TopoIIα + 50 μM doxorubicin and Lane L: linearized kDNA marker. (B) Lanes K: kDNA only, Lane D: decatenated kDNA only, Lane T: kDNA + TopoIIα, Lane 31, 32 and 42–47: kDNA + TopoIIα + compounds **31**, **32** and **42**–**47**, respectively, Lane I: kDNA + TopoIIα + 50 μM doxorubicin and Lane L: linearized kDNA marker. Catenated kDNA does not migrate out of the loading wells.

an extended conformation. This different arrangement may be accounted for the presence of benzene type or naphthalene type of amides. Besides the arrangement of the compounds, the formation of hydrogen bonds is considered (Fig. 8). In compounds **43** and **45**, the C-3 hydroxyl group on the naphthoquinone ring forms hydrogen bonds with NH group of K798. These amino acid residues (K798) are conserved among TopoII family and found in loop region close to active site residue (Y805) of hTopoIIα [31]. The more hydrogen bonding interaction in compound **43** may relate to its toxicity and hTopoIIα inhibitory activity. The hydrogen bonding formation also emphasizes the importance of the hydroxyl group at this position as it was observed in the naphthoquione esters [21]. In another compounds, such as compounds **23** and **27**, pi–sigma interaction with conserved residue A801 was observed, while this interaction cannot be seen in the less active compounds **21** and **25**. Collectively, this result correlated well with that of cytotoxicity assay and hTopoIIα inhibitory activity.

3. Conclusion

With regards to the excellent anticancer activity of rhinacanthins and related naphthoquinone esters, sixteen new naphthoquinone amides were synthesized by a new route with high yield. All synthetic naphthoquinone amides, naphthamides and benzamides, were evaluated for anticancer activity against three cancer cell lines (KB, NCI-H187, and MCF-7) and also toxicity to normal Vero cell lines. From the cytotoxicity test, naphthamides showed stronger inhibition than benzamides, but naphthamides with methoxyl group on C-1 of naphthalene ring inhibited cancer cells less than benzamides with the same substituent. The presence

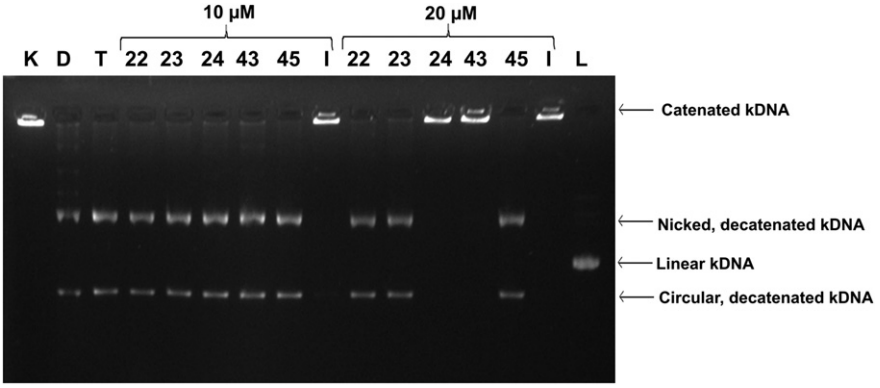


Fig. 5. Topoisomerase IIα inhibitory activity of selected five naphthoquinone amides (**22**–**24**, **43** and **45**). The compounds were examined in final concentration of 10 and 20 μM, respectively, as designated. Lanes K: kDNA only, Lane D: decatenated kDNA only, Lane T: kDNA + TopoIIα, Lane 22, 23, 24, 43 and 45: kDNA + TopoIIα + compounds **22**, **23**, **24**, **43** and **45**, respectively, Lane I: kDNA + TopoIIα + doxorubicin and Lane L: linearized kDNA marker. Catenated kDNA does not migrate out of the loading wells.

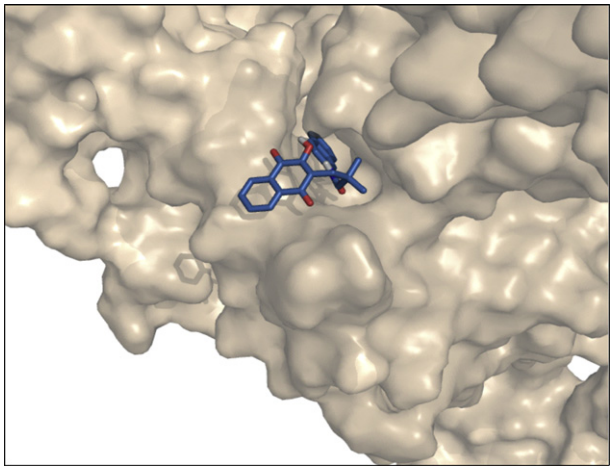


Fig. 6. Surfaced view of DNA-binding pocket. The DNA-binding domain is represented as a molecular surface (gray) and compound **23** is represented in stick and colored by the atom type (carbon, marine blue; oxygen, red; hydrogen, white). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of hydroxyl group or methoxyl group on C-3 of naphthoquinone nucleus did not alter the cytotoxicity whereas naphthoquinone esters [21] with C-3 hydroxyl group showed stronger anticancer activity compared to those with methoxyl group. Interestingly, most of naphthoquinone amides showed weak toxicity against normal Vero cell lines and much less toxic than the previous naphthoquinone esters.

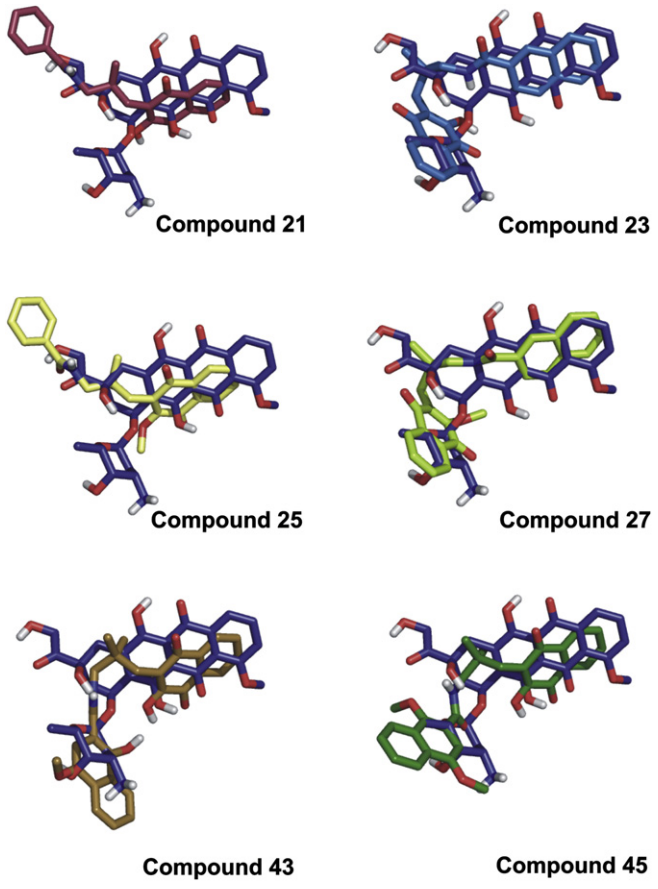


Fig. 7. Molecular docking of doxorubicin (dark blue) and naphthoquinone amide compounds **21**, **23**, **25**, **27**, **43** and **45** in the DNA-binding domain. Compounds **21**, **23**, **25**, **27**, **43** and **45** are shown in stick and colored by the atom type (carbon: violet, blue, yellow, light green, brown, and green, respectively; oxygen: red; hydrogen: white and nitrogen: blue). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The decatenation assay revealed that compounds **24** and **43** at 20 μM can inhibit hTopoIIα activity while three other compounds, namely compounds **22**, **23**, and **45**, exhibited hTopoIIα inhibitory activities at final concentration of 50 μM. Molecular docking analysis revealed the different spatial arrangement between naphthoquinone amides containing benzene group and naphthalene group; this finding is in agreement with hTopoIIα inhibitory assay. Interestingly, naphthamide **24** exhibited a low toxicity against Vero cell lines but relatively potent inhibition against the tested cancer cell lines as well as inhibited hTopoIIα activity. Therefore, the development of this compound can lead to a higher hTopoIIα inhibitor and eventually an anticancer drug.

4. Experimental section

4.1. Chemistry

Melting points were determined on a Fisher John apparatus and MEI-TEMP capillary melting point apparatus and are uncorrected. The infrared (IR) spectra were recorded on a Perkin–Elmer 2000 Fourier transform infrared spectrophotometer, which the wavenumbers are expressed in $\tilde{\nu}$ (cm^{-1}). NMR spectra were obtained on a VARIAN ^{UNITY} INOVA 400 MHz spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. The chemical shifts are expressed in δ (ppm); coupling constants (J) are expressed in Hz. High resolution mass spectral data (HRMS) were performed at Department of Chemistry, Faculty of Science, Chiangmai University and Mahidol University, Thailand, and were found to be within 0.4% of theoretical values. Thin-layer chromatography (TLC) analyses were carried out on pre-coated aluminum sheet silica gel 60 F_{254}. Flash column chromatography was performed on silica gel (230–400 mesh, Merck 9385). All reagents and solvents were used as received from Merck, Fluka, Aldrich, and Across Chemical. Unless otherwise noted in the case of anhydrous conditions, purifications were accomplished according to the standard procedure outlined in Vogel's Text Book of Practical Organic Chemistry.

4.1.1. *Methyl 2-((1-methoxynaphthalen-2-yl)methyl)-2-methylpropanoate (**3**)*

1.6 M *n*-Butyl lithium (3.74 mL, 5.976 mmol) was added dropwise to a stirred solution of diisopropylamine (0.84 mL, 5.976 mmol) in dry tetrahydrofuran (THF) (15 mL) at 0 °C under nitrogen atmosphere. After stirring for 45 min, isobutyronitrile (0.54 mL, 5.976 mmol) was slowly added at −78 °C to the reaction mixture and stirring was continued for 1 h. A solution of bromide **2** (1.00 g, 3.984 mmol) and hexamethylphosphoramide (HMPA) (1.00 mL, 5.976 mmol) in dry THF (5 mL) was added dropwise to the reaction mixture at the same temperature. After stirring for 2 h at −78 °C, the reaction mixture was quenched with saturated ammonium chloride solution and then extracted with diethyl ether (3 × 50 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography, eluting with 5% ethyl acetate–hexane to give the desired product **3** as a colorless solid (0.853 g, 90%). mp: 60–61 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03–8.00 (m, 1H, ArH), 7.80–7.76 (m, 1H, ArH), 7.55 (d, J = 8.4 Hz, 1H, ArH), 7.43 (d, J = 8.5 Hz, 1H, ArH), 7.48–7.39 (m, 2H, ArH), 3.84 (s, 3H, OCH_3), 2.99 (s, 2H, CH_2–Ar), 1.32 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.76 (C), 134.58 (C), 128.82 (CH), 128.11 (CH), 127.68 (C), 126.05 (CH), 126.01 (CH), 125.28 (C), 124.26 (C–N), 124.04 (CH), 122.29 (CH), 62.00 (OCH_3), 39.77 (CH_2), 33.74 (C), 26.55 (2× CH_3);

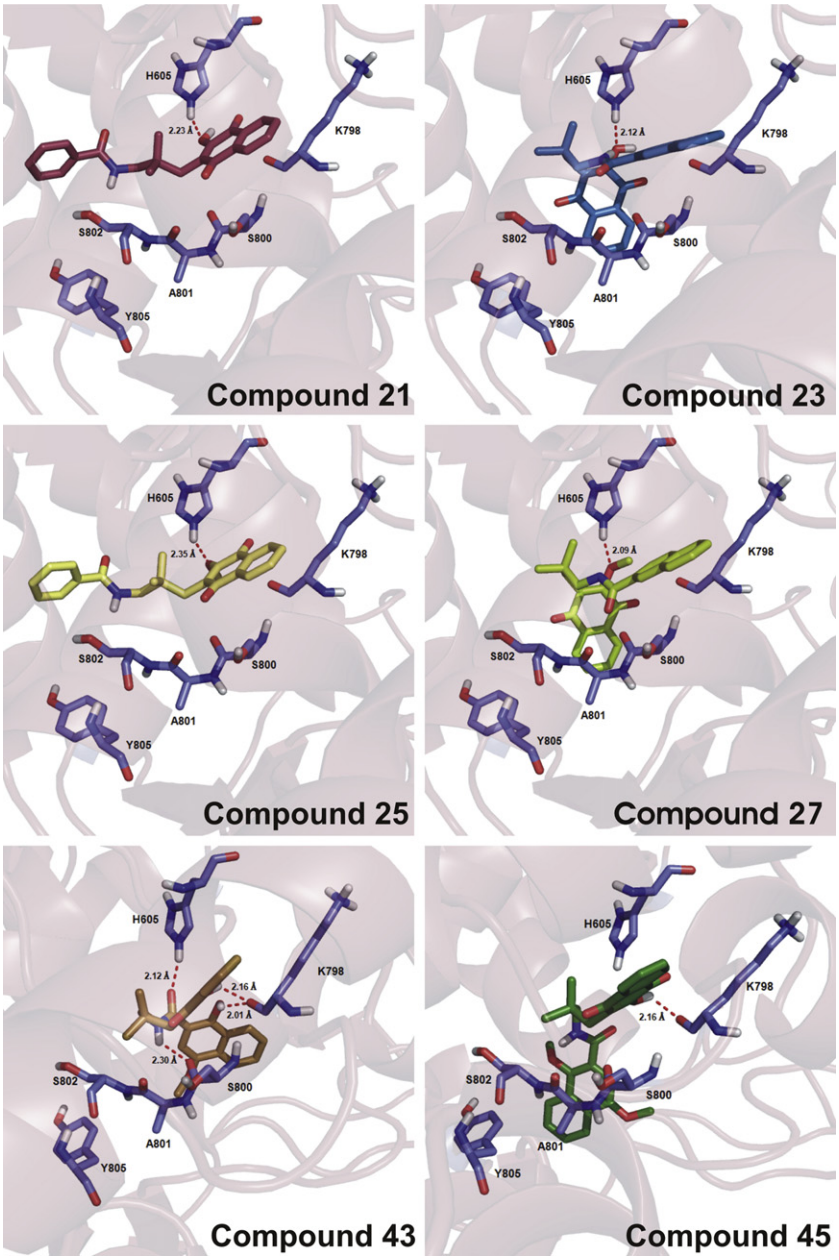


Fig. 8. View of naphthoquinone amides in DNA-binding domain of hTopoIIα. The amino acids involved in the interaction of naphthoquinone amides are depicted in stick representation and colored by the atom type (carbon, blue slate; oxygen, red; hydrogen, white and nitrogen, blue). The dotted red lines represented the hydrogen bonding interaction. Compounds **21**, **23**, **25**, **27**, **43** and **45** are shown in stick and colored by the atom type (carbon: violet, blue, yellow, light green, brown, and green, respectively; oxygen: red; hydrogen: white and nitrogen: blue). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

IR (KBr): $\tilde{\nu}$ = 3054 (CH), 2978, 2935 (CH_3), 2870, 2840 (CH_2), 2233 (C–N), 1597, 1572, 1466, 1370, 1236 (C=C), 1082 (C–O); HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{17}NO$: 240.1388, found: 240.1388.

*4.1.2. 3-(1-Methoxynaphthalen-2-yl)-2,2-dimethylpropan-1-amine (**4**)*

A solution of nitrile **3** (826.9 mg, 3.46 mmol) in dry THF (10 mL) was added dropwise over 5 min to a stirred and ice-cooled suspension of lithium aluminum hydride (262.95 mg, 6.92 mmol) in dry THF (10 mL). After stirring for 3 h at room temperature, the reaction mixture was quenched with ethyl acetate and water. The aqueous phase was extracted with diethyl ether (3 × 30 mL) and the combined organic layers were washed with water and brine. The organic phase was dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 2% v/v methanol:dichloromethane to afford product **4** as a yellow oil (773.5 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03–7.98 (m, 1H, ArH), 7.77–7.73 (m, 1H, ArH), 7.46 (d, *J* = 8.4 Hz, 1H, ArH), 7.42 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 1H, ArH), 7.37 (ddd, *J* = 8.1, 6.8, 1.4 Hz, 1H, ArH), 7.21 (d, *J* = 8.4 Hz, 1H, ArH), 3.83 (s, 3H, OCH_3), 2.64 (s, 2H, CH_2–Ar), 2.35 (s, 2H, CH_2–N), 0.85 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.29 (C), 133.97 (C), 130.48 (CH), 127.87 (CH), 127.83 (C), 127.48 (C), 125.72 (CH), 125.43 (CH), 123.08 (CH), 122.21 (CH), 61.68 (OCH_3), 52.24 (CH_2N), 38.80 (CH_2), 37.22 (C), 25.39 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3382, 3306 (NH_2), 3050 (CH), 2955 (CH_3), 2867 (CH_2), 1598, 1571, 1505, 1470, 1371 (C=C), 1232 (C–N), 1081 (C–O); HRMS

(ESI+): m/z $[M + H]^+$ calcd for $C_{16}H_{21}NO$: 244.1701, found: 244.1700.

4.1.3. N-(3-(1-Methoxynaphthalen-2-yl)-2,2-dimethylpropyl)-2-benzamide (**9**)

4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) (838 mg, 3.03 mmol) was added to a mixture of benzoic acid (**5**) (369 mg, 3.03 mmol) and amine **4** (613 mg, 2.52 mmol) in MeOH (50 mL) at room temperature. After 1 h with stirring at room temperature, the MeOH was removed by evaporation. The resulting residue was dissolved in ether, and washed successively with saturated sodium carbonate, water, 1 N HCl, water and brine and dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash column chromatography eluting with 10% v/v ethyl acetate–hexane to give amide **9** as a colorless oil (861 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.04$ (dd, $J = 8.3$, 0.6 Hz, 1H, ArH), 7.81–7.75 (m, 3H, ArH), 7.60 (t, $J = 6.3$ Hz, 1H, ArH), 7.53 (d, $J = 8.5$ Hz, 1H, ArH), 7.50–7.45 (m, 1H, ArH), 7.45–7.35 (m, 4H, ArH), 7.25 (d, $J = 8.5$ Hz, 1H, ArH), 3.91 (s, 3H, OCH_3), 3.01 (d, $J = 6.6$ Hz, 2H, CH_2–NH), 2.70 (s, 2H, CH_2–Ar), 1.03 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 167.43$ (C=O), 153.47 (C), 135.43 (C), 134.15 (C), 131.07 (CH), 130.14 (CH), 128.43 (2× CH), 128.08 (CH), 127.47 (C), 127.03 (C), 126.87 (2× CH), 126.15 (CH), 125.82 (CH), 123.94 (CH), 121.92 (CH), 62.19 (OCH_3), 47.13 (CH_2N), 39.35 (CH_2), 37.50 (C), 26.41 (2× CH_3); IR (KBr): $\tilde{\nu} = 3370$ (NH), 3054 (CH), 2960, 2937 (CH_3), 2869, 2833 (CH_2), 1655, 1646 (C=O), 1578, 1542, 1535, 1467, 1368, 1295 (C=C), 1232 (C–N), 1080 (C–O); HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{23}H_{25}NO_2$: 348.1964, found: 348.1968.

4.1.4. 2-Methoxy-N-(3-(1-methoxynaphthalen-2-yl)-2,2-dimethylpropyl)benzamide (**10**)

4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) (137 mg, 0.494 mmol) was added to a mixture of 2-methoxy benzoic acid (**6**) (75 mg, 0.494 mmol) and amine **4** (100 mg, 0.412 mmol) in MeOH (10 mL) at room temperature. After 1 h with stirring at room temperature, the MeOH was evaporated. The resulting residue was dissolved in ether, and washed successively with saturated sodium carbonate, water, 1 N HCl, water and brine and dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash column chromatography eluting with 15% v/v ethyl acetate–hexane to give **10** as a colorless oil (125.8 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.09$ (dd, $J = 7.8$, 1.9 Hz, 1H, ArH), 8.05–8.00 (m, 1H, ArH), 8.00–7.96 (m, 1H, ArH), 7.76–7.72 (m, 1H, ArH), 7.46 (d, $J = 8.4$ Hz, 1H, ArH), 7.44–7.33 (m, 3H, ArH), 7.21 (d, $J = 8.4$ Hz, 1H, ArH), 7.01 (td, $J = 7.5$, 1.0 Hz, 1H, ArH), 6.91 (dd, $J = 8.3$, 0.7 Hz, 1H, ArH), 3.90 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.25 (d, $J = 6.2$ Hz, 2H, CH_2–NH), 2.71 (s, 2H, CH_2–Ar), 0.95 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 165.58$ (C=O), 157.23 (C), 154.29 (C), 134.07 (C), 132.27 (CH), 132.16 (CH), 130.36 (CH), 127.94 (CH), 127.77 (C), 126.97 (C), 125.77 (CH), 125.51 (CH), 123.28 (CH), 122.74 (C), 122.09 (CH), 121.28 (CH), 111.36 (CH), 61.61 (OCH_3), 56.01 (OCH_3), 48.83 (CH_2N), 39.68 (CH_2), 37.12 (C), 25.57 (2× CH_3); IR (KBr): $\tilde{\nu} = 3405$ (NH), 3052 (CH), 2950, 2923 (CH_3), 2852 (CH_2), 1655 (C=O), 1599, 1535, 1466, 1370, 1298, 1238 (C=C), 1082 (C–O), 1021 (C–N); HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{24}H_{27}NO_3$: 378.2069, found: 378.2070.

4.1.5. N-(3-(1-Methoxynaphthalen-2-yl)-2,2-dimethylpropyl)-2-naphthamide (**11**)

4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) (63 mg, 0.227 mmol) was added to a mixture of naphthoic acid (**7**) (39 mg, 0.227 mmol) and amine **4** (50 mg, 0.206 mmol) in MeOH (4 mL) at room temperature. After 1 h with stirring at room temperature, the MeOH was evaporated. The resulting residue was dissolved in ether, and washed successively with saturated sodium carbonate, water, 1 N hydrochloric acid, water and brine and dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash column chromatography (15% AcOEt–hexane) to give **11** as a colorless oil (80.1 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.27$ (d, $J = 0.9$ Hz, 1H, ArH), 8.08–8.03 (m, 1H, ArH), 7.86–7.76 (m, 6H, ArH), 7.54 (d, $J = 8.4$ Hz, 1H, ArH), 7.52–7.45 (m, 3H, ArH), 7.42 (ddd, $J = 6.8$, 6.1, 1.4 Hz, 1H, ArH), 7.26 (d, $J = 8.5$ Hz, 1H, ArH), 3.94 (s, 3H, OCH_3), 3.05 (d, $J = 6.6$ Hz, 2H, CH_2–NH), 2.73 (s, 2H, CH_2–Ar), 1.05 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 167.46$ (C=O), 153.47 (C), 134.62 (C), 134.17 (C), 132.74 (C), 132.71 (C), 130.14 (CH), 128.83 (CH), 128.25 (CH), 128.12 (CH), 127.73 (CH), 127.48 (C), 127.38 (CH), 127.17 (CH), 127.07 (C), 126.61 (CH), 126.21 (CH), 125.85 (CH), 124.00 (CH), 123.79 (CH), 121.92 (CH), 62.25 (OCH_3), 47.21 (CH_2N), 39.38 (CH_2), 37.56 (C), 26.48 (2× CH_3); IR (KBr): $\tilde{\nu} = 3357$ (N–H), 3055 (CH), 2958, 2922 (CH_3), 2863, 2857 (CH_2), 1647 (C=O), 1540, 1465, 1435, 1365, 1299 (C=C), 1229 (C–N), 1080 (C–O); HRMS (ESI+): m/z $[M]^+$ calcd for $C_{27}H_{27}NO_2$: 420.1939, found: 420.1935.

4.1.6. 1-Methoxy-N-(3-(1-methoxynaphthalen-2-yl)-2,2-dimethylpropyl)-2-naphthamide (**12**)

4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) (273.4 mg, 0.988 mmol) was added to a mixture of 2-methoxy naphthoic acid (**8**) (199.8 mg, 0.988 mmol) and amine **4** (200 mg, 0.823 mmol) in MeOH (12 mL) at room temperature. After 3 h with stirring at room temperature, the MeOH was evaporated. The resulting residue was dissolved in ether, and washed successively with saturated sodium carbonate, water, 1 N HCl, water and brine and dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash column chromatography eluting with 10% v/v ethyl acetate–hexane to give **12** as a colorless oil (272.7 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.51$ (t, $J = 6.1$ Hz, 1H), 8.25–8.20 (m, 1H), 8.09 (d, $J = 8.6$ Hz, 1H), 8.09–8.05 (m, 1H), 7.90–7.85 (m, 1H), 7.84–7.81 (m, 1H), 7.71–7.67 (m, 1H), 7.59–7.54 (m, 3H), 7.50 (ddd, $J = 8.3$, 6.8, 1.5 Hz, 1H), 7.45 (ddd, $J = 8.0$, 6.8, 1.4 Hz, 1H), 7.29 (d, $J = 8.4$ Hz, 1H), 4.07 (s, 3H), 3.94 (s, 3H), 3.27 (d, $J = 6.5$ Hz, 2H), 2.79 (s, 2H), 1.08 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 166.13$ (C=O), 154.84 (C), 154.22 (C), 136.29 (C), 134.14 (C), 130.46 (CH), 128.12 (CH), 128.00 (CH), 127.68 (C), 127.63 (C), 127.59 (CH), 127.16 (CH), 126.83 (C), 126.42 (CH), 125.84 (CH), 125.59 (CH), 124.34 (CH), 123.38 (CH), 123.14 (C), 122.77 (CH), 122.07 (CH), 63.25 (OCH_3), 61.80 (OCH_3), 47.75 (CH_2N), 39.60 (CH_2), 37.35 (C), 26.00 (2× CH_3); IR (KBr): $\tilde{\nu} = 3393$ (NH), 3053 (CH), 2959, 2929 (CH_3), 2863, 2841 (CH_2), 1651 (C=O), 1521, 1468, 1444, 1370, 1339 (C=C), 1207 (C–N), 1081 (C–O); HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_{28}H_{29}NO_3$: 450.2045, found: 450.2049.

4.1.7. N-(3-(1-Hydroxynaphthalen-2-yl)-2,2-dimethylpropyl)-2-benzamide (**13**)

Boron tribromide (0.34 mL, 3.618 mmol) was added dropwise over 2 min at −78 °C to a stirred solution of methyl naphthyl ether **9** (861 mg, 2.411 mmol) in dry dichloromethane (50 mL) and the reaction mixture was stirred for 10 min. The reaction mixture was cooled to 0 °C then cold water was added to the reaction mixture and extracted with dichloromethane (3 × 30 mL). The combined organic phases were washed with water, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 20% v/v ethyl acetate–hexane to afford product **13** as a colorless oil (767.7 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.11$–8.07 (m, 1H, ArH), 7.73–7.69 (m, 1H, ArH), 7.64–7.59 (m, 3H, ArH), 7.39–7.34 (m, 2H, ArH), 7.31 (d, $J = 8.0$ Hz, 2H, ArH), 7.27–7.23 (m, 1H, ArH), 7.21 (d, $J = 7.8$ Hz, 2H, ArH), 7.12 (d, $J = 8.4$ Hz, 1H, ArH), 3.08 (d, $J = 6.6$ Hz, 2H, CH_2–NH), 2.72 (s, 2H, CH_2–Ar), 0.92 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 168.05$ (C=O), 149.13 (C), 134.43 (C), 133.55 (C), 131.32 (CH), 130.84 (CH), 128.45 (2× CH), 127.78 (CH), 126.87 (2× CH), 125.57 (CH), 125.35 (CH), 125.05 (C), 120.90 (CH), 119.98 (CH), 119.69 (C), 48.18 (CH_2N), 39.82 (CH_2), 37.34 (C), 26.39

(2× CH_3); IR (KBr): $\tilde{\nu}$ = 3351 (NH), 3188 (OH), 3055 (CH), 2960, 2922 (CH_3), 2869 (CH_2), 1644 (C=O), 1574, 1548, 1538, 1470, 1308, 1355, 1265, 1232 (C=C), 1184 (C–N), 1077 (C–O); HRMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{23}NO_2$: 241.1295, found: 241.1292.

4.1.8. 2-Hydroxy-N-(3-(1-hydroxynaphthalen-2-yl)-2,2-dimethylpropyl)benzamide (**14**)

Boron tribromide (0.1 mL, 1.020 mmol) was added dropwise over 2 min at 0 °C to a stirred solution of methyl naphthyl ether **10** (175 mg, 0.464 mmol) in dry dichloromethane (20 mL) and the reaction mixture was further stirred at room temperature for 2 h. The reaction mixture was cooled to 0 °C then cold water was added to the reaction mixture and extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with water, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 10% v/v ethyl acetate–hexane to afford product **14** as a pale yellow oil (154.6 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.42 (s, 1H, PhOH), 7.96–7.92 (m, 1H, ArH), 7.79–7.75 (m, 1H, ArH), 7.46 (ddd, *J* = 8.3, 6.8, 1.5 Hz, 1H, ArH), 7.42 (ddd, *J* = 8.0, 6.8, 1.3 Hz, 1H, ArH), 7.38 (d, *J* = 8.4 Hz, 1H, ArH), 7.36–7.33 (m, 1H, ArH), 7.27 (ddd, *J* = 8.6, 7.3, 1.6 Hz, 1H, ArH), 7.18 (d, *J* = 8.4 Hz, 1H, ArH), 7.16 (dd, *J* = 8.0, 1.6 Hz, 1H, ArH), 6.90–6.87 (m, 1H, ArH), 6.67 (ddd, *J* = 8.0, 7.2, 1.2 Hz, 1H, ArH), 6.14 (s, 1H, OH), 3.13 (d, *J* = 6.6 Hz, 2H, CH_2–NH), 2.76 (s, 2H, CH_2–Ar), 0.99 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.99 (C=O), 161.45 (C), 148.24 (C), 133.92 (CH), 133.54 (C), 130.68 (CH), 128.22 (CH), 125.86 (CH), 125.83 (CH), 125.20 (CH), 124.33 (C), 120.75 (CH), 119.75 (C), 119.63 (CH), 118.62 (CH), 118.51 (CH), 114.57 (C), 47.23 (CH_2N), 39.74 (CH_2), 37.30 (C), 26.33 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3404 (NH), 3363 (OH), 3269 (OH), 3062 (CH), 2960, 2929 (CH_3), 2869 (CH_2), 1640 (C=O), 1593, 1539, 1492, 1369, 1305, 1272, 1254 (C=C), 1227 (C–N), 1178, 1148 (C–O); HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{23}NO_3$: 350.1756, found: 350.1761.

4.1.9. N-(3-(1-Hydroxynaphthalen-2-yl)-2,2-dimethylpropyl)-2-naphthamide (**15**)

Boron tribromide (0.07 mL, 0.756 mmol) was added dropwise over 5 min at 0 °C to a stirred solution of methyl naphthyl ether **11** (200 mg, 0.504 mmol) in dry dichloromethane (10 mL) and the reaction mixture was stirred for 10 min. The reaction mixture was cooled to 0 °C then cold water was added to the reaction mixture and extracted with dichloromethane (3 × 30 mL). The combined organic phases were washed with water, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 20% v/v ethyl acetate–hexane to afford product **15** as a colorless oil (170 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13–8.10 (m, 1H, ArH), 8.09 (d, *J* = 0.6 Hz, 1H, ArH), 7.76–7.64 (m, 5H, ArH), 7.47–7.37 (m, 4H, ArH), 7.35–7.31 (m, 2H, ArH), 7.15 (d, *J* = 8.4 Hz, 1H, ArH), 3.19 (d, *J* = 6.6 Hz, 2H, CH_2–NH), 2.78 (s, 2H, CH_2–Ar), 0.98 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.34 (C=O), 149.53 (C), 134.74 (C), 133.84 (C), 132.69 (C), 131.70 (C), 131.05 (CH), 129.17 (CH), 128.41 (CH), 128.03 (CH), 127.70 (CH), 127.63 (CH), 126.63 (CH), 125.79 (CH), 125.56 (CH), 125.53 (C), 123.58 (CH), 121.46 (CH), 120.33 (C), 120.27 (CH), 48.34 (CH_2N), 40.10 (CH_2), 37.52 (C), 26.61 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3362 (OH), 3355 (N–H), 1644 (C=O), 1547, 1548, 1538, 1470, 1355, 1265 (C=C), 1232 (C–N), 1077 (C–O); HRMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{25}NO_2$: 406.1778, found: 406.1784.

4.1.10. 1-Hydroxy-N-(3-(1-hydroxynaphthalen-2-yl)-2,2-dimethylpropyl)-2-naphthamide (**16**)

Boron tribromide (0.15 mL, 1.544 mmol) was added dropwise over 2 min at 0 °C to a stirred solution of methyl naphthyl ether **12** (300 mg, 0.702 mmol) in dry dichloromethane (30 mL) and the reaction mixture was further stirred at room temperature for 2 h. The reaction mixture was cooled to 0 °C then cold water was added to the reaction mixture and extracted with dichloromethane (3 × 30 mL). The combined organic phases were washed with water, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 7% v/v ethyl acetate–hexane to afford product **16** as a pale yellow oil (207.6 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.86 (s, 1H, OH), 8.32 (dd, *J* = 8.2, 0.7 Hz, 1H, ArH), 7.98 (d, *J* = 8.4 Hz, 1H, ArH), 7.79–7.75 (m, 1H, ArH), 7.62–7.58 (m, 1H, ArH), 7.49–7.44 (m, 2H, ArH), 7.44–7.39 (m, 2H, ArH), 7.38 (d, *J* = 8.4 Hz, 1H, ArH), 7.18 (d, *J* = 8.4 Hz, 1H, ArH), 7.12 (d, *J* = 8.8 Hz, 1H, ArH), 7.04 (d, *J* = 8.8 Hz, 1H, ArH), 6.28 (s, 1H, OH), 3.15 (d, *J* = 6.5 Hz, 2H, CH_2–NH), 2.77 (s, 2H, CH_2–Ar), 0.99 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.69 (C=O), 160.46 (C), 148.32 (C), 136.13 (C), 133.55 (C), 130.71 (CH), 128.69 (CH), 128.20 (CH), 127.20 (CH), 125.83 (CH), 125.80 (CH), 125.72 (CH), 125.65 (C), 124.37 (C), 123.77 (CH), 120.70 (CH), 120.69 (CH), 119.72 (C), 119.70 (CH), 118.06 (CH), 106.88 (C), 47.30 (CH_2N), 39.73 (CH_2), 37.28 (C), 26.33 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3375 (NH), 3239 (OH), 3056 (CH), 2958, 2921 (CH_3), 2865 (CH_2), 1609 (C=O), 1595, 1554, 1503, 1469, 1394, 1288 (C=C), 1226 (C–N), 1181 (C–O); HRMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{25}NO_3$: 422.1732, found: 422.1733.

4.1.11. N-(3-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl)-2-benzamide (**17**)

A solution of Fremmy's salt (1.6799 g, 6.268 mmol) in water (10 mL) was added to a stirred solution of **13** (767.7 mg, 2.238 mmol) in MeOH–DMF (3:1) (20 mL). After stirring for 10 h at room temperature, cold water was added and the reaction mixture was extracted with dichloromethane (3 × 30 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 15% v/v ethyl acetate–hexane to afford product **17** as a yellow solid (547.6 mg, 70%). mp: 155–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09–8.06 (m, 1H, ArH), 8.03–8.00 (m, 1H, ArH), 7.95–7.91 (m, 2H, ArH), 7.71–7.67 (m, 2H, ArH), 7.52–7.40 (m, 4H, ArH), 6.80 (s, 1H, ArH), 3.06 (d, *J* = 6.7 Hz, 2H, CH_2–NH), 2.49 (s, 2H, CH_2–Ar), 0.98 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.85 (C=O), 184.37 (C=O), 167.25 (C=O), 148.11 (C), 138.95 (CH), 134.69 (C), 134.19 (CH), 133.78 (CH), 132.07 (C), 131.88 (C), 131.33 (CH), 128.57 (2× CH), 127.07 (CH), 127.01 (2× CH), 126.18 (CH), 47.05 (CH_2N), 38.08 (CH_2), 37.40 (C), 26.04 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3405 (NH), 3066 (CH), 2962, 2922 (CH_3), 2870 (CH_2), 1667, 1660, 1651 (C=O), 1595, 1532, 1325, 1300, 1273 (C=C), 1184 (C–N); HRMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{21}NO_3$: 370.1419, found: 370.1422.

4.1.12. N-(3-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl)-2-hydroxybenzamide (**18**)

A solution of Fremmy's salt (492 mg, 1.836 mmol) in water (6 mL) was added to a stirred solution of **14** (80 mg, 0.229 mmol) in MeOH–DMF (3:1) (20 mL). After stirring for 7 h at room temperature, cold water was added and the reaction mixture was extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 10% v/v ethyl acetate–hexane to afford product **18** as a yellow solid (81.5 mg, 98%). mp: 168 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.58 (s, 1H, PhOH), 8.16 (ddd, *J* = 3.5, 2.3, 0.5 Hz, 1H, ArH), 8.08 (ddd, *J* = 4.0, 2.3, 0.5 Hz, 1H, ArH), 7.94 (t, *J* = 6.0 Hz, 1H, N*H*–CH_2),

7.83 (dd, J = 7.9, 1.5 Hz, 1H, ArH), 7.80–7.73 (m, 2H, ArH), 7.42 (ddd, J = 8.5, 7.3, 1.5 Hz, 1H, ArH), 7.00–6.96 (m, 1H, ArH), 6.95 (dd, J = 7.0, 1.0 Hz, 1H, ArH), 6.86 (s, 1H, ArH), 3.07 (d, J = 6.7 Hz, 2H, CH_2–NH), 2.53 (d, J = 0.6 Hz, 2H, CH_2–Ar), 1.05 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.31 (C=O), 184.26 (C=O), 170.02 (C=O), 161.78 (C), 147.77 (C), 139.30 (CH), 134.39 (CH), 134.00 (CH), 133.87 (CH), 132.07 (C), 131.80 (C), 127.17 (CH), 126.26 (CH), 125.60 (CH), 118.72 (CH), 118.50 (CH), 114.49 (C), 46.12 (CH_2N), 38.09 (CH_2), 37.38 (C), 26.15 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3404 (NH), 3062 (CH), 2963, 2920 (CH_3), 2870 (CH_2), 1663, 1647 (C=O), 1536, 1491, 1369, 1330, 1303, 1274, 1254 (C=C), 1228 (C–N); HRMS (ESI+): m/z [M + H]$^+$ calcd for $C_{22}H_{21}NO_4$: 364.1549, found: 364.1554.

4.1.13. N-(3-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl)-2-naphthamide (**19**)

A solution of Fremmy's salt (142 mg, 0.532 mmol) in water (3 mL) was added to a stirred solution of **15** (34 mg, 0.089 mmol) in MeOH–DMF (3:1) (4 mL) and 1 M NaOAc 0.12 mL. After stirring for 7 h at room temperature, cold water was added and the reaction mixture was extracted with dichloromethane (3 × 10 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 20% v/v ethyl acetate–hexane to afford product **19** as a yellow oil (31.1 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (s, 1H, ArH), 8.12–8.09 (m, 1H, ArH), 8.05–8.01 (m, 1H, ArH), 8.00 (dd, J = 8.6, 1.8 Hz, 1H, ArH), 7.94 (dd, J = 6.4, 2.9 Hz, 1H, ArH), 7.90 (d, J = 8.6 Hz, 1H, ArH), 7.84 (dd, J = 6.5, 2.8 Hz, 1H, ArH), 7.72–7.68 (m, 1H, ArH), 7.64 (t, J = 6.6 Hz, 1H, ArH), 7.52–7.48 (m, 1H, ArH), 6.83 (s, 1H, ArH), 3.12 (d, J = 6.6 Hz, 1H, CH_2–NH), 2.53 (s, 1H, CH_2–Ar), 1.02 (s, 1H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.95 (C=O), 184.42 (C=O), 167.32 (C=O), 148.17 (C), 139.03 (CH), 134.77 (C), 134.24 (CH), 133.83 (CH), 132.78 (C), 132.13 (C), 131.92 (C), 129.12 (CH), 128.44 (CH), 127.72 (CH), 127.67 (CH), 127.54 (CH), 127.13 (CH), 126.63 (CH), 126.24 (CH), 123.66 (CH), 47.19 (CH_2N), 38.17 (CH_2), 37.50 (C), 26.14 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3404 (NH), 3058 (CH), 2962, 2926 (CH_3), 2870 (CH_2), 1663 (C=O), 1595, 1535, 1327, 1301, 1272 (C=C), 1202 (C–N); HRMS (ESI+): m/z [M + Na]$^+$ calcd for $C_{26}H_{23}NO_3$: 420.1576, found: 420.1571.

4.1.14. N-(3-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl)-1-hydroxy-2-naphthamide (**20**)

A solution of Fremmy's salt (804 mg, 3.0 mmol) in water (5 mL) was added to a stirred solution of **16** (200 mg, 0.5 mmol) in MeOH–DMF (3:1) (20 mL). After stirring for 6 h at room temperature, cold water was added and the reaction mixture was extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 8% v/v ethyl acetate–hexane to afford product **20** as a yellow solid (179.8 mg, 87%). mp: 154–155 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45–8.40 (m, 1H, ArH), 8.21–8.17 (m, 1H, ArH), 8.11–8.06 (m, 1H, ArH), 7.97 (t, J = 6.2 Hz, 1H, NH–CH_2), 7.81 (d, J = 8.8 Hz, 1H, ArH), 7.80–7.75 (m, 3H, ArH), 7.58 (ddd, J = 8.2, 6.9, 1.4 Hz, 1H, ArH), 7.51 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H, ArH), 7.39 (d, J = 8.7 Hz, 1H, ArH), 6.88 (s, 1H, ArH), 3.12 (d, J = 6.6 Hz, 2H, CH_2–NH), 2.56 (s, 2H, CH_2–Ar), 1.07 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.33 (C=O), 184.33 (C=O), 170.74 (C=O), 160.73 (C), 147.88 (C), 139.30 (CH), 136.28 (C), 134.40 (CH), 133.89 (CH), 132.11 (C), 131.85 (C), 128.72 (CH), 127.28 (CH), 127.23 (CH), 126.28 (CH), 125.74 (C), 125.72 (C), 125.70 (CH), 123.83 (CH), 121.21 (CH), 118.24 (CH), 106.98 (C), 46.21 (CH_2N), 38.16 (CH_2), 37.45 (C), 26.20 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3400 (NH), 3055 (CH), 2961, 2921 (CH_3), 2863 (CH_2), 1661, 1622 (C=O), 1594, 1540, 1504, 1470, 1394, 1332, 1302, 1274, 1255 (C=C), 1210 (C–N), 1178 (C–O); HRMS (ESI+): m/z [M + Na]$^+$ calcd for $C_{26}H_{23}NO_4$: 436.1525, found: 436.1524.

4.1.15. N-(3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl)-2-benzamide (**21**)

The mixture of naphthoquinone **17** (506 mg, 1.457 mmol), *tert*-butyl hydroperoxide (TBHP) (70% in H_2O) (2.5 mL, 17.478 mmol) in THF (35 mL) was stirred at room temperature for 15 min. Triton B (40% in H_2O) (1.7 mL, 4.370 mmol) was added dropwise to the reaction mixture and continuously stirred for 30 min. The reaction mixture was cooled to 0 °C, acidified with 10% HCl to pH = 1, extracted with dichloromethane (3 × 30 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 20% v/v ethyl acetate–hexane to afford product **21** as a yellow solid (499 mg, 94%). mp: 144–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (ddd, J = 7.7, 1.4, 0.5 Hz, 1H, ArH), 8.05 (ddd, J = 7.5, 1.5, 0.5 Hz, 1H, ArH), 7.96–7.95 (m, 1H, ArH), 7.94–7.93 (m, 1H, ArH), 7.82 (t, J = 6.1 Hz, 1H, NH–CH_2), 7.72 (td, J = 7.6, 1.5 Hz, 1H, ArH), 7.66 (td, J = 7.5, 1.4 Hz, 1H, ArH), 7.49–7.40 (m, 4H, ArH), 3.07 (d, J = 6.7 Hz, 2H, CH_2–NH), 2.57 (s, 2H, CH_2–Ar), 0.98 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.29 (C=O), 180.88 (C=O), 167.24 (C=O), 155.17 (C), 135.17 (CH), 134.97 (C), 133.34 (CH), 132.78 (C), 131.21 (CH), 129.34 (C), 128.55 (2× CH), 127.27 (CH), 127.06 (2× CH), 126.37 (CH), 121.50 (C), 47.31 (CH_2N), 38.57 (CH_2), 31.99 (C), 26.40 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3379 (NH), 3064 (CH), 2962, 2925 (CH_3), 2865 (CH_2), 1664, 1647 (C=O), 1596, 1577, 1536, 1490, 1362, 1274, 1216 (C=C), 1183 (C–N), 1129 (C–O); HRMS (ESI+): m/z [M + Na]$^+$ calcd for $C_{22}H_{21}NO_4$: 386.1368, found: 386.1367.

4.1.16. 2-Hydroxy-N-(3-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl)benzamide (**22**)

A mixture of naphthoquinone **18** (15 mg, 0.041 mmol) and *tert*-butyl hydroperoxide (TBHP) (70% in H_2O) (0.071 mL, 0.495 mmol) in THF (2 mL) was stirred at room temperature for 15 min. Triton B (40% in H_2O) (0.06 mL, 0.164 mmol) was added dropwise to the reaction mixture and continuously stirred for 5 min. The reaction mixture was cooled to 0 °C, acidified with 10% HCl to pH 1, extracted with dichloromethane (3 × 15 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 20% v/v ethyl acetate–hexane to afford product **22** as a yellow solid (14.5 mg, 93%). mp: 182–183 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.65 (s, 1H, PhOH), 8.24–8.20 (m, 1H, ArH), 8.13 (ddd, J = 7.7, 1.4, 0.4 Hz, 1H, ArH), 8.08–8.05 (m, 1H, ArH), 7.79 (dd, J = 7.9, 1.6 Hz, 1H, ArH), 7.74 (td, J = 7.6, 1.5 Hz, 1H, ArH), 7.68 (td, J = 7.5, 1.4 Hz, 1H, ArH), 7.36 (ddd, J = 8.7, 7.2, 1.6 Hz, 1H, ArH), 6.94 (dd, J = 8.4, 0.9 Hz, 1H, ArH), 6.90 (ddd, J = 8.0, 7.3, 1.2 Hz, 1H, ArH), 3.04 (d, J = 6.8 Hz, 2H, CH_2–NH), 2.56 (s, 2H, CH_2–Ar), 0.99 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.69 (C=O), 180.81 (C=O), 170.01 (C=O), 161.80 (C), 155.43 (C), 135.27 (CH), 133.86 (CH), 133.49 (CH), 132.72 (C), 129.32 (C), 127.37 (CH), 126.48 (CH), 125.70 (CH), 121.18 (C), 118.68 (CH), 118.47 (CH), 114.73 (C), 46.57 (CH_2N), 38.54 (C), 31.95 (C), 26.42 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3425 (OH), 3381 (NH), 3055 (CH), 2957, 2924 (CH_3), 2851 (CH_2), 1675, 1640 (C=O), 1596, 1546, 1367, 1273 (C=C), 1221 (C–N), 1178 (C–O); HRMS (ESI+): m/z [M + H]$^+$ calcd for $C_{22}H_{21}NO_5$: 380.1498, found: 380.1502.

4.1.17. N-(3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl)-2-naphthamide (**23**)

The mixture of naphthoquinone **19** (40 mg, 0.1 mmol), TBHP (70% in H_2O) (0.17 mL, 1.2 mmol) in THF (3 mL) was stirred at room

temperature for 15 min. Triton B (40% in H_2O) (0.12 mL, 0.3 mmol) was added dropwise to the reaction mixture and continuously stirred for 30 min. The reaction mixture was cooled to 0 °C, acidified with 10% HCl to pH 1, extracted with dichloromethane (3 × 15 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 20% v/v ethyl acetate–hexane to afford the product **23** as a yellow solid (36 mg, 87%). mp: 134–135 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47 (d, J = 1.3 Hz, 1H, ArH), 8.12 (ddd, J = 7.7, 1.3, 0.4 Hz, 1H, ArH), 8.05 (ddd, J = 7.5, 1.4, 0.4 Hz, 1H, ArH), 8.01 (dd, J = 8.6, 1.8 Hz, 1H, ArH), 7.99–7.95 (m, 1H, ArH), 7.93 (dd, J = 6.5, 2.9 Hz, 1H, ArH), 7.89 (d, J = 8.7 Hz, 1H, ArH), 7.83 (dd, J = 6.5, 2.8 Hz, 1H, ArH), 7.72 (td, J = 7.6, 1.5 Hz, 1H, ArH), 7.66 (td, J = 7.5, 1.4 Hz, 1H, ArH), 7.51–7.47 (m, 2H, ArH), 3.13 (d, J = 6.7 Hz, 2H, CH_2–NH), 2.61 (s, 2H, CH_2–Ar), 1.02 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.32 (C=O), 180.90 (C=O), 167.28 (C=O), 155.20 (C), 135.18 (CH), 134.71 (C), 133.34 (CH), 132.80 (C), 132.19 (C), 129.35 (C), 129.12 (CH), 128.36 (CH), 127.69 (CH), 127.65 (CH), 127.43 (CH), 127.29 (CH), 126.54 (CH), 126.38 (CH), 123.73 (CH), 121.52 (C), 47.46 (CH_2N), 38.63 (CH_2), 32.06 (C), 26.45 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3378 (NH), 3058 (CH), 2962, 2921 (CH_3), 2870 (CH_2), 1663, 1646 (C=O), 1595, 1536, 1365, 1300, 1273 (C=C), 1215 (C–N), 1130 (C–O); HRMS (ESI+): m/z [M + Na]$^+$ calcd for $C_{26}H_{23}NO_4$: 436.1525, found: 436.1518.

4.1.18. 1-Hydroxy-N-(3-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl)-2-naphthamide (*24*)

A mixture of naphthoquinone **20** (20 mg, 0.048 mmol), *tert*-butyl hydroperoxide (TBHP) (70% in H_2O) (0.08 mL, 0.580 mmol) in THF (2 mL) was stirred at room temperature for 15 min. Triton B (40% in H_2O) (0.08 mL, 0.192 mmol) was added dropwise to the reaction mixture and continuously stirred for 10 min. The reaction mixture was cooled to 0 °C, acidified with 10% HCl to pH 1, extracted with dichloromethane (3 × 15 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 15% v/v ethyl acetate–hexane to afford product **24** as a yellow solid (16.3 mg, 78%). mp: 214–215 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40–8.35 (m, 1H, ArH), 8.29–8.22 (m, 1H, ArH), 8.17–8.14 (m, 1H, ArH), 8.09–8.05 (m, 1H, ArH), 7.78 (d, J = 8.8 Hz, 1H, ArH), 7.73 (dd, J = 7.6, 1.4 Hz, 1H, ArH), 7.72 (d, J = 7.8 Hz, 1H, ArH), 7.68 (td, J = 7.5, 1.3 Hz, 1H, ArH), 7.62 (s, 1H), 7.52 (ddd, J = 8.2, 7.0, 1.4 Hz, 1H, ArH), 7.46 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H, ArH), 7.32 (d, J = 8.8 Hz, 1H, ArH), 3.09 (d, J = 6.5 Hz, 2H, CH_2–NH), 2.59 (s, 2H, CH_2–Ar), 1.01 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.67 (C=O), 180.82 (C=O), 170.69 (C=O), 160.69 (C), 155.37 (C), 136.23 (C), 135.29 (CH), 133.48 (CH), 132.76 (C), 129.32 (C), 128.61 (CH), 127.41 (CH), 127.27 (CH), 126.47 (CH), 125.62 (CH), 123.83 (CH), 121.38 (CH), 121.24 (C), 118.13 (CH), 107.20 (C), 46.64 (CH_2N), 38.59 (CH_2), 32.00 (C), 26.44 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3391 (NH), 3364 (OH), 3062 (CH), 2957, 2926 (CH_3), 2870 (CH_2), 1671, 1626 (C=O), 1596, 1547, 1503, 1463, 1363, 1276 (C=C), 1216 (C–N), 1177 (C–O); HRMS (ESI+): m/z [M + Na]$^+$ calcd for $C_{26}H_{23}NO_5$: 452.1474, found: 452.1485.

4.1.19. N-(3-(3-Methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl)benzamide (*25*)

To the stirred solution of naphthoquinone alcohol **21** (24.6 mg, 0.068 mmol) in acetone (3 mL) was added K_2CO_3 (12.2 mg, 0.088 mmol). The reaction mixture was stirred for 1 h at room temperature until the color of the reaction was changed from yellow to dark red. Then Me_2SO_4 (0.008 mL, 0.088 mmol) was added dropwise to the dark red solution and continuously stirred for 8 h at room temperature. The reaction mixture was cooled to 0 °C, acidified with 10% HCl to pH 1, extracted with dichloromethane (3 × 15 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 20% v/v ethyl acetate–hexane to afford product **25** as a yellow oil (21.4 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04–8.01 (m, 1H, ArH), 7.99–7.96 (m, 1H, ArH), 7.94–7.93 (m, 1H, ArH), 7.93–7.91 (m, 1H, ArH), 7.77 (t, J = 6.2 Hz, 1H, ArH), 7.67–7.64 (m, 1H, ArH), 7.64–7.62 (m, 1H, ArH), 7.47–7.39 (m, 3H, ArH), 4.11 (s, 3H, OCH_3), 3.03 (d, J = 6.5 Hz, 2H, CH_2NH), 2.55 (s, 2H, CH_2–Ar), 0.95 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.86 (C=O), 181.07 (C=O), 167.19 (C=O), 159.75 (C), 134.94 (C), 133.94 (CH), 133.54 (CH), 131.67 (C), 131.42 (C), 131.17 (CH), 128.49 (2× CH), 126.98 (2× CH), 126.54 (CH), 126.18 (CH), 61.15 (OCH_3), 47.36 (CH_2N), 38.12 (CH_2), 31.90 (C), 26.36 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3380 (NH), 3063 (CH), 2962, 2921 (CH_3), 2872 (CH_2), 1663, 1646 (C=O), 1598, 1576, 1536, 1489, 1365, 1271 (C=C), 1216 (C–N), 1130 (C–O); HRMS (ESI+): m/z [M + Na]$^+$ calcd for $C_{23}H_{23}NO_4$: 400.1519, found: 400.1517.

4.1.20. 2-Methoxy-N-(3-(3-methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl)benzamide (*26*)

To a stirred solution of naphthoquinone alcohol **22** (40 mg, 0.105 mmol) in acetone (3 mL), K_2CO_3 (17 mg) was added. The reaction mixture was stirred for at room temperature until the color of the reaction was changed from yellow to dark red. Then Me_2SO_4 (0.01 mL) was added dropwise to the dark red solution and continuously stirred for 8 h at room temperature. The reaction mixture was cooled to 0 °C, acidified with 10% HCl to pH 1, extracted with dichloromethane (3 × 15 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 15% v/v ethyl acetate–hexane to afford product **26** as a yellow oil (34 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.61 (t, J = 5.8 Hz, 1H, ArH), 8.13 (dd, J = 7.8, 1.7 Hz, 1H, ArH), 8.00–7.95 (m, 2H, ArH), 7.64–7.60 (m, 2H, ArH), 7.37 (ddd, J = 8.3, 7.3, 1.9 Hz, 1H, ArH), 7.00 (ddd, J = 7.8, 7.4, 1.0 Hz, 1H, ArH), 6.94 (dd, J = 8.3, 0.5 Hz, 1H, ArH), 4.09 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 3.15 (d, J = 6.3 Hz, 2H, CH_2–NH), 2.58 (s, 2H, CH_2–Ar), 0.94 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.09 (C=O), 181.34 (C=O), 165.42 (C=O), 159.23 (C), 157.60 (C), 133.79 (CH), 133.27 (CH), 132.39 (CH), 132.34 (CH), 131.99 (C), 131.84 (C), 131.51 (C), 126.35 (CH), 126.04 (CH), 122.10 (C), 121.08 (CH), 111.23 (CH), 60.95 (OCH_3), 55.88 (OCH_3), 48.34 (CH_2N), 37.68 (CH_2), 32.14 (C), 26.16 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3377 (NH), 3068 (CH), 2959, 2921 (CH_3), 2851 (CH_2), 1724, 1643 (C=O), 1599, 1538, 1475, 1464, 1364, 1299, 1268 (C=C), 1216 (C–N), 1022 (C–O); HRMS (ESI+): m/z [M + Na]$^+$ calcd for $C_{24}H_{25}NO_5$: 430.1625, found: 430.1633.

4.1.21. N-(3-(3-Methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl)-2-naphthamide (*27*)

To the stirred solution of naphthoquinone alcohol **23** (25 mg, 0.06 mmol) in acetone (3 mL) was added K_2CO_3 (12 mg, 0.091 mmol). The reaction mixture was stirred for 1 h at room temperature until the color of the reaction was changed from yellow to dark red. Then Me_2SO_4 (0.009 mL) was added dropwise to the dark red solution and continuously stirred for 9 h at room temperature. The reaction mixture was cooled to 0 °C, acidified with 10% HCl to pH 1, extracted with dichloromethane (3 × 15 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 15% v/v ethyl acetate–hexane to afford product **27** as a yellow oil (22.31 mg, 87%). ^{1}H NMR

(400 MHz, $CDCl_3$): δ = 8.46 (s, 1H, ArH), 8.08–8.03 (m, 1H, ArH), 8.01 (dd, J = 2.3, 1.1 Hz, 1H, ArH), 7.99 (dd, J = 2.8, 1.1 Hz, 1H, ArH), 7.93 (dd, J = 6.0, 2.8 Hz, 1H, ArH), 7.88 (d, J = 8.6 Hz, 1H, ArH), 7.83 (dd, J = 6.3, 2.9 Hz, 1H, ArH), 7.68–7.62 (m, 2H, ArH), 7.52–7.45 (m, 2H, ArH), 4.13 (s, 3H, OCH_3), 3.09 (d, J = 6.4 Hz, 2H, CH_2–NH), 2.60 (s, 2H, CH_2–Ar), 0.99 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.93 (C=O), 181.14 (C=O), 167.28 (C=O), 159.81 (C), 134.70 (C), 134.00 (CH), 133.60 (CH), 132.79 (C), 132.21 (C), 131.74 (C), 131.55 (C), 131.49 (C), 129.08 (CH), 128.36 (CH), 127.69 (CH), 127.59 (CH), 127.43 (CH), 126.62 (CH), 126.55 (CH), 126.24 (CH), 123.72 (CH), 61.22 (OCH_3), 47.55 (CH_2N), 38.22 (CH_2), 32.02 (C), 26.47 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3378 (NH), 3058 (CH), 2961, 2925 (CH_3), 2870 (CH_2), 1711, 1660, 1646 (C=O), 1597, 1536, 1466, 1366, 1299, 1271 (C=C), 1216 (C–N), 1129 (C–O); HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_{27}H_{25}NO_4$: 450.1676, found: 450.1672.

4.1.22. 1-Methoxy-N-(3-(3-methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl)-2-naphthamide (**28**)

To a stirred solution of naphthoquinone alcohol **24** (20 mg, 0.045 mmol) in acetone (2.5 mL) was added K_2CO_3 (8.1 mg, 0.059 mmol). The reaction mixture was stirred for 1 h at room temperature until the color of the reaction was changed from yellow to dark red. Then Me_2SO_4 (0.007 mL, 0.059 mmol) was added dropwise to the dark red solution and continuously stirred for 6 h at room temperature. The reaction mixture was cooled to 0 °C, acidified with 10% HCl to pH 1, extracted with dichloromethane (3 × 15 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 18% v/v ethyl acetate–hexane to afford product **28** as a yellow oil (17.6 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.58 (t, J = 6.2 Hz, 1H, N*H*–CH_2), 8.15 (dd, J = 6.2, 3.6 Hz, 1H, ArH), 8.06 (d, J = 8.7 Hz, 1H, ArH), 8.02–7.99 (m, 1H, ArH), 7.99–7.96 (m, 1H, ArH), 7.81 (dd, J = 6.0, 3.4 Hz, 1H, ArH), 7.64–7.60 (m, 3H, ArH), 7.51 (t, J = 3.4 Hz, 1H, ArH), 7.49 (t, J = 3.4 Hz, 1H, ArH), 4.11 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 3.24 (d, J = 6.4 Hz, 2H, C*H*$_2$–NH), 2.64 (s, 2H, CH_2–Ar), 0.99 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.06 (C=O), 181.30 (C=O), 165.94 (C=O), 159.28 (C), 155.18 (C), 136.45 (C), 133.85 (CH), 133.29 (CH), 133.03 (C), 132.11 (C), 131.85 (C), 131.50 (C), 128.12 (CH), 127.65 (CH), 127.61 (C), 127.13 (CH), 126.46 (CH), 126.40 (CH), 126.09 (CH), 124.40 (CH), 122.97 (CH), 63.48 (OCH_3), 61.09 (OCH_3), 48.59 (OCH_3), 37.82 (CH_2), 32.31 (C), 26.28 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3380 (NH), 3060 (CH), 2961, 2928 (CH_3), 2870, 2850 (CH_2), 1660, 1644, 1634 (C=O), 1596, 1538, 1520, 1455, 1371, 1338, 1273 (C=C), 1216 (C–N), 1082 (C–O); HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_{28}H_{27}NO_5$: 480.1781, found: 480.1779.

4.1.23. N-(3-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl)-2-methoxybenzamide (**29**)

To the stirred solution of naphthoquinone alcohol **18** (50 mg, 0.138 mmol) in acetone (4 mL) K_2CO_3 (25 mg) was added. The reaction mixture was stirred for at room temperature until the color of the reaction was changed from yellow to dark red. Then Me_2SO_4 (0.017 mL) was added dropwise to the dark red solution and continuously stirred for 8 h at room temperature. The reaction mixture was cooled to 0 °C, acidified with 10% HCl to pH 1, extracted with dichloromethane (3 × 15 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 15% v/v ethyl acetate–hexane to afford product **29** as a yellow oil (48.9 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (t, J = 5.7 Hz, 1H, N*H*–CH_2), 8.12 (dd, J = 7.8, 1.9 Hz, 1H, ArH), 8.03–7.97 (m, 2H, ArH), 7.66–7.63 (m, 2H, ArH), 7.37 (ddd, J = 8.3, 7.3, 1.9 Hz, 1H, ArH), 7.00 (ddd, J = 8.3, 7.6, 1.0 Hz, 1H, ArH), 6.94–6.91 (m, 1H, ArH), 6.79 (s, 1H, ArH), 4.01 (s, 3H, OCH_3), 3.18 (d, J = 6.3 Hz, 2H, C*H*$_2$–NH), 2.52 (s, 2H, CH_2–Ar), 0.96 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.76 (C=O), 184.62 (C=O), 165.43 (C=O), 157.54 (C), 148.71 (C), 138.10 (CH), 133.77 (CH), 133.60 (CH), 132.55 (CH), 132.38 (CH), 132.09 (C), 132.03 (C), 126.81 (CH), 125.98 (CH), 121.71 (C), 121.13 (CH), 111.19 (CH), 55.91 (OCH_3), 48.24 (CH_2N), 38.22 (CH_2), 36.87 (C), 25.83 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3383 (NH), 3072 (CH), 2962 (CH_3), 2871, 2841 (CH_2), 1667, 1657, 1651 (C=O), 1598, 1538, 1484, 1470, 1328, 1302, 1274, 1240 (C=C), 1106 (C–O), 1022 (C–N); HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_{23}H_{23}NO_4$: 400.1525, found: 400.1525.

4.1.24. N-(3-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl)-1-methoxy-2-naphthamide (**30**)

To a stirred solution of naphthoquinone alcohol **20** (50 mg, 0.121 mmol) in acetone (4 mL), K_2CO_3 (22 mg) was added. The reaction mixture was stirred for at room temperature until the color of the reaction was changed from yellow to dark red. Then Me_2SO_4 (0.015 mL) was added dropwise to the dark red solution and continuously stirred for 8 h at room temperature. The reaction mixture was cooled to 0 °C, acidified with 10% HCl to pH 1, extracted with dichloromethane (3 × 15 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 15% v/v ethyl acetate–hexane to afford product **30** as a yellow oil (49.7 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (t, J = 6.3 Hz, 1H, N*H*–CH_2), 8.16–8.13 (m, 1H, ArH), 8.06 (d, J = 8.7 Hz, 1H, ArH), 8.04–8.01 (m, 1H, ArH), 8.00–7.97 (m, 1H, ArH), 7.82–7.79 (m, 1H, ArH), 7.65–7.61 (m, 3H, ArH), 7.51 (dd, J = 6.3, 3.3 Hz, 2H, ArH), 6.82 (s, 1H, ArH), 4.07 (s, 3H, OCH_3), 3.30 (d, J = 6.4 Hz, 2H, C*H*$_2$–NH), 2.58 (s, 2H, CH_2–Ar), 1.01 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.42 (C=O), 188.21 (C=O), 184.65 (C=O), 155.29 (C), 148.55 (C), 138.27 (CH), 136.55 (C), 133.77 (CH), 133.65 (CH), 132.12 (C), 128.27 (C), 128.15 (CH), 127.75 (CH), 127.51 (C), 127.02 (CH), 126.88 (CH), 126.49 (C), 126.46 (CH), 126.05 (CH), 124.49 (CH), 122.98 (CH), 63.52 (OCH_3), 48.74 (CH_2N), 38.39 (CH_2), 36.93 (C), 25.83 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3381 (NH), 3060 (CH), 2963, 2929 (CH_3), 2870, 2851 (CH_2), 1663 (C=O), 1595, 1531, 1521, 1451, 1370, 1333, 1300, 1272 (C=C), 1205 (C–N), 1081 (C–O); HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{27}H_{25}NO_4$: 450.1681, found: 450.1686.

4.1.25. N-(3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl)-2-methoxybenzamide (**31**)

A mixture of naphthoquinone **29** (40 mg, 0.106 mmol), *tert*-butyl hydroperoxide (TBHP) (70% in H_2O) (0.14 mL, 0.954 mmol) in THF (2 mL) was stirred at room temperature for 15 min. Triton B (40% in H_2O) (0.13 mL, 0.318 mmol) was added dropwise to the reaction mixture and continuously stirred for 10 min. The reaction mixture was cooled to 0 °C, acidified with 10% HCl to pH 1, extracted with dichloromethane (3 × 15 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 15% v/v ethyl acetate–hexane to afford product **31** as a yellow solid (36.27 mg, 87%). mp: 162 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71 (t, J = 5.8 Hz, 1H, N*H*–CH_2), 8.19 (dd, J = 7.8, 1.8 Hz, 1H, ArH), 8.12–8.09 (m, 1H, ArH), 8.09–8.06 (m, 1H, ArH), 7.74 (td, J = 7.5, 1.5 Hz, 1H, ArH), 7.70–7.63 (m, 2H, ArH and OH), 7.42 (ddd, J = 8.2, 7.4, 1.9 Hz, 1H, ArH), 7.05 (td, J = 7.8, 0.9 Hz, 1H, ArH), 6.98 (d, J = 8.3 Hz, 1H, ArH), 4.05 (s, 3H, OCH_3), 3.23 (d, J = 6.4 Hz, 2H, C*H*$_2$–NH), 2.64 (s, 2H, CH_2–Ar), 1.01 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.43 (C=O), 181.09 (C=O), 165.48 (C=O), 157.63 (C), 154.67 (C), 134.95 (CH), 133.03 (CH), 132.86 (C), 132.38 (2× CH), 129.38 (C),

127.00 (CH), 126.16 (CH), 122.12 (C), 121.88 (C), 121.07 (CH), 111.21 (CH), 55.87 (OCH_3), 48.22 (CH_2N), 38.18 (CH_2), 32.14 (C), 26.16 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3373 (NH), 3171 (OH), 3074 (CH), 2962, 2925 (CH_3), 2870 (CH_2), 1667, 1650, 1644 (C=O), 1597, 1538, 1484, 1462, 1361, 1272, 1241, 1216 (C=C), 1130 (C–O), 1023 (C–N); HRMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{23}NO_5$: 416.1474, found: 416.1472.

4.1.26. N-(3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl)-1-methoxy-2-naphthamide (**32**)

A mixture of naphthoquinone **30** (40 mg, 0.094 mmol), *tert*-butyl hydroperoxide (TBHP) (70% in H_2O) (0.12 mL, 0.842 mmol) in THF (4 mL) was stirred at room temperature for 15 min. Triton B (40% in H_2O) (0.11 mL, 0.281 mmol) was added dropwise to the reaction mixture and continuously stirred for 10 min. The reaction mixture was cooled to 0 °C, acidified with 10% HCl to pH 1, extracted with dichloromethane (3 × 15 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 15% v/v ethyl acetate–hexane to afford product **32** as a yellow solid (34.86 mg, 84%). mp: 128–129 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.65 (t, *J* = 6.2 Hz, 1H, N*H*–CH_2), 8.14 (dd, *J* = 6.3, 3.5 Hz, 1H, ArH), 8.06 (d, *J* = 8.6 Hz, 1H, ArH), 8.06 (dd, *J* = 8.1, 1.5 Hz, 1H, ArH), 8.01 (dd, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.79 (dd, *J* = 6.1, 3.3 Hz, 1H, ArH), 7.67 (td, *J* = 7.6, 1.4 Hz, 1H, ArH), 7.62–7.58 (m, 2H, ArH), 7.50 (d, *J* = 3.3 Hz, 1H, ArH), 7.48 (d, *J* = 3.2 Hz, 1H, ArH), 4.06 (s, 3H, OCH_3), 3.27 (d, *J* = 6.4 Hz, 2H, C*H*$_2$–NH), 2.64 (s, 2H, CH_2–Ar), 1.02 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.42 (C=O), 181.04 (C=O), 165.98 (C=O), 155.22 (C), 154.67 (C), 136.43 (C), 134.95 (CH), 133.00 (CH), 132.82 (C), 129.34 (C), 128.09 (CH), 127.62 (CH), 127.57 (C), 127.09 (CH), 127.04 (CH), 126.36 (CH), 126.15 (CH), 124.36 (CH), 122.97 (CH), 122.50 (C), 121.72 (C), 63.49 (OCH_3), 48.57 (CH_2N), 38.19 (CH_2), 32.32 (C), 26.22 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3377 (NH), 3058 (CH), 2959, 2924 (CH_3), 2852 (CH_2), 1727, 1662, 1646 (C=O), 1528, 1459, 1367, 1272 (C=C), 1213 (C–N), 1083 (C–O); HRMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{27}H_{25}NO_5$: 466.1625, found: 466.1623.

4.1.27. N-(3-(1-Hydroxynaphthalen-2-yl)-2,2-dimethylpropyl)-2,5-dimethoxybenzamide (**36**)

To the solution of **4** (100 mg, 0.411 mmol) in dry dichloromethane (15 mL) under nitrogen atmosphere was added boron tribomide (0.047 mL) dropwise at 0 °C. The reaction mixture was continuously stirred at room temperature for 7 h. The reaction mixture was cooled to 0 °C then neutralized by adding ammonia dropwise, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The crude residue **33** (101.3 mg) was further underwent amide formation without purification. 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) (137 mg, 0.494 mmol) was added to a mixture of 2,5-dimethoxybenzoic acid (**34**) (75 mg, 0.494 mmol) and crude amine **33** (101.3 mg, 0.412 mmol) in MeOH (10 mL) at room temperature. After 1 h with stirring at room temperature, the MeOH was evaporated. The resulting residue was dissolved in ether, and washed successively with saturated sodium carbonate, water, 1 N HCl, water and brine and dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash column chromatography eluting with 15% v/v ethyl acetate–hexane to give **36** as a colorless oil (100 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39 (t, *J* = 5.9 Hz, 1H, N*H*–CH_2), 8.22–8.19 (m, 1H, ArH), 8.11 (s, 1H, OH), 7.76 (d, *J* = 3.3 Hz, 1H, ArH), 7.69 (dd, *J* = 7.1, 2.2 Hz, 1H, ArH), 7.41–7.38 (m, 1H, ArH), 7.37–7.34 (m, 1H, ArH), 7.26 (d, *J* = 8.3 Hz, 1H, ArH), 7.09 (d, *J* = 8.4 Hz, 1H, ArH), 6.95 (dd, *J* = 9.0, 3.3 Hz, 1H, ArH), 6.86 (d, *J* = 9.0 Hz, 1H, ArH), 3.89 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.29 (d, *J* = 6.5 Hz, 2H, C*H*$_2$–NH), 2.76 (s, 2H, CH_2–Ar), 0.97 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.16 (C=O), 154.01 (C), 151.81 (C), 150.06 (C), 143.26 (C), 131.33 (CH), 127.31 (CH), 125.56 (CH), 125.41 (C), 124.97 (CH), 121.99 (CH), 121.70 (C), 119.80 (CH), 118.91 (CH), 117.87 (C), 115.61 (CH), 113.02 (CH), 56.69 (OCH_3), 55.91 (OCH_3), 49.50 (CH_2N), 39.99 (CH_2), 37.47 (C), 26.77 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3380 (NH), 3169 (OH), 3056 (CH), 2960, 2929 (CH_3), 2865, 2833 (CH_2), 1638 (C=O), 1605, 1579, 1535, 1493, 1466, 1360, 1280 (C=C), 1218 (C–N), 1043, 1023 (C–O); HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{27}NO_4$: 416.1832, found: 416.1839.

4.1.28. N-(3-(1-Hydroxynaphthalen-2-yl)-2,2-dimethylpropyl)-1,4-dimethoxy-2-naphthamide (**37**)

To a solution of **4** (200 mg, 0.822 mmol) in dry dichloromethane (25 mL) under nitrogen atmosphere was added boron tribomide (0.09 mL, 0.986 mmol) dropwise at 0 °C. The reaction mixture was continuously stirred at room temperature for 7 h. The reaction mixture was cooled to 0 °C then neutralized by adding ammonia dropwise, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The crude residue **33** (212.1 mg) was further underwent amide formation without purification. 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) (307.2 mg, 1.110 mmol) was added to a mixture of 2,5-dimethoxy naphthoic acid (**35**) (257.7 mg, 1.110 mmol) and amine **33** (212.1 mg, 0.925 mmol) in MeOH (30 mL) at room temperature. After 1 h with stirring at room temperature, the MeOH was evaporated. The resulting residue was dissolved in ether, and washed successively with saturated sodium carbonate, water, 1 N hydrochloric acid, water and brine and dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash column chromatography eluting with 15% v/v ethyl acetate–hexane to give **37** as a colorless oil (247.8 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.64 (t, *J* = 6.3 Hz, 1H, N*H*–CH_2), 8.25 (d, *J* = 2.8 Hz, 1H, ArH), 8.24 (d, *J* = 2.6 Hz, 1H, ArH), 8.06–8.03 (m, 1H, ArH), 7.90 (s, 1H, OH), 7.76 (dd, *J* = 6.8, 2.5 Hz, 1H, ArH), 7.56–7.55 (m, 1H, ArH), 7.55–7.53 (m, 1H, ArH), 7.47 (s, 1H, ArH), 7.45–7.41 (m, 2H, ArH), 7.35 (d, *J* = 8.4 Hz, 1H, ArH), 7.18 (d, *J* = 8.4 Hz, 1H, ArH), 3.97 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.40 (d, *J* = 6.5 Hz, 2H, C*H*$_2$–NH), 2.88 (s, 2H, CH_2–Ar), 1.07 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.71 (C=O), 152.04 (C), 149.83 (C), 148.93 (C), 133.59 (C), 131.13 (CH), 128.40 (C), 128.05 (C), 127.50 (CH), 127.22 (CH), 127.02 (CH), 125.50 (CH), 125.25 (C), 125.05 (CH), 122.61 (CH), 122.54 (CH), 121.52 (CH), 121.40 (C), 119.23 (CH), 118.55 (C), 103.66 (CH), 63.36 (OCH_3), 55.78 (OCH_3), 49.41 (CH_2N), 40.01 (CH_2), 37.48 (C), 26.52 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3347 (NH), 3226 (OH), 3057 (CH), 2960, 2936 (CH_3), 2868 (CH_2), 1638 (C=O), 1594, 1534, 1458, 1371, 1268, 1235 (C=C), 1205 (C–N), 1116, 1091 (C–O); HRMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{28}H_{29}NO_4$: 466.1989, found: 466.1998.

4.1.29. N-(3-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl)-2,5-dimethoxybenzamide (**38**)

A solution of Fremmy's salt (2.673 g, 9.973 mmol) in water (18 mL) was added to a stirred solution of **36** (654 mg, 1.662 mmol) in MeOH–DMF (3:1) (50 mL). After stirring for 7 h at room temperature, cold water was added and the reaction mixture was extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 10% v/v ethyl acetate–hexane to afford product **38** as a yellow solid (524.6 mg, 78%). mp: 118–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54 (t, *J* = 5.8 Hz, 1H, N*H*–CH_2), 8.03–8.00 (m, 1H, ArH), 8.00–7.97 (m, 1H, ArH), 7.70 (d, *J* = 3.2 Hz, 1H, ArH), 7.66–7.63 (m, 2H, ArH), 6.92 (dd, *J* = 9.0, 3.2 Hz,

1H, ArH), 6.86 (d, J = 9.0 Hz, 1H, ArH), 6.79 (s, 1H, ArH), 3.97 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.19 (d, J = 6.3 Hz, 2H, CH_2–NH), 2.52 (d, J = 0.6 Hz, 2H, CH_2–Ar), 0.96 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.72 (C=O), 184.63 (C=O), 165.20 (C=O), 153.79 (C), 151.85 (C), 148.72 (C), 138.08 (CH), 133.77 (CH), 133.59 (CH), 132.10 (C), 132.04 (C), 126.83 (CH), 125.99 (CH), 122.19 (C), 119.26 (CH), 115.65 (CH), 112.82 (CH), 56.49 (OCH_3), 55.82 (OCH_3), 48.40 (CH_2N), 38.24 (CH_2), 36.86 (C), 25.84 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3379 (NH), 3062 (CH), 2961, 2934 (CH_3), 2863, 2833 (CH_2), 1664, 1660, 1651 (C=O), 1593, 1547, 1538, 1494, 1470, 1366, 1328, 1304, 1275 (C=C), 1216 (C–N), 1042, 1021 (C–O); HRMS (ESI+): m/z [M + Na]$^+$ calcd for $C_{24}H_{25}NO_5$: 430.1625, found: 430.1620.

4.1.30. N-(3-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl)-1,4-dimethoxy-2-naphthamide (**39**)

A solution of Fremmy's salt (783 mg, 2.922 mmol) in water (9 mL) was added to a stirred solution of **37** (216 mg, 0.487 mmol) in MeOH–DMF (3:1) (20 mL). After stirring for 7 h at room temperature, cold water was added and the reaction mixture was extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 10% v/v ethyl acetate–hexane to afford product **39** as a yellow solid (209 mg, 94%). mp: 140 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.73 (t, J = 5.6 Hz, 1H, NH–CH_2), 8.28 (d, J = 7.8 Hz, 1H, ArH), 8.16 (d, J = 8.3 Hz, 1H, ArH), 8.13–8.08 (m, 1H, ArH), 8.08–8.03 (m, 1H, ArH), 7.73–7.68 (m, 2H, ArH), 7.63–7.57 (m, 2H, ArH), 7.49 (s, 1H, ArH), 6.90 (s, 1H, ArH), 4.10 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 3.39 (d, J = 6.2 Hz, 2H, CH_2–NH), 2.67 (s, 2H, CH_2–Ar), 1.10 (s, 6H, 2× CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.82 (C=O), 184.69 (C=O), 166.00 (C=O), 151.99 (C), 149.03 (C), 148.59 (C), 138.23 (CH), 133.76 (CH), 133.64 (CH), 132.10 (C), 132.04 (C), 128.39 (C), 128.21 (C), 127.19 (CH), 126.99 (CH), 126.88 (CH), 126.03 (CH), 122.79 (CH), 122.59 (CH), 121.65 (C), 103.81 (CH), 63.45 (OCH_3), 55.83 (OCH_3), 48.88 (CH_2N), 38.39 (CH_2), 36.94 (C), 25.86 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3381 (NH), 3072 (CH), 2961, 2929 (CH_3), 2871, 2841 (CH_2), 1661, 1613 (C=O), 1594, 1520, 1456, 1371, 1302, 1271 (C=C), 1204 (C–N), 115, 1091 (C–O); HRMS (ESI+): m/z [M + Na]$^+$ calcd for $C_{28}H_{27}NO_5$: 480.1781, found: 480.1776.

4.1.31. N-(3-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl)-2-hydroxy-5-methoxybenzamide (**40**)

Boron tribromide (0.004 mL, 0.04 mmol) was added dropwise over 1 min at −78 °C to a stirred solution of methyl ether **38** (12 mg, 0.03 mmol) in dry dichloromethane (1.5 mL) and the reaction mixture was further stirred at the same temperature for 2 h. The reaction mixture was cooled to 0 °C then cold water was added to the reaction mixture and extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with water, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 10% v/v ethyl acetate–hexane to afford product **40** as a pale yellow solid (10.4 mg, 90%). mp: 132–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.00 (s, 1H, OH), 8.09–8.06 (m, 1H, ArH), 8.05–8.02 (m, 1H, ArH), 7.88 (t, J = 6.3 Hz, 1H, NH–CH_2), 7.75–7.68 (m, 2H, ArH), 7.34 (d, J = 2.9 Hz, 1H, ArH), 7.00 (dd, J = 9.0, 2.9 Hz, 1H, ArH), 6.88 (d, J = 9.0 Hz, 1H, ArH), 6.82 (s, 1H, ArH), 3.86 (s, 3H, OCH_3), 3.01 (d, J = 6.7 Hz, 2H, CH_2–NH), 2.49 (s, 2H, CH_2–Ar), 1.00 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.49 (C=O), 184.24 (C=O), 169.75 (C=O), 155.92 (C), 151.85 (C), 147.74 (C), 139.42 (CH), 134.49 (CH), 133.91 (CH), 132.09 (C), 131.81 (C), 127.13 (CH), 126.33 (CH), 121.30 (CH), 119.28 (CH), 114.18 (C), 109.38 (CH), 55.95 (OCH_3), 46.11 (CH_2N), 38.01 (CH_2), 37.46 (C), 26.20 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3400 (NH), 3070 (CH), 2959, 2924 (CH_3), 2871, 2848 (CH_2), 1664, 1660, 1644 (C=O), 1599, 1548, 1538, 1494, 1371, 1331, 1303, 1275, 1240 (C=C), 1179 (C–N), 1039 (C–O); HRMS (ESI+): m/z [M + Na]$^+$ calcd for $C_{23}H_{23}NO_5$: 416.1468, found: 416.1467.

4.1.32. N-(3-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl)-1-hydroxy-4-methoxy-2-naphthamide (**41**)

Boron tribromide (0.022 mL, 0.236 mmol) was added dropwise over 2 min at −78 °C to a stirred solution of methyl naphthyl ether **39** (90 mg, 0.197 mmol) in dry dichloromethane (10 mL) and the reaction mixture was further stirred at the same temperature for 2 h. The reaction mixture was cooled to 0 °C then cold water was added to the reaction mixture and extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with water, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 10% v/v ethyl acetate–hexane to afford product **41** as a pale yellow solid (67.4 mg, 77%). mp: 132–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.47 (s, 1H, Ar–OH), 8.35 (ddd, J = 8.1, 1.5, 0.7 Hz, 1H, ArH), 8.15 (ddd, J = 8.3, 1.4, 0.7 Hz, 1H, ArH), 8.07–8.02 (m, 2H, ArH), 7.94 (t, J = 6.3 Hz, 1H, NH–CH_2), 7.75–7.68 (m, 2H, ArH), 7.55 (ddd, J = 8.3, 6.9, 1.5 Hz, 1H, ArH), 7.50 (ddd, J = 8.2, 6.9, 1.4 Hz, 1H, ArH), 7.16 (s, 1H, ArH), 6.84 (s, 1H, ArH), 4.11 (s, 3H, OCH_3), 3.05 (d, J = 6.6 Hz, 2H, CH_2–NH), 2.52 (s, 2H, CH_2–Ar), 1.03 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.67 (C=O), 184.20 (C=O), 170.65 (C=O), 154.98 (C), 147.80 (C), 139.48 (CH), 134.54 (CH), 133.92 (CH), 132.10 (C), 131.82 (C), 128.87 (C), 128.29 (CH), 127.03 (CH), 126.47 (C), 126.38 (CH), 123.71 (CH), 121.69 (CH), 105.62 (C), 98.42 (CH), 55.73 (OCH_3), 46.03 (CH_2N), 37.95 (CH_2), 37.61 (C), 26.26 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3390 (NH), 3070 (CH), 2956, 2923 (CH_3), 2853 (CH_2), 1658, 1628 (C=O), 1596, 1552, 1458, 1389, 1366, 1336, 1300, 1275 (C=C), 1233 (C–N), 1115, 1098 (C–O); HRMS (ESI+): m/z [M + Na]$^+$ calcd for $C_{27}H_{25}NO_5$: 466.1625, found: 466.1628.

4.1.33. 2-Hydroxy-N-(3-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl)-5-methoxybenzamide (**42**)

A mixture of naphthoquinone **40** (58 mg, 0.147 mmol), *tert*-butyl hydroperoxide (TBHP) (70% in H_2O) (0.25 mL, 1.769 mmol) in THF (6 mL) was stirred at room temperature for 15 min |Triton B (40% in H_2O) (0.17 mL, 0.442 mmol) was added dropwise to the reaction mixture and continuously stirred for 10 min. The reaction mixture was cooled to 0 °C, acidified with 10% HCl to pH 1, extracted with dichloromethane (3 × 15 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 15% v/v ethyl acetate–hexane to afford product **42** as a yellow solid (33.7 mg, 56%). mp: 164–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (t, J = 6.2 Hz, 1H, NH–CH_2), 8.09 (dd, J = 7.7, 1.2 Hz, 1H, ArH), 8.06 (dd, J = 7.6, 1.2 Hz, 1H, ArH), 7.73 (td, J = 7.5, 1.5 Hz, 1H, ArH), 7.67 (td, J = 7.5, 1.4 Hz, 1H, ArH), 7.64 (s, 1H, PhOH), 7.36 (d, J = 2.9 Hz, 1H, ArH), 6.98 (dd, J = 9.0, 2.9 Hz, 1H, ArH), 6.88 (d, J = 9.0 Hz, 1H, ArH), 3.84 (s, 3H, OCH_3), 3.02 (d, J = 6.6 Hz, 2H, CH_2–NH), 2.56 (s, 2H, CH_2–Ar), 0.99 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.80 (C=O), 180.75 (C=O), 169.70 (C=O), 155.90 (C), 155.53 (C), 151.80 (C), 135.28 (CH), 133.52 (CH), 132.72 (C), 129.31 (C), 127.29 (CH), 126.50 (CH), 121.11 (C), 121.06 (CH), 119.17 (CH), 114.42 (C), 109.57 (CH), 55.94 (OCH_3), 46.59 (CH_2N), 38.60 (CH_2), 31.96 (C), 26.48 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3361 (NH), 3213 (OH), 3075 (CH), 2960, 2925 (CH_3), 2870, 2851 (CH_2), 1672, 1648, 1644 (C=O), 1601, 1548, 1494, 1462, 1366, 1274, 1218 (C=C), 1130 (C–N), 1057, 1041 (C–O); HRMS (ESI+): m/z [M + Na]$^+$ calcd for $C_{23}H_{23}NO_6$: 432.1418, found: 432.1423.

4.1.34. 1-Hydroxy-N-(3-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl)-4-methoxy-2-naphthamide (**43**)

A mixture of naphthoquinone **41** (70 mg, 0.158 mmol), *tert*-butyl hydroperoxide (TBHP) (70% in H_2O) (0.27 mL, 1.894 mmol) in THF (7 mL) was stirred at room temperature for 15 min. Triton B (40% in H_2O) (0.19 mL, 0.474 mmol) was added dropwise to the reaction mixture and continuously stirred for 10 min. The reaction mixture was cooled to 0 °C, acidified with 10% HCl to pH 1, extracted with dichloromethane (3 × 15 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 15% v/v ethyl acetate–hexane to afford product **43** as a yellow solid (38.9 mg, 54%). mp: 203–204 °C; ^{1}H NMR (400 MHz, [D_6] Acetone): δ = 14.02 (s, 1H, Ar–OH), 8.67 (s, 1H, ArH), 8.37–8.33 (m, 1H, ArH), 8.21–8.15 (m, 2H, ArH), 8.08–8.05 (m, 1H, ArH), 7.86 (td, J = 7.5, 1.5 Hz, 1H, ArH), 7.81 (td, J = 7.5, 1.4 Hz, 1H, ArH), 7.65 (ddd, J = 8.3, 6.9, 1.5 Hz, 1H, ArH), 7.59 (ddd, J = 8.2, 6.9, 1.4 Hz, 1H, ArH), 7.40 (s, 1H, ArH), 4.12 (s, 3H, OCH3), 3.27 (d, J = 6.4 Hz, 2H, C*H*2–NH), 2.71 (s, 2H, CH2–Ar), 1.06 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, [D_6] Acetone): δ = 187.33 (C=O), 180.74 (C=O), 167.37 (C=O), 156.61 (C), 154.94 (C), 152.40 (C), 136.08 (C), 135.38 (CH), 133.90 (CH), 133.87 (C), 133.74 (C), 131.03 (C), 128.87 (CH), 127.26 (CH), 126.98 (CH), 126.48 (CH), 124.03 (C), 122.37 (CH), 121.49 (C), 99.82 (CH), 56.06 (OCH_3), 47.72 (CH_2N), 39.10 (CH_2), 32.54 (C), 26.71 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3446 (OH), 3365 (NH), 3070 (CH), 2957, 2924 (CH_3), 2851 (CH_2), 1670, 1625 (C=O), 1599, 1547, 1461, 1365, 1340, 1290, 1274 (C=C), 1218 (C–N), 1119, 1099 (C–O); HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_{27}H_{25}NO_6$: 482.1574, found: 182.1571.

4.1.35. N-(3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl)-2,5-dimethoxybenzamide (**44**)

A mixture of naphthoquinone **38** (300 mg, 0.736 mmol), *tert*-butyl hydroperoxide (TBHP) (70% in H_2O) (1.26 mL, 8.835 mmol) in THF (30 mL) was stirred at room temperature for 15 min. Triton B (40% in H_2O) (0.87 mL, 2.209 mmol) was added dropwise to the reaction mixture and continuously stirred for 10 min. The reaction mixture was cooled to 0 °C, acidified with 10% HCl to pH 1, extracted with dichloromethane (3 × 15 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 15% v/v ethyl acetate–hexane to afford product **44** as a yellow solid (210.7 mg, 68%). mp: 215–216 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.76 (t, J = 6.1 Hz, 1H, N*H*–CH_2), 8.06 (ddd, J = 7.7, 1.4, 0.4 Hz, 1H, ArH), 8.05–8.01 (m, 1H, ArH), 7.72 (d, J = 3.1 Hz, 1H, ArH), 7.73–7.67 (m, 1H, ArH), 7.63 (td, J = 7.5, 1.4 Hz, 1H, ArH), 7.53 (s, 1H, OH), 6.93 (dd, J = 8.9, 3.2 Hz, 1H, ArH), 6.87 (d, J = 8.9 Hz, 1H, ArH), 3.96 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.18 (d, J = 6.4 Hz, 2H, C*H*$_2$–NH), 2.59 (s, 2H, CH_2–Ar), 0.97 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.39 (C=O), 181.11 (C=O), 165.25 (C=O), 154.61 (C), 153.78 (C), 151.97 (C), 134.97 (CH), 133.04 (CH), 132.88 (C), 129.37 (C), 127.03 (CH), 126.17 (CH), 122.59 (C), 121.87 (C), 119.13 (CH), 115.67 (CH), 112.90 (CH), 56.51 (OCH_3), 55.83 (OCH_3), 48.37 (CH_2N), 38.17 (CH_2), 32.17 (C), 26.17 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3380 (NH), 2959 (CH_3), 2863, 2833 (CH_2), 1639 (C=O), 1533, 1492, 1461, 1362, 1274 (C=C), 1215 (C–N), 1046, 1019 (C–O); HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_{24}H_{25}NO_6$: 446.1574, found: 446.1573.

4.1.36. N-(3-(3-Hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl)-1,4-dimethoxy-2-naphthamide (**45**)

A mixture of naphthoquinone **39** (50 mg, 0.109 mmol), *tert*-butyl hydroperoxide (TBHP) (70% in H_2O) (0.19 mL, 1.311 mmol) in THF (6 mL) was stirred at room temperature for 15 min. Triton B (40% in H_2O) (0.13 mL, 0.327 mmol) was added dropwise to the reaction mixture and continuously stirred for 10 min. The reaction mixture was cooled to 0 °C, acidified with 10% HCl to pH 1, extracted with dichloromethane (3 × 15 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 15% v/v ethyl acetate–hexane to afford product **45** as a yellow solid (37.4 mg, 72%). mp: 128 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.79 (t, J = 5.9 Hz, 1H, N*H*–CH_2), 8.22–8.18 (m, 1H, ArH), 8.10–8.05 (m, 2H, ArH), 8.01 (ddd, J = 7.5, 1.3, 0.4 Hz, 1H, ArH), 7.68 (td, J = 7.6, 1.4 Hz, 1H, ArH), 7.61 (td, J = 7.5, 1.3 Hz, 1H, ArH), 7.56 (s, 1H, Ar–OH), 7.53–7.49 (m, 2H, ArH), 7.42 (s, 1H, ArH), 4.01 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.28 (d, J = 6.4 Hz, 2H, C*H*$_2$–NH), 2.65 (s, 2H, CH_2–Ar), 1.02 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.37 (C=O), 181.08 (C=O), 166.02 (C=O), 154.59 (C), 151.91 (C), 148.98 (C), 134.96 (CH), 133.00 (CH), 132.85 (C), 129.34 (C), 128.31 (C), 128.28 (C), 127.07 (CH), 127.05 (CH), 126.88 (CH), 126.15 (CH), 122.79 (CH), 122.54 (CH), 121.97 (C), 121.75 (C), 103.97 (CH), 63.42 (OCH_3), 55.80 (OCH_3), 48.76 (CH_2N), 38.21 (CH_2), 32.37 (C), 26.26 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3371 (NH), 3070 (CH), 2959, 2928 (CH_3), 2848 (CH_2), 1657, 1650, 1644 (C=O), 1594, 1531, 1461, 1371, 1273 (C=C), 1215 (C–N), 1116, 1091 (C–O); HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_{28}H_{27}NO_6$: 496.1731, found: 496.1734.

4.1.37. 2,5-Dimethoxy-N-(3-(3-methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl)benzamide (**46**)

To a stirred solution of naphthoquinone alcohol **44** (50 mg, 0.118 mmol) in acetone (6 mL), K_2CO_3 (19.6 mg) was added. The reaction mixture was stirred for at room temperature until the color of the reaction was changed from yellow to dark red. Then Me_2SO_4 (0.01 mL) was added dropwise to the dark red solution and continuously stirred for 8 h at room temperature. The reaction mixture was cooled to 0 °C, acidified with 10% HCl to pH 1, extracted with dichloromethane (3 × 15 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 15% v/v ethyl acetate–hexane to afford product **46** as a yellow oil (49.4 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.69 (t, J = 5.9 Hz, 1H, N*H*–CH_2), 8.00–7.95 (m, 2H, ArH), 7.70 (d, J = 3.2 Hz, 1H, ArH), 7.63–7.62 (m, 1H, ArH), 7.62–7.60 (m, 1H, ArH), 6.92 (dd, J = 8.9, 3.2 Hz, 1H, ArH), 6.87 (d, J = 8.9 Hz, 1H, ArH), 4.09 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.15 (d, J = 6.3 Hz, 2H, C*H*$_2$–NH), 2.58 (s, 2H, CH_2–Ar), 0.94 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.04 (C=O), 181.34 (C=O), 165.19 (C=O), 159.20 (C), 153.78 (C), 151.92 (C), 133.78 (CH), 133.26 (CH), 131.97 (C), 131.84 (C), 131.51 (C), 126.36 (CH), 126.03 (CH), 122.58 (C), 119.09 (CH), 115.64 (CH), 112.93 (CH), 60.94 (OCH_3), 56.52 (OCH_3), 55.80 (OCH_3), 48.48 (CH_2N), 37.65 (CH_2), 32.16 (C), 26.16 (2× CH_3); IR (KBr): $\tilde{\nu}$ = 3371 (NH), 3070 (CH), 2958, 2929 (CH_3), 2863, 2833 (CH_2), 1668, 1658, 1651 (C=O), 1601, 1576, 1538, 1494, 1463, 1337, 1310, 1277, 1263 (C=C), 1217 (C–N), 1041, 1022 (C–O); HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_{25}H_{27}NO_6$: 460.1731, found: 460.1733.

4.1.38. 1,4-Dimethoxy-N-(3-(3-methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-dimethylpropyl)-2-naphthamide (**47**)

To a stirred solution of naphthoquinone alcohol **45** (13 mg, 0.032 mmol) in acetone (1 mL), K_2CO_3 (5.2 mg, 0.038 mmol) was added. The reaction mixture was stirred for at room temperature until the color of the reaction was changed from yellow to dark red. Then Me_2SO_4 (0.003 mL, 0.063 mmol) was added dropwise to the dark red solution and continuously stirred for 8 h at room temperature. The reaction mixture was cooled to 0 °C, acidified

with 10% HCl to pH 1, extracted with dichloromethane (3 × 15 mL). The combined organic phases were washed with water and brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography eluting with 15% v/v ethyl acetate–hexane to afford product **47** as a yellow oil (10.1 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.72$ (t, $J = 6.1$ Hz, 1H, N*H*–CH_2), 8.22–8.18 (m, 1H, ArH), 8.10–8.07 (m, 1H, ArH), 8.02–7.99 (m, 1H, ArH), 7.98–7.95 (m, 1H, ArH), 7.63–7.60 (m, 2H, ArH), 7.53–7.49 (m, 2H, ArH), 7.41 (s, 1H, ArH), 4.11 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.25 (d, $J = 6.4$ Hz, 2H, C*H*$_2$–NH), 2.65 (s, 2H, CH_2–Ar), 0.99 (s, 6H, 2× CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 186.01$ (C═O), 181.31 (C═O), 165.99 (C═O), 159.24 (C), 151.92 (C), 148.91 (C), 133.82 (CH), 133.26 (CH), 132.12 (C), 131.85 (C), 131.49 (C), 128.29 (C), 127.05 (CH), 126.89 (CH), 126.44 (CH), 126.06 (CH), 122.76 (CH), 122.54 (CH), 122.02 (C), 103.96 (CH), 63.38 (OCH_3), 61.07 (OCH_3), 55.80 (OCH_3), 48.75 (CH_2N), 37.80 (CH_2), 32.33 (C), 26.29 (2× CH_3); IR (KBr): $\tilde{\nu} = 3389$ (NH), 3070 (CH), 2952, 2927 (CH_3), 2848 (CH_2), 1660, 1652 (C═O), 1596, 1521, 1457, 1369, 1336, 1264 (C═C), 1215 (C–N), 1159, 1111, 1091 (C–O); HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{29}H_{29}NO_6$: 488.2073, found: 488.2082.

4.2. Rezasurin microplate assay (REMA) [28]

Novel naphthoquinone amides were subjected to cytotoxic evaluation against three cancerous human-cell lines: KB (epidermoid carcinoma of oral cavity, ATCC CCL-17), NCI-H187 (small cell lung carcinoma, ATCC CRL-5804), and MCF-7 (breast adenocarcinoma, ATCC HTB-22) cell lines. Cells at a logarithmic growth phase were harvested and diluted to 7×10^4 cells/mL for KB and 9×10^4 cells/mL for NCI-H187 and MCF-7 in fresh medium. Successively, 5 mL of a test sample diluted in 0.5% DMSO and 45 mL of cell suspension were added into 384-well plates. The plates were incubated at 37 °C in 5% CO_2 incubator. After the incubation period (3 days for KB and MCF-7 and 5 days for NCI-H187), 12.5 mL of 62.5 mg/mL resazurin solution was added to each well, and the plates were then incubated at 37 °C for 4 h. Fluorescence signals were measured using SpectraMax M5 multi-detection microplate reader (Molecular Devices, USA) at the excitation and emission wavelengths of 530 nm and 590 nm, respectively. Dose response curves were plotted from 6 concentrations of 2-fold serially diluted test compounds and the 50% inhibition concentration (IC_{50}) was determined by curve fitting using the SOFTMax Pro software (Molecular Devices, USA). Doxorubicin and 0.5% DMSO were used as a positive and a negative control, respectively.

4.3. Green fluorescent protein (GFP)-based assay [29]

The GFP-expressing Vero cell lines were generated in-house by stably transfecting the African green monkey kidney cell lines (Vero, ATCC CCL-81), with pEGFP-N1 plasmid (Clontech). The cell lines were maintained in minimal essential medium supplemented with 10% heat-inactivated fetal bovine serum, 2 mM L-glutamine, 1 mM sodium pyruvate, 1.5 g/L sodium bicarbonate and 0.8 mg/mL geneticin, at 37 °C in a humidified incubator with 5% CO_2. The assay was carried out by adding 45 μL of cell suspension at 3.3×10^4 cells/mL to each well of 384-well plates containing 5 μL of test compounds previously diluted in 0.5% DMSO, and then incubating for 4 days in 37 °C incubator with 5% CO_2. Fluorescence signals were measured by using SpectraMax M5 multi-detection microplate reader (Molecular Devices, USA) in the bottom-reading mode with excitation and emission wavelengths of 485 and 535 nm. Fluorescence signal at day 4 was subtracted with background fluorescence at day 0. IC_{50} values were obtained as previously described in Section 4.2.

4.4. Topoisomerase assay

Human Topoisomerase IIα activity was determined using Topisomerase II assay kit (TopGEN Inc.). The reaction mixture containing 60 ng of kintoplast DNA (kDNA) and 2 units of human Topoisomerase IIα was incubated with and without naphthoquinone amide derivatives at 37 °C for 1 h in complete assay buffer (50 mM Tris-Cl pH 8.0, 150 mM NaCl, 10 mM $MgCl_2$, 0.5 mM dithiothreitol, and 2 mM ATP). Doxorubicin was used as a positive control while decatenated and linearized kDNA were used as markers. The reaction in a final volume of 20 μl was stopped by adding stop buffer/gel loading dye (1% Sarkosyl, 0.025% bromophenol blue and 5% glycerol). Reaction products were run on 1% agarose gel in 0.5x TBE buffer with 0.5 μg/ml ethidium bromide included in the gel. Electrophoresis was performed at 50 V for 1.30 h. After electrophoresis, the gel was destained with distilled water for 30 min and photographed over a UV transilluminator using DNr Bio-Imaging system. One unit of Topoisomerase II is defined as the amount of enzyme that decatenates 0.2 μg of kDNA in 30 min at 37 °C.

4.5. Molecular docking studies

The protein structure of human TopoIIα (hTopoIIα) was modeled by SWISS-MODEL using *Saccharomyces cerevisiae* TopoII as a template (PDB: 1BJT) [32]. The crystal structure of *S. cerevisiae* TopoII was solved at 2.50 Å resolutions. The sequence identity between human TopoIIα and the template was 42.9%. The structure of hTopoIIα was modeled using residues from 425 to 1203. Naphthoquinone amide structures were built and optimized at the calculation level hf/6-31g with Gaussian 03. Gasteiger charges were added by using AutoDock4.0 which was employed for all docking calculations. All hydrogen atoms were added and water molecules were removed from the protein structure. Lamarckian genetic algorithm (LGA) was used in this study. Default search parameters were used except for 100 docking runs. The grid size was set to 60 × 60 × 60 points with a grid spacing of 0.375 Å. The structures with relative lower binding free energy and the most cluster members were chosen for the optimum docking conformation. Three-dimensional structures with the best-docked conformation were visualized and analyzed by PyMOL v.0.99 and Discovery Studio 2.5 (Accelrys, Inc., CA, USA).

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References

[1] P. Panichayupakaranant, W. Meerungrueang, Effect of medium composition and light on root and rhinacanthin formation in *Rhinacanthus nasutus* cultures, Pharm. Biol. 48 (2010) 1192–1197.
[2] H. Liu, External Ointment Tianguaxuanjunjing for Treating Skin Disease and Its Preparation, Faming Zhuanli Shenqing Gongkai Shuomingshu, 2009, CN 100468058.
[3] X. Wang, G. Ding, External Chinese Medicine for Treating Psoriasis and Its Production Process, Faming Zhuanli Shenqing Gongkai Shuomingshu, 2009, CN 100347561.
[4] N. Takagi, K. Yoshida, I. Utada, M. Tsukamoto, T. Hozumi, Cosmetic/cosmetic Containing Moor Hot Spring Water, Jpn. Kokai Tokkyo Koho, 2000, JP 2000239146.

[5] N. Siriwatanametanon, B.L. Fiebich, T. Efferth, J.M. Prieto, M. Heinrich, Traditionally used Thai medicinal plants: in vitro anti-inflammatory, anticancer and antioxidant activities, J. Ethnopharmacol. 130 (2010) 196–207.
[6] H. Wang, J. Hao, W. Mu, Stemona-rhinacanthus Communis Effervescent Tablet for Treating Gynecologic Inflammation and Its Preparation, Faming Zhuanli Shenqing Gongkai Shuomingshu, 2006, CN 1879830.
[7] Y. Qian, A Traditional Chinese Medicine for Treating Hepatitis B and Its Preparation Method, Faming Zhuanli Shenqing, 2009, CN 101390970.
[8] P. Siripong, K. Kanokmedakul, S. Piyaviriyagul, J. Yahuafai, R. Champai, S. Ruchirawat, N. Oku, Anticancer naphthoquinone esters from *Rhinacanthus nasutus* Kurz. roots on various cancer cells, J. Trad. Med. 23 (2006) 166–172.
[9] P. Khanittha, C.P. Wild, U. Vinitketkumneun, Thai medicinal plants modulate nitric oxide and tumor necrosis factor-α in J774.2 mouse macrophages, J. Ethnopharmacol. 95 (2004) 183–189.
[10] P. Kupradinun, P. Siripong, R. Chanpai, S. Piyaviriyagul, A. Rungsipipat, S. Wangnaitham, Effects of *Rhinacanthus nasutus* Kurz on colon carcinogenesis in mice, Asian Pac. J. Cancer P 10 (2009) 103–106.
[11] P. Siripong, J. Yahuafai, K. Shimizu, K. Ichikawa, S. Yonezawa, T. Asai, K. Kanokmedakul, S. Ruchirawat, N. Oku, Antitumor activity of liposomal naphthoquinone esters isolated from Thai medicinal plant: *Rhinacanthus nasutus* Kurz, Biol. Pharm. Bull. 29 (2006) 2279–2283.
[12] P. Siripong, C. Hahnvajanawong, J. Yahuafai, S. Piyaviriyakul, K. Kanokmedhakul, N. Kongkathip, S. Ruchirawat, N. Oku, Induction of apoptosis by rhinacanthone isolated from *Rhinacanthus nasutus* roots in human cervical carcinoma cells, Biol. Pharm. Bull. 32 (2009) 1251–1260.
[13] P. Siripong, J. Yahuafai, K. Shimizu, K. Ichikawa, S. Yonezawa, T. Asai, K. Kanokmedhakul, S. Ruchirawat, N. Oku, Induction of apoptosis in tumor cells by three naphthoquinone esters isolated from Thai medicinal plant: *Rhinacanthus nasutus* Kurz, Biol. Pharm. Bull. 29 (2006) 2070–2076.
[14] T.S. Wu, H.J. Tien, M.Y. Yeh, K.H. Lee, Isolation and cytotoxicity of rhinacanthin A and B, two naphthoquinones, from *Rhinacanthus nasutus*, Phytochemistry 27 (1988) 3787–3788.
[15] T.S. Wu, C.C. Yang, P.L. Wu, L.K. Liu, A quinol and steroids from the leaves and stems of *Rhinacanthus nasutus*, Phytochemistry 40 (1995) 1247–1249.
[16] M.R. Kernan, A. Sendl, J.L. Chen, S.D. Jolad, P. Blanc, J.T. Murphy, C.A. Stoddart, W. Nanakorn, M.J. Balick, E.J. Rozhon, Two new lignans with activity against influenza virus from the medicinal plant *Rhinacanthus nasutus*, J. Nat. Prod. 60 (1997) 635–637.
[17] T.S. Wu, H.C. Hsu, P.L. Wu, Y.L. Leu, Y.Y. Chan, C.Y. Chern, M.Y. Yeh, H.J. Tien, Naphthoquinone esters from the root of *Rhinacanthus nasutus*, Chem. Pharm. Bull. 46 (1998) 413–418.
[18] T.S. Wu, H.C. Hsu, P.L. Wu, C.M. Teng, Y.C. Wu, Rhinacanthin-Q, a naphthoquinone from *Rhinacanthus nasutus* and its biological activity, Phytochemistry 49 (1998) 2001–2003.
[19] R.S. Thirumurugan, S. Kavimani, R.S. Srivastava, Antitumour activity of rhinacanthone against Dalton's ascetic lymphoma, Biol. Pharm. Bull. 23 (2000) 1438–1440.
[20] N. Kongkathip, B. Kongkathip, P. Siripong, C. Sangma, S. Luangkamin, M. Niyomdecha, S. Pattanapa, S. Piyaviriyagul, P. Kongsaeree, Potent antitumor activity of synthetic 1,2-naphthoquinones and 1,4-naphthoquinones, Bioorg. Med. Chem. 11 (2003) 3179–3191.
[21] N. Kongkathip, S. Luangkamin, B. Kongkathip, C. Sangma, R. Grigg, P. Kongsaevee, S. Prabpai, N. Pradidphol, S. Piyaviriyagul, P. Siripong, Synthesis of novel rhinacanthins and related anticancer naphthoquinone esters, J. Med. Chem. 47 (2004) 4427–4438.
[22] N. Kongkathip, N. Pradidphol, K. Hasitapan, B. Kongkathip, Synthesis and anticancer evaluation of naphthoquinone esters with 2′-cyclopentyl and 2′-cyclohexyl substituents, Biosci. Biotechnol. Biochem. 74 (2010) 1205–1214.
[23] M. Palomba, A. Pau, G. Boatto, B. Asproni, L. Auzzas, R. Cerri, L. Arenare, W. Filippelli, G. Falcone, G. Motola, Anti-inflammatory and analgesic amides: new developments, Arch. Pharm. (Weinheim) 333 (2000) 17–26.
[24] R.P. Tangallapally, R. Yendapally, R.E. Lee, A.J. Lenaerts, Synthesis and evaluation of cyclic secondary amine substituted phenyl and benzyl nitrofuranyl amides as novel antituberculosis agents, J. Med. Chem. 48 (2005) 8261–8269.
[25] M. Kunishima, C. Kawachi, J. Morita, K. Terao, F. Iwasaki, S. Tani, 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride: an efficient condensing agent leading to the formation of amides and esters, Tetrahedron 55 (1999) 13159–13170.
[26] M. Kunishima, C. Kawachi, K. Hioki, K. Terao, S. Tani, Formation of carboxamides by direct condensation of carboxylic acids and amines in alcohols using a new alcohol- and watersoluble condensing agent: DMT-MM, Tetrahedron 57 (2001) 1551–1558.
[27] A.M. Echavarren, N. Tamayo, M.C. Paredesh, Synthesis of the benzo[*b*]carbazoloquinone with the structure proposed for prekinamycin, Tetrahedron Lett. 34 (1993) 4713–4716.
[28] J.O. Brien, I. Wilson, T. Orton, F. Pognan, Investigation of the alamar blue (resazurin) fluorescent dye for the assessment of mammalian cell cytotoxicity, Eur. J. Biochem. 267 (2000) 5421–5426.
[29] L. Hunt, M. Jordan, M. De Jesus, F.M. Wurm, GFP-expressing mammalian cells for fast, sensitive, noninvasive cell growth assessment in a kinetic mode, Biotechnol. Bioeng. 65 (1999) 201–205.
[30] M.T. Muller, K. Helal, S. Soisson, J.R. Spitzner, A rapid and quantitative microtiter assay for eukaryotic topoisomerase II, Nucleic Acids Res. 17 (1989) 9499.
[31] N. Suda, Y. Nakagawa, A. Kikuchi, M. Sawada, Y. Takami, H. Funahashi, A. Nakao, S. Yoshida, M. Suzuki, Function of the loop residue Thr792 in human DNA topoisomerase IIα, Biochem. Biophys. Res. Commun. 303 (2003) 46–51.
[32] J.M. Berger, D. Fass, C.E. Bogden, Quaternary changes in topoisomerase II may direct orthogonal movement of two DNA strands, Nat. Struct. Biol. 6 (1999) 322–326.