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Studies toward the Development of Antiproliferative Neoclerodanes from Salvinorin A

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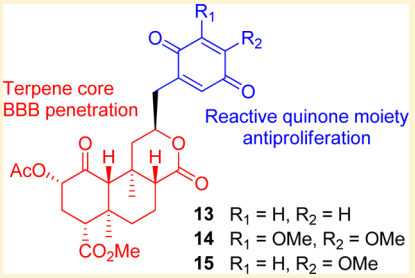
Supporting Information

ABSTRACT: The success rate for central nervous system (CNS) drug candidates in the clinic is relatively low compared to the industry average across other therapeutic areas. Penetration through the blood–brain barrier (BBB) to reach the therapeutic target is a major obstacle in development. The rapid CNS penetration of salvinorin A has suggested that the neoclerodane nucleus offers an excellent scaffold for developing antiproliferative compounds that enter the CNS. The Liebeskind–Srogl reaction was used as the main carbon–carbon bond-forming step toward the synthesis of quinone-containing salvinorin A analogues. Quinone-containing salvinorin A analogues were shown to have antiproliferative activity against the MCF7 breast cancer cell line, but show no significant activity at the κ-opioid receptors. In an in vitro model of BBB penetration, quinone-containing salvinorin A analogues were shown to passively diffuse across the cell monolayer. The analogues, however, are substrates of P-glycoprotein, and thus further modification of the molecules is needed to reduce the affinity for the efflux transporter.



In 2010, it was estimated that approximately 688 000 people in the United States are living with primary tumors of the brain and central nervous system (CNS), 138 000 of which are living with malignant tumors and 550 000 with nonmalignant tumors.[1] According to the Central Brain Tumor Registry of the United States (CBTRUS), approximately 69 720 new cases of primary tumors and nonmalignant brain and CNS tumors were expected to be diagnosed in 2013 in the United States. One of the most prevalent primary tumors in the CNS is gliomas. Seventy percent of all CNS gliomas are malignant, and this type of CNS cancer has been shown to be the most frequent and lethal of the cancers originating in the CNS, with a high rate of recurrence and mortality.[2,3] Several therapeutic strategies are available; however, they are not efficient for every patient with recurrent glioblastoma, and prognosis remains uncertain. Thus, new agents and novel diagnostic tools are necessary for the improvement of the outcome for glioblastoma patients. The discovery of novel biological probes could help us gain a better understanding of this disease state, which could in turn assist in faster diagnosis of affected patients, providing them with a greater survival rate.

The use of natural products has been documented in many ancient civilizations that were utilizing natural products in their ethnomedicinal traditions and spiritual practices. They represent secondary metabolites that are produced by various organisms in response to external stimuli such as temperature, growth, infection, and stress from competition.[4] Natural products have played a major role in the discovery and development of drugs for the treatment of various human diseases.[5] That natural products are well represented in the pharmaceutical industry is demonstrated by the fact that one-third of the top-selling drugs in the world are natural products or natural product derivatives.[4] Natural products as well as natural product derived entities have contributed to the development of various anti-infectives, anticholesteromics, and antitumor agents, most of which are still actively used in the clinic.[6] Because of the vast structural diversity that nature has provided, it is safe to say that further investigation into natural products and their derivatives can provide us with novel drug entities and biological probes.

Nakijiquinones are marine sesquiterpene quinones that were isolated from an Okinawan sponge of the Spongiidae family in the early 1990s.[7] These natural products possess three distinct structural elements: a terpene core, an amino acid side chain, and a central *p*-quinoid moiety (examples in Chart 1).[7−12] Upon their isolation, this family of quinones was shown to be the first naturally occurring inhibitors of the Her-2/Neu receptor tyrosine kinase.[8] Cytotoxicity assays in murine leukemia and human epidermoid carcinoma cells demonstrated IC_{50} values for several of the isolated quinones in the range 0.5 to 6 μg/mL, making them compounds of pronounced interest.[7,8,10]

Recently, some clerodane diterpenes have also demonstrated cytotoxicity against several cell lines.[13−16] Therefore, it is unclear whether the antiproliferative activity of the nakijiquinones is due to the quinone, the terpene core, or their combination. The terpene core of these molecules, however, offers few options for structural manipulation and compound optimization.

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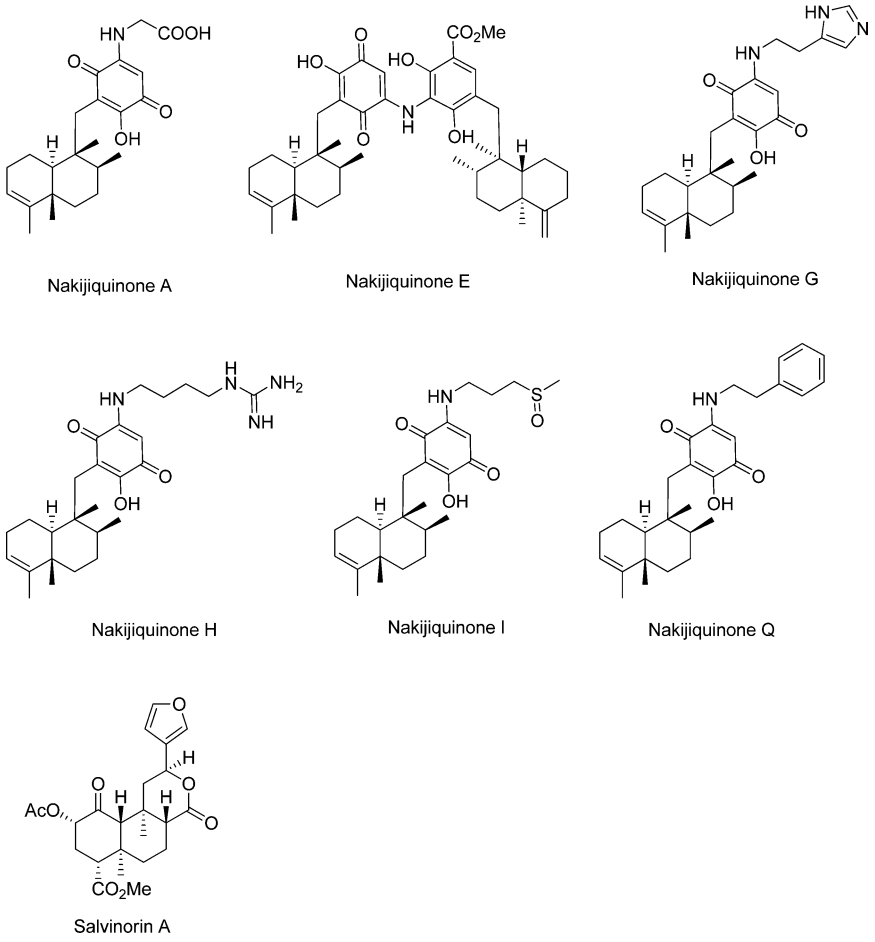
Chart 1. Examples of Nakijiquinones Isolated from an Okinawan Sponge of the Spongiidae Family and Salvinorin A



One clerodane that has not been explored for its cytotoxic activity is salvinorin A.[17−19] Previous studies have shown that salvinorin A, a potent κ-opioid receptor (KOP) agonist, is able to cross the blood−brain barrier (BBB) within 1 min of intravenous or inhaled administration,[20−22] although it is a substrate for P-glycoprotein (P-gp).[21] On the basis of its rapid CNS penetration, the neoclerodane nucleus offers an excellent scaffold for the development of CNS cancer probes that could be used as potential diagnostic tools. In addition, the salvinorin A nucleus offers additional opportunities for optimizing the activity of such biological probes due to the various chemical handles already present in the salvinorin A diterpene core.

Therefore, we hypothesized that a combination of the salvinorin A nucleus and the nakijiquinone *p*-quinoid moiety will result in a novel scaffold that is expected to pass the BBB and have antiproliferative activity (Figure 1). As a first step, we evaluated a series of quinone-containing analogues similar in structure to the quinone moiety in the nakijiquinones. It was envisioned that these modifications would provide an initial proof of concept before embarking on a more complex synthetic undertaking. The resulting molecules showed no activity at the KOP, but exhibited antiproliferative activity against cancer cell lines. Finally, the salvinorin A quinones are predicted to rapidly cross the BBB by passive diffusion and are an important starting point for the development of novel probes for studying CNS cancers.

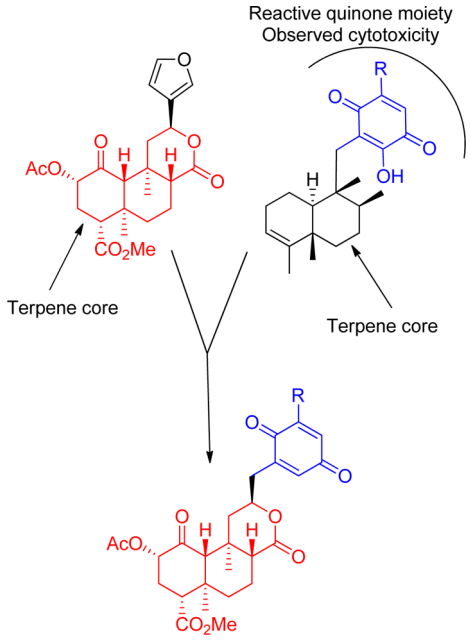


Figure 1. Design strategy.

RESULTS AND DISCUSSION

Chemistry. The use of the Liebeskind−Srogl reaction as the main carbon−carbon bond cross-coupling step was based on the recent observation that the mild coupling conditions of this

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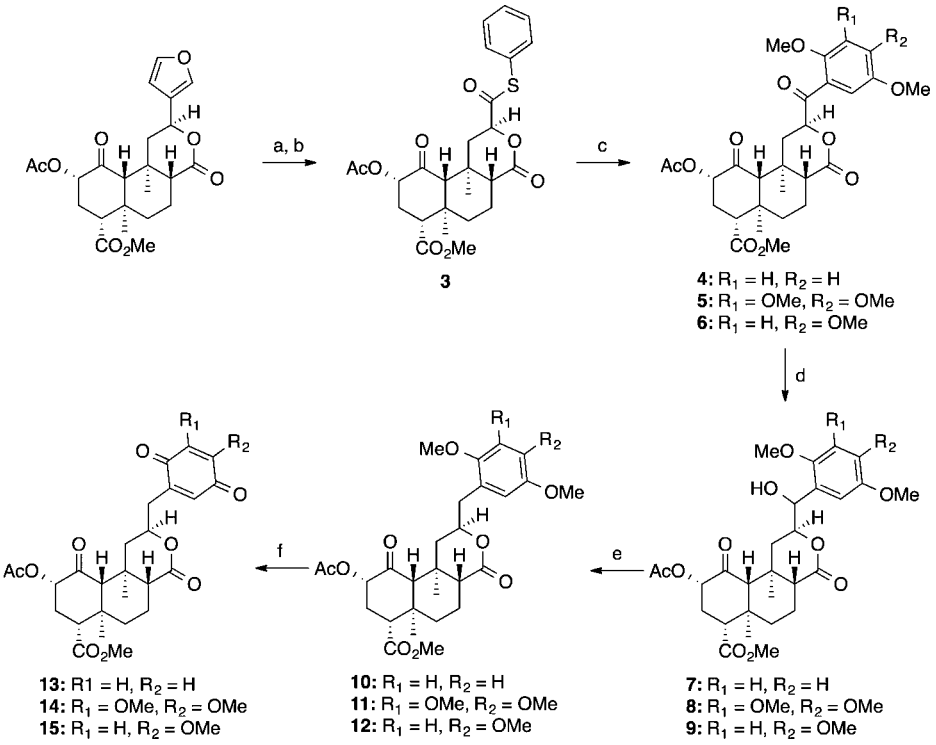
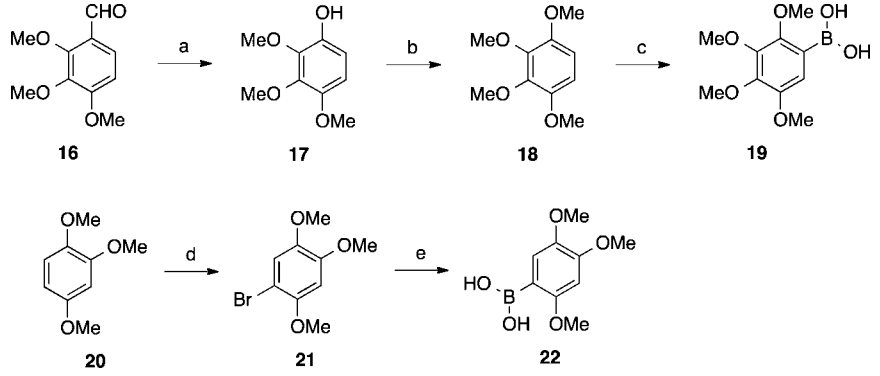
Scheme 1[a]



[a]Reagents and conditions: (a) $NaIO_4$, $RuCl_3{\cdot}3H_2O$, $CCl_4/CH_3CN/H_2O$; (b) PhSH, CDMT, NMM, THF; (c) CuTC, $Pd(dba)_2$, $RB(OH)_2$, $P(OEt)_3$, THF; (d) (*R*)-(+)-2-methyl CBS reagent, borane-dimethyl sulfide complex, toluene, −78 to −30 °C; (e) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt; (f) CAN, CH_3CN, rt.

Scheme 2[a]



[a]Reagents and conditions: (a) H_2O_2, H_2SO_4, MeOH; (b) K_2CO_3, MeI, acetone; (c) *n*-BuLi, $B(OMe)_3$, THF, −78 °C to rt; (d) Br_2, CH_2Cl_2, 0 °C; (e) *n*-BuLi, trimethyborate, THF, −78 °C.

reaction, which utilize bis(dibenzylideneacetone)palladium(0), copper(I) thiophene carboxylate, and triethylphosphite at ambient temperature, are well tolerated by the salvinorin A scaffold.[23] As described previously, salvinorin A was isolated from *Salvia divinorum* leaves and subjected to oxidative degradation utilizing sodium periodate and ruthenium(III) chloride to yield the corresponding carboxylic acid in 74% yield. The resulting acid was then esterified with thiophenol to yield thioester **3** in 60% yield (Scheme 1).[21] Thioester **3** was used as the key intermediate for the synthesis of our targeted quinones. The reaction of **3** with several different boronic acids yielded aromatic ketones **4**−**6** in 48%, 79%, and 90% yield, respectively. Ketones **4**−**6** were reduced using Corey−Bakshi−Shibata (CBS) conditions to yield benzylic alcohols **7**−**9** in 64−90% yield. Deoxygenation of **7**−**9** was accomplished using trimethylsilane and boron trifluoride diethyl etherate to give methylene analogues **10**−**12**. Finally, oxidation of **10**−**12** with ceric ammonium nitrate (CAN) gave quinones **13**−**15** in 28−72% yield.

Several of the necessary boronic acids were prepared following published reports.[24,25] 2,3,4,5-Tetramethoxyphenylboronic acid was synthesized following and slightly modifying conditions proposed by Tremblay and co-workers (Scheme 2).[24] Oxidation of 2,3,4-trimethoxybenzaldehyde (**16**) with hydrogen peroxide afforded phenol **17** in 84% yield. Methylation of **17** with iodomethane under basic conditions gave 1,2,3,4-tetramethoxybenzene (**18**) in 67% yield. Treatment of **18** with *n*-butyllithium followed by trimethylborate

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gave boronic acid **19** in 52% yield. 2,4,5-Trimethoxyphenylboronic acid was prepared following conditions proposed by Sutherland and co-workers.[25] The reaction of 1,2,4-trimethoxybenzene **20** with bromine gave bromobenzene **21** in 96% yield. Treatment of **21** with *n*-butyllithium followed by trimethylborate afforded boronic acid **22** in 38% yield.

Biological Testing. Two natural product scaffolds were utilized to afford analogues in which the C-12 furanyl moiety of salvinorin A was replaced with functionalized *p*-benzoquinone groups, which were tested for activity at KOP as well as antiproliferative properties. Analogues **13**−**15** were subjected to a calcium mobilization assay, which is a functional assay that will determine their activity at the KOP (Table 1). Salvinorin A showed full efficacy and potency (EC_{50} of 1.7 ± 0.6 nM), consistent with previous observations.[26] Analogues **13**−**15** showed little to no agonist activity at the KOP, which is consistent with observed SAR trends, wherein replacing the furan ring of salvinorin A generally reduces affinity, efficacy, and potency for the KOP.[26]

Table 1. KOP Activity Using a Calcium Mobilization Assay

cmpd	EC_{50} (nM)[a]	E_{max}[b]
Salvinorin A	1.7 ± 0.6	103 ± 2
13	2500 ± 900	27 ± 4
14	>10 000[c]	ND[d]
15	>10 000[c]	ND[d]

[a]EC_{50} = concentration for 50% maximal response; mean ± SEM, n = 2. [b]E_{max} = % stimulation compared to (−)-U-69,593; mean ± SEM n = 2. [c]EC_{50} could not be calculated because no activity was observed. [d]ND = not determined.

To determine whether the salvinorin A-derived analogues exhibited antiproliferative activity, their effects on the growth of the MCF7 breast cancer cell line were tested (Table 2). The positive controls geldanamycin (GDA) and 1,4-benzoquinone (1,4-BQ) inhibited over 80% of cell growth compared to DMSO-treated controls, with potencies of 0.04 and 2.57 μM, respectively. Similarly, salvinorin A-derived analogues, **13**−**15**, show antiproliferative efficacy, inhibiting between 77% and 86% of cell growth, with potencies of 6.54, 2.70, and 5.84 μM, respectively. Salvinorin A did not show any detectable antiproliferative effects, suggesting that the activity of analogues **13**−**15** is due primarily to the quinone moiety. Similar results were obtained from an additional breast cancer cell line (SKBr3; data not shown). Additional information is needed before a conclusion about an optimal substitution pattern for the quinone ring can be reached.

Table 2. Antiproliferative Activity in MCF7 Breast Cancer Cell Line

cmpd	IC_{50} (μM)[a]	% inhibition[b]
GDA	0.04 ± 0.02	81 ± 3
1,4-BQ	2.57 ± 0.81	85 ± 0.3
salvinorin A	>100[c]	ND[d]
13	6.54 ± 1.57	77 ± 8
14	2.70 ± 0.91	86 ± 3
15	5.84 ± 0.50	83 ± 4

[a]IC_{50} = concentration for 50% growth inhibition. Data are mean ± SEM, n = 2−5. [b]% growth inhibition compared to DMSO-treated cells. Data are mean ± SEM, n = 2−5. [c]IC_{50} could not be calculated because no inhibition occurred. [d]ND = not determined.

Salvinorin A-derived analogues were tested in an in vitro model of BBB penetration (Table 3). The MDCK-MDR1 cell line (Madin-Darby canine kidney cells stably transfected with MDR1; MDR1, multidrug resistance gene 1) has been useful in determining whether compounds may passively diffuse across a cell monolayer and whether they may be substrates for P-gP, an important efflux transporter in the BBB and gene product of MDR1.[27,28] Caffeine, which is not a P-gp substrate, shows high transport from the apical to the basolateral side of the cell monolayer with and without P-gp inhibition by verapamil (73.0% and 85.9% transport, respectively),[29] indicative of passive diffusion and limited efflux by P-gp. In contrast, prazosin, a known P-gp substrate,[30] shows significantly less transport from the apical to basolateral side of the membrane. Pretreatment with verapamil, however, significantly increases the transport of prazosin to the basolateral side, indicating that the control compound prazosin passively diffuses across the monolayer and is actively effluxed by P-gp. Salvinorin A and the two benzoquinoids **14** and **15** show similar results to prazosin, suggesting that they passively diffuse across the cell monolayer and are actively effluxed by P-gp, consistent with salvinorin A being a known P-gp substrate.[21,31] Therefore, these benzoquinoids are predicted to rely heavily on passive diffusion to enter the brain, similar to salvinorin A.[20−22] Since the short duration of action of salvinorin A is due in part to its affinity for the P-gp, manipulation of the salvinorin A scaffold may be necessary to reduce efflux, in order to pursue novel cancer therapies and/or diagnostic probes based on this approach. Alternatively, a targeting strategy may be utilized to direct the compounds to cancer cells.

Table 3. In Vitro Model of Brain Penetration in MDCK-MDR1 Cells (% Transport[a])

	pretreatment	
cmpd	vehicle[b]	verapamil[c]
caffeine	85.9 ± 2.4###	73.0 ± 17.8
prazosin	6.7 ± 1.8	35.5 ± 2.1***
salvinorin A	21.2 ± 3.2	54.2 ± 3.4**
14	5.0 ± 1.5	47.2 ± 11.9**
15	9.7 ± 3.4	38.4 ± 5.3**

[a]% transport equals ratio of basolateral to apical concentration of test compound. Data are mean ± SEM; n = 3−5. [b]One-way ANOVA: $F_{(4,13)} = 93.33$, $p < 0.0001$; Bonferroni post-test ###$p < 0.001$ versus all other compounds after vehicle pretreatment. [c]**$p < 0.01$, ***$p < 0.001$ versus vehicle pretreatment, Student's t test.

The similarity between two natural products, the plant-derived diterpenoid salvinorin A and the marine sponge derived nakijiquinone family of natural products, prompted an idea that a combination of the two scaffolds may yield biological probes that could have potential in CNS-related cancers. Several compounds were synthesized with similarities to both scaffolds, i.e., salvinorin A analogues that possess a C-12 quinone instead of a furanyl moiety. These benzoquinoids exhibited negligible activity at the KOP receptors, but exhibited moderate antiproliferative activity due to the quinonoid moiety. Finally, the salvinorin A-derived benzoquinoids are predicted to passively diffuse across a membrane, but are subject to active efflux by P-gp. These promising results are indicative of the possibility for use of these salvinorin A-derived compounds as

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biological probes in the study of certain brain cancers. This represents the first report of salvinorin A-derived compounds that exhibit antiproliferative activity.

EXPERIMENTAL SECTION

General Experimental Procedures. Unless otherwise indicated, all reagents were purchased from commercial sources and were used without further purification. Melting points were determined on a Thomas-Hoover capillary melting apparatus. NMR spectra were recorded on a Bruker DRX-400 with a qnp probe or a Bruker AV-500 with a cryoprobe using δ values in ppm (TMS as internal standard) and J (Hz) assignments of ^{1}H resonance coupling. HRMS data were collected on either an LCT Premier (Waters Corp., Milford, MA, USA) TOF mass spectrometer or an Agilent 6890 N gas chromatograph in conjunction with a Quarto Micro GC mass spectrometer (Micromass Ltd., Manchester, UK). TLC was performed on 0.25 mm Analtech GHLF silica gel plates using EtOAc/*n*-hexanes, in 1:1 v/v ratio, as the solvent unless otherwise noted. Spots on TLC were visualized by UV (254 or 365 nm), if applicable, and phosphomolybdic acid in EtOH. Column chromatography was performed with silica gel (40−63 μm particle size) from Sorbent Technologies (Atlanta, GA, USA). Analytical HPLC was carried out on an Agilent 1100 Series capillary HPLC system with diode array detection at 254 nm on an Agilent Eclipse XDB-C_{18} column (250 × 10 mm, 5 μm) with isocratic elution in CH_3CN/H_2O (3:2, v/v) unless otherwise specified.

General Procedure A: Liebskind−Srogl Coupling Reaction. Thioester **3** (1 equiv), appropriate boronic acid (3 equiv), bis(dibenzylideneacetone)palladium(0) (5 mol %), and copper(I) thiophene carboxylate (1.5 equiv) were placed in a 100 mL round-bottom flask and flushed twice with argon. Anhydrous THF was added immediately followed by triethylphosphite (20 mol %, color change from red to green with a brown tint). The reaction was allowed to stir at ambient temperature and upon completion (TLC monitoring) was diluted with Et_2O (30 mL). The organic portion was washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using mixtures of EtOAc/*n*-hexanes.

General Procedure B: CBS Reduction. The corresponding aromatic ketone (1 equiv) was placed in a round-bottom flask and flushed three times with argon. A solution of (*R*)-(+)-2-methyl-CBS-oxazaborolidine (1 M in toluene, 1 equiv) was added, the temperature was cooled to −78 °C, and the solution was allowed to stir for 5 min. A solution of borane-dimethyl sulfide complex (2 M in diethyl ether, 1 equiv) was added dropwise, and the mixture was warmed to −30 °C and allowed to stir until completion (TLC monitoring). Upon completion, MeOH (1 mL), H_2O (0.5 mL), and Et_2O (5 mL) were added, and the mixture was warmed to room temperature over a period of 1 h. H_2O (20 mL) and Et_2O (20 mL) were added, and the two layers separated. The aqueous layer was washed with two additional portions of Et_2O, the combined organic layers were washed with brine and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using mixtures of EtOAc/*n*-hexanes.

General Procedure C: Deoxygenation Procedure. The corresponding alcohol (1 equiv, 0.21 mmol) was placed in a round-bottom flask and flushed with argon. CH_2Cl_2 (10 mL) was added, and the mixture was cooled to 0 °C. Triethylsilane (2 equiv) was added, and the mixture was stirred for 2 min. Boron trifluoride diethyl etherate (2 equiv) was added dropwise, and the resulting mixture was allowed to stir at 0 °C until completion (TLC monitoring). The reaction was quenched with H_2O, and the mixture was warmed to ambient temperature. The mixture was extracted with EtOAc (3 × 20 mL), dried (Na_2SO_4), and concentrated to dryness under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using mixtures of EtOAc/*n*-hexanes.

General Procedure D: Quinone Formation. An aqueous solution of ceric(IV) ammonium nitrate (2−3 equiv, 0.42 mmol, 1.4 mL) was added dropwise to a solution of salvinorin A derivative (1 equiv, 0.21 mmol) in MeCN (7 mL) at ambient temperature. The reaction was stirred until completion (TLC monitoring), CH_2Cl_2 (20 mL) was added, and the resulting mixture was washed with H_2O and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel using mixtures of EtOAc/*n*-hexanes.

(2*S*,4a*R*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-Methyl 9-Acetoxy-2-(2,5-dimethoxybenzoyl)-6a,10b-dimethyl-4,10-dioxododecahydro-1*H*-benzo[*f*]isochromene-7-carboxylate (4). Compound **4** was synthesized from compound **3** using general procedure A and commercially available 2,5-dimethoxyphenylboronic acid to afford 0.250 g (48% yield) of a white solid, mp = 97−100 °C. TLC system: 45% EtOAc/55% *n*-hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, J = 3.2 Hz, 1H), 7.10 (dd, J = 9.0, 3.2 Hz, 1H), 6.93 (d, J = 9.0 Hz, 1H), 5.95 (t, J = 8.1 Hz, 1H), 5.13−5.03 (m, 1H), 3.90 (s, 3H), 3.80 (s, 3H), 3.71 (s, 4H), 2.78−2.66 (m, 2H), 2.31−2.22 (m, 2H), 2.19−2.07 (m, 7H), 1.80−1.60 (m, 3H), 1.54 (td, J = 13.4, 3.8 Hz, 1H), 1.42 (s, 3H), 1.40−1.32 (m, 1H), 1.07 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.84, 196.68, 171.61, 169.78, 153.78, 153.42, 124.04, 122.28, 114.45, 113.45, 79.12, 74.86, 65.02, 56.20, 55.84, 53.31, 51.96, 49.45, 42.04, 38.04, 37.88, 35.58, 30.75, 20.64, 18.31, 16.68, 16.05; HRMS (m/z) [M + Na]$^+$ calcd for $C_{28}H_{34}NaO_{10}$ 553.2050, found 553.2063.

(2*S*,4a*R*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-Methyl 9-Acetoxy-2-[(2,5-dimethoxyphenyl)(hydroxy)methyl]-6a,10b-dimethyl-4,10-dioxododecahydro-1*H*-benzo[*f*]isochromene-7-carboxylate (7). Compound **7** was synthesized from compound **4** using general procedure B to afford 0.31 g (90% yield) of a white solid, mp = 125−128 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (dd, J = 11.1, 2.5 Hz, 1H), 6.85−6.70 (m, 2H), 5.27 (dd, J = 5.2, 3.1 Hz, 1H), 5.12 (dd, J = 12.4, 7.5 Hz, 1H), 3.78−3.76 (m, 5H), 3.72 (d, J = 4.7 Hz, 3H), 2.80−2.70 (m, 2H), 2.35−2.19 (m, 2H), 2.19−2.09 (m, 5H), 2.02 (dd, J = 11.5, 3.3 Hz, 1H), 1.87 (dd, J = 13.2, 6.1 Hz, 1H), 1.75 (dt, J = 10.1, 2.9 Hz, 1H), 1.60−1.52 (m, 3H), 1.30 (s, 3H), 1.06 (d, J = 6.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.16, 172.13, 171.67, 169.60, 153.82, 150.10, 127.29, 113.79, 113.21, 111.26, 78.80, 74.92, 70.54, 64.28, 55.92, 55.72, 53.44, 51.94, 50.56, 42.13, 38.10, 34.85, 34.81, 30.91, 20.60, 18.18, 16.15, 15.21; HRMS (m/z) [M + Na]$^+$ calcd for $C_{28}H_{36}NaO_{10}$ 555.2206; found 555.2217.

(2*S*,4a*R*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-Methyl 9-Acetoxy-2-(2,5-dimethoxybenzyl)-6a,10b-dimethyl-4,10-dioxododecahydro-1*H*-benzo[*f*]isochromene-7-carboxylate (10). Compound **10** was synthesized from compound **7** using general procedure C to afford 0.11 g (36% yield) of a white solid, mp = 96−98 °C. TLC system: 40% EtOAc/60% *n*-hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79−6.73 (m, 3H), 5.12 (dd, J = 11.6, 8.4 Hz, 1H), 4.76 (dq, J = 11.3, 5.6 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.72 (s, 3H), 2.91 (dd, J = 5.8, 2.7 Hz, 2H), 2.73 (dd, J = 11.7, 5.2 Hz, 1H), 2.33−2.23 (m, 3H), 2.17 (s, 3H), 2.14−2.06 (m, 2H), 1.92−1.83 (m, 1H), 1.79−1.71 (m, 1H), 1.59−1.49 (m, 2H), 1.33 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.11, 171.61, 171.58, 169.88, 153.31, 151.83, 125.67, 117.47, 112.57, 111.30, 75.05, 64.20, 55.79, 55.73, 53.58, 51.96, 51.23, 42.25, 42.15, 38.22, 37.22, 35.08, 30.81, 20.60, 18.16, 16.31, 15.18; HRMS (m/z) [M + Na]$^+$ calcd for $C_{28}H_{36}NaO_9$ 539.2257; found 539.2269.

(2*S*,4a*R*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-Methyl 9-Acetoxy-2-[(3,6-dioxocyclohexa-1,4-dien-1-yl)methyl]-6a,10b-dimethyl-4,10-dioxododecahydro-1*H*-benzo[*f*]isochromene-7-carboxylate (13). Compound **13** was synthesized from compound **10** using general procedure D to afford 0.04 g (39% yield) of a yellow solid, mp = dec at 212−214 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.80−6.72 (m, 2H), 6.70 (dd, J = 2.3, 1.2 Hz, 1H), 5.14 (dd, J = 11.5, 8.5 Hz, 1H), 4.69 (dddd, J = 11.9, 9.6, 4.9, 3.2 Hz, 1H), 3.73 (s, 3H), 2.81−2.70 (m, 2H), 2.60−2.50 (m, 1H), 2.39 (dd, J = 13.3, 4.8 Hz, 1H), 2.34−2.25 (m, 2H), 2.18 (s, 3H), 2.12 (d, J = 3.7 Hz, 1H), 1.97 (dd, J = 11.5, 3.1 Hz, 1H), 1.81−1.74 (m, 1H), 1.65−1.57 (m, 1H), 1.53 (s, 1H), 1.35 (s, 3H), 1.32−1.22 (m, 1H), 1.09 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.91, 187.17, 187.10, 171.50, 170.74, 170.00, 143.61, 136.61, 136.59, 135.20, 75.11, 75.03, 64.04, 53.60, 52.00, 51.41, 43.04, 42.09, 38.14, 36.78, 35.26, 30.75, 20.59, 18.12, 16.37, 15.17; HRMS (m/z) [M + K]$^+$ calcd for $C_{26}H_{30}KO_9$ 525.1527, found 525.1528; HPLC t_R = 6.424; purity = 99.2%.

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(2*S*,4a*R*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-Methyl 9-Acetoxy-6a,10b-dimethyl-4,10-dioxo-2-(2,3,4,5-tetramethoxybenzoyl)-dodecahydro-1*H*-benzo[*f*]isochromene-7-carboxylate (5). Compound **5** was synthesized from compound **3** using general procedure A and 2,3,4,5-tetramethoxyphenylboronic acid[24] to afford 0.57 g (79% yield) of an amorphous solid. TLC system: 45% EtOAc/55% *n*-hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (s, 1H), 5.88 (t, *J* = 8.2 Hz, 1H), 5.13−5.04 (m, 1H), 3.98 (s, 3H), 3.94 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H), 3.72 (s, 3H), 2.71 (ddd, *J* = 12.1, 8.3, 2.5 Hz, 2H), 2.28 (td, *J* = 9.5, 2.2 Hz, 2H), 2.18−2.17 (m, 3H), 2.14−2.13 (m, 3H), 2.12 (s, 1H), 1.76 (dt, *J* = 13.4, 3.2 Hz, 1H), 1.72−1.58 (m, 2H), 1.43 (s, 3H). 1.07 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.81, 196.30, 171.58, 171.37, 169.80, 149.46, 148.77, 148.54, 146.62, 122.46, 107.23, 78.79, 74.89, 64.92, 62.02, 61.25, 56.16, 53.38, 51.97, 49.51, 42.07, 38.38, 37.91, 35.55, 30.95, 30.71, 20.60, 18.29, 16.51, 16.05; HRMS (*m*/*z*) [M + Na]$^+$ calcd for $C_{30}H_{38}NaO_{12}$ 613.2261, found 613.2289.

(2*S*,4a*R*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-Methyl 9-Acetoxy-2-(hydroxy(2,3,4,5-tetramethoxyphenyl)methyl)-6a,10b-dimethyl-4,10-dioxododecahydro-1*H*-benzo[*f*]isochromene-7-carboxylate (8). Compound **8** was synthesized from compound **5** using general procedure B to afford 0.78 g (89% yield) of a white solid, mp = 104−107 °C. TLC system: 55% EtOAc/44% *n*-hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.65 (s, 1H), 5.26 (dd, J = 4.7, 2.9 Hz, 1H), 5.11 (dd, *J* = 12.2, 7.7 Hz, 1H), 4.73 (ddd, *J* = 11.5, 5.8, 3.0 Hz, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.83 (d, *J* = 5.1 Hz, 6H), 3.72 (s, 3H), 2.96 (s, 1H), 2.88 (s, 1H), 2.74 (dd, *J* = 12.7, 4.1 Hz, 1H), 2.65 (d, *J* = 4.9 Hz, 1H), 2.31−2.22 (m, 2H), 2.17 (s, 2H), 2.12 (s, 3H), 1.97 (td, *J* = 13.2, 12.6, 7.0 Hz, 2H), 1.81−1.74 (m, 1H), 1.31 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.18, 171.89, 171.55, 169.53, 149.68, 146.51, 144.04, 142.65, 125.54, 104.67, 79.77, 74.90, 70.07, 64.23, 61.07, 61.05, 60.99, 56.33, 53.51, 51.91, 50.64, 42.19, 38.14, 34.81, 34.62, 30.82, 20.50, 18.12, 16.15, 15.14; HRMS (*m*/*z*) [M + Na]$^+$ calcd for $C_{30}H_{40}NaO_{12}$ 615.2418, found 615.2435.

(2*S*,4a*R*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-Methyl 9-Acetoxy-6a,10b-dimethyl-4,10-dioxo-2-(2,3,4,5-tetramethoxybenzyl)-dodecahydro-1*H*-benzo[*f*]isochromene-7-carboxylate (11). Compound **11** was synthesized from compound **8** using general procedure C to afford 0.42 g (55% yield) of a white solid, mp = 91−94 °C. TLC system: 45% EtOAc/55% *n*-hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.45 (s, 1H), 5.12 (dd, *J* = 11.5, 8.4 Hz, 1H), 4.71 (dq, *J* = 11.3, 5.5 Hz, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.80 (d, *J* = 9.0 Hz, 6H), 3.72 (s, 3H), 2.88 (qd, *J* = 13.8, 5.9 Hz, 2H), 2.77−2.70 (m, 1H), 2.33−2.22 (m, 3H), 2.16 (s, 3H), 2.10 (d, *J* = 3.9 Hz, 2H), 1.87 (dd, *J* = 11.6, 3.1 Hz, 1H), 1.80−1.72 (m, 1H), 1.59−1.49 (m, 2H), 1.34 (s, 3H), 1.30−1.24 (m, 1H), 1.08 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.14, 171.58, 171.49, 169.85, 149.22, 146.94, 145.69, 141.92, 123.97, 108.53, 77.69, 75.05, 64.12, 61.15, 61.06, 61.04, 56.23, 53.57, 51.97, 51.28, 42.28, 42.14, 38.20, 36.72, 35.07, 30.78, 20.58, 18.17, 16.33, 15.18; HRMS (*m*/*z*) [M + Na]$^+$ calcd for $C_{30}H_{40}NaO_{11}$ 599.2468, found 599.2459.

(2*S*,4a*R*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-Methyl 9-Acetoxy-2-[(4,5-dimethoxy-3,6-dioxocyclohexa-1,4-dien-1-yl)methyl]-6a,10b-dimethyl-4,10-dioxododecahydro-1*H*-benzo[*f*]isochromene-7-carboxylate (14). Compound **14** was synthesized from compound **11** using general procedure D to afford 0.11 g (28% yield) of an orange solid, mp = 102−104 °C. TLC system: 55% EtOAc/45% *n*-hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.55−6.48 (m, 1H), 5.14 (dd, *J* = 11.7, 8.3 Hz, 1H), 4.68 (dddd, *J* = 11.7, 9.5, 4.7, 3.2 Hz, 1H), 4.02 (s, 3H), 4.00 (s, 3H), 3.73 (s, 3H), 2.80−2.70 (m, 2H), 2.54 (ddd, *J* = 14.6, 9.3, 1.1 Hz, 1H), 2.38 (dd, *J* = 13.3, 4.9 Hz, 1H), 2.34−2.26 (m, 2H), 2.18 (s, 3H), 2.14−2.09 (m, 2H), 2.00−1.93 (m, 1H), 1.81−1.75 (m, 1H), 1.60−1.51 (m, 2H), 1.34 (s, 3H), 1.30−1.21 (m, 1H), 1.09 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.92, 183.85, 183.80, 171.51, 170.80, 169.98, 145.04, 144.87, 141.74, 133.24, 75.19, 75.02, 64.01, 61.31, 61.24, 53.58, 52.00, 51.38, 42.97, 42.08, 38.12, 36.43, 35.25, 30.74, 20.59, 18.11, 16.36, 15.17; HRMS (*m*/*z*) [M + Na]$^+$ calcd for $C_{28}H_{34}NaO_{11}$ 569.1999, found 569.1960; HPLC t_R = 6.959; purity = 98.1%.

(2*S*,4a*R*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-Methyl 9-Acetoxy-6a,10b-dimethyl-4,10-dioxo-2-(2,4,5-trimethoxybenzoyl)dodecahydro-1*H*-benzo[*f*]isochromene-7-carboxylate (6). Compound **6** was synthesized from compound **3** using general procedure A and 2,4,5-trimethoxyphenylboronic acid[25] to afford 1.01 g (90% yield) of a white solid, mp = 103−106 °C. TLC system: 60% EtOAc/40% *n*-hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (s, 1H), 6.47 (s, 1H), 5.94 (dd, *J* = 8.8, 7.3 Hz, 1H), 5.07 (ddd, *J* = 10.8, 9.3, 1.0 Hz, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 3.87 (s, 3H), 3.70 (s, 3H), 2.78 (dd, *J* = 13.7, 8.8 Hz, 1H), 2.72−2.65 (m, 1H), 2.30−2.22 (m, 2H), 2.21−2.07 (m, 6H), 1.74 (dt, *J* = 12.9, 3.1 Hz, 1H), 1.65 (ddd, *J* = 14.8, 11.6, 3.3 Hz, 1H), 1.57−1.49 (m, 1H), 1.42 (s, 3H), 1.35−1.27 (m, 1H), 1.06 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.89, 171.94, 171.63, 169.81, 155.64, 155.37, 143.68, 118.18, 114.77, 112.83, 96.12, 78.93, 74.89, 65.22, 56.30, 56.26, 56.20, 53.30, 51.95, 49.16, 42.07, 38.37, 37.88, 35.62, 30.76, 20.66, 18.35, 16.95, 16.00; HRMS (*m*/*z*) [M + K]$^+$ calcd for $C_{29}H_{36}KO_{11}$ 599.1895, found 599.1903.

(2*S*,4a*R*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-Methyl 9-Acetoxy-2-(hydroxy(2,4,5-trimethoxyphenyl)methyl)-6a,10b-dimethyl-4,10-dioxododecahydro-1*H*-benzo[*f*]isochromene-7-carboxylate (9). Compound **9** was synthesized from compound **6** using general procedure B to afford 0.78 g (64% yield) of a white solid, mp = 133−136 °C. TLC system: 60% EtOAc/40% *n*-hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.49 (s, 1H), 5.28 (dd, *J* = 5.0, 2.8 Hz, 1H), 5.15−5.05 (m, 1H), 4.75 (ddd, *J* = 11.6, 5.8, 3.0 Hz, 1H), 3.90 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 3.71 (s, 3H), 2.74 (dd, *J* = 12.7, 4.2 Hz, 1H), 2.63 (d, *J* = 5.2 Hz, 1H), 2.32−2.19 (m, 2H), 2.14 (d, *J* = 19.1 Hz, 5H), 2.02−1.94 (m, 1H), 1.91 (dd, *J* = 13.2, 5.8 Hz, 1H), 1.80−1.72 (m, 1H), 1.58−1.50 (m, 2H), 1.30 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.19, 172.04, 171.63, 169.55, 150.16, 149.20, 143.24, 117.56, 111.01, 96.89, 79.36, 74.93, 69.90, 64.31, 56.73, 56.12, 56.02, 53.56, 51.94, 50.67, 42.23, 38.20, 34.85, 34.74, 30.89, 20.55, 18.18, 16.18, 15.19; HRMS (*m*/*z*) [M + K]$^+$ calcd for $C_{29}H_{38}KO_{11}$ 601.2051, found 601.2029.

(2*S*,4a*R*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-Methyl 9-Acetoxy-6a,10b-dimethyl-4,10-dioxo-2-(2,4,5-trimethoxybenzyl)dodecahydro-1*H*-benzo[*f*]isochromene-7-carboxylate (12). Compound **12** was synthesized from compound **9** using general procedure C to afford 0.42 g (56% yield) of a white solid, mp = 108−111 °C. TLC system: 55% EtOAc/45% *n*-hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.70 (s, 1H), 6.51 (s, 1H), 5.15−5.01 (m, 1H), 4.71 (dd, *J* = 11.4, 5.5 Hz, 1H), 3.89 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 3.71 (s, 3H), 2.96−2.80 (m, 2H), 2.76−2.67 (m, 1H), 2.32−2.21 (m, 3H), 2.17 (s, 3H), 2.07 (d, *J* = 11.7 Hz, 2H), 1.85−1.71 (m, 2H), 1.57−1.46 (m, 2H), 1.32 (s, 3H), 1.20 (dd, *J* = 13.5, 11.6 Hz, 1H), 1.07 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.13, 171.65, 171.60, 169.89, 151.77, 148.48, 142.77, 115.84, 115.16, 97.43, 77.47, 75.07, 64.24, 56.62, 56.18, 56.15, 53.60, 51.95, 51.20, 42.18, 41.92, 38.23, 36.07, 35.02, 30.80, 20.60, 18.15, 16.32, 15.20; HRMS (*m*/*z*) [M + K]$^+$ calcd for $C_{29}H_{38}KO_{10}$ 585.2102, found 585.2084.

(2*S*,4a*R*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-Methyl 9-Acetoxy-2-[(4-methoxy-3,6-dioxocyclohexa-1,4-dien-1-yl)methyl]-6a,10b-dimethyl-4,10-dioxododecahydro-1*H*-benzo[*f*]isochromene-7-carboxylate (15). Compound **15** was synthesized from compound **12** using general procedure D to afford 0.50 g (72% yield) of a yellow solid, mp = 127−130 °C. TLC system: 60% EtOAc/40% *n*-hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.63 (t, *J* = 1.1 Hz, 1H), 5.93 (s, 1H), 5.14 (dd, *J* = 11.6, 8.4 Hz, 1H), 4.70 (dddd, *J* = 14.6, 8.6, 4.8, 3.3 Hz, 1H), 3.83 (s, 3H), 3.73 (s, 3H), 2.83−2.71 (m, 2H), 2.56 (ddd, *J* = 14.4, 9.2, 1.0 Hz, 1H), 2.38 (dd, *J* = 13.3, 4.9 Hz, 1H), 2.34−2.28 (m, 2H), 2.18 (s, 4H), 2.11 (d, *J* = 4.1 Hz, 2H), 2.00−1.94 (m, 1H), 1.82−1.75 (m, 1H), 1.54 (d, *J* = 12.9 Hz, 1H), 1.35 (s, 3H), 1.27 (t, *J* = 12.5 Hz, 1H), 1.09 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.90, 187.00, 181.77, 171.52, 170.77, 169.98, 158.75, 144.44, 133.15, 107.66, 75.35, 75.02, 64.04, 56.31, 53.59, 52.00, 51.40, 43.01, 42.08, 38.14, 36.65, 35.26, 30.76, 20.60, 18.11, 16.37, 15.17; HRMS (*m*/*z*) [M + K]$^+$ calcd for $C_{27}H_{32}KO_{10}$ 555.1633, found 555.1678; HPLC t_R = 6.049; purity = 95.4%.

Calcium Mobilization Assay. The assay was performed as described previously.[23,32] Briefly, CHO cells stably expressing KOP R-Gαq_{16} were maintained in F-12 media with 10% FBS, 1% penicillin and streptomycin, and 0.2% normocin (Life Technologies, Carlsbad, CA, USA) at 37 °C and 5% CO_2. Cells were plated at 30 000 cells/well

in the same media in a black Costar 96-well optical bottom plate and incubated at 37 °C overnight. The media was replaced with fluorescent calcium dye (Calcium 5 dye, Molecular Devices, Sunnyvale, CA, USA) in 225 μL of assay buffer (HBSS buffer containing 20 mM HEPES, 0.25% BSA, 1% DSMO, and 10 μM probenecid (Sigma, St. Louis, MO, USA)), and cells were incubated for 1 h at 37 °C. Stock solutions (10 mM) were prepared for all compounds in DMSO. Stocks were used to make fresh serial dilutions in DMSO for each experiment and diluted to 10× in assay buffer. Cells were stimulated with 25 μL of 10× compounds using the Flexstation 3 plate-reader, and the change in fluorescence over baseline was recorded for 60 s. Maximum change over baseline was determined from two independent experiments performed on different days (n = 2). For each experiment, 10-point dose−response curves spanning at least seven log units were generated in duplicate (two wells per dose per compound) for each compound. The dose range for salvinorin A was chosen based on literature precedent[26] and to provide clear lower and upper asymptotes for the semilog plots of the dose−response curves. The dose range for test compounds began at the highest concentration allowed by solubility (10 μM). Data from each experiment were analyzed separately using nonlinear regression (GraphPad Prism 5.0, San Diego, CA, USA) to determine the potency (EC_{50}) and efficacy (E_{max}) values.

Antiproliferation Assay.[33] MCF7 and SKBr3 cells were maintained in Advanced DMEM/F12 (1:1; Life Technologies) supplemented with L-glutamine (2 mM), streptomycin (500 μg/mL), penicillin (100 units/mL), and 10% FBS at 37 °C and 5% CO_2. Cells were grown to confluence, seeded (2000 cells/well, 100 μL total media) in clear, flat-bottom 96-well plates, and allowed to attach overnight. Stock solutions (10 mM) were prepared for all compounds in DMSO. Stocks were used to make fresh dilutions in DMSO for each experiment. Six-point dose−response curves were generated in duplicate (two wells per dose per compound) using the following dose ranges: GDA, 1 nM to 1 μM; all test compounds, 100 nM to 100 μM. Compounds were added (1% DMSO final concentration), and cells were incubated at 37 °C for 72 h. After 72 h, cell growth was determined using an MTS/PMS cell proliferation kit (Promega) per the manufacturer's instructions. Cells incubated in 1% DMSO were used as controls (i.e., 0% inhibition), and the relative growth of cells incubated with each compound concentration was normalized to DMSO-treated controls. Data from at least two independent experiments performed on different days ($n \geq 2$) were analyzed by nonlinear regression using GraphPad Prism 5.0 to generate IC_{50} and % inhibition values.

In Vitro Predictive Model of BBB Penetration. MDCK-MDR1 cells (Madin-Darby canine kidney cells stably transfected with MDR1, which codes for P-gp) obtained from The Netherlands Cancer Institute were maintained in DMEM/F12 (Life Technologies) media with 10% FBS and antibiotics at 37 °C and 5% CO_2. MDCK-MDR1 cells were plated (40 000 cells/well) on semipermeable membranes in a 24-well Transwell system with a 0.4 μm membrane pore size, and media was changed the next day. Cells were grown to confluence (generally 3 to 4 days after plating), and growth media was replaced with transport media (Hanks' balanced salt solution supplemented with 25 mM glucose and 25 mM HEPES) containing vehicle or verapamil (100 μM) for 15 min at 37 °C. Transport media was replaced with fresh transport media containing 10 μM test compound (and vehicle or verapamil) on the apical chamber and incubated at 37 °C for 60 min. The concentration of DMSO was maintained at 1% throughout the experiment to facilitate solubility and minimize aggregation. Samples (20 μL) from the apical and basolateral chambers were collected and analyzed by LC/MS for the presence of test compound (LC/MS details below). The difference in peak areas between the apical and basolateral sides with account of volume differences in each side was used to determine transport across a monolayer.[34−36] Caffeine, which penetrates the BBB efficiently, was used as a positive control for membrane permeability. Prazosin was used as a control for P-gp-mediated transport, and 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-*N*-{[4-(methanesulfonamidomethyl)-cyclohexyl]methyl}-4-methylpyrazole-3-carboxamide was used as a negative control for transport across MDCK-MDR1 monolayers (data not shown).[30,37] Transepithelial electrical resistance was randomly monitored in monolayers prior to the assay to ensure development of resistance and monolayer integrity using chopstick-style electrodes (EVOM, World Precision Instruments). Each study was conducted with one or two independent samples of each compound and controls. Studies were repeated two or three times, and data were averaged to produce mean and SEM; therefore, each value represents data from n = 3−5 independent measurements.

LC/MS Methods. Sample preparation: 20 μL of media was mixed with 180 μL of 0.1% HCO_2H in MeCN. Samples were centrifuged, and 100 μL of supernatant was mixed with 300 μL of 50:50 MeOH/H_2O in 96-well plates. Sample analysis was conducted in positive electrospray mode using an Applied Biosystems API 5000 triple quadrupole mass spectrometer (Framingham, MA, USA) interfaced to a Waters Acquity UPLC system (Waters Corporation, Milford, MA, USA). Chromatography was accomplished using a Phenomenex Luna C_{18} column (50 mm × 2 mm i.d., 5 μm particle size) fitted with a guard cartridge. Injection volumes were 20 μL. Two mobile phase solutions were used: (A) 0.1% HCO_2H with 10 mM ammonium formate in H_2O; (B) 0.1% HCO_2H with 10 mM ammonium formate in MeOH. The flow rate was 0.5 mL/min. Initial chromatographic conditions were 90% A held for 1 min, decreasing to 5% A over 2.5 min, and held for 1 min before returning to initial conditions. Compound **14** was monitored with a multiple reaction monitoring (MRM) transition of 547.18 → 487.00 with DP = 186, CE = 17, and CXP = 20. Compound **15** was monitored with an MRM transition of 517.35 → 457.20 with DP = 201, CE = 17, and CXP = 18. Salvinorin A was monitored with an MRM transition of 433.19 → 373.30 with DP = 141, CE = 15, and CXP = 30. Prazosin was monitored with an MRM transition of 384.19 → 247.00 with DP = 186, CE = 39, and CXP = 18. Caffeine was monitored with an MRM transition of 195.32 → 138.00 with DP = 86, CE = 25, and CXP = 22. Mass spectrometer parameters were as follows: CUR = 10, GS1 = 40, GS2 = 60, IS = 2000, TEM = 650 °C, CAD = 5.

■ ASSOCIATED CONTENT

Supporting Information

Supporting data including HPLC, ^{1}H NMR, and ^{13}C NMR spectra of compounds **13**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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