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Synthetic methods for the preparation of ARQ 501 (β-Lapachone) human blood metabolites

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Abstract—ARQ 501 (3,4-dihydro-2,2-dimethyl-2H-naphthol[1,2-*b*] pyran-5,6-dione), a synthetic version of β-Lapachone, is a promising anti-cancer agent currently in multiple Phase II clinical trials. Promising anti-cancer activity was observed in Phase I and Phase II trials. Metabolism by red blood cells of drugs is an understudied area of research and the metabolites arising from oxidative ring opening (**M2** and **M3**), decarbonylation/ring contraction (**M5**), and decarbonylation/oxidation (**M4** and **M6**) of ARQ 501 offer a unique opportunity to provide insight into these metabolic processes. Since these metabolites were not detected in in vitro incubations of ARQ 501 with liver microsomes and were structurally diverse, confirmation by chemical synthesis was considered essential. In this report, we disclose the synthetic routes employed and the characterization of the reference standards for these blood metabolites as well as additional postulated structures, which were not confirmed as metabolites.

1. Introduction

β-Lapachone (3,4-dihydro-2,2-dimethyl-2H-naphthol[1,2-*b*] pyran-5,6-dione), a natural product found in Pau d'arco trees (*Tabebuia impetiginosa*), has broad anti-cancer activities. ARQ 501, a fully synthetic version of β-Lapachone, elevates E2F-1 levels leading to the activation of the cell cycle checkpoint which results in the selective apoptotic cell death of cancer cells[1] and is effective against human ovarian cancer and prostate cancer xenografts in mice.[2] ARQ 501 is currently in multiple Phase II clinical trials and promising anti-cancer activity has been observed.

The majority of drugs are metabolized by the liver with other tissues such as the gastrointestinal tract, the lungs, the skin, and the kidneys providing almost all the remainder. There have been countless reports in the scientific community describing studies to elucidate these processes. However, blood is generally assumed to be an inert vehicle for the transportation of drugs to target tissues and is frequently not studied for its metabolic effects on drug molecules.[3] In the course of developing pharmacokinetic methods for ARQ 501, it was observed that not only did ARQ 501 partition into red blood cells but was also metabolized rapidly in whole blood although not in plasma.[4]

Figure 1 shows the results from in vitro time course studies on the metabolism of [^{14}C] ARQ 501 incubated in human whole blood. Detection and identification of metabolites was based on radioactive peak monitoring and molecular ion detection using an accurate radioisotope counting (LC-ARC) system.[4] After 180 min incubation at 37 °C, ARQ 501 yielded four major metabolites (**M1**, **M2**, **M3**, and **M5**) and two minor metabolite peaks (**M4** and **M6**). These metabolites were not detected in in vitro incubations of ARQ 501 with liver microsomes or hepatocytes. They therefore represented a unique opportunity to examine the effects of an understudied metabolizing system (red blood cells) on a promising Phase II drug.

Herein, we describe the preparation of these novel ARQ 501 human blood metabolites. In addition, we describe the synthesis of several postulated metabolites suggested by accurate mass measurements which failed to match the chromatographic retention times and so were ruled out as metabolites in this study.

Keywords: Synthesis; Human; Blood; Metabolites; ARQ 501; β-Lapachone.
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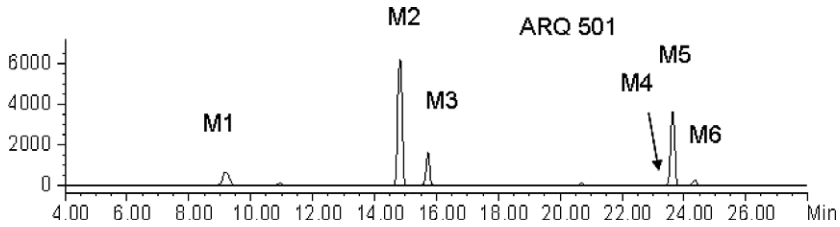


Figure 1. Radiochromatograms of [^{14}C] ARQ 501 incubated in human whole blood at rt for 180 min.

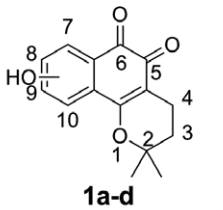
2. Results and discussion

2.1. Synthesis of postulated but unconfirmed metabolites, M1

Accurate mass measurement experiments indicated that metabolite **M1** was produced by the oxidation of ARQ 501. A characteristic product ion at *m*/*z* 121 localized the oxidation to the phenyl ring. Hydroxylated ring variants of ARQ 501 **1a**–**d** were thus postulated (Fig. 2) and prepared as shown in Scheme 1. Methoxytetralones **2a**–**d** were oxidized to the corresponding methoxy-substituted 2-hydroxy-[1,4]-naphthoquinones **3a**–**d** using the literature procedures.[5] The methoxy-substituted ARQ 501 isomers **5a**–**d** were synthesized through allylation followed by cyclization in concentrated sulfuric acid. The treatment of **5a**–**d** with boron tribromide followed by concentrated sulfuric acid provided the corresponding hydroxylated compounds **1a**–**d**.[6] The demethylation of **5d** proceeded in excellent yield (93%) to provide **1d**, presumably due to the neighboring carbonyl group assistance, while the demethylation of **5a**–**c** provided low yields (7–27%) of the corresponding products **1a**–**c**. We ascribe this to the competing destruction of the dihydropyran ring by boron tribromide. Disappointingly, the chromatographic retention time of **M1** did not match either of these hydroxylated ARQ 501 compounds. **M1** eluted much earlier and the structure remains unconfirmed.

2.2. Synthesis of blood metabolites M2–M6

Metabolites **M2**, **M3**, **M5**, and **M6** have not been previously reported in the literature. **M2** and **M3** are products of oxidative ring opening of ARQ 501. Metabolite **M2** was synthesized concisely from ARQ 501 in two steps as shown in Scheme 2. The oxidation of ARQ 501 with MCPBA (*m*-chloroperoxybenzoic acid) was followed by aqueous hydrolysis. No epoxidation was observed of the double bond in the MCPBA oxidation reaction. Cyclic anhydride **6** and metabolite **M2** were characterized by 1D and 2D NMR analysis.



1a-d

a: 10-OH; **b**: 9-OH; **c**: 8-OH; **d**: 7-OH

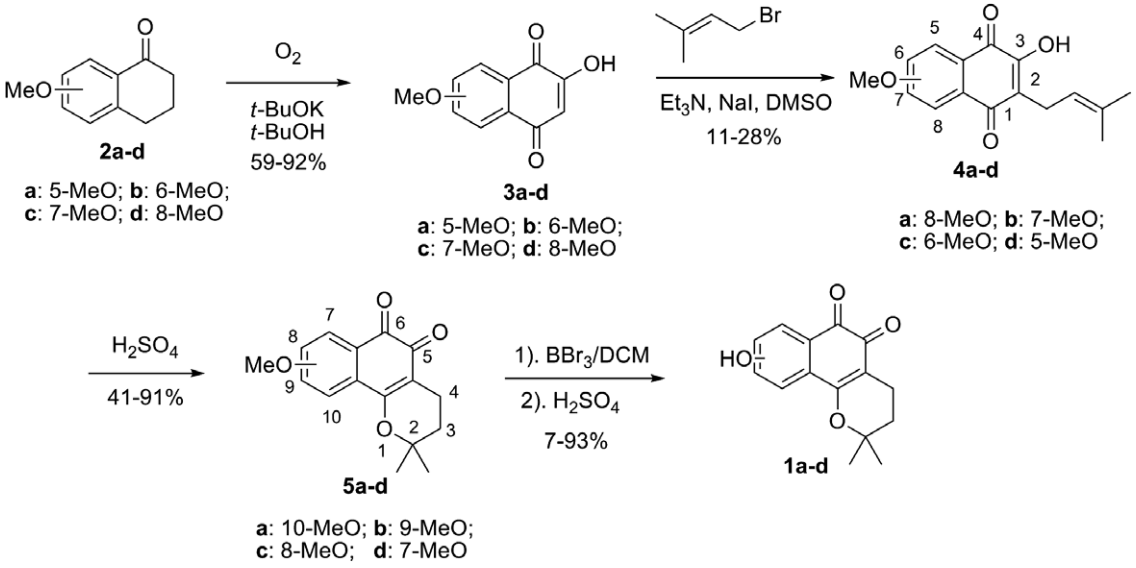
Figure 2. Postulated metabolite structures of **M1**.

Metabolite **M3** was prepared by regio-specific hydrogenation of the cyclic anhydride **6** using catalytic palladium over barium sulfate as shown in Scheme 3. The reduction occurred exclusively at the carbonyl attached to the pyran ring, no reduction of the carbonyl attached to benzene ring or hydrogenation of the double bond was detected. The structure of metabolite **M3** was assigned by 1D and 2D NMR analysis. The gHMBC (gradient Heteronuclear Multiple Bond Correlation spectroscopy) of **M3** showed the expected three bond correlations of the 4-proton with aldehyde carbon and aldehyde proton with the 4-carbon (Fig. 3). This experiment confirmed that the aldehyde is on the pyran ring and the carboxylic acid is on the phenyl ring.

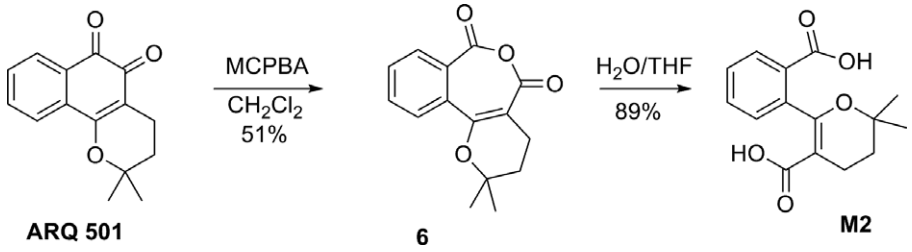
Metabolite **M4** was prepared as shown in Scheme 4. The allylation of 4-hydroxycoumarin **7** with 3,3-dimethylallylbromide provided intermediate **8**, which was cyclized by treatment with sulfuric acid to give metabolite **M4**.[7] The structure of metabolite **M4** was assigned by 1D and 2D NMR analysis.

Metabolite **M5** was synthesized by an analogous reaction sequence as described for metabolite **M4** except that 1,3-indanedione **9** was used as a starting material. The allylation of indanedione **9** gave intermediate **10**, and the cyclization of **10** with sulfuric acid in THF gave metabolite **M5** (Scheme 5). The structure of metabolite **M5** was assigned by 1D and 2D NMR analysis.

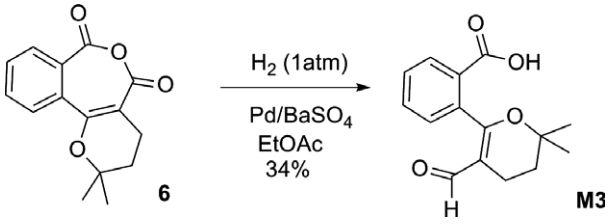
Prior to the synthesis of the standard which confirmed the structure of **M4**, it was postulated that the accurate mass of **M4** ($C_{14}H_{14}O_3$) corresponded to a phenyl ring hydroxylated form of **M5** (Fig. 4). Two of these postulated metabolites (**11b** and **11c**) were prepared as shown in Scheme 6. Compound **3c** was converted to its corresponding iodonium ylide **12**, which was then thermally transformed to 5-methoxyindan-1,3-dione **13**, a method described in the literature.[8] Following allylation and cyclization, a mixture of methoxy-substituted ring contraction compounds **15b** and **15c** was obtained in a 5:2 ratio. Demethylation of **15b** and **15c** with boron tribromide resulted in 6:1 mixture of **11b** and **11c**. The structures of **11b** and **11c** were assigned based on ^{1}H NMR analysis. In compound **11b**, the chemical shift of the phenolic proton appears at lower field (δ 10.22) due to its relationship to *para*-electron-withdrawing carbonyl group, as compared to that in **11c** (δ 10.00) whose electron-withdrawing carbonyl group is in the *meta*-posi-



Scheme 1. Synthetic route for postulated structures **1a**–**d**.



Scheme 2. Synthesis of metabolite **M2**.



Scheme 3. Synthesis of metabolite **M3**.

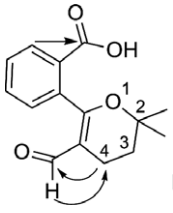


Figure 3. Key gHMBC correlations of **M3**, the direction of the arrows indicates proton to carbon correlations.

tion. In compound **11c**, the C6 proton is in the *ortho*-position relative to the electron-donating phenol group, and appears at higher field (δ 6.72) than the corresponding C6 proton in compound **11b** (δ 7.13) where the C6 is in *meta*-position relative to the phenol group. However, chromatographic retention time of **M4** matched neither **11b** nor **11c**. The synthesis of **11a** and **11d** was not pursued after the match of **M4** was confirmed with the lactone compound as shown in Scheme 4.

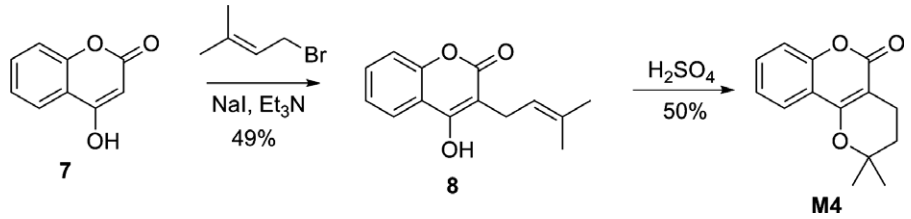
Metabolite **M6** was prepared as shown in Scheme 7. The bromination of 2-acetylbenzoic acid **16**, followed by cyclization with sodium acetate provided lactone **18**.[9] The allylation of **18** afforded intermediate **19**, which was cyclized with sulfuric acid to give **M6**.

3. Summary

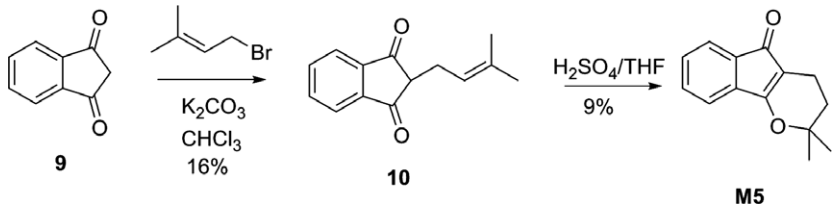
The objective of the present work was to provide structurally unambiguous reference standards, which could be used to elucidate the underlying mechanisms by which ARQ 501 is metabolized by red blood cells.

The five major human blood metabolites of ARQ 501 (**M2**–**M6**) confirmed in this work indicate that at least one metabolite, **M5** a novel decarbonylation/ring contraction product, may arise from a heretofore unknown mechanism. In addition, metabolites **M2** and **M3** were confirmed as oxidative ring opening products, and **M4** and **M6** as decarbonylation/oxidation products.

With these structurally diverse metabolites available, work is underway to identify the enzymes responsible for the biotransformations of ARQ 501 in red blood cells. Thus, this work provides materials with which to



Scheme 4. Synthesis of metabolite **M4**.



Scheme 5. Synthesis of metabolite **M5**.

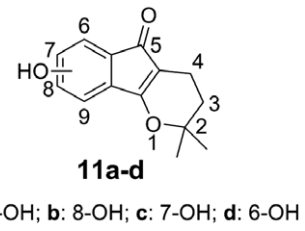


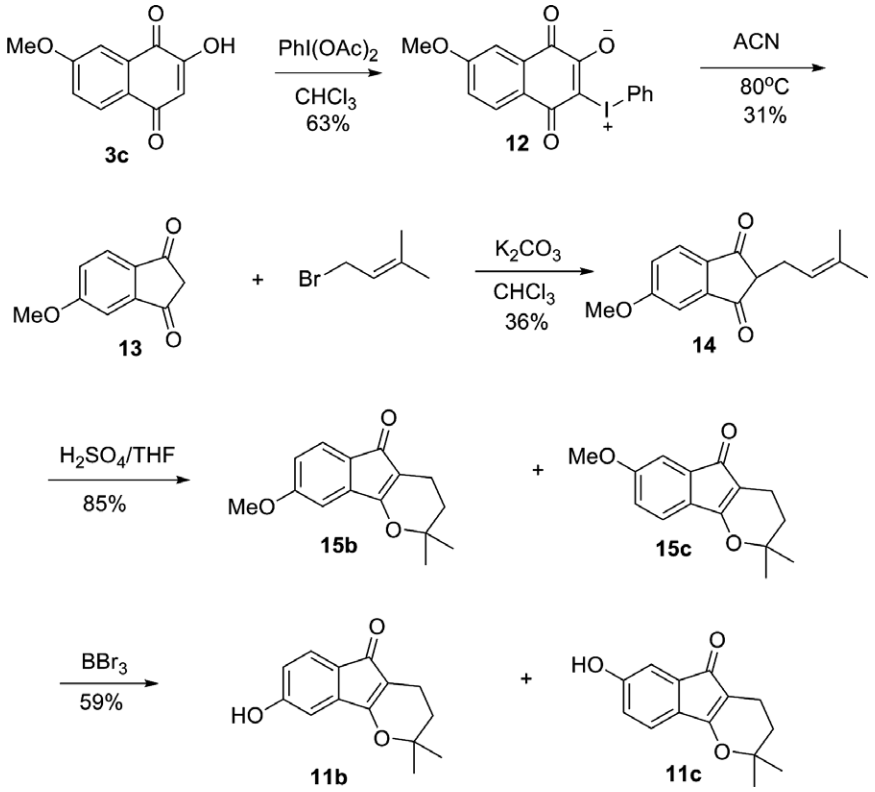
Figure 4. Postulated structures of **M4**.

study an often neglected route of metabolism (blood) of a drug.

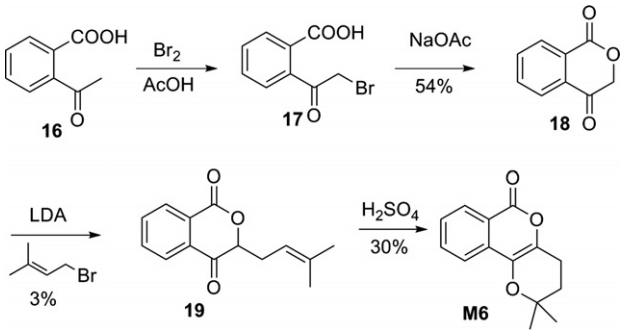
Metabolites (**M2**–**M6**) have been studied in pre-clinical models and do not show anti-cancer activity.

4. Experimentals

NMR spectra were recorded on a Varian Mercury 400 MHz NMR spectrometer and calibrated using tetra-



Scheme 6. Synthetic scheme for postulated structures **11b** and **11c**.



Scheme 7. Synthesis of metabolite **M6**.

methylsilane as an internal reference. Mass spectra were obtained on a Waters Micromass ZQ mass spectrometer.

4.1. Synthesis of 8-methoxy-1-tetralone (2a)

A solution of 2-methoxy-6-methylbenzoic acid ethyl ester (3.88 g, 20 mmol) in anhydrous tetrahydrofuran (25 mL) was added dropwise into a solution of lithium diisopropylamide (LDA) (13.75 mL, 22 mmol, 1.6 M in tetrahydrofuran) at −78 °C over 15 min. Methyl acrylate (4.5 mL, 50 mmol) was added and the reaction was warmed to 0 °C and kept at that temperature for 5 h. The reaction was quenched by the addition of saturated ammonium chloride (100 mL) and extracted with dichloromethane (3× 200 mL). The combined organic layers were evaporated under reduced pressure and the resulting residue dissolved in a mixture of methanol/concentrated hydrochloric acid (4:1, 500 mL) and heated at reflux overnight. The reaction mixture was evaporated to dryness under reduced pressure and extracted with dichloromethane (3× 100 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (5–35% ethyl acetate in hexane) to give the product (1.22 g, 34%) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42 (t, J = 8.2 Hz, 1H), 6.94 (d, J = 8.2 Hz, 1H), 6.87 (d, J = 7.4 Hz, 1H), 3.77 (s, 3H), 2.86 (t, J = 6.2 Hz, 2H), 2.50–2.51 (m, 2H), 1.93 (t, J = 6.2 Hz, 2H); LCMS: m/z 177 $[M+H]^+$.

4.2. Synthesis of 2-hydroxy-8-methoxy-[1,4]naphthoquinone (3a)

Oxygen gas was bubbled into a solution of potassium *tert*-butoxide (1 M in *tert*-butanol, 60 mL, 60 mmol) for 30 min, 8-methoxytetralone (**2a**) (1.22 g, 6.93 mmol) was added, and oxygen was bubbled through the reaction mixture for an additional 4 h. The mixture was cooled to 0 °C, quenched by the addition of 1 M hydrochloric acid (100 mL), and extracted with dichloromethane (3× 500 mL). The combined organic layers were extracted with 1 M sodium hydroxide (3× 200 mL), re-acidified with concentrated hydrochloric acid (20 mL), and extracted with dichloromethane (3× 500 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give the product as an orange solid (1.03 g, 73%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.36 (br s, 1H), 7.76 (t, J = 8.2 Hz, 1H), 7.56 (d, J = 8.6 Hz, 1H), 7.49 (d, J = 8.6 Hz, 1H), 6.08 (s, 1H), 3.93 (s, 3H); LCMS: m/z 205 $[M+H]^+$.

4.3. Synthesis of 2-hydroxy-7-methoxy-[1,4]naphthoquinone (3b)

Compound **3b** was synthesized from **2b** in 69% yield using the same procedure as described for **3a**. Mp 220–222 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.58 (s, 1H), 7.89 (d, J = 8.6 Hz, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.35 (dd, J = 8.6, 2.5 Hz, 1H), 6.10 (s, 1H), 3.92 (s, 3H); LCMS: m/z 205 $[M+H]^+$.

4.4. Synthesis of 2-hydroxy-6-methoxy-[1,4]naphthoquinone (3c)

Compound **3c** was synthesized from **2c** in 59% yield using the same procedure as described for **3a**. Mp 222–224 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.82 (br s, 1H), 7.96 (d, J = 8.6 Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H), 7.29 (d, J = 8.6 Hz, 1H), 3.92 (s, 3H); LCMS: m/z 204 $[M+H]^+$.

4.5. Synthesis of 2-hydroxy-5-methoxy-[1,4]naphthoquinone (3d)

Compound **3d** was prepared in 92% yield from **2d** using the same procedure as described for **3a**.

4.6. Synthesis of 3-hydroxy-5-methoxy-2-(3-methylbut-2-en-1-yl)-1,4-naphthoquinone (4a)

To a solution of 2-hydroxy-8-methoxy-[1,4]naphthoquinone (**3a**) (1.03 g, 5.0 mmol) in anhydrous dimethylsulfoxide (5 mL) were added 3,3-dimethylallyl bromide (0.65 mL, 5.55 mmol), triethylamine (0.77 mL, 5.55 mmol), and sodium iodide (831 mg, 5.55 mmol). The mixture was stirred at rt for 2 h, heated at 45 °C for 4 h and then poured into water (100 mL), extracted with dichloromethane (3× 200 mL), washed successively with 10% sodium bicarbonate (200 mL), brine (200 mL), and dried over sodium sulfate. After filtration and evaporation of the solvent under reduced pressure, the orange residue was purified by silica gel chromatography (10–30% ethyl acetate in hexane) to give the product as a yellow solid (150 mg, 11%). Mp 171–173 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.70 (s, 1H), 7.77 (t, J = 7.8 Hz, 1H), 7.61 (d, J = 7.0 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 5.12 (m, 1H), 3.92 (m, 3H), 3.10 (d, J = 7.0 Hz, 2H); LCMS: m/z 273 $[M+H]^+$.

4.7. Synthesis of 3-hydroxy-6-methoxy-2-(3-methyl-bu-2-enyl)-[1,4]naphthoquinone (4b)

Compound **4b** was prepared in 21% yield from **3b** using the same procedure as described for **4a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 2.8 Hz, 1H), 7.20 (dd, J = 8.8, 2.8 Hz, 1H), 5.20

(m, 1H), 3.29 (d, J = 6.8 Hz, 2H), 1.79 (s, 3H), 1.69 (s, 3H); LCMS: m/z 273 $[M+H]^+$.

4.8. Synthesis of 2-hydroxy-6-methoxy-3-(3-methylbut-2-en-1-yl)naphthoquinone (4c)

Compound **4c** was prepared in 18% yield from **3c** using the same procedure as described for **4a**. Mp 113–115 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (br s, 1H), 7.95 (d, J = 8.6 Hz, 1H), 7.41 (d, J = 2.7 Hz, 1H), 7.28 (dd, J = 2.7, 8.6 Hz, 1H), 5.12 (m, 1H), 3.92 (s, 3H), 3.14 (d, J = 7.0 Hz, 2H), 1.70 (s, 3H), 1.62 (s, 3H); LCMS: m/z 273 $[M+H]^+$. Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92. Found: C, 70.76; H, 5.69.

4.9. Synthesis of 3-hydroxy-8-methoxy-2-(3-methyl-bu-2-enyl)-[1,4]naphthoquinone (4d)

Compound **4d** was prepared in 28% yield from **3d** using the same procedure as described for **4a**. Mp 122–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.74 (m, 1H), 7.63–7.59 (m, 1H), 7.33 (d, J = 8.8 Hz, 1H), 7.07 (s, 1H), 5.24–5.20 (m, 1H), 4.01 (s, 3H), 3.28 (d, J = 8.0 Hz, 2H), 1.79 (s, 3H), 1.67 (s, 3H); LCMS: m/z 273 $[M+H]^+$.

4.10. Synthesis of 7-methoxy-2,2-dimethyl-3,4-dihydro-2H-benzo[*h*]chromene-5,6-dione (5a)

Concentrated sulfuric acid (5 mL) was added to 3-hydroxy-5-methoxy-2-(3-methylbut-2-en-1-yl)-1,4-naphthoquinone (**4a**) (150 mg, 0.87 mmol) at rt. The mixture was stirred for 1 h and then diluted with ice water (100 mL). The resulting solution was extracted with ethyl acetate (3× 100 mL), washed with brine (100 mL), dried over sodium sulfate, and concentrated under reduced pressure. The crude solid was purified by silica gel chromatography (30–50% ethyl acetate in hexane) to give the product as an orange solid (62 mg, 41%). Mp 156–157 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.57 (t, J = 7.8 Hz, 1H), 7.48 (d, J = 7.4 Hz, 1H), 3.97 (s, 3H), 2.54 (t, J = 6.6 Hz, 1H), 1.84 (t, J = 6.6 Hz, 2H); LCMS: m/z 273 $[M+H]^+$.

4.11. Synthesis of 8-methoxy-2,2-dimethyl-3,4-dihydro-2H-benzo[*h*]chromene-5,6-dione (5b)

Compound **5b** was synthesized in 91% yield from **4b** using the same procedure as described for **5a**. Mp 162–163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.8 Hz, 1H), 7.55 (d, J = 2.0 Hz, 1H), 7.11 (dd, J = 8.4, 2.4 Hz, 1H), 3.84 (s, 3H), 2.54 (t, J = 6.4 Hz, 2H), 1.83 (t, J = 6.4 Hz, 2H), 1.45 (s, 6H); LCMS: m/z 273 $[M+H]^+$.

4.12. Synthesis of 9-methoxy-2,2-dimethyl-3,4-dihydro-2H-benzo[*h*]chromene-5,6-dione (5c)

Compound **5c** was prepared in 72% yield from **4c** using the same procedure as described for **5a**. Mp 158–160 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, J = 8.6 Hz, 1H), 7.20 (d, J = 2.3 Hz, 1H), 7.12 (dd, J = 2.7, 8.6 Hz, 1H), 3.90 (s, 3H), 2.39 (t, J = 6.6 Hz, 2H), 1.82 (t, J = 6.6 Hz, 2H) 1.41 (s, 6H); LCMS: m/z 273 $[M+H]^+$.

4.13. Synthesis of 10-methoxy-2,2-dimethyl-3,4-dihydro-2H-benzo[*h*]chromene-5,6-dione (5d)

Compound **5d** was prepared in 67% yield from **4d** using the same procedure as described for **5a**. Mp 145–146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.8 Hz, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 4.00 (s, 3H), 2.60 (t, J = 6.8 Hz, 2H), 1.79 (t, J = 6.8 Hz, 2H), 1.41 (s, 6 H); LCMS: m/z 273 $[M+H]^+$.

4.14. Synthesis of 7-hydroxy-2,2-dimethyl-3,4-dihydro-2H-benzo[*h*]chromene-5,6-dione (1a)

To a solution of 7-methoxy-2,2-dimethyl-3,4-dihydro-2H-benzo[*h*]chromene-5,6-dione (**5a**) (50 mg, 0.18 mmol) in anhydrous dichloromethane at 0 °C was added boron tribromide (0.71 mL, 0.71 mmol, 1.0 M in dichloromethane) dropwise. After stirring for 15 min, the mixture was allowed to warm to rt and stirred for 2 h. The reaction mixture was quenched by the addition of ice water (15 mL), and extracted with dichloromethane (3× 20 mL). The combined organic layers were dried and concentrated under reduced pressure. The resulting residue was taken up in a concentrated sulfuric acid (5 mL) and stirred at rt for 30 min. The mixture was diluted with water (20 mL) and extracted with dichloromethane (3× 20 mL). The combined extracts were dried, concentrated under reduced pressure, and purified by silica gel chromatography (20–80% ethyl acetate in hexane) to give the product as a red-orange solid (13.6 mg, 27%). Mp 163–165 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.75 (s, 1H), 7.68 (t, J = 7.8 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.12 (d, J = 7.8 Hz, 1H), 2.54 (t, J = 6.6 Hz, 1H), 1.82 (t, J = 6.6 Hz, 2H); LCMS: m/z 259 $[M+H]^+$.

4.15. Synthesis of 8-hydroxy-2,2-dimethyl-3,4-dihydro-2H-benzo[*h*]chromene-5,6-dione (1b)

Compound **1b** was prepared in 17% yield from compound **5b** using the same procedure as described for **1a**. Mp 211–213 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 2.8 Hz, 1H), 7.09 (dd, J = 8.8, 2.8 Hz, 1H), 2.35 (t, J = 6.4 Hz, 2H), 1.80 (t, J = 6.4 Hz, 2H), 1.40 (s, 6H); LCMS: m/z 259 $[M+H]^+$.

4.16. Synthesis of 9-hydroxy-2,2-dimethyl-3,4-dihydro-2H-benzo[*h*]chromene-5,6-dione (1c)

Compound **1c** was prepared in 7% yield from **5c** using the same procedure as described for **1a**. Mp 257–260 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.89 (br s, 1H), 7.82 (d, J = 8.6 Hz, 1H), 7.14 (d, J = 2.3 Hz, 1H), 7.12 (dd, J = 2.3, 8.6 Hz, 1H), 3.90 (s, 3H), 2.38 (t, J = 6.6 Hz, 2H) 1.80 (t, J = 6.6 Hz, 2H) 1.40 (s, 6H); LCMS: m/z 273 $[M+H]^+$.

4.17. Synthesis of 10-hydroxy-2,2-dimethyl-3,4-dihydro-2H-benzo[*h*]chromene-5,6-dione (1d)

Compound **1d** was prepared in 93% yield from **5d** using the same procedure as described for **1a**. Mp 150–152 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.39 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.21 (d, J = 1.6 Hz, 1H), 2.60 (t, J = 8.0 Hz, 2H), 1.83 (t, J = 8.0 Hz, 2H), 1.43 (s, 6H); LCMS: m/z 258 $[M+H]^+$.

4.18. Synthesis of 2,2-dimethyl-3,4-dihydro-2H-1,6-dioxan-dibenzo[*a*,*c*]cycloheptene-5,7-dione (6)

A solution of MCPBA (77%, 493 mg, 2.2 mmol) in dichloromethane (10 mL) was dried over sodium sulfate. The dried solution was added to a solution of ARQ 501 (484 mg, 2 mmol) in dichloromethane (10 mL) and the resulting mixture stirred at rt for 24 h. After concentrating the reaction mixture, dichloromethane (5 mL) was added and the white solid was filtered off. The filtrate was concentrated under reduced pressure and the residue purified by chromatography on a silica gel (1–20% ethyl acetate in hexane) to provide 2,2-dimethyl-3,4-dihydro-2H-1,6-dioxan-dibenzo[*a*,*c*]cycloheptene-5,7-dione (**6**) as a white solid (265 mg, 51%). Mp 104–107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.80 (m, 2H), 7.65 (td, J = 8.0, 1.2 Hz, 1H), 7.54 (td, J = 8.0, 1.2 Hz, 1H), 2.66 (t, J = 6.8 Hz, 2H), 1.83 (t, J = 6.8 Hz, 2H), 1.42 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.17, 161.70, 156.27, 133.12, 131.67, 130.83, 130.72, 129.55, 126.99, 104.89, 77.99, 31.87, 26.81, 22.06; LCMS: m/z 259 $[M+H]^+$.

4.19. Synthesis of 2-(2-carboxy-phenyl)-6,6-dimethyl-5,6-dihydro-4H-pyran-3-carboxylic acid (M2)

2,2-Dimethyl-3,4-dihydro-2H-1,6-dioxan-dibenzo[*a*,*c*]cycloheptene-5,7-dione (**6**) (52 mg, 0.2 mmol) was dissolved in a mixture of THF (5 mL) and water (3 mL), and the resulting solution stirred at rt for 14 h. The reaction mixture was extracted with ethyl acetate (3× 5 mL) and the combined organic extracts dried over sodium sulfate. After filtration and concentration under reduced pressure, ether (5 mL) was added to the residue and the white solid collected by filtration to give 2-(2-carboxy-phenyl)-6,6-dimethyl-5,6-dihydro-4H-pyran-3-carboxylic acid (**M2**) (49 mg, 89%). Mp 185–187 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.00 (br, 2H), 7.79 (d, J = 7.2 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 2.33 (t, J = 6.4 Hz, 2H), 1.69 (t, J = 6.4 Hz, 2H), 1.26 (s, 6H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 169.01, 168.04, 162.82, 139.62, 131.65, 131.07, 130.86, 129.94, 128.54, 100.99, 76.82, 32.30, 26.85, 20.28; LCMS: m/z 299 $[M+Na]^+$, 277 $[M+H]^+$, 259 $[M+H-H_2O]^+$; HRMS: Calcd 277.1076. Found: 277.1080.

4.20. Synthesis of 2-(3-formyl-6,6-dimethyl-5,6-dihydro-4H-pyran-2-yl)-benzoic acid (M3)

To a solution of 2,2-dimethyl-3,4-dihydro-2H-1,6-dioxan-dibenzo[*a*,*c*]cycloheptene-5,7-dione (**6**) (200 mg, 0.78 mmol) in ethyl acetate (10 mL) was added Pd/$BaSO_4$ (30 mg). A hydrogen balloon was attached and the system was evacuated and filled with hydrogen three times. The reaction mixture was stirred under hydrogen for 6 h (LCMS showed 60% of product formation with 36% of starting material). The reaction mixture was filtered and concentrated to dryness under reduced pressure. The residue was purified by preparative reverse phase HPLC to afford 2-(3-formyl-6,6-dimethyl-5,6-dihydro-4H-pyran-2-yl)-benzoic acid (**M3**) as a white solid (68 mg, 34%). Mp 146–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.10 (dd, J = 8.0, 1.2 Hz, 1H), 7.61 (td, J = 7.6, 1.2 Hz, 1H), 7.56 (td, J = 7.6, 1.6 Hz, 1H), 7.40 (dd, J = 7.2, 1.2 Hz, 1H), 2.43 (t, J = 6.8 Hz, 2H), 1.79 (t, J = 6.4 Hz, 2H), 1.37 (s, 6 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 191.57, 172.54, 171.26, 135.10, 132.65, 132.48, 131.60, 130.16, 130.10, 114.02, 79.58, 31.87, 26.73, 16.11; LCMS: m/z 261 $[M+H]^+$; HRMS: Calcd 261.1127. Found: 261.1136.

4.21. Synthesis of 2,2-dimethyl-3,4-dihydro-2H-pyrano[3,2-*c*]chromen-5-one (M4)

To a solution of 4-hydroxycoumarine (**7**) (0.30 g, 1.85 mmol) in DMSO (10 mL) was added 3,3-dimethylallyl bromide (0.24 mL, 2.04 mmol), sodium iodide (0.28 g, 1.85 mmol), and triethylamine (0.28 mL, 2.04 mmol). The reaction was stirred at rt for 2 h, then heated at 45 °C for 3 h. A mixture of ethyl acetate and water (5:1, 180 mL) was added to the reaction mixture. The organic layer was separated and washed with water (30 mL), brine (50 mL), dried over sodium sulfate, filtered, and concentrated to dryness under reduced pressure. The crude product was purified by silica gel chromatography (15% ethyl acetate in hexane) to afford intermediate **8** as a white solid (0.21 g, 49%). LC/MS was used to confirm the expected $[M+H]^+$ of 231 m/z. Intermediate **8** (40 mg) was dissolved in concentrated sulfuric acid (2 mL) and stirred at rt for 1 h. Ice water (30 mL) was added to quench the reaction. The reaction mixture was extracted with ethyl acetate (3× 80 mL) and the combined organic extracts were washed with water (50 mL), brine (50 mL), dried over sodium sulfate, filtered, and concentrated to dryness under reduced pressure. The crude product was purified by silica gel chromatography (20% ethyl acetate in hexane) to afford 2,2-dimethyl-3,4-dihydro-2H-pyrano[3,2-*c*]chromen-5-one (**M4**) as a white solid (20 mg, 50 %). Mp 115–117 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (d, J = 7.2 Hz, 1H), 7.61 (t, J = 8.0 Hz, 1H), 7.39–7.33 (m, 2H), 2.45 (t, J = 6.4 Hz, 2H), 1.87 (t, J = 6.4 Hz, 2H), 1.41 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.52, 159.38, 152.67, 131.44, 123.85, 122.65, 116.74, 116.43, 99.84, 78.31, 32.14, 26.84, 17.59; LCMS: m/z 231 $[M+H]^+$; HRMS: Calcd 231.1021. Found: 231.1025.

4.22. Synthesis of 2-(3-methylbut-2-enyl)-indan-1,3-dione (10)

To a solution of 1,3-indanedione (**9**) (146 mg, 1.0 mmol) in chloroform (2 mL) were added 3,3-dimethylallyl bromide (149 mg, 1.0 mmol) and potassium carbonate (138 mg, 1.0 mmol). The reaction mixture was stirred at rt for 18 h and then filtered to remove the solid. The filtrate was immediately loaded onto a silica gel column and eluted with 10% ethyl acetate in hexane to give 2-(3-methylbut-2-enyl)-indan-1,3-dione (**10**) as a yellow solid (35 mg, 16%). Mp 63–65 °C; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.98–7.95 (m, 2H), 7.85–7.82 (m, 2H), 5.01 (t, $J = 1.2$ Hz, 1H), 3.06 (t, $J = 5.2$ Hz, 1H), 2.72 (t, $J = 6.8$ Hz, 2H), 1.63 (s, 3H), 1.57 (s, 3H); LCMS: m/z 215 $[M+H]^+$.

4.23. Synthesis of 2,2-dimethyl-3,4-dihydro-2H-indeno[1,2-*b*]pyran-5-one (M5)

Concentrated sulfuric acid (5 mL) was added dropwise to a solution of 2-(3-methylbut-2-en-1-yl)-1H-indene-1,3(2H)-dione (**10**) (1.5 g, 7.0 mmol) in THF (100 mL) at rt. The mixture was stirred for 1 h and then diluted with ice water (100 mL). The resulting solution was extracted with ethyl acetate (3× 100 mL), washed with brine (100 mL), dried over sodium sulfate, and concentrated under reduced pressure. The crude solid was purified by preparative reverse phase HPLC and silica gel chromatography (100% $CHCl_3$) to give 2,2-dimethyl-3,4-dihydro-2H-indeno[1,2-*b*]pyran-5-one (**M5**) (130 mg, 8.6%) as a yellow solid. Mp 53–55 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.41–7.29 (m, 3H), 7.12 (d, $J = 6.8$ Hz, 1H), 2.20 (t, $J = 6.4$ Hz, 2H), 1.78 (t, $J = 6.4$ Hz, 2H), 1.41 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 193.62, 173.99, 138.69, 133.99, 131.89, 129.82, 120.91, 117.64, 106.51, 81.28, 32.86, 26.78, 14.47; LCMS: m/z 215 $[M+H]^+$; HRMS: Calcd 215.1076. Found: 215.1080.

4.24. Synthesis of 7-methoxy-1,4-dioxo-3-(phenyliodonio)-1,4-dihydronaphthalen-2-olate (12)

(Diacetoxyiodo)benzene (7.6 g, 23.6 mmol) was added to a suspension of 2-hydroxy-7-methoxy-[1,4]naphthoquinone (**3c**) (4.8 g, 23.6 mmol) in chloroform (50 mL) at 0 °C. The reaction mixture was warmed and stirred at rt for 5 h. After concentration under reduced pressure, ethyl acetate (50 mL) was added to the residue and the light orange solid product (**12**) was collected by filtration (6.1 g, 63 %). Mp 204–209 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (d, $J = 8.8$ Hz, 1H), 7.86–7.82 (m, 2H), 7.55–7.49 (m, 1H), 7.43–7.37 (m, 3H), 7.34 (dd, $J = 8.4$, 2.8 Hz, 1H), 3.90 (s, 3H); LCMS: m/z 407 $[M+H]^+$.

4.25. Synthesis of 5-methoxy-indan-1,3-dione (13)

7-Methoxy-1,4-dioxo-3-(phenyliodonio)-1,4-dihydronaphthalen-2-olate (**12**) (3.0 g, 7.39 mmol) as a suspension in acetonitrile was refluxed overnight. The reaction mixture was cooled to rt, and filtered. The filtrate was concentrated under reduced pressure and the residue purified by chromatography on a silica gel (5–40% ethyl acetate in hexane) to give the product as a yellowish solid (0.4 g, 31%). Mp 118–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, $J = 6.8$, 2.8 Hz, 1H), 7.36–7.32 (m, 2H), 3.96 (s, 3H), 3.23 (s, 2H); LCMS: m/z 177 $[M+H]^+$.

4.26. Synthesis of 5-methoxy-2-(3-methyl-but-2-enyl)-indan-1,3-dione (14)

A mixture of 5-methoxy-indan-1,3-dione (**13**) (400 mg, 2.27 mmol), 3,3-dimethylallyl bromide (370 mg, 2.48 mmol), and potassium carbonate (941 mg, 6.81 mmol) in dichloromethane (25 mL) was stirred at rt. The reaction was followed closely by LC/MS. The reaction was stopped when the monoallylation product (30%) no longer increased, while the diallylation product (20%) increased more rapidly. The reaction mixture was filtered through Celite and the filtrate concentrated under reduced pressure. The residue was purified by chromatography on a silica gel (1–20% ethyl acetate in hexane) to provide the product (201 mg, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, $J = 7.6$, 2.8 Hz, 1H), 7.35–7.31 (m, 2H), 5.03–4.98 (m, 1H), 3.96 (s, 3H), 3.05 (t, $J = 5.6$ Hz, 1H), 2.70 (t, $J = 6.8$ Hz, 2H), 1.63 (s, 3H), 1.57 (s, 3H); LCMS: m/z 245 $[M+H]^+$.

4.27. Synthesis of 8-methoxy-2,2-dimethyl-3,4-dihydro-2H-indeno[1,2-*b*]pyran-5-one (15b) and 7-methoxy-2,2-dimethyl-3,4-dihydro-2H-indeno[1,2-*b*]pyran-5-one (15c)

5-Methoxy-2-(3-methyl-but-2-enyl)-indan-1,3-dione (**14**) (201 mg, 0.82 mmol) was dissolved in THF (5 mL). Concentrated sulfuric acid was added dropwise until the solution turned to orange-dark brown. The reaction mixture was stirred at rt until the reaction was complete as indicated by LC/MS. The reaction mixture was then poured into ice water (50 mL) and extracted with ethyl acetate (3× 50 mL). The combined organic extracts were washed with water (3× 50 mL) and dried over sodium sulfate. After filtration and concentration under reduced pressure, the residue was purified by chromatography on a silica gel (5–40% ethyl acetate in hexane) to give the product (clear oil) (172 mg, 85%) as an approximately 5:2 mixture of two regio-isomers with the major product identified as **15b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, $J = 8.0$ Hz, 1H), 6.68 (d, $J = 2.4$ Hz, 1H), 6.60 (dd, $J = 7.6$, 2.4 Hz, 1H), 3.82 (s, 3H), 2.29 (t, $J = 6.4$ Hz, 2H), 1.75 (t, $J = 6.4$ Hz, 2H), 1.42 (s, 6H); LCMS: m/z 245 $[M+H]^+$. Compound **15c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, $J = 2.0$ Hz, 1H), 6.98 (d, $J = 8.0$ Hz, 1H), 6.67 (dd, $J = 8.0$, 2.4 Hz, 1H), 3.80 (s, 3H), 2.29 (t, $J = 6.4$ Hz, 2H), 1.75 (t, $J = 6.4$ Hz, 2H), 1.42 (s, 6H).

4.28. Synthesis of 8-hydroxy-2,2-dimethyl-3,4-dihydro-2H-indeno[1,2-*b*]pyran-5-one (11b) and 7-hydroxy-2,2-dimethyl-3,4-dihydro-2H-indeno[1,2-*b*]pyran-5-one (11c)

An anhydrous dichloromethane solution (3.0 mL) of a mixture of **15b** and **15c** (5:2 ratio) (100 mg, 0.41 mmol) was cooled to 0 °C and boron tribromide (1 M in dichloromethane, 1.0 mL) was added dropwise. The resulting solution was warmed to rt and stirred for 2 h. LC/MS indicated completion of the reaction and the reaction was quenched with ice water (15 mL) and extracted with dichloromethane (3× 15 mL). The combined organics were washed with water (4× 15 mL) and dried over sodium sulfate. After filtration and concentration under reduced pressure, the residue was purified by chromatography on silica gel (10–50% ethyl acetate in hexane) to afford the product as an approximately 6:1 mixture of two regio-isomers (56 mg, 59%) with the major product identified as **11b**: ^{1}H NMR (400 MHz, DMSO-d_6) δ

10.22 (s, 1H), 7.13 (d, J = 7.6 Hz, 1H), 6.56–6.50 (m, 2H), 2.15 (t, J = 6.4 Hz, 2H), 1.74 (t, J = 6.4 Hz, 2H), 1.38 (s, 6H); LCMS: m/z 231 $[M+H]^+$. Compound **11c**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.00 (s, 1H), 6.91 (d, J = 7.6 Hz, 1H), 6.72 (d, J = 2.0 Hz, 1H), 6.62 (dd, J = 8.0, 2.4 Hz, 1H), 2.15 (t, J = 6.4 Hz, 2H), 1.74 (t, J = 6.4 Hz, 2H), 1.38 (s, 6H).

4.29. Synthesis of isochroman-1,4-dione (18)

To a solution of 2-acetylbenzoic acid (**16**) (3.19 g, 19.4 mmol) in a mixture of acetic acid/toluene (2:1, 60 mL) was added bromine (1.0 mL, 19.4 mmol) via syringe. The reaction mixture was heated at 50 °C for 18 h, cooled to rt, and then concentrated under reduced pressure. The crude product was purified by silica gel chromatography (30–70% ethyl acetate in hexane) to give a mixture of 2-(2-bromoacetyl)-benzoic acid (**17**) and isochroman-1,4-dione (**18**) (3.8 g). The mixture was dissolved in methanol (250 mL), and sodium acetate (205 mg, 2.5 mmol) added in portions at rt. The resulting mixture was stirred at rt for 4 h, poured into water (100 mL), extracted with ethyl acetate (3× 100 mL), washed with brine (200 mL), and dried over sodium sulfate. After filtration and concentration under reduced pressure, the yellow residue was purified by silica gel chromatography (30–75% ethyl acetate/hexane) to give isochroman-1,4-dione (**18**) (1.7 g, 54%) as a white solid. Mp 151–154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32–8.29 (m, 1H), 8.12–8.08 (m, 1H), 7.93–7.83 (m, 2H), 5.15 (s, 2H); LCMS: m/z 163 $[M+H]^+$.

4.30. Synthesis of 3-(3-methyl-but-2-enyl)-isochroman-1,4-dione (19)

To a solution of isochroman-1,4-dione (**18**) (502 mg, 3.09 mmol) in THF (5 mL) at −78 °C was added dropwise lithium diisopropyl amide (prepared by the addition of n-BuLi (2.1 mL, 3.3 mmol, 1.6 M in hexane) to diisopropylamine (0.48 mL, 3.3 mmol)) at −78 °C. After stirring for 30 min, 3,3-dimethylallyl bromide (506 mg, 3.4 mmol) in THF (1 mL) was added dropwise and the resulting solution was stirred for 1 h at −78 °C. After warming to room temperature, the reaction was quenched with water (5 mL), extracted with dichloromethane (3× 5 mL), and dried over sodium sulfate. After filtration and concentration under reduced pressure, the residue was purified by silica gel chromatography (5–50% ethyl acetate in hexane) to give 3-(3-methyl-but-2-enyl)-isochroman-1,4-dione as an oil (**19**) (20 mg, 2.8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, J = 8.0, 1.2 Hz, 1H), 8.06 (dd, J = 6.8, 2.0 Hz, 1H), 7.88–7.79 (m, 2H), 5.14 (t, J = 5.2 Hz, 1H), 5.04–4.98 (m, 1H), 2.87–2.69 (m, 2H), 1.61 (s, 3H), 1.57 (s, 3H); LCMS: m/z 231 $[M+H]^+$.

4.31. Synthesis of 2,2-dimethyl-3,4-dihydro-2H-pyrano[3,2-*c*]isochromen-6-one (M6)

Concentrated sulfuric acid (1 mL) was added dropwise to 3-(3-methyl-but-2-enyl)-isochroman-1,4-dione (**19**) (20 mg, 0.08 mmol) at rt. The mixture was stirred for 30 min and then diluted with ice water (2 mL). The resulting solution was extracted with dichloromethane (3× 5 mL), washed with brine (5 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude solid was purified by silica gel chromatography (5–30% ethyl acetate in hexane) to give 2,2-dimethyl-3,4-dihydro-2H-pyrano[3,2-*c*] isochromen-6-one (**M6**) (6 mg, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 7.8 Hz, 1H), 7.74–7.72 (m, 2H), 7.49–7.47 (m, 1H), 2.65 (t, J = 6.6 Hz, 2H), 1.90 (t, J = 6.6 Hz, 2H), 1.39 (s, 6H); LCMS: m/z 231 $[M+H]^+$; HRMS: Calcd 231.1021. Found: 231.1024.

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