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Ground state oxygen in synthesis of cyclic peroxides. Part 1: Benzo fused ketals

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Abstract—A thiol-olefin-cooxygenation (TOCO) radical chain reaction involving ground state molecular oxygen converts 2′-isopropenyl acetophenones directly into cyclic peroxy hemiketal products with three new bonds. Starting with 4-*t*-butylbenzenethiol, this TOCO process proceeds reproducibly on gram scale in 86% yield. Hemiketal → ketal and sulfide → sulfone transformations finally provide a series of sulfonyl cyclic peroxy ketals. The in vitro antimalarial activities of some of these structurally simple benzo-fused cyclic peroxides are reported.

1. Introduction

Among the methods for preparing dialkyl peroxides such as 1,2-dioxetanes and antimalarial 1,2,4-trioxanes, dioxygenation using photochemically-generated singlet molecular oxygen is the most popular.[1–3] Unfortunately, however, preparation of multigram amounts of antimalarial trioxanes is not practical using singlet molecular oxygen due to the short lifetime and high reactivity of this high energy species. Thus, even though our research program of antimalarial trioxane drug development successfully identified two safe, efficacious, and structurally simple antimalarial trioxanes, scale-up synthesis was unsuccessful.[4,5] As part of a general program eventually to synthesize trioxanes using ground state molecular oxygen, we report here non-singlet (i.e., triplet, ground state) molecular oxygen synthesis of simple benzo-fused cyclic peroxy ketals. This research builds on our previous report about some potent antimalarial cyclic peroxy ketals (e.g., sulfone **1** with $IC_{50}=31$ nM)[6] and on the recent successful application of thiol-olefin-cooxygenation (TOCO) chemistry for rapid and efficient conversion of limonene (**2**) into some antimalarially potent sulfonyl endoperoxides (Scheme 1 and Fig. 1).[7,8]

2. Results and discussion

Starting with commercial 2′-bromoacetophenone, Wittig methylenation, lithium–bromide exchange, addition to acetaldehyde, and oxidation produced 2′-isopropenyl acetophenone (**5**) in high yield (Scheme 2). Using a balloon filled with molecular oxygen and a short irradiation time, as recently described in a modified TOCO protocol,[9] TOCO chemistry produced the benzo-fused cyclic peroxy hemiketal **7** in 57% yield as a 9:5 ratio of diastereomers (Scheme 2). The high yield of this TOCO process is due in large part to the ease with which the benzenethiolate radical adds to the isopropenyl group to generate a tertiary benzylic carbon-centered radical; this relatively stable radical reacts with ground-state molecular oxygen to form a peroxy radical, which can abstract a hydrogen atom from benzenethiol, thereby propagating this radical chain reaction. The putative intermediate hydroperoxy ketone **6** is not observed, but it presumably rapidly cyclizes into the isolated peroxy hemiketal product **7**.

Based on our previous finding that cyclic peroxy hemiketals have considerably less antimalarial potency than the

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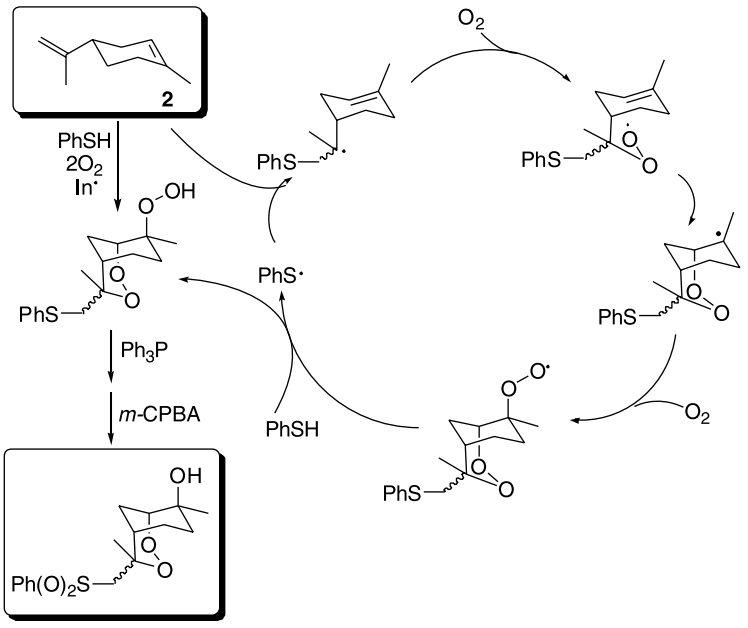


Scheme 1. Thiol olefin cooxygenation (TOCO) followed by sulfide oxidation.

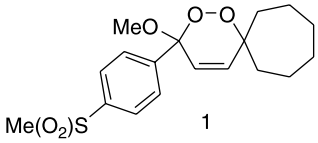
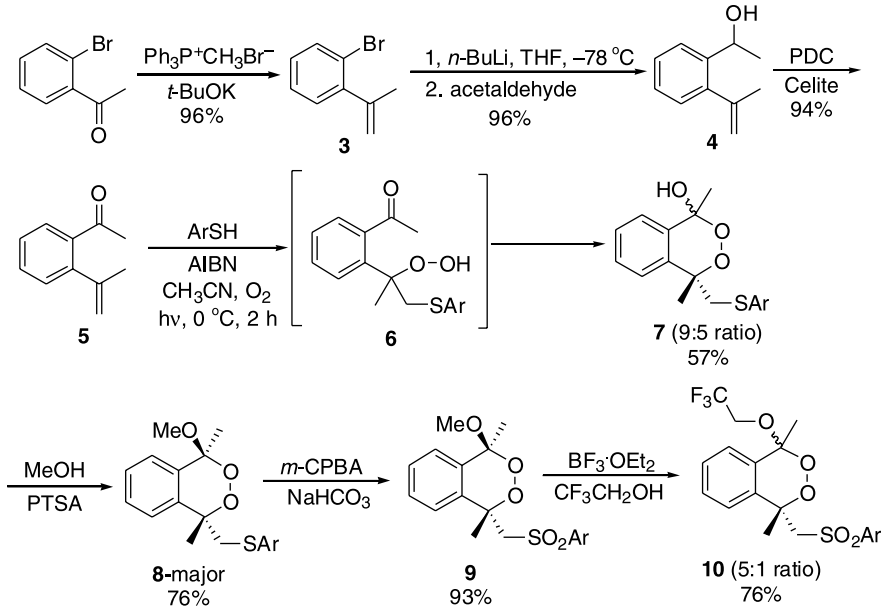


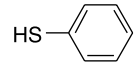
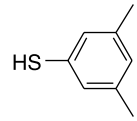
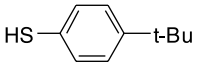
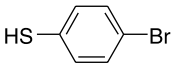
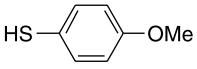
Figure 1.

corresponding ketals,[6] hemiketal **7** was converted directly into ketal **8** (Scheme 2). Based also on the previous finding that sulfanyl endoperoxides have considerably less antimalarial potency than the corresponding sulfonyl endoperoxides,[8] the major diastereomer of sulfide **8** was oxidized into sulfone **9**. Confirmation of the relative stereochemistry of crystalline sulfone **9** by X-ray crystallography revealed that the two methyl groups on the 1,2-dioxin ring are trans-oriented. Dissolved in 40:60 DMSO/H_2O buffered at pH 7.4, sulfone **9** was stable; after 4 days at 25 °C, less than 1% decomposition was determined by calibrated HPLC analysis. Finally, with the intention of further diminishing any possible hydrolysis of the peroxy ketal functionality under physiological (pH 7.4) conditions, the methoxy group was replaced by a less basic (i.e., less easily protonated) trifluoroethoxy group in the form of ketal sulfone **10** (Scheme 2). In this way, a series of commercial benzenethiols led to the series of benzo-fused cyclic peroxy ketals shown in Table 1. The most outstanding chemical result in this series is that 4-*t*-butylbenzenethiol, a mercaptan having almost no unpleasant odor, achieves the 3-bond-forming TOCO process in 86% yield even on gram scale.



Scheme 2. Synthesis of ketal endoperoxides via the TOCO process. Yields and ratios are for Ar=Ph.

Table 1. Benzo fused ketal analogs via the TOCO process

Entry	HS-Ar	Yield (%)			
		7	**8′** major + **8″** minor	**9**	**10′** major + **10″** minor
a		57% (1.8:1)	76% (9:1)	93	76% (5:1)[a]
b		60% (2:1)	76% (2.7:1)	83	74% (5:1)
c		86% (1.4:1)	89% (6:1)	97	65% (5:1)
d		71% (2.8:1)	84% (3.4:1)	89	90% (5:1)
e		72% (1.5:1)	83% (2.4:1)	94	91% (6:1)

[a] Inseparable mixture by HPLC.

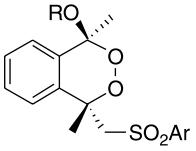
The in vitro antimalarial potencies of several of these sulfonyl cyclic peroxy ketals was determined using our standard protocol[10] and are shown in Table 2.

To encumber the ketal region and thus to retard possible hydrolysis of the peroxy ketal functionality under physiological conditions, a sterically hindered version carrying a tertiary butyl group was prepared in good yield as a 1:1 mixture of diastereomers (Scheme 3). The sulfonyl *t*-butyl peroxy ketal **12** diastereomer where the methoxy is cis to the sulfonyl was only weakly active as an antimalarial.

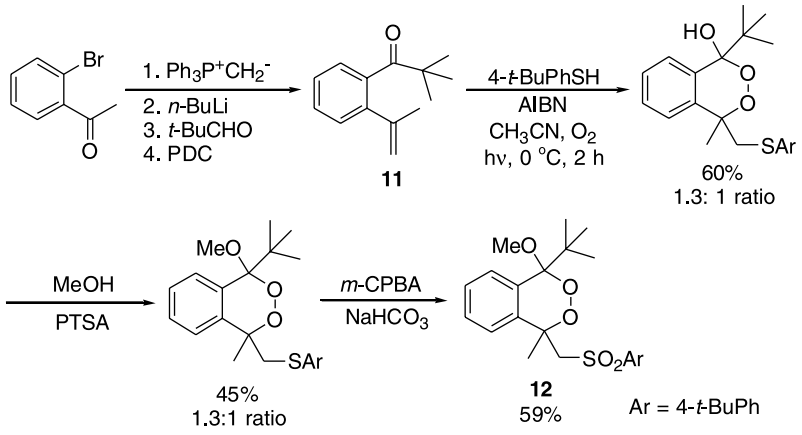
3. Conclusions

In conclusion, TOCO radical chain reactions using ground state molecular oxygen lead, in good yield, to a series of benzo-fused cyclic peroxy ketals. These reactions are easily scaled up to multigram quantities of products. The relatively

Table 2. Antimalarial activity against *Plasmodium falciparum* (NF54)

	Ar	R	IC_{50} (nM)[a]
	4-*t*-BuPh	Me	540
	4-BrPh	Me	820
	Ph[b]	CF_3CH_2	480
	Artemisinin		7.9 ± 0.87

[a] The standard deviation for each set of quadruplicates was an average of 8.0% (≤16%) of the mean. R^2 values for the fitted curves were ≥0.983. Artemisinin activity is the mean ± standard deviation of the concurrent control (n=3).
[b] Mixture of isomers.



Scheme 3. Synthesis of a hindered ketal endoperoxide via the TOCO process.

weak in vitro antimalarial activities of these cyclic peroxy ketals, however, make them unpromising for chemotherapy of malaria.

4. Experimental

4.1. General

4.1.1. 1-Bromo-2-isopropenyl-benzene 3. To a suspension of methyltriphenylphosphonium bromide (8.57 g, 24.0 mmol) in THF (60 mL) at room temperature was added a solution of potassium *tert*-butoxide (1.0 M in THF, 24.0 mL, 24.0 mmol). After being stirred for 5 min, the reaction mixture was treated with a solution of 2′-bromoacetophenone (3.98 g, 20 mmol) in THF (40 mL) via cannula. The reaction mixture was stirred for 3 h at room temperature before it was quenched with the addition of saturated aqueous ammonium chloride (40 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3×40 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified via flash column chromatography (100% hexanes) to give 1-bromo-2-isopropenyl-benzene (3.78 g, 96% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, J=8.0, 1.2 Hz, 1H), 7.26 (dt, J=7.2, 1.2 Hz, 1H), 7.19 (dd, J=7.6, 2.0 Hz, 1H), 7.13–7.09 (m, 1H), 5.24–5.22 (m, 1H), 4.94–4.93 (m, 1H), 2.10–2.09 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 144.8, 132.7, 129.7, 128.3, 127.2, 121.5, 116.0, 23.5; IR (CH_2Cl_2, film) 3081, 3053, 2970, 1917, 1805, 1641, 1469, 1433, 1371, 1025, 903, 758, 653 cm^{-1}; TLC R_f (hexane)=0.83; HRMS (CI) m/z calcd for C_9H_9Br $(M)^+$ 195.9888, found 195.9876.

4.1.2. Alcohol 4. To a solution of 1-bromo-2-isopropenyl-benzene (1.97 g, 10 mmol) in THF (15 mL) at −78 °C, was added a solution of *n*-BuLi (1.6 M in hexanes, 7.5 mL, 12 mmol). After being stirred for 30 min at −78 °C, acetaldehyde (0.84 mL, 15 mmol) was added neat. The reaction mixture was stirred at −78 °C for 30 min then at room temperature for 1 h before it was quenched with the addition of saturated aqueous ammonium chloride (25 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3×40 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified via flash column chromatography (20% ethyl acetate in hexanes) to give alcohol (1.55 g, 96% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (ddd, J=7.6, 1.2, 0.4 Hz, 1H), 7.41 (td, J=7.6, 1.6 Hz, 1H), 7.31 (td, J=7.6, 1.6 Hz, 1H), 7.27 (ddd, J=7.6, 1.2, 0.4 Hz, 1H), 5.25–5.22 (m, 1H), 5.18 (quint, J=1.6 Hz, 1H), 4.90 (m, 1H), 2.10 (br s, 1H), 2.09–2.07 (m, 3H), 1.49–1.45 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 142.3, 142.0, 127.9, 127.4, 127.1, 125.2, 115.5, 66.6, 25.6, 25.0; IR (CH_2Cl_2, film) 3746, 3076, 2971, 2929, 1640, 1486, 1445, 1434, 1372, 1299, 1196, 1073, 1004, 900, 759 cm^{-1}; TLC R_f (hexane/Et_2O 2:1)=0.64; HRMS (EI) m/z calcd for $C_{11}H_{14}O$ $(M)^+$ 162.1039, found 162.1098.

4.1.3. Ketone 5. To a solution of alcohol **4** (1.19 g, 7.36 mmol) in CH_2Cl_2 (25 mL) was added pyridinium dichromate (PDC, 5.54 g, 14.7 mmol) and Celite® (5.50 g) at 25 °C under argon atmosphere. After being stirred for 2 days, the reaction mixture was diluted with EtOAc and filtered through a pad of silica gel. The filtrate was concentrated in vacuo and then purified by flash column chromatography (10% EtOAc in petroleum ether) to give ketone **4** (1.11 g, 94%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (ddd, J=7.6, 1.2, 0.4 Hz, 1H), 7.39 (td, J=7.6, 1.6 Hz, 1H), 7.29 (td, J=7.6, 1.2 Hz, 1H), 7.25 (dd, J=7.6, 1.2 Hz, 1H), 5.16–5.15 (m, 1H), 4.88 (m, 1H), 2.47 (m, 3H), 2.11 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.6, 145.1, 142.5, 139.3, 130.6, 128.4, 127.8, 127.1, 116.2, 29.9, 23.9; IR (neat, film) 3062, 2973, 2918, 2855, 1691, 1635, 1595, 1441, 1355, 1275, 1243, 956, 904, 770, 758 cm^{-1}; TLC R_f (hexane/Et_2O)=0.80; HRMS (EI) m/z calcd for $C_{11}H_{12}O$ $(M)^+$ 160.0883, found 160.0888.

4.1.4. Hemiketal 7c. To a solution of ketone **5** (2.12 g, 13.2 mmol) in acetonitrile (220 mL) under argon was added 2,2′-azobisisobutyronitrile (AIBN, 152 mg, 0.926 mmol) and 4-*tert*-butylthiophenol (2.85 mL, 16.5 mmol). The reaction vessel was flushed with oxygen for 10 min at 0 °C and then kept under a positive pressure of oxygen with two balloons. The reaction mixture was stirred vigorously and irradiated using a mercury UV lamp (450 W, Ace Glass) at a distance of 10 cm at 0 °C. After 2 h, the reaction was flushed with argon and then concentrated in vacuo. The crude product was then purified by flash silica gel column chromatography (10% EtOAc in hexanes) to yield hemiketal **7c** (4.06 g, 11.3 mmol, 86%) as a yellow oil as a mixture of two diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.44 (m, 1H), 7.33–7.26 (m, 7H), 3.78 (s, 1H), 3.70 (d, J=13.6 Hz, 1H), 3.39 (d, J=13.6 Hz, 1H), 1.69 (s, 3H), 1.60 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 137.7, 135.3, 133.4, 129.6, 128.1, 127.6, 125.8, 125.8, 124.7, 99.2, 81.9, 43.4, 34.3, 31.2, 23.8, 22.4; IR (CH_2Cl_2, film) 3415, 2962, 2862, 1492, 1444, 1364, 1148, 1120, 935, 892, 824, 764 cm^{-1}; HRMS (EI) m/z calcd for $C_{21}H_{26}O_3SNa$ $(M+Na)^+$ 381.14948, found 381.14871.

4.1.5. Ketone 11. Ketone **11** was synthesized as above with substitution of trimethylacetaldehyde in place of acetaldehyde. After three steps from 2′-bromoacetophenone, ketone **11** was isolated as a colorless oil (104 mg, 0.512 mmol, 36% from alcohol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.26 (m, 3H), 7.11 (d, J=7.2 Hz, 1H), 5.17 (m, 1H), 4.97 (s, 1H), 2.14 (s, 3H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.0, 144.4, 139.9, 135.8, 128.4, 127.3, 126.5, 125.7, 117.6, 78.6, 27.7, 24.1; IR (CH_2Cl_2, film) 3488.6, 3061.9, 2968.8, 2870.0, 1987.1, 1633.4, 1478.5, 1460.0, 1392.0, 1363.6, 1278.6, 1259.5, 1191.1, 1173.0, 1035.9, 768.0, 734.4 cm^{-1}; HRMS (FAB-MS) m/z calcd for $C_{14}H_{18}O$ $(M+H)^+$ 203.14359, found 203.14416.

4.2. General procedure for the TOCO process

A solution of ketone (1.0 mmol), 2,2′-azobisisobutyronitrile (AIBN, 0.07 mmol) and thiophenol (1.25 mmol) in acetonitrile (17 mL) was thoroughly flushed with oxygen for 10 min at 0 °C and then kept under a positive pressure of pure oxygen with the aid of two oxygen balloons. The reaction mixture was stirred vigorously and UV irradiated at

0 °C using an externally mounted medium-pressure mercury lamp (450 W, Ace Glass) at a distance of 15 cm. After 2 h at 0 °C, the reaction mixture was concentrated in vacuo and the residue was subjected to flash column chromatography to give corresponding hemiketals.

4.3. General procedure for the methylation of the alcohol

To a solution of the above hemiketals (0.15 mmol) in MeOH (3 mL) was added *p*-toluenesulfonic acid monohydrate (0.015 mmol) at 25 °C. After being stirred for 24 h at 25 °C, the reaction mixture was concentrated in vacuo and the residue was subjected to flash column chromatography to give the corresponding methoxy ketal sulfides.

4.4. General procedure for oxidation of methoxy ketal sulfides to methoxy ketal sulfones

To a solution of methoxy ketal sulfide (0.15 mmol) in CH_2Cl_2 (6 mL), was added 3-chloroperoxybenzoic acid (*m*-CPBA, 77% max, 0.36 mmol) and sodium bicarbonate (0.86 mmol). After being stirred for 4 h at 25 °C, the reaction was quenched by the addition of water and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$. After filtration and concentration in vacuo, the residue was purified via flash column chromatography (25% ethyl acetate in hexanes). The products were further purified using normal-phase high-performance liquid chromatography (HPLC) prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 5% EtOAc in hexanes, 2.0 mL/min, 264 nm].

4.5. Conversion of methoxy ketal sulfones to trifluoroethoxy ketal sulfones

To a solution of methoxy ketal (0.13 mmol) in trifluoroethanol (3 mL) at 0 °C, was added dropwise boron trifluoride diethyl etherate (0.066 mmol, 0.5 equiv). After stirring for 3 h at 0 °C, the reaction mixture was warmed to room temperature and further stirred for 1 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (3 mL) and extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. After filtration and concentration in vacuo, the residue was purified via flash column chromatography (20% ethyl acetate in hexanes). The products were further purified using normal-phase HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 5% EtOAc in hexanes, 2.0 mL/min, 264 nm].

4.5.1. From thiophenol.

4.5.1.1. Compound 8′a. Colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.22 (m, 8H), 7.18–7.13 (m, 1H), 3.69 (d, J=17.6 Hz, 1H), 3.43 (s, 3H), 3.38 (d, J=18.0 Hz, 1H), 1.61 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 137.1, 134.0, 129.4, 128.8, 128.1, 127.6, 126.0, 125.9, 124.5, 101.8, 81.5, 51.2, 43.1, 22.3, 22.3; IR (neat, film) 3060, 2990, 2937, 2832, 1583, 1480, 1439, 1371, 1298, 1275, 1154, 1131, 1043, 875, 763, 739, 691 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{20}O_3SNa$ $(M+Na)^+$339.1025, found 339.1024.

4.5.1.2. Compound 9a. White solid: mp 97–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dm, J=7.6 Hz, 2H), 7.62 (tt, J=7.6, 1.6 Hz, 1H),7.53 (tm, J=7.6 Hz, 2H), 7.34–7.29 (m, 4H), 3.95 (d, J=14.8 Hz, 1H), 3.58 (d, J=14.8 Hz, 1H), 3.30 (s, 3H), 1.87 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 137.5, 133.5, 133.5, 128.9, 128.5, 128.1, 125.9, 124.5, 101.5, 79.7, 61.9, 51.2, 22.5, 22.1; IR ($CDCl_3$, film) 3066, 2996, 2940, 1448, 1375, 1308, 1147, 1085, 1043, 876, 761, 688 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{20}O_5SNa$ $(M+Na)^+$371.0924, found 371.0909.

4.5.1.3. Compound 10′a. Colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94–7.89 (m, 2H), 7.64 (tt, J=7.6, 1.2 Hz, 1H), 7.56–7.51 (m, 2H), 7.42–7.33 (m, 4H), 3.66 (dq, J=12.0, 8.4 Hz, 1H), 3.91 (d, J=14.8 Hz, 1H), 4.02 (dq, J=11.6, 8.8 Hz, 1H), 3.58 (d, J=14.8 Hz, 1H),, 1.90 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 137.9, 133.6, 131.4, 129.2, 129.0, 128.6, 128.1, 126.1, 124.6, 123.6 (q, J=276 Hz), 102.0, 80.0, 62.4 (q, J=35 Hz), 61.6, 23.6, 22.5; IR (neat, film) 3067, 2996, 2942, 2835, 1586, 1448, 1378, 1321, 1286, 1151, 1085, 968, 902, 764, 688 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{19}F_3O_5SNa$ $(M+Na)^+$439.0797, found 439.0808.

4.5.1.4. Compound 8′b. Colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.26 (m, 4H), 6.95 (s, 2H), 6.78 (s, 1H), 3.51 (d, J=13.2 Hz, 1H), 3.43 (s, 3H), 3.38 (d, J=13.2 Hz, 1H), 2.25 (s, 6H), 1.63 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 138.3, 136.6, 134.0, 128.0, 127.8, 127.6, 125.8, 124.6, 101.7, 81.5, 51.2, 43.0, 22.3, 22.3, 21.1; IR (CH_2Cl_2, film) 2989, 2937, 1599, 1582, 1447, 1370, 1298, 1274, 1131, 1043, 896, 875, 762 cm^{-1}; TLC R_f (hexane/Et_2O 2:1)=0.58; HRMS (ESI) *m/z* calcd for $C_{20}H_{24}O_3SNa$ $(M+Na)^+$367.1338, found 367.1328. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 10% EtOAc in hexanes, 2.0 mL/min, 264 nm, t_R =15.3 min].

4.5.2. From 3,5-dimethylthiophenol.

4.5.2.1. Compound 8″b. Colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.31 (m, 3H), 7.22–7.20 (m, 1H), 6.97 (s, 2H), 6.79 (s, 1H), 3.57 (d, J=13.6 Hz, 1H), 3.43 (d, J=13.6 Hz, 1H), 3.33 (s, 3H), 2.26 (s, 6H), 1.69 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 138.4, 136.6, 134.4, 128.0, 128.0, 127.4, 127.3, 125.8, 124.2, 102.9, 82.1, 51.9, 43.4, 24.4, 24.2, 21.2; IR (CH_2Cl_2, film) 2987, 2929, 1594, 1575, 1445, 1369, 1268, 1128, 1042, 849, 762 cm^{-1}; TLC R_f (hexane/Et_2O 2:1)=0.64; HRMS (ESI) *m/z* calcd for $C_{20}H_{24}O_3SNa$ $(M+Na)^+$367.1338, found 367.1332. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 10% EtOAc in hexanes, 2.0 mL/min, 264 nm, t_R=13.5 min].

4.5.2.2. Compound 9b. Colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.50 (m, 2H), 7.35–7.29 (m, 4H), 7.21–7.20 (m, 1H), 3.90 (d, J=14.8 Hz, 1H), 3.61 (d, J=14.8 Hz, 1H), 3.33 (s, 3H), 2.36 (br s, 6H), 1.87 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 139.0, 137.3, 135.0, 133.5, 128.3, 128.0, 125.8, 125.4, 124.7, 101.5, 79.8, 61.9, 51.2, 22.7, 22.0, 21.1; IR (CH_2Cl_2, film)

2972, 2941, 2835, 1608, 1456, 1378, 1318, 1302, 1139, 1104, 1046, 878, 768, 683 cm^{-1}; TLC R_f (hexane/Et_2O 2:1)=0.14; HRMS (ESI) *m/z* calcd for $C_{20}H_{24}O_5SNa$ $(M+Na)^+$ 399.1237, found 399.1237. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 30% EtOAc in hexanes, 3.0 mL/min, 264 nm, t_R=9.5 min].

4.5.2.3. Compound 10′b. Colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (br s, 2H), 7.41–7.33 (m, 4H), 7.22 (br s, 1H), 4.06 (dq, J=11.8, 8.4 Hz, 1H), 3.85 (d, J=14.8 Hz, 1H), 3.68 (dq, J=11.8, 8.8 Hz, 1H), 3.60 (d, J=14.8, 8.8 Hz, 1H), 2.37 (s, 6H), 1.88 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 139.1, 137.8, 135.2, 131.4, 129.0, 128.5, 126.0, 125.4, 124.9, 123.6 (q, J=276 Hz), 62.4 (q, J=35 Hz), 61.6, 23.6, 22.7, 21.1; IR (CH_2Cl_2, film) 2987, 2929, 1608, 1453, 1378, 1321, 1286, 1144, 1083, 967, 902, 858, 765, 684 cm^{-1}; TLC R_f (hexane/EtOAc 2:1)=0.68; HRMS (ESI) *m/z* calcd for $C_{21}H_{23}F_3O_5SNa$ $(M+Na)^+$ 467.1110, found 467.1093. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 30% EtOAc in hexanes, 2.0 mL/min, 264 nm, t_R=13.0 min].

4.5.2.4. Compound 10″b. Colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.48–7.47 (m, 2H), 7.35–7.32 (m, 3H), 7.22–7.18 (m, 2H), 3.78–3.68 (m, 3H), 3.53 (dq, J=12.0, 8.8 Hz, 1H), 2.36 (s, 6H), 1.89 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 139.2, 138.4, 135.3, 132.1, 128.9, 128.2, 125.9, 125.5, 124.1, 123.5 (q, J=276 Hz), 63.1, 62.0 (q, J=35 Hz), 24.4, 24.3, 21.1; IR (CH_2Cl_2, film) 2987, 2929, 1604, 1449, 1372, 1319, 1280, 1140, 966, 898, 855, 763, 681 cm^{-1}; TLC R_f (hexane/EtOAc 2:1)=0.68; HRMS (ESI) *m/z* calcd for $C_{21}H_{23}F_3O_5SNa$ $(M+Na)^+$ 467.1110, found 467.1097. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 30% EtOAc in hexanes, 2.0 mL/min, 264 nm, t_R=13.7 min].

4.5.3. From 4-*t*-butylthiophenol.

4.5.3.1. Compound 8′c. Colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.26 (m, 8H), 3.68 (d, J=13.2 Hz, 1H), 3.43 (s, 3H), 3.36 (d, J=13.6 Hz, 1H), 1.62 (s, 3H), 1.61 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 138.3, 134.0, 133.5, 129.6, 128.0, 127.5, 125.8, 124.5, 101.7, 81.5, 51.1, 43.6, 34.4, 31.2, 22.3; IR (CH_2Cl_2, film) 2962, 1490, 1457, 1371, 1272, 1191, 1130, 1044, 875, 823, 762 cm^{-1}; TLC R_f (hexane/Et_2O 2:1)=0.64; HRMS (ESI) *m/z* calcd for $C_{22}H_{28}O_3SNa$ $(M+Na)^+$ 395.1651, found 395.1641. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 10% EtOAc in hexanes, 3.0 mL/min, 264 nm, t_R=9.5 min].

4.5.3.2. Compound 8″c. Colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.35 (m, 1H), 7.33–7.26 (m, 6H), 7.21–7.18 (m, 1H), 3.58 (d, J=13.6 Hz, 1H), 3.43 (d, J=13.6 Hz, 1H), 3.32 (s, 3H), 1.69 (s, 3H), 1.67 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 139.2, 134.4, 133.6, 130.0, 128.0, 127.4, 125.9, 125.8, 124.1, 102.8, 82.2, 51.9, 44.0, 34.4, 31.2, 24.3, 24.3; IR (CH_2Cl_2, film) 2963, 2868, 1490, 1447, 1369, 1269, 1188, 1120, 1044, 879, 825, 762 cm^{-1}; TLC R_f (hexane/Et_2O 2:1)=0.72; HRMS (ESI) *m/z* calcd for $C_{22}H_{28}O_3SNa$ $(M+Na)^+$ 395.1651, found 395.1648. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 5% EtOAc in hexanes, 2.0 mL/min, 264 nm, t_R=18.4 min].

4.5.3.3. Compound 9c. Colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.84–7.82 (m, 2H), 7.53–7.51 (m, 2H), 7.32–7.26 (m, 4H), 3.90 (d, J=14.8 Hz, 1H), 3.58 (d, J=14.8 Hz, 1H), 3.30 (s, 3H), 1.87 (s, 3H), 1.44 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 137.7, 137.4, 133.5, 128.4, 128.0, 127.9, 125.9, 125.8, 124.6, 101.5, 79.7, 61.9, 51.0, 35.2, 31.0, 22.5, 21.9; IR (CH_2Cl_2, film) 2964, 1595, 1398, 1319, 1151, 1108, 1085, 1043, 762 cm^{-1}; TLC R_f (hexane/EtOAc 2:1)=0.63; HRMS (ESI) *m/z* calcd for $C_{22}H_{28}O_5SNa$ $(M+Na)^+$ 427.1550, found 427.1541. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 30% EtOAc in hexanes, 3.0 mL/min, 264 nm, t_R=12.9 min].

4.5.3.4. Compound 10′c. Colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.84–7.81 (m, 2H), 7.55–7.51 (m, 2H), 7.38–7.32 (m, 4H), 4.03 (dq, J=11.8, 8.8 Hz, 1H), 3.86 (d, J=14.8 Hz, 1H), 3.67 (dq, J=12.0, 8.4 Hz, 1H), 3.59 (d, J=14.8 Hz, 1H), 1.88 (s, 3H), 1.52 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 137.9, 137.7, 131.4, 129.1, 128.5, 127.9, 126.1, 124.8, 123.6 (q, J=280 Hz), 102.0, 80.1, 62.3 (q, J=35 Hz), 61.7, 35.2, 31.1, 23.6, 22.6; IR (CH_2Cl_2, film) 2965, 2872, 1595, 1453, 1320, 1288, 1153, 1084, 968, 902, 842, 765, 573 cm^{-1}; TLC R_f (hexane/EtOAc 2:1)=0.66; HRMS (ESI) *m/z* calcd for $C_{23}H_{27}F_3O_5SNa$ $(M+Na)^+$ 495.1423, found 495.1426. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 30% EtOAc in hexanes, 3.0 mL/min, 264 nm, t_R=7.9 min].

4.5.3.5. Compound 10″c. Colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.82–7.79 (m, 2H), 7.54–7.50 (m, 2H), 7.36–7.33 (m, 3H), 7.21–7.18 (m, 1H), 3.77 (d, J=15.2 Hz, 1H), 3.69 (d, J=15.2 Hz, 1H), 3.68 (dq, J=11.8, 8.8 Hz, 1H), 3.49 (dq, J=11.8, 8.8 Hz, 1H), 1.91 (s, 3H), 1.64 (s, 3H), 1.56 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 138.5, 138.0, 132.0, 129.0, 128.2, 127.9, 126.0, 126.0, 124.1, 123.5 (q, J=276 Hz), 63.2, 62.0 (q, J=35 Hz), 35.2, 31.0, 24.3, 24.1; IR (CH_2Cl_2, film) 2966, 1595, 1493, 1453, 1399, 1375, 1319, 1286, 1152, 1084, 968, 903, 836, 790, 767 cm^{-1}; TLC R_f (hexane/EtOAc 2:1)=0.66; HRMS (ESI) *m/z* calcd for $C_{23}H_{27}F_3O_5SNa$ $(M+Na)^+$ 495.1423, found 495.1408. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 30% EtOAc in hexanes, 3.0 mL/min, 264 nm, t_R=8.2 min].

4.5.3.6. Compound 8′d. Colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 7.26–7.20 (m, 3H), 3.66 (d, J=13.6 Hz, 1H), 3.42 (s, 3H), 3.32 (d, J=13.2 Hz, 1H), 1.61 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 136.3, 133.9, 131.7, 130.9, 128.1, 127.7, 125.9, 124.3, 119.7, 101.7, 81.3, 51.2, 43.1, 22.2, 22.2; IR (CH_2Cl_2, film) 2989, 2927, 2826, 1473, 1368,

1297, 1272, 1126, 1086, 1041, 1006, 870, 805, 760 cm^{-1}; TLC R_f (hexane/Et_2O 2:1)=0.58; HRMS (ESI) *m/z* calcd for $C_{18}H_{19}BrO_3SNa$ $(M+Na)^+$417.0130, found 417.0126. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 20% EtOAc in hexanes, 2.0 mL/min, 264 nm, t_R=11.4 min].

4.5.4. From 4-bromothiophenol.

4.5.4.1. Compound 8″d. Colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.29 (m, 5H), 7.22 (dt, J=8.4, 2.0 Hz, 2H), 7.17–7.14 (m, 1H), 3.56 (d, J=13.6 Hz, 1H), 3.39 (d, J=14.0 Hz, 1H), 3.30 (s, 3H), 1.68 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 136.4, 134.5, 131.8, 131.3, 128.1, 127.5, 125.8, 123.9, 120.0, 102.8, 82.1, 51.7, 43.5, 24.3, 24.0; IR (CH_2Cl_2, film) 2989, 2927, 1474, 1370, 1269, 1189, 1091, 1007, 866, 808, 762 cm^{-1}; TLC R_f (hexane/Et_2O 2:1)=0.64; HRMS (ESI) *m/z* calcd for $C_{18}H_{19}BrO_3SNa$ $(M+Na)^+$417.0130, found 417.0141. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 20% EtOAc in hexanes, 2.0 mL/min, 264 nm, t_R=10.7 min].

4.5.4.2. Compound 9d. Colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J=8.8 Hz, 2H), 7.67 (d, J=8.4 Hz, 2H), 7.34–7.25 (m, 4H), 1.84 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 137.3, 133.3, 132.1, 129.8, 128.7, 128.5, 128.1, 125.9, 124.2, 101.4, 79.5, 61.7, 51.1, 22.2, 21.9; IR (CH_2Cl_2, film) 2990, 2940, 2831, 1574, 1449, 1389, 1320, 1148, 1084, 1067, 1010, 876, 762 cm^{-1}; TLC R_f (hexane/EtOAc 2:1)=0.57; HRMS (ESI) *m/z* calcd for $C_{18}H_{19}BrO_5SNa$ $(M+Na)^+$449.0029, found 449.0031. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 30% EtOAc in hexanes, 2.0 mL/min, 264 nm, t_R=14.1 min].

4.5.4.3. Compound 10′d. White solid: mp 129–130 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81–7.78 (m, 2H), 7.70–7.67 (m, 2H), 7.41–7.31 (m, 4H), 4.01 (dq, J=11.8, 8.4 Hz, 1H), 3.91 (d, J=14.8 Hz, 1H), 3.65 (dq, J=11.6, 8.8 Hz, 1H), 3.54 (d, J=14.8 Hz, 1H), 1.86 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 137.8, 132.3, 131.2, 129.7, 129.3, 128.9, 128.6, 126.2, 124.4, 123.5 (q, J=276 Hz), 62.3 (q, J=35 Hz), 61.5, 23.5, 22.3; IR (CH_2Cl_2, film) 3078, 2991, 2933, 1575, 1451, 1390, 1322, 1277, 1150, 1125, 1083, 1068, 1010, 967 cm^{-1}; TLC R_f (hexane/EtOAc 2:1)=0.73; HRMS (ESI) *m/z* calcd for $C_{19}H_{18}BrF_3O_5SNa$ $(M+Na)^+$516.9903, found 516.9916. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 40% EtOAc in hexanes, 2.0 mL/min, 264 nm, t_R=10.2 min].

4.5.4.4. Compound 10″d. Colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.76–7.73 (m, 2H), 7.66–7.63 (m, 2H), 7.36–7.33 (m, 3H), 7.15–7.13 (m, 1H), 3.74–3.69 (m, 3H), 3.54 (dq, J=11.8, 8.4 Hz, 1H), 1.87 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 137.9, 132.3, 132.2, 129.8, 129.1, 128.3, 127.6, 126.0, 123.9, 123.5 (q, J=276 Hz), 63.1, 61.8 (q, J=35 Hz), 24.2, 23.9; IR (CH_2Cl_2, film) 2920, 2854, 1574, 1390, 1324, 1282, 1150, 1084, 1010, 967, 824, 766 cm^{-1}; TLC R_f (hexane/EtOAc 2:1)=0.73; HRMS (ESI) *m/z* calcd for $C_{19}H_{18}BrF_3O_5SNa$ $(M+Na)^+$516.9903, found 516.9902. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 40% EtOAc in hexanes, 2.0 mL/min, 264 nm, t_R=14.0 min].

4.5.5. From 4-methoxythiophenol.

4.5.5.1. Compound 8′e. Colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.33 (m, 3H), 7.32–7.28 (m, 2H), 7.26–7.23 (m, 1H), 6.83–6.79 (m, 2H), 3.78 (s, 3H), 3.61 (d, J=13.6 Hz, 1H), 3.41 (s, 3H), 3.27 (d, J=13.6 Hz, 1H), 1.59 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 138.4, 133.9, 133.0, 127.9, 127.5, 127.5, 125.8, 124.5, 114.5, 101.7, 81.6, 55.3, 51.2, 45.3, 22.3, 22.2; IR (CH_2Cl_2, film) 2977, 2925, 2820, 1592, 1494, 1443, 1370, 1284, 1245, 1179, 1130, 1042, 875, 762 cm^{-1}; TLC R_f (hexane/Et_2O 2:1)=0.44; HRMS (ESI) *m/z* calcd for $C_{19}H_{22}O_4SNa$ $(M+Na)^+$369.1131, found 369.1129. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 20% EtOAc in hexanes, 2.0 mL/min, 264 nm, t_R=12.2 min].

4.5.5.2. Compound 8″e. Colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.34 (m, 3H), 7.32–7.28 (m, 2H), 7.17–7.15 (m, 1H), 6.81–6.79 (m, 2H), 3.78 (s, 3H), 3.51 (d, J=13.6 Hz, 1H), 3.35 (d, J=13.6 Hz, 1H), 3.31 (s, 3H), 1.66 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 139.2, 134.4, 133.4, 128.0, 127.6, 127.3, 125.8, 124.1, 102.8, 82.3, 55.3, 51.8, 45.6, 24.3, 24.2; IR (CH_2Cl_2, film) 2984, 2937, 2834, 1592, 1494, 1442, 1369, 1284, 1245, 1180, 1129, 1034, 827, 763 cm^{-1}; TLC R_f (hexane/Et_2O 2:1)=0.44; HRMS (ESI) *m/z* calcd for $C_{19}H_{22}O_4SNa$ $(M+Na)^+$369.1131, found 369.1128. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 40% EtOAc in hexanes, 2.0 mL/min, 264 nm, t_R=9.8 min].

4.5.5.3. Compound 9e. White solid: mp 134–135 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86–7.84 (m, 2H), 7.32–7.26 (m, 4H), 6.99–6.97 (m, 2H), 3.92 (d, J=15.2 Hz, 1H), 3.86 (s, 3H), 3.53 (d, J=14.8 Hz, 1H), 3.31 (s, 3H), 1.85 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 137.6, 133.4, 132.4, 130.2, 128.4, 128.0, 125.9, 124.4, 114.1, 101.5, 79.7, 62.0, 55.6, 51.2, 22.4, 22.1; IR (CH_2Cl_2, film) 2983, 2934, 2834, 1596, 1498, 1444, 1320, 1260, 1142, 1087, 804, 741 cm^{-1}; TLC R_f (hexane/EtOAc 2:1)=0.35; HRMS (ESI) *m/z* calcd for $C_{19}H_{22}O_6SNa$ $(M+Na)^+$401.1029, found 401.1029. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 40% EtOAc in hexanes, 2.0 mL/min, 264 nm, t_R=16.9 min].

4.5.5.4. Compound 10′e. Colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.86–7.82 (m, 2H), 7.42–7.33 (m, 4H), 7.01–6.97 (m, 2H), 4.05 (dq, J=11.8, 8.4 Hz, 1H), 3.88 (s, 3H), 3.87 (d, J=14.8 Hz, 1H), 3.66 (dq, J=11.8, 8.8 Hz, 1H), 3.54 (d, J=14.8 Hz, 1H), 1.86 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 138.1, 132.3, 131.3, 130.3, 129.1, 128.5, 126.1, 124.6 (q, J=276 Hz),

114.2, 62.4 (q, $J=35$ Hz), 61.8, 55.7, 23.7, 22.4; IR (CH_2Cl_2, film) 2992, 2938, 2839, 1596, 1498, 1377, 1321, 1286, 1143, 1085, 1024, 967, 901, 836 cm^{-1}; TLC R_f (hexane/EtOAc 2:1)=0.57; HRMS (ESI) *m/z* calcd for $C_{20}H_{21}F_3O_6SNa$ $(M+Na)^+$ 469.0903, found 469.0904. This product was further purified using HPLC prior to antimalarial testing [semi-preparative Silica gel column (1×25 cm), 50% EtOAc in hexanes, 2.0 mL/min, 264 nm, $t_R=11.5$ min].

4.5.5.5. Compound 12. White solid: mp 120–123 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, $J=8.8$ Hz, 2H), 7.55 (d, $J=8.4$ Hz, 2H), 7.42 (d, $J=7.6$ Hz, 1H), 7.36 (m, 2H), 7.30 (m, 1H), 3.95 (br d, $J=12.0$ Hz, 1H), 3.71 (d, $J=15.2$ Hz, 1H), 3.21 (br s, 3H), 1.81 (br s, 3H), 1.34 (s, 9H), 0.79 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 141.7, 137.8, 128.2, 128.2, 128.0, 127.4, 126.9, 126.0, 124.8, 106.6, 79.5, 50.8, 41.4, 35.2, 31.1, 26.4, 26.2, 23.8; IR (CH_2Cl_2, film) 2964, 2360, 1726, 1595, 1462, 1393, 1319, 1291, 1199, 1150, 1107, 1084, 960, 845, 760, 576, 520 cm^{-1}; HRMS (FAB-MS) *m/z* calcd for $C_{25}H_{34}O_5S$ $(M+Na)^+$ 469.20247, found 469.20237.

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