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Developing Potent Human Uric Acid Transporter 1 (hURAT1) Inhibitors

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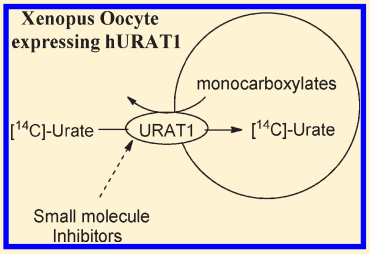
ABSTRACT: The kidneys are a vital organ in the human body. They serve several purposes including homeostatic functions such as regulating extracellular fluid volume and maintaining acid−base and electrolyte balance and are essential regarding the excretion of metabolic waste. Furthermore, the kidneys play an important role in uric acid secretion/reabsorption. 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 ^{14}C-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. As compared to dimethoxy analogues, monophenols formed on the C ring showed the best in vitro inhibitory potential. Compounds with submicromolar (i.e., IC_{50} < 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 levels, which crystallize and deposit into joints and/or surrounding tissues.[3]

Hyperuricemia may result from the overproduction 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 a subsequent increase in serum urate levels. Recent studies suggest that high levels of uric acid play a pivotal role in other 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 levels 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 that lower serum urate levels. A purine xanthine oxidase inhibitor, allopurinol **3** has been the most commonly used urate-lowering drug in the United States. 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 nonpurine 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 that act directly on the renal tubule, increasing uric acid renal excretion by inhibiting urate reabsorption 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 levels.[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 natrium-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

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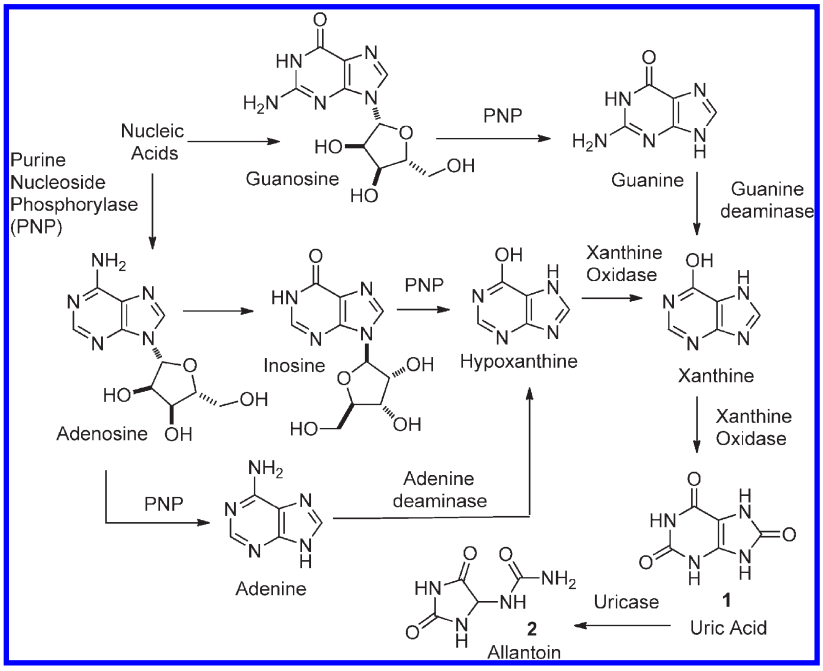

Figure 1. Nucleic acid catabolism.

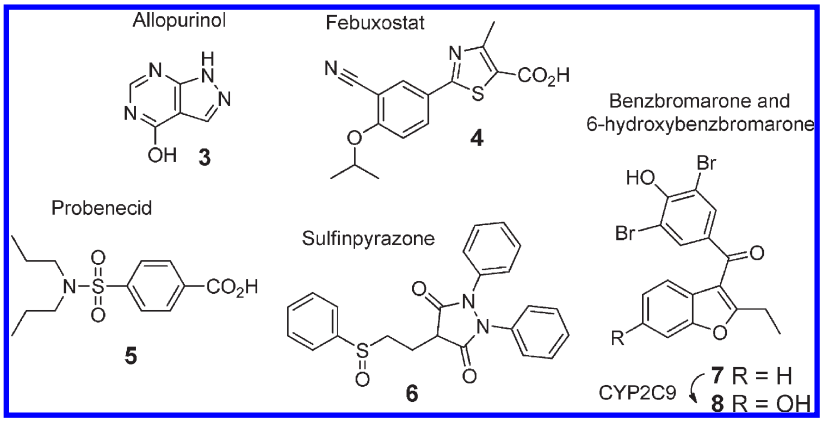

Figure 2. Chemical structures for allopurinol (**3**), febuxostat (**4**), probenecid (**5**), sulfinpyrazone (**6**), benzbromarone (**7**), and 6-hydroxybenzbromarone (**8**).

surface contains transporters that 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 United States has been very high. In 2001, kidney disease was ranked as the ninth leading cause of death in the United States.[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 United States. Metabolized by CYP2C9 (major) and CYP2C19 (minor), idiosyncratic hepatotoxic events associated with **7** are hypothesized to result from CYP biotransformation downstream from initial metabolite, 6-hydroxybenzbromarone **8** (Figure 2).[21] In 2008, Lee and co-workers 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** 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 ^{14}C-uric acid uptake via hURAT1. We have prepared and tested a series of 2-ethyl-benzofurans as described below.

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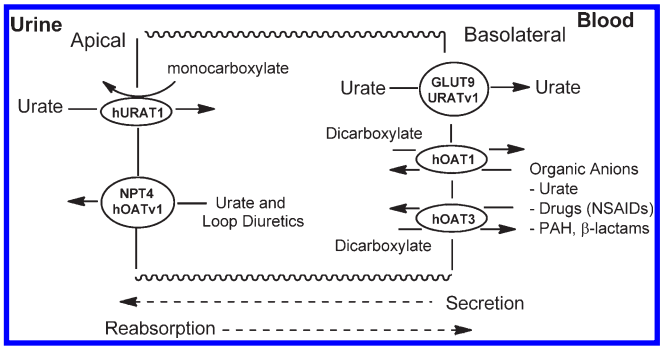

Figure 3. Transporters in renal tubular cells: urate secretion/reabsorption.

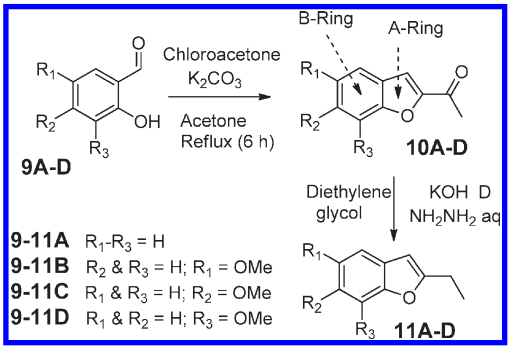

Figure 4. Synthesis of 2-ethylbenzofurans.

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**−**D**. Benzaldehydes were coupled with chloroacetone under basic conditions (K_2CO_3) to produce an SN_2 reaction—Williamson's ether synthesis[23]—to afford 2-(2-oxopropoxy)benzaldehydes, which subsequently endured a tandem base-catalyzed intramolecular aldol condensation[24] reaction to produce the corresponding 1-(benzofuran-2-yl)ethanone, **10A**−**D**. Herein, we will refer to the bicyclic structure thus formed as the "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 reaction[24] 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 AA, 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**−**D**; Figure 5), we observed altered reactivity to produce various regioisomers. The 5-methoxy analogue **11B**

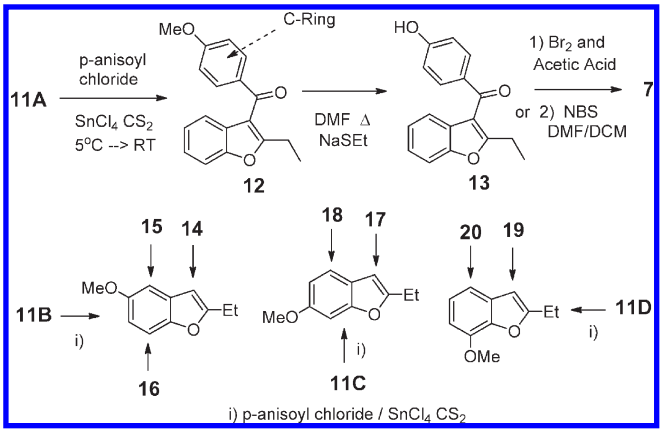

Figure 5. Synthesis of benzbromarone methoxy-(2-ethylbenzofuran-(yl)(4-methoxyphenyl)methanones.

produced three products **14**−**16** (the 3-, 4-, and 7-substituted analogues, respectively), while 6-methoxy **11C** afforded two products **17** and **18** (the 3- and 4-substituted analogues, respectively), and 7-methoxy **11D** generated two products, **19** and **20** (the 3- and 4-substituted analogues, respectively). The formation and isolation of the various dimethoxy benzofuran analogues (**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 the B ring. Compounds **14**−**20** were converted to their corresponding mono- or diphenolic analogues (**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 analogues 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 dibromo and diphenolic analogues, **41** to **42** and **43** to **44**, respectively.

The 6-methoxy analogue **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 3 mol equiv of NBS, compound **30** produced tribromo analogue **46**. Another example of a tribrominated product was observed when (2-ethyl-7-hydroxybenzofuran-4-yl)(4-hydroxyphenyl)methanone **38** was reacted with 2 mol equiv 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 analogue **37** produced monobrominated **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,b, 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

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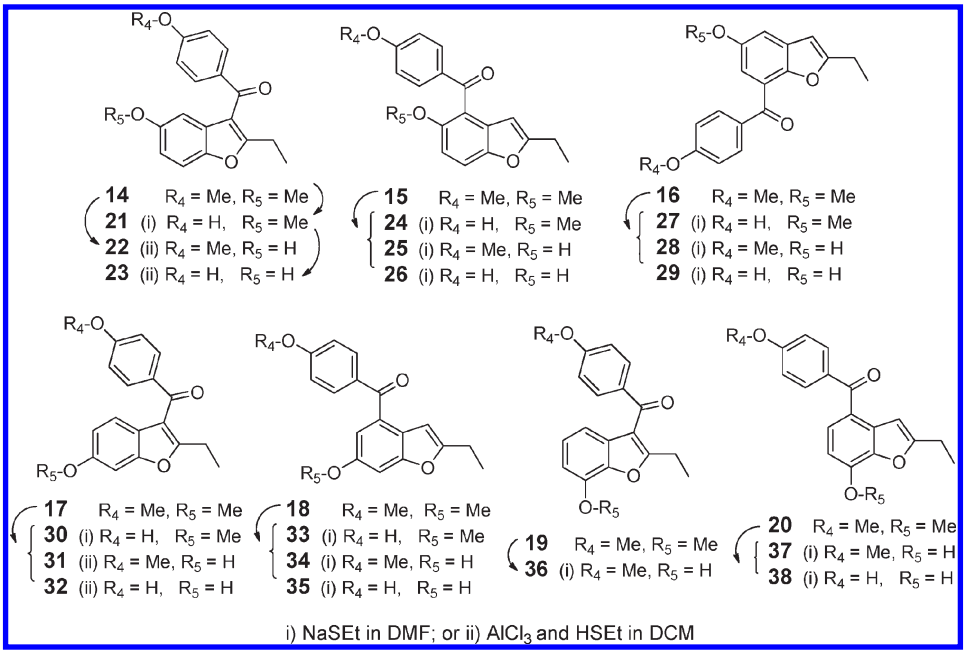

Figure 6. Formation of mono- and diphenolic compounds (**21**−**38**).

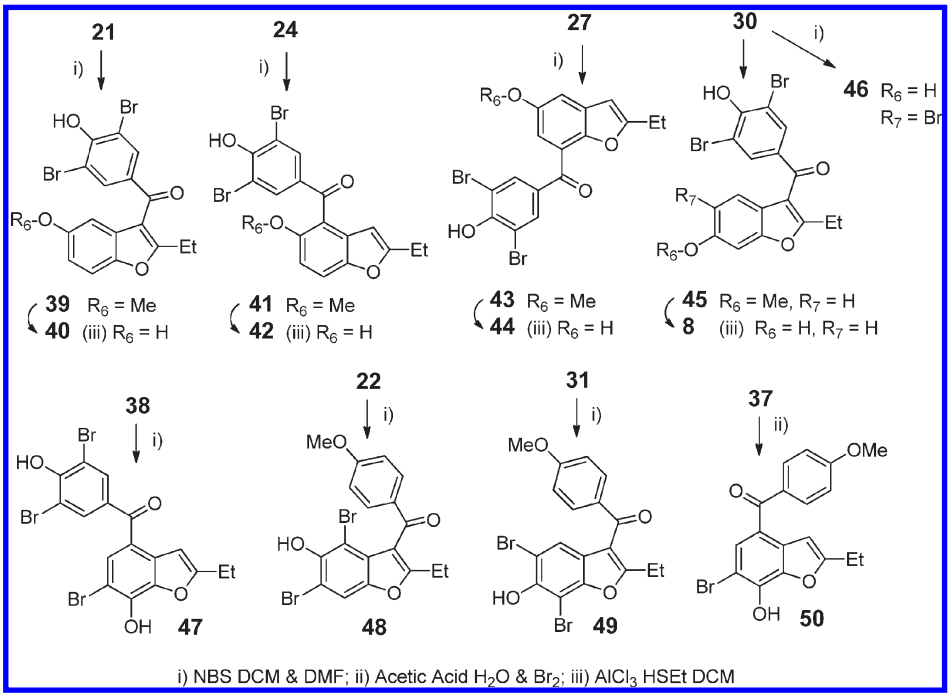

Figure 7. Formation of mono-, di-, and tribrominated compounds (**39**−**50**).

presumed to be the major transporter responsible for the reabsorption of uric acid from the urine.[3,9,11] Time-dependent ^{14}C-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 ^{14}C-uric acid uptake (10.0 μM extracellular) displayed linear influx for at least 2 h. Because 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 2 h. Furthermore, as we are clearly operating under linear influx conditions, we selected the 60 min time point to generate the in vitro IC_{50} values.

As summarized in Table 1, we tested compounds **5**, **7**, **8**, and **12**−**50**. Injecting benzbromarone inside the oocyte and conducting the experiment with only extracellular ^{14}C-uric acid does not readily inhibit ^{14}C-uric acid uptake (data not shown); therefore, the site of inhibitor is crucial, and the data support the notion that inhibitor interactions occur on the apical side.

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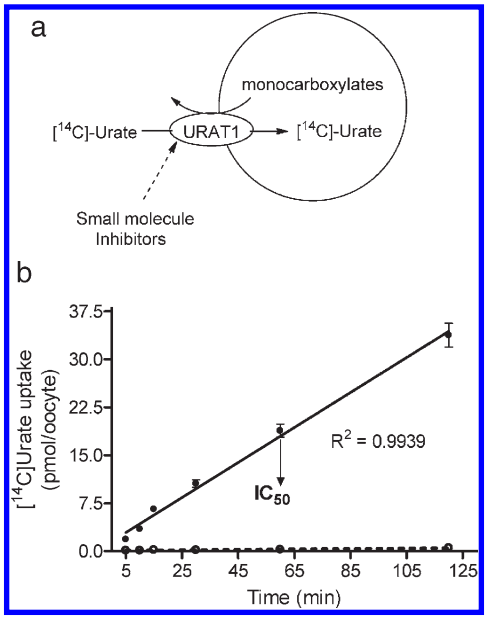

Figure 8. (a) Oocytes expressing hURAT1 and ^{14}C-urate uptake. (b) Oocytes expressing hURAT1 and displayed linear time-dependent ^{14}C-uric acid uptake: ○ = control, and ● = hURAT1 (n = 8 ± SD).

We initially conducted a general screen in which ^{14}C-uric acid (10.0 μM) and test compound (50 μM) 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 μM test compound produced ≥60% inhibition, we conducted a second set of experiments with varying concentrations (i.e., 5, 10, 50, 100, and 500 nM and 5, 10, and 50 μM) of the test compound. The data were used to estimate IC_{50} values, the concentration of compound reducing ^{14}C-uric acid uptake in hURAT1 expressing oocytes by 50% as compared to control. The IC_{50} values were generated using a sigmoidal dose−response (variable slope) relationship.

The ability to prepare a variety of different benzofuran analogues provided us with the ability to probe the structure−activity relationship (SAR) of benzbromarone-related compounds. The data summarized in Table 1 illustrate that **7** has very potent hURAT1 inhibitor potential. The 6-hydroxy-metabolite **8** was a weaker inhibitor than parent drug **7**: IC_{50} = 138 versus 26 nM, respectively. These data are comparable to data produced via Madin−Darby canine kidney cells (MDCK)-hURAT1 where 200 and 35 nM (5.7-fold difference) were reported, respectively.[29] Compound **12** with one methoxy group in the C ring and dimethoxy analogues (**14**−**20**, Figure 6) at 50 μM produced weak-to-no ^{14}C-urate transport inhibition. Two dimethoxy compounds (**14** and **19**) displayed weak inhibition, and 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 IC_{50} value changing from >50 to 2.8 μM. Halogenation of **13** to give **7** results in an inhibitor with very potent activity, a low nanomolar inhibitor (i.e., IC_{50} < 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 μM versus 3.9 μM). Comparing **30** and **32** (IC_{50} of 3.9 vs 1.1 μM) illustrates

Table 1. Summary of Compounds in Vitro Data[a]

compound	% inhibition at 50 μM	IC_{50}
probenecid (**5**)	35.7 ± 2.6	86.39 ± 0.07 μM
7	99.9 ± 0.1	26 ± 3 nM
8	99.8 ± 0.2	138 ± 88 nM
12	13.3 ± 5.7	ND
13	90.8 ± 0.9	2.80 ± 0.18 μM
14	24.3 ± 5.4	ND
15	6.1 ± 4.3	ND
16	5.2 ± 4.8	ND
17	6.2 ± 9.6	ND
18	1.5 ± 5.6	ND
19	17.2 ± 6.0	ND
20	7.4 ± 11.2	ND
21	92.7 ± 0.8	2.46 ± 0.90 μM
22	12.9 ± 8.0	ND
23	96.5 ± 0.5	2.49 ± 0.14 μM
24	88.2 ± 0.8	6.68 ± 0.09 μM
25	28.7 ± 5.4	ND
26	51.5 ± 4.0	ND
27	60.0 ± 2.5	33.65 ± 0.13 μM
28	9.3 ± 5.3	ND
29	41.0 ± 0.6	ND
30	92.7 ± 0.8	3.92 ± 0.17 μM
31	48.3 ± 3.9	ND
32	92.1 ± 0.9	1.13 ± 0.11 μM
33	62.4 ± 1.8	19.69 ± 0.20 μM
34	12.4 ± 4.7	ND
35	41.0 ± 5.5	ND
36	18.2 ± 7.3	ND
37	0.8 ± 8.7	ND
38	93.8 ± 0.7	3.94 ± 0.15 μM
39	99.9 ± 0.1	42 ± 9 nM
40	99.9 ± 0.1	189 ± 90 nM
41	99.6 ± 0.4	358 ± 130 nM
42	99.9 ± 0.1	83 ± 10 nM
43	99.0 ± 0.1	1.44 ± 0.14 μM
44	99.8 ± 0.2	287 ± 118 nM
45	99.9 ± 0.1	111 ± 14 nM
46	98.1 ± 0.2	1.65 ± 0.12 μM
47	99.9 ± 0.1	177 ± 80 nM
48	76.5 ± 1.2	23.46 ± 0.27 μM
49	99.8 ± 0.2	667 ± 88 nM
50	99.3 ± 0.3	772 ± 215 nM

[a] ND, no data.

that a methoxy on the B ring was less potent (higher IC_{50} value) than the corresponding diphenol analogue. The 6-methoxy regioisomers such as **18**, as compared to demethoxylated analogues **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 and Table 1), cleavage of **14** produced **21**−**23** using different reaction conditions, whereas **16** was used to produce **27**−**29**. Comparing the 3-yl series also illustrates the importance of the C ring phenol (IC_{50} **22** ≫ **21** = **23**) inhibitor activity.

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Deprotection of **15** was used to produce **24**−**26** (Figure 6), whereas compound **20** was used to produced **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 analogues, 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 C ring 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 analogues) 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 analogues) 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 μM vs 287 nM) shows an example where the B ring −OH takes an important role to enhance inhibitor activity. Therefore, functional group biotransformations (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**, and **39**−**50**) with low IC_{50} values (<1.0 μM) 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 analogues 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 analogues are known to undergo phase I metabolism to afford mono- and diphenolic analogues, a biotransformation that may lead to altered inhibitory activity. These results provide our initial groundwork 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 reabsorption and secretion pathways (i.e., URATv1, hOATs, 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, concentrated 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, NBS, bromine (Br_2), ammonium chloride (NH_4Cl), sodium ethanethiolate (NaSEt), and formic acid were purchased from Sigma-Aldrich Chemical Co. (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 (H_2O) were purchased from Fisher Scientific (Pittsburgh, PA). The NMR solvents $CDCl_3$, DMSO-d_6, and D_2O 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 ^{13}C 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 a Leap autosampler (LEAP Technologies, Carrboro, NC) was used. Liquid chromatography employed an Agilent Technologies, Zorbax extended-C18 50 mm × 4.6 mm, 5 μm column at 40 °C with a flow rate of 0.4 mL/min. The mobile phase consisted of A, 10 mM (NH_4OAc) and 0.1% formic acid in H_2O, and B, 50:50 ACN:MeOH. The chromatography method used was 95% A for 1.0 min, ramped to 95% B at 3.0 min, and held for 4.5 min, and 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 electrospray 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) quadruple one (Q1) and (Q3) were set on Unit resolution; (vii) dwell time was set at 200 ms; 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). K_2CO_3 (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 were 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 SiO_2 chromatography (2:1, Hex:EtOAc) to afford a light yellow solid (12.3 g, 59.9 mmol, 91% yield). ^1H NMR (400 MHz) $CDCl_3$: 7.72−7.70 (d, 1H), 7.59−7.57 (d, 1H), 7.51−7.45 (m, 2H), 7.33−7.29 (t, 1H), 2.61 (s, 3H). ^{13}C NMR (100 MHz) $CDCl_3$: 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). Yield, 85%. ^1H NMR (400 MHz) $CDCl_3$: 7.47−7.43 (m, 2H), 7.10−7.08 (m, 2H), 3.85 (s, 3H), 2.59 (s, 3H). ^{13}C NMR (100 MHz) $CDCl_3$: 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). Yield, 83%. ^1H NMR (400 MHz) $CDCl_3$: 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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). Yield, 91%. ^1H NMR (400 MHz) $CDCl_3$: 7.48 (s, 1H), 7.28−7.20 (m, 2H), 6.95−6.94 (d, 1H), 4.02 (s, 3H), 2.63 (s, 3H). ^{13}C NMR (100 MHz) $CDCl_3$: 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% aqueous 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 $MgSO_4$, filtered, concentrated under reduced pressure, and purified via SiO_2 chromatography (4:1, Hex:EtOAc) to afford a light yellow oil (6.05 g, 41.3 mmol, 55% yield). ^{1}H NMR (400 MHz) $CDCl_3$: 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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 analogues were prepared

2-Ethyl-5-methoxybenzofuran (11B). Yield, 68%. ^{1}H NMR (400 MHz) $CDCl_3$: 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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). Yield, 90%. ^{1}H NMR (400 MHz) $CDCl_3$: 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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). Yield, 91%. ^{1}H NMR (400 MHz) $CDCl_3$: 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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 CS_2 (50 mL). The reaction vessel was capped with a sure-seal, and a N_2 balloon was 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 was extracted with EtOAc (4 × 100 mL). The organic phase was washed with dilute HCl (0.5 N, 30 mL), followed by H_2O (30 mL), 1.0 M NaOH (30 mL), $NaHCO_3$(aq) (30 mL), and saturated NaCl(aq) (30 mL). The organic phase was dried ($MgSO_4$), filtered, concentrated under reduced pressure, and purified via SiO_2 chromatography (10:1:0.25, Hex:EtOAc:MeOH) to afford **12** as a light yellow solid (4.61 g, 16.4 mmol, 96% yield). ^{1}H NMR (400 MHz) $CDCl_3$: 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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 of NH_4Cl(aq)] and extracted with EtOAc (4 × 75 mL). The organic phase was washed with H_2O, followed by NaCl(aq). The organic phase was then dried ($MgSO_4$), filtered, concentrated under reduced pressure, and purified via SiO_2 chromatography (4:1, Hex:EtOAc) to give **13** as a white solid (857 mg, 3.22 mmol, 90% yield). ^{1}H NMR (400 MHz) $CDCl_3$: 10.4 (bs, 1H; exchangeable in D_2O), 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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, Br_2 (138 μL) was added. After 15 min, the mixture was quenched with H_2O (35 mL) and extracted with EtOAc (3 × 70 mL). The organic phase was washed NaCl(aq) (2 × 50 mL) and dried ($MgSO_4$), filtered, concentrated under reduced pressure, and purified via SiO_2 chromatography (3:1, Hex:EtOAc) to give **7** as a light red solid (176 mg, 0.469 mmol, 35% yield). ^{1}H NMR (400 MHz) DMSO-d_6: 10.2 (bs, 1H; exchangeable in D_2O), 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). ^{13}C NMR (100 MHz) DMSO-d_6: 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 → 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 (1.0 mL) was added. The reaction mixture was allowed to warm to room temperature 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 (four times, 10 mL each) and then brine. The organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude material was purified twice by column chromatography on SiO_2 (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**), and (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 CS_2 (100 mL). The reaction vessel was capped with a sure-seal, and a N_2 balloon was 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 room temperature (3 h), diluted with H_2O (40 mL), and extracted with EtOAc (4 × 150 mL). The organic phase was washed with dilute HCl (0.5 N, 75 mL), followed by H_2O (75 mL), 1.0 M NaOH(aq) (75 mL), $NaHCO_3$(aq) (75 mL), and NaCl(aq) (75 mL). The organic phase was dried ($MgSO_4$), filtered, concentrated under reduced pressure, and purified via SiO_2 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). Compound **14**: A light yellow oil (1.80 g, 5.80 mmol, 16.8% yield). ^{1}H NMR (400 MHz) $CDCl_3$: 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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 → 135.1 *m*/*z*; GS1 and GS2 at 25, DP = 46, CE = 29, CXP = 8, t_R = 4.64 min. Compound **15**: A light yellow oil (702 mg, 2.26 mmol, 7% yield). ^{1}H NMR (400 MHz) $CDCl_3$: 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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 → 203.1 *m*/*z*; GS1 and GS2 at 25, DP = 41, CE = 21, CXP = 12, t_R = 4.48 min. Compound **16**: A white solid (4.61 g, 14.9 mmol, 43% yield). ^{1}H NMR (400 MHz) $CDCl_3$: 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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 → 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.

*(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 CS_2 (100 mL), the vessel was capped with a sure-seal, and a N_2 balloon was 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 room temperature (3.0 h). The contents were diluted (H_2O, 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), $NaHCO_3$(aq) (75 mL), and saturated NaCl(aq) (75 mL). The organic phase was dried ($MgSO_4$), filtered, concentrated under reduced pressure, and purified via SiO_2 chromatography (10:1, Hex:EtOAc) to afford two products (**17**:**18**) in a 5.3:1.0 ratio. Compound **17**: A light yellow solid (7.92 g, 25.5 mmol, 72% yield). ^{1}H NMR (400 MHz) $CDCl_3$: 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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. Compound **18**: A light yellow solid (1.50 g, 4.80 mmol, 14% yield). ^{1}H NMR (400 MHz) $CDCl_3$: 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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 from 5.3:1.0 at 5 °C to 2.6:1.0 at room temperature.

*(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 CS_2 (35 mL). The RBF was capped with a sure-seal, and a N_2 balloon was attached. The vessel 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 h) and warmed to room temperature (3 h). The contents were diluted (H_2O, 40 mL) and extracted with EtOAc (4 × 100 mL). The organic phase was washed with HCl(aq) (0.5 N, 40 mL), followed by H_2O (40 mL), $NaHCO_3$(aq) (40 mL), and NaCl(aq) (40 mL). The organic phase was dried ($MgSO_4$), filtered, concentrated under reduced pressure, and purified via SiO_2 chromatography (10:1, Hex:EtOAc) to afford two products **19**:**20** 1.0:9.7 ratio. Compound **19**: A light yellow oil (559 mg, 1.8 mmol, 8% yield). ^{1}H NMR (400 MHz) $CDCl_3$: 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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. Compound **20**: A light yellow solid (5.43 g, 17.5 mmol, 78% yield). ^{1}H NMR (400 MHz) $CDCl_3$: 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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 room temperature.

*(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 NH_4Cl(aq) and extracted with EtOAc (4 × 70 mL). The organic phase was washed with H_2O and NaCl(aq), dried ($MgSO_4$), filtered, concentrated under reduced pressure, and purified via SiO_2 chromatography (4:1, Hex:EtOAc) to afford **21** as a yellow solid (706 mg, 2.38 mmol, 73% yield). ^{1}H NMR (400 MHz) $CDCl_3$: 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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), $AlCl_3$ (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 (Na_2SO_4), filtered, concentrated under reduced pressure, and purified via SiO_2 chromatography (Hex:EtOAc, 4:1) to give **22** (0.148 g, 0.499 mmol, 77% yield) as a white solid. ^{1}H NMR (400 MHz) $CDCl_3$: 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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), $AlCl_3$ (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 H_2O/HCl and extracted (DCM, 3 × 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 **23** (10.3 mg, 0.046 mmol, 25% yield) as a yellow solid. ^{1}H 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). ^{13}C 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 of NH_4Cl(aq)] and extracted with EtOAc (4 × 75 mL). The organic phase was washed with H_2O and NaCl(aq), dried ($MgSO_4$), filtered, concentrated under reduced pressure, and purified by SiO_2 chromatography (4:1, Hex:EtOAc) to afford **24** as a light yellow solid (631 mg, 2.13 mmol, 94% yield). ^{1}H NMR (400 MHz) DMSO-d_6: 10.4 (bs, 1H; exchangeable in D_2O), 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). ^{13}C 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 NH_4Cl(aq) (2 vol) and extracted with EtOAc (3 × 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) **24** (111.5 mg, 60% yield) as a light yellow solid and (ii) **25** (4.8 mg, 0.0161 mmol, 2.5% yield) as a yellow solid. ^{1}H NMR (400 MHz) $CDCl_3$: 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 → 189.0 *m/z*; GS1 and GS2 at 25, CAD = 5, DP = 71, CE = 29, CXP = 12, t_R = 4.80 min. (iii) Compound **26** (8.5 mg, 0.0301 mmol, 5% yield) as a yellow foam. ^{1}H 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 → 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 of NH_4Cl(aq)] and extracted with EtOAc (4 × 125 mL). The organic phase was washed with H_2O and 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). ^{1}H 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 → 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 ± 5 °C, 1.0 h) and then quenched with NH_4Cl(aq) (2 vol), and extracted with EtOAc (3 × 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. ^{1}H NMR (400 MHz) $CDCl_3$: 11.9 (s, 1H), 7.74−7.72 (d, 2H), 7.63 (s, 1H), 7.07 (s, 1H), 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 → 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 ± 5 °C, 16 h). Next, the reaction mixture was quenched with NH_4Cl(aq) and extracted with EtOAc (3 × 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. ^{1}H 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 → 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 of saturated NH_4Cl(aq)] and extracted with EtOAc (4 × 150 mL). The organic phase was washed with H_2O, followed by NaCl(aq) and then dried ($MgSO_4$). The material was filtered, concentrated under reduced pressure, and purified via SiO_2 chromatography (4:1, Hex:EtOAc) to afford **30** as a yellow solid (1.54 g, 5.20 mmol, 81% yield). ^{1}H NMR (400 MHz) $CDCl_3$: 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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 $AlCl_3$ (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). Afterward, the reaction was quenched (1.0 N HCl, 5 mL) and extracted (DCM). The organic phase was washed with NaCl(aq), dried (Na_2SO_4), filtered, concentrated under reduced pressure, and then purified via SiO_2 chromatography (Hex:EtOAc, 4:1) to give (i) **31** (107.8 mg, 0.364 mmol, 56% yield) as a yellow foam. ^{1}H NMR (400 MHz) DMSO-d_6: 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). ^{13}C NMR (100 MHz) DMSO-d_6: 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. (ii) Compound **32** (14.7 mg, 0.052 mmol, 8% yield) as a light yellow solid. ^{1}H NMR (400 MHz) DMSO-d_6: 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). ^{13}C NMR (100 MHz) DMSO-d_6: 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). Afterward, the reaction was quenched [2 vol of NH_4Cl(aq)] and extracted with EtOAc (4 × 70 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 (4:1, Hex:EtOAc) to afford **33** as a yellow solid (308 mg, 1.04 mmol, 46% yield). ^{1}H NMR (400 MHz) DMSO-d_6: 10.4 (bs, 1H; exchangeable in D_2O), 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). ^{13}C NMR (100 MHz) DMSO-d_6: 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. ^{1}H NMR (400 MHz) $CDCl_3$: 7.79−7.77 (d, 2H), 7.28−7.26 (d, 1H), 7.21 (bs, 1H; exchangeable in D_2O), 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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 NH_4Cl(aq) and extracted with EtOAc (3 ×

40 mL). The organic phase was washed with NaCl(aq) (2 vol), dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified via SiO_2 chromatography (Hex:EtOAc, 4:1) to give (i) **33** (98.0 mg, 0.330 mmol, 51% yield) as a white solid and (ii) **34** (21.7 mg, 0.0732 mmol, 11% yield) as a yellow solid. ^{1}H NMR (400 MHz) $CDCl_3$: 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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. (iii) Compound **35** (5.7 mg, 0.020 mmol, 3% yield) as a yellow solid. ^{1}H NMR (400 MHz) $CDCl_3$: 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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 NH_4Cl(aq) (2 vol) and extracted with EtOAc (3 × 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 **36** (22 mg, 0.074 mmol, 23% yield) as a light yellow solid. ^{1}H NMR (400 MHz) $CDCl_3$: 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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 of NH_4Cl(aq) and extracted with EtOAc (3 × 50 mL). The organic phase was washed with NaCl(aq) (40 mL) and dried ($MgSO_4$), filtered, concentrated under reduced pressure, and purified via SiO_2 chromatography (3:1, Hex:EtOAc) to give **37** as an off-white solid (451 mg, 1.52 mmol, 86% yield). ^{1}H NMR (400 MHz) DMSO-d_6: 10.9 (s, 1H; exchangeable in D_2O), 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). ^{13}C 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 of NH_4Cl(aq) and extracted with EtOAc (4 × 100 mL). The organic phase was dried ($MgSO_4$), filtered, concentrated under reduced pressure, and purified via SiO_2 chromatography (2:1, Hex:EtOAc) to give **38** as an off-white solid (1.17 g, 4.14 mmol, 93% yield). ^{1}H NMR (400 MHz) DMSO-d_6: 10.9 (bs, 1H; exchangeable in D_2O), 10.3 (bs, 1H; exchangeable in D_2O), 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). ^{13}C 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 room temperature and stirred (17 h). The mixture was quenched with H_2O (10 mL) and diluted with DCM (20 mL), and the organic phase was washed four times with H_2O and NaCl(aq) and then dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified via SiO_2 chromatography (Hex:EtOAc, 4:1) to give **39** (0.050 g, 0.110 mmol, 22% yield) as a light orange solid. ^{1}H NMR (400 MHz) $CDCl_3$: 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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**).* $AlCl_3$ (0.041 g, 0.310 mmol) was added 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 (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography on SiO_2 (hexanes:EtOAc, 4:1) to give **40** as a white solid (11.0 mg, 0.025 mmol, 38% yield). ^{1}H NMR (400 MHz) $CDCl_3$: 9.26 (s, 1H; exchangeable D_2O), 7.88 (s, 2H), 7.42−7.40 (d, 1H), 6.74−6.73 (bd, 2H; 1 exchangeable in D_2O), 2.78−2.72 (q, 2H), 1.25−1.21 (t, 3H). ^{13}C NMR (100 MHz) $CDCl_3$: 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 room temperature (17 h). The reaction mixture was quenched with H_2O and washed with NaCl(aq). 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 **41** (0.110 g, 0.242 mmol, 51% yield) as a white solid. ^{1}H NMR (400 MHz) $CDCl_3$: 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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**).* $AlCl_3$ (0.065 g, 0.486 mmol) was added 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 (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography on SiO_2 (Hex:EtOAc, 4:1) to give **42** as a yellow solid (15.2 mg, 0.0345 mmol, 33% yield). ^{1}H NMR (400 MHz) $CDCl_3$: 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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 room temperature (17 h). The mixture was diluted with H_2O and diluted with DCM (20 mL), and the organic phase was washed four times with H_2O and then NaCl(aq). 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 **43** (145 mg, 0.319 mmol, 63% yield) as a white solid. ^{1}H NMR (400 MHz) $CDCl_3$: 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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**).* $AlCl_3$ (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 H_2O/1.0 N HCl (1 vol) and extracted with DCM (3 × 30 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 **44** (53.9 mg, 0.122 mmol, 65% yield) as a yellow solid. ^{1}H 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). ^{13}C 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 room temperature (20 h) and then quenched with water (5 mL) and diluted with additional DCM (10 mL). The material was washed with H_2O (10 mL) and then with NaCl(aq) (10 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 **45** (0.148 g, 0.326 mmol, 64% yield) as a light yellow solid. ^{1}H 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). ^{13}C 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-hydroxy-benzofuran-3-yl)methanone.* In a RBF/SB cooled with an ice/NaCl bath, ethanethiol (HSEt, 1.29 mL) was added followed by $AlCl_3$ (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). Afterward, 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 (Na_2SO_4), filtered, concentrated under reduced pressure, and purified via SiO_2 chromatography (Hex:EtOAc, 4:1) to give **8** (226 mg, 0.514 mmol, 78% yield) as a light brown foam. ^{1}H 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). ^{13}C 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 to room temperature (17 h). The mixture was quenched with H_2O (1 vol) and diluted with DCM (30 mL). The organic phase was washed four times with H_2O and then NaCl(aq). 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 **46** (0.146 g, 0.274 mmol, 54% yield) as an off-white solid. ^{1}H NMR (400 MHz) DMSO-d_6: 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). ^{13}C NMR (100 MHz) DMSO-d_6: 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 was 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 room temperature (17 h). The reaction mixture was quenched with H_2O and diluted with DCM (30 mL). The organic phase was washed four times with H_2O and NaCl(aq) and then dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified twice via SiO_2 chromatography (Hex:EtOAc, 4:1) to give **47** (125 mg, 0.241 mmol, 45% yield) as a white solid. ^{1}H NMR (400 MHz) $CDCl_3$: 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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.

*(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 was 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 room temperature (18 h). The reaction mixture was quenched with H_2O and diluted with DCM (30 mL). The organic phase was washed four times with H_2O and NaCl(aq) and then dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified twice via SiO_2 chromatography (Hex:EtOAc, 4:1) to give **48** (7.9 mg, 0.0174 mmol, 17% yield) as an orange oil. ^{1}H NMR (400 MHz) $CDCl_3$: 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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. 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.

*(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 room temperature (17 h). Next, the mixture was quenched with water and diluted with DCM (30 mL). The organic phase was washed four times with H_2O and NaCl(aq) and then dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified via SiO_2 chromatography (Hex:EtOAc, 4:1) to give **49** (27.0 mg, 0.0594 mmol, 35% yield) as a yellow oil. ^{1}H NMR (400 MHz) $CDCl_3$: 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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 μL) followed by Br_2 (74 μL) were added. The mixture was stirred (5 min) and quenched with H_2O (5 mL), and the mixture was extracted with EtOAc

(3 × 50 mL). The organic phase was dried ($MgSO_4$), filtered, concentrated under reduced pressure, and purified via SiO_2 chromatography (3:1, Hex:EtOAc) to afford **50** as a light red solid (176 mg, 0.469 mmol, 69% yield). ^{1}H NMR (400 MHz) $CDCl_3$: 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). ^{13}C NMR (100 MHz) $CDCl_3$: 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 → 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. [^{14}C]Urate (55 mCi/mmol) was purchased from Moravek (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.

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). The polyadenylation of cRNA at the 3′-end was performed using poly(A) tailing kit (Ambion). Female *Xenopus* frogs (African clawed frogs, 95−120 g) were purchased from Sato Zoushoku (Chiba, Japan) and nurtured in tap water (19 ± 3 °C). Oocytes (1.23 ± 0.10 mg/oocyte) isolated from *Xenopus laevis* were defolliculated with 1.0 mg/mL collagenase in Ca^{2+}-free solution (96.0 mM NaCl, 2.0 mM KCl, 1.0 mM $MgCl_2 \cdot 6H_2O$, and 5.0 mM HEPES, pH 7.5) at 25 ± 2 °C for 2.0 h. The oocytes were washed in Ca^{2+}-free solution and transferred to ND96 buffer (96.0 mM NaCl, 2.0 mM KCl, 1.0 mM $CaCl_2$, 1.0 mM $MgCl_2 \cdot 6H_2O$, 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 °C for 2−3 days in ND96 solution containing gentamicin (50 μg/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 [^{14}C]urate (10 μM) with or without test compound. The uptake was terminated by washing the oocytes with ice-cold uptake solution (five times at 1.0 mL each) after 60 min of incubation. The oocytes were solubilized with 5% (w/v) SDS, and the radioactivity content was determined using liquid scintillation counter (Aloka 3100; Aloka Co., Ltd. Tokyo, Japan). The urate uptake by noninjected (control) oocytes was subtracted from oocytes expressing hURAT1. The data are presented (Table 1) and reported as the % of inhibition. The IC_{50} data were conducted using different compound concentrations (i.e., 5, 10, 50, 100, and 500 nM and 5, 10, and 50 μM). All screening data are expressed as means ± SEMs (n = 5−7), and the IC_{50} values are means ± SDs (n = 5−7).

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ABBREVIATIONS USED

hURAT1; SLC22A12, human uric acid transporter 1; GLUT9, URATv1; SLC2A9, glucose transporter 9, voltage-dependent uric acid transporter 1; NPT4; SLC17A3, natrium-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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