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Synthesis and Characterization of 1,4-Benzodioxane-6-Carboxylic Acid Amide Analogs

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Abstract

A library of new 1,4-benzodioxane-6-carboxylic acid amide analogs was designed and synthesized. These analogs were obtained in six steps from gallic acid. Firstly, esterification of the commercially available gallic acid in methanol in the presence of sulfuric acid afforded methyl 3,4,5-trihydroxybenzoate (**9**) in satisfactory yield. The ester **9** was then reacted with an excess of 1,2-dibromoethane in the presence of K_2CO_3 in acetone to furnish the 6,8-disubstituted-1,4-benzodioxane (**10**) in 45% yield. The reaction of **10** with various mercaptans gave the sulfide derivative **11**, **12**, and **13** in moderate yield. Subsequent hydrolysis of the methyl ester in **13** followed by conversion to the acid chloride and reaction of the acid chloride intermediate with different commercially available primary and secondary amines gave the amide analogs **18** - **32** with an average yield of 43%. Conversion of the sulfide group in Compound **23** to Sulfoxide **33** or Sulfone **34** was accomplished by reaction with either 30% H_2O_2/TeO_2 or 30% H_2O_2, respectively. The structures of the synthesized compounds were characterized using FTIR, ^{1}H-NMR, ^{13}C-NMR, and high-resolution ESI-MS.

Keywords

Gallic Acid, 1,4-Benzodioxane Derivatives, Prostate Cancer, Anticancer Drugs

1. Introduction

The 1,4-benzodioxane is an important scaffold in some biologically useful natural products including some lignin and neolignan natural products such as Silybin (**1**) and Purpurenol (**2**) (Figure 1). Hence, the 1,4-bezodioxane has not only

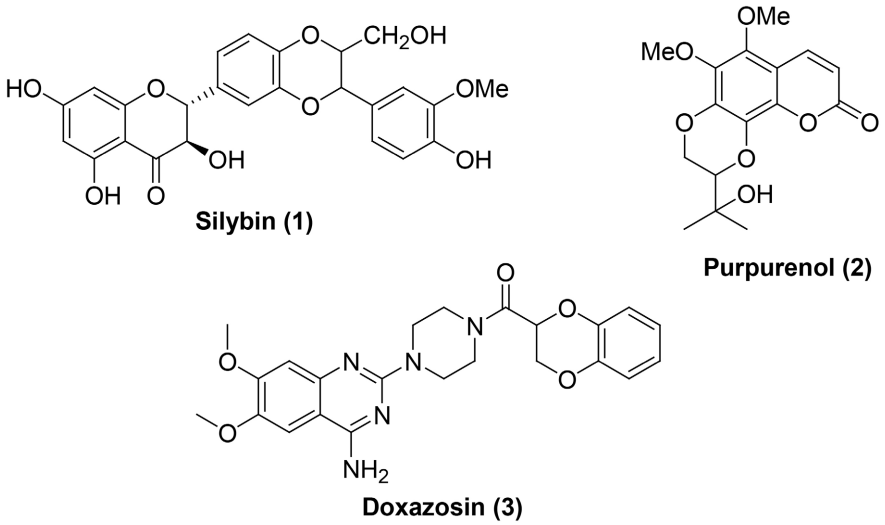


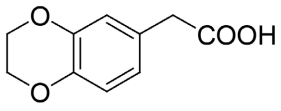
Figure 1. Chemical structure of Silybin (**1**), Purpurenol (**2**) and Doxazosin (**3**).

received attention for its synthesis, but more importantly, it has received significant attention in medicinal and pharmaceutical research. Some 1,4-benzodioxanes have demonstrated hepatoprotective, antioxidant, cytotoxic, and antimicrobial activities in addition to properties that suggest therapeutic applications in areas such as antidepressant, antihyperglycemic, and potential for the treatment of other diseases [1]-[7].

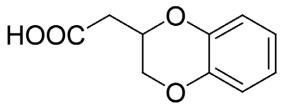
The 1,4-benzodioxane moiety is a significant part of doxazosin (**3**, marketed as CARDURA in the United States, **Figure 1**), a drug used in the treatment of hypertension and benign prostatic hyperplasia (BPH) [6] [7].

Various 1,4-benzodioxane derivatives have been shown to display notable anti-inflammatory and anticancer activities [3] [8]-[13]. For example, Vazquez, et al demonstrated that 2,3-dihydro-1,4-benzodioxin analog bearing an acetic acid substituent displayed anti-inflammatory activity. A study of the structure-activity relationships demonstrated that the relative position of the acetic acid group for optimum anti-inflammatory activities was at position-6 (**4**, **Figure 2**). The regioisomer with the acetic acid substituent at position-2 (Compound **5**, **Figure 2**), showed mediocre anti-inflammatory activity [3] [4].

Of particular interest is the discovery of the 1,4-benzodioxane bisamide chemical probe, CCT251236 (**6**, **Figure 3**), which was reported as an HSF1 pathway inhibitor that showed growth inhibitory activities in the human ovarian carcinoma xenograft model [12]. The 1,4-benzodioxane moiety was found to be critical to the growth inhibitory activities of this compound and attempts to replace this moiety resulted in compounds with reduced or loss of growth inhibitory activity. Another benzodioxane derivative (**7**, **Figure 3**) was recently reported as a potent inhibitor of the physiologically important p38α MAPK pathway [13]. The p38α MAPK pathway is important in a number of physiological processes including cancer and chronic graft-versus-host disease which can present a risk factor in various types of transplants including transplants for certain cancer patients. Both

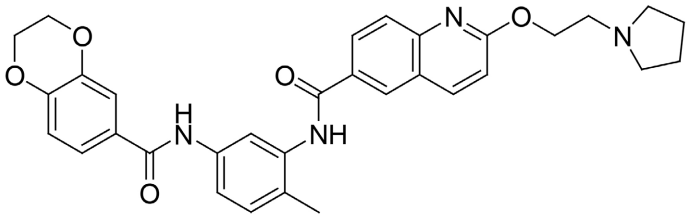


(2,3-dihydrobenzo [1,4]dioxin-6-yl)acetic acid (4)



(2,3-dihydrobenzo [1,4]dioxin-2-yl)acetic acid (5)

Figure 2. Chemical structure of (2,3-dihydrobenzo [1,4] dioxin-6-yl) acetic acid (**4**) and (2,3-dihydrobenzo [1,4] dioxin-2yl) acetic acid (**5**).



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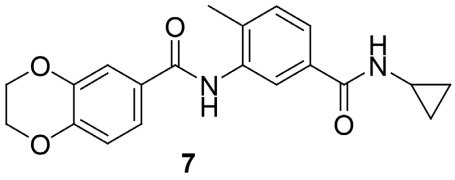

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Figure 3. Chemical structure of 1,4-benzodioxane bisamides[12,13] (**6**) and (**7**).

benzodioxane derivatives, CCT251236 (**6**) and Compound **7**, possess a benzamide moiety at position-6 of the 1,4-benzodioxane template.

In our continuous efforts to develop novel small organic molecules for studies on Metastatic Castration-Resistant Prostate Cancer (MCRPC), we designed some 1,4-benzodioxane derivatives with a benzamide moiety at position-6. This paper presents the synthesis and characterization of new 1,4-benzodioxane-6-carboxylic acid amide analogs from gallic acid as a readily available starting material as shown in **Figure 4**.

2. Results and Discussion

In our synthesis of the new 1,4-benzodioxane-6-carboxylic acid amide analogs, we found gallic acid to be an attractive, inexpensive, and readily available starting material that is perfectly suited with a carboxylic acid group to create the 6-substituted 1,4-benzodioxane with the potential to further functionalize position-8 of the benzodioxane scaffold for wider SAR studies. Consequently, the 1,4-benzodioxane derivatives were synthesized in six steps by chemical transformation of gallic acid as outlined in **Figures 5-8**.

Firstly, the Fischer esterification of the commercially available gallic acid in methanol with sulfuric acid readily afforded methyl 3,4,5-trihydroxybenzoate (**9**) in good yield [14]. The subsequent reaction of ester **9** with 1,2-dibromoethane in the presence of K_2CO_3 in acetone gave the 1,4-benzodioxane ring yielding methyl 8-(2-bromoethoxy)-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxylate (**10**). The formation of Compound **10** was confirmed by the study of its ^{1}H- and ^{13}C-NMR spectra. Furthermore, the molecular ion region of the mass spectrum (EI) confirmed the presence of the M^+ and M + 2 peaks in about 1:1 ratio typical for compounds containing one bromine atom. To incorporate diversity at position-8

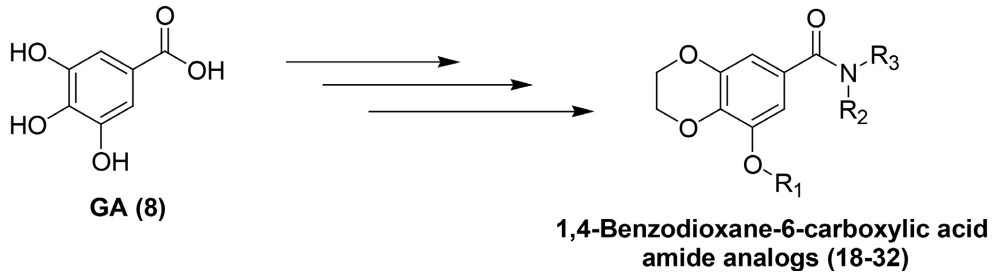
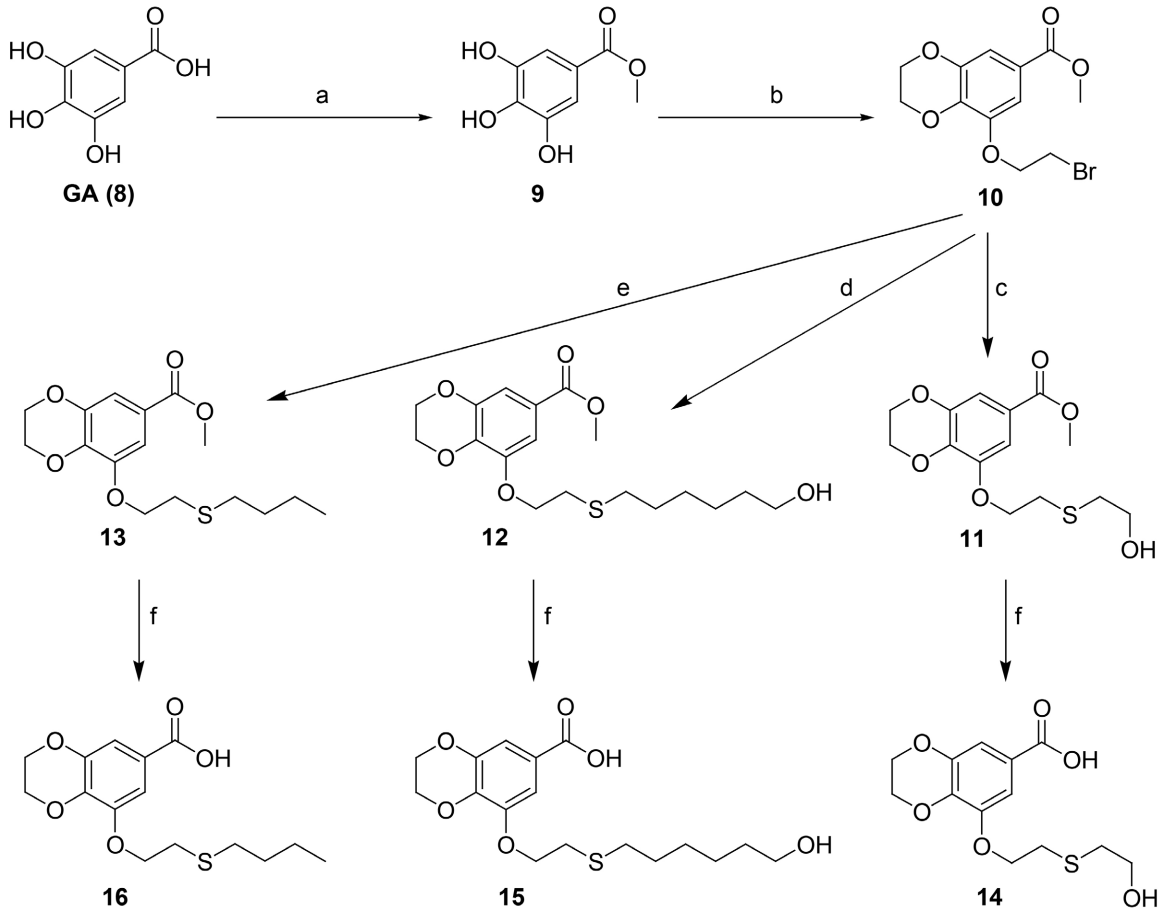


Figure 4. Chemical transformation of gallic acid to 1,4-benzodioxane moiety.



Reagents and conditions: (a) CH_3OH/H_2SO_4, reflux, 90%; (b) 1,2-Dibromoethane, K_2CO_3, acetone, reflux, 47%; (c) 2-mercaptoethanol, K_2CO_3, DMF, reflux, 53%; (d) 6-mercaptohexanol , K_2CO_3, DMF, reflux, 37%; (e) Butanethiol, K_2CO_3, DMF, reflux, 49%, (f) 1. NaOH (2N), MeOH, reflux 2. HCl, 64-83%.

Figure 5. Schematic diagram for stepwise conversion of gallic acid to 8-alkoxy-1,4-benzodioxane-6-carboxylic acids.

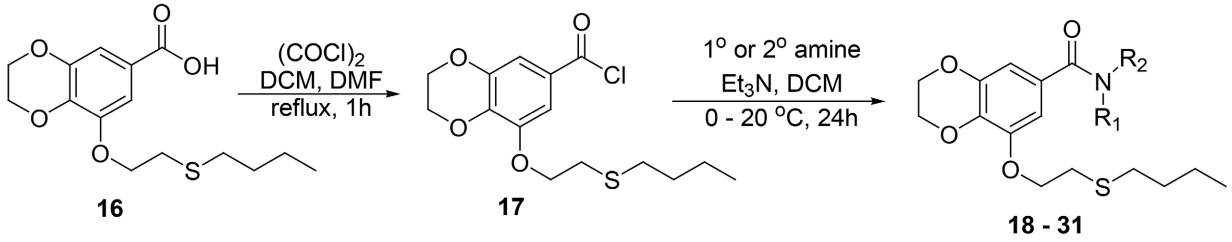


Figure 6. Conversion of carboxylic acid analog **16** to 1,4-benzodioxane-6-carboxylic acid amide derivatives (**18** - **31**).

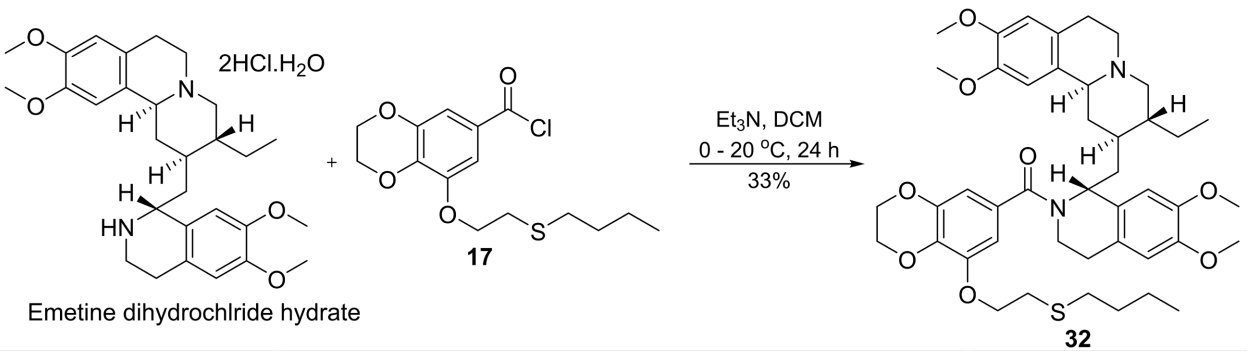


Figure 7. Reaction of emetine dihydrochloride with 1,4-benzodioxane-6-carbonyl chloride **17** to form an emetine-benzodioxane conjugate **32.**

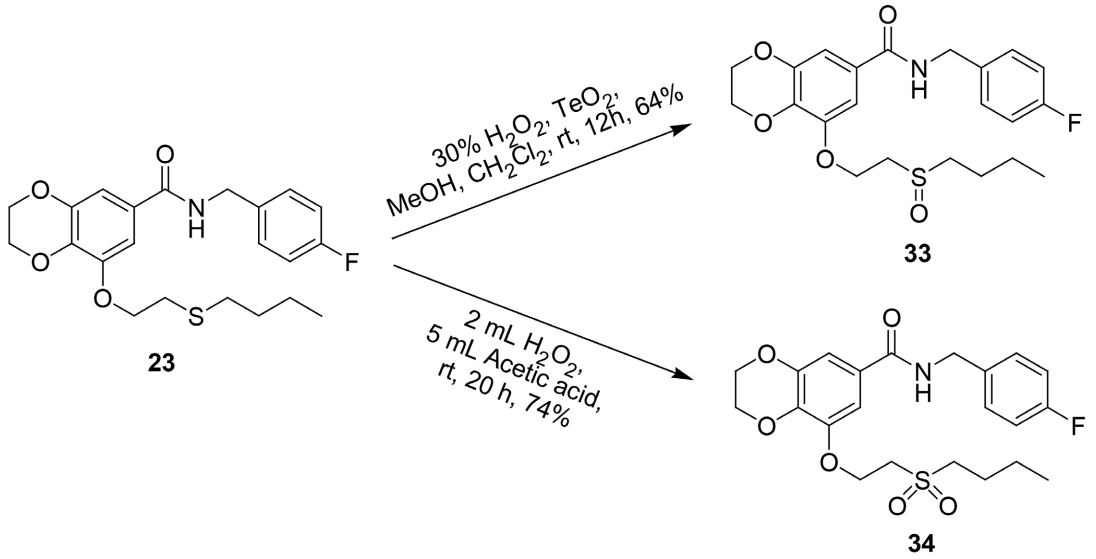
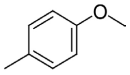
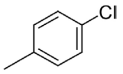
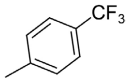
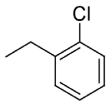
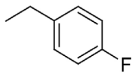
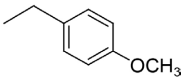
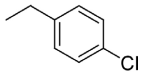
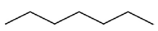
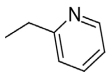
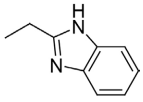
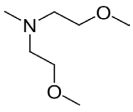


Figure 8. Oxidation of sulfide moiety in Compound **23** to form Sulfoxide **33** and Sulfone **34**.

for SAR studies, we elected to incorporate a sulfur-containing group in position-8 based on other work in our group as well as the biological importance of sulfur-containing compounds [15] [16] [17]. Hence, benzodioxane derivative **10** was subsequently reacted with selected mercaptans to afford the three thia-analogs **11**, **12** and **13**. To accomplish our goal to synthesize a small library of the 1,4-benzodioxane-6-carboxylic acid amide analogs for initial bioassay screening, one of these, Compound **13**, was reacted further as outlined in **Figures 5-7**. Incorporation of benzamide group at position-6 of Compound **13** was achieved by initial base-induced hydrolysis of the ester group in **13** to furnish the carboxylic acid **16** (**Figure 5**) followed by the conversion of **16** to the acid chloride **17** using oxalyl chloride, and the reaction of acid chloride **17** with various primary and secondary amines to obtain the 1,4-benzodioxane-6-carboxylic acid amide analogs **18** to **32** (as shown in **Figure 6** and in **Table 1**) including the emetine derivative **32** (**Figure 7**). The relatively low yield of Compound **28** is attributed to the loss of substantial amount of this compound during several trituration steps because of difficulties in purification.

Table 1. Set of R (aliphatic and aromatic) groups in 6-substituted 1,4-benzodioxane analogs (**18** - **31**).

Compound	R_1	R_2
18	H	
19	H	
20	H	
21	H	
22	H	
23	H	
24	H	
25	H	
26	H	
27	H	
28	H	
29		
30		
31		

Upon purification by trituration or column chromatography on silica gel, the pure products were characterized by FTIR, ^{1}H-NMR, and ^{13}C NMR spectroscopy as well as by high-resolution ESI-MS. Fourier transform infrared spectra of 1,4-benzodioxane analogs (**18** to **32**) is characterized by the presence of the amide C=O stretching vibration between 1626 and 1676 cm^{-1}, and the N-H stretching between 3275 - 3346 cm^{-1} for Compounds **18** to **28**. The ^{1}H-NMR spectra of the 1,4-benzodioxane-6-carboxylic acid amide analogs **18** to **32** displayed the proton chemical shift values of the two methylene groups sandwiched between the oxygen atoms in the 1,4-benzodioxane ring as multiplets between 4.25 and 4.30 ppm (for two protons each) consistent with literature values [9],

while the protons of the methylene protons adjacent to the ether oxygen at position-8 appeared as a triplet at about 4.2 ppm. The methylene groups adjacent to the sulfur atom appeared as triplets at about 2.6 and 2.9 ppm [17]. In the C-13 NMR spectra of Compounds **18** to **32**, the amide carbonyl carbon appeared at 164 ppm, while the sp^3 carbons at positions 2 and 3 of the 1,4-benzodioxane ring could be seen at 64 ppm. On the other hand, the sp^3 carbon atom adjacent to the ether oxygen at position-8 occurred at 69 ppm. All of Compounds **18** to **32** were studied by high-resolution ESI-MS to obtain exact masses consistent with each compound.

In order to study the effect of the oxidation state of the sulfur atom on the biological activities of one of these 1,4-benzodioxane analogs, Compound **23** was further converted to the Sulfoxide **33** and Sulfone **34** derivatives. The reaction of Compound **23** with excess 30% H_2O_2 afforded the Sulfone **34** in 74% yield, while the reaction of **23** with 30% H_2O_2 in the presence of TeO_2 furnished the Sulfoxide **33** in 64% yield without over oxidation to the sulfone (**Figure 8**) [18]. The spectra data of Compounds **33** and **34** including the high-resolution ESI-MS studies were consistent with the formation of sulfoxide and sulfone, respectively.

3. Conclusion

In this paper, we designed and synthesized a library of 1,4-benzodioxane-6-carboxylic acid amide analogs via a six-step reaction sequence. All the synthesized compounds were characterized by infrared spectroscopy, nuclear magnetic resonance spectroscopy, and high-resolution electrospray ionization mass spectrometry to confirm the structure of the compounds.

4. Experimental Section

General. Infrared (IR) spectra were obtained on a Perkin Elmer PE 100 spectrometer with an Attenuated Total Reflectance (ATR) window. ^{1}H- and ^{13}C-NMRs were performed on the Bruker Avance 400 MHz spectrometer. All compounds were analyzed in deuterated chloroform ($CDCl_3$), deuterated dimethyl sulfoxide (DMSO-d6) or deuterated methanol (MeOD-d4). The chemical shifts are in δ units (ppm) from TMS (0.00 ppm), $CDCl_3$ (7.26 ppm), $(CD_3)_2SO$ (2.52 ppm) or CD_3OD (3.31) as the internal standard for ^{1}H-NMR; and $CDCl_3$ (77.00 ppm), $(CD_3)_2SO$ (39.50 ppm) or CD_3OD (49.00) for ^{13}C-NMR. The apparent resonance multiplicity is described as s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet) and m (multiplet). High-resolution electrospray ionization mass spectrometry was recorded on Agilent Technologies 6224 TOF LCMS. The mass spectra showed signals corresponding to M + H, 2M + H, M + Na and 2M + Na. Additionally, the chlorinated and brominated derivatives showed corresponding M + 2 + H peaks. Thin layer chromatography (TLC) analysis was carried out on 5 × 20 cm plate coated with silica gel GF254 type 60 (25 - 250 mesh).

Methyl 3,4,5-trihydroxybenzoate (9)

To a stirred solution of gallic acid (508 mg, 2.99 mmol) in MeOH (20 mL), conc. H_2SO_4 (0.18 mL, 3.4 mmol) was added. The reaction mixture was refluxed for 2 h, and then evaporated. The residue was taken up in water and extracted with ethyl acetate three times. The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford the methyl gallate as a white solid (495 mg, 90%). Mp 202˚C - 204˚C. IR (cm^{-1}): 3460, 3301, 3085, 3017, 2954, 1691, 1615, 1540, 1470, 1456, 1436, 1383, 1308, 1247, 1193, 1097, 1034, 1002, 917, 892, 866, 806, 765, 746, 733. ^1H NMR (400 MHz, MeOD) δ 3.80 (3H, s), 4.88 (3H, s), 7.03 (2H, s). ^{13}C NMR (100 MHz, MeOD) δ 52.3 (1C), 110.0 (2C), 121.4 (1C), 139.7 (1C), 146.5 (2C), 169.0 (1C). MS (EI, M^+) m/z 184.1 (100%)

Methyl 8-(2-bromoethoxy)-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxylate (10)

To a stirred solution of methyl gallate (1.0532 g, 5.72 mmol) and potassium carbonate K_2CO_3 (3.7977 g, 27.48 mmol) in acetone (45 mL), 1,2-dibromoethane (2.40 mL, 27.85 mmol) in 5 mL acetone was added drop wise at RT. The reaction mixture was reflux for 18 hrs. The resulting mixture was cooled, filtered and the filtrate was evaporated. The residue was taken up in 25 mL CH_2Cl_2, washed with water (2 × 25 mL) and an aqueous NaOH (2N) solution (2 × 25 mL), and then water (2 × 25 mL) and brine (25 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to obtain a white solid (0.85 g, 47%). Mp 105˚C - 107˚C. IR (cm^{-1}): 2996, 2948, 2882, 1698, 1592, 1506, 1433, 1389, 1375, 1348, 1323, 1271, 1246, 1201, 1185, 1171, 1126, 1071, 1053, 1036, 1002, 977, 935, 903, 883, 872, 832, 786, 765, 726, 696. ^1H NMR (400 MHz, $CDCl_3$) δ 3.61 (2H, t, J = 6.4 Hz), 3.80 (3H, s), 4.20 - 4.22 (2H, m), 4.28 - 4.32 (4H, m), 7.11 (1H, d, J = 1.2 Hz), 7.22 (1H, d, J = 1.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5 (1C), 52.1 (1C), 63.9 (1C), 64.7 (1C), 68.9 (1C), 107.4 (1C), 113.0 (1C), 122.1 (1C), 137.9 (1C), 143.8 (1C), 146.9 (1C), 166.4 (1C). ESI-TOF-MS m/z: **317.0018/319.0001**, ($[C_{12}H_{13}{}^{79/81}BrO_5 + H]^+$ calcd. 317.0025/319.0005); **338.9852/340.9813**, ($[C_{12}H_{13}{}^{79/81}BrO_5 + Na]^+$ calcd. 338.9838/340.9824).

Methyl 8-(2-((2-hydroxyethyl)thio)ethoxy)-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxylate (11)

To a stirred solution of bromo derivative (**10**) (313 mg, 0.99 mmol) in *N*,*N*-dimethylformamide (4.0 mL) was added 2-mercaptoethanol (0.1 mL, 1.3 mmol) and potassium carbonate (268 mg, 1.93 mmol). The reaction was heated at 60˚C for 24 h, and then cooled to room temperature. The reaction was diluted with ethyl acetate (20 mL), and washed with water (5 × 20 mL), brine (20 mL), dried over anhydrous magnesium sulfate, and concentrated under vacuum to give a white paste material. The crude product was purified by column chromatography over silica gel using gradient elution. Hexane was employed to elute nonpolar impurities followed by elution with 20% to 35% of EtOAc in hexane to obtain the desired product (164 mg, 53%). IR (cm^{-1}): 3444, 2930, 2870, 1712,

1591, 1505, 1433, 1317, 1242, 1204, 1040, 999, 885, 764. ^{1}HNMR (400 MHz, $CDCl_3$): δ 2.85 (2H, t, J = 5.6 Hz), 2.99 (2H, t, J = 6.8 Hz), 3.80 (2H, t, J = 5.6 Hz), 3.88 (3H, s), 4.25 (2H, t, J = 6.8 Hz), 4.26 - 4.28 (2H, m), 4.35 - 4.38 (2H, m), 7.19 (1H, d, J = 1.6 Hz), 7.28 (1H, d, J = 2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.3 (1C), 35.7 (1C), 52.1 (1C), 60.9 (1C), 63.9 (1C), 64.7 (1C), 68.9 (1C), 106.7 (1C), 112.7 (1C), 122.1 (1C), 137.7 (1C), 143.8 (1C), 147.4 (1C), 166.6 (1C). ESI-TOF-MS m/z: **337.0662**, ($[C_{14}H_{18}O_6S + Na]^+$ calcd. 337.0722).

Methyl 8-(2-(butylthio)ethoxy)-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxylate (13)

To a stirred solution of bromo derivative (**10**) (0.6512 g, 2.05 mmol) in *N*,*N*-dimethylformamide (5.0 mL) was added butanethiol (0.3 mL, 2.67 mmol) and potassium carbonate (0.4824 g, 3.49 mmol). The reaction was heated at 60˚C for 24 h, and then cooled to room temperature. The reaction was diluted with ethyl acetate (20 mL), and washed with water (5 × 20 mL), brine (20 mL), dried over anhydrous magnesium sulfate, and concentrated under vacuum to give oily residue. The crude product was purified by column chromatography over silica gel using gradient elution. Hexane was employed to elute nonpolar impurities followed by elution with 20% to 35% of EtOAc in hexane to obtain the desired product (355 mg, 53%). IR (cm^{-1}): 2922, 1712, 1592, 1506, 1431, 1388, 1373, 1342, 1314, 1203, 1130, 1065, 1049, 1022, 1002, 964, 881, 759, 730, 699. ^{1}H NMR (400 MHz, DMSO-d6): δ 0.88 (3H, t, J = 7.2 Hz), 1.32 - 1.41 (2H, m), 1.45 - 1.56 (2H, m), 2.63 (2H, t, J = 7.20 Hz), 2.85 (2H, t, J = 6.8 Hz), 3.8 (3H, s), 4.15 (2H, t, J = 6.4 Hz), 4.25 - 4.32 (4H, m), 7.09 (1H, d, J = 2 Hz), 7.10 (1H, d, J = 2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5 (1C), 21.3 (1C), 30.0 (1C), 31.2, (1C), 31.3 (1C), 52.0 (1C), 63.8 (1C), 64.2 (1C), 68.7 (1C), 106.2 (1C), 111.3 (1C), 121.1 (1C), 137.7 (1C), 143.6 (1C), 147.5 (1C), 165.7 (1C). ESI-TOF-MS m/z: **327.1262**, ($[C_{16}H_{22}O_5S + H]^+$ calcd. 327.1266).

8-(2-((2-hydroxyethyl)thio)ethoxy)-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxylic acid (14)

A solution of **11** (126.1 mg, 0.40 mmol) and NaOH (2N, 10 mL) in methanol (10 mL) was refluxed for 8 h. The reaction mixture was concentrated under vacuum and the resulting mixture acidified with conc. HCl to give a white precipitate which was filtered under suction, washed with water and allowed to dry in a vacuum oven to obtain a white solid (77.6 mg, 64%). Mp: 148˚C - 150˚C. IR (cm^{-1}): 3500 - 2400, 3414, 2959, 2883, 2621, 1682, 1591, 1507, 1434, 1393, 1352, 1315, 1263, 1211, 1160, 1123, 1101, 1040, 986, 963, 919, 883, 846, 820, 760, 731, 705, 689. ^{1}H NMR (400 MHz, DMSO-d6): δ 2.68 (2H, t, J = 6.8 Hz), 2.89 (2H, t, J = 6.4 Hz), 3.56 (2H, q, J = 5.6 and 12.4 Hz), 4.14 (2H, t, J = 6.8 Hz), 4.25 - 4.26 (2H, m), 4.28 - 4.30 (2H, m), 4.79 (1H, t, J = 5.2 Hz), 7.07 (1H, d, J = 1.6 Hz), 7.10 (1H, d, J = 1.6 Hz), 12.76 (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.6 (1C), 30.4 (1C), 61.0 (1C), 63.8 (1C), 64.2 (1C), 68.6 (1C), 106.5 (1C), 111.5 (1C), 122.3 (1C), 137.4 (1C), 143.5 (1C), 147.4 (1C), 166.8 (1C). ESI-TOF-MS m/z: **323.0564**, ($[C_{13}H_{16}O_6S + Na]^+$ calcd. 323.0565).

8-(2-((6-hydroxyhexyl)thio)ethoxy)-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxylic acid (15)

To a stirred solution of bromo derivative (**10**) (1.1596 g, 3.66 mmol) in *N*,*N*-dimethylformamide (4.0 mL) was added 6-mercaptohexanol (0.65 mL, 4.75 mmol) and potassium carbonate (859.1 mg, 6.22 mmol). The reaction was heated at 60˚C for 24 h, and then cooled to room temperature. The reaction was diluted with ethyl acetate (20 mL), and washed with water (5 × 20 mL), brine (20 mL), dried over anhydrous magnesium sulfate, and concentrated under vacuum to give a white paste material (**12**). Since purification was difficult at this step, the residual white paste (492.3 mg, 1.5661 mmol) and NaOH (2N, 15 mL) in methanol (15 mL) was refluxed for 8 h. The reaction mixture was concentrated under vacuum and the resulting mixture acidified with conc. HCl to give a white precipitate which was filtered under suction, washed with water and allowed to dry in a vacuum oven to obtain Compound **15** as a white solid (392.0 mg, 83% yield). Mp: 138˚C - 140˚C. IR (cm^{-1}): 3500 - 2400, 3435, 2930, 2855, 1680, 1590, 1507, 1463, 1432, 1383, 1364, 1347, 1310, 1260, 1243, 1204, 1120, 1042, 988, 966, 924, 887, 875, 766, 731, 701, 687. ^{1}H NMR (400 MHz, DMSO-d6): δ 1.26 - 1.64 (8H, m), 2.62 (2H, t, J = 7.2 Hz), 2.69 (1H, t, 7.2 Hz), 2.85 (2H, t, J = 6.4 Hz), 3.37 (2H, t, J = 6.4), 4.138 (2H, t, J = 6.4), 4.25 - 4.30 (4H, m), 7.07 (1H, J = 2Hz), 7.09 (1H, J = 1.6 Hz), 12.78 (1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.1 (1C), 28.2 (1C), 29.3 (1C), 30.0 (1C), 31.6 (1C), 32.5 (1C), 60.6 (1C), 63.8 (1C), 64.2 (1C), 68.6 (1C), 106.4 (1C), 111.5 (1C), 122.3 (1C), 137.4 (1C), 143.4 (1C), 147.3 (1C), 166.8 (1C). ESI-TOF-MS m/z: **379.1191**, ($[C_{17}H_{24}O_6S + Na]^+$ calcd. 379.1191).

8-(2-butylsulfanyl-ethoxy)-2,3-dihydro-benzo[1,4]dioxine-6-carboxylic acid (16)

A solution of **13** (321.5 mg, 0.9850 mmol) and NaOH (2N, 10 mL) in methanol (10 mL) was stirred and refluxed for 8 h. The reaction mixture was concentrated under vacuum and the resulting mixture acidified with conc. HCl to give a white precipitate which was filtered under suction, washed with water and allowed to dry in a vacuum oven to obtain a white solid (232.1 mg, 75.4%). Mp: 122˚C - 123˚C. IR (cm^{-1}): 3400 - 2400, 2954, 2927, 2859, 2580, 1674, 1591, 1509, 1434, 1422, 1389, 1372, 1350, 1317, 1269, 1249, 1215, 1125, 1058, 1045, 970, 948, 919, 885, 868, 778, 763, 732, 711, 695. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, J =7.2 Hz), 1.38 - 1.47 (2H, m), 1.57 - 1.65 (2H, m), 2.64 (2H, t, J = 7.2 Hz), 2.95 (2H, t, J = 7.2 Hz), 4.23 (2H, t, J = 6.8 Hz), 4.28 (2H, s), 4.38 (2H, s), 7.26 (1H, s), 7.36 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (1C), 22.0 (1C), 30.5 (1C), 31.8 (1C), 32.3 (1C), 63.9 (1C), 64.8 (1C), 68.9 (1C), 107.2 (1C), 113.3 (1C), 113.3 (1C), 121.0 (1C), 138.5 (1C), 143.8 (1C), 147.6 (1C), 171.2 (1C). TOF-MS m/z: **335.0922**, ($[C_{15}H_{20}O_5S + Na]^+$ calcd. 335.0929).

Formation of 1,4-benzodioxane-6-carboxylic acid amide analogs (18) to (31)

To a stirred solution of **16** (200 mg, 0.64 mmol) and *N*,*N*-dimethylformamide (2 drops) in anhydrous dichloromethane (15 mL) at 0˚C - 5˚C, oxalyl chloride (0.11 mL, 1.31 mmol) was added. The reaction mixture was refluxed for 1 h un-

der nitrogen. The resulting mixture was concentrated under vacuum. This resulted in yellow oil, **17**, which was used for the next step without further purification.

To a stirred solution of the amine in anhydrous CH_2Cl_2 (10 mL) was added a solution of acid chloride (**17**) in CH_2Cl_2 dropwise at 0˚C - 5˚C. The reaction mixture was stirred for two hours at 0˚C, and at room temperature for overnight. CH_2Cl_2 (15 mL) was then added to the reaction mixture and the resulting mixture washed with H_2O (25 mL), HCl (1N, 2 × 25 mL), H_2O (25 mL), and brine (25 mL). The organic layer was dried over anhydrous $MgSO_4$ followed by solvent removal in-vacuo. The residue was triturated with hexane to obtain the product or purified by column chromatography on silica gel using 20% EtOAc in Hexane for **21**, 40% EtOAc in Hexane for **29 - 30**, and 5% MeOH in DCM for **31**.

8-(2-(butylthio)ethoxy)-N-phenyl-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxamide (18)

(166 mg, 47%). Mp: 68˚C - 70˚C. IR (cm^{-1}): 3276, 2956, 2928, 2872, 1642, 1588, 1528, 1500, 1463, 1439, 1385, 1367, 1346, 1320, 1274, 1225, 1202, 1120, 1035, 925, 888, 870, 800, 750, 726, 690. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (3H, t, J = 7.6 Hz), 1.37 - 1.46 (2H, m), 1.56 - 1.63 (2H, m), 2.62 (2H, t, J = 7.2 Hz), 2.94 (2H, t, J = 7.2 Hz), 4.21 (2H, t, J = 7.2 Hz), 4.27 - 4.29 (2H, m), 4.34 - 4.36 (2H, m), 7.01 (1H, d, J = 2.0 Hz), 7.11 - 7.15 (2H, m), 7.36 (2H, t, J = 7.6 Hz), 7.62 (2H, d, J = 8.0 Hz), 7.84 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6 (1C), 21.9 (1C), 30.6 (1C), 31.8, (1C), 32.3 (1C), 64.1 (1C), 64.6 (1C), 68.9 (1C), 105.2 (1C), 108.9 (1C), 120.1 (2C), 124.4 (1C), 127.0 (1C), 129.0 (2C), 136.6 (1C), 138.0 (1C), 143.8 (1C), 148.1 (1C), 165.0 (1C). ESI-TOF-MS m/z: **388.1574**, ($[C_{21}H_{25}NO_4S + H]^+$ calcd. 388.1583).

8-(2-(butylthio)ethoxy)-N-(4-methoxyphenyl)-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxamide (19)

(134 mg, 47%). Mp: 136˚C - 138˚C. IR (cm^{-1}): 3282, 2954, 2926, 2870, 1634, 1588, 1512, 1500, 1463, 1427, 1411, 1349, 1318, 1278, 1228, 1204, 1181, 1117, 1060, 1043, 1030, 976, 929, 890, 827, 811, 757, 725, 672. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (3H, t, J = 7.2 Hz), 1.37 - 1.46 (2H, m), 1.56 - 1.63 (2H, m), 2.62 (2H, t, J = 7.6 Hz), 2.94 (2H, t, J = 7.2 Hz), 3.80 (3H, s), 4.22 (2H, t, J = 7.2 Hz), 4.27 - 4.29 (2H, m), 4.33 - 4.36 (2H, m) 6.89 (2H, d, J = 9.2 Hz), 6.99 (1H, d, J = 2.0 Hz), 7.11 (1H, d, J = 2.0 Hz), 7.51 (2H, d, J = 8.8 Hz), 7.69 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6 (1C), 22.0 (1C), 30.7 (1C), 31.8, (1C), 32.3 (1C), 55.5 (1C), 64.1 (1C), 64.6 (1C), 69.0 (1C), 105.3 (1C), 108.9 (1C), 114.2 (2C), 122.0 (2C), 127.1 (1C), 131.1 (1C), 136.6 (1C), 143.8 (1C), 148.1 (1C), 156.5 (1C), 164.9 (1C). ESI-TOF-MS m/z: **418.1678**, ($[C_{22}H_{27}NO_5S + H]^+$ calcd. 418.1688).

8-(2-(butylthio)ethoxy)-N-(4-chlorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxamide (20)

(108 mg, 37%). Mp: 105˚C - 107˚C. IR (cm^{-1}): 3275, 2977, 2956, 2926, 2870, 1643, 1588, 1525, 1527, 1501, 1458, 1428, 1398, 1362, 1323, 1266, 1239, 1221,

1198, 1122, 1067, 1046, 1031, 1008, 887, 849, 818, 791, 735, 703, 682. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (3H, t, J = 7.3 Hz), 1.37 - 1.46 (2H, m), 1.56 - 1.63 (2H, m), 2.62 (2H, t, J = 7.2 Hz), 2.95 (2H, t, J = 7.2 Hz), 4.22 (2H, t, J = 6.8 Hz), 4.29 - 4.30 (2H, m), 4.35 - 4.36 (2H, m) 7.00 (1H, s), 7.10 (1H, s), 7.32 (2H, d, J = 8.8 Hz), 7.58 (2H, d, J = 8.8 Hz), 7.78 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (1C), 22.0 (1C), 30.7 (1C), 31.8 (1C), 32.3 (1C), 64.1, (1C), 64.7 (1C), 69.0 (1C), 105.2 (1C), 108.9 (1C), 121.3 (2C), 126.6 (1C), 129.1 (2C), 129.4 (1C), 136.6 (1C), 136.8 (1C), 143.9 (1C), 148.2 (1C), 164.9 (1C). ESI-TOF-MS m/z: **422.1137**, ($[C_{21}H_{24}ClNO_4S + H]^+$ calcd. 422.1193).

8-(2-(butylthio)ethoxy)-N-(4-(trifluoromethyl)phenyl)-2,3-dihydrobenzo [*b*][1,4]dioxine-6-carboxamide (21)

(218 mg, 80%). Mp: 176˚C - 178˚C. IR (cm^{-1}): 3286, 2957, 2928, 2872, 1653, 1590, 1525, 1502, 1463, 1430, 1406, 1385, 1351, 1321, 1245, 1265, 1225, 1202, 1155, 1114, 1065, 1037, 1018, 891, 839, 757, 742, 699, 675. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (3H, t, J = 7.3 Hz), 1.37 - 1.46 (2H, m), 1.56 - 1.64 (2H, m), 2.63 (2H, t, J = 7.4 Hz), 2.96 (2H, t, J = 7.1 Hz), 4.24 (2H, t, J = 7.2 Hz), 4.29 - 4.32 (2H, m), 4.36 - 4.38 (2H, m) 7.01 (1H, d, J = 2.0 Hz), 7.11 (1H, d, J = 2.0 Hz), 7.62 (2H, d, J = 8.6 Hz), 7.76 (2H, d, J = 8.4 Hz), 7.86 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (1C), 14.2 (1C), 22.0 (1C), 29.7 (1C), 30.7 (1C), 31.8, (1C), 32.4 (1C), 50.9 (1C), 60.4 (1C), 64.1 (1C), 64.7 (1C), 69.0 (1C), 105.3 (1C), 109.1 (1C), 119.6 (1C), 126.3 - 126.4 (2C), 137.1 (1C), 141.1 (1C), 143.9 (1C), 148.2 (1C), 165.1 (1C). ESI-TOF-MS m/z: **456.1456**, ($[C_{22}H_{24}F_3NO_4S + H]^+$ calcd. 456.1456).

8-(2-(butylthio)ethoxy)-N-(2-chlorobenzyl)-2,3-dihydrobenzo[*b*][1,4]dio xine-6-carboxamide (22)

(107 mg, 35%). Mp: 88˚C - 90˚C. IR (cm^{-1}): 3273, 2956, 2928, 2872, 1636, 1589, 1538, 1497, 1463, 1442, 1427, 1383, 1366, 1345, 1316, 1272, 1247, 1210, 1119, 1069, 1040, 933, 910, 887, 853, 812, 747, 727, 679. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (3H, t, J = 7.3 Hz), 1.36 - 1.45 (2H, m), 1.55 - 1.62 (2H, m), 2.61 (2H, t, J = 7.4 Hz), 2.93 (2H, t, J = 7.2 Hz), 4.20 (2H, t, J = 7.2 Hz), 4.25 - 4.27 (2H, m), 4.31 - 4.34 (2H, m), 4.69 (2H, d, J = 6.0 Hz), 6.50 (1H, t, J = 5.4 Hz), 6.89 (1H, d, J = 1.9 Hz), 7.06 (1H, d, J = 1.9 Hz), 7.23 - 7.26 (2H, m), 7.37 - 7.39 (1H, m), 7.44 - 7.46 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (1C), 22.0 (1C), 30.6 (1C), 31.8, (1C), 32.3 (1C), 42.1 (1C), 64.1 (1C), 64.6 (1C), 68.9 (1C), 105.2 (1C), 108.8 (1C), 126.3 (1C), 127.1 (1C), 129.0 (1C), 129.6 (1C), 130.4 (1C), 133.7 (1C), 135.6 (1C), 136.4 (1C), 143.7 (1C), 148.0 (1C), 166.6 (1C). ESI-TOF-MS m/z: **436.1341**, ($[C_{22}H_{26}ClNO_4S + H]^+$ calcd. 436.1349).

8-(2-(butylthio)ethoxy)-N-(4-fluorobenzyl)-2,3-dihydrobenzo[*b*][1,4]dio xine-6-carboxamide (23)

(126.1 mg, 41%). Mp: 121˚C - 122˚C. IR (cm^{-1}): 3264, 2961, 2930, 2873, 1629, 1589, 1538, 1496, 1460, 1427, 1385, 1367, 1344, 1318, 1273, 1210, 1156, 1116, 1069, 1043, 1016, 998, 958, 909, 886, 853, 822, 810, 726, 697, 681. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (3H, t, J = 7.3 Hz), 1.36 - 1.46 (2H, m), 1.55 - 1.63 (2H, m), 2.61 (2H, t, J = 7.4 Hz), 2.94 (2H, t, J = 7.2 Hz), 4.21 (2H, t, J = 7.2 Hz), 4.25 - 4.28 (2H, m), 4.31 - 4.34 (2H, m), 4.58 (2H, d, J = 5.7 Hz), 6.29 (1H, dist t), 6.89

(1H, d, J = 2 Hz), 7.00 - 7.05 (2H, m), 7.06 (1H, d, J = 2 Hz), 7.29 - 7.33 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (1C), 22.0 (1C), 30.6 (1C), 31.8, (1C), 32.3 (1C), 43.4 (1C), 64.1 (1C), 64.6 (1C), 68.9 (1C), 105.2 (1C), 108.8 (1C), 115.5 (1C), 115.7 (1C), 126.3 (1C), 129.5 (1C), 129.6 (1C), 134.1 (1C), 136.5 (1C), 143.8 (1C), 148.0 (1C), 162.3 (1C, JC-F = 245 Hz), 166.6 (1C). ESI-TOF-MS m/z: **420.1617**, ($[C_{22}H_{26}FNO_4S + H]^+$ calcd. 420.1645).

8-(2-(butylthio)ethoxy)-N-(4-methoxybenzyl)-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxamide (24)

(139 mg, 46%). Mp: 120˚C - 121˚C. IR (cm^{-1}): 3283, 2956, 2927, 2875, 1634, 1612, 1590, 1537, 1501, 1463, 1428, 1389, 1349, 1310, 1273, 1250, 1211, 1174, 1127, 1066, 1037, 963, 930, 910, 885, 819, 769, 718, 680. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (3H, t, J = 7.2 Hz), 1.36 - 1.46 (2H, m), 1.55 - 1.61 (2H, m), 2.61 (2H, t, J = 7.2 Hz), 2.93 (2H, t, J = 7.2 Hz), 3.80 (3H, s), 4.21 (2H, t, J = 7.2 Hz), 4.22 - 4.26 (2H, m), 4.32 - 4.34 (2H, m) 4.54 (2H, d, J = 5.2 Hz), 6.21 (1H, dist. t), 6.87 - 6.89 (3H, m), 7.06 (1H, d, J = 2.0 Hz), 7.26 - 7.28 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6 (1C), 22.0 (1C), 30.6 (1C), 31.8 (1C), 32.3 (1C), 43.7, (1C), 55.3 (1C), 64.1 (1C), 64.6 (1C), 68.9 (1C), 105.2 (1C), 108.8 (1C), 114.2 (2C), 126.5 (1C), 129.3 (1C), 130.3 (1C), 131.5 (1C), 136.4 (1C), 143.7 (1C), 147.9 (1C), 159.1 (1C), 166.5 (1C). ESI-TOF-MS m/z: **432.1859**, ($[C_{23}H_{29}NO_5S + H]^+$ calcd. 432.1845).

8-(2-(butylthio)ethoxy)-N-(4-chlorobenzyl)-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxamide (25)

(120.7 mg, 41%). Mp: 115˚C - 117˚C. IR (cm^{-1}): 3275, 2956, 2928, 2870, 1633, 1590, 1538, 1493, 1463, 1427, 1406, 1388, 1345, 1317, 1272, 1228, 1211, 1122, 1090, 1067, 1043, 1015, 958, 886, 855, 800, 781, 726, 681. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (3H, t, J = 7.2 Hz), 1.37 - 1.46 (2H, m), 1.56 - 1.63 (2H, m), 2.62 (2H, t, J = 7.6 Hz), 2.94 (2H, t, J = 7.2 Hz), 4.21 (2H, t, J = 7.2 Hz), 4.25 - 4.27 (2H, m), 4.33 - 4.35 (2H, m) 4.58 (2H, d, J = 6.0 Hz), 6.89 (1H, d, J = 2.0 Hz), 7.06 (1H, d, J = 2.0 Hz), 7.28 - 7.29 (2H, m), 7.31 (2H, t, J = 2.0 Hz), 7.32 - 7.34 (1H, dist. t). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (1C), 22.0 (1C), 30.7 (1C), 31.8 (1C), 32.3 (1C), 43.4, (1C), 64.1 (1C), 64.6 (1C), 69.0 (1C), 105.2 (1C), 108.8 (1C), 126.2 (1C), 128.9 (2C), 129.2 (2C), 133.4 (1C), 136.6 (C), 136.8 (1C), 143.8 (1C), 148.0 (1C), 166.7 (1C). ESI-TOF-MS m/z: **436.1349**, ($[C_{22}H_{26}ClNO_4S + H]^+$ calcd. 436.1349).

8-(2-(butylthio)ethoxy)-N-hexyl-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxamide (26)

(108 mg, 38%). Mp: 98˚C - 100˚C. IR (cm^{-1}): 3286, 2955, 2926, 2858, 1631, 1589, 1539, 1499, 1463, 1426, 1381, 1367, 1346, 1316, 1273, 1251, 1209, 1117, 1068, 1042, 960, 927, 889, 854, 767, 724, 679. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 - 0.94 (6H, m), 1.25 - 1.46 (8H, m), 1.56 - 1.63 (4H, m), 2.62 (2H, t, J = 7.3 Hz), 2.94 (2H, dist. t), 3.38 - 3.43 (2H, q, J = 6.9 Hz), 4.21 (2H, t, J = 7.2), 4.25 - 4.28 (2H, m), 4.32 - 4.34 (2H, m), 5.99 (1H, dist. t), 6.86 (1H, d, J = 1.9 Hz), 7.03 (1H, d, J = 1.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (1C), 14.0 (1C), 22.0 (1C),

22.5, (1C), 26.6 (1C), 29.6 (1C), 30.6 (1C), 31.5 (1C), 31.8 (1C), 32.3 (1C), 40.1 (1C), 64.1 (1C), 64.6 (1C), 68.9 (1C), 136.8 (1C), 105.2 (1C), 108.6 (1C), 127.0 (1C), 136.2 (1C), 143.7 (1C), 147.9 (1C), 166.7 (1C). ESI-TOF-MS m/z: **396.2206**, ($[C_{21}H_{33}NO_4S + H]^+$ calcd. 396.2209).

8-(2-(butylthio)ethoxy)-N-(pyridin-2-ylmethyl)-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxamide (27)

(121 mg, 30%). Mp: 142˚C - 143˚C. IR (cm^{-1}): 3259, 2951, 2926, 2872, 2574, 1640, 1621, 1588, 1538, 1495, 1465, 1426, 383, 1345, 1318, 1250, 1227, 1207, 1120, 1072, 1040, 1003, 960, 885, 760, 727. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (3H, t, J = 7.3 Hz), 1.35 - 1.44 (2H, m), 1.53 - 1.61 (2H, m), 2.62 (2H, t, J = 7.3 Hz), 2.93 (2H, t, J = 7.0 Hz), 4.21 - 4.28 (4H, m), 4.29 - 4.32 (2H, m), 4.97 (2H, d, J = 6.1 Hz) 7.21 - 7.22 (2H, m), 7.74 (1H, t, J = 6.6 Hz), 7.98 (1H, d, J = 7.9 Hz), 8.27 - 8.31 (1H, m), 8.66 (1H, d, J = 5.2 Hz), 8.78 (1H, t, J = 5.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (1C), 22.0 (1C), 30.7 (1C), 31.8, (1C), 32.2 (1C), 40.4 (1C), 63.9 (1C), 64.6 (1C), 69.0 (1C), 105.0 (1C), 110.3 (1C), 124.7 (1C), 125.0 (1C), 127.1 (1C), 136.8 (1C), 141.6 (1C), 143.9 (1C), 144.8 (1C), 147.8 (1C), 154.4 (1C), 167.1 (1C). ESI-TOF-MS m/z: **403.1672**, ($[C_{21}H_{26}N_2O_4S + H]^+$ calcd. 403.1692).

N-((1*H*-benzo[d]imidazol-2-yl)methyl)-8-(2-(butylthio)ethoxy)-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxamide (28)

(58.8 mg, 19.4%). Mp: 216˚C - 218˚C. IR (cm^{-1}): 3346, 3185, 2926, 2870, 1642, 1587, 1548, 1498, 1459, 1370, 1343, 1320, 1273, 1252, 1227, 1211, 1117, 1067, 1041, 1003, 968, 936, 884, 866, 842, 767, 736. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (3H, t, J = 7.6 Hz), 1.33 - 1.41 (2H, m), 1.49 - 1.56 (2H, m), 2.49 (2H, t, J = 7.2 Hz), 2.83 (2H, t, J = 7.2 Hz), 4.07 (2H, t, J = 6.8 Hz), 4.20 (2H, br s), 4.30 (2H, br s), 4.78 (2H, d, J = 4.8 Hz) 7.20 - 7.26 (5H, m), 7.55 (2H, br s), 9.15 (1H, dist. t). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (1C), 21.9 (1C), 30.6 (1C), 31.8, (1C), 32.2 (1C), 38.3 (1C), 64.0 (1C), 64.6 (1C), 68.7 (1C), 105.0 (1C), 109.9 (1C), 123.0 (1C), 125.0 (1C), 136.7 (1C), 143.8 (1C), 147.8 (1C), 152.5 (1C), 168.6 (1C). ESI-TOF-MS m/z: **442.1788**, ($[C_{23}H_{27}N_3O_4S + H]^+$ calcd. 442.1801).

8-(2-(butylthio)ethoxy)-*N*,*N*-bis(2-methoxyethyl)-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxamide (29)

(89.1 mg, 30%). IR (cm^{-1}): 2946, 2927, 2873, 1628, 1588, 1509, 1455, 1424, 1380, 1365, 1338, 1304, 1272, 1246, 1211, 1193, 1114, 1056, 1043, 1015, 9640, 925, 888, 863, 766, 742. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (3H, t, J = 7.3 Hz), 1.36 - 1.45 (2H, m), 1.55 - 1.63 (2H, m), 2.61 (2H, t, J = 7.4 Hz), 2.93 (2H, t, J = 7.3 Hz), 3.34 (6H, s), 3.50 - 3.63 (8H, m), 4.16 (2H, t, J = 7.9 Hz), 4.24 - 4.27 (2H, m), 4.31 - 4.33 (2H, m), 6.65 (1H, d, J = 1.8 Hz), 6.67 (1H, d, J = 1.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6 (1C), 21.9 (1C), 30.6 (1C), 31.8, (1C), 32.3 (1C), 58.9 (1C), 64.2 (1C), 64.5 (1C), 68.8 (1C), 70.7 (1C), 105.2 (1C), 109.6 (1C), 128.4 (1C), 134.4 (1C), 143.8 (1C), 147.6 (1C), 171.6 (1C). ESI-TOF-MS m/z: **428.2104**, ($[C_{21}H_{33}NO_6S + H]^+$ calcd. 428.2107).

8-(2-(butylthio)ethoxy)-2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)(morpholin

o)methanone (30)

(61.5 mg, 25%). IR (cm^{-1}): 2956, 2927, 2857, 1633, 1613, 1589, 1509, 1455, 1421, 1382, 1367, 1342, 1307, 1273, 1249, 1212, 1122, 1066, 1045, 1028, 970, 931, 888, 862, 820, 758, 741, 692. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (3H, t, J = 7.9 Hz), 1.38 - 1.45 (2H, m), 1.55 - 1.63 (2H, m), 2.61 (2H, t, J = 7.2 Hz), 2.93 (2H, t, J = 7.2 Hz), 3.62 - 3.68 (8H, m), 4.16 (2H, t, J = 7.2 Hz), 4.25 - 4.27 (2H, m), 4.31 - 4.33 (2H, m) 6.58 (1H, d, J = 1.9 Hz), 6.60 (1H, d, J = 1.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8 (1C), 22.1 (1C), 24.1 (1C), 29.8 (1C), 30.8, (1C), 32.0 (1C),32.5 (1C), 64.3 (1C), 64.7 (1C), 67.0 (1C), 69.2 (1C), 105.4 (1C), 109.7 (1C), 127.2 (1C), 135.2 (1C), 144.0 (1C), 148.2 (1C), 170.1 (1C). ESI-TOF-MS m/z: **382.1692**, ($[C_{19}H_{27}NO_5S + H]^+$ calcd. 382.1688).

[8-(2-butylsulfanyl-ethoxy)-2,3-dihydro-benzo[1,4]dioxin-6-yl]-piperidin-1-yl-methanone (31)

(81 mg, 31%). IR (cm^{-1}): 2927, 2857, 2577, 1676, 1631, 1590, 1508, 1432, 1372, 1349, 1321, 1269, 1249, 1212, 1115, 1058, 1044, 948, 885, 868, 763, 732, 711, 695, 667. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, J = 7.2 Hz), 1.25 - 1.68 (10H, m), 2.63 (2H, t, J = 7.2 Hz), 2.95 (2H, t, J = 7.6 Hz), 4.22 (2H, t, J = 7.2 Hz), 4.27 - 4.29 (2H, m), 4.36 - 4.38 (2H, m), 7.25 (1H, d, J = 2 Hz), 7.35 (1H, d, J = 2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (1C), 22.0 (2C), 24.4 (1C), 26.1 (1C), 30.5 (1C), 30.6 (1C), 31.8 (1C), 32.3 (2C), 63.9 (1C), 64.8 (1C), 68.8 (1C), 107.1 (1C), 113.3 (1C), 121.1 (1C), 138.4 (1C), 143.7 (1C), 147.6 (1C), 170.8 (1C). ESI-TOF-MS m/z: **380.1892**, ($[C_{20}H_{29}NO_4S + H]^+$ calcd. 380.1896).

[8-(2-butylsulfanyl-ethoxy)-2,3-dihydro-benzo[1,4]dioxin-6-yl]-[1-(3-ethyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-2-ylmethyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-methanone (32)

To a stirred solution of **16** (225 mg, 0.68 mmol) and *N*,*N*-dimethylformamide (2 drops) in anhydrous dichloromethane (15 mL) at 0 - 5˚C, oxalyl chloride (0.11 mL, 1.31 mmol) was added. The reaction mixture was refluxed for 1 h under nitrogen. The resulting mixture was concentrated under vacuum. This resulted in yellow oil, **17**, which was used for the next step without further purification.

To a stirred solution of triethylamine (0.1 mL) in CH_2Cl_2 (10 mL) at room temperature was added emetine dihydrochloride (200 mg, 0.36 mmol). After all the emetine was completely dissolved, a solution of acid chloride **17** in CH_2Cl_2 (5 mL) was added dropwise at 0˚C - 5˚C. The reaction mixture was stirred at room temperature for 24 h. CH_2Cl_2 (15 mL) was then added to the mixture and the resulting mixture washed with distilled water (2 × 25 mL), and brine (25 mL). The organic layer was dried over anhydrous $MgSO_4$ followed by solvent removal in-vacuo. The residue was applied onto a silica gel column and eluted with 10% methanol in ethyl acetate. The yellow solid obtained was further dried in a vacuum oven to obtain a powdery yellow solid (95 mg, 33%).

Mp: 115˚C - 117˚C. IR (cm^{-1}): 2929, 2865, 2825, 2749, 1610, 1626, 1588, 1509, 1458, 1425, 1364, 1339, 1252, 1203, 1120, 1030, 928, 888, 859, 766. ^{1}H NMR (400

MHz, $CDCl_3$) δ 0.89 - 0.95 (6H, m), 1.31 - 1.48 (4H, m), 1.50 - 1.54 (1H, m), 1.56 - 1.66 (3H, m), 1.68 - 2.36 (1H, m), 2.56 - 2.65 (3H, m), 2.67 - 2.89 (3H, m), 2.91 - 2.99 (3H, m), 2.99 - 3.46 (3H, m), 3.49 - 3.71 (3H, m), 3.79 - 3.89 (9H, m), 3.92 - 4.11 (2H, m), 4.13 - 4.40 (11H, m), 4.46 - 4.54 (1H, m), 6.54 - 6.59 (4H, m), 7.23 (1H, d, J = 2Hz), 7.43 (1H, d, J = 2.4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 22.9, 29.1, 30.7, 31.8, 32.4, 40.5, 48.7, 52.4, 55.8 - 56.2 (4C), 64.2, 64.5, 104.6, 108.8, 110.0, 111.2, 111.4, 124.4, 128.7, 134.7, 170.2; ESI-TOF-MS m/z: **775.3985**, ($[C_{44}H_{58}N_2O_8S + H]^+$ calcd. 775.3992).

Transformation of the sulfide to sulfoxide or sulfone analogs

8-(2-(Butylsulfinyl)ethoxy)-N-(4-fluorobenzyl)-2,3-dihydrobenzo[*b*][1,4] dioxine-6-carboxamide (33)

Hydrogen peroxide (30 wt%, 0.08 mL) was added dropwise to a mixture of **23** (150 mg, 0.36 mmol) and tellurium dioxide (6.00 mg, 0.036 mmol) in MeOH: CH_2Cl_2 (1:1, 8 mL). The mixture was stirred at room temperature for 12 h. The solvent was evaporated in vacuo, and water (20 mL) was added to the reaction mixture and then extracted with CH_2Cl_2 (2 × 20 mL). The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was triturated with hexane to obtain **33** as a light yellow solid (99 mg, 64%).

Mp: 141˚C - 143˚C. IR (cm^{-1}): 3287, 2954, 2924, 2872, 1632, 1606, 1589, 1537, 1510, 1500, 1466, 1423, 1392, 1367, 1348, 1311, 1274, 1249, 1230, 1209, 1160, 1125, 1097, 1067, 1027, 982, 972, 911, 887, 858, 834, 820, 773, 760, 725, 702, 678. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (3H, t, J = 7.2 Hz), 1.38 - 1.53 (2H, m), 1.68 - 1.76 (2H, m), 2.78 (2H, t, J = 8 Hz), 2.96 - 3.02 (1H, m), 3.13 - 3.20 (1H, m), 4.22 - 4.23 (2H, m), 4.26 - 4.27 (2H, m), 4.40 - 4.42 (2H, m), 4.51 (2H, d, J = 5.6 Hz), 6.96 (2H, t, J = 8.8), 7.08 (1H, d, J = 1.6 Hz), 7.10 (1H, d, J = 2 Hz), 7.26 - 7.30 (2H, m), 7.43 (1H, t, J = 6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5 (1C), 21.9 (1C), 24.5 (1C), 43.1, (1C), 51.2 (1C), 52.5 (1C), 61.7 (1C), 63.9 (1C), 64.4 (1C), 105.3 (1C), 110.1 (1C), 115.1 (1C), 115.3 (1C), 126.2 (1C), 129.3 (1C), 129.4 (1C), 134.4 (1C), 136.3 (1C), 143.7 (1C), 146.9 (1C), 161.9 (1C, d, JC-F= 244), 166.5 (1C). ESI-TOF-MS m/z: **436.1584**, ($[C_{22}H_{26}FNO_5S + H]^+$ calcd. 436.1594).

8-(2-(Butylsulfonyl)ethoxy)-N-(4-fluorobenzyl)-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxamide (34)

To a stirred solution of **23** (150 mg, 0.36 mmol) in acetic acid (5 mL), hydrogen peroxide (2 mL, 30 wt%) was added in one portion and the resulting mixture was stirred at room temperature for 20 h. The mixture was then poured onto crushed ice resulting in the formation of a white precipitate. The precipitate was separated by filtration, washed with cold water and dried to provide **34** as a white solid (120 mg, 74%).

Mp: 166˚C - 168˚C. IR (cm^{-1}): 3407, 2956, 2938, 2875, 1651, 1633, 1588, 1546, 1501, 1464, 1428, 1388, 1344, 1314, 1286, 1269, 1212, 1157, 1117, 1070, 1036, 1015, 972, 930, 909, 886, 858, 821, 759, 724, 663. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (3H, t, J = 7.6 Hz), 1.42 - 1.52 (2H, m), 1.83 - 1.90 (2H, m), 3.21 - 3.25 (2H,

m), 3.41 (2H, t, J = 5.2 Hz), 4.26 - 4.29 (4H, m), 4.44 (2H, t, J = 5.2 Hz), 4.56 (2H, d, J = 5.6 Hz), 6.50 (1H, dist t), 6.97 (1H, d, J = 2 Hz), 7.02 (2H, t, J = 8.8 Hz), 7.05 (1H, d, J = 1.6 Hz), 7.28 - 7.32 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (1C), 22.0 (1C), 30.6 (1C), 31.8, (1C), 32.3 (1C), 43.4 (1C), 64.1 (1C), 64.6 (1C), 68.9 (1C), 105.2 (1C), 108.8 (1C), 115.5 (1C), 115.7 (1C), 126.3 (1C), 129.5 (1C), 129.6 (1C), 134.0 (1C), 136.5 (1C), 143.8 (1C), 148.0 (1C), 162.2 (1C, d, JC-F = 245 Hz), 166.6 (1C). ESI-TOF-MS m/z: **452.1556**, ($[C_{22}H_{26}FNO_6S + H]^+$ calcd. 452.1543).

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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