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Synthesis and Evaluation of the Analogues of Penicillide against Cholesterol Ester Transfer Protein†

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A series of penicillide analogues, with modifications at C-3 and C-9 positions, are synthesized as potential cholesteryl ester transfer protein (CETP) inhibitors. The preliminary *in vitro* inhibition assay provided some valuable structure-activity relationship information about penicillide.

Keywords cross-coupling, lactone, inhibitors, cholesterol ester transfer protein, penicillide

Introduction

Cholesteryl ester transfer protein (CETP), a plasma glycoprotein responsible for the transfer of cholesteryl esters from the cardioprotective high density lipoprotein cholesterol (HDL-C) to the potentially atherogenic low or very low density lipoprotein cholesterol (LDL-C or VLDL-C), has been viewed as a promising therapeutic target for treatment of dyslipidaemia.[1] Up to now, several CETP inhibitors have evolved into human clinical trials, including torcetrapid, anacetrapid, dalcetrapid and evacetrapid.[2] However, some of them are not successful at late-stage of clinical development. For example, torcetrapid was withdrawn in phase III due to its increased risk in cardiovascular events, possibly associated with torcetrapid-specific off-target effects involving increasing aldosterone level and extending QT interval.[3] Nowadays, the natural product-based strategy to discover novel CETP inhibitors becomes an alternative approach in this medical field, due to its relatively higher statistic probability of success in drug development.[4]

Penicillide (Figure 1), is a metabolite produced by a filamentous fungus (*Penicillium* sp.), which was isolated and identified by Sassa, Udagawa, and co-workers.[5] Recently, its derivative **1**, which was identified by optimization through medicinal chemistry efforts in Bayer Pharma (Figure 1),[6] showed sufficient stability in rat plasma along with potent CETP inhibition (IC_{50} = 15 nmol•L^{-1}). This tricyclic skeleton fused by an eight-membered lactone, as well as its potential application as CETP inhibitor, attracted our greatest interest. Just recently, we accomplished the total synthesis of racemic penicillide.[7] As a continuation of this work, herein we present the synthesis of a variety of penicillide analogues and the preliminary data of their CETP inhibition.

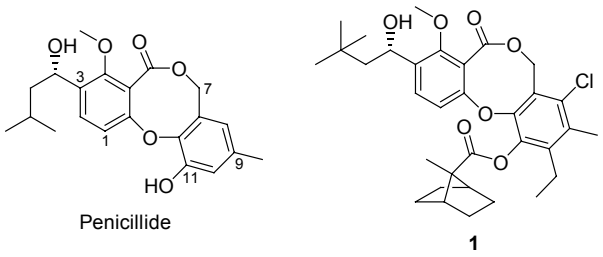

Figure 1 The structures of penicillide and its representative derivative as CETP inhibitor.

Results and Discussion

Although the co-crystal structure of CETP and a natural substrate has been disclosed,[8] the detailed binding domain for the CETP inhibitors including **1** is not yet fully elucidated due to the large pocket.[9] Due to the limitation of semi-synthesis starting from penicillide, previous SAR study was focused on various *O*-substituents at C-11 position, as well as different alkyl side chains at C-3 position.[5] Therefore, we became interested in exploring analogues at C-9 position to probe its steric and lipophilic requirement. In addition, we would

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† Dedicated to Professor Guoqiang Lin on the Occasion of his 70th birthday.

like to find out the effect of hydroxyl group at C-3 side chain by replacing it with proton or fluorine.

Several penicillide analogues, as shown in Figure 2, were designed to target the above ideas, and their retro synthetic analysis led to the advanced intermediate aryl bromide **10**[7] and the corresponding phenols **8** with pre-installed substituents. These two building blocks could go through Ullmann coupling reaction and further lactonization to give the tricyclic core, then the aldehyde group would allow for nucleophilic attack by various organometalics to afford alcohols, in which the hydroxy group could be further reduced or replaced by fluorine.

As shown in Scheme 1, our synthesis started from commercially available 2,3-dihydroxybenzaldehyde. Selective benzylation of one phenolic hydroxyl group was conducted, according to the known method,[10] using NaH (2.0 equiv.) and benzyl bromide (1.0 equiv.) to obtain compound **2** in 65% yield. The reduction of **2** by $NaBH_4$ in MeOH at r.t. produced **7a** in 98% yield, and subsequent protection of the free hydroxyl with THP afforded the desired phenol **8a** in 96% yield.

Next, we turned to the preparation of substituted phenols **8b**—**8c** and **8e**—**8g**. The bromination of **2** was achieved using NBS/NH_4OAc in CH_3CN to give the bromide **3a** in 85% yield,[11] which allowed for the introduction of 4-methoxyphenyl or methyl groups through Suzuki or Negishi coupling. The Suzuki reaction of **3a** with 4-methoxyphenylboronic acid produced **3c** in 84% yield,[13] which was subjected to further reduction and THP protection as above to give the desired phenol **8c** in 79% yield over two steps. The Negishi reaction of **3a** or **3b** with Me_2Zn did not provide the desired product with an acceptable yield, thus required the protection of hydroxy group. Fortunately, the silyl protected bromide **4** reacted smoothly with Me_2Zn in the presence of $Pd(dppf)Cl_2$ in refluxing 1,4-dioxane, affording the aldehyde **5** in 82% yield.[12] Further reduction of the aldehyde and subsequent modifications of protection groups resulted in the desired phenol **8b** in 72% yield over three steps.

As for the preparation of phenols **8e**—**8g**, the formation of C—S bond usually requires aryl iodide substrate. Thus, the iodide **3b** was produced from **2** using ICl/Pyridine in 88% yield.[11] After the selective THP protection of benzylic hydroxy group, the desired sulfone **8e** was successfully obtained in 52% yield through an *L*-proline-promoted CuI-catalyzed coupling reaction.[14] Due to its low reactivity in the following Ullmann coupling with the bromide **10**, the corresponding alkylthio ethers **8f**—**8g** were prepared as follows. The two hydroxy groups in **7d** was protected as acetonide **9** using 2,2-dimethoxypropane in 95% yield, which was then converted to corresponding thioethers according to Ma's protocol.[15] The subsequent cleavage of the ketal protecting group and selective THP protection of the benzylic hydroxy afforded the desired phenols **8f** and **8g** successfully in 66% and 68% yields (based on **9**), respectively.

With the desired phenols (**8a**—**8c**, **8e**—**8g**) in hand, the advanced intermediate **10**, prepared from the commercially available 5-amino-2-methylphenol in 7 steps,[7] was coupled with them through Ullmann reaction under our previous conditions (Scheme 2).[7] This transformation was catalyzed by Cu powder/CuO system in the presence of DMAP in refluxing CH_3CN. The phenols bearing electron-donating groups could be converted into the desired aryl ethers (**11a**—**11c**, **11f**—**11g**) in satisfying yields, while the phenol (**8e**) bearing a methylsulfonyl group gave **11e** (R^3=SO_2Me) in quite low yield (18%), possibly due to an unfavorable electronic effect of the strong electron-withdrawing group.

The sequence to construct the tricyclic core from aryl ethers (**11a**—**11c**, **11f**—**11g**) is similar to our previous synthesis of penicillide.[7] Removal of the THP protecting group under acidic conditions led to the aldehydes (**12a**—**12c**, **12f**—**12g**). Then, the formyl group was protected as its dimethyl acetal by the treatment with MeOH in the presence of a catalytic amount of TsOH. The subsequent saponification of the ester with KOH in refluxing MeOH and acidification with aqueous 3 N HCl gave the acids (**13a**—**13c**, **13f**—**13g**) in excellent yields, which were further cyclized using the Mukaiyama's reagent[16] in refluxing MeCN for 12 h to afford the desired lactones (**14a**—**14c**, **14f**—**14g**) in satisfactory yields

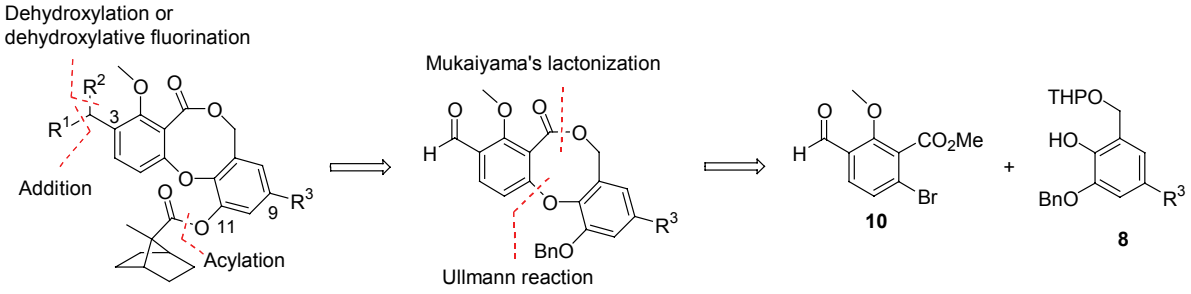

Figure 2 The retro synthetic analysis of designed compounds.

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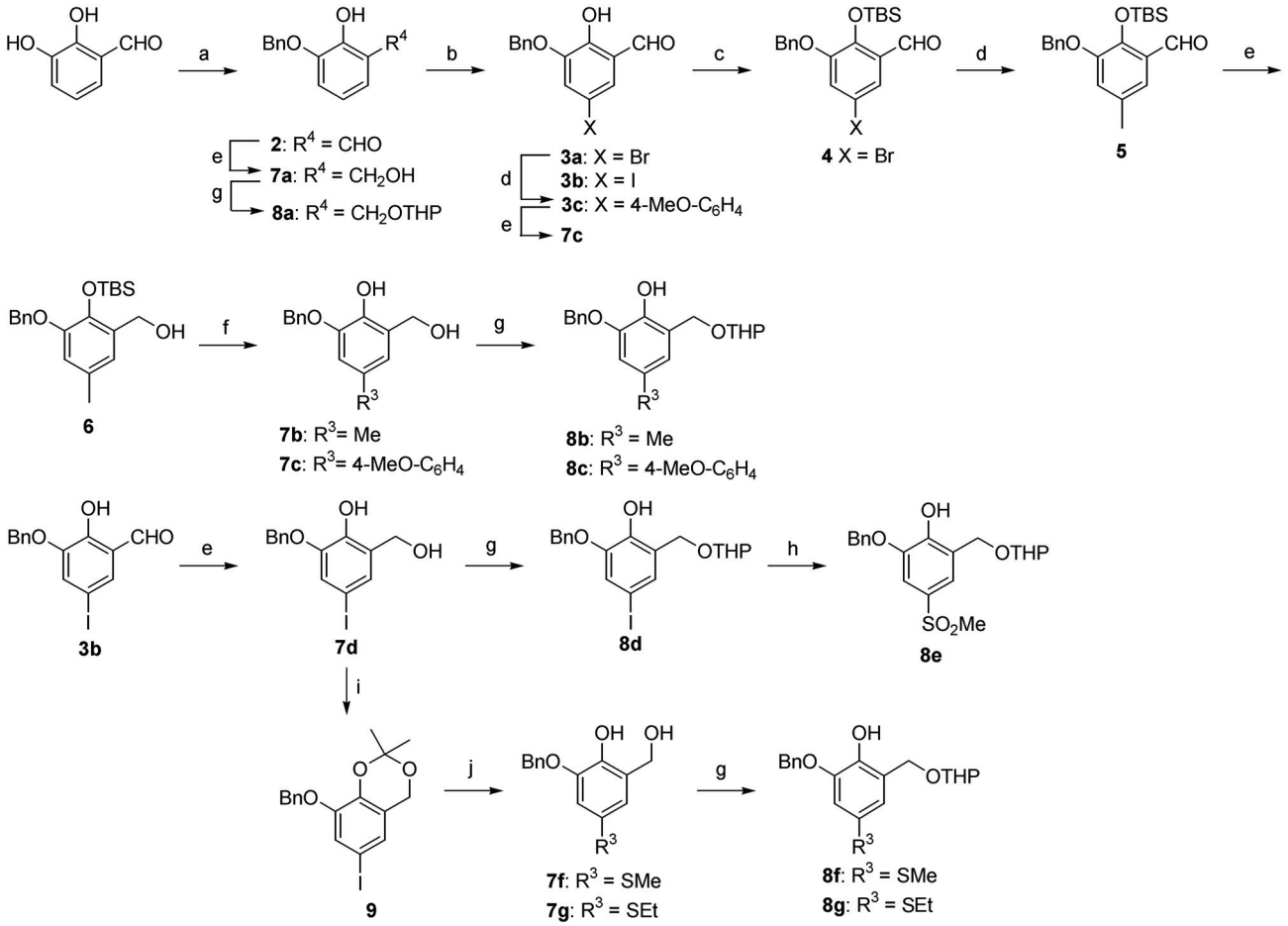
Scheme 1 The synthesis of the suitable phenols **8**



Reagents and conditions: a. NaH (2.0 equiv.), r.t., 1 h, then BnBr/THF, r.t., 4 h, 65%; b. for **3a**: NBS, NH_4OAc, CH_3CN, r.t., 4 h, 85%; for **3b**: ICl/Pyridine, $CHCl_3$, r.t., overnight, 88%; c. TBSCl, $(i\text{-}Pr)_2NEt$, DMF, r.t., 1 h, for **4**: 95%; d. for **5**: Me_2Zn, $Pd(dppf)Cl_2$ (cat.), 1,4-dioxane, reflux, 1 h, 82% (based on **4**); for **3c**: $ArB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, MeOH, 80 °C, overnight, 84%; e. $NaBH_4$, MeOH, r.t., 4 h, for **7a**: 98%; for **6**: 91%; for **7c**: 86%; for **7d**: 95%; f. $n\text{-}BuN_4F\cdot xH_2O$, THF, r.t., 30 min, 94%; g. 3,4-dihydro-2*H*-pyran, $p\text{-}TsOH\cdot H_2O$ (cat.), CH_2Cl_2, 0 °C, 1 h, for **8a**: 96%; for **8b**: 84%; for **8c**: 92%; for **8d**: quantitative yield; for **8f**: 78%; for **8g**: 82%; h. CuI/*L*-proline, $MeSO_2Na$, NaOH, DMSO, 95 °C, 52%; i. 2,2-dimethoxypropane, TsOH, CH_2Cl_2, r.t., overnight, 95%; j. (i) CuI, S, K_2CO_3, DMF, 90 °C; (ii) $NaBH_4$, 0－40 °C; (iii) MeI, r.t.; k. aq. 1 mol·L^{-1} HCl, THF/H_2O, reflux, for **7f**: 84%; for **7g**: 83% (overall yield from **9**).

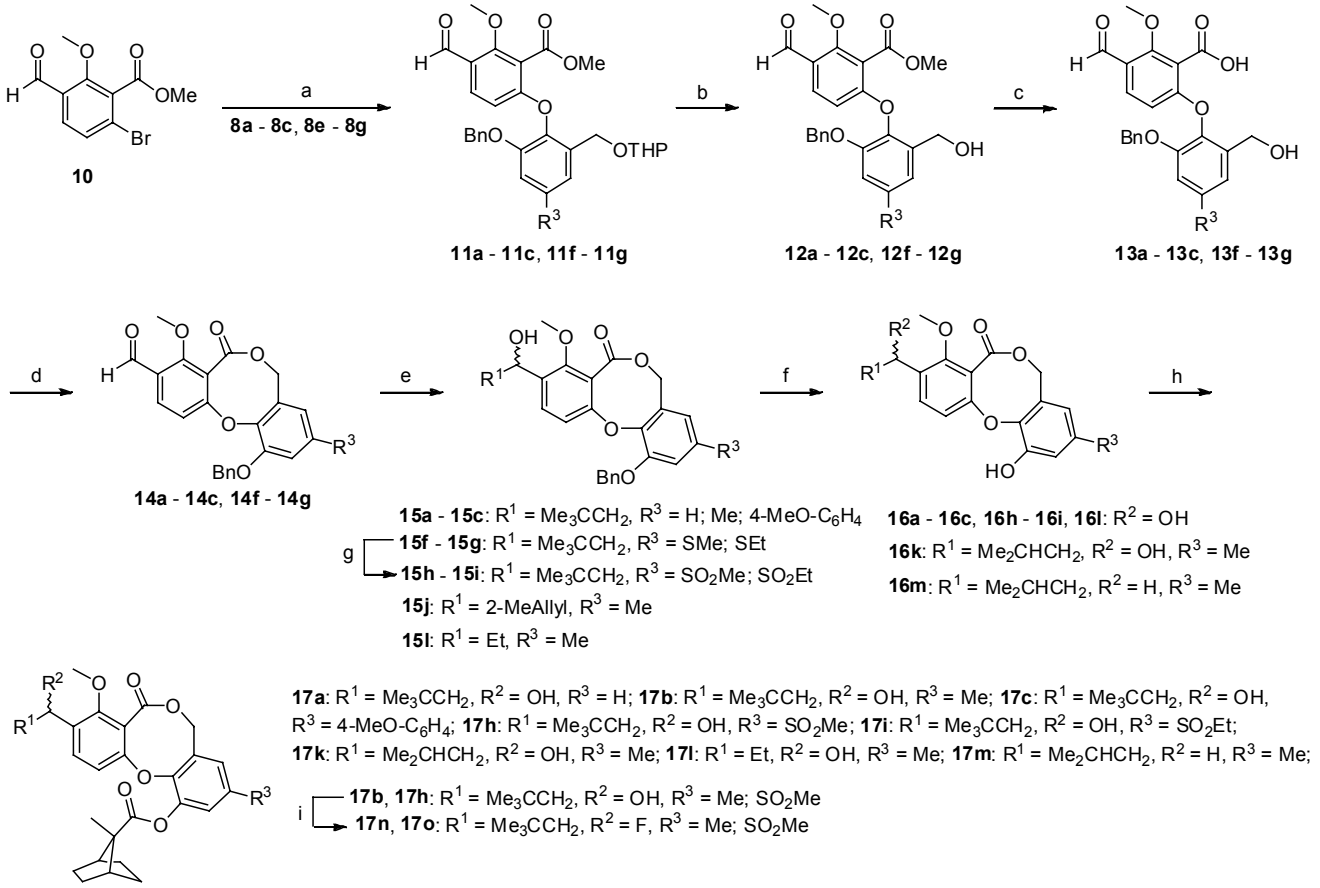
The introduction of C-3 alkyl chains was realized through the reaction with the fresh-prepared neopentylmagnesium chloride to give the corresponding adducts (**15a**－**15c**, **15f**－**15g**) in acceptable yields. Among them, the alkylthio ethers (**15f**－**15g**) were selectively oxidized by oxone to give the alkylsulfonyl compounds (**15h**－**15i**) in almost quantitative yields.[17]

Attempts to obtain **15k** (R^1＝Me_2CHCH_2, R^3＝Me) by a direct nucleophilic addition of 2-methylpropyl Grignard reagent or (2-methylpropyl)lithium to compound **14b** (R^3＝Me) mainly resulted in the corresponding benzyl alcohol due to the reduction of the formyl group. Alternatively, a 2-methylprop-2-en-1-yl Grignard reagent was applied to react with **14b** in anhydrous THF at 0－10 ℃ for 1 h, giving **15j** in 82% yield. In a similar way, EtMgBr was added to **14b**, producing **15l** in 57% yield.

The selective removal of the protective benzyl group in compound **15** (**15a**－**15c**, **15h**, **15i**, **15l**) was realized by hydrogenation in the presence of 10% Pd/C in AcOEt/MeOH at room temperature to give the phenols (**16a**－**16c**, **16h**, **16i**, **16k**, **16l**) in excellent yields. However, **15f**－**15g** did not react under the same conditions due to the toxicity of alkylthio ether to the catalyst. In the case of **15j**, both the C－C double bond and the benzyl group were reduced to give **16k** (65%), together with the further dehydroxylated product **16m** (34%).

Acylation of the resulting phenols (**16a**－**16c**, **16h**, **16i**, **16k**, **16l**, **16m**) with the bulky aliphatic acyl chloride, which was *in situ* prepared from 7-methylbicyclo-[2.2.1]heptane-7-carboxylic acid[18] and oxalyl dichloride, was conducted after the treatment with NaH, leading to the desired products (**17a**－**17c**, **17h**, **17i**, **17k**, **17l**, **17m**) in rewarding yields. Furthermore, **17b** and **17h** could be fluorinated with DAST at －78 ℃[19] to furnish the dehydroxy fluorinated products **17n** (74%)

Scheme 2 The synthetic route to the target compounds



Reagents and conditions: a. Cu, CuO, DMAP, CH_3CN, reflux, 12 h, for **11a**: 73%; **11b**: 60%; **11c**: 69%; **11f**: 67%; **11g**: 70%; b. *p*-TsOH•H_2O, *i*-PrOH/H_2O, reflux, 12 h, for **12a**: 88%; **12b**: 93%; **12c**: 95%; **12f**: 85%; **12g**: quant. yield; *c*. (i) *p*-TsOH•H_2O, MeOH, 1 h; (ii) KOH, reflux, 12 h, then aq. 3 mol•L^{-1} HCl; d. Et_3N, 2-chloro-1-methylpyridinium iodide (Mukaiyama's reagent), CH_3CN, reflux, overall yields based on **12**, for **14a**: 55%; **14b**: 51%; **14c**: 18%; **14f**: 67%; **14g**: 56%; e. Me_3CCH_2MgCl, 2-methylallyl magnesium chloride or EtMgBr, THF, -10 ℃, 1 h, **15a**: 97%; **15b**: 98%; **15c**: 77%; **15f**: 83%; **15g**: 68%; **15j**: 82%; **15l**: 57%; f. 10% Pd/C, H_2 (1 atm), MeOH/AcOEt, r.t., 3 h, for **16a**: 85%; **16b**: 87%; **16c**: 93%; **16h**: quant. yield; **16i**: quant. yield; **16l**: quant. yield; **16k**: 65% together with **16m**: 35%; g. Oxone, THF/H_2O, 0 ℃—r.t., for **15h**: 94%; **15i**: 93%; h. NaH, RCOCl, THF, r.t., 1 h, for **17a**: 58%; **17b**: 89%; **17c**: 72%; **17h**: 89%; **17i**: 87%; **17k**: 86%; **17l**: 76%; **17m**: 87%; i. DAST, CH_2Cl_2, –78 ℃—r.t., for **17n**: 74%; **17o**: 80%.

and **17o** (80%), respectively.

The synthetic penicillide analogues (**17a** — **17c**, **17h**, **17i**, **17k**—**17o**) were tested in inhibiting CETP-mediated transfer of ^{3}H-CE from HDL to LDL in human serum,[1c, 20] with the data shown in Table 1. The preliminary results indicated that the C-9 methyl group (Table 1, R^3) in penicillide could be replaced with hydrogen (**17a**, **17b**), but an aromatic substitution (**17c**) or a small hydrophilic group (**17h**, **17i**) significantly reduced the inhibition. The side-chain modification (Table 1, R^1) suggested that this moiety might tolerate a lipophilic group with different steric bulkiness, particularly the Et group gave an increasing inhibition (**17b**, **17k**, **17l**). However, the free hydroxyl (Table 1, R^2) in the side chain played an important role in retaining the inhibition, as its replacement by hydrogen or an H-bond acceptor (fluorine atom) dramatically decreased the inhibition (**17b**, **17m**, **17n**, **17o**).

Conclusions

In summary, we synthesized a series of the penicillide analogues, with modification at C-3 and C-9 positions. The preliminary data in inhibiting CETP suggested the importance of the H-bond donator in the side chain of penicillide, the more tolerance of C-3 alkyl chain, as well as the less tolerance at C-9 position in order to retain CETP inhibition.

Experimental

General information: Solvents were distilled from the appropriate drying agents before use. All the reagents were purchased from Acros, Alfa Aesar, and National Chemical Reagents Group Co. Ltd, P. R. China. Unless otherwise stated, all the reactions were performed under Ar. Column chromatography: Commercial silica gel (Qingdao Hai Yang Chemical Group Co.; 300—400 mesh). Spots on the TLC plates (GF 254,

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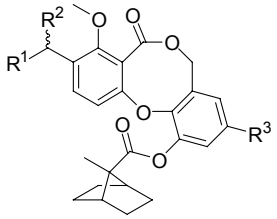
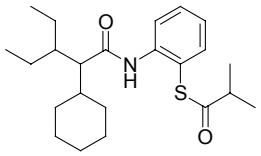
Table 1 The inhibition of the penicillide analogues against CETP



Compd.	R^1	R^2	R^3	Inhibition[a]
17a	Me_3CCH_2	OH	H	56
17b	Me_3CCH_2	OH	Me	59 (3)[b]
17c	Me_3CCH_2	OH	4-MeO-C_6H_4	8
17h	Me_3CCH_2	OH	SO_2Me	10
17i	Me_3CCH_2	OH	SO_2Et	0
17k	Me_2CHCH_2	OH	Me	96 (63)[b]
17l	Et	OH	Me	89 (89)[b]
17m	Me_2CHCH_2	H	Me	16
17n	Me_3CCH_2	F	Me	25
17o	Me_3CCH_2	F	SO_2Me	0
	 Dalcetrapid			100 (82)[b]

[a] The inhibition at 10 μmol•L^{-1} of tested compounds. [b] In the parentheses, the inhibition at 1 μmol•L^{-1}.

Yantai Jiangyou Silica R&D Co. Ltd., P. R. China) were detected under UV light or with iodine. The meltimg points of some compounds were obtained in an uncorrected melting instrument. ^{1}H and ^{13}C NMR spectra: Varian Mercury-Plus (300 or 400 MHz for ^{1}H, and 100 MHz for ^{13}C) spectrometer; chemical shifts δ in ppm, with residual $CHCl_3$ [δ (H) 7.26; δ (C) 77.0] as internal standard; J in Hz. EI-MS, ESI-MS and HR-APCI/ESI-MS: Finnigan Mat-95 mass spectrometer; in *m/z*.

3-(Benzyloxy)-2-hydroxybenzaldehyde (**2**): To a suspension of 60% NaH (5.80 g, 144 mmol) in dry THF (150 mL) was added dropwise a solution of 2,3-dihydroxybenzaldehyde (10.0 g, 72 mmol) in dry THF under stirring. The resulting mixture was stirred at r.t. for 1 h. Then benzyl bromide (12.3 g, 72 mmol) was added dropwise at 25 ℃ and continued to stir for 24 h. After the reaction was quenched with H_2O (300 mL), the mixture was acidified with aq. HCl to pH＝2 and extracted with CH_2Cl_2 (100 mL×3). The combined organic phases were washed with 1 mol•L^{-1} HCl, dried over $MgSO_4$ and concentrated. The residue was subjected to column chromatography (short SiO_2 column, petroleum ether/AcOEt＝20∶1) to give the crude product, which was further purified by recrystalization from EtOH: white solid **2** (10.7 g, 65%). TLC (petroleum ether/AcOEt＝10∶1): R_f 0.42. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 11.12 (s, 1H, OH), 9.92 (s, 1H, CHO), 7.47－7.32 (m, 5H, ArH), 7.20 (dd, J＝7.8, 1.4 Hz, 1H, ArH), 7.13 (d, J＝7.8 Hz, 1H, ArH), 6.90 (dd, J＝7.8 Hz, J'＝7.8 Hz, 1H, ArH), 5.20 (s, 2H, CH_2). MS (ESI): 229.1 [M＋H].

3-(Benzyloxy)-5-bromo-2-hydroxybenzaldehyde (**3a**): To a solution of **2** (4.00 g, 17.5 mmol) in MeCN (90 mL), was added $AcONH_4$ (137 mg, 1.75 mmol) and NBS (3.28 g, 18.4 mmol). The resulting mixture was stirred for 4 h at r.t., then concentrated. H_2O (100 mL) was added to the residue, the mixture was extracted with AcOEt (30 mL×3), the combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was subjected to column chromatography (SiO_2 petroleum ether/AcOEt＝20∶1) to give a yellowish solid **3a** (4.59 g, 85%). m.p. 116－117 ℃; TLC (petroleum ether/CH_2Cl_2＝2∶1): R_f 0.35. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 10.96 (s, 1H, OH), 9.86 (s, 1H, CHO), 7.46－7.35 (m, 5H, ArH), 7.33 (d, J＝2.4 Hz, 1H, ArH), 7.23 (d, J＝2.0 Hz, 1H, ArH), 5.16 (s, 2H, CH_2). MS (ESI): 329.0, 331.1 [M＋Na].

3-(Benzyloxy)-5-iodo-2-hydroxybenzaldehyde (**3b**): A solution of ICl (1.29 g, 7.95 mmol) in $CHCl_3$ (8 mL) was added dropwise to pyridine (20 mL) at r.t. After the mixture was stirred for 15 min, it was added to a solution of 2,3-dihydroxybenzaldehyde (1.01 g, 6.00 mmol) in $CHCl_3$ (10 mL), and the resulting mixture was stirred at r.t. for 6 h. After the reaction was completed (monitored by TLC), the reaction mixture was evaporated *in vacuo*, and the residue was diluted with $CHCl_3$ (50 mL), washed with 1 N HCl aq. (50 mL), 5% NaS_2O_3 aq. (50 mL), and water (50 mL). The organic phase was dried over Na_2SO_4. After filtered and evaporated, the residue was purified by column chromatography (SiO_2 petroleum ether/AcOEt＝20∶1) to give a yellowish solid **3b** (1.59 g, 88%). m.p. 87－88 ℃; TLC (petroleum ether/AcOEt＝4∶1): R_f 0.29. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 11.01 (s, 1H, OH), 9.84 (s, 1H, CHO), 7.50－7.20 (m, 7H, ArH), 5.13 (s, 2H, OCH_2). MS (ESI): 276.9 [M–H].

5-(Benzyloxy)-4-hydroxy-4'-methoxy-[1,1'-biphenyl]-3-carbaldehyde (**3c**): A dry flask was charged with **3a** (1.04 g, 3.40 mmol), 4-methoxyphenylboronic acid (0.62 g, 4.08 mmol), $Pd(PPh_3)_4$ (0.35 g, 0.34 mmol), 2 N K_2CO_3 (3.4 mL, 6.08 mmol) and MeOH (15 mL), the resulting mixture was stirred at 80 ℃ overnight. The solid was removed by filtration through a pad of celite, the filtrate was evaporated, and the residue was diluted with water/AcOEt (100 mL/100 mL). After separation, the organic phase was washed with water (100 mL), brine (100 mL), dried over $MgSO_4$, and concentrated. The residue was subjected to column chromatography (SiO_2, AcOEt/petroleum ether＝1∶20) to give a white solid **3c** (0.95 g, 84%). TLC (petroleum ether/AcOEt 10∶1): R_f 0.16. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 11.00 (s, 1H, OH), 9.98 (s, 1H, CHO), 7.49－7.47 (m, 2H, ArH), 7.41－7.33 (m, 7H, ArH), 6.97－6.95 (m, 2H, ArH), 5.25 (s, 2H, CH_2), 3.85 (s, 3H, OCH_3); ^{13}C NMR

($CDCl_3$, 100 MHz) δ: 196.5, 159.1, 151.1, 147.3, 136.4, 132.8, 132.0, 128.6 (2C), 128.1, 127.6 (2C), 127.4 (2C), 122.9, 121.0, 119.7, 114.3 (2C), 71.5, 55.3. MS (ESI): 335.2 [M＋H]. HRMS (APCI): Calcd for $C_{21}H_{19}O_4$ [M＋H]: 335.1283, found 335.1262

3-(Benzyloxy)-5-bromo-2-{[(*tert*-butyl)dimethylsilyl]-oxy}benzaldehyde (**4**): To a solution of **3a** (307 mg, 1.1 mmol) in DMF (1 mL) was added *N*,*N*-diisopropyl-ethylamine (0.35 mL, 2.0 mmol). After the mixture was stirred for 10 min, *t*-$BuMe_2SiCl$ (301 mg, 2.0 mmol) was added, and the resulting mixture was stirred at r.t. for 1 h. The reaction was quenched with H_2O (50 mL), the mixture was extracted with AcOEt (50 mL×3), the combined organic extracts were washed with H_2O, brine, dried over $MgSO_4$, and concentrated. The residue was subjected to column chromatography (SiO_2, petroleum ether/AcOEt＝100∶1) to give a yellow solid **4** (401 mg, 95%). m.p. 74－75 ℃; TLC (petroleum ether/AcOEt＝15∶1): R_f 0.78. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 10.40 (s, 1H), 7.52 (d, J＝2.4 Hz, 1H), 7.42－7.41 (m, 5H), 7.21 (d, J＝2.4 Hz, 1H), 5.03 (s, 2H), 0.92 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 188.7, 151.3, 148.5, 135.0, 128.9, 128.7 (2C), 128.4 (2C), 121.9, 121.1, 113.7, 71.4, 25.7 (3C), 18.7, 4.3 (2C). ESI-MS: 421.1, 423.1 [M＋H].

3-(Benzyloxy)-2-{[(*tert*-butyl)dimethylsilyl]oxy}-5-methylbenzaldehyde (**5**): To a flame-dried flask were added **4** (2.21 g, 5.24 mmol), [Pd(dppf)Cl_2] (58 mg, 0.08 mmol), 1.2 mol•L^{-1} dimethylzinc in toluene (5.2 mL, 6.29 mmol) and dry 1,4-dioxane (15 mL), the resulting suspension was heated at 110 ℃ for 1 h. After cooling, the mixture was quenched with aq. 1 N HCl (50 mL) and extracted with AcOEt (50 mL×2). The combined extracts were washed with H_2O, brine, dried over $MgSO_4$, and concentrated. The residue was subjected to column chromatography (SiO_2, petroleum ether/AcOEt ＝40∶1) to give a yellow solid **5** (1.53 g, 82%). m.p. 72－73 ℃; TLC (petroleum ether/AcOEt＝15∶1): R_f 0.57. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 10.46 (s, 1H), 7.44 －7.35 (m, 5H), 7.21 (s, 1H), 6.94 (d, J＝1.6 Hz, 1H), 5.05 (s, 2H), 2.28 (s, 3 H), 0.94 (s, 9H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 190.5, 150.1, 147.2, 136.0, 130.9, 128.6 (2C), 128.3, 128.2 (2C), 127.7, 119.7, 119.2, 71.0, 25.8 (3C), 21.0, 18.8, –4.3 (2C). MS (ESI): 357.2 [M＋H].

(3-(Benzyloxy)-2-((*tert*-butyldimethylsilyl)oxy)-5-methylphenyl)methanol (**6**): $NaBH_4$ (378 mg, 10.0 mmol) was added in portions to a stirred solution of **5** (891 mg, 2.5 mmol) in MeOH (200 mL) at 0 ℃. The resulting mixture was stirred for 4 h at r.t. and then concentrated. The residue was dissolved in aq. 3 N HCl (50 mL), then extracted with CH_2Cl_2 (20 mL×3). The combined CH_2Cl_2 extracts were washed with H_2O (50 mL×3), dried over Na_2SO_4, and concentrated to give a colorless oil **6** (812 mg, 91%). TLC (petroleum ether/AcOEt＝ 10∶1): R_f 0.41. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.42－7.30 (m, 5H), 6.75 (s, 1H), 6.68 (s, 1H), 5.02 (s, 2H), 4.67 (s, 2H), 2.26 (s, 3H), 2.23 (s, 1H), 0.94 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 148.9, 140.1, 136.5, 132.0, 130.7, 128.4 (2C), 128.2 (2C), 128.0, 121.0, 113.1, 70.6, 61.7, 25.9 (3C), 21.0, 18.6, 4.0 (2C). MS (ESI): 381.2 [M＋Na].

2-(Benzyloxy)-6-(hydroxymethyl)phenol (**7a**): Prepared according to the procedure for **6** except that a different substrate **2** was used. Colorless oil, yield: 98%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.42－7.36 (m, 5H, ArH), 6.91－6.79 (m, 3H, ArH), 6.08 (s, 1H, OH), 5.11 (s, 2H, CH_2), 4.74 (s, 2H, CH_2), 2.33 (br s, 1H, OH). MS (ESI): 253.0 [M＋Na].

3-(Benzyloxy)-2-(hydroxy)-5-methylbenzenemethanol (**7b**): To a cold (0 ℃) solution of **6** (323 mg, 0.90 mmol) in dry THF (9 mL) was added Bu_4NF•xH_2O (471 mg, 1.8 mmol). The resulting mixture was stirred at r.t. for 0.5 h. The reaction was quenched with H_2O (20 mL), then extracted with AcOEt (20 mL×3), the combined organic extracts were washed with H_2O, brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (SiO_2, petroleum ether/AcOEt＝4∶1) to give a colorless oil **7b** (206 mg, 94%). TLC (petroleum ether/AcOEt＝3∶1): R_f 0.26. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.43－7.37 (m, 5H, ArH), 6.73 (s, 1H, ArH), 6.70 (s, 1H, ArH), 5.91 (s, 1H, OH), 5.09 (s, 2H, CH_2), 4.70 (s, 2H, CH_2), 2.36 (s, 1H, OH), 2.28 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 145.4, 141.5, 136.3, 129.2, 128.7 (2C), 128.3, 127.8 (2C), 126.3, 121.5, 112.6, 71.1, 61.8, 21.0. MS (ESI): 267.1 [M＋Na].

3-(Benzyloxy)-5-(hydroxymethyl)-4'-methoxy-[1,1'-biphenyl]-4-ol (**7c**): Prepared according to the procedure for **6** except that a different substrate **3c** was used. colorless oil, yield: 86%. TLC (petroleum ether/AcOEt＝3∶1): R_f 0.21. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.45－7.44 (m, 7H, ArH), 7.08－7.07 (m, 2H, ArH), 6.96－6.94 (m, 2H, ArH), 6.10 (s, 1H, OH), 5.17 (s, 2H, CH_2), 4.79 (s, 2H, CH_2), 3.84 (s, 3H, OCH_3) , 2.40 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 158.7, 145.8, 143.0, 136.2, 133.5, 132.9, 128.7 (2C), 128.4, 127.8 (2C), 127.7 (2C), 126.8, 119.5, 114.1 (2C), 110.5, 71.3, 61.8, 55.3. MS (ESI): 335.2 [M–H]. HRMS (APCI): Calcd for $C_{21}H_{19}O_4$ [M–H]: 335.1284, found: 335.1261.

2-(Benzyloxy)-6-(hydroxymethyl)-4-iodophenol (**7d**): Prepared according to the procedure for **6** except that a different substrate **3b** was used. Colorless oil, yield: 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50－7.32 (m, 5H), 7.24 (s, 1H), 7.17 (d, J＝1.7 Hz, 1H), 6.08 (s, 1H), 5.06 (s, 2H), 4.66 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.4, 143.8, 135.6, 129.9, 128.9, 128.8 (2C), 128.6, 128.0 (2C), 120.6, 80.7, 71.5, 60.8. MS (ESI): 379.0 [M＋Na]. HRMS (EI): Calcd for $C_{14}H_{13}IO_3$ [M]: 355.9909, found: 355.9909.

8-(Benzyloxy)-6-iodo-2,2-dimethyl-4*H*-benzo[*d*][1,3]-dioxine (**9**): To a solution of **7d** (7.08 g, 19.9 mmol) in dry CH_2Cl_2 (100 mL) were added $TsOH$•H_2O (0.380 g, 2.0 mmol) and 2,2-dimethoxypropane (12.3 mL, 99.5 mmol), the resulting mixture continued to stir at r.t. for 0.5 h. The reaction solution was washed with sat. aq.

$NaHCO_3$ (100 mL), brine (100 mL), and dried over Na_2SO_4. The solvent was evaporated and the residue was subjected to column chromatography (SiO_2, petroleum ether/AcOEt＝4∶1), giving a colorless oil **9** (7.00 g, 95%). TLC R_f＝0.8 (petroleum ether/AcOEt＝1∶3). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.45－7.29 (m, 5H), 7.06 (s, 1H), 6.93 (d, J＝1.0 Hz, 1H), 5.10 (s, 2H), 4.77 (s, 2H), 1.57 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.2, 141.8, 136.6, 128.5 (2C), 127.9, 127.2, 126.1, 122.5, 122.3 (2C), 100.1, 81.2, 71.4, 60.0, 24.6 (2C). MS (ESI): 418.9 [M＋Na]. HRMS (ESI): Calcd for $C_{17}H_{17}IO_3Na$ [M＋Na]: 419.0120, found: 419.0114.

2-(Benzyloxy)-6-(hydroxymethyl)-4-(methylthio)phenol (**7f**): A dry flask was charged with **9** (0.198 g, 0.50 mmol), CuI (10 mg, 0.050 mmol), sulfur powder (48 mg, 1.5 mmol), K_2CO_3 (0.138 g, 1.0 mmol) and dry DMF (2.0 mL), the mixture was stirred at 90 ℃ for 10 h. After **9** disappeared as monitored by TLC (R_f 0.19, petroleum ether/AcOEt＝1∶10), the reaction mixture was cooled, and $NaBH_4$ (57 mg, 1.5 mmol) was added. The resulting mixture was stirred at 40 ℃ overnight, leading to the corresponding thiol (TLC: R_f 0.19, petroleum ether/AcOEt＝10∶1). After that, CH_3I (50 μL, 1.5 mmol) was added to the reaction mixture in one portion, and the reaction was stirred at r.t. overnight. The reaction mixture was diluted with AcOEt (10 mL), filtered through a pad of celite, and the filtrate was poured into a solution of water (40 mL) and sat. aq. NH_4Cl (20 mL), then extracted with AcOEt (20 mL×3). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4, and evaporated. The residue was subjected to column chromatography (SiO_2, petroleum ether/AcOEt＝5∶1, R_f 0.60), yielding 0.181 g of methylthio compound as a colorless oil.

The above methylthio compound was dissolved in aq. 1 N HCl (6.0 mL) and THF (6.0 mL), and refluxed for 2 h. After cooled, the solution was diluted with AcOEt (20 mL) and water (20 mL). The aq. phase was extracted with AcOEt (20 mL×2), and the combined organic phases were washed with brine (50 mL), dried over Na_2SO_4, and evaporated. The residue was subjected to column chromatography (petroleum ether/AcOEt＝5∶1), furnishing a colorless oil **7f** (0.116 g, 84% overall yield). TLC R_f 0.54 (petroleum ether/AcOEt＝3∶1). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.73－7.29 (m, 5H), 7.10－6.70 (m, 2H), 6.06 (s, 1H), 5.08 (s, 2H), 4.69 (s, 2H), 2.42 (s, 3H), 2.38 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.8, 142.4, 136.0, 128.7 (2C), 128.5, 128.0, 127.9 (2C), 127.2, 121.4, 112.9, 71.4, 61.4, 18.1. MS (ESI): 275.0 [M–H]. HRMS (ESI): Calcd for $C_{15}H_{15}O_3S$ [M–H]: 275.0742, found: 275.0755.

2-(Benzyloxy)-4-(ethylthio)-6-(hydroxymethyl)phenol (**7g**): Prepared according to the procedure for **7f** except that a different substrate (EtI) was used. Colorless oil, yield: 83%. TLC R_f 0.18 (petroleum ether/AcOEt＝4∶1). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.39－7.34 (m, 5H), 6.95 (s, 2H), 6.28 (s, 1H), 5.06 (s, 2H), 4.66 (s, 2H), 2.80 (q, J＝7.2 Hz, 2H), 2.62 (brs, 1H), 1.20 (t, J＝7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.6, 143.2, 136.0, 128.7 (2C), 128.4, 127.8 (2C), 127.1, 125.5, 124.5, 115.5, 71.2, 61.3, 29.8, 14.5. MS (ESI): 289.1 [M–H]. HRMS (ESI): Calcd for $C_{16}H_{18}NaO_3S$ [M＋Na]: 313.0874, found: 313.0853.

2-(Benzyloxy)-6-(((tetrahydro-2*H*-pyran-2-yl)oxy)-methyl)phenol (**8a**): To a cold (－10 ℃) solution of **7a** (0.300 g, 1.3 mmol) in dry CH_2Cl_2 (20 mL) was added $TsOH•H_2O$ (0.024 g, 0.13 mmol), the resulting mixture was stirred at –10 ℃ for 15 min. Then 3,4-dihydro-2*H*-pyran (0.35 mL, 3.84 mmol) was added dropwise and the solution was stirred at r.t. overnight. The reaction was quenched with Et_3N (1 mL), the mixture was washed with brine, dried over $MgSO_4$, and evaporated. The residue was subjected to column chromatography (SiO_2, petroleum ether/AcOEt＝20∶1) to give a white solid **8a** (0.393 g, 96%). m.p. 76－77 ℃; TLC (petroleum ether/AcOEt＝6∶1): R_f 0.60. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.44－7.33 (m, 5H, ArH), 6.94 (dd, J＝7.6, 1.2 Hz, 1H, ArH), 6.87 (dd, J＝7.8, 1.2 Hz, 1H, ArH), 6.80 (dd, J＝7.8 Hz, J'＝7.8 Hz, 1H, ArH), 6.38 (s, 1H, OH), 5.11 (s, 2H, CH_2), 4.86 (d, J＝12.0 Hz, 1H, CH_2), 4.76 (t, J＝3.8 Hz, 1H, CH_2), 4.63 (d, J＝12.0 Hz, 1H, CH_2), 3.96－3.93 (m, 1H, CH_2), 3.58－3.55 (m, 1H, CH_2), 1.86－1.52 (m, 6H). MS (ESI): 337.2 [M＋Na].

2-(Benzyloxy)-4-methyl-6-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)phenol (**8b**): Prepared according to the procedure for **8a** except that a different substrate **7b** was used. White solid, yield: 84%. m.p. 98－99 ℃; TLC R_f 0.67 (petroleum ether/AcOEt＝4∶1). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.44－7.34 (m, 5H), 6.74 (s, 1H), 6.71 (s, 1H), 6.23 (s, 1H), 5.08 (s, 2H), 4.82 (d, J＝12.0 Hz, 1H), 4.75 (t, J＝3.3 Hz, 1H), 4.58 (d, J＝12.0 Hz, 1H), 4.00－3.95 (m, 1H), 3.60－3.50 (m, 1H), 2.26 (s, 3H), 1.88－1.53 (m, 6H). MS (ESI): 351.1 [M＋Na]. HRMS (ESI): Calcd for $C_{20}H_{23}O_4$ [M–H]: 327.1597, found: 328.1610.

3-(Benzyloxy)-4'-methoxy-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-[1,1'-biphenyl]-4-ol (**8c**): Prepared according to the procedure for **8a** except that a different substrate **7c** was used. White solid, yield: 92%. m.p. 83－84 ℃; TLC R_f 0.57 (petroleum ether/AcOEt＝3∶1). ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.46－7.35 (m, 7H, ArH), 7.12 (d, J＝1.6 Hz, 1H, ArH), 7.07 (d, J＝2.0 Hz, 1H, ArH), 6.95－6.92 (m, 2H, ArH), 6.40 (s, 1H, OH), 5.17 (s, 2H, CH_2), 4.90 (d, J＝12.0 Hz, 1H, CH_2), 4.79 (t, J＝3.5 Hz, 1H, CH), 4.67 (d, J＝12.0 Hz, 1H, CH_2), 4.01－3.95 (m, 1H, CH_2), 3.83 (s, 3H, OCH_3), 3.60－3.56 (m, 1H, CH_2), 1.89－1.54 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 158.6, 146.2, 143.6, 136.5, 133.7, 132.6, 128.6 (2C), 128.2, 127.8 (2C), 127.7 (2C), 124.0, 120.3, 114.0 (2C), 111.0, 98.2, 71.3, 64.9, 62.5, 55.3, 30.5, 25.3, 19.5. MS (ESI): 443.2 [M＋Na]. HRMS (APCI): Calcd for $C_{26}H_{27}O_5$ [M–H]: 419.1859, found: 419.1823.

2-(Benzyloxy)-4-iodo-6-(((tetrahydro-2*H*-pyran-2-yl)-oxy)methyl)phenol (**8d**): Prepared according to the pro-

cedure for **8a** except that a different substrate **7d** was used. White solid, quantitative yield. TLC R_f 0.1 (petroleum ether/AcOEt＝4∶1). The crude product was directly used in next step.

2-(Benzyloxy)-4-(methylsulfonyl)-6-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)phenol (**8e**): A dry flask was charged with **8d** (0.127 g, 0.29 mmol), CuI (6 mg, 0.03 mmol), CH_3SO_2Na (0.036 g, 0.35 mmol), *L*-proline (12 mg, 0.06 mmol), NaOH (5 mg, 0.1 mmol) and dry DMSO (2 mL), the mixture was stirred at 85 ℃ for 36 h. After cooled, the reaction mixture was diluted with AcOEt (40 mL) and filtered through a pad of celite. The filtrate was washed with a solution of water 40 (mL) and sat. aq. NH_4Cl (20 mL), the separated aq. phase was extracted with AcOEt (20 mL×4), and the combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, and subjected to column chromatography (SiO_2, petroleum ether/AcOEt＝2.8∶1), yielding a white solid **8e** (59 mg, 52%). TLC R_f 0.1 (petroleum ether/AcOEt＝4∶1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (s, 1H), 7.47－7.35 (m, 6H), 7.04 (d, J＝6.3 Hz, 1H), 5.17 (s, 2H), 4.89 (d, J＝12.8 Hz, 1H), 4.75 (s, 1H), 4.62 (d, J＝12.8 Hz, 1H), 4.00－3.95 (m, 1H), 3.60－3.50 (m, 1H), 3.00 (s, 3H), 1.88－1.56 (m, 6H). MS (ESI): 391.1 [M–H].

2-(Benzyloxy)-4-(methylthio)-6-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)phenol (**8f**): Prepared according to the procedure for **8a** except that a different substrate **7f** was used. White solid, yield: 78%. TLC R_f 0.74 (petroleum ether/AcOEt＝4∶1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.51－7.29 (m, 4H), 6.94 (d, J＝2.0 Hz, 1H), 6.89 (d, J＝2.0 Hz, 1H), 6.35 (s, 1H), 5.10 (s, 2H), 4.82 (d, J＝12.3 Hz, 1H), 4.80－4.70 (m, 1H), 4.59 (d, J＝12.3 Hz, 1H), 4.00－3.95 (m, 1H), 3.60－3.50 (m, 1H), 2.41 (s, 3H), 1.89－1.50 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.2, 143.0, 136.2, 128.6 (2C), 128.3, 127.7 (2C), 127.5, 124.6, 122.2, 113.4, 98.2, 71.3, 64.5, 62.4, 30.5, 25.3, 19.4, 18.1. HRMS (ESI): Calcd for $C_{20}H_{23}O_4S$ [M–H]: 359.1317, found 359.1337.

2-(Benzyloxy)-4-(ethylthio)-6-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)phenol (**8g**): Prepared according to the procedure for **8a** except that a different substrate **7g** was used. White solid, yield: 82%. TLC R_f 0.6 (petroleum ether/AcOEt＝5∶1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46－7.29 (m, 5H), 7.02 (d, J＝1.2 Hz, 1H), 6.95 (s, 1H), 6.42 (s, 1H), 5.09 (s, 2H), 4.82 (d, J＝12.3 Hz, 1H), 4.80－4.70 (m, 1H), 4.59 (d, J＝12.3 Hz, 1H), 3.94 (dd, J＝13.6, 5.8 Hz, 1H), 3.60－3.50 (m, 1H), 2.80 (q, J＝7.3 Hz, 2H), 1.90－1.69 (m, 2H), 1.69－1.49 (m, 4H), 1.20 (t, J＝7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.9, 143.6, 136.2, 128.6 (2C), 128.2, 127.6 (2C), 125.2, 125.1, 124.4, 115.9, 98.2, 71.2, 64.4, 62.4, 30.4, 29.8, 25.3, 19.4, 14.5. MS (ESI): 397.1 [M＋Na]. HRMS (ESI): Calcd for $C_{21}H_{26}NaO_4S$ [M＋Na]: 397.1449, found 397.1430.

Methyl 6-(2-(Benzyloxy)-6-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)phenoxy)-3-formyl-2-methoxybenzoate (**11a**): To a flame-dried flask were added **8a** (1.12 g, 3.55 mmol), **10** (0.808 g, 2.96 mmol), activated Cu powder (0.474 g, 7.40 mmol), CuO black (0.592 g, 7.40 mmol), DMAP (1.08 g, 8.88 mmol) and dry MeCN (25 mL), the resulting suspension was refluxed for 17 h. After cooling, the mixture was diluted with CH_2Cl_2 (20 mL) and filtered through a pad of celite, the filter cake was washed with CH_2Cl_2 (10 mL×3), the filtrate was concentrated, and the residue was subjected to column chromatography (SiO_2, petroleum ether/AcOEt＝6∶1) to give a yellowish oil **11a** (1.10 g, 73%). TLC (petroleum ether/AcOEt＝10∶1): R_f 0.11. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 10.22 (s, 1H, CHO), 7.71 (d, J＝4.7 Hz, 1H, ArH), 7.27－7.13 (m, 7H, ArH), 6.99 (dd, J＝8.1, 1.4 Hz, 1H, ArH), 6.43 (d, J＝8.8 Hz, 1H, ArH), 5.02 (s, 2H, CH_2), 4.73 (d, J＝12.0 Hz, 1H, CH_2), 4.67－4.66 (m, 1H, CH), 4.48 (d, J＝12.0 Hz, 1H, CH_2), 3.99 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 3.83－3.76 (m, 1H, CH_2), 3.51－3.45 (m, 1H, CH_2), 1.65－1.43 (m, 6H). MS (ESI): 529.2 [M＋Na].

Methyl 6-(2-(benzyloxy)-4-methyl-6-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)phenoxy)-3-formyl-2-methoxybenzoate (**11b**): Prepared according to the procedure for **11a** except that a different substrate **8b** was used. Yellowish oil, yield: 60%. TLC R_f 0.09 (petroleum ether/AcOEt＝10∶1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 10.22 (s, 1H, CHO), 7.76 (d, J＝8.7 Hz, 1H, ArH), 7.28－7.16 (m, 5H, ArH), 6.94 (s, 1H, ArH), 6.83 (s, 1H, ArH), 6.46 (d, J＝9.1 Hz, 1H, ArH), 5.00 (s, 2H, CH_2), 4.69 (d, J＝12 Hz, 1H, CH_2), 4.75－4.60 (m, 1H, CH), 4.43 (d, J＝12 Hz, 1H, CH_2), 3.99 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.85－3.75 (m, 1H, CH_2), 3.55－3.40 (m, 1H, CH_2), 2.36 (s, 3H, CH_3), 1.66－1.41 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 187.7, 165.3, 161.7, 161.5, 150.1, 138.3, 136.5, 136.4, 132,2, 131.0, 128.2 (2C), 127.6, 126.7 (2C), 122.9, 122.5, 117.8, 114.9, 110.3, 98.4, 70.4, 64.7, 64.3, 61.8, 52.6, 30.2, 25.3, 21.4, 19.0. MS (ESI): 543.4 [M＋Na]. HRMS (ESI): Calcd for $C_{30}H_{32}O_8Na$ [M＋Na]: 543.1995, found 543.1968.

Methyl 6-((3-(benzyloxy)-4'-methoxy-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)-[1,1'-biphenyl]-4-yl)oxy)-3-formyl-2-methoxybenzoate (**11c**): Prepared according to the procedure for **11a** except that a different substrate **8c** was used. Yellowish oil, yield: 69%. TLC R_f 0.32 (petroleum ether/AcOEt＝5∶1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 10.23 (s, 1H, CHO), 7.74 (d, J＝8.7 Hz, 1H, ArH), 7.50－7.47 (m, 2H, ArH), 7.31－7.16 (m, 7H, ArH), 7.00－6.97 (m, 2H, ArH), 6.53 (d, J＝8.7 Hz, 1H, ArH), 5.08 (s, 2H, CH_2), 4.77 (d, J＝12 Hz, 1H, CH_2), 4.71－4.70 (m, 1H, CH), 4.51 (d, J＝12 Hz, 1H, CH_2), 4.00 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.84－3.78 (m, 1H, CH_2), 3.52－3.47 (m, 1H, CH_2), 1.64－1.42 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 187.8, 165.3, 161.7, 161.3, 159.3, 150.5, 139.6, 139.4, 136.3, 132.9, 132.8, 131.1, 128.3 (2C), 128.1 (2C), 127.7, 126.8 (2C), 123.1, 120.3, 117.9, 114.2 (2C), 112.6, 110.4, 98.5, 70.6, 64.8, 64.4, 61.8, 55.3, 52.7, 30.2, 25.3, 19.1. MS (ESI): 635.1 [M＋Na]. HRMS (ESI): Calcd for $C_{36}H_{37}O_9$ [M＋H]: 613.2438,

found 613.2395.

Methyl 6-(2-(benzyloxy)-4-(methylthio)-6-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)phenoxy)-3-formyl-2-methoxybenzoate (**11f**): Prepared according to the procedure for **11a** except that a different substrate **8f** was used. Yellowish oil, yield: 67%. TLC R_f 0.12 (petroleum ether/AcOEt=10∶1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.21 (s, 1H), 7.72 (d, J=8.9 Hz, 1H), 7.35−7.19 (m, 3H), 7.20−7.10 (m, 1H), 7.14 (s, 1H), 7.01 (s, 1H), 6.88 (s, 1H), 6.45 (d, J=8.8 Hz, 1H), 5.00 (s, 2H), 4.68 (d, J=12.5 Hz, 1H), 4.66 (s, 1H), 4.44 (d, J=12.5 Hz, 1H), 3.98 (s, 3H), 3.94 (s, 3H), 3.90−3.70 (m, 1H), 3.55−3.45 (m, 1H), 2.48 (s, 3H), 1.69−1.32 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 187.7, 165.2, 161.7, 161.2, 150.4, 138.1, 136.6, 136.0, 133.2, 131.0, 128.2, 127.7, 126.7, 123.1, 119.4, 117.8, 112.4, 110.1, 98.4, 70.6, 64.7, 64.0, 61.8, 52.6, 30.2, 25.2, 19.0, 16.1. MS (ESI): 575.2 [M+Na]. HRMS (ESI): Calcd for $C_{30}H_{32}NaO_8S$ [M+Na]: 575.1716, found 575.1719.

Methyl 6-(2-(benzyloxy)-4-(ethylthio)-6-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)phenoxy)-3-formyl-2-methoxybenzoate (**11g**): Prepared according to the procedure for **11a** except that a different substrate **8g** was used. White solid, yield: 70%. TLC R_f 0.11 (petroleum ether/AcOEt=10∶1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.21 (s, 1H), 7.72 (d, J=8.8 Hz, 1H), 7.31−7.19 (m, 3H), 7.17−7.11 (m, 2H), 7.09 (d, J=2.0 Hz, 1H), 6.95 (d, J=2.0 Hz, 1H), 6.46 (d, J=8.8 Hz, 1H), 5.00 (s, 2H), 4.70−4.66 (m, 2H), 4.44 (d, J=12.3 Hz, 1H), 3.98 (s, 3H), 3.94 (s, 3H), 3.90−3.70 (m, 1H), 3.55−3.45 (m, 1H), 2.93 (q, J=7.4 Hz, 2H), 1.60−1.35 (m, 6H), 1.29 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 187.7, 165.2, 161.7, 161.2, 150.4, 138.7, 136.1, 134.9, 133.3, 131.1, 128.3 (2C), 127.8, 126.8 (2C), 123.2, 121.9, 117.9, 114.6, 110.3, 98.4, 70.6, 64.8, 64.0, 61.9, 52.7, 30.2, 27.9, 25.3, 19.0, 14.3. HRMS (ESI): Calcd for $C_{31}H_{34}NaO_8S$ [M+Na]: 589.1827, found 589.1849.

Methyl 6-(2-(benzyloxy)-6-(hydroxymethyl)phenoxy)-3-formyl-2-methoxybenzoate (**12a**): To a flame-dried flask were added **11a** (1.01 g, 2.0 mmol), TsOH•H_2O (2 mg), *i*-PrOH (10 mL), and H_2O (3 mL), and the resulting solution was refluxed overnight. After cooling, the mixture was extracted with AcOEt (30 mL×3). The combined extracts were washed with H_2O, brine, dried over Na_2SO_4, and concentrated. The residue was subjected to column chromatography (SiO_2, petroleum ether/AcOEt=3∶1) to give a colorless oil **12a** (0.72 g, 88%). TLC (petroleum ether/AcOEt=3∶1): R_f 0.14. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 10.20 (s, 1H, CHO), 7.73 (d, J=8.6 Hz, 1H, ArH), 7.26−7.14 (m, 6H, ArH), 7.07 (d, J=7.2 Hz, 1H, ArH), 6.99 (d, J=8.4 Hz, 1H, ArH), 6.43 (d, J=9.0 Hz, 1H, ArH), 5.02 (s, 2H, CH_2), 4.60 (s, 2H, CH_2), 3.98 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 2.74 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 187.7, 165.5, 161.9, 160.7, 150.5, 140.2, 136.3, 135.3, 131.6, 128.3 (2C), 127.8, 126.8 (2C), 126.7, 123.4, 121.3, 117.5, 114.0, 110.0, 70.5, 64.7, 60.5, 52.9. MS (EI): 422 [M]. HRMS (ESI): calcd for $C_{24}H_{22}O_7Na$ [M+Na]: 445.1263, found 445.1262.

Methyl 6-(2-(benzyloxy)-6-(hydroxymethyl)-4-methylphenoxy)-3-formyl-2-methoxybenzoate (**12b**): Prepared according to the procedure for **12a** except that a different substrate **11b** was used. Colorless oil, yield: 93%. TLC R_f 0.20 (petroleum ether/AcOEt=3∶1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 10.22 (s, 1H, CHO), 7.74 (d, J=9.0 Hz, 1H, ArH), 7.29−7.16 (m, 5H, ArH), 6.88 (s, 1H, ArH), 6.83 (s, 1H, ArH), 6.46 (d, J=9.0 Hz, 1H, ArH), 5.02 (s, 2H, CH_2), 4.56 (s, 2H, CH_2), 3.40 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 2.78 (br s, 1H, OH), 2.35 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 187.7, 165.6, 161.9, 160.9, 150.2, 138.0, 136.8, 136.3, 134.6, 131.6, 128.3 (2C), 127.7, 126.7 (2C), 123.3, 121.9, 117.4, 114.7, 109.9, 70.5, 64.7, 60.7, 52.9, 21.4. MS (ESI): 459.3 [M+Na]. HRMS (ESI): Calcd for $C_{25}H_{24}O_7Na$ [M+Na]: 459.1420, found 459.1409.

Methyl 6-((3-(benzyloxy)-5-(hydroxymethyl)-4'-methoxy-[1,1'-biphenyl]-4-yl)oxy)-3-formyl-2-methoxybenzoate (**12c**): Prepared according to the procedure for **12a** except that a different substrate **11c** was used. Colorless oil, yield: 95%. TLC R_f 0.14 (petroleum ether/AcOEt=3∶1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 10.23 (s, 1H, CHO), 7.77 (d, J=9.1 Hz, 1H, ArH), 7.49−7.46 (m, 2H, ArH), 7.29−7.16 (m, 7H, ArH), 6.99−6.96 (m, 2H, ArH), 6.53 (d, J=9.1 Hz, 1H, ArH), 5.09 (s, 2H, CH_2), 4.65 (d, J=6.0 Hz, 2H, CH_2), 4.01 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 2.74 (t, J=6.0 Hz, 1H, OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 187.7, 165.5, 161.9, 160.8, 159.4, 150.7, 139.7, 139.2, 136.2, 135.2, 132.7, 131.6, 128.4 (2C), 128.1 (2C), 127.9, 126.9 (2C), 123.5, 119.8, 117.5, 114.2 (2C), 112.5, 110.1, 70.7, 64.8, 61.0, 55.3, 52.9. MS (ESI): 528.7 [M+H]. HRMS (APCI): calcd for $C_{31}H_{29}O_8$ [M+H]: 529.1862, found 529.1850.

Methyl 6-(2-(benzyloxy)-6-(hydroxymethyl)-4-(methylthio)phenoxy)-3-formyl-2-methoxybenzoate (**12f**): Prepared according to the procedure for **12a** except that a different substrate **11f** was used. Colorless oil, quantitative yield. TLC R_f 0.15 (petroleum ether/AcOEt=3∶1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.20 (s, 1H), 7.73 (d, J=8.8 Hz, 1H), 7.33−7.19 (m, 3H), 7.19−7.08 (m, 2H), 6.96 (s, 1H), 6.88 (d, J=1.5 Hz, 1H), 6.45 (d, J=8.8 Hz, 1H), 5.01 (s, 2H), 4.57 (d, J=3.8 Hz, 2H), 3.98 (s, 3H), 3.95 (s, 3H), 2.92 (brs, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 187.6, 165.5, 161.8, 160.7, 150.5, 137.6, 137.0, 135.9, 135.5, 131.6, 128.3, 127.8, 126.8, 123.4, 118.7, 117.4, 112.1, 109.8, 70.6, 64.7, 60.4, 52.8, 16.0. HRMS (ESI): Calcd for $C_{25}H_{25}O_7S$ [M+H]: 469.1321, found 469.1324.

Methyl 6-(2-(benzyloxy)-4-(ethylthio)-6-(hydroxymethyl)phenoxy)-3-formyl-2-methoxybenzoate (**12g**): Prepared according to the procedure for **12a** except that a different substrate **11g** was used. Colorless oil, quantitative yield. TLC R_f 0.18 (petroleum ether/AcOEt=3∶1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.16 (s, 1H), 7.70 (d, J=8.8 Hz, 1H), 7.26−7.18 (m, 3H), 7.16−

7.09 (m, 2H), 7.07 (d, J=1.8 Hz, 1H), 6.93 (d, J=1.8 Hz, 1H), 6.44 (d, J=8.8 Hz, 1H), 4.98 (s, 2H), 4.57 (s, 2H), 3.95 (s, 3H), 3.90 (s, 3H), 3.51 (brs, 1H), 2.89 (q, J=7.3 Hz, 2H), 1.26 (t, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 187.8, 165.5, 161.8, 160.8, 150.4, 138.0, 136.1, 135.8, 135.2, 131.6, 128.3 (2C), 127.8, 126.8 (2C), 123.4, 120.9, 117.5, 114.1, 110.0, 70.6, 64.7, 59.9, 52.8, 27.8, 14.2. HRMS (APCI): Calcd for $C_{26}H_{27}O_7S$ [M+H]: 483.1477, found 483.1454.

6-(2-(Benzyloxy)-6-(hydroxymethyl)phenoxy)-3-formyl-2-methoxybenzoic acid (**13a**): To a solution of **12a** (0.655 g, 1.55 mmol) in MeOH (12 mL) was added TsOH•H_2O (55 mg, 0.32 mmol), and the resulting mixture was stirred at r.t. for 1 h. Then NaOH tablets (0.722 g, 18.5 mmol) were added, and the mixture was refluxed overnight. After cooling, the MeOH was evaporated, the mixture was acidified with aq. 3 N HCl to adjust pH=3−4. The mixture was extracted with AcOEt (30 mL×4) and the combined extracts were concentrated to give a colorless oil **13a** (837 mg, almost quantitative yield), which was used in next step without further purification.

13b, **13c**, **13f**, **13g** were prepared according to the above operation except for different substrates used. The spetral data of **13b** are presented as an example: ^{1}H NMR (DMSO, 400 MHz) δ: 10.11 (s, 1H, CHO), 7.67 (d, J=8.8 Hz, 1H, ArH), 7.25−7.18 (m, 5H, ArH), 7.03 (s, 1H, ArH), 6.98 (s, 1H, ArH), 6.38 (d, J=8.8 Hz, 1H, ArH), 5.08 (s, 2H, CH_2), 4.37 (s, 2H, CH_2), 3.97 (s, 3H, OCH_3), 2.34 (s, 3H, CH_3). MS (ESI): 421.0 [M–H].

11-(Benzyloxy)-4-methoxy-5-oxo-5,7-dihydrodibenzo[*b*,*g*][1,5]dioxocine-3-carbaldehyde (**14a**): To a solution of 2-chloro-1-methylpyridinium iodide (1.42 g, 5.57 mmol) in dry MeCN (40 mL) was added a solution of the above crude **13a** (0.568 g, 1.39 mmol) in dry MeCN (10 mL) and Et_3N (4.4 mL, 31.6 mmol) at 80 ℃ by a syringe pump within 5 h. The resulting mixture was refluxed for another 8 h. After cooling to r.t., the mixture was concentrated, the residue was dissolved in CH_2Cl_2 (30 mL) and filtered through a pad of SiO_2, the filter cake was washed with CH_2Cl_2 (10 mL×5). The filtrate was washed with H_2O (30 mL×3), dried over $MgSO_4$, and concentrated. The residue was subjected to column chromatography (SiO_2, CH_2Cl_2) to give a white solid **14a** (0.261 g, 55% based on **12a**). m.p. 123−124 ℃; TLC (petroleum ether/AcOEt=2∶1): R_f 0.67. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 10.35 (s, 1H, CHO), 7.99 (d, J=8.6 Hz, 1H, ArH), 7.50−7.34 (m, 5H, ArH), 7.08−7.01 (m, 3H, ArH), 6.67 (d, J=7.1 Hz, 1H, ArH), 5.22 (s, 2H, CH_2), 5.18 (s, 2H, CH_2), 4.12 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 187.7, 166.0, 161.2, 157.6, 150.7, 145.2, 136.4, 133.3, 128.7 (2C), 128.1, 127.8, 127.2 (2C), 127.1, 125.2, 121.1, 120.5, 118.7, 115.9, 71.2, 68.9, 64.6. MS (ESI): 391.2 [M+H]. HRMS (ESI): Calcd for $C_{23}H_{18}O_6Na$ [M + Na]: 413.1001, found 413.0987.

11-(Benzyloxy)-4-methoxy-9-methyl-5-oxo-5,7-dihydrodibenzo[*b*,*g*][1,5]dioxocine-3-carbaldehyde (**14b**): Prepared according to the procedure for **14a** except that a different substrate **13b** was used, a white solid **14b** (51% based on **12b**). m.p. 57−58 ℃; TLC (petroleum ether/AcOEt=2∶1): R_f 0.80. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 10.35 (d, J=0.6 Hz, 1H, CHO), 7.98 (d, J=8.6 Hz, 1H, ArH), 7.51−7.35 (m, 5H, ArH), 7.03 (dd, J=8.6, 0.6 Hz, 1H, ArH), 6.89 (d, J=1.4 Hz, 1H, ArH), 6.48 (d, J=1.4 Hz, 1H, ArH), 5.20 (s, 2H, CH_2), 5.13 (s, 2H, CH_2), 4.12 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 187.8, 166.1, 161.2, 158.0, 150.4, 143.2, 136.5, 135.3, 133.3, 128.7 (2C), 128.1, 127.32, 127.27 (2C), 127.0, 121.5, 120.6, 118.7, 116.6, 71.3, 69.0, 64.7, 21.2. MS (ESI): 427.0 [M+Na]. HRMS (ESI): Calcd for $C_{24}H_{20}O_6Na$ [M + Na]: 427.1158, found 427.1133.

11-(Benzyloxy)-4-methoxy-9-(4-methoxyphenyl)-5-oxo-5,7-dihydrodibenzo[*b*,*g*][1,5]dioxocine-3-carbaldehyde (**14c**): Prepared according to the procedure for **14a** except that a different substrate **13c** was used, a yellowish oil **14c** (18% based on **12c**). TLC (petroleum ether/AcOEt=2∶1): R_f 0.58. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 10.37 (s, 1H, CHO), 8.02 (d, J=8.7 Hz, 1H, ArH), 7.54−7.51 (m, 2H, ArH), 7.45−7.36 (m, 5H, ArH), 7.23 (d, J=2.0 Hz, 1H, ArH), 7.08 (dd, J=8.7, 0.8 Hz, 1H, ArH), 6.97−6.94 (m, 2H, ArH), 6.83 (d, J=2.0 Hz, 1H, ArH), 5.28 (s, 2H, CH_2), 5.23 (s, 2H, CH_2), 4.14 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 187.8, 166.0, 161.2, 159.5, 157.7, 150.8, 144.2, 138.3, 136.4, 133.4, 132.2, 128.7 (2C), 128.2, 128.0 (2C), 127.8, 127.4 (2C), 127.1, 120.6, 119.4, 118.8, 114.4, 114.3 (2C), 71.5, 69.1, 64.7, 55.3. HRMS (APCI): Calcd for $C_{30}H_{25}O_7$ [M+H]: 497.1600, found 497.1599.

11-(Benzyloxy)-4-methoxy-9-(methylthio)-5-*oxo*-5,7-dihydrodibenzo[*b*,*g*][1,5]dioxocine-3-carbaldehyde (**14f**): Prepared according to the procedure for **14a** except that a different substrate **13f** was used, a yellowish solid **14f** (67% based on **12f**). m.p. 99−100 ℃; TLC (petroleum ether/AcOEt=2∶1): R_f 0.61. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.33 (s, 1H), 7.98 (d, J=8.5 Hz, 1H), 7.55−7.30 (m, 5H), 7.02 (d, J=8.5 Hz, 1H), 6.96 (d, J=2.1 Hz, 1H), 6.54 (d, J=2.1 Hz, 1H), 5.20 (s, 2H), 5.13 (s, 2H), 4.11 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 187.8, 165.9, 161.2, 157.7, 150.8, 143.1, 136.2, 135.6, 133.4, 128.8, 128.3, 128.2, 127.4 (2C), 127.2, 120.5, 119.1, 118.7, 114.5, 71.5, 68.8, 64.7, 16.4. MS (ESI): 436.9 [M+H]. HRMS (ESI): Calcd for $C_{24}H_{21}O_6S$ [M+H]: 437.1059, found 437.1066.

11-(Benzyloxy)-9-(ethylthio)-4-methoxy-5-oxo-5,7-dihydrodibenzo[*b*,*g*][1,5]dioxocine-3-carbaldehyde (**14g**): Prepared according to the procedure for **14a** except that a different substrate **13g** was used, a yellowish solid **14g** (56% based on **12g**). m.p. 143−144 ℃; TLC (petroleum ether/acetone=4∶1): R_f 0.30. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.34 (s, 1H), 8.00 (d, J=8.5 Hz, 1H), 7.48 (d, J=7.3 Hz, 2H), 7.45−7.31 (m, 3H), 7.03 (d, J=8.5 Hz, 2H), 6.63 (d, J=1.7 Hz, 1H), 5.21 (s, 2H), 5.13 (s, 2H), 4.11 (s, 3H), 2.84 (q, J=7.3 Hz, 2H), 1.23 (t, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ:

187.7, 165.9, 161.2, 157.6, 150.6, 143.6, 136.1, 133.5, 133.4, 128.7, 128.3, 128.0, 127.3, 127.1, 121.8, 120.4, 118.7, 116.8, 71.4, 68.8, 64.7, 28.2, 14.2. MS (ESI): 451.1 [M＋H]. HRMS (APCI): Calcd for $C_{25}H_{23}O_6S$ [M＋H]: 451.1215, found 451.1224.

11-(Benzyloxy)-3-(1-hydroxy-3,3-dimethylbutyl)-4-methoxydibenzo[*b*,*g*][1,5]dioxocin-5(7*H*)-one (**15a**): A dry flask was charged with fresh magnesium sheet (1.05 g, 44 mmol) and anhydrous ether (5.0 mL) and stirred at r.t. under Ar atmosphere, then a grain of iodine was added. After red color disappeared, a solution (1 mL) of neopentyl bromide (5 mL) in anhydrous ether (10 mL) was added dropwise to keep the reaction solution refluxing, and the reaction mixture continued to reflux for 12 h. The solution was used directly in next step.

To a cold (－10 ℃) solution of **14a** (0.150 g, 0.38 mmol) in dry THF (10 mL) was added a THF solution (0.9 mL) of fresh-prepared neopentylmagnesium bromide, and the mixture was stirred at －10 ℃ for 1 h. After cautiously quenched with sat. aq. NH_4Cl, the mixture was extracted with AcOEt (30 mL×3), the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (SiO_2, petroleum ether/AcOEt ＝4∶1) to give a white solid **15a** (0.173 mg, 97%). m.p. 176－177 ℃; TLC (petroleum ether/AcOEt＝2∶1): R_f 0.5. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.59 (d, J＝8.6 Hz, 1H, ArH), 7.51－7.48 (m, 2H, ArH), 7.42－7.33 (m, 3H, ArH), 7.05－6.95 (m, 3H, ArH), 6.65 (d, J＝7.3 Hz, 1H, ArH), 5.22 (s, 2H, CH_2), 5.19－5.16 (m, 1H, CH), 5.14 (s, 2H, CH_2), 3.98 (s, 3H, OCH_3), 1.87 (d, J＝4.8 Hz, 1H, OH), 1.69－1.59 (m, 2H, CH_2), 1.03 (s, 9H, *t*-Bu-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 167.3, 154.1, 152.0, 150.6, 146.3, 137.6, 136.7, 131.0, 128.6 (2C), 128.0, 127.8, 127.2 (2C), 124.5, 121.3, 119.4, 118.0, 116.0, 71.4, 69.0, 66.5, 62.7, 52.2, 30.7, 30.1 (3C). MS (ESI): 463.1 [M＋H]. HRMS (ESI): Calcd for $C_{28}H_{29}O_6$ [M–H]: 461.1964, found 461.1966.

11-(Benzyloxy)-3-(1-hydroxy-3,3-dimethylbutyl)-4-methoxy-9-methyldibenzo[*b*,*g*][1,5]dioxocin-5(7*H*)-one (**15b**): Prepared according to the procedure for **15a** except that a different substrate **14b** was used, a white solid **15b**, yield: 98%. m.p. 143－144 ℃; TLC (petroleum ether/AcOEt＝3∶1): R_f 0.44. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.57 (d, J＝8.2 Hz, 1H, ArH), 7.51－7.49 (m, 2H, ArH), 7.42－7.31 (m, 3H, ArH), 6.94 (d, J＝7.8 Hz, 1H, ArH), 6.85 (s, 1H, ArH), 6.44 (s, 1H, ArH), 5.19 (s, 2H, CH_2), 5.18－5.14 (m, 1H, CH), 5.08 (s, 2H, CH_2), 3.95 (s, 3H, OCH_3), 2.25 (s, 3H, CH_3), 2.12 (br s, 1H, OH), 1.68－1.53 (m, 2H, CH_2), 1.02 (s, 9H, CMe_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 167.5, 153.9, 152.0, 150.2, 144.0, 137.5, 136.7, 134.4, 130.9, 128.5 (2C), 127.9, 127.23, 127.16 (2C), 121.6, 119.3, 118.0, 116.5, 71.2, 69.0, 66.3, 62.5, 52.1, 30.6, 30.0 (3C), 21.0. MS (ESI): 477.2 [M＋H]. HRMS (APCI): Calcd for $C_{29}H_{33}O_6$ [M＋H]: 477.2277, found 477.2278.

11-(Benzyloxy)-3-(1-hydroxy-3,3-dimethylbutyl)-4-methoxy-9-(4-methoxyphenyl)dibenzo[*b*,*g*][1,5]dioxocin-5(7*H*)-one (**15c**): Prepared according to the procedure for **15a** except that a different substrate **14c** was used, a yellowish solid **15c**, yield: 77%. m.p. 85－86 ℃; TLC (petroleum ether/AcOEt＝5∶1): R_f 0.30. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.60 (d, J＝8.6 Hz, 1H, ArH), 7.54－7.51 (m, 2H, ArH), 7.43－7.34 (m, 5H, ArH), 7.19 (d, J＝1.6 Hz, 1H, ArH), 6.99 (d, J＝8.6 Hz, 1H, ArH), 6.95－6.92 (m, 2H, ArH), 6.80 (d, J＝1.6 Hz, 1H, ArH), 5.27 (s, 2H, CH_2), 5.20－5.10 (m, 2H), 5.18 (s, 2H), 3.99 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 1.93 (br s, 1H, OH), 1.70－1.55 (m, 2H, CH_2), 1.03 (s, 9H, CMe_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 167.3, 159.3, 154.0, 152.0, 150.6, 145.2, 137.6, 137.5, 136.6, 132.3, 131.0, 128.6 (2C), 128.0, 127.9 (2C), 127.8, 127.3 (2C), 119.5, 119.3, 118.0, 114.4, 114.2 (2C), 71.5, 69.2, 66.4, 62.6, 55.3, 52.2, 30.7, 30.0 (3C). MS (ESI): 568.7 [M＋H]. HRMS (APCI): Calcd for $C_{35}H_{37}O_7$ [M＋H]: 569.2539, found 569.2534.

11-(Benzyloxy)-3-(1-hydroxy-3,3-dimethylbutyl)-4-methoxy-9-(methylthio)dibenzo[*b*,*g*][1,5]dioxocin-5(7*H*)-one (**15f**): Prepared according to the procedure for **15a** except that a different substrate **14f** was used, a white solid **15f**, yield: 83%. m.p. 155－156 ℃; TLC (petroleum ether/CH_2Cl_2＝3∶1): R_f 0.21. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 (d, J＝8.5 Hz, 1H), 7.50 (s, 1H), 7.48 (s, 1H), 7.46－7.27 (m, 3H), 6.95－6.93 (m, 2H), 6.54 (d, J＝1.7 Hz, 1H), 5.20 (s, 2H), 5.19－5.13 (m, 1H), 5.09 (s, 2H), 3.97 (s, 3H), 2.40 (s, 3H), 1.99 (brs, 1H), 1.71－1.64 (m, 1H), 1.60－1.50 (m, 1H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.3, 154.0, 151.9, 150.7, 144.1, 137.7, 136.5, 134.4, 131.0, 128.7 (2C), 128.1 (2C), 127.3 (2C), 119.4, 119.2, 117.9, 114.7, 71.4, 68.8, 66.4, 62.6, 52.2, 30.7, 30.1 (3C), 16.5. HRMS (ESI): Calcd for $C_{29}H_{32}NaO_6S$ [M＋Na]: 531.1817, found 531.1828.

11-(Benzyloxy)-9-(ethylthio)-3-(1-hydroxy-3,3-dimethylbutyl)-4-methoxydibenzo[*b*,*g*][1,5]dioxocin-5(7*H*)-one (**15g**): Prepared according to the procedure for **15a** except that a different substrate **14g** was used, a yellowish solid **15g**, yield: 68%. m.p. 48－49 ℃; TLC (petroleum ether/AcOEt＝2∶1): R_f 0.66. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59 (d, J＝8.5 Hz, 1H), 7.49 (d, J＝7.3 Hz, 2H), 7.44－7.30 (m, 3H), 7.01 (d, J＝2.0 Hz, 1H), 6.94 (d, J＝8.4 Hz, 1H), 6.63 (d, J＝2.0 Hz, 1H), 5.21 (s, 2H), 5.19－5.13 (m, 1H), 5.09 (s, 2H), 3.97 (s, 3H), 2.83 (q, J＝7.3 Hz, 2H), 1.96 (brs, 1H), 1.70－1.60 (m, 1H), 1.56 (dd, J＝14.5, 2.8 Hz, 1H), 1.21 (t, J＝7.3 Hz, 3H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.2, 154.1, 151.8, 150.6, 144.8, 137.8, 136.4 132.4, 131.0, 128.7 (2C), 128.1, 128.1, 127.3 (2C), 122.4, 119.2, 118.0, 117.3, 71.5, 68.8, 66.4, 62.7, 52.2, 30.7, 30.1 (3C), 28.5, 14.3. MS (ESI): 505.1 [M–OH]. HRMS (ESI): Calcd for $C_{30}H_{34}NaO_6S$ [M＋Na]: 545.1974, found 545.1979.

11-(Benzyloxy)-3-(1-hydroxy-3,3-dimethylbutyl)-4-methoxy-9-(methylsulfonyl)dibenzo[*b*,*g*][1,5]dioxocin-5(7*H*)-one (**15h**): To a solution of **15f** (0.152 g, 0.30

mmol) in THF/H_2O (10 mL, *V*/*V*＝1∶2) was added oxane (0.370 g, 0.40 mmol) in one portion at 0 ℃, and stirred at r.t. for 3 h. Then water (10 mL) was added to the reaction mixture, and the resulting mixture was extracted with AcOEt (30 mL×2). The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (SiO_2, petroleum ether/acetone＝1.8∶1) to give a yellowish solid **15h** (0.152 mg, 94%). m.p. 127－128 ℃; TLC (petroleum ether/acetone＝2∶1): R_f 0.38. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.62 (d, *J*＝8.5 Hz, 1H), 7.58 (d, *J*＝2.0 Hz, 1H), 7.50 (d, *J*＝7.0 Hz, 2H), 7.45－7.32 (m, 3H), 7.27 (d, *J*＝1.9 Hz, 1H), 6.90 (d, *J*＝8.5 Hz, 1H), 5.26 (s, 2H), 5.21－5.10 (m, 3H), 3.95 (s, 3H), 2.99 (s, 3H), 1.63 (dd, *J*＝14.5, 8.7 Hz, 1H), 1.54 (dd, *J*＝14.5, 2.6 Hz, 1H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.0, 154.4, 151.4, 151.0, 150.2, 139.1, 136.4, 135.7, 131.7, 129.1 (2C), 129.0, 128.8, 127.8 (2C), 121.1, 119.0, 118.1, 114.2, 71.8, 68.6, 66.5, 63.1, 52.5, 44.8, 31.0, 30.4 (3C). MS (ESI): 523.2 [M–OH]. HRMS (ESI): Calcd for $C_{29}H_{32}NaO_8S$ [M＋Na]: 563.1716, found 563.1721.

11-(Benzyloxy)-9-(ethylsulfonyl)-3-(1-hydroxy-3,3-dimethylbutyl)-4-methoxydibenzo[*b*,*g*][1,5]dioxocin-5(7*H*)-one (**15i**): Prepared according to the procedure for **15h** except that a different substrate **15g** was used, a white solid **15i**: 93%. m.p. 220－221 ℃; TLC (petroleum ether/acetone＝2∶1): R_f 0.36. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64 (d, *J*＝8.5 Hz, 1H), 7.52 (d, *J*＝1.9 Hz, 1H), 7.49 (d, *J*＝7.2 Hz, 2H), 7.44－7.31 (m, 3H), 7.24 (d, *J*＝1.8 Hz, 1H), 6.93 (d, *J*＝8.5 Hz, 1H), 5.28 (s, 2H), 5.24－5.14 (m, 3H), 3.98 (s, 3H), 3.04 (q, *J*＝7.4 Hz, 2H), 1.99 (d, *J*＝2.9 Hz, 1H), 1.70－1.60 (m, 1H), 1.56 (dd, *J*＝14.5, 2.6 Hz, 1H), 1.18 (t, *J*＝7.4 Hz, 3H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.6, 154.2, 151.0, 150.7, 150.0, 138.7, 135.4, 134.0, 131.3, 128.8 (2C), 128.6, 128.4, 127.4 (2C), 121.6, 118.8, 117.8, 114.9, 71.5, 68.4, 66.3, 62.8, 52.2, 50.7, 30.7, 30.1 (3C), 7.4. MS (ESI): 537.3 [M–OH]. HRMS (ESI): Calcd for $C_{30}H_{34}NaO_8S$ [M＋Na]: 577.1872, found 577.1868.

11-(Benzyloxy)-3-(1-hydroxy-3-methylbut-3-en-1-yl)-4-methoxy-9-methyl-5*H*,7*H*-dibenzo[*b*,*g*][1,5]-dioxocin-5-one (**15j**): Prepared according to the procedure for **15a** except that a different Grignard reagent (2-methylprop-2-en-1-yl magnesium chloride) was used, a yellowish solid **15j**, yield: 82%. m.p. 55－56 ℃; TLC (petroleum ether/AcOEt＝2∶1): R_f 0.50. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.62 (d, *J*＝8.6 Hz, 1H), 7.60－7.30 (m, 5H), 6.96 (d, *J*＝8.6 Hz, 1H), 6.86 (s, 1H), 6.46 (s, 1H), 5.19 (s, 2H), 5.08－5.14 (m, 3H), 4.93 (s, 1H), 4.84 (s, 1H), 3.98 (s, 3H), 2.47 (dd, *J*＝13.6, 3.2 Hz, 1H), 2.35－2.28 (m, 1H), 2.26 (s, 3H), 1.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 167.4, 154.5, 152.3, 150.2, 144.0, 142.3, 136.7, 135.0, 134.4, 130.9, 128.6 (2C), 127.9, 127.3, 127.2 (2C), 121.6, 119.3, 118.0, 116.5, 114.2, 71.3, 69.0, 65.5, 47.3, 29.6, 22.2, 21.0. MS (ESI): 443.0 [M–OH]. HRMS(APCI): Calcd for $C_{28}H_{29}O_6$ [M＋H]: 461.1964, found 461.1979.

11-(Benzyloxy)-3-(1-hydroxypropyl)-4-methoxy-9-methyldibenzo[*b*,*g*][1,5]dioxocin-5(7*H*)-one (**15l**): Prepared according to the procedure for **15b** except that a different Grignard reagent (ethyl magnesium bromide) was used, a white solid **15l**, yield: 57%. m.p. 106－107 ℃; TLC (petroleum ether/AcOEt＝2∶1): R_f 0.37. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57－7.46 (m, 3H), 7.44－7.29 (m, 3H), 6.95 (d, *J*＝8.4 Hz, 1H), 6.86 (s, 1H), 6.45 (s, 1H), 5.19 (s, 2H), 5.09 (s, 2H), 4.92 (t, *J*＝6.3 Hz, 1H), 3.95 (s, 3H), 2.25 (s, 3H), 2.21 (brs, 1H), 1.89－1.64 (m, 2H), 0.95 (t, *J*＝7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.5, 154.8, 152.3, 150.3, 144.0, 136.8, 135.5, 134.5, 131.2, 128.6 (2C), 128.0, 127.3, 127.2 (2C), 121.6, 119.4, 118.0, 116.6, 71.3, 69.8, 69.1, 62.8, 31, 21.1, 10.3. MS (ESI): 417.3 [M–OH]. HRMS (ESI): Calcd for $C_{26}H_{26}NaO_6$ [M＋Na]: 457.1627, found 457.1614.

11-Hydroxy-3-(1-hydroxy-3,3-dimethylbutyl)-4-methoxydibenzo[*b*,*g*][1,5]dioxocin-5(7*H*)-one (**16a**): To a solution of **15a** (42 mg, 0.09 mmol) in EtOH/AcOEt (10 mL, *V*/*V*＝1∶2) was added 10% Pd/C (4 mg), and the resulting mixture was stirred under H_2 (balloon) at r.t. for 3 h (TLC monitoring). The mixture was diluted with CH_2Cl_2 (20 mL), then filtered through a pad of celite, the filter cake was washed with AcOEt, and the combined filtrate was concentrated. The residue was subjected to column chromatography (SiO_2, petroleum ether/AcOEt＝3∶1) to give a white solid **16a** (29 mg, 85%). TLC (petroleum ether/AcOEt＝2∶1): R_f 0.47. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.53 (d, *J*＝8.7 Hz, 1H, ArH), 7.03 (d, *J*＝7.9 Hz, 1H, ArH), 6.97－6.93 (m, 1H, ArH), 6.83 (d, *J*＝8.7 Hz, 1H, ArH), 6.82 (s, 1H, OH), 6.54 (d, *J*＝7.5 Hz, 1H, ArH), 5.15－5.12 (m, 3H), 3.97 (s, 3H, OCH_3), 2.28 (br s, 1H, OH), 1.64－1.51 (m, 2H, CH_2), 1.01 (s, 9H, CMe_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 167.8, 153.7, 150.8, 147.9, 143.4, 138.1, 130.9, 126.1, 124.9, 120.2, 119.2, 117.6, 117.3, 69.1, 66.4, 62.4, 52.3, 30.7, 30.0 (3C). MS (ESI): 373.0 [M＋H]. HRMS (ESI): Calcd for $C_{21}H_{24}O_6Na$ [M＋Na]: 395.1471, found 395.1462.

11-Hydroxy-3-(1-hydroxy-3,3-dimethylbutyl)-4-methoxy-9-methyldibenzo[*b*,*g*][1,5]dioxocin-5(7*H*)-one (**16b**): Prepared according to the procedure for **16a** except that a different substrate **15b** was used, a white solid **16b**, yield: 87%. m.p. 114－115 ℃; TLC (petroleum ether/AcOEt＝2∶1): R_f 0.42. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.52 (d, *J*＝8.7 Hz, 1H, ArH), 6.84 (s, 1H, ArH), 6.81 (d, *J*＝8.7 Hz, 1H, ArH), 6.76 (br s, 1H, OH), 6.34 (s, 1H, ArH), 5.15－5.04 (m, 3H), 3.96 (s, 3H, OCH_3), 2.31 (br s, 1H, OH), 2.23 (s, 3H, CH_3), 1.64－1.50 (m, 2H, CH_2), 1.01 (s, 9H, CMe_3). MS (ESI): 387.0 [M＋H].

11-Hydroxy-3-(1-hydroxy-3,3-dimethylbutyl)-4-methoxy-9-(4-methoxyphenyl)dibenzo[*b*,*g*][1,5]dioxocin-5(7*H*)-one (**16c**): Prepared according to the procedure for **16a** except that a different substrate **15c** was used, a white solid **16c**, yield: 93%. TLC (petroleum ether/

AcOEt=2∶1): R_f 0.24. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.55 (d, J=8.2 Hz, 1H, ArH), 7.42−7.39 (m, 2H, ArH), 7.21 (d, J=2.0 Hz, 1H, ArH), 6.95−6.92 (m, 2H, ArH), 6.87 (d, J=8.2 Hz, 1H, ArH), 6.81 (br s, 1H, OH), 6.71 (d, J=2.0 Hz, 1H, ArH), 5.17−5.14 (m, 3H), 3.98 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 2.24 (br s, 1H, OH), 1.66−1.52 (m, 2H, CH_2), 1.02 (s, 9H, CMe_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 167.8, 159.3, 153.8, 151.0, 147.9, 142.4, 138.1, 137.9, 132.1, 131.0, 127.9 (2C), 126.2, 119.2, 118.5, 117.6, 115.4, 114.2 (2C), 69.3, 66.4, 62.4, 55.3, 52.3, 30.7, 30.1 (3C). MS (ESI): 478.9 [M+H]. HRMS (APCI): calcd for $C_{28}H_{31}O_7$ [M+H]: 479.2070, found 479.2066.

11-Hydroxy-3-(1-hydroxy-3,3-dimethylbutyl)-4-methoxy-9-(methylsulfonyl)dibenzo[*b*,*g*][1,5]dioxocin-5(7*H*)-one (**16h**): Prepared according to the procedure for **16a** except that a different substrate **15h** was used, a white solid **16h**, yield: 98%. TLC (petroleum ether/acetone=2∶1): R_f 0.23. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85 (brs, 1H), 7.62−7.49 (m, 2H), 7.15 (d, J=1.8 Hz, 1H), 6.79 (d, J=8.5 Hz, 1H), 5.23−4.91 (m, 3H), 3.94 (s, 3H), 3.02 (s, 3H), 2.69 (brs, 1H), 1.69−1.55 (m, 1H), 1.55−1.45 (m, 1H), 1.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.6, 153.8, 149.7, 149.0, 147.4, 138.9, 136.51, 131.4, 127.4, 119.5, 118.2, 117.5, 116.7, 68.6, 66.3, 62.5, 52.2, 44.4, 30.7, 30.1 (3C). MS (ESI): 433.1 [M–OH]. HRMS (ESI): calcd for $C_{22}H_{26}NaO_8S$ [M+Na]: 473.1246, found 473.1245.

9-(Ethylsulfonyl)-11-hydroxy-3-(1-hydroxy-3,3-dimethylbutyl)-4-methoxydibenzo[*b*,*g*][1,5]dioxocin-5(7*H*)-one (**16i**): Prepared according to the procedure for **16a** except that a different substrate **15i** was used, a white solid **16i**, yield: 87%. TLC (petroleum ether/acetone=2∶1): R_f 0.20. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.80 (brs, 1H), 7.56 (d, J=8.5 Hz, 1H), 7.49 (d, J=2.0 Hz, 1H), 7.11 (d, J=2.0 Hz, 1H), 6.80 (d, J=8.5 Hz, 1H), 5.37−4.94 (m, 3H), 3.95 (s, 3H), 3.08 (q, J=7.4 Hz, 2H), 1.66−1.58 (m, 1H), 1.56−1.44 (m, 1H), 1.25 (t, J=7.4 Hz, 3H), 1.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.6, 153.8, 149.7, 148.9, 147.4, 138.9, 134.5, 131.4, 127.2, 120.3, 118.3, 117.5, 68.6, 66.2, 62.4, 52.3, 50.6, 30.7, 30.0 (3C), 7.4. MS (ESI): 447.1 [M–OH]. HRMS (ESI): Calcd for $C_{23}H_{28}NaO_8S$ [M+Na]: 487.1403, found 487.1406.

11-Hydroxy-3-(1-hydroxy-3-methylbutyl)-4-methoxy-9-methyldibenzo[*b*,*g*][1,5]dioxocin-5(7*H*)-one (**16k**) and 11-hydroxy-3-isopentyl-4-methoxy-9-methyldibenzo[*b*,*g*][1,5]dioxocin-5(7*H*)-one (**16m**): To a solution of **15j** (202 mg, 0.44 mmol) in MeOH/AcOEt (6 mL, *V*/*V*=5∶1) was added 10% Pd/C (20 mg), the resulting mixture was stirred under H_2 (balloon) at r.t. for 3 h (TLC monitoring). After addition of CH_2Cl_2 (20 mL), the mixture was filtered through a pad of celite, the filter cake was washed with AcOEt, the combined filtrates were concentrated, and the residue was subjected to column chromatography (SiO_2, petroleum ether/AcOEt=2∶5) to give a white solid **16k** (106 mg, 65%) and a white solid **16m** (54 mg, 35%). **16k**: TLC (petroleum ether/AcOEt=2∶1): R_f 0.46. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.52 (d, J=8.6 Hz, 1H), 6.84 (s, 1H), 6.83 (d, J=8.6 Hz, 1H), 6.64 (brs, 1H), 6.35 (s, 1H), 5.10−4.90 (m, 3H), 3.96 (s, 3H), 2.23 (s, 3H), 1.85−1.75 (m, 1H), 1.75−1.55 (m, 1H), 1.55−1.35 (m, 1H), 0.97 (d, J=6.8 Hz, 3H), 0.95 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 167.9, 154.3, 151.2, 147.5, 141.3, 136.9, 135.0, 131.1, 125.7, 120.7, 119.3, 117.8, 117.7, 69.2, 66.6, 62.7, 47.6, 24.9, 23.4, 21.8, 20.8. MS (ESI): 355.0 [M–OH]. HRMS (APCI): Calcd for $C_{21}H_{25}O_6$ [M+H]: 373.1651, found 373.1654. **16m**: TLC (petroleum ether/AcOEt=1∶2): R_f 0.46. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30−7.25 (m, 1H), 6.85−6.70 (m, 2H), 6.37 (s, 1H), 6.26 (s, 1H), 5.06 (s, 2H), 3.94 (s, 3H), 2.70−2.50 (m, 2H), 2.23 (s, 3H), 1.70−1.50 (m, 1H), 1.50−1.40 (m, 2H), 0.94 (d, J=6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.0, 155.8, 150.4, 147.6, 141.7, 135.5, 135.1, 134.1, 126.1, 121.11, 120.6, 117.7, 117.6, 69.3, 62.9, 40.0, 28.3, 27.6, 22.8 (2C), 21.2. MS (ESI): 357.2 [M+H]. HRMS (APCI): Calcd for $C_{21}H_{25}O_5$ [M+H]: 357.1702, found 357.1709.

11-Hydroxy-3-(1-hydroxypropyl)-4-methoxy-9-methyldibenzo[*b*,*g*][1,5]dioxocin-5(7*H*)-one (**16l**): Prepared according to the procedure for **16a** except that a different substrate **15l** was used. The crude product was used directly in next step for **17l**.

9-(1-Hydroxy-3,3-dimethylbutyl)-8-methoxy-7-oxo-5,7-dihydrodibenzo[*b*,*g*][1,5]dioxocin-1-yl 7-methylbicyclo[2.2.1]heptane-7-carboxylate (**17a**): To a solution of 7-methylbicyclo[2.2.1]heptane-7-carboxylic acid[18] (500 mg, 3.24 mmol) in CH_2Cl_2 (4.0 mL) was added a drop of dry DMF at 0 ℃, followed by oxalyl dichloride (0.34 mL, 3.9 mmol). The resulting solution was stirred at r.t. for 1 h, then evaporated *in vacuo* and diluted with anhydrous THF (64 mL), giving the acyl chloride solution (*ca*. 0.05 mol•L^{-1}) for the next step.

A dry flask was charged with NaH (60%, 8 mg, 0.172 mmol) under Ar atmosphere, a solution of **16a** (58 mg, 0.156 mmol) in dry THF (4 mL) was added, and the resulting mixture was stirred at r.t. for 1 h. Then the acyl chloride solution (4 mL, about 0.20 mmol) was added dropwise. The reaction mixture was stirred at r.t. overnight. After evaporation, the residue was purified by preparative TLC (petroleum ether/AcOEt=3∶1), giving a white solid **17a** (46 mg, 58%). m.p. 156−157 ℃; TLC (petroleum ether/AcOEt=3∶1): R_f 0.42. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.61 (d, J=8.2 Hz, 1H, ArH), 7.09−7.07 (m, 2H, ArH), 7.00 (d, J=8.6 Hz, 1H, ArH), 6.96−6.92 (m, 1H, ArH), 5.18−5.11 (m, 3H), 3.98 (s, 3H, OCH_3), 2.40−2.25 (m, 2H), 1.97−1.84 (m, 5H), 1.70−1.55 (m, 2H, CH_2), 1.45 (s, 3H, CH_3), 1.34−1.32 (m, 4H), 1.03 (s, 9H, CMe_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 175.3, 167.1, 153.9, 151.2, 148.4, 142.3, 138.3, 131.1, 127.6, 127.2, 124.5, 124.2, 119.6, 118.3, 69.1, 66.4, 63.0, 58.6, 52.3, 42.0, 30.7, 30.1, 29.4, 27.8, 17.1. HRMS (APCI): Calcd for $C_{30}H_{35}O_7$ [M–H]: 507.2383, found 507.2375.

9-(1-Hydroxy-3,3-dimethylbutyl)-8-methoxy-3-meth-

yl-7-oxo-5,7-dihydrodibenzo[*b*,*g*][1,5]dioxocin-1-yl 7-methylbicyclo[2.2.1]heptane-7-carboxylate (**17b**): Prepared according to the procedure for **17a** except that a different substrate **16b** was used, a white solid **17b**, yield: 89%. m.p. 175－176 ℃; TLC (petroleum ether/AcOEt＝2∶1): R_f 0.64. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (d, J＝8.5 Hz, 1H), 6.99 (d, J＝8.5 Hz, 1H), 6.88 (d, J＝1.5 Hz, 1H), 6.74 (s, 1H), 5.24－5.11 (m, 1H), 5.07 (s, 2H), 3.97 (s, 3H), 2.33 (s, 2H), 2.28 (s, 3H), 2.01－1.79 (m, 5H), 1.67 (dd, J＝14.5, 8.7 Hz, 1H), 1.62－1.49 (m, 1H), 1.45 (s, 3H), 1.40－1.20 (m, 4H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.4, 167.2, 153.9, 151.4, 146.1, 141.8, 138.0, 134.2, 131.1, 127.6, 127.1, 124.7, 119.7, 118.3, 69.1, 66.4, 62.9, 58.6, 52.2, 41.96, 41.95, 30.7, 30.1, 29.4, 27.8, 20.5, 17.1. MS (ESI): 505.3 [M–OH]. HRMS (ESI): Calcd for $C_{31}H_{38}NaO_7$ [M＋Na]: 545.2515, found 545.2516.

9-(1-Hydroxy-3,3-dimethylbutyl)-8-methoxy-3-(4-methoxyphenyl)-7-oxo-5,7-dihydrodibenzo[*b*,*g*][1,5]dioxocin-1-yl 7-methylbicyclo[2.2.1]heptane-7-carboxylate (**17c**): Prepared according to the procedure for **17a** except that a different substrate **16c** was used, a yellowish oil **17c**, yield: 72%. TLC (petroleum ether/AcOEt＝3∶1): R_f 0.37. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.63 (d, J＝8.6 Hz, 1H, ArH), 7.43－7.40 (m, 2H, ArH), 7.20 (s, 1H, ArH), 7.08 (s, 1H, ArH), 7.04 (d, J＝8.6 Hz, 1H, ArH), 6.95－6.93 (d, J＝8.6 Hz, 2H, ArH), 5.19－5.16 (m, 3H), 3.99 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 2.35 (s, 2H), 2.00－1.85 (m, 5H), 1.71－1.56 (m, 2H, CH_2), 1.48 (s, 3H, CH_3), 1.35－1.33 (m, 4H), 1.03 (s, 9H, CMe_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 191.0, 175.3, 167.1, 159.5, 153.9, 151.3, 147.2, 142.4, 138.3, 137.4, 131.4, 131.2, 128.0, 127.6, 125.3, 122.4, 118.4, 114.3, 69.3, 66.4, 63.0, 58.6, 55.3, 52.3, 42.0, 30.7, 30.1, 29.4, 27.8, 17.2. HRMS (APCI): Calcd for $C_{37}H_{41}O_8$ [M–H]: 613.2802, found 613.2816.

9-(1-Hydroxy-3,3-dimethylbutyl)-8-methoxy-3-(methylsulfonyl)-7-oxo-5,7-dihydrodibenzo[*b*,*g*][1,5]dioxocin-1-yl 7-methylbicyclo[2.2.1]heptane-7-carboxylate (**17h**): Prepared according to the procedure for **17a** except that a different substrate **16h** was used, a white solid **17h**, yield: 89%. m.p. 188－189 ℃; TLC (petroleum ether/AcOEt＝1∶1): R_f 0.40. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75－7.63 (m, 2H), 7.59 (d, J＝2.0 Hz, 1H), 6.99 (d, J＝8.5 Hz, 1H), 5.29－4.94 (m, 3H), 3.98 (s, 3H), 3.07 (s, 3H), 2.33 (s, 2H), 1.98 (d, J＝4.4 Hz, 1H), 1.93－1.86 (m, 4H), 1.68－1.61 (m, 1H), 1.57 (dd, J＝14.5, 2.3 Hz, 1H), 1.46 (s, 3H), 1.40－1.20 (m, 4H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.7, 166.2, 154.1, 152.7, 150.0, 142.9, 139.4, 135.9, 131.5, 128.8, 126.9, 124.1, 119.0, 118.0, 68.4, 66.2, 63.1, 58.6, 52.3, 44.7, 42.02, 42.01, 30.7, 30.1 (3C), 29.3, 27.7, 17.1. MS (ESI): 569.2 [M–OH]. HRMS (ESI): Calcd for $C_{31}H_{38}NaO_9S$ [M＋Na]: 609.2134, found 609.2123.

3-(Ethylsulfonyl)-9-(1-hydroxy-3,3-dimethylbutyl)-8-methoxy-7-oxo-5,7-dihydrodibenzo[*b*,*g*][1,5]dioxocin-1-yl 7-methylbicyclo[2.2.1]heptane-7-carboxylate (**17i**): Prepared according to the procedure for **17a** except that a different substrate **16i** was used, a white solid **17i**, yield: 87%. m.p. 125－126 ℃; TLC (petroleum ether/AcOEt＝1∶1): R_f 0.71. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (d, J＝8.5 Hz, 1H), 7.62 (s, 1H), 7.54 (s, 1H), 7.00 (d, J＝8.5 Hz, 1H), 5.20－5.10 (m, 3H), 3.98 (s, 3H), 3.13 (q, J＝7.4 Hz, 2H), 2.33 (s, 2H), 2.01 (d, J＝4.3 Hz, 1H), 1.93 (d, J＝8.0 Hz, 2H), 1.86 (d, J＝8.1 Hz, 2H), 1.74－1.52 (m, 2H), 1.46 (s, 3H), 1.39－1.24 (m, 7H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.6, 166.2, 154.0, 152.6, 150.0, 142.8, 139.3, 133.9, 131.4, 128.6, 127.5, 124.8, 118.9, 117.9, 68.3, 66.1, 63.0, 58.5, 52.2, 50.7, 41.9, 30.6, 30.0 (3C), 29.2, 27.6, 17.0, 7.3. MS (ESI): 583.3 [M–OH]. HRMS (ESI): Calcd for $C_{32}H_{40}NaO_9S$ [M＋Na]: 623.2291, found 623.2297.

9-(1-Hydroxy-3-methylbutyl)-8-methoxy-3-methyl-7-oxo-5,7-dihydrodibenzo[*b*,*g*][1,5]dioxocin-1-yl 7-methylbicyclo[2.2.1]heptane-7-carboxylate (**17k**): Prepared according to the procedure for **17a** except that a different substrate **16k** was used, a white solid **17k**, yield: 86%. TLC (petroleum ether/AcOEt＝3∶1): R_f 0.33. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 (d, J＝8.6 Hz, 1H), 7.00 (d, J＝8.5 Hz, 1H), 6.88 (d, J＝1.6 Hz, 1H), 6.74 (d, J＝1.5 Hz, 1H), 5.09－5.07 (m, 3H), 3.97 (s, 3H), 2.32 (s, 2H), 2.28 (s, 3H), 2.03 (d, J＝4.1 Hz, 1H), 1.97 (d, J＝8.5 Hz, 2H), 1.85 (d, J＝9.7 Hz, 2H), 1.79 (dd, J＝13.6, 7.0 Hz, 1H), 1.75－1.65 (m, 1H), 1.60－1.50 (m, 1H), 1.45 (s, 3H), 1.40－1.20 (m, 4H), 0.97 (dd, J＝9.2, 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.6, 167.4, 154.6, 151.7, 146.3, 142.0, 137.1, 134.5, 131.3, 127.8, 127.3, 125.0, 120.0, 118.6, 69.3, 66.8, 63.3, 58.8, 47.7, 42.2, 42.1, 29.6, 28.0, 25.1, 23.6, 22.0, 20.8, 17.3. MS (ESI): 531.2 [M＋Na]. HRMS (ESI): Calcd for $C_{30}H_{36}NaO_7$ [M＋Na]: 531.2359, found 531.2342.

9-(1-Hydroxypropyl)-8-methoxy-3-methyl-7-oxo-5,7-dihydrodibenzo[*b*,*g*][1,5]dioxocin-1-yl 7-methylbicyclo-[2.2.1]heptane-7-carboxylate (**17l**): Prepared according to the procedure for **17a** except that a different substrate **16l** was used, a yellowish oil **17l**, yield: 76%. TLC (petroleum ether/AcOEt＝2∶1): R_f 0.34. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56 (d, J＝8.5 Hz, 1H), 7.00 (d, J＝8.5 Hz, 1H), 6.88 (d, J＝1.5 Hz, 1H), 6.74 (d, J＝1.4 Hz, 1H), 5.06 (s, 2H), 4.92 (dd, J＝10.0, 6.6 Hz, 1H), 3.96 (s, 3H), 2.32 (s, 2H), 2.28 (s, 3H), 2.17 (d, J＝4.0 Hz, 1H), 2.00－1.95 (m, 2H), 1.90－1.80 (m, 2H), 1.81－1.72 (m, 2H), 1.45 (s, 3H), 1.37－1.28 (m, 4H), 0.96 (t, J＝7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.4, 167.2, 154.7, 151.5, 146.1, 141.8, 136.1, 134.3, 131.3, 127.6, 127.1, 124.8, 119.8, 118.3, 69.7, 69.1, 63.1, 58.6, 42.0, 41.9, 31.0, 29.4, 27.8, 20.5, 17.1, 10.3. MS (ESI): 503.2 [M＋Na]. HRMS (ESI): Calcd for $C_{28}H_{32}NaO_7$ [M＋Na]: 503.2046, found 503.2049.

9-Isopentyl-8-methoxy-3-methyl-7-oxo-5,7-dihydrodibenzo[*b*,*g*][1,5]dioxocin-1-yl 7-methylbicyclo[2.2.1]-heptane-7-carboxylate (**17m**): Prepared according to the procedure for **17a** except that a different substrate **16m** was used, a white solid **17m**, yield: 87%. m.p. 186－187 ℃; TLC (petroleum ether/AcOEt＝4∶1): R_f 0.75. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (d, J＝8.4 Hz, 1H),

6.92 (d, J=8.4 Hz, 1H), 6.87 (d, J=1.6 Hz, 1H), 6.73 (d, J=1.5 Hz, 1H), 5.05 (s, 2H), 3.93 (s, 3H), 2.62 (t, J=8.0 Hz, 2H), 2.40−2.20 (m, 2H), 2.28 (s, 3H), 1.98 (d, J=8.4 Hz, 2H), 1.90−1.75 (m, 2H), 1.65−1.55 (m, 1H), 1.45 (s, 3H), 1.38−1.21 (m, 6H), 0.95 (d, J=6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.6, 167.6, 155.6, 150.4, 146.5, 142.0, 135.2, 134.2, 134.1, 127.9, 127.4, 124.8, 120.6, 118.3, 69.3, 63.1, 58.8, 42.2, 41.8, 40.0, 29.6, 29.5, 28.2, 28.0, 27.9, 27.4, 22.6, 20.7, 17.3. MS (ESI): 493.3 [M+H]. HRMS (APCI): Calcd for $C_{30}H_{37}O_6$ [M+H]: 493.2590, found 493.2602.

9-(1-Fluoro-3,3-dimethylbutyl)-8-methoxy-3-methyl-7-oxo-5,7-dihydrodibenzo[*b*,*g*][1,5]dioxocin-1-yl 7-methylbicyclo[2.2.1]heptane-7-carboxylate (**17n**): To a solution of **17b** (0.102 g, 0.19 mmol) in CH_2Cl_2 (2.0 mL) was added dropwise DAST (52 μL, 0.24 mmol) at −78 ℃. The resulting mixture was stirred at this temperature for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ (5 mL), the mixture was extracted with AcOEt (30 mL×3), and the combined organic phases were washed with brine (30 mL), dried over Na_2SO_4, and evaporated. The residue was subjected to column chromatography (SiO_2, petroleum ether/AcOEt = 9 ∶ 1), giving a white solid **17n** (74 mg, 74%). m.p. 152−153 ℃; TLC (petroleum ether/AcOEt=3 ∶ 1): R_f 0.80. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56 (d, J=8.5 Hz, 1H), 7.02 (d, J=8.5 Hz, 1H), 6.88 (d, J=1.6 Hz, 1H), 6.74 (d, J=1.4 Hz, 1H), 6.00−5.80 (m, 1H), 5.05 (d, J=13.9 Hz, 2H), 3.97 (s, 3H), 2.33 (s, 2H), 2.29 (s, 3H), 2.02−1.77 (m, 5H), 1.65−1.55 (m, 1H), 1.45 (s, 3H), 1.39−1.29 (m, 4H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.4, 167.0, 153.8 (d, J=5.4 Hz), 152.2, 146.1, 141.9, 134.4, 133.8 (d, J=21.6 Hz), 130.8, 130.7, 127.7, 127.1, 124.9 118.4, 87.3 (d, J=170.3 Hz), 77.4, 77.0, 76.7, 69.2, 62.9, 58.6, 50.4 (d, J=22.4 Hz), 42.0, 31.6, 30.5, 29.8, 29.4, 27.8, 22.7, 20.6, 17.2, 14.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −176.57 (s). MS (ESI): 547.3 [M+Na]. HRMS (ESI): Calcd for $C_{31}H_{37}FO_6Na$ [M+Na]: 547.2466, found 547.2460.

9-(1-Fluoro-3,3-dimethylbutyl)-8-methoxy-3-(methylsulfonyl)-7-oxo-5,7-dihydrodibenzo[*b*,*g*][1,5]dioxocin-1-yl 7-methylbicyclo[2.2.1]heptane-7-carboxylate (**17o**): Prepared according to the procedure for **17n** except that a different substrate **17h** was used, a white solid **17o**, yield: 80%. m.p. 207−208 ℃; TLC (petroleum ether/AcOEt=1 ∶ 1): R_f 0.70. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (d, J=2.2 Hz, 1H), 7.65−7.53 (m, 2H), 7.03 (d, J=8.5 Hz, 1H), 5.90 (dd, J=48.6, 8.7 Hz, 1H), 5.15 (d, J=13.7 Hz, 2H), 3.98 (s, 3H), 3.07 (s, 3H), 2.33 (s, 2H), 2.01−1.76 (m, 5H), 1.65−1.50 (m, 1H), 1.46 (s, 3H), 1.40−1.30 (m, 4H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.8, 166.0, 154.03 (d, J=5.4 Hz), 152.6, 150.8, 143.0, 136.2, 135.1 (d, J=22.0 Hz), 131.1, 131.0, 128.8, 126.9, 124.3, 118.1, 87.2 (d, J=171.1 Hz), 68.4, 63.2, 58.7, 50.4 (d, J=22.3 Hz), 44.7, 42.1, 30.5, 29.8, 29.4, 27.8, 17.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ: −177.57 (s). MS (ESI): 589.3 [M+H]. HRMS (ESI): Calcd for $C_{31}H_{37}FNaO_8S$ [M+Na]: 611.2091, found 611.2098.

Assay of CETP inhibition

After preincubation with compounds diluted in DMSO for 4 h at 37 ℃, aliquots of plasma were mixed with [^{3}H]CE-HDL (8 μg/mL) and LDL (60 μg/mL) in a total volume of 200 μL buffer containing 50 mmol•L^{-1} Tris-HCl (pH 7.4), 150 mmol•L^{-1} NaCl, 1 mmol•L^{-1} EDTA and 1% bovine serum albumin. The mixture was kept in incubator for 16 h at 37 ℃. Then 20 μL of precipitating reagent (dextran sulfate/$MgCl_2$=0.45%/0.23 mol•L^{-1}) was added and the mixture was centrifuged at 1000 g for 15 min at 4 ℃. Half of the supernatant was collected and its radioactivity was measured in a liquid scintillation counter. The inhibition rate was determined according to the following equation:

$$\%\text{inhibition} = 1 - (CPM_{blank} - CPM_{test})/(CPM_{blank} - CPM_{control}) \times 100\%$$

'Test' samples contained plasma with inhibitor compounds diluted by DMSO, while 'Control' samples contained plasma with DMSO. 'Blank' samples were prepared as 'control' samples but incubated at 4 ℃ instead of 37 ℃ for 16 h.

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