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Synthesis and biological evaluation of structurally diverse α -conformationally restricted chalcones and related analogues†

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Numerous members of the combretastatin and chalcone families of natural products function as inhibitors of tubulin polymerization through a binding interaction at the colchicine site on β -tubulin. These molecular scaffolds inspired the development of many structurally modified derivatives and analogues as promising anticancer agents. A productive design blueprint that involved molecular hybridization of the pharmacophore moieties of combretastatin A-4 (CA4) and the chalcones led to the discovery of two promising lead molecules referred to as KGP413 and SD400. The corresponding water-soluble phosphate prodrug salts of KGP413 and SD400 selectively damaged tumor-associated vasculature, thus highlighting the potential development of these molecules as vascular disrupting agents (VDAs). These previous studies prompted our current investigation of conformationally restricted chalcones. Herein, we report the synthesis of cyclic chalcones and related analogues that incorporate structural motifs of CA4, and evaluation of their cytotoxicity against human cancer cell lines [NCI-H460 (lung), DU-145 (prostate), and SK-OV-3 (ovarian)]. While these molecules proved inactive as inhibitors of tubulin polymerization ($IC_{50} > 20 \mu M$), eight molecules demonstrated good antiproliferative activity ($GI_{50} < 20 \mu M$) against all three cancer cell lines, and compounds 2j and 2l demonstrated sub-micromolar cytotoxicity. To the best of our knowledge these molecules represent the most potent (based on GI_{50}) cyclic chalcones known to date, and are promising lead molecules for continued investigation.

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1. Introduction

Within the stilbene and flavonoid classes of natural products, the combretastatins and chalcones represent two distinct secondary metabolites which exemplify promising anticancer lead agents.^{1–6} These natural products and related analogues function as inhibitors of tubulin polymerization through a binding interaction at the colchicine site, located at the subunit interface of the tubulin α,β -heterodimer.^{7–11} The net

result is disruption of cellular processes necessary for cell proliferation.^{12,13} In addition to the antimitotic activity inherent to these analogues, disruption of tubulin polymerization also directly correlates with their anti-vascular activity.^{14–23}

Molecular hybridization of the pharmacophoric moieties (trimethoxy aryl ring and *p*-methoxyphenolic ring) of combretastatin A-4 (CA4) and the chalcones (α,β -unsaturated ketone) led to the discovery of two highly potent lead anticancer agents referred to as KGP413 (ref. 25) and SD400 (ref. 26 and 27) (Fig. 1). These hybrid molecules demonstrated potent cytotoxicity as evidenced by low nM GI_{50} values (SRB assay) across NCI-H460, DU-145, and SK-OV-3 cell lines for KGP413 (ref. 25), and a low nM IC_{50} value (MTT assay) against the K562 cell line for SD400.^{26,27} In addition, these two hybrid molecules functioned as vascular disrupting agents (VDAs^{25,26}), which target tumor-associated microvessels, resulting in loss of nutrients, oxygen deprivation and subsequent necrosis. Dihydronaphthalene and benzosuberene molecular scaffolds bearing the CA4 substitution pattern have provided access to highly potent VDAs (for example, KGP03 and KGP18 respectively (Fig. 1)).^{25,33–37} Furthermore, the SAR study of 2-arylidenebenzocycloalkanones by Dimmock demonstrated the correlation between the spatial arrangement of

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Fig. 1 Representative natural products and synthetic analogues that bind to the colchicine site resulting in inhibition of tubulin polymerization, including: colchicine,²⁴ combretastatin analogues [CA4 and its corresponding water-soluble phosphate prodrug salt CA4P (prodrug itself inactive with tubulin)],^{1,2} chalcones,⁷ dihydronaphthalene analogue (KGP03 (ref. 25)), benzosuberene analogue (KGP18 (ref. 33, 35 and 36)), and chalcone analogues (KGP413 (ref. 25) and SD400 (ref. 26 and 27)).

the aryl rings and bioactivity.³⁸ Several of the cyclic chalcone analogues evaluated by Dimmock displayed low μM IC₅₀ values in several cancer cell lines, demonstrating the potential utility of cyclic chalcones as anticancer agents.^{39–42} Surprisingly, very few examples of cyclic chalcones as colchicine binding site inhibitors have been reported in the literature.^{43,44} Furthermore, no examples (to the best of our knowledge) are reported which merge the salient features of CA4 with the 2-arylidenebenzocycloalkanones scaffold, where the *p*-methoxy-phenolic ring is the A ring and the trimethoxy-aryl moiety is the B ring (Fig. 2).

Herein, we report the design, synthesis, and preliminary biological evaluation of novel tetralone and benzosuberone cyclic chalcones. Functionalized analogues of this nature bear structural similarity to CA4, KGP03, KGP18, and KGP413 (Fig. 1). Selection of the chalcone molecules identified for synthesis was guided, in part, by our previous SAR investigations related to dihydronaphthalene and benzosuberene-based mole-

cules designed to function as inhibitors of tubulin polymerization and as VDAs.^{25,33–36} In addition, oxime derivatives were prepared to serve as a latentiation point for the potential conversion to water-soluble phosphate prodrug salts.⁴⁵ Studies by Qin and co-workers investigated chalcones and corresponding oxime analogues, in which the oximes demonstrated a general trend of slightly enhanced antiproliferative activity (IC₅₀ values) compared to the parent chalcone (Fig. 3).^{44,46–48} The dihydronaphthalene chalcones were converted to their corresponding naphthol isomers to investigate correlation of the fused aromatic ring and exocyclic methylene bridge carbon inherent to these naphthol analogues with their associated biological activity (Fig. 3).^{50–52} The structure of diol analogue 3c is intriguing since it offers a unique opportunity to undergo oxidative conversion (*in vivo*) to generate a highly reactive quinone intermediate similar to the mechanism attributed to combretastatin A-1 (CA1), which leads to enhanced antitumor efficacy (*in vivo*) of CA1 related to formation of the corresponding CA1

Fig. 2 Molecular hybridization strategy utilizing the 2-arylidenebenzocycloalkanone scaffold investigated by Dimmock (R = H or 3,4,5-OCH₃) and the CA4 substitution pattern to generate conformationally restricted chalcones as colchicine binding site inhibitors (R = H, Br, OH, NO₂, NH₂, CN).

Fig. 3 Analogues synthesized from chalcones: (a) photoisomerization to *Z*-isomer; (b) Wolff-Kishner reduction to cyclopropa[*a*]-naphthalene; (c) ketoxime for phosphate salt attachment; (d) microwave-assisted isomerization to naphthol.

ortho-quinone.^{53,54} The dihydronaphthalene chalcones were also converted to cyclopropane derivatives utilizing Wolff-Kishner reduction conditions (Fig. 3).^{55–58} Ty and coworkers reported the synthesis of enantiomerically pure cyclopropyl analogues of CA4 to evaluate the effects of stereochemistry on biological activity.⁵⁹ We report synthetic strategies directed toward the preparation of conformationally restricted chalcones and corresponding derivatives, along with evaluation of inhibition of tubulin polymerization (cell-free assay) and cytotoxicity against NCI-H460 (non-small cell lung carcinoma), DU-145 (prostate carcinoma), and SK-OV-3 (ovarian adenocarcinoma) human cancer cell lines.

2. Results and discussion

2.1. Synthesis

Chalcone analogues were prepared by a Claisen-Schmidt condensation between the appropriate tetralone or benzo-

suberone and 3,4,5-trimethoxybenzaldehyde (Scheme 1).⁶⁰ The condensation reaction times varied depending on the functionalization inherent to the tetralone and benzo-suberone precursors. Microwave-assisted reaction conditions were utilized when appropriate, and the yields were above 95% after 30 min. Due to steric interactions, the *E*-isomer was exclusively observed, and it should be noted that the phenol-substituted chalcone **2c** underwent photoisomerization to the corresponding *Z*-isomer upon exposure to 365 nm UV-light (observed by ¹H NMR and by 2D TLC). However, the *Z*-chalcone underwent isomerization back to the *E*-form relatively quickly (upon termination of UV-light exposure) and was not isolated (Fig. 3). Related photoisomerization of chalcone analogues has been previously observed.^{61–65}

The structural overlap between KGP413 and SD400 suggested that appropriate *Z*-chalcone analogues could potentially demonstrate similar biological activity to these highly potent VDAs. However, the *E*-chalcone (Scheme 1) was

Scheme 1 Reagents and conditions: (a) 3,4,5-trimethoxybenzaldehyde, KOH, MeOH, rt, 12–24 h; (b) 3,4,5-trimethoxybenzaldehyde, KOH, MeOH, MW, 110 °C, 1 h; (c) CuCN, NMP, MW, 160 °C, 30 min.

Scheme 2 Reagents and conditions: (a) KOH, MeOH, MW, 160 °C, 30 min; (b) BCl₃, CH₂Cl₂, 0 °C, 30 min; (c) Na₂S₂O₄, H₂O:EtOH (1:1), MW, 160 °C, 30 min.

exclusively obtained due to the unfavorable steric interaction between the aryl and carbonyl groups. Therefore, it was envisioned that isomerization of the chalcone analogues to their corresponding naphthol derivatives (Scheme 2) would impart rotational freedom to the trimethoxy aryl ring, providing access to conformations not possible in the chalcone series. Aromatization to the naphthol was accomplished using microwave-assisted reaction conditions in the presence of strong base. This transformation proceeded through either a stepwise synthesis or a one-pot reaction from the corresponding tetralone and aldehyde. It should be noted that the isomerization only occurred at high temperature (MW, 160 °C) and was not observed in the microwave-assisted Claisen-Schmidt condensation. Quantitative isomerization to naphthol derivatives was observed for all chalcone analogues evaluated. However, it proved necessary to install an isopropyl protecting group (**2d**) in order to isomerize the phenolic chalcone to the corresponding naphthol **3c** (Scheme 2). The

tetralone and benzosuberone chalcone analogues were converted to their corresponding oxime derivatives upon treatment with hydroxyl amine and sodium acetate (Scheme 3).⁴⁸ The cyclopropane derivatives were prepared using standard Wolff-Kishner reduction conditions (Scheme 4). The relative stereochemistry of compounds **5a** and **5b** was confirmed by X-ray crystallography, and the anticipated 1:1 ratio of enantiomers was evidenced by polarimetry (from lack of appreciable rotation).

2.2. Biological evaluation

Chalcones (**2a–2l**), naphthols (**3a–3f**), oximes (**4b** and **4c**), and cyclopropane analogues (**5a** and **5b**) were evaluated for their ability to inhibit the polymerization of purified tubulin. While the chalcones, oximes, and cyclopropane analogues were found to be inactive (IC₅₀ > 20 μM), one member of the naphthol series (**3a**) demonstrated weak inhibition of tubulin

Scheme 3 Reagents and conditions: (a) hydroxylamine hydrochloride, NaOAc, MeOH, reflux, 6 h.

Scheme 4 Reagents and conditions: (a) hydrazine monohydrate, KOH, diethylene glycol, 150 °C for 90 min then 195 °C for 4 h.

polymerization ($IC_{50} = 17 \mu M$). The naphthol scaffold was envisioned to adopt a favorable conformation for binding to the colchicine site due to the bond rotation provided by the methylene bridge. Inhibition of colchicine binding was investigated for compounds **2j** and **2l**; however, both molecules demonstrated very weak competition (14% and 0.34%, respectively, at a $5 \mu M$ concentration), providing further confirmation that the tubulin-microtubule protein system was not the primary molecular target for this series of molecules. Considering our previous SAR studies surrounding dihydronaphthalene and benzosuberene inhibitors of tubulin polymerization^{25,33–37} and related chalcone^{25–32} analogues reported in the literature, the lack of binding interaction at the colchicine site and accompanying lack of inhibition of tubulin polymerization was somewhat surprising and unexpected. Encouragingly, several molecules from the chalcone and naphthol series (**2c**, **2h**, **2i**, **2k**, **3a**, and **3b**) demonstrated low-micromolar cytotoxicity ($GI_{50} < 20 \mu M$), and two analogues (**2j** and **2l**) demonstrated sub-micromolar cytotoxicity against NCI-H460 (lung), DU-145 (prostate), and SK-OV-3 (ovarian) human cancer cell lines (Table 1). The naphthol series displayed a general trend of enhanced potency (GI_{50}) compared to the parent chalcones. Five compounds (**2c**, **2f**, **2j**, **2l**, and **3a**) were evaluated for potential cytotoxicity against a non-tumor cell line [human umbilical vein endothelial cells (HUVECs)]. Compounds **2c**, **2f**, and **3a** demonstrated relatively uniform minimal cytotoxicity across all four cell lines, while compound **2j** demonstrated a moderate (10-fold) decrease in cytotoxicity against HUVECs in comparison to the

cancer cell lines. Interestingly, compound **2l** demonstrated an approximately 100-fold decrease in cytotoxicity against HUVECs in comparison to the cancer cell lines evaluated. It is noteworthy that the sub-micromolar cytotoxicity demonstrated by compounds **2j** and **2l** represent, to the best of our knowledge, the most cytotoxic (based on GI_{50}) cyclic chalcones known to date. Having established that tubulin is not the primary target for the cytotoxicity demonstrated by this subset of molecules, it is intriguing to consider alternative molecular targets and pathways that have been previously established for other chalcone analogues, including MDM2-p53, proteasomes, NF-kappa B, IL-6/JAK/STAT3, VEGF, and caspases.⁴⁹

3. Conclusion

In summary, we utilized molecular scaffolds inherent to the natural product CA4 and our biologically active synthetic dihydronaphthalene and benzosuberene lead molecules to generate structurally modified cyclic chalcones and related analogues. Synthetic routes were developed and optimized for these compounds. All analogues were evaluated for inhibition of tubulin polymerization and for their cytotoxicity against human cancer cell lines. While these molecules proved inactive as inhibitors of tubulin polymerization ($IC_{50} > 20 \mu M$), enhanced cytotoxicity (sub-micromolar) was observed for two compounds (**2j** and **2l**) against the three human cancer cell lines evaluated in this study. In addition, compound **2l** demonstrated nearly a 100-fold decrease in cytotoxicity against a non-cancer cell line (HUVECs). These cyclic chalcones represent interesting starting points for further structural refinement in order to enhance potency and further evaluate the mechanism of action.

4. Experimental section

4.1. Chemistry

4.1.1. Experimental procedures for tetralone and benzosuberone intermediates. Procedures for the synthesis of tetralone (**1b–1f**) and benzosuberone (**1h–1l**) intermediates can be found in our previously published work.^{25,33,66}

4.1.2. Experimental procedures for chalcone synthesis

4.1.2.1. (*E*)-6-Methoxy-2-(3,4,5-trimethoxybenzylidene)-3,4-dihydronaphthalen-1(2H)-one (2a**).** KOH (3.33 g, 59.6 mmol) was dissolved in methanol (300 mL), and 6-methoxy-1-tetralone (3.50 g, 19.9 mmol) and 3,4,5-trimethoxy benzaldehyde (3.90 g, 19.9 mmol) were added to the solution. The reaction was stirred at room temperature for 12 h. The mixture was neutralized with 2 M HCl and extracted with CH_2Cl_2 . The organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, EtOAc/hexanes) afforded **2a** (6.34 g, 53.6 mmol, 90% yield) as yellow crystals. 1H NMR ($CDCl_3$, 500 MHz): δ 8.05 (1H, d, $J = 8.7$ Hz), 7.72 (1H, s), 6.83 (1H, dd, $J = 8.7, 2.4$ Hz), 6.66 (1H, d, $J = 2.2$ Hz), 6.62 (2H, s), 3.85 (3H, s), 3.84 (6H, s), 3.82 (3H, s), 3.10 (2H, t, $J = 5.8$ Hz), 2.88

Table 1 Cytotoxicity of the target chalcone, naphthol, oxime, and cyclopropane analogues

Compound	GI_{50} (μM) SRB assay ^a		
	NCI-H460	DU-145	SK-OV-3
2a	22.4	22.6	40.3
2b	22.6	27.6	29.6
2c	6.44	5.49	6.29
2e	36.3	37.6	23.5
2f	46.4	32.4	>135
2g	44.4	57.2	33.3
2h	6.57	9.71	12.0
2i	4.44	9.91	8.50
2j	0.635	0.456	0.941
2k	5.96	5.94	16.1
2l	0.733	0.237	0.936
3a	13.4	8.84	7.50
3b	5.92	6.17	18.3
3c	24.4	23.4	21.9
3e	22.9	18.6	21.0
3f	65.2	49.7	16.4
4b	47.0	50.1	80.1
4c	22.8	23.9	38.2
5a	38.8	41.1	54.5
5b	59.2	61.5	108
CA4	0.005	0.00602	0.00506
Doxorubicin	0.0547	0.1081	0.0875
Paclitaxel	0.00165	0.00152	0.00136

^a Average of 3 $\geq$ n independent determinations.

(2H, t, $J = 6.5$ Hz). ^{13}C NMR (CDCl_3 , 126 MHz): δ 186.5, 163.5, 153.0, 145.6, 138.4, 136.1, 135.0, 131.5, 130.6, 126.9, 113.3, 112.2, 107.1, 60.9, 56.2, 55.4, 29.2, 27.3. HRMS: Obsd 377.1362 $[\text{M} + \text{Na}^+]$, calcd for $\text{C}_{21}\text{H}_{22}\text{NaO}_5^+$: 377.1359. HPLC retention time – 8.17 min.

4.1.2.2. (*E*)-5-Bromo-6-methoxy-2-(3,4,5-trimethoxybenzylidene)-3,4-dihydronaphthalen-1(2H)-one (**2b**). KOH (0.67 g, 11.9 mmol) was dissolved in methanol (100 mL), and 5-bromo-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (**1b**) (1.01 g, 3.96 mmol) and 3,4,5-trimethoxy benzaldehyde (0.78 g, 3.96 mmol) were added to the solution. The reaction was stirred at room temperature for 12 h. The mixture was neutralized with 2 M HCl and extracted with CH_2Cl_2 . The organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, EtOAc/hexanes) afforded **2b** (1.34 g, 3.09 mmol, 78% yield) as white crystals. ^1H NMR (CDCl_3 , 500 MHz): δ 8.16 (1H, d, $J = 8.7$ Hz), 7.75 (1H, s), 6.93 (1H, d, $J = 8.7$ Hz), 6.66 (2H, s), 3.99 (3H, s), 3.89 (9H, s), 3.14 (2H, t, $J = 5.8$ Hz), 3.09 (2H, t, $J = 6.2$ Hz). ^{13}C NMR (CDCl_3 , 126 MHz): δ 186.1, 159.5, 152.9, 144.0, 136.5, 133.7, 131.5, 129.3, 129.3, 128.1, 109.8, 107.1, 60.8, 56.3, 56.0, 28.8, 26.5. HRMS: Obsd 455.0465 $[\text{M} + \text{Na}^+]$, calcd for $\text{C}_{21}\text{H}_{21}\text{BrNaO}_5^+$: 455.0464. HPLC retention time – 11.55 min.

4.1.2.3. (*E*)-5-Hydroxy-6-methoxy-2-(3,4,5-trimethoxybenzylidene)-3,4-dihydronaphthalen-1(2H)-one (**2c**). KOH (0.36 g, 6.40 mmol) was dissolved in methanol (15 mL) in a 20 mL microwave vial, and 5-hydroxy-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (**1c**) (0.41 g, 2.13 mmol) and 3,4,5-trimethoxy benzaldehyde (0.42 g, 2.13 mmol) were added to the solution. The reaction mixture was subjected to microwave irradiation at 110 °C for 1 h. The mixture was neutralized with 2 M HCl and extracted with CH_2Cl_2 . The organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, EtOAc/hexanes) afforded **2c** (0.59 g, 1.59 mmol, 75% yield) as a yellow solid. ^1H NMR (CDCl_3 , 500 MHz): δ 7.78 (1H, d, $J = 8.6$ Hz), 7.75 (1H, s), 6.89 (1H, d, $J = 8.6$ Hz), 6.67 (2H, s), 5.72 (1H, s), 3.97 (3H, s), 3.89 (3H, s), 3.88 (6H, s), 3.12 (2H, t, $J = 5.9$ Hz), 2.97 (2H, t, $J = 6.5$ Hz). ^{13}C NMR (CDCl_3 , 126 MHz): δ 187.2, 153.0, 141.5, 136.2, 135.2, 135.1, 131.5, 129.1, 121.2, 116.3, 115.3, 110.0, 108.7, 107.2, 61.0, 56.2, 56.1, 26.7, 21.6. HRMS: Obsd 393.1311 $[\text{M} + \text{Na}^+]$, calcd for $\text{C}_{21}\text{H}_{22}\text{NaO}_6^+$: 393.1309. HPLC retention time – 4.84 min.

4.1.2.4. (*E*)-5-Isopropoxy-6-methoxy-2-(3,4,5-trimethoxybenzylidene)-3,4-dihydronaphthalen-1(2H)-one (**2d**). KOH (0.29 g, 5.12 mmol) was dissolved in methanol (15 mL) in a 20 mL microwave vial, and 5-isopropoxy-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (**1d**) (0.41 g, 1.71 mmol) and 3,4,5-trimethoxy benzaldehyde (0.34 g, 1.71 mmol) were added to the solution. The reaction mixture was subjected to microwave irradiation at 110 °C for 1 h. The mixture was neutralized with 2 M HCl and extracted with CH_2Cl_2 . The organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification by flash column

chromatography (silica gel, EtOAc/hexanes) afforded (*E*)-5-isopropoxy-6-methoxy-2-(3,4,5-trimethoxybenzylidene)-3,4-dihydronaphthalen-1(2H)-one **2d** (0.57 g, 1.39 mmol, 81% yield) as a yellow solid. ^1H NMR (CDCl_3 , 600 MHz): δ 7.95 (1H, d, $J = 8.7$ Hz), 7.79 (1H, s), 6.94 (1H, d, $J = 8.7$ Hz), 6.69 (2H, s), 4.45 (1H, p, $J = 6.2$ Hz), 3.94 (3H, s), 3.92 (3H, s), 3.91 (6H, s), 3.11 (2H, t, $J = 6.4$ Hz), 3.01 (2H, t, $J = 6.4$ Hz), 1.30 (6H, d, $J = 6.2$ Hz). ^{13}C NMR (CDCl_3 , 151 MHz): δ 187.1, 157.0, 153.1, 142.8, 138.5, 137.9, 136.1, 135.1, 131.5, 127.4, 125.2, 110.3, 107.2, 74.9, 61.0, 56.2, 55.8, 27.1, 23.0, 22.6.

4.1.2.5. (*E*)-6-Methoxy-5-nitro-2-(3,4,5-trimethoxybenzylidene)-3,4-dihydronaphthalen-1(2H)-one (**2e**). KOH (0.15 g, 2.71 mmol) was dissolved in methanol (5 mL) in a 5 mL microwave vial, and 6-methoxy-5-nitro-3,4-dihydronaphthalen-1(2H)-one (**1e**) (0.21 g, 0.95 mmol) and 3,4,5-trimethoxy benzaldehyde (0.19 g, 0.95 mmol) were added to the solution. The reaction mixture was subjected to microwave irradiation at 110 °C for 1 h. The mixture was neutralized with 2 M HCl and extracted with CH_2Cl_2 . The organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, EtOAc/hexanes) afforded **2e** (0.35 g, 0.87 mmol, 91% yield) as yellow crystals. ^1H NMR (CDCl_3 , 500 MHz): δ 8.27 (1H, d, $J = 8.9$ Hz), 7.81 (1H, s), 7.06 (1H, d, $J = 8.9$ Hz), 6.65 (2H, s), 3.98 (3H, s), 3.89 (3H, s), 3.88 (6H, s), 3.16 (2H, t, $J = 5.8$ Hz), 2.86 (2H, t, $J = 6.5$ Hz). ^{13}C NMR (CDCl_3 , 126 MHz): δ 185.1, 154.3, 153.2, 139.8, 139.0, 138.0, 136.0, 133.0, 132.1, 130.8, 126.9, 110.9, 107.3, 61.0, 56.7, 56.2, 26.3, 23.8. HRMS: Obsd 422.1209 $[\text{M} + \text{Na}^+]$, calcd for $\text{C}_{21}\text{H}_{21}\text{NNaO}_7^+$: 422.1210. HPLC retention time – 8.33 min.

4.1.2.6. (*E*)-5-Amino-6-methoxy-2-(3,4,5-trimethoxybenzylidene)-3,4-dihydronaphthalen-1(2H)-one (**2f**). KOH (0.48 g, 8.50 mmol) was dissolved in methanol (25 mL), and 5-amino-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (**1f**) (0.55 g, 2.88 mmol) and 3,4,5-trimethoxy benzaldehyde (0.55 g, 2.80 mmol) were added to the solution. The reaction was stirred at room temperature for 24 h. The mixture was neutralized with 2 M HCl and extracted with CH_2Cl_2 . The organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, EtOAc/hexanes) afforded **2f** (0.47 g, 1.20 mmol, 46% yield) as yellow crystals. ^1H NMR (CDCl_3 , 500 MHz): δ 7.75 (2H, d, $J = 8.5$ Hz), 6.88 (1H, d, $J = 8.6$ Hz), 6.68 (2H, s), 3.97 (3H, s), 3.92 (3H, s), 3.91 (6H, s), 3.84 (2H, s), 3.18 (2H, t, $J = 6.5$ Hz), 2.78 (2H, t, $J = 6.5$ Hz). ^{13}C NMR (CDCl_3 , 151 MHz): δ 187.5, 153.1, 150.9, 138.4, 135.8, 135.0, 132.3, 131.6, 127.6, 127.0, 120.1, 108.6, 107.2, 61.0, 56.2, 55.7, 26.6, 23.1. HRMS: Obsd 392.1470 $[\text{M} + \text{Na}^+]$, calcd for $\text{C}_{21}\text{H}_{23}\text{NNaO}_5^+$: 392.1468. HPLC retention time – 4.49 min.

4.1.2.7. (*E*)-2-Methoxy-5-oxo-6-(3,4,5-trimethoxybenzylidene)-5,6,7,8-tetrahydronaphthalene-1-carbonitrile (**2g**). CuCN (2.00 g, 22.3 mmol) and (*E*)-5-bromo-6-methoxy-2-(3,4,5-trimethoxybenzylidene)-3,4-dihydronaphthalen-1(2H)-one (**2b**) (0.40 g, 0.93 mmol) were dissolved in *N*-methyl-2-pyrrolidone (10 mL) in a 20 mL microwave vial. The reaction mixture was subjected to microwave irradiation at 160 °C for 30 minutes.

The reaction mixture was filtered through Celite with CH_2Cl_2 . The organic layer was collected and washed with H_2O . The organic layer was dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, EtOAc/hexanes) afforded **2g** (0.34 g, 0.88 mmol, 95% yield) as white crystals. ^1H NMR (CDCl_3 , 600 MHz): δ 8.34 (1H, d, J = 8.9 Hz), 7.81 (1H, s), 7.00 (1H, d, J = 8.9 Hz), 6.68 (2H, s), 4.04 (3H, s), 3.91 (3H, s), 3.90 (6H, s), 3.21 (2H, t, J = 6.5 Hz), 3.15 (2H, t, J = 6.3 Hz). ^{13}C NMR (CDCl_3 , 151 MHz): δ 185.1, 164.9, 153.2, 148.7, 138.9, 137.8, 134.9, 133.2, 130.8, 127.3, 114.5, 109.9, 107.4, 100.9, 61.0, 56.6, 56.2, 27.2, 26.5. HRMS: Obsd 402.1317 [$\text{M} + \text{Na}^+$], calcd for $\text{C}_{22}\text{H}_{21}\text{NNaO}_5^+$: 402.1313. HPLC retention time – 5.91 min.

4.1.2.8. (E)-2-Methoxy-6-(3,4,5-trimethoxybenzylidene)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (2h). KOH (0.18 g, 3.18 mmol) was dissolved in methanol (25 mL), and 2-methoxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (0.20 g, 1.06 mmol) and 3,4,5-trimethoxy benzaldehyde (0.21 g, 1.06 mmol) were added to the solution. The reaction was stirred at room temperature for 12 h. The mixture was neutralized with 2 M HCl and extracted with CH_2Cl_2 . The organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, EtOAc/hexanes) afforded **2h** (0.20 g, 0.55 mmol, 52% yield) as yellow crystals. ^1H NMR (CDCl_3 , 600 MHz): δ 7.83 (1H, d, J = 8.5 Hz), 7.70 (1H, s), 6.89 (1H, dd, J = 8.5, 2.1 Hz), 6.77 (2H, s), 6.74 (1H, d, J = 1.9 Hz), 3.92 (6H, s), 3.91 (3H, s), 3.89 (3H, s), 2.91 (2H, t, J = 6.8 Hz), 2.66 (2H, t, J = 6.8 Hz), 2.11 (2H, p, J = 6.8 Hz). ^{13}C NMR (CDCl_3 , 151 MHz): δ 196.9, 163.0, 153.2, 142.2, 138.6, 137.9, 137.6, 131.8, 131.5, 131.4, 114.5, 112.0, 106.8, 61.0, 56.2, 55.4, 32.5, 26.5, 25.3. HRMS: Obsd 391.172 [$\text{M} + \text{Na}^+$], calcd for $\text{C}_{22}\text{H}_{24}\text{NaO}_5^+$: 391.1516. HPLC retention time – 8.42 min.

4.1.2.9. (E)-1-Bromo-2-methoxy-6-(3,4,5-trimethoxybenzylidene)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (2i). KOH (0.30 g, 5.37 mmol) was dissolved in methanol (25 mL), and 1-bromo-2-methoxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (0.48 g, 1.79 mmol) and 3,4,5-trimethoxy benzaldehyde (0.35 g, 1.79 mmol) were added to the solution. The reaction was stirred at room temperature for 12 h. The mixture was neutralized with 2 M HCl and extracted with CH_2Cl_2 . The organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, EtOAc/hexanes) afforded **2i** (1.34 g, 3.09 mmol, 78% yield) as white crystals. ^1H NMR (CDCl_3 , 600 MHz): δ 7.77 (1H, s), 7.72 (1H, d, J = 8.5 Hz), 6.88 (1H, d, J = 8.6 Hz), 6.73 (2H, s), 3.96 (3H, s), 3.89 (6H, s), 3.89 (3H, s), 3.20 (2H, t, J = 6.7 Hz), 2.59 (2H, t, J = 6.7 Hz), 2.06 (2H, p, J = 6.8 Hz). ^{13}C NMR (CDCl_3 , 151 MHz): δ 196.2, 159.0, 153.2, 140.7, 138.7, 138.4, 137.0, 133.3, 131.1, 129.7, 113.5, 109.6, 106.8, 61.0, 56.5, 56.2, 30.9, 25.2, 25.1. HRMS: Obsd 469.0621 [$\text{M} + \text{Na}^+$], calcd for $\text{C}_{22}\text{H}_{23}\text{BrNaO}_5^+$: 469.0621. HPLC retention time – 13.24 min.

4.1.2.10. (E)-1-Hydroxy-2-methoxy-6-(3,4,5-trimethoxybenzylidene)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (2j). KOH (0.28 g, 4.97 mmol) was dissolved in

methanol (25 mL), and 1-hydroxy-2-methoxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (0.34 g, 1.66 mmol) and 3,4,5-trimethoxy benzaldehyde (0.36 g, 1.82 mmol) were added to the solution. The reaction was stirred at room temperature for 12 h. The mixture was neutralized with 2 M HCl and extracted with CH_2Cl_2 . The organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, EtOAc/hexanes) afforded **2j** (0.05 g, 0.12 mmol, 38% yield) as a yellow solid. ^1H NMR (CDCl_3 , 600 MHz): δ 7.74 (1H, s), 7.42 (1H, d, J = 8.4 Hz), 6.87 (1H, d, J = 8.4 Hz), 6.78 (2H, s), 5.77 (1H, s), 3.99 (3H, s), 3.92 (6H, s), 3.92 (3H, s), 3.04 (2H, t, J = 6.7 Hz), 2.65 (2H, t, J = 6.7 Hz), 2.09 (2H, p, J = 6.7 Hz). ^{13}C NMR (CDCl_3 , 151 MHz): δ 187.2, 153.0, 141.5, 136.2, 135.2, 135.1, 131.5, 129.1, 121.2, 116.3, 115.3, 110.0, 108.7, 107.2, 61.0, 56.2, 56.1, 26.7, 21.6. HRMS: Obsd 407.1469 [$\text{M} + \text{Na}^+$], calcd for $\text{C}_{22}\text{H}_{24}\text{NaO}_6^+$: 407.1465. HPLC retention time – 5.88 min.

4.1.2.11. (E)-2-Methoxy-1-nitro-6-(3,4,5-trimethoxybenzylidene)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (2k). KOH (0.06 g, 1.02 mmol) was dissolved in methanol (10 mL), and 2-methoxy-1-nitro-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (0.08 g, 0.34 mmol) and 3,4,5-trimethoxy benzaldehyde (0.07 g, 0.34 mmol) were added to the solution. The reaction was stirred at room temperature for 12 h. The mixture was neutralized with 2 M HCl and extracted with CH_2Cl_2 . The organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, EtOAc/hexanes) afforded **2k** (0.35 g, 0.87 mmol, 91% yield) as yellow crystals. ^1H NMR (CDCl_3 , 600 MHz): δ 7.92 (1H, d, J = 8.5 Hz), 7.79 (1H, s), 7.05 (1H, d, J = 8.6 Hz), 6.75 (2H, s), 3.99 (3H, s), 3.92 (9H, s), 2.82 (2H, t, J = 6.6 Hz), 2.68 (2H, t, J = 6.6 Hz), 2.15 (2H, p, J = 6.8 Hz). ^{13}C NMR (CDCl_3 , 126 MHz): δ 207.0, 153.5, 153.3, 141.0, 139.3, 139.0, 132.7, 132.4, 130.7, 110.6, 106.9, 61.0, 56.6, 56.2, 26.4, 26.1, 25.0. HRMS: Obsd 436.1366 [$\text{M} + \text{Na}^+$], calcd for $\text{C}_{22}\text{H}_{23}\text{NNaO}_7^+$: 436.1367. HPLC retention time – 9.58 min.

4.1.2.12. (E)-1-Amino-2-methoxy-6-(3,4,5-trimethoxybenzylidene)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (2l). KOH (0.07 g, 1.31 mmol) was dissolved in methanol (10 mL), and 1-amino-2-methoxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (0.09 g, 0.44 mmol) and 3,4,5-trimethoxy benzaldehyde (0.09 g, 0.44 mmol) were added to the solution. The reaction was stirred at room temperature for 24 h. The mixture was neutralized with 2 M HCl and extracted with CH_2Cl_2 . The organic layers were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, EtOAc/hexanes) afforded **2l** (0.13 g, 0.34 mmol, 78% yield) as yellow crystals. ^1H NMR (CDCl_3 , 600 MHz): δ 7.73 (1H, s), 7.28 (1H, d, J = 8.4 Hz), 6.78 (1H, d, J = 8.4 Hz), 6.73 (2H, s), 3.91 (3H, s), 3.88 (6H, s), 3.88 (3H, s), 2.84 (2H, t, J = 6.7 Hz), 2.61 (2H, t, J = 6.7 Hz), 2.04 (2H, p, J = 6.8 Hz). ^{13}C NMR (CDCl_3 , 126 MHz): δ 197.3, 153.2, 150.9, 138.5, 137.7, 137.6, 132.7, 132.1, 131.5, 124.2, 120.8, 108.1, 106.8, 61.0, 56.2, 55.7, 25.5, 25.4, 24.6. HRMS: Obsd 406.1629 [$\text{M} + \text{Na}^+$], calcd for $\text{C}_{22}\text{H}_{25}\text{NNaO}_5^+$: 406.1625. HPLC retention time – 5.68 min.

4.1.3. Experimental procedures for naphthol synthesis

4.1.3.1. 6-Methoxy-2-(3,4,5-trimethoxybenzyl)naphthalen-1-ol (3a). (*E*)-6-Methoxy-2-(3,4,5-trimethoxybenzylidene)-3,4-dihydronaphthalen-1(2*H*)-one (2a) (0.26 g, 0.72 mmol) and KOH (0.12 g, 2.16 mmol) were dissolved in methanol (5 mL). The reaction mixture was subjected to microwave irradiation at 160 °C for 30 min. The reaction mixture was neutralized with 2 M HCl and extracted with CH₂Cl₂. The organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, EtOAc/hexanes) afforded 3a (0.22 g, 0.61 mmol, 84% yield) as an orange oil. ¹H NMR (CDCl₃, 600 MHz): δ 8.07 (1H, d, *J* = 9.1 Hz), 7.35 (1H, d, *J* = 8.3 Hz), 7.25 (1H, d, *J* = 8.3 Hz), 7.15 (1H, dd, *J* = 9.1, 2.5 Hz), 7.12 (1H, d, *J* = 2.4 Hz), 6.48 (2H, s), 5.44 (1H, s), 4.09 (2H, s), 3.94 (3H, s), 3.85 (3H, s), 3.79 (6H, s). ¹³C NMR (CDCl₃, 126 MHz): δ 157.7, 153.5, 149.5, 136.6, 135.3, 135.2, 129.5, 123.0, 120.2, 119.3, 117.9, 117.7, 105.7, 105.4, 60.9, 56.1, 55.3, 37.0. HRMS: Obsd 355.1545 [M + H⁺], calcd for C₂₁H₂₃O₅⁺: 355.1540. HPLC retention time – 6.82 min.

4.1.3.2. 5-Bromo-6-methoxy-2-(3,4,5-trimethoxybenzyl)naphthalen-1-ol (3b). (*E*)-5-Bromo-6-methoxy-2-(3,4,5-trimethoxybenzylidene)-3,4-dihydronaphthalen-1(2*H*)-one (2b) (0.21 g, 0.48 mmol) and KOH (0.08 g, 1.45 mmol) were dissolved in methanol (5 mL). The reaction mixture was subjected to microwave irradiation at 160 °C for 30 min. The reaction mixture was neutralized with 2 M HCl and extracted with CH₂Cl₂. The organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, EtOAc/hexanes) afforded 3b (0.19 g, 0.45 mmol, 93% yield) as white crystals. ¹H NMR (CDCl₃, 600 MHz): δ 8.18 (1H, d, *J* = 9.2 Hz), 7.81 (1H, d, *J* = 8.7 Hz), 7.38 (1H, d, *J* = 8.7 Hz), 7.24 (1H, d, *J* = 9.2 Hz), 6.47 (2H, s), 5.46 (1H, s), 4.09 (2H, s), 4.04 (3H, s), 3.85 (3H, s), 3.78 (6H, s). ¹³C NMR (CDCl₃, 126 MHz): δ 153.9, 153.6, 149.5, 136.8, 134.7, 133.6, 130.8, 122.8, 121.4, 118.7, 118.0, 112.7, 108.3, 105.3, 60.9, 57.0, 56.1, 37.1. HRMS: Obsd 457.0443 [M + Na⁺], calcd for C₂₁H₂₁(⁸¹Br)NaO₅⁺: 457.0443. HPLC retention time – 9.28 min.

4.1.3.3. 2-Methoxy-6-(3,4,5-trimethoxybenzyl)naphthalene-1,5-diol (3c). (*E*)-5-Isopropoxy-6-methoxy-2-(3,4,5-trimethoxybenzylidene)-3,4-dihydronaphthalen-1(2*H*)-one (2d) (0.32 g, 0.78 mmol) and KOH (0.13 g, 2.33 mmol) were dissolved in methanol (5 mL). The reaction mixture was subjected to microwave irradiation at 160 °C for 30 min. The reaction mixture was neutralized with 2 M HCl and extracted with CH₂Cl₂. The organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Isomerization to 3d was confirmed by ¹H NMR of the crude reaction mixture. ¹H NMR (CDCl₃, 600 MHz): δ 7.87 (1H, d, *J* = 9.2 Hz), 7.75 (1H, d, *J* = 8.6 Hz), 7.27 (1H, s), 7.25 (1H, d, *J* = 8.6 Hz), 6.50 (2H, s), 4.67 (1H, hept, *J* = 6.1 Hz), 4.09 (2H, s), 3.98 (3H, s), 3.85 (3H, s), 3.81 (6H, s), 1.39 (6H, d, *J* = 6.2 Hz). The crude reaction mixture was then dissolved in CH₂Cl₂ (5 mL) and cooled to 0 °C. BCl₃ (0.27 mL, 0.27 mmol) was added, and the solution was stirred at 0 °C for 30 min. The reaction

mixture was quenched with H₂O and extracted with CH₂Cl₂. The organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, EtOAc/hexanes) afforded 2-methoxy-6-(3,4,5-trimethoxybenzyl)naphthalene-1,5-diol 3c (0.23 g, 0.62 mmol, 79% overall yield) as a brown solid. ¹H NMR (CDCl₃, 600 MHz): δ 7.75 (1H, d, *J* = 8.6 Hz), 7.68 (1H, d, *J* = 9.1 Hz), 7.27 (1H, d, *J* = 8.6 Hz), 7.26 (1H, d, *J* = 9.1 Hz), 6.49 (2H, s), 6.03 (1H, s), 5.22 (1H, s), 4.10 (2H, s), 4.02 (3H, s), 3.85 (3H, s), 3.80 (6H, s). ¹³C NMR (CDCl₃, 126 MHz): δ 153.6, 149.1, 141.5, 139.6, 136.7, 135.1, 128.6, 124.5, 121.2, 117.9, 113.0, 112.5, 105.4, 60.9, 57.1, 56.1, 37.2. HRMS: Obsd 393.1360 [M + H⁺], calcd for C₂₁H₂₂NaO₆⁺: 393.1309. HPLC retention time – 4.51 min.

4.1.3.4. 6-Methoxy-5-nitro-2-(3,4,5-trimethoxybenzyl)naphthalen-1-ol (3e). (*E*)-6-Methoxy-5-nitro-2-(3,4,5-trimethoxybenzylidene)-3,4-dihydronaphthalen-1(2*H*)-one (2e) (0.25 g, 0.63 mmol) and KOH (0.11 g, 1.88 mmol) were dissolved in methanol (5 mL). The reaction mixture was subjected to microwave irradiation at 160 °C for 30 min. The reaction mixture was neutralized with 2 M HCl and extracted with CH₂Cl₂. The organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, EtOAc/hexanes) afforded 3e (0.19 g, 0.48 mmol, 76% yield) as a brown solid. ¹H NMR (CDCl₃, 500 MHz): δ 8.29 (1H, d, *J* = 9.4 Hz), 7.36 (1H, d, *J* = 8.7 Hz), 7.25 (1H, d, *J* = 9.4 Hz), 7.20 (1H, d, *J* = 8.6 Hz), 6.41 (2H, s), 5.68 (1H, s), 4.05 (2H, s), 4.00 (3H, s), 3.81 (3H, s), 3.75 (6H, s). ¹³C NMR (CDCl₃, 126 MHz): δ 153.7, 149.8, 148.7, 136.8, 135.7, 134.2, 132.4, 126.4, 126.2, 120.1, 118.9, 112.6, 112.1, 105.3, 60.9, 57.0, 56.1, 37.0. HRMS: Obsd 422.1208 [M + Na⁺], calcd for C₂₁H₂₁NNaO₇⁺: 422.1210. HPLC retention time – 6.62 min.

4.1.3.5. 5-Amino-6-methoxy-2-(3,4,5-trimethoxybenzyl)naphthalen-1-ol (3f). 6-Methoxy-5-nitro-2-(3,4,5-trimethoxybenzyl)naphthalen-1-ol (3e) (0.25 g, 0.63 mmol) and sodium dithionite (0.11 g, 1.88 mmol) were dissolved in H₂O:ethanol (1:1, 10 mL). The reaction mixture was subjected to microwave irradiation at 160 °C for 30 min. The reaction mixture was extracted with EtOAc. The organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, EtOAc/hexanes) afforded 3f (0.19 g, 0.48 mmol, 76% yield) as a reddish solid. ¹H NMR (CDCl₃, 600 MHz): δ 7.60 (1H, d, *J* = 9.1 Hz), 7.34 (1H, d, *J* = 8.6 Hz), 7.21 (2H, dd, *J* = 10.9, 8.9 Hz), 6.47 (2H, s), 5.67 (1H, s), 4.27 (2H, s), 4.08 (2H, s), 3.96 (3H, s), 3.84 (3H, s), 3.77 (6H, s). ¹³C NMR (CDCl₃, 151 MHz): δ 153.5, 149.6, 142.8, 136.6, 135.6, 129.5, 128.2, 124.5, 121.0, 117.7, 113.0, 112.7, 111.7, 105.5, 60.9, 56.6, 56.1, 36.7. HRMS: Obsd 370.1652 [M + H⁺], calcd for C₂₁H₂₄NO₅⁺: 370.1649. HPLC retention time – 3.53 min.

4.1.4. Experimental procedure for oxime synthesis

4.1.4.1. (*E*)-5-Bromo-6-methoxy-2-((*E*)-3,4,5-trimethoxybenzylidene)-3,4-dihydronaphthalen-1(2*H*)-one oxime (4b)⁴⁸. (*E*)-5-Bromo-6-methoxy-2-(3,4,5-trimethoxybenzylidene)-3,4-dihydronaphthalen-1(2*H*)-one (2b) (1.01 g, 2.31 mmol),

hydroxylamine hydrochloride (0.24 g, 3.47 mmol), and sodium acetate (0.28 g, 3.47 mmol) were dissolved in methanol (100 mL). The reaction mixture was refluxed for 6 h. The reaction mixture was quenched with H₂O and extracted with EtOAc. The organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, EtOAc/hexanes) afforded **4b** (0.57 g, 1.27 mmol, 52% yield) as a white solid. ¹H NMR ((CD₃)₂SO, 500 MHz): δ 11.33 (1H, s), 7.82 (1H, d, *J* = 8.8 Hz), 7.10 (1H, s), 7.01 (1H, d, *J* = 8.9 Hz), 6.63 (2H, s), 3.84 (3H, s), 3.72 (6H, s), 3.60 (3H, s), 2.58 (2H, m), 1.50 (2H, m). ¹³C NMR ((CD₃)₂SO, 126 MHz): δ 156.2, 154.2, 152.9, 138.5, 137.9, 136.8, 125.8, 125.3, 113.1, 110.9, 105.6, 66.2, 60.4, 56.8, 56.2, 33.7, 26.5, 23.0. HRMS: Obsd 448.0756 [M + H⁺], calcd for C₂₁H₂₃BrNO₅⁺: 448.0754. HPLC retention time – 3.41 min.

4.1.4.2. (E)-5-Hydroxy-6-methoxy-2-((E)-3,4,5-trimethoxybenzylidene)-3,4-dihydronaphthalen-1(2H)-one oxime (4c)⁴⁸. (E)-5-Hydroxy-6-methoxy-2-(3,4,5-trimethoxybenzylidene)-3,4-dihydronaphthalen-1(2H)-one (**2c**) (0.11 g, 0.30 mmol), hydroxylamine hydrochloride (0.03 g, 0.45 mmol), and sodium acetate (0.04 g, 0.45 mmol) were dissolved in methanol (10 mL). The reaction mixture was refluxed for 6 h. The reaction mixture was quenched with H₂O and extracted with EtOAc. The organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, EtOAc/hexanes) afforded **4c** (0.05 g, 0.14 mmol, 45% yield) as a white solid. ¹H NMR ((CD₃)₂SO, 600 MHz): δ 11.13 (1H, s), 8.60 (1H, s), 7.32 (1H, d, *J* = 8.6 Hz), 7.08 (1H, s), 6.87 (1H, d, *J* = 8.7 Hz), 6.65 (2H, s), 3.81 (3H, s), 3.77 (6H, s), 3.65 (3H, s), 2.54 (2H, d, *J* = 5.2 Hz), 1.59 (1H, m), 1.49 (1H, m). ¹³C NMR ((CD₃)₂SO, 151 MHz): δ 155.0, 153.0, 147.8, 143.3, 138.3, 136.8, 125.6, 124.3, 105.6, 66.6, 60.4, 56.3, 33.9, 23.1, 19.2. HRMS: Obsd 386.1599 [M + H⁺], calcd for C₂₁H₂₄NO₆⁺: 386.1598. HPLC retention time – 1.55 min.

4.1.5. Experimental procedure for cyclopropa[a]naphthalene synthesis

4.1.5.1. 5-Methoxy-1-(3,4,5-trimethoxyphenyl)-1a,2,3,7b-tetrahydro-1H-cyclopropa[a]naphthalene (5a)^{55–58}. A mixture of hydrazine monohydrate (4.26 mL, 85.1 mmol), KOH (4.52 g, 80.5 mmol), diethylene glycol (75 mL), and (E)-6-methoxy-2-(3,4,5-trimethoxybenzylidene)-3,4-dihydronaphthalen-1(2H)-one (**2a**) (1.77 g, 5.01 mmol) was heated at 150 °C for 90 min. H₂O generated during the reaction and excess hydrazine hydrate were removed by distillation. The reaction mixture was then heated to 195 °C for an additional 4 h. The reaction mixture was poured over ice and extracted with CH₂Cl₂. The organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, EtOAc/hexanes) afforded **5a** (1.61 g, 4.70 mmol, 94% yield) as white crystals. ¹H NMR (CDCl₃, 500 MHz): δ 7.18 (1H, d, *J* = 8.3 Hz), 6.71 (1H, dd, *J* = 8.3, 2.6 Hz), 6.64 (1H, d, *J* = 2.4 Hz), 6.32 (2H, s), 3.85 (6H, s), 3.82 (3H, s), 3.78 (3H, s), 2.59 (2H, m), 2.25 (1H, ddt, *J* = 13.1, 4.8, 2.3 Hz), 2.18 (1H, t, *J* = 4.4 Hz), 2.14 (1H, dd, *J* = 8.6, 3.8 Hz),

1.94 (1H, dq, *J* = 7.8, 2.4 Hz), 1.82 (1H, tdd, *J* = 12.9, 6.5, 3.3 Hz). ¹³C NMR (CDCl₃, 126 MHz): δ 157.4, 153.2, 138.4, 134.8, 129.3, 129.2, 129.2, 114.3, 111.6, 110.0, 102.4, 97.3, 60.9, 56.1, 55.3, 27.7, 26.3, 26.0. HRMS: Obsd 377.1662 [M + Na⁺], calcd for C₂₁H₂₄NaO₄⁺: 363.1567. HPLC retention time – 11.76 min.

4.1.5.2. 4-Bromo-5-methoxy-1-(3,4,5-trimethoxyphenyl)-1a,2,3,7b-tetrahydro-1H-cyclopropa[a]naphthalene (5b)^{55–58}. A mixture of hydrazine monohydrate (2.55 mL, 52.0 mmol), KOH (2.76 g, 49.3 mmol), diethylene glycol (75 mL), and (E)-5-bromo-6-methoxy-2-(3,4,5-trimethoxybenzylidene)-3,4-dihydronaphthalen-1(2H)-one (**2b**) (1.33 g, 3.06 mmol) was heated at 150 °C for 90 min. H₂O generated during the reaction and excess hydrazine hydrate were removed by distillation. The reaction mixture was then heated to 195 °C for an additional 4 h. The reaction mixture was poured over ice and extracted with CH₂Cl₂. The organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (silica gel, EtOAc/hexanes) afforded **5b** (1.09 g, 2.60 mmol, 85% yield) as white crystals. ¹H NMR (CDCl₃, 500 MHz): δ 7.18 (1H, d, *J* = 8.3 Hz), 6.73 (1H, d, *J* = 8.3 Hz), 6.32 (2H, s), 3.87 (3H, s), 3.85 (6H, s), 3.82 (3H, s), 3.23 (1H, dd, *J* = 16.9, 5.2 Hz), 2.30 (2H, m), 2.15 (2H, d, *J* = 6.8 Hz), 1.95 (1H, m), 1.80 (1H, dtd, *J* = 13.3, 6.8, 5.7, 3.3 Hz). ¹³C NMR (CDCl₃, 126 MHz): δ 153.8, 153.3, 138.0, 136.0, 134.5, 131.4, 127.8, 114.7, 109.6, 102.4, 56.4, 56.1, 28.0, 26.6, 25.7, 24.8, 19.0. HRMS: Obsd 441.0672 [M + Na⁺], calcd for C₂₁H₂₃BrNaO₄⁺: 441.0672. HPLC retention time – 15.10 min.

4.1.6. Confirmation that target molecules are not PAINS molecules. Each target molecule and several common motifs were screened using the zinc15 docking algorithm (<http://zinc15.docking.org/patterns/home>), which provided confirmation that the reported chalcones and corresponding analogues are not pan assay interference compounds (PAINS). A molecule previously identified as a PAIN molecule was screened to provide positive confirmation that the algorithm was functioning accurately.⁶⁷

4.2. Biological evaluation

4.2.1. Cell lines and sulforhodamine B (SRB) assay. Inhibition of growth of human cancer cells was assessed using the sulforhodamine B assay (SRB), as previously described.^{68–70} Briefly, cancer cell lines (DU-145, SK-OV-3, and NCI-H460) (obtained from ATCC) were plated at 7000–8000 cells/well into 96-well plates using DMEM supplemented with 5% fetal bovine serum/1% gentamicin sulfate and incubated for 24 h at 37 °C in a humidified incubator in a 5% CO₂ atmosphere. Compounds to be tested were dissolved in DMSO to generate a 10 mg mL^{−1} stock solution. Serial dilutions were made and added to the plates. Doxorubicin and paclitaxel were used as positive controls. After a 48 h treatment, the cells were fixed with trichloroacetic acid (10% final concentration), washed with water, dried, stained with a SRB dye containing 1% acetic acid, washed to remove excess dye with 1% acetic acid, and dried. SRB dye was solubilized with 200 μL of 10 mM

Tris solution per well, and absorbances were measured at wavelength 540 nm and normalized to values at wavelength 630 nm using an automated BioTek plate reader. A growth inhibition of 50% (GI₅₀ or the drug concentration causing 50% reduction in the net protein increase) was calculated from the absorbance data.

4.2.2. HUVEC growth and sulforhodamine B (SRB) assay. HUVECs were obtained from Invitrogen, and grown and maintained in M200 (ATCC) media supplemented with VEGF growth factor kit (ATCC), 1% gentamicin sulfate, and 1% amphotericin B in collagen I coated T75 flasks. Cells were removed from the T75 flasks using Tryple reagent and plated into 96 well plates (Corning Costar) at a concentration of 9000 cells/well in 100 µL of media for an SRB assay. Cells were allowed 48 hours to plate down prior to treatment. Compounds were serially diluted using 10-fold dilutions in M200 media supplemented with LSGS growth kit, 1% gentamicin sulfate, and 1% amphotericin B. GI₅₀ values were calculated as the drug concentration that inhibited growth by 50%. The use of the LSGS growth kit was to approximate a more normal and less activated phenotype typical of normal endothelium.

4.2.3. Tubulin assays. Inhibition of tubulin polymerization and percent inhibition of [³H]colchicine binding to tubulin were performed as described previously.²⁵

Conflicts of interest

A portion of the work presented in this manuscript was funded through Mateon Therapeutics, Inc. (formerly OXiGENE Inc.), and this relationship is properly indicated in the acknowledgement section. One of the authors (KGP) is a current shareholder. We are pleased with this productive and useful long-term scientific collaboration and funding relationship with Mateon Therapeutics, Inc., and it is important to note that there is no actual conflict of interest associated with the science presented in this manuscript.

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