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Developing Potent Human Uric Acid Transporter 1 (hURAT1) Inhibitors

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Abstract

The kidneys are a vital organ in the human body. They serve several purposes including homeostatic functions such as regulating extracellular fluid volume, maintaining acid-base and electrolyte balance, and are essential regarding the excretion of metabolic waste. Furthermore, the kidneys play an important role in uric acid secretion/re-absorption. Abnormalities associated with kidney transporters have been associated with various diseases, such as gout. The current study utilized *Xenopus* oocytes expressing human uric acid transporter 1 (hURAT1; SLC22A12) as an *in vitro* method to investigate novel compounds and their ability to inhibit ¹⁴C-uric acid uptake via hURAT1. We have prepared and tested a series of 2-ethyl-benzofuran compounds and probed the hURAT1 *in vitro* inhibitor structure-activity relationship (SAR). Compared to di-methoxy analogs, mono-phenols formed on the C-Ring showed the best *in vitro* inhibitory potential. Compounds with sub-micromolar (*i.e.* IC₅₀ < 1000 nM) inhibitors were prepared by brominating the corresponding phenols to produce compounds with potent uricosuric activity.

Introduction

In humans, purine nucleotides, nucleosides, and bases (*i.e.* adenine, inosine, and guanine) are metabolically degraded to urate (uric acid **1**, Figure 1) via xanthine. Many organisms, from bacteria to mammals, possess the enzyme uricase and metabolize **1** to the more water soluble allantoin **2**. However uricase is absent in humans.^{1,2} Urate functions as an antioxidant in the blood, but high levels of uric acid (a condition known as hyperuricemia) can precipitate gout. Gout is a medical condition commonly associated with repeated episodes of acute inflammatory arthritis caused by elevated urate blood level which crystallize and deposit into joints and/or surrounding tissues.³

Hyperuricemia may result from the over production of uric acid or from insufficient renal elimination. For example, as cancer cells are destroyed, the elevated uric acid production may contribute to hyperuricemia, limiting the aggressiveness of cancer chemotherapy. Lifestyle and diet are also well known contributors to elevated serum urate.⁴ As we age, renal function declines, resulting in lower urate excretion with subsequent increase in serum urate level. Recent studies suggest that high levels of uric acid play a pivotal role in other

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important diseases such as hypertension, insulin resistance, diabetes, chronic renal disease, diabetic renal disease, and cardiovascular disease.^{4–5} Hence, drugs that influence uric acid serum level are therapeutically important.

Currently, there are several drug strategies to control urate levels (Figure 2). There are only a few commercially available small molecule drugs administered in the United States (US) that lower serum urate level. A purine xanthine oxidase inhibitor, allopurinol **3** has been the most commonly used urate-lowering drug in the US. While clearly effective, only about 40% of patients are able to meet treatment goals via **3**, and it occasionally causes Stevens Johnson syndrome, which may be fatal.⁶ A second drug, febuxostat **4** functions as a non-purine xanthine oxidase inhibitor. Compound **4** has been associated with cardiovascular complications causing the Food and Drug Administration (FDA) to require a cautionary statement on the drug insert. Uricosurics, such as probenecid **5**, sulfinpyrazone **6** and benzbromarone **7**, are drugs which act directly on the renal tubule, increasing uric acid renal excretion by inhibiting urate re-absorption via one or more transporter proteins.³ More recently, rasburicase and pegloticase have been developed as injectable protein formulations to provide temporary blood uricase activity as an adjunct in cancer chemotherapy or for treatment of refractory gout.⁷

In healthy humans, renal elimination plays a primary role in controlling uric acid serum level.^{8–10} Urate is readily filtered by the kidney; it is both reabsorbed and secreted along the nephron. The cells lining the nephron contain specific transporters. In humans, the apical surface contains human uric acid transporter 1 (hURAT1; SLC22A12)^{3,11} and the sodium-dependent phosphate transporter 4, also called voltage-dependent human organic anion transporter 1 (NPT4, hOATv1; SLC17A3).^{12–14} Apical transporters are in contact with the urine. The basolateral surface contains transporters which are in contact with the blood and include the facilitative glucose transporter 9, also called the voltage-dependent uric acid transporter 1 (GLUT9, URATv1; SLC2A9),^{15–17} and human organic anion transporter proteins 1 (hOAT1; SLC22A6) and 3 (hOAT3; SLC22A8).¹⁸ In addition to urate, hOAT1 and hOAT3 have broad substrate specificity and are known to transport NSAIDs, β -lactams, and *p*-aminohippuric acid (Figure 3). The prevalence rate for kidney disease in the US has been very high. In 2001, kidney disease was ranked as the ninth leading cause of death in the US.¹⁹ A relationship has been observed between hyperuricemia and hypertension, diabetes, renal disease and cardiovascular disease.²⁰ Given these considerations, the development of novel compounds that could lower uric acid serum levels could be therapeutically important.

A drug with potent uricosuric activity, benzbromarone **7** effectively reduces serum urate levels, with most people achieving normal uric acid values. Administered clinically in Japan and previously in Europe, benzbromarone is not approved in the US. Metabolized by CYP2C9 (major) and CYP2C19 (minor), idiosyncratic hepatotoxic events associated with **7** are hypothesized to result from CYP biotransformation down-stream from initial metabolite, 6-hydroxybenzbromarone **8** (Figure 2).²¹ In 2008, Lee and coworkers compared oral *in vivo* efficacy and concluded that **7** (100 mg/kg) produces a greater physiological effect (*i.e.* lowers urate level) than **4** (300 mg/day) or **5** (1000 mg/day).²² Furthermore, previous results from our laboratories illustrated that **7** and **8** to have potent hURAT1 inhibitor properties.^{3,11} Thus we sought to prepare a series of compounds and probe the structural requirement(s) related to hURAT1 inhibition. The current study utilized *Xenopus* oocytes expressing hURAT1 as an *in vitro* method to investigate novel compounds for their ability to inhibit ¹⁴C-uric acid uptake via hURAT1. We have prepared and tested a series of 2-ethyl-benzofurans as described below.

Results and Discussion

Part One: Compound Synthesis

As summarized in Figure 4, our chemical synthesis utilized a series of commercially available 2-hydroxy-benzaldehydes **9A–9D**. Benzaldehydes were coupled with chloroacetone under basic conditions (K_2CO_3) to produce an SN_2 reaction – Williamson's ether synthesis²³ – to afford 2-(2-oxopropoxy)benzaldehydes which subsequently endured a tandem base catalyzed intramolecular aldol condensation²⁴ reaction to produce the corresponding 1-(benzofuran-2-yl)ethanone, **10A–D**. Herein, we will refer to the bicyclic structure thus formed as 'A-Ring' and 'B-Ring', respectively (Figure 4). Ketones **10A–D** were reduced using classic Wolff-Kishner reduction conditions (hydrazine and base with heating)²³ to afford 2-ethylbenzofurans **11A–D**.

Compound **11A** was subjected to an aromatic electrophilic substitution reaction²⁴ using p-anisoyl chloride (4-methoxybenzoyl chloride) under acid conditions ($SnCl_4$) to produce (2-ethylbenzofuran-3-yl)(4-methoxyphenyl)methanone **12** (Figure 5). Herein, we refer to the additional ring thus added as the C-Ring. The para-methoxy group on the C-ring was demethylated under basic conditions ($NaSEt/DMF$)²⁵ to afford phenol **13**, which was consequently dibrominated to afford benzbromarone **7**. Two different reaction conditions to dibrominate phenol **13** were investigated. The first conditions utilized Br_2 in acetic acid, while the second used *N*-bromosuccinimide (NBS) in a mixture of DMF and DCM.²⁴ In our hands, the use of NBS consistently produced higher yields of **7**.

When we conducted analogous electrophilic substitution reactions, but with electronically donating methoxy groups on the B-Ring (*i.e.* **11B–11D**; Figure 5), we observed altered reactivity to produce various regioisomers. The 5-methoxy analog **11B** produced three products **14–16** (the –3, –4, and –7 substituted analogs, respectively), while 6-methoxy **11C** afforded two products **17** and **18** (the –3 and –4 substituted analogs, respectively), and 7-methoxy **11D** generated two products, **19** and **20** (the –3 and –4 substituted analogs, respectively). The formation and isolation of the various dimethoxy benzofuran analogs (**14–20**) provided us with the unique opportunity to probe the importance of the C-Ring and its connectivity attached to either the A-Ring or B-ring. Compounds **14–20** were converted to their corresponding mono- or di-phenolic analogs (**21–38**; Figure 6) using one of two different deprotection conditions. The reaction conditions were either i) basic via $NaSEt$ in DMF; or ii) acidic using $AlCl_3$ and $HSEt$ in DCM.²⁵

As summarized in Figure 7, we sought to prepare analogs of **7**. We prepared C-Ring dibromo-phenolic compounds and subsequent deprotection ($AlCl_3/HSEt$) of the second methoxy group to afford the corresponding diphenolic compounds. In the case of the 5-methoxy series, compound **21** was halogenated to **39** with subsequent conversion to diphenol **40**. The two other 5-methoxy isomers, (2-ethyl-5-methoxybenzofuran-4-yl)(4-hydroxyphenyl)methanone **24** and (2-ethyl-5-methoxybenzofuran-7-yl)(4-hydroxyphenyl)methanone **27** were also converted to their di-bromo and diphenolic analogs, **41** to **42** and **43** to **44**, respectively.

The 6-methoxy analog **30** was dibrominated to **45**, and deprotected to afford **8**, an authentic sample of **7**'s major metabolite produced by human liver microsomes via CYP2C9 (major) and CYP2C19 (minor).²¹ When we used three mol equivalents of NBS, compound **30** produced tribromo analog **46**. Another example of a tribrominated product was observed when (2-ethyl-7-hydroxybenzofuran-4-yl)(4-hydroxyphenyl)methanone **38** was reacted with two mol equivalents of NBS to produce **47**. Lastly, examples of brominating the B-Ring included halogenation of 5-hydroxy **22** and 6-hydroxy **31** to produce **48** and **49**, respectively; whereas the 7-hydroxy analog **37** produced mono-brominated **50**.

Part Two: Inhibitor Studies

We have previously used the *Xenopus* oocyte expression system and have found it to be a very useful single cell *in vitro* tool to probe drug molecules and their interactions with specific transporter proteins.^{26–28} As depicted and shown in Figure 8a and Figure 8b, respectively, we successfully incorporated functional hURAT1 into oocytes. The *in vitro* expressing oocyte system mimics hURAT1 *in vivo*, an influx transporter protein located at the apical surface of renal tubular cells (Figure 3) and presumed to be the major transporter responsible for the reabsorption of uric acid from the urine.^{3,9,11} Time dependent ¹⁴C-uric acid uptake experiments (0 – 120 min) were conducted in oocytes not expressing hURAT1 (control) and oocytes expressing hURAT1, showing that hURAT1 was incorporated as an influx transporter. The ¹⁴C-uric acid uptake (10.0 μ M extracellular) displayed linear influx for at least two hours. Since we know that hURAT1 operates as a monocarboxylate exchanger (*i.e.* lactate, malate, nicotinate, etc),^{3,9,11} these data illustrate that we have not depleted the intracellular concentration of monocarboxylates within the two hours. Furthermore, as we are clearly operating under linear influx conditions, we selected the 60 min time point to generate the *in vitro* IC₅₀ values.

As summarized in Table 1, we tested compounds **5**, **7**, **8** and **12–50**. Injecting benzobromarone inside the oocyte and conducting the experiment with only extracellular ¹⁴C-uric acid does not readily inhibit ¹⁴C-uric acid uptake (data not shown); therefore, the site of inhibitor is crucial and the data supports the notion that inhibitor interactions occur on the apical side. We initially conducted a general screen in which ¹⁴C-uric acid (10.0 μ M) and test compound (50 μ M) were placed in the extracellular fluid and radioactivity inside the oocyte was analyzed after 60 min. Except for weak inhibitor probenecid **5**, when the initial screen using 50 μ M test compound produced $\geq 60\%$ inhibition, we conducted a second set of experiments with varying concentrations (*i.e.* 5, 10, 50, 100, 500 nM, and 5, 10 and 50 μ M) of the test compound. The data were used to estimate IC₅₀ values, the concentration of compound reducing ¹⁴C-uric acid uptake in hURAT1 expressing oocytes by 50% compared to control. The IC₅₀ values were generated using a sigmoidal dose-response (variable slope) relationship.

The ability to prepare a variety of different benzofuran analogs provided us with the ability to probe the structure-activity relationship of benzobromarone-related compounds. The data summarized in Table 1 illustrates that **7** has very potent hURAT1 inhibitor potential. The 6-hydroxy-metabolite **8** was a weaker inhibitor than parent drug **7**; IC₅₀ 138 nM versus 26 nM, respectively. These data are comparable to data produced via MDCK-hURAT1 where 200 nM and 35 nM (5.7-fold difference) were reported, respectively.²⁹ Compound **12** with one methoxy group in the C-Ring and dimethoxy analogs (**14–20**, Figure 6) at 50 μ M produced weak-to-no ¹⁴C-urate transport inhibition. Two di-methoxy-compounds (**14** and **19**) displayed weak inhibition, both have the C-Ring connected at benzofuran position three. If one compares **12** to benzarone **13** (Figure 5), the importance for the phenolic –OH in the C-Ring becomes clear with the IC₅₀ value changing from $>50\mu$ M to 2.8 μ M. Halogenation of **13** to give **7** results in an inhibitor with very potent activity, a low-nano-molar inhibitor (*i.e.* IC₅₀ < 50 nM).

Metabolite **8** was prepared from **17**. The C-Ring deprotection to give **30** (Figure 6) followed by halogenation produced **45** (Figure 7), and then deprotection gave authentic metabolite **8**. Compound **30** versus B-Ring phenol **31** (Figure 6) also shows the more potent C-Ring phenol inhibitor trend ($>50\mu$ M versus 3.9 μ M). Comparing **30** and **32** (IC₅₀ of 3.9 μ M versus 1.1 μ M) illustrates that a methoxy on the B-Ring was less potent (higher IC₅₀ value) than the corresponding diphenol analog. The 6-methoxy regioisomers such as **18**, compared to demethoxylated analogs **33**, **34** and **35**, displayed the following inhibitory trend: (**18**, di-MeO $<$ **34**, C-Ring -OMe $<$ **35**, di-OH $<$ **33**, B-ring -OMe). Looking at the 5-methoxy series

(Figure 6, Table 1), cleavage of **14** produced **21**, **22**, and **23** using different reaction conditions; whereas **16** was used to produce **27**, **28** and **29**. Comparing the 3-yl series also illustrates the importance of the C-Ring phenol (IC_{50} **22** $\gg$ **21** = **23**) inhibitor activity.

Deprotection of **15** was used to produce **24**, **25** and **26** (Figure 6); whereas compound **20** was used to produce **37** and **38** and cleavage of **19** afforded **36**. Comparing **27–29** (Table 1) further illustrates the importance of the C-Ring phenol and how a diphenol may or may not be detrimental to inhibitor activity. Compounds **39–50** (Figure 7 and Table 1) were all brominated analogs, with either one (**50**), two (**40–45**, **48** and **49**), or three (**46** and **47**) bromine atoms. Compounds containing a methoxy on the B-Ring, and dibromo-phenol functionality on the CRing, were more potent inhibitors when the C-Ring was connected to the A-Ring (**39** and **45**) than versus the B-Ring (**41** and **43**). Furthermore, a general trend of decreased inhibitor potency (*i.e.* increased IC_{50}) was observed when **39** and **45** (C-Ring connected to A-Ring analogs) were demethoxylated to **40** and **8**, respectively. Conversely, more potent inhibitors (*i.e.* lower IC_{50}) were produced when **41** and **43** (C-Ring connected to B-Ring analogs) were demethoxylated to **42** and **44**, respectively. Therefore, while a vast amount of the current data supports the importance of the C-Ring dibromo-phenol, **43** versus **44** (1.44 μ M versus 287 nM) shows an example where the B-Ring –OH takes an important role to enhance inhibitor activity. Therefore, functional group bio-transformations (*e.g.* CYP catalyzed MeO- to HO-) are very important chemical attributes to consider when designing future URAT1 inhibitors. Overall, we have prepared compounds (*i.e.* **7**, **8**, **39–50**) with low IC_{50} values (<1.0 μ M) with some having excellent (<200 nM) inhibitory potency. These experimental data provide insight into structural requirements for the development of potent uricosuric activity and warrant continued investigation into the SAR of hURAT1.

Conclusion

The current study prepared a series of benzbromarone analogs and probed hURAT1 inhibitor SAR. The presented data provide insight into structural requirements; for example, a phenol on the C-Ring containing bromine atoms in the two ortho position(s) affords potent hURAT1 inhibitors. The data also illustrate the important consequence of biotransformation pathways. Dimethoxy analogs are known to undergo phase I metabolism to afford mono- and diphenolic analogs, a biotransformation which may lead to altered inhibitory activity. These results provide our initial ground work regarding uric acid transporter inhibitors. Our future efforts will focus on additional compound synthesis, *in vitro* metabolism, and rodent pharmacokinetic (PK) experiments. Furthermore, we plan to examine other transporter proteins involved in urate re-absorption and secretion pathways (*i.e.* URATv1, hOAT's, etc), and ultimately compare the SAR overlap between the different renal tubular cell transporters.

Experimental Section

Materials and Methods

Benzaldehyde, chloroacetone, silica gel (70–230 mesh), diethylene glycol (DEG), hydrazine (55% aqueous solution), potassium hydroxide (KOH), anhydrous magnesium sulfate ($MgSO_4$), anhydrous sodium sulfate (Na_2SO_4), carbon disulfide (CS_2), p-anisoyl chloride, tin (IV) chloride, conc. hydrochloric acid (HCl), sodium bicarbonate ($NaHCO_3$), sodium chloride (NaCl), 2-hydroxy-5-methoxybenzaldehyde, 2-hydroxy-3-methoxybenzaldehyde (o-vanillin), 2-hydroxy-4-methoxybenzaldehyde, 2-hydroxybenzaldehyde, *N*-bromosuccinimide (NBS), bromine (Br_2), ammonium chloride (NH_4Cl), sodium ethanethiolate (NaSEt), and formic acid were purchased from Sigma-Aldrich Chemical Company (St. Louis, MO). Acetone, hexanes (Hex), ethyl acetate (EtOAc), potassium carbonate (K_2CO_3), dimethylformamide (DMF), methylene chloride (DCM), sodium

hydroxide (NaOH), HPLC grade methanol (MeOH), HPLC grade acetonitrile (ACN), isopropanol, acetic acid (AA), and HPLC grade water (H₂O) were purchased from Fisher Scientific (Pittsburgh, PA). The NMR solvents CDCl₃, DMSO-d₆, and D₂O were purchased from either Sigma-Aldrich or Cambridge Isotope Laboratories, Inc. (Andover, MA). Reactions were monitored via Silica gel IB2-F thin layer chromatography (TLC) plates, and were purchased from J.T. Baker (Phillipsburg, NJ).

The ¹H and ¹³C NMR spectra were recorded using a 400 MHz Bruker NMR, Avance III 400. The chemical shifts are reported in ppm. An Applied Biosystems Sciex 4000 (Applied Biosystems; Foster City, CA) was equipped with a Shimadzu HPLC (Shimadzu Scientific Instruments, Inc.; Columbia, MD) and Leap auto-sampler (LEAP Technologies; Carrboro, NC) was used. Liquid chromatography employed an Agilent Technologies, Zorbax extended-C18 50 × 4.6 mm, 5 micron column at 40 °C with a flow-rate of 0.4 mL/min. The mobile phase consisted of A: 10 mM (NH₄OAc), 0.1% formic acid in H₂O, and B: 50:50 ACN:MeOH. The chromatography method used was 95% A for 1.0 min; ramped to 95% B at 3.00 min and held for 4.5 min, lastly, brought back to 95% A at 8.5 min and held for 1.0 min (9.5 min total run time). Unless specifically denoted for an individual compound, compounds were monitored via electro-spray ionization positive ion mode (ESI+) using the following conditions: i) an ion-spray voltage of 5500 V; ii) temperature, 450 °C; iii) curtain gas (CUR; set at 10) and Collisionally Activated Dissociation (CAD; set at 5) gas were nitrogen; iv) Ion Source gas one (GS1) and two (GS2) were set at either 20 or 25, and specifically denoted in the individual compound section; v) entrance potential was set at 10 V; vi) quadrupole one (Q1) and (Q3) were set on Unit resolution; vii) dwell time was set at 200 msec; and viii) declustering potential (DP), collision energy (CE), and collision cell exit potential (CXP) are voltages (V). Samples (10 µL) were analyzed by LC/MS-MS. As judged by TLC, NMR and LC/MS-MS analysis, all purified compounds were > 95% pure.

Chemical Synthesis

2-Ethyl-benzofurans: 1-(benzofuran-2-yl)ethanone (10A): K₂CO₃ (13.6 g) was added to a dry round bottom flask (RBF; 250 mL) containing a stir bar (SB). The contents were diluted with anhydrous acetone (140 mL) and stirred while benzaldehyde (10.0 g; 81.9 mmol) was added dropwise (2–3 min). Next, chloroacetone (8.75 g; 94.6 mmol) was added (2–3 min). A reflux condenser was attached and contents heated to reflux (6 h). The contents were cooled to ambient temperature and Büchner filtered; the solid was rinsed with acetone (2 × 50 mL). The filtrate was concentrated under reduced pressure and purified via SiO₂ chromatography (2:1; Hex:EtOAc) to afford a light yellow solid (12.3 g; 59.9 mmol; 91% yield). ¹H-NMR (400 MHz) CDCl₃: 2–7.70 (d, 1H), 7.59–7.57 (d, 1H), 7.51–7.45 (m, 2H), 7.33–7.29 (t, 1H), 2.61 (s, 3H); ¹³C-NMR (100 MHz) CDCl₃: 188.7, 155.7, 152.7, 128.4, 127.1, 124.0, 123.4, 113.2, 112.5, 26.6. Using analogous procedures, the following analogs were prepared: **1-(5-methoxybenzofuran-2-yl)ethanone (10B):** (85% yield). ¹H-NMR (400 MHz) CDCl₃: 7.47–7.43 (m, 2H), 7.10–7.08 (m, 2H), 3.85 (s, 3H), 2.59 (s, 3H); ¹³C-NMR (100 MHz) CDCl₃: 188.6, 156.6, 153.3, 150.9, 127.6, 118.5, 113.5, 113.2, 103.9, 55.8, 26.4. **1-(6-methoxybenzofuran-2-yl)ethanone (10C):** (83% yield). ¹H-NMR (400 MHz) CDCl₃: 7.56–7.54 (d, 1H), 7.44 (s, 1H), 7.03 (s, 1H), 6.95–6.92 (d, 1H), 3.87 (s, 3H), 2.56 (s, 3H); ¹³C-NMR (100 MHz) CDCl₃: 187.9, 161.2, 157.3, 152.3, 123.7, 120.3, 114.4, 113.9, 95.6, 55.7, 26.2. **1-(7-methoxybenzofuran-2-yl)ethanone (10D):** (91% yield). ¹H-NMR (400 MHz) CDCl₃: 7.48 (s, 1H), 7.28–7.20 (m, 2H), 6.95–6.94 (d, 1H), 4.02 (s, 3H), 2.63 (s, 3H); ¹³C-NMR (100 MHz) CDCl₃: 188.8, 153.0, 146.1, 145.3, 128.7, 124.6, 115.1, 112.8, 109.4, 56.1, 26.7.

2-ethylbenzofuran (11A): Ketone (12.1 g; 75.5 mmol) in a RBF/SB (500 mL) was mixed with DEG (290 mL) and heated (120 – 130 °C). The mixture was stirred and hydrazine (16.1

g; 55% aq solution) was added dropwise (15–20 min). The mixture was heated (180 – 190 °C; 10 min) and then decreased to 120 – 130 °C. Next, KOH (13.2 g) was carefully added in portions and heated (120 – 130 °C; 6 h). The contents were diluted with ice water (220 – 230 mL) and extracted (DCM; 4 × 350 mL). The organic phase was dried over anhydrous MgSO₄, filtered, concentrated under reduced pressure, and purified via SiO₂ chromatography (4:1; Hex:EtOAc) to afford a light yellow oil (6.05 g; 41.3 mmol; 55% yield). ¹H-NMR (400 MHz) CDCl₃: 7.51-7.47 (d, 1H), 7.42-7.40 (d, 1H), 7.50-7.22 (m, 2H), 6.38 (s, 1H), 2.83-2.77 (q, 2H), 1.34-1.32 (t, 3H); ¹³C-NMR (100 MHz) CDCl₃: 161.1, 154.8, 129.1, 123.2, 122.5, 120.3, 110.8, 101.1, 21.9, 12.0. Using analogous procedures, the following analogs were prepared: **2-ethyl-5-methoxybenzofuran (11B)**: (68% yield). ¹H-NMR (400 MHz) CDCl₃: 7.35-7.32 (d, 1H), 6.97 (s, 1H), 6.82-6.80 (dd, 1H), 6.28 (s, 1H), 3.83 (s, 3H), 2.79-2.75 (q, 2H), 1.33-1.27 (t, 3H); ¹³C-NMR (100 MHz) CDCl₃: 160.2, 157.3, 155.6, 122.4, 120.3, 111.1, 100.7, 95.9, 55.8, 21.9, 12.1.

2-ethyl-6-methoxybenzofuran (11C): (90% yield). ¹H-NMR (400 MHz) CDCl₃: 7.32-7.29 (d, 1H), 6.97 (s, 1H), 6.83-6.80 (dd, 1H), 6.32 (1H), 3.83 (s, 3H), 2.79-2.75 (q, 2H), 1.35-1.29 (t, 3H); ¹³C-NMR (100 MHz) CDCl₃: 162.0, 155.8, 149.7, 129.7, 111.4, 111.1, 103.3, 101.1, 56.0, 22.0, 12.0. **2-ethyl-7-methoxybenzofuran (11D)**: (91% yield). ¹H-NMR (400 MHz) CDCl₃: 7.12-7.08 (m, 2H), 6.74-6.72 (d, 1H), 6.37 (s, 1H), 4.00 (s, 3H), 2.83-2.81 (q, 2H), 1.35-1.31 (t, 3H); ¹³C-NMR (100 MHz) CDCl₃: 161.3, 145.0, 143.8, 130.7, 123.2, 112.9, 105.4, 101.5, 56.0, 21.9, 12.1.

(2-ethylbenzofuran-3-yl)(4-methoxyphenyl)methanone (12): Benzofuran (**11A**; 2.50 g; 17.1 mmol) in a RBF/SB (250 mL) was diluted with CS₂ (50 mL). The reaction vessel was capped with a sure-seal and a N₂ balloon attached. The vessel was cooled in an ice bath (30 min). Next, p-anisoyl chloride (1.3 mol equiv.) was added dropwise (3–4 min) followed by tin (IV) chloride (1.3 mol equiv.) added dropwise (5–7 min). The contents were stirred (3 h) and warmed to ambient temperature (3 h). Water (40 mL) was added and the mixture extracted with EtOAc (4 × 100 mL). The organic phase was washed with dilute HCl (0.5 N, 30 mL), followed by H₂O (30 mL), 1.0 M NaOH (30 mL), NaHCO₃ aq (30 mL) and saturated NaCl aq (30 mL). The organic phase was dried (MgSO₄), filtered, concentrated under reduced pressure, and purified via SiO₂ chromatography (10:1:0.25; Hex:EtOAc:MeOH) to afford **12** a light yellow solid (4.61 g; 16.4 mmol; 96% yield). ¹H-NMR (400 MHz) CDCl₃: 7.86-7.83 (d, 2H), 7.48-7.46 (d, 1H), 7.40-7.38 (d, 1H), 7.29-7.25 (t, 1H), 7.21-7.17 (t, 1H), 6.99-6.94 (d, 2H), 3.89 (s, 3H), 2.94-2.88 (q, 2H), 1.35-1.29 (t, 3H); ¹³C-NMR (100 MHz) CDCl₃: 190.6, 165.5, 163.6, 153.7, 132.0, 131.8, 127.3, 124.3, 123.5, 121.4, 116.3, 113.8, 111.0, 55.6, 21.8, 12.5. LC/MS-MS: 281.1 → 135.1 *m/z*; GS1 and GS2 at 25, DP = 66, CE = 29, CXP = 8, *t_R* = 4.73 min.

(2-ethylbenzofuran-3-yl)(4-hydroxyphenyl)methanone (13): In a RBF/SB (50 mL), benzofuran (**12**; 1.00 g; 3.57 mmol) was diluted with DMF (18 mL) and NaSEt (455 mg) was added. The mixture was heated (125–130 °C; 1.0 h). Next, the mixture was quenched (2 vol NH₄Cl aq) and extracted with EtOAc (4 × 75 mL). The organic phase was washed with H₂O, followed by NaCl aq. The organic phase was then dried (MgSO₄), filtered, concentrated under reduced pressure and purified via SiO₂ chromatography (4:1; Hex:EtOAc) to give **13** as a white solid (857 mg; 3.22 mmol; 90% yield). ¹H-NMR (400 MHz) CDCl₃: 10.4 (bs, 1H; exchangeable in D₂O), 7.80-7.78 (d, 2H), 7.49-7.47 (d, 1H), 7.43-7.41 (d, 1H), 7.30-7.26 (t, 1H), 7.22-7.18 (t, 1H), 6.98-6.94 (d, 2H), 2.95-2.89 (q, 2H), 1.36-1.32 (t, 3H); ¹³C-NMR (100 MHz) CDCl₃: 192.1, 165.9, 161.5, 153.6, 132.2, 130.9, 129.0, 124.4, 123.5, 121.1, 116.1, 115.6, 111.0, 21.8, 12.2. LC/MS-MS: 267.0 → 121.2 *m/z*; GS1 and GS2 at 20, DP = 46, CE = 29, CXP = 6, *t_R* = 4.31 min.

(3,5-dibromo-4-hydroxyphenyl)(2-ethylbenzofuran-3-yl)methanone (7): In a RBF/SB (50 mL), hydroxy-benzofuran (**13**; 318 mg; 1.19 mmol) was diluted with AA (20 mL) and then Br₂ (138 μ L) was added. After 15 min, the mixture was quenched with H₂O (35 mL) and extracted with EtOAc (3 $\times$ 70 mL). The organic phase was washed NaCl aq (2 $\times$ 50 mL) and dried (MgSO₄), filtered, concentrated under reduced pressure, and purified via SiO₂ chromatography (3:1; Hex:EtOAc) to give **7** as a light red solid (176 mg; 0.469 mmol; 35% yield). ¹H-NMR (400 MHz) DMSO-d₆: 10.2 (bs, 1H; exchangeable in D₂O), 7.91 (s, 2H), 7.66-7.64 (d, 1H), 7.43-7.41 (d, 1H), 7.36-7.33 (t, 1H), 7.29-7.27 (d, 1H), 2.83-2.77 (q, 2H), 1.28-1.24 (t, 3H); ¹³C-NMR (100 MHz) DMSO-d₆: 187.5, 165.8, 156.1, 153.5, 133.7, 132.3, 126.9, 125.2, 124.3, 121.2, 115.6, 112.2, 111.7, 21.84, 12.4. LC/MS-MS: 424.9 $\rightarrow$ 278.8 *m/z*; GS1 and GS2 at 20, DP = 96, CE = 37, CXP = 16, *t_R* = 4.65 min. Alternatively, NBS was used as a brominating agent. In a RBF/SB (50 mL) NBS (0.200 g, 1.13 mmol) mixed in DCM (9.0 mL) was diluted with DMF (0.33 mL) at -10 °C (ice-brine cooling bath) for 10 min. Next, **13** (0.150 g, 0.563 mmol) in DCM (1 mL) was added. The reaction mixture was allowed to warm to RT and stirred (17 h). The reaction mixture was quenched (water; 5 mL) and diluted with DCM (30 mL). The organic phase was washed with water (4 times; 10 mL each) and then brine. The organic phase was dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude material was purified twice by column chromatography on SiO₂ (Hex:EtOAc; 4:1) to afford **7** (192 mg, 0.460 mmol, 82%) as a white solid.

(2-ethyl-5-methoxybenzofuran-3-yl)(4-methoxyphenyl)methanone (14), (2-ethyl-5-methoxybenzofuran-4-yl)(4-methoxyphenyl)methanone (15) (2-ethyl-5-methoxybenzofuran-7-yl)(4-methoxyphenyl)methanone (16): Benzofuran (**11B**; 6.10 g; 34.6 mmol) in a RBF/SB (250 mL) was diluted with CS₂ (100 mL). The reaction vessel was capped with a sure-seal and a N₂ balloon attached. The RBF was cooled in an ice bath (30 min) and *p*-anisoyl chloride (1.3 mol equiv.) was added dropwise (3–4 min); next, tin (IV) chloride (1.3 mol equiv.) was added dropwise (5–7 min) and the mixture was stirred (3 h). The contents were warmed to RT (3 h), diluted with H₂O (40 mL), and extracted with EtOAc (4 $\times$ 150 mL). The organic phase was washed with dilute HCl (0.5 N, 75 mL), followed by H₂O (75 mL), 1.0 M NaOH aq (75 mL), NaHCO₃ aq (75 mL) and NaCl aq (75 mL). The organic phase was dried (MgSO₄), filtered, concentrated under reduced pressure and purified via SiO₂ chromatography (10:1:0.25; Hex:EtOAc:MeOH) to afford three products (**14**:**15**:**16** in a ratio of 2.6:1.0:6.6). **14**: A light yellow oil (1.80 g; 5.80 mmol; 16.8% yield) ¹H-NMR (400 MHz) CDCl₃: 7.86-7.82 (d, 2H), 7.36-7.34 (d, 1H), 6.97-6.93 (m, 3H), 6.88-6.85 (dd, 1H), 3.89 (s, 3H), 3.74 (s, 3H), 2.87-2.79 (q, 2H), 1.32-1.28 (t, 3H); ¹³C-NMR (100 MHz) CDCl₃: 190.7, 166.1, 163.5, 156.4, 148.7, 131.9, 131.7, 127.9, 116.5, 113.7, 113.0, 111.4, 104.0, 55.9, 55.6, 22.1, 12.4. LC/MS-MS: 311.1 $\rightarrow$ 135.1 *m/z*; GS1 and GS2 at 25, DP = 46, CE = 29, CXP = 8, *t_R* = 4.64 min. **15**: A light yellow oil (702 mg; 2.26 mmol; 7% yield) ¹H-NMR (400 MHz) CDCl₃: 7.84-7.81 (d, 2H), 7.44-7.41 (d, 1H), 6.92-6.86 (m, 3H), 6.20 (s, 1H), 3.86 (s, 3H), 3.73 (s, 3H), 2.76-2.70 (q, 2H), 1.28-1.23 (t, 3H); ¹³C-NMR (100 MHz) CDCl₃: 194.3, 163.7, 163.4, 153.1, 149.8, 132.3, 131.1, 129.4, 119.9, 113.6, 112.5, 108.1, 100.7, 57.1, 55.5, 22.0, 11.7. LC/MS-MS: 311.1 $\rightarrow$ 203.1 *m/z*; GS1 and GS2 at 25, DP = 41, CE = 21, CXP = 12, *t_R* = 4.48 min. **16**: A white solid (4.61 g; 14.9 mmol; 43% yield) ¹H-NMR (400 MHz) CDCl₃: 7.82-7.79 (d, 2H), 7.38 (s, 1H), 6.99 (s, 1H), 6.90-6.87 (d, 2H), 6.37 (s, 1H), 3.86 (s, 3H), 3.73 (s, 3H), 2.82-2.77 (q, 2H), 1.35-1.31 (t, 3H); ¹³C-NMR (100 MHz) CDCl₃: 194.9, 163.8, 163.5, 153.9, 148.8, 132.4, 131.7, 131.2, 125.2, 113.5, 111.6, 102.4, 101.5, 56.3, 55.5, 22.1, 11.9. LC/MS-MS: 311.1 $\rightarrow$ 203.1 *m/z*; GS1 and GS2 at 25, DP = 51, CE = 25, CXP = 12, *t_R* = 4.49 min. Investigating the influence of temperature on product ratio, the ratios of isolated **14**:**15**:**16** were 2.6:1.0:6.6 at 5 °C and 1.1:1.0:2.7 at room temperature (RT).

(2-ethyl-6-methoxybenzofuran-3-yl)(4-methoxyphenyl)methanone (17) and (2-ethyl-6-methoxybenzofuran-4-yl)(4-methoxyphenyl)methanone (18): In a RBF/SB (250 mL),

benzofuran (**11C**; 6.27 g; 35.6 mmol) was diluted with CS₂ (100 mL) and the vessel capped with a sure-seal and a N₂ balloon attached. The RBF was cooled in an ice bath (30 min) and p-anisoyl chloride (1.3 mol equiv.) was added dropwise (3–4 min); next, tin (IV) chloride (1.3 mol equiv.; 5–7 min) was added. The mixture was stirred (3.0 h) and warmed to RT (3.0 h). The contents were diluted (H₂O; 40 mL) and extracted with EtOAc (4 × 150 mL). The organic phase was washed with dilute HCl (0.5 N, 75 mL), followed by water (75 mL), 1.0 M NaOH (75 mL), NaHCO₃ aq (75 mL) and saturated NaCl aq (75 mL). The organic phase was dried (MgSO₄), filtered, concentrated under reduced pressure, and purified via SiO₂ chromatography (10:1; Hex:EtOAc) to afford two products (**17:18**) in a 5.3:1.0 ratio. **17**: A light yellow solid (7.92 g; 25.5 mmol; 72% yield). ¹H-NMR (400 MHz) CDCl₃: 7.85–7.81 (d, 2H), 7.27–7.25 (d, 1H), 7.01 (s, 1H), 6.96–6.94 (d, 2H), 6.83–6.80 (d, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 2.89–2.83 (q, 2H), 1.33–1.29 (t, 3H); ¹³C-NMR (100 MHz) CDCl₃: 190.5, 164.5, 163.5, 158.0, 154.7, 132.1, 131.7, 121.5, 120.6, 116.2, 113.7, 112.1, 95.9, 55.8, 55.5, 21.8, 12.5. LC/MS-MS: 311.1 → 135.1 *m/z*; GS1 and GS2 at 25, DP = 56, CE = 31, CXP = 9, t_R = 4.65 min. **18**: A light yellow solid (1.50 g; 4.80 mmol; 14% yield) ¹H-NMR (400 MHz) CDCl₃: 7.81–7.78 (d, 2H), 7.42 (s, 1H), 7.03 (s, 1H), 6.91–6.88 (d, 2H), 6.32 (s, 1H), 3.87 (s, 3H), 3.75 (s, 3H), 2.79–2.75 (q, 2H), 1.34–1.31 (t, 3H); ¹³C-NMR (100 MHz) CDCl₃: 195.3, 163.4, 161.1, 156.6, 155.2, 132.4, 131.3, 125.2, 121.8, 121.0, 113.5, 100.9, 94.5, 56.1, 55.5, 21.8, 12.0. LC/MS-MS: 311.1 → 203.1 *m/z*; GS1 and GS2 at 25, DP = 56, CE = 25, CXP = 14, t_R = 4.48 min. Investigating the influence of temperature on product ratio, the ratios of isolated **17:18** changed with 5.3:1.0 at 5 °C to 2.6:1.0 at RT.

(2-ethyl-7-methoxybenzofuran-3-yl)(4-methoxyphenyl)methanone (19) and (2-ethyl-7-methoxybenzofuran-4-yl)(4-methoxyphenyl)methanone (20): In a RBF/SB (100 mL), benzofuran (**11D**; 3.96 g; 22.5 mmol) was diluted in CS₂ (35 mL). The RBF was capped with a sure-seal and a N₂ balloon attached. The vessel was cooled in an ice bath (30 min) and p-anisoyl chloride (1.3 mol equiv.) added dropwise (3–4 min); next, tin (IV) chloride (1.3 mol equiv.; 5–7 min) was added. The mixture was stirred (3 h) and warmed to RT (3 h). The contents were diluted (H₂O; 40 mL) and extracted with EtOAc (4 × 100 mL). The organic phase was washed with HCl aq (0.5 N, 40 mL), followed by H₂O (40 mL), NaHCO₃ aq (40 mL) and NaCl aq (40 mL). The organic phase was dried (MgSO₄), filtered, concentrated under reduced pressure, and purified via SiO₂ chromatography (10:1; Hex:EtOAc) to afford two products **19:20** 1.0:9.7 ratio. **19**: A light yellow oil (559 mg; 1.8 mmol; 8% yield) ¹H-NMR (400 MHz) CDCl₃: 7.81–7.78 (d, 2H), 7.51–7.49 (d, 1H), 7.00–6.95 (d, 2H), 6.86 (s, 1H), 6.75–6.72 (d, 1H), 4.07 (s, 3H), 3.87 (s, 3H), 2.85–2.82 (q, 2H), 1.37–1.32 (t, 3H); ¹³C-NMR (100 MHz) CDCl₃: 194.5, 163.3, 162.8, 148.0, 143.8, 132.2, 131.6, 131.5, 128.5, 123.1, 113.5, 104.3, 102.7, 56.3, 55.5, 21.9, 11.9. LC/MS-MS: 311.0 → 203.1 *m/z*; GS1 and GS2 at 25, DP = 51, CE = 27, CXP = 14, t_R = 4.47 min. **20**: A light yellow solid (5.43 g; 17.5 mmol; 78% yield) ¹H-NMR (400 MHz) CDCl₃: 7.83–7.81 (d, 2H), 7.18–7.17 (d, 2H), 6.92–6.90 (d, 2H), 6.43 (s, 1H), 4.04 (s, 3H), 3.87 (s, 3H), 2.87–2.81 (q, 2H), 1.38–1.33 (t, 3H); ¹³C-NMR (100 MHz) CDCl₃: 194.9, 163.4, 162.8, 145.0, 142.8, 133.8, 132.4, 131.7, 126.0, 124.0, 113.9, 113.4, 101.6, 60.9, 55.5, 21.7, 11.8. LC/MS-MS: 311.1 → 135.0 *m/z*; GS1 and GS2 at 25, DP = 56, CE = 31, CXP = 8, t_R = 4.54 min. Investigating the influence of temperature on product ratio, the ratios of isolated **19:20** changed with reaction temperature from 1.0:9.7 at 5 °C to 1.0:9.0 at RT.

(2-ethyl-5-methoxybenzofuran-3-yl)(4-hydroxyphenyl)methanone (21): In a RBF/SB (50 mL), benzofuran (**15**; 1.01 g; 3.25 mmol) was diluted with DMF (15 mL). To the reaction mixture, NaSEt (405 mg) was added and heated (115–120 °C; 0.25 h). The reaction was quenched with the addition of 2 volumes of NH₄Cl aq and extracted with EtOAc (4 × 70 mL). The organic phase was washed with H₂O, NaCl aq, dried (MgSO₄), filtered, concentrated under reduced pressure, and purified via SiO₂ chromatography (4:1; Hex:EtOAc) to afford **21** as a yellow solid (706 mg; 2.38 mmol; 73% yield). ¹H-NMR (400

MHz) CDCl₃: 10.5 (bs, 1H), 7.80-7.77 (d, 2H), 7.37-7.35 (d, 1H), 6.95-6.93 (m, 3H), 6.89-6.86 (dd, 1H), 3.73 (s, 3H), 2.89-2.83 (q, 2H), 1.32-1.29 (t, 3H); ¹³C-NMR (100 MHz) CDCl₃: 191.8, 166.6, 161.1, 156.3, 148.6, 132.1, 131.2, 127.7, 116.3, 115.5, 113.0, 111.4, 104.0, 55.9, 22.0, 12.2. LC/MS-MS: 297.0 → 121.2 *m/z*; GS1 and GS2 at 25, DP = 41, CE = 31, CXP = 6, *t_R* = 4.30 min.

(2-ethyl-5-hydroxybenzofuran-3-yl)(4-methoxyphenyl)methanone (22): In a RBF/SB (50 mL), AlCl₃ (0.403 g, 3.03 mmol) and ethanethiol (HSEt; 0.829 mL) were cooled in an ice bath (20 min). Compound **14** (0.20 g, 0.644 mmol) was dissolved in DCM (4.3 mL), added and stirred (1.0 h). Next, the reaction mixture was quenched with 1.0 N HCl, and extracted with DCM (4 × 75 mL). The organic phase was dried (Na₂SO₄), filtered, concentrated under reduced pressure, and purified via SiO₂ chromatography (Hex:EtOAc; 4:1) to give **22** (0.148 g, 0.499 mmol, 77% yield) as a white solid. ¹H-NMR (400 MHz) CDCl₃: 7.82-7.79 (d, 2H), 7.32-7.30 (d, 1H), 7.22-7.21 (s, 1H), 6.98-6.95 (d, 2H), 6.85-6.82 (d, 1H), 3.88 (s, 3H), 2.79-2.73 (q, 2H), 1.30-1.26 (t, 3H); ¹³C-NMR (100 MHz); CDCl₃: 191.8, 166.6, 163.5, 153.0, 148.5, 131.8, 131.6, 127.9, 116.3, 113.8, 113.1, 111.3, 106.5, 55.5, 22.1, 12.2. LC/MS-MS: 297.0 → 135.0 *m/z*; GS1 and GS2 at 25, CAD=5, DP = 66, CE = 31, CXP = 8, *t_R* = 4.25 min.

(2-ethyl-5-hydroxybenzofuran-3-yl)(4-hydroxyphenyl)methanone (23): In a RBF/SB (50 mL), AlCl₃ (0.114 g, 0.857 mmol) and HSEt (0.234 mL) were added. Compound **21** (0.054 g, 0.182 mmol) in DCM (1.3 mL) was added (0 °C) and stirred (1.0 h). The reaction mixture was quenched with H₂O/HCl and extracted (DCM; 3 × 75 mL). The organic phase was washed with NaCl aq, dried (Na₂SO₄), filtered, concentrated under reduced pressure and purified via SiO₂ chromatography (Hex:EtOAc; 4:1) to give **23** (10.3 mg, 0.046 mmol, 25% yield) as a yellow solid. ¹H-NMR (400 MHz) DMSO-*d*₆: 10.4 (s, 1H), 9.2 (s, 1H), 7.66-7.64 (d, 2H), 7.40-7.37 (d, 1H), 6.88-6.86 (d, 2H), 6.72-6.69 (m, 2H), 2.78-2.72 (q, 2H), 1.22-1.19 (t, 3H); ¹³C-NMR (100 MHz) DMSO-*d*₆: 189.9, 165.2, 162.5, 154.3, 147.6, 132.0, 130.3, 128.0, 116.2, 115.7, 113.4, 111.8, 105.9, 21.7, 12.6. LC/MS-MS: 283.1 → 121.2 *m/z*; GS1 and GS2 at 25, DP = 66, CE = 29, CXP = 6, *t_R* = 3.97 min.

(2-ethyl-5-methoxybenzofuran-4-yl)(4-hydroxyphenyl)methanone (24): In a RBF/SB (50 mL), **15** (701 mg; 2.26 mmol) was dissolved with DMF (15 mL). NaSEt (285 mg) was added and the mixture was heated (115–120 °C; 0.5 h). Next, the reaction mixture was quenched (2 vol NH₄Cl aq) and extracted with EtOAc (4 × 75 mL). The organic phase was washed with H₂O, NaCl aq, dried (MgSO₄), filtered, concentrated under reduced pressure, and purified by SiO₂ chromatography (4:1; Hex:EtOAc) to afford **24** as a light yellow solid (631 mg; 2.13 mmol; 94% yield). ¹H-NMR (400 MHz) DMSO-*d*₆: 10.4 (bs, 1H; exchangeable in D₂O), 7.59-7.57 (d, 3H), 7.05-7.03 (d, 1H), 6.83-6.81 (d, 2H), 6.19 (s, 1H), 3.67 (s, 3H), 2.75-2.69 (q, 2H), 1.21-1.17 (t, 3H); ¹³C-NMR (100 MHz) DMSO-*d*₆: 193.3, 163.4, 162.9, 152.7, 149.4, 132.4, 129.2, 128.5, 120.0, 115.8, 112.7, 108.8, 100.7, 57.0, 21.6, 12.0. LC/MS-MS: 297.0 → 203.0 *m/z*; GS1 and GS2 at 20, DP = 66, CE = 23, CXP = 14, *t_R* = 4.17 min.

(2-ethyl-5-hydroxybenzofuran-4-yl)(4-methoxyphenyl)methanone (25) and (2-ethyl-5-hydroxybenzofuran-4-yl)(4-hydroxyphenyl)methanone (26): In a RBF/SB (25 mL), **15** (0.200 g, 0.644 mmol) was dissolved with DMF (4.5 mL). NaSEt (0.270 g, 3.22 mmol) was added and the mixture was heated (110 ± 5 °C; 19 h). The mixture was quenched with NH₄Cl aq (2 vol.) and extracted with EtOAc (3 × 75 mL). The organic phase was washed with NaCl aq, dried (Na₂SO₄), filtered, concentrated under reduced pressure, and purified via SiO₂ chromatography (Hex:EtOAc; 4:1) to give: i) **24** (111.5 mg, 60% yield) as a light yellow solid, ii) **25** (4.8 mg, 0.0161 mmol, 2.5 % yield) as a yellow solid, ¹H-NMR (400 MHz) CDCl₃: 11.5 (s, 1H), 7.69-7.66 (d, 2H), 7.52-7.49 (d, 1H), 6.99-6.95 (d, 2H),

6.91-6.89 (d, 1H), 5.60 (s, 1H), 3.91 (s, 3H), 2.68-2.53 (q, 2H), 1.21-1.17 (t, 3H); ^{13}C -NMR (100 MHz) CDCl_3 : 199.1, 163.0, 162.3, 159.4, 148.4, 132.2, 131.4, 129.5, 118.3, 113.6, 113.2, 111.8, 102.9, 55.5, 21.8, 11.8. LC/MS-MS: 297.0 $\rightarrow$ 189.0 m/z ; GS1 and GS2 at 25, CAD=5, DP = 71, CE = 29, CXP = 12, t_R = 4.80 min and, iii) **26** (8.5 mg, 0.0301 mmol, 5% yield) as a yellow foam. ^1H -NMR (400 MHz) CDCl_3 : 11.5 (bs, 1H), 7.65-7.61 (d, 2H), 7.52-7.50 (d, 1H), 6.93-6.89 (m, 3H), 5.60 (s, 1H), 5.24 (bs, 1H), 2.68-2.63 (q, 2H), 1.21-1.17 (t, 3H); ^{13}C -NMR (100 MHz) CDCl_3 : 199.1, 162.4, 159.4, 159.3, 148.5, 132.4, 131.6, 129.5, 118.4, 115.2, 113.2, 111.7, 102.8, 21.8, 11.8. LC/MS-MS: 283.1 $\rightarrow$ 189.0 m/z ; GS1 and GS2 at 25, CAD=5, DP = 66, CE = 29, CXP = 12, t_R = 4.26 min.

(2-ethyl-5-methoxybenzofuran-7-yl)(4-hydroxyphenyl)methanone (27): In a RBF/SB (50 mL), **16** (2.17 g; 6.99 mmol) dissolved in DMF (26 mL) was added and stirred. NaSEt (884 mg) was added and heated (100–105 °C; 3.0 h). The reaction mixture was quenched (2 vol NH_4Cl aq) and extracted with EtOAc (4 $\times$ 125 mL). The organic phase was washed with H_2O , NaCl aq, dried (MgSO_4), filtered, concentrated under reduced pressure, and purified via SiO_2 chromatography (2:1; Hex:EtOAc) to afford **27** as a light yellow sticky solid (908 mg; 3.06 mmol; 44% yield). ^1H -NMR (400 MHz) CDCl_3 : 10.3 (bs, 1H), 7.78-7.75 (d, 2H), 7.39 (s, 1H), 7.02 (s, 1H), 6.87-6.83 (d, 2H), 6.38 (s, 1H), 3.74 (s, 3H), 2.82-2.77 (q, 2H), 1.30-1.26 (t, 3H); ^{13}C -NMR (100 MHz) CDCl_3 : 192.0, 165.0, 161.4, 157.8, 154.5, 132.1, 130.9, 121.3, 120.3, 116.0, 115.5, 112.2, 95.7, 55.7, 21.8, 12.3. LC/MS-MS: 297.0 $\rightarrow$ 203.1 m/z ; GS1 and GS2 at 25, DP = 36, CE = 27, CXP = 14, t_R = 4.20 min.

(2-ethyl-5-hydroxybenzofuran-7-yl)(4-methoxyphenyl)methanone (28): In a RBF/SB (25 mL), **16** (0.200 g, 0.644 mmol) was diluted with DMF (4.5 mL) and NaSEt (0.108 g, 1.28 mmol) was added. The mixture was heated (110 $\pm$ 5 °C, 1.0 h) and then quenched with NH_4Cl aq, (2 vol) and extracted with EtOAc (3 $\times$ 75 mL). The organic phase was dried (Na_2SO_4), filtered, concentrated under reduced pressure and purified via SiO_2 chromatography (Hex:EtOAc; 4:1) to give: i) **27** (97.0 mg, 0.327 mmol, 51% yield) as a white solid, and ii) **28** (8.1 mg, 0.027 mmol, 4% yield) as a yellow solid. ^1H -NMR (400 MHz) CDCl_3 : 11.9 (s, 1H), 7.74-7.72 (d, 2H), 7.63 (s, 1H), 7.07 (s, 1), 7.02-7.00 (d, 2H), 6.36 (s, 1H), 3.91 (s, 3H), 2.81-2.76 (q, 2H), 1.35-1.31 (t, 3H); ^{13}C -NMR (100 MHz); CDCl_3 : 199.9, 167.1, 162.6, 158.9, 147.6, 136.6, 131.6, 130.8, 115.2, 114.3, 113.6, 107.1, 101.6, 55.5, 22.1, 11.5. LC/MS-MS: 297.0 $\rightarrow$ 135.0 m/z ; GS1 and GS2 at 25, DP = 106, CE = 33, CXP = 8, t_R = 4.82 min.

(2-ethyl-5-hydroxybenzofuran-7-yl)(4-hydroxyphenyl)methanone (29): In a RBF/SB (25 mL), **16** (0.200 g, 0.644 mmol) was added and diluted with DMF (4.5 mL). NaSEt (0.270 g, 3.22 mmol) was added and the contents were stirred and heated (110 $\pm$ 5 °C; 16 h). Next, the reaction mixture was quenched with NH_4Cl aq, and extracted with EtOAc (3 $\times$ 75 mL). The organic phase was washed with NaCl aq, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified via SiO_2 chromatography (Hex:EtOAc; 4:1) to give: i) **27** (82.0 mg, 0.276 mmol, 43% yield) as an off-white solid, and ii) **29** (21.3 mg, 0.075 mmol, 12% yield) as a yellow solid. ^1H -NMR (400 MHz) CDCl_3 : 11.9 (bs, 2H), 7.69-7.67 (d, 2H), 7.62 (s, 1H), 7.07 (s, 1H), 6.95-6.93 (d, 2H), 6.36 (s, 1H), 2.80-2.78 (q, 2H), 1.35-1.32 (t, 3H); ^{13}C -NMR (100 MHz) CDCl_3 : 200.0, 167.2, 159.1, 158.8, 147.6, 136.8, 131.9, 131.0, 115.2, 115.1, 114.4, 107.2, 101.7, 22.1, 11.5. LC/MS-MS: 283.1 $\rightarrow$ 121.2 m/z ; GS1 and GS2 at 25, DP = 61, CE = 33, CXP = 6, t_R = 4.37 min.

(2-ethyl-6-methoxybenzofuran-3-yl)(4-hydroxyphenyl)methanone (30): In a RBF/SB (100 mL), benzofuran (**17**; 2.00 g; 6.44 mmol) was diluted with DMF (25 mL). The mixture was stirred while NaSEt (820 mg) was added and the contents were warmed (105–110 °C; 1.0 h). The mixture was quenched (2 vol saturated NH_4Cl aq) and extracted with EtOAc (4 $\times$ 150 mL). The organic phase was washed with H_2O , followed by NaCl aq, and then dried

(MgSO₄). The material was filtered, concentrated under reduced pressure and purified via SiO₂ chromatography (4:1; Hex:EtOAc) to afford **30** as a yellow solid (1.54 g; 5.20 mmol; 81% yield). ¹H-NMR (400 MHz) CDCl₃: 10.3 (bs, 1H), 7.79-7.78 (d, 2H), 7.28-7.26 (d, 1H), 7.02-7.01 (d, 1H), 6.93-6.91 (d, 2H), 6.84-6.82 (dd, 1H), 3.85 (s, 3H), 2.90-2.84 (q, 2H), 1.33-1.29 (t, 3H); ¹³C-NMR (100 MHz) CDCl₃: 191.8, 165.0, 161.0, 157.9, 154.6, 132.1, 131.2, 121.4, 120.3, 116.0, 115.5, 112.2, 95.8, 55.7, 21.8, 12.4. LC/MS-MS: 297.0 → 121.2 *m/z*; GS1 and GS2 at 25, DP = 46, CE = 27, CXP = 6, *t_R* = 4.28 min.

(2-ethyl-6-hydroxybenzofuran-3-yl)(4-methoxyphenyl)methanone (31) and (2-ethyl-6-hydroxybenzofuran-3-yl)(4-hydroxyphenyl)methanone (32): A RBF/SB containing AlCl₃ (0.403 g, 3.03 mmol) was cooled with an ice/NaCl bath (10 min) and then HSEt (0.829 mL) was added and mixed. Compound **17** (0.200 g, 0.644 mmol) in DCM (4.3 mL) was added and stirred (1.0 h). Afterwards, the reaction was quenched (1.0 N HCl; 5 mL) and extracted (DCM). The organic phase was washed with NaCl aq, dried (Na₂SO₄), filtered, concentrated under reduced pressure, and then purified via SiO₂ chromatography (Hex:EtOAc; 4:1) to give: i) **31** (107.8 mg, 0.364 mmol, 56% yield) as a yellow foam. ¹H-NMR (400 MHz) DMSO-d₆: 7.86-7.84 (d, 2H), 7.21-7.19 (d, 1H), 7.00 (s, 1H), 6.96-6.94 (d, 2H), 6.79-6.76 (m, 2H), 3.88 (s, 3H), 2.88-2.82 (q, 2H), 1.32-1.28 (t, 3H); ¹³C-NMR (100 MHz) DMSO-d₆: 191.5, 164.8, 163.6, 154.5, 154.1, 131.8, 131.7, 121.4, 120.2, 116.0, 113.7, 112.6, 98.1, 55.5, 21.7, 12.4. LC/MS-MS: 297.0 → 135.1 *m/z*; GS1 and GS2 at 25, CAD = 6, DP = 66, CE = 31, CXP = 8, *t_R* = 4.24 min; and, ii) **32** (14.7 mg, 0.052 mmol, 8% yield) as a light yellow solid. ¹H-NMR (400 MHz) DMSO-d₆: 10.4 (bs, 1H), 9.6 (bs, 1H), 7.67-7.65 (d, 2H), 7.14-7.12 (d, 1H), 6.94-6.93 (d, 1H), 6.88-6.86 (d, 2H), 6.73-6.71 (d, 1H), 2.75-2.69 (q, 2H), 1.21-1.18 (t, 3H); ¹³C-NMR (100 MHz) DMSO-d₆: 189.9, 162.8, 162.5, 156.0, 154.6, 132.0, 130.3, 121.3, 119.1, 116.1, 115.7, 113.1, 97.9, 21.6, 12.8. LC/MS-MS: 283.0 → 121.2 *m/z*; GS1 and GS2 at 25, CAD = 5, DP = 41, CE = 29, CXP = 6, *t_R* = 4.45 min.

(2-ethyl-6-methoxybenzofuran-4-yl)(4-hydroxyphenyl)methanone (33): In a RBF/SB, **18** (700 mg; 2.26 mmol) was diluted with DMF (11 mL). To the mixture NaSEt (367 mg) was added and the contents were warmed (105–110 °C; 3.0 h). Afterwards, the reaction was quenched (2 vol NH₄Cl aq) and extracted with EtOAc (4 × 70 mL). The organic phase was washed with H₂O, NaCl aq, dried (MgSO₄), filtered, concentrated under reduced pressure, and purified via SiO₂ chromatography (4:1; Hex:EtOAc) to afford **33** as a yellow solid (308 mg; 1.04 mmol; 46% yield). ¹H-NMR (400 MHz) DMSO-d₆: 10.4 (bs, 1H; exchangeable in D₂O), 7.59-7.57 (d, 2H), 7.38 (s, 1H), 7.33 (s, 1H), 6.84-6.82 (d, 2H), 6.53 (s, 1H), 3.70 (s, 3H), 2.84-2.77 (q, 2H), 1.28-1.25 (t, 3H); ¹³C-NMR (100 MHz) DMSO-d₆: 194.3, 162.6, 160.9, 156.1, 154.9, 132.5, 129.5, 125.8, 121.7, 120.3, 115.6, 101.5, 95.7, 56.5, 21.6, 12.2. ¹H-NMR (400 MHz) CDCl₃: 7.79-7.77 (d, 2H), 7.28-7.26 (d, 1H), 7.21 (bs, 1H; exchangeable in D₂O), 7.02-7.01 (d, 1H), 6.93-6.91 (d, 2H), 6.84-6.81 (dd, 1H), 3.85 (s, 3H), 2.90-2.84 (q, 2H), 1.33-1.29 (t, 3H); ¹³C-NMR (100 MHz) CDCl₃: 191.5, 165.0, 160.8, 157.9, 154.6, 132.1, 131.5, 121.4, 120.4, 116.0, 115.4, 112.2, 95.8, 55.8, 21.8, 12.4. LC/MS-MS: 297.0 → 121.2 *m/z*; GS1 and GS2 at 20, DP = 41, CE = 29, CXP = 6, *t_R* = 4.27 min.

(2-ethyl-6-hydroxybenzofuran-4-yl)(4-methoxyphenyl)methanone (34) and (2-ethyl-6-hydroxybenzofuran-4-yl)(4-hydroxyphenyl)methanone (35): In a RBF/SB (15 mL), **18** (0.200 g, 0.644 mmol) was diluted with DMF (3.0 mL). To the mixture NaSEt (0.108 g, 1.29 mmol) was added and the contents were heated (110 ± 5 °C; 4.0 h). Additional NaSEt (0.108 g, 1.29 mmol) was added and heated (14 h). Next, the reaction was quenched with NH₄Cl aq and extracted with EtOAc (3 × 40 mL). The organic phase was washed with NaCl aq (2 vol), dried (Na₂SO₄), filtered, concentrated under reduced pressure, and purified via SiO₂ chromatography (Hex:EtOAc; 4:1) to give: i) **33** (98.0 mg, 0.330 mmol, 51% yield) as a white solid, ii) **34** (21.7 mg, 0.0732 mmol, 11% yield) as a yellow solid. ¹H-NMR (400

MHz) CDCl₃: 12.2 (bs, 2H), 7.73-7.69 (m, 3H), 7.04 (s, 1H), 7.02-6.99 (d, 2H), 6.25, (s, 1H), 3.91 (s, 3H), 2.77-2.75 (q, 2H), 1.33-1.30 (t, 3H); ¹³C-NMR (100 MHz) CDCl₃: 200.2, 162.7, 161.9, 161.0, 159.2, 131.7, 131.0, 125.4, 121.5, 116.1, 113.6, 100.8, 99.5, 55.5, 21.7, 11.7. LC/MS-MS: 297.0 → 135.1 *m/z*; GS1 and GS2 at 25, DP = 61, CE = 29, CXP = 8, *t_R* = 4.90 min; and, iii) **35** (5.7 mg, 0.020 mmol, 3% yield) as a yellow solid. ¹H-NMR (400 MHz) CDCl₃: 12.1 (bs, 2H), 7.70 (s, 1H), 7.69-7.65 (d, 2H), 7.05 (s, 1H), 6.96-6.93 (d, 2H), 6.26 (s, 1H), 2.79-2.73 (q, 2H), 1.33-1.30 (t, 3H); ¹³C-NMR (100 MHz) CDCl₃: 200.2, 161.9, 161.0, 159.3, 158.9, 132.0, 131.3, 125.4, 121.5, 116.1, 115.2, 100.8, 99.5, 21.7, 11.7. LC/MS-MS: 283.1 → 121. *m/z*; GS1 and GS2 at 25, DP = 46, CE = 31, CXP = 6, *t_R* = 4.44 min.

(2-ethyl-7-hydroxybenzofuran-3-yl)(4-methoxyphenyl)methanone (36): In a RBF/SB, **19** (0.100 g, 0.322 mmol) was diluted with DMF (3.0 mL) and NaSEt (0.081 g, 0.966 mmol) was added and heated (105–115 °C; 21 h). The reaction was quenched with NH₄Cl aq (2 vol) and extracted with EtOAc (3 × 75 mL). The organic phase was washed with NaCl aq, dried (Na₂SO₄), filtered, concentrated under reduced pressure, and purified via SiO₂ chromatography (Hex:EtOAc; 4:1) to give **36** (22 mg, 0.074 mmol, 23% yield) as a light yellow solid. ¹H-NMR (400 MHz) CDCl₃: 12.9 (s, 1H), 7.74-7.71 (d, 2H), 7.46-7.43 (d, 2H), 7.01-6.99 (d, 2H), 6.97-6.94 (d, 1H), 6.42 (s, 1H), 3.90 (s, 3H), 2.91-2.85 (q, 2H), 1.39-1.36 (t, 3H); ¹³C-NMR (100 MHz) CDCl₃: 200.3, 165.7, 162.6, 149.5, 142.7, 136.5, 131.7, 131.0, 127.5, 114.7, 113.6, 110.1, 102.2, 55.5, 22.1, 11.8. LC/MS-MS: 296.8 → 135.1 *m/z*; GS1 and GS2 at 25, CAD=4, DP = 56, CE = 39, CXP = 10, *t_R* = 4.76 min.

(2-ethyl-7-hydroxybenzofuran-4-yl)(4-methoxyphenyl)methanone (37): In a RBF/SB (50 mL), **20** (548 mg; 1.77 mmol) was diluted with DMF (8.0 mL). NaSEt (224 mg) was added and warmed (80–85 °C; 20 min). The reaction mixture was quenched with 1.2 vol NH₄Cl aq and extracted with EtOAc (3 × 50 mL). The organic phase was washed with NaCl aq (40 mL) and dried (MgSO₄), filtered, concentrated under reduced pressure, and purified via SiO₂ chromatography (3:1; Hex:EtOAc) to give **37** as an off-white solid (451 mg; 1.52 mmol; 86% yield). ¹H-NMR (400 MHz) DMSO-*d*₆: 10.9 (s, 1H; exchangeable in D₂O), 7.70-7.67 (d, 2H), 7.36-7.34 (d, 1H), 7.08-7.06 (d, 2H), 6.82 (s, 1H), 6.76-6.74 (d, 1H), 3.85 (s, 3H), 2.85-2.80 (q, 2H), 1.32-1.26 (t, 3H); ¹³C-NMR (100 MHz) DMSO-*d*₆: 193.4, 162.9, 162.5, 146.6, 143.1, 131.9, 131.6, 131.5, 129.1, 121.0, 114.0, 109.3, 102.8, 55.8, 21.5, 12.1. LC/MS-MS: 297.0 → 135.1 *m/z*; GS1 and GS2 at 25, DP = 41, CE = 29, CXP = 8, *t_R* = 4.19 min.

(2-ethyl-7-hydroxybenzofuran-4-yl)(4-hydroxyphenyl)methanone (38): In a RBF/SB (100 mL), **20** (1.38 g; 4.46 mmol) was dissolved with DMF (20 mL). NaSEt (1.13 g) was added and warmed (105–110 °C; 4.5 h). The mixture was then quenched with 2 vol NH₄Cl aq and extracted with EtOAc (4 × 100 mL). The organic phase was dried (MgSO₄), filtered, concentrated under reduced pressure and purified via SiO₂ chromatography (2:1; Hex:EtOAc) to give **38** as an off-white solid (1.17 g; 4.14 mmol; 93% yield). ¹H-NMR (400 MHz) DMSO-*d*₆: 10.9 (bs, 1H; exchangeable in D₂O), 10.3 (bs, 1H; exchangeable in D₂O), 7.61-7.59 (d, 2H), 7.35-7.30 (d, 1H), 6.89-6.86 (d, 2H), 6.79 (s, 1H), 6.75-6.73 (d, 1H), 2.86-2.79 (q, 2H), 1.29-1.25 (t, 3H); ¹³C-NMR (100 MHz) DMSO-*d*₆: 193.5, 162.9, 161.6, 146.6, 143.3, 132.5, 131.7, 130.2, 129.0, 121.4, 115.5, 109.4, 103.0, 21.7, 12.3. LC/MS-MS: 283.1 → 121.2 *m/z*; GS1 and GS2 at 25, DP = 51, CE = 29, CXP = 6, *t_R* = 3.89 min.

(3,5-dibromo-4-hydroxyphenyl)(2-ethyl-5-methoxybenzofuran-3-yl)methanone (39): In a RBF/SB, NBS (0.180 g, 1.05 mmol) in DCM (8.0 mL) was added. Next, DMF (0.3 mL) was added and the mixture was cooled (ice-brine cooling bath; 10 min). Compound **21** (0.150 g, 0.506 mmol) in DCM (1.0 mL) was added. The mixture was then warmed to RT and stirred (17 h). The mixture was quenched with H₂O (10 mL), diluted with DCM (20

mL) and the organic phase was washed four times with H₂O, NaCl aq, and then dried (Na₂SO₄), filtered, concentrated under reduced pressure, and purified via SiO₂ chromatography (Hex:EtOAc; 4:1) to give **39** (0.050 g, 0.110 mmol, 22% yield) as a light orange solid. ¹H-NMR (400 MHz) CDCl₃: 8.00 (s, 2H), 7.39-7.36 (d, 1H), 6.93-6.89 (m, 2H), 6.43 (bs, 1H), 3.77 (s, 3H), 2.89-2.83 (q, 2H), 1.36-1.32 (t, 3H); ¹³C-NMR (100 MHz) CDCl₃: 187.7, 167.2, 156.7, 153.1, 148.7, 133.7, 133.5, 127.1, 115.6, 113.6, 111.6, 110.0, 103.5, 55.9, 22.2, 12.2. LC/MS-MS: 454.9 → 278.8 *m/z*; GS1 and GS2 at 25, CAD=4, DP = 71, CE = 37, CXP = 18, *t_R* = 4.59 min.

(3,5-dibromo-4-hydroxyphenyl)(2-ethyl-5-hydroxybenzofuran-3-yl)methanone (40):

AlCl₃ (0.041 g, 0.310 mmol) was added dropwise at -10 °C to ethanethiol (0.084 mL). This solution was added to a solution of **39** (39.0 mg, 0.066 mmol) in DCM (1.0 mL) at 0 °C. The reaction mixture was stirred at this temperature for 1.0 h and then quenched by the addition of water and 1.0 N HCl. The aqueous phase was extracted with DCM (3 × 30 mL) and the combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude material was purified by column chromatography on SiO₂ (hexanes:EtOAc, 4:1) to give **40** as a white solid (11.0 mg, 0.025 mmol, 38% yield). ¹H-NMR (400 MHz) CDCl₃: 9.26 (s, 1H; exchangeable D₂O), 7.88 (s, 2H), 7.42-7.40 (d, 1H), 6.74-6.73 (bd, 2H; 1 exchangeable in D₂O), 2.78-2.72 (q, 2H), 1.25-1.21 (t, 3H); ¹³C-NMR (100 MHz) CDCl₃: 187.6, 166.5, 154.5, 147.6, 133.6, 127.6, 115.6, 113.7, 112.1, 112.0, 110.0, 109.0, 105.8, 21.9, 12.5. LC/MS-MS: 440.9 → 278.9 *m/z*; GS1 and GS2 at 25, CAD=4, DP = 121, CE = 39, CXP = 16, *t_R* = 4.31 min.

(3,5-dibromo-4-hydroxyphenyl)(2-ethyl-5-methoxybenzofuran-4-yl)methanone (41):

In a RBS/SB, NBS (0.168 g, 0.945 mmol) in DCM (7.4 mL) was added. Next, DMF (0.28 mL) was added and the mixture was cooled in an ice bath (10 min). Compound **24** (0.140 g, 0.472 mmol) in DCM (1.0 mL) was added and warmed to RT (17 h). The reaction mixture was quenched with H₂O and washed with NaCl aq. The organic phase was dried (Na₂SO₄), filtered, concentrated under reduced pressure, and purified via SiO₂ chromatography (Hex:EtOAc; 4:1) to give **41** (0.110 g, 0.242 mmol, 51% yield) as a white solid. ¹H-NMR (400 MHz) CDCl₃: 7.94 (s, 2H), 7.49-7.47 (d, 1H), 6.89-6.87 (d, 1H), 6.30 (s, 1H), 3.73 (s, 3H), 2.79-2.74 (q, 2H), 1.31-1.28 (t, 3H); ¹³C-NMR (100 MHz) CDCl₃: 191.8, 164.0, 153.5, 153.0, 149.8, 133.8, 133.1, 129.8, 117.9, 113.6, 109.7, 107.7, 100.7, 56.7, 21.9, 11.6. LC/MS-MS: 454.9 → 203.2 *m/z*; GS1 and GS2 at 25, CAD=4, DP = 26, CE = 33, CXP = 14, *t_R* = 4.42 min.

(3,5-dibromo-4-hydroxyphenyl)(2-ethyl-5-hydroxybenzofuran-4-yl)methanone (42):

AlCl₃ (0.065 g, 0.486 mmol) was added dropwise at -10 °C to ethanethiol (0.133 mL). This solution was added to a solution of **41** (47.0 mg, 0.103 mmol) in DCM (1.0 mL) at 0 °C. The reaction mixture was stirred at this temperature for 1.0 h and then quenched by the addition of water and 1.0 N HCl. The aqueous phase was extracted with DCM (3 × 30 mL) and the combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude material was purified by column chromatography on SiO₂ (hexanes:EtOAc, 4:1) to give **42** as a yellow solid (15.2 mg, 0.0345 mmol, 33% yield). ¹H-NMR (400 MHz) CDCl₃: 11.4 (s, 1H), 7.84 (s, 2H), 7.57-7.54 (d, 1H), 6.92-6.89 (d, 1H), 5.64 (s, 1H), 2.72-2.67 (q, 2H), 1.24-1.21 (t, 3H); ¹³C-NMR (100 MHz) CDCl₃: 195.9, 163.2, 159.9, 152.7, 148.5, 133.9, 133.3, 129.2, 119.3, 113.4, 110.8, 109.8, 102.4, 21.8, 12.0. LC/MS-MS: 441.0 → 189.0 *m/z*; GS1 and GS2 at 25, CAD = 4, DP = 76, CE = 39, CXP = 12, *t_R* = 4.57 min.

(3,5-dibromo-4-hydroxyphenyl)(2-ethyl-5-methoxybenzofuran-7-yl)methanone (43):

In a RBS/SB, NBS (0.180 g, 1.05 mmol) in DCM (8.0 mL) was added. Next, DMF (0.3 mL) was added and the mixture was cooled in an ice bath (10 min). Compound **27** (0.150 g,

0.506 mmol) in DCM (1.0 mL) was added and warmed to RT (17 h). The mixture was diluted with H₂O, diluted with DCM (20 mL) and the organic phase was washed four times with H₂O and then NaCl aq. The organic phase was dried (Na₂SO₄), filtered, concentrated under reduced pressure and purified via SiO₂ chromatography (Hex:EtOAc; 4:1) to give **43** (145 mg, 0.319 mmol, 63% yield) as a white solid. ¹H-NMR (400 MHz) CDCl₃: 7.92 (s, 2H), 7.43 (s, 1H), 7.03 (s, 1H), 6.40 (s, 1H), 3.74 (s, 3H), 2.84-2.78 (q, 2H), 1.36-1.33 (t, 3H); ¹³C-NMR (100 MHz) CDCl₃: 192.4, 164.5, 153.9, 152.8, 148.8, 133.9, 133.2, 132.7, 123.4, 111.9, 109.6, 102.4, 101.5, 56.1, 22.0, 11.7. LC/MS-MS: 454.9 → 203.2 *m/z*; GS1 and GS2 at 25, CAD=4, DP = 86, CE = 35, CXP = 12, *t_R* = 4.47 min.

(3,5-dibromo-4-hydroxyphenyl)(2-ethyl-5-hydroxybenzofuran-7-yl)methanone (44): AlCl₃ (0.117 g, 0.880 mmol) and ethanethiol (0.241 mL) were mixed in a RBF/SB and cooled with an ice bath. Next, compound **43** (0.085 g, 0.187 mmol) in DCM (1.3 mL) was added and stirred (1.0 h). The mixture was quenched with H₂O/1.0 N HCl (1 vol) and extracted with DCM (3 × 30 mL). The organic phase was dried (Na₂SO₄), filtered, concentrated under reduced pressure and purified via SiO₂ chromatography (Hex:EtOAc; 4:1) to give **44** (53.9 mg, 0.122 mmol, 65% yield) as a yellow solid. ¹H-NMR (400 MHz) DMSO-*d*₆: 10.9 (bs, 1H), 10.2 (s, 1H), 7.80 (s, 2H), 7.47 (s, 1H), 7.02 (s, 1H), 6.57 (s, 1H), 2.80-2.74 (q, 2H), 1.27-1.23 (t, 3H); ¹³C-NMR (100 MHz) DMSO-*d*₆: 193.9, 165.4, 155.1, 153.7, 148.0, 134.3, 134.0, 132.2, 120.2, 112.3, 111.8, 106.8, 102.1, 21.8, 12.0. LC/MS-MS: 441.0 → 189.0 *m/z*; GS1 and GS2 at 25, CAD=4, DP = 60, CE = 37, CXP = 18, *t_R* = 4.81 min.

(3,5-dibromo-4-hydroxyphenyl)(2-ethyl-6-methoxybenzofuran-3-yl)methanone (45): In a RBF/SB (50 mL), NBS (0.180 g, 1.05 mmol) in DCM (8.0 mL) was added and followed by the addition of DMF (0.3 mL). The mixture was cooled in an ice/NaCl bath (10 min), and then benzofuran (**30**; 0.150 g, 0.506 mmol) in DCM (1.0 mL) was added. The mixture was warmed to RT (20 h) and then quenched with water (5 mL) and diluted with additional DCM (10 mL). The material was washed with H₂O (10 mL) and then with NaCl aq (10 mL). The organic phase was dried (Na₂SO₄), filtered, concentrated under reduced pressure and purified via SiO₂ chromatography (Hex:EtOAc; 4:1) to give **45** (0.148 g, 0.326 mmol, 64% yield) as a light yellow solid. ¹H-NMR (400 MHz) DMSO-*d*₆: 11.0 (s, 1H), 7.90 (s, 2H), 7.29-7.27 (m, 2H), 6.91-6.88 (d, 1H), 3.80 (s, 3H), 2.78-2.73 (q, 2H), 1.26-1.25 (t, 3H); ¹³C-NMR (100 MHz) DMSO-*d*₆: 187.6, 164.9, 158.2, 154.6, 133.6, 132.2, 121.4, 119.8, 115.4, 113.0, 112.0, 96.6, 56.2, 21.8, 12.5. LC/MS-MS: 454.9 → 278.8 *m/z*; GS1 and GS2 at 25, CAD=5, DP = 76, CE = 35, CXP = 18, *t_R* = 4.58 min.

6-Hydroxy-Benzbromarone (8); (3,5-dibromo-4-hydroxyphenyl)(2-ethyl-6-hydroxybenzofuran-3-yl)methanone: In a RBF/SB cooled with an ice/NaCl bath, ethanethiol (HSEt; 1.29 mL) was added followed by AlCl₃ (0.414 g, 3.11 mmol). Compound **45** (0.300 g, 0.661 mmol) in DCM (10 mL) was added and stirred (1.5 h). Afterwards, the reaction mixture was quenched with 1.0 N HCl (5 mL) and extracted with DCM (3 × 40 mL). The organic phase was washed with NaCl aq, and then dried (Na₂SO₄), filtered, concentrated under reduced pressure, and purified via SiO₂ chromatography (Hex:EtOAc; 4:1) to give **8** (226 mg, 0.514 mmol, 78% yield) as a light brown foam. ¹H-NMR (400 MHz) DMSO-*d*₆: 10.9 (bs, 1H), 9.7 (s, 1H), 7.88 (s, 2H), 7.19-7.17 (d, 1H), 6.95 (s, 1H), 6.75-6.72 (d, 2H), 2.74 – 2.69 (q, 2H), 1.23-1.19 (t, 3H); ¹³C-NMR (100 MHz) DMSO-*d*₆: 187.7, 164.4, 156.2, 155.4, 154.7, 133.6, 133.0, 121.4, 118.6, 115.5, 113.4, 112.0, 98.0, 21.8, 12.6. LC/MS-MS: 441.0 → 278.9 *m/z*; GS1 and GS2 at 25, CAD=4, DP = 101, CE = 35, CXP = 18, *t_R* = 4.20 min.

(5-bromo-2-ethyl-6-methoxybenzofuran-3-yl)(3,5-dibromo-4-hydroxyphenyl)methanone (46): In a RBF/SB, NBS (0.270 g, 1.52 mmol) in DCM (3.9

mL) was diluted with DMF (0.3 mL) and cooled in an ice bath (10 min). Compound **30** (0.150 g, 0.506 mmol) dissolved in DCM (1.0 mL) was added and the reaction mixture was warmed up to RT (17 h). The mixture was quenched with H₂O (1 vol) and diluted with DCM (30 mL). The organic phase was washed four times with H₂O, and then NaCl aq. The organic phase was dried (Na₂SO₄), filtered, concentrated under reduced pressure and purified via SiO₂ chromatography (Hex:EtOAc; 4:1) to give **46** (0.146 g, 0.274 mmol 54% yield) as an off-white solid. ¹H-NMR (400 MHz) DMSO-d₆: 11.1 (bs, 1H), 7.91 (s, 2H), 7.60 (s, 1H), 7.51 (s, 1H), 3.90 (s, 3H), 2.76-2.71 (q, 2H), 1.25-1.24 (t, 3H); ¹³C-NMR (100 MHz) DMSO-d₆: 187.2, 165.7, 155.6, 153.8, 153.7, 133.7, 132.6, 124.3, 121.0, 114.9, 112.0, 107.5, 97.0, 57.3, 22.0, 12.4. LC/MS-MS: 532.9 → 453.9 *m/z* (M-Br); GS1 and GS2 at 25, CAD=5, DP = 70, CE = 31, CXP = 30, *t_R* = 4.70 min.

(6-bromo-2-ethyl-7-hydroxybenzofuran-4-yl)(3,5-dibromo-4-

hydroxyphenyl)methanone (47): In a RBF/SB, NBS (0.189 g, 1.06 mmol) diluted with DCM (9.0 mL) was mixed with DMF (0.31 mL) and the mixture cooled in an ice bath (10 min). Compound **38** (0.150 g, 0.531 mmol) in DCM (1.0 mL) was added and warmed to RT (17 hr). The reaction mixture was quenched with H₂O and diluted with DCM (30 mL). The organic phase was washed four times with H₂O, NaCl aq, and then dried (Na₂SO₄), filtered, concentrated under reduced pressure, and purified twice via SiO₂ chromatography (Hex:EtOAc; 4:1) to give **47** (125 mg, 0.241 mmol, 45% yield) as a white solid. ¹H-NMR (400 MHz) CDCl₃: 7.91 (s, 2H), 7.62 (s, 1H), 6.77 (s, 1H), 6.20 (bs, 2H), 2.88-2.82 (q, 2H), 1.38-1.34 (t, 3H); ¹³C-NMR (100 MHz) CDCl₃: 190.4, 164.7, 152.8, 142.5, 141.7, 133.8, 132.9, 131.7, 130.1, 122.1, 109.9, 103.1, 102.7, 21.9, 11.7. LC/MS-MS: 520.9 (M+2, isotope mass → 278.8 *m/z*; GS1 and GS2 at 25, CAD=4, DP = 101, CE = 37, CXP = 18, *t_R* = 4.36 min. LC/MS-MS: 454.9 → 135.1 *m/z*; GS1 and GS2 at 25, CAD = 4, DP = 61, CE = 37, CXP = 8, *t_R* = 4.56 min.

(4,6-dibromo-2-ethyl-5-hydroxybenzofuran-3-yl)(4-methoxyphenyl)methanone (48): In a RBF/SB, NBS (0.036 g, 0.203 mmol) diluted with DCM (1.0 mL) was mixed with DMF (0.06 mL) and the mixture cooled in an ice bath (10 min). Compound **22** (0.030 g, 0.101 mmol) in DCM (0.8 mL) was added and warmed to RT (18 hr). The reaction mixture was quenched with H₂O and diluted with DCM (30 mL). The organic phase was washed four times with H₂O, NaCl aq, and then dried (Na₂SO₄), filtered, concentrated under reduced pressure, and purified twice via SiO₂ chromatography (Hex:EtOAc; 4:1) to give **48** (7.9 mg, 0.0174 mmol, 17% yield) as an orange oil. ¹H-NMR (400 MHz) CDCl₃: 7.85-7.83 (d, 2H), 7.65 (s, 1H), 6.95-6.92 (d, 2H), 5.77 (s, 1H), 3.88 (s, 3H), 2.72-2.66 (q, 2H), 1.27-1.23 (t, 3H); ¹³C-NMR (100 MHz) CDCl₃: 189.9, 164.1, 162.5, 147.9, 146.1, 132.0, 128.0, 116.6, 114.3, 114.1, 114.0, 105.8, 99.6, 55.5, 21.2, 12.2.

(5,7-dibromo-2-ethyl-6-hydroxybenzofuran-3-yl)(4-methoxyphenyl)methanone (49): In a RBF/SB, NBS (0.060 g, 0.337 mmol) diluted in DCM (2.0 mL) was mixed with DMF (0.1 mL) and the mixture was cooled in an ice bath (10 min). Compound **31** (0.050 g, 0.169 mmol) in DCM (1.0 mL) was added and the mixture was warmed to RT (17 h). Next, the mixture was quenched with water and diluted with DCM (30 mL). The organic phase was washed four times with H₂O, NaCl aq, and then dried (Na₂SO₄), filtered, concentrated under reduced pressure, and purified via SiO₂ chromatography (Hex:EtOAc; 4:1) to give **49** (27.0 mg, 0.0594 mmol, 35% yield) as a yellow oil. ¹H-NMR (400 MHz) CDCl₃: 7.82-7.80 (d, 2H), 7.57 (s, 1H), 6.99-6.97 (d, 2H), 5.93 (bs, 1H), 3.91 (s, 3H), 2.88-2.82 (q, 2H), 1.35-1.31 (t, 3H); ¹³C-NMR (100 MHz) CDCl₃: 189.5, 165.4, 163.8, 151.1, 146.9, 131.6, 131.3, 122.8, 122.1, 116.2, 113.9, 106.1, 91.8, 55.6, 21.9, 12.3. LC/MS-MS: 454.9 → 135.1 *m/z*; GS1 and GS2 at 25, CAD=4, DP = 71, CE = 37, CXP = 8, *t_R* = 4.56 min.

(6-bromo-2-ethyl-7-hydroxybenzofuran-4-yl)(4-methoxyphenyl)methanone (50): In a RBF/SB, compound **37** (203 mg; 0.685 mmol) was diluted with AA (12 mL) and stirred. Next, water (250 μ L) followed by Br₂ (74 μ L) were added. The mixture was stirred (5 min) and quenched with H₂O (5 mL) and the mixture was extracted with EtOAc (3 $\times$ 50 mL). The organic phase was dried (MgSO₄), filtered, concentrated under reduced pressure, and purified via SiO₂ chromatography (3:1; Hex:EtOAc) to afford **50** as a light red solid (176 mg; 0.469 mmol; 69% yield). ¹H-NMR (400 MHz) CDCl₃: 7.81-7.78 (d, 2H), 7.64 (s, 1H), 6.99-6.96 (d, 2H), 6.78 (s, 1H), 6.00 (bs, 1H), 3.90 (s, 3H), 2.86-2.80 (q, 2H), 2.10 (s, 1H), 1.35-1.29 (t, 3H); ¹³C-NMR (100 MHz) CDCl₃: 193.6, 164.1, 163.2, 142.7, 141.5, 132.4, 131.6, 130.8, 130.4, 123.2, 113.9, 103.0, 102.9, 55.6, 21.9, 11.8. LC/MS-MS: 375.0 $\rightarrow$ 135.0 m/z ; GS1 and GS2 at 25, DP = 66, CE = 27, CXP = 8, t_R = 4.42 min.

Functional analysis via oocytes expressing hURAT1

Sodium pyruvate and sodium dodecyl sulfate (SDS) were obtained from Sigma–Aldrich Chemical Co. (St. Louis, MO, USA). [¹⁴C]Urate (55 mCi/mmol) was purchased from Moravsek (Brea, CA). Gentamicin sulfate and other chemicals for solution preparation were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). N-(2-hydroxyethyl)piperazine-N'-(2-ethane sulfonic acid) (HEPES) was purchased from Dojindo Laboratories (Kumamoto, Japan). Collagenase type I from *Clostridium histolyticum* was purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA)

cRNA synthesis and oocyte injection—The hURAT1 (pcDNA3.1) plasmids were linearized with *EcoRV*. The cRNAs were synthesized *in vitro* with T7 RNA polymerase using mMessage mMachine® High yield capped RNA transcription kit (Ambion, Austin, TX, USA). The polyadenylation of cRNA at 3'-end was performed using poly(A) tailing kit (Ambion, Austin, TX, USA). Female *Xenopus* frogs (African clawed frogs; 95–120 g) were purchased from Sato Zoushoku (Chiba, Japan) and nurtured in tap water (19 $\pm$ 3 $^{\circ}$ C). Oocytes (1.23 $\pm$ 0.10 mg/oocyte) isolated from *Xenopus laevis* were defolliculated with 1.0 mg/mL collagenase in Ca²⁺-free solution (96.0 mM NaCl, 2.0 mM KCl, 1.0 mM MgCl₂·6H₂O and 5.0 mM HEPES, pH 7.5) at 25 $\pm$ 2 $^{\circ}$ C for 2.0 h. The oocytes were washed in Ca²⁺-free solution and transferred to ND96 buffer (96.0 mM NaCl, 2.0 mM KCl, 1.0 mM CaCl₂, 1.0 mM MgCl₂·6H₂O and 5.0 mM HEPES, pH 7.5). Defolliculated *Xenopus* oocytes (stage IV and V) were injected with 25 ng of capped cRNA and incubated at 18 $^{\circ}$ C for 2–3 days in ND96 solution containing gentamicin (50 μ g/mL) and 2.5 mM sodium pyruvate.

Inhibition study—After incubation of cRNA-injected oocytes (2–3 days), uptake experiments were performed at room temperature in Cl[−]-free uptake solution (Cl[−] in ND96 solution was replaced with gluconate). The uptake experiments were initiated by replacing the initial bath solutions with uptake solutions containing radiolabeled [¹⁴C]urate (10 μ M) with or without test compound. The uptake was terminated by washing the oocytes with ice-cold uptake solution (5 times @ 1.0 mL each) after 60 min of incubation. The oocytes were solubilized with 5% (w/v) SDS and the radioactivity content determined using liquid scintillation counter (Aloka 3100; Aloka Co., Ltd. Tokyo, Japan). The urate uptake by non-injected (control) oocytes was subtracted from oocytes expressing hURAT1. The data are presented (Table 1) and reported as the % of inhibition. The IC₅₀ data were conducted using different compound concentrations (*i.e.* 5, 10, 50, 100, 500 nM, and 5, 10 and 50 μ M). All screening data are expressed as mean $\pm$ S.E.M (n = 5–7), and the IC₅₀ values are mean $\pm$ SD (n = 5–7).

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Abbreviations

hURAT1; SLC22A12	Human Uric Acid Transporter 1
GLUT9, URATv1, SLC2A9	Glucose Transporter 9, voltage-dependent uric acid transporter 1
NPT4; SLC17A3	Sodium-dependent phosphate transporter 4
hOATv1	voltage-dependent human Organic Anion Transporter 1
hOAT1; SLC22A6	human Organic Anion Transporter 1
hOAT3; SLC22A8	human Organic Anion Transporter 3
SAR	Structure-Activity Relationship
PK	Pharmacokinetic
FDA	Food and Drug Administration
MDCK	Madin-Darby Canine Kidney Cells

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Figure 1.
Nucleic acid catabolism

Figure 2. Chemical Structures for allopurinol (**3**), febuxostat (**4**), probenecid (**5**), sulfipyrazone (**6**), benzbromarone (**7**), and 6-hydroxybenzbromarone (**8**).

Figure 3.
Transporters in renal tubular cells: Urate Secretion/Reabsorption

Figure 4.
Synthesis of 2-ethylbenzofurans

Figure 5.
Synthesis of benzbromarone methoxy-(2-ethylbenzofuran-yl)(4-methoxyphenyl)methanones

Figure 6.
Formation of mono- and diphenolic compounds (21–38)

Figure 7.
Formation of mono-, di-, and tri-brominated compounds (39–50)

Figure 8.

Figure 8a Oocytes expressing hURAT1 and ¹⁴C-urate uptake

Figure 8b Oocytes expressing hURAT1 and displayed linear time-dependent ¹⁴C-uric acid uptake, ○ = control, and ● = hURAT1 (n=8 ± SD).

Table 1Summary of compounds *in vitro* data

Compound	% Inhibition @ 50 μ M	IC ₅₀
Probenecid (5)	35.7 $\pm$ 2.6	86.39 $\pm$ 0.07 μ M
7	99.9 $\pm$ 0.1	26 $\pm$ 3 nM
8	99.8 $\pm$ 0.2	138 $\pm$ 88 nM
12	13.3 $\pm$ 5.7	ND
13	90.8 $\pm$ 0.9	2.80 $\pm$ 0.18 μ M
14	24.3 $\pm$ 5.4	ND
15	6.1 $\pm$ 4.3	ND
16	5.2 $\pm$ 4.8	ND
17	6.2 $\pm$ 9.6	ND
18	1.5 $\pm$ 5.6	ND
19	17.2 $\pm$ 6.0	ND
20	7.4 $\pm$ 11.2	ND
21	92.7 $\pm$ 0.8	2.46 $\pm$ 0.90 μ M
22	12.9 $\pm$ 8.0	ND
23	96.5 $\pm$ 0.5	2.49 $\pm$ 0.14 μ M
24	88.2 $\pm$ 0.8	6.68 $\pm$ 0.09 μ M
25	28.7 $\pm$ 5.4	ND
26	51.5 $\pm$ 4.0	ND
27	60.0 $\pm$ 2.5	33.65 $\pm$ 0.13 μ M
28	9.3 $\pm$ 5.3	ND
29	41.0 $\pm$ 0.6	ND
30	92.7 $\pm$ 0.8	3.92 $\pm$ 0.17 μ M
31	48.3 $\pm$ 3.9	ND
32	92.1 $\pm$ 0.9	1.13 $\pm$ 0.11 μ M
33	62.4 $\pm$ 1.8	19.69 $\pm$ 0.20 μ M
34	12.4 $\pm$ 4.7	ND
35	41.0 $\pm$ 5.5	ND
36	18.2 $\pm$ 7.3	ND
37	0.8 $\pm$ 8.7	ND
38	93.8 $\pm$ 0.7	3.94 $\pm$ 0.15 μ M
39	99.9 $\pm$ 0.1	42 $\pm$ 9 nM
40	99.9 $\pm$ 0.1	189 $\pm$ 90 nM
41	99.6 $\pm$ 0.4	358 $\pm$ 130 nM
42	99.9 $\pm$ 0.1	83 $\pm$ 10 nM
43	99.0 $\pm$ 0.1	1.44 $\pm$ 0.14 μ M
44	99.8 $\pm$ 0.2	287 $\pm$ 118 nM
45	99.9 $\pm$ 0.1	111 $\pm$ 14 nM
46	98.1 $\pm$ 0.2	1.65 $\pm$ 0.12 μ M
47	99.9 $\pm$ 0.1	177 $\pm$ 80 nM

Compound	% Inhibition @ 50 μ M	IC ₅₀
48	76.5 $\pm$ 1.2	23.46 $\pm$ 0.27 μ M
49	99.8 $\pm$ 0.2	667 $\pm$ 88 nM
50	99.3 $\pm$ 0.3	772 $\pm$ 215 nM

ND = no data