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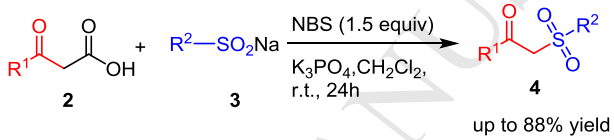

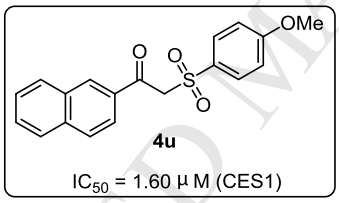

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ABSTRACT

A *N*-bromosuccinimide (NBS) mediated decarboxylative sulfonylation of *β*-keto acids with sodium sulfinates is developed. The transformation exhibits a broad substrate scope and good functional group tolerance. Preliminary mechanistic studies showed that this reaction is likely to proceed through a nucleophilic substitution of *β*-keto acid with sulfonyl bromide pathway. All synthesized *β*-keto sulfones were evaluated the inhibitory effect against human carboxylesterase 1 (CES1). This investigation offers an expedient strategy for efficient synthesis of *β*-keto sulfones that are widely present in biologically active natural products and pharmaceutical agents.

1. Introduction

Sulfones not only belong to key structural motifs distributed in biologically active molecules and functional materials but also act as versatile precursors for organic chemistry.[1] Among those, *β*-keto sulfones are prominent in medicinal chemistry owing to their remarkable pharmaceutical properties, i.e., antagonists of bacterial quorum sensing in Vibrio harveyi **1a**,[2] and inhibitors of LpxC **1b** and MMP **1c** (Fig. 1)[3]. They also play a crucial role in synthetic applications for natural products and various important structural components such as disubstituted acetylenes,[4] allenes, vinylsulfones,[5] ketones,[6] polyfunctionalized 4H-pyrans,[7] and optically active *β*-hydroxysulfones.[8] Recognizing the great importance of *β*-keto sulfones, the formation of Csp^3-SO_2R bond has been of intensive research area. Recently, many efforts have been achieved in the development of efficient synthetic processes for these scaffolds.[9] However, most of them require transition-metal catalysts, expensive reagents, relatively complicated or harsh reaction conditions, and have limited substrate scopes. Therefore, the development of new strategies for the synthesis of *β*-keto sulfones is highly desirable, which continue to be a challenging issue.

The decarboxylative reaction of *β*-keto acids and its subsequent functionalization have been an attractive topic in organic synthesis and play a crucial role in fine chemicals, material science, and medicinal chemistry.[10] A large array of *β*-keto acids transformation systems for carbon-carbon and carbon-hetero bond forming reactions have been well established in the past decades.[11] Despite these notable achievements, however, little progress has been made in the development of a carbon-sulfur version for this important reaction. In light of the literature precedence[2-11] and continuation of our work on the utility of *β*-keto acids for carbon-carbon and carbon-hetero bond forming reactions,[12] we thought it would be of interest to develop a method by a decarboxylative sulfonylation of *β*-keto acids using sodium sulfinates (easily prepared, bench-top stable, non-odorous solids). Herein, we report a one-pot chemoselective synthesis of *β*-keto sulfones via decarboxylative coupling of *β*-keto acids with sodium sulfinates through a *N*-bromosuccinimide (NBS)-promoted pathway. In addition, all synthetic *β*-keto sulfones compounds have been screened for inhibitory effects against human carboxylesterase 1 (CES1) using D-Luciferin methyl ester (DME) as specific optical substrate.[13] Primary structure-activity relationships (SAR) analysis of all tested *β*-keto sulfones compounds provide insights into the fine relationships linking

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between the inhibitory effects on CES1 and the substituent-properties of these compounds. Guided by these SARs, we design and synthesize a novel *β*-keto sulfone compound leading to a dramatically increase of the inhibitory effects against CES1.

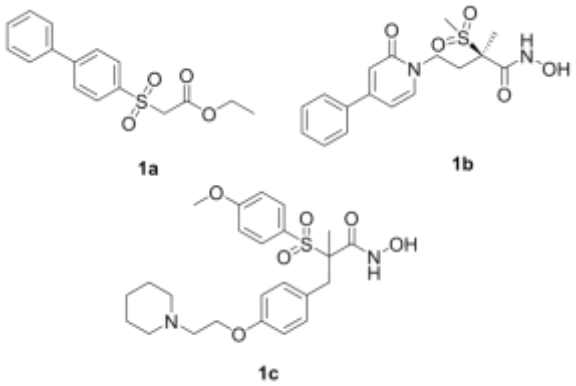


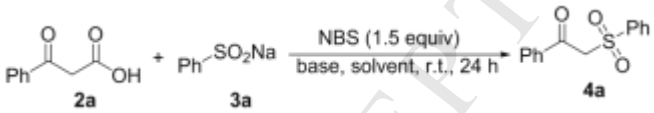
Fig.1 Bioactive molecules having *β*-keto sulfone core.

2. Results and discussion

2.1. Optimization of Reaction Conditions

We commenced the initial condition-screening experiments by utilizing benzoylacetic acid **2a** and sodium sulfinate **3a** as the model substrates (Table 1). To our delight, the desired *β*-keto sulfone product **4a** was obtained in a 28% yield by using *N*-bromosuccinimide (NBS, 1.5 equiv.) at room temperature in CH_2Cl_2 for 24 h under air (Table 1, entry 1). To promote the yield of **4a**, further studies surveyed a series of bases (Table 1, entries 2-7). The switching of base from K_2CO_3 to various other bases proves K_3PO_4 as the optimum base, where the yield of **4a** could be increased to 88% (Table 1, entry 6). Further screening of solvents revealed that CH_2Cl_2 is superior to H_2O, CH_3CN, THF , MeOH and DMF (Table 1, entries 8-12).

Table 1. Optimization and screening of the reaction conditions[a]



Entry	Base	Solvent	Yield (%) [b]
1	none	CH_2Cl_2	28
2	K_2CO_3	CH_2Cl_2	64
3	Et_3N	CH_2Cl_2	51
4	iPr_2NEt	CH_2Cl_2	52
5	KOH	CH_2Cl_2	43
6	K_3PO_4	CH_2Cl_2	88
7	Na_3PO_4	CH_2Cl_2	82
8	K_3PO_4	H_2O	18
9	K_3PO_4	CH_3CN	67
10	K_3PO_4	THF	57
11	K_3PO_4	CH_3OH	55
12	K_3PO_4	DMF	47

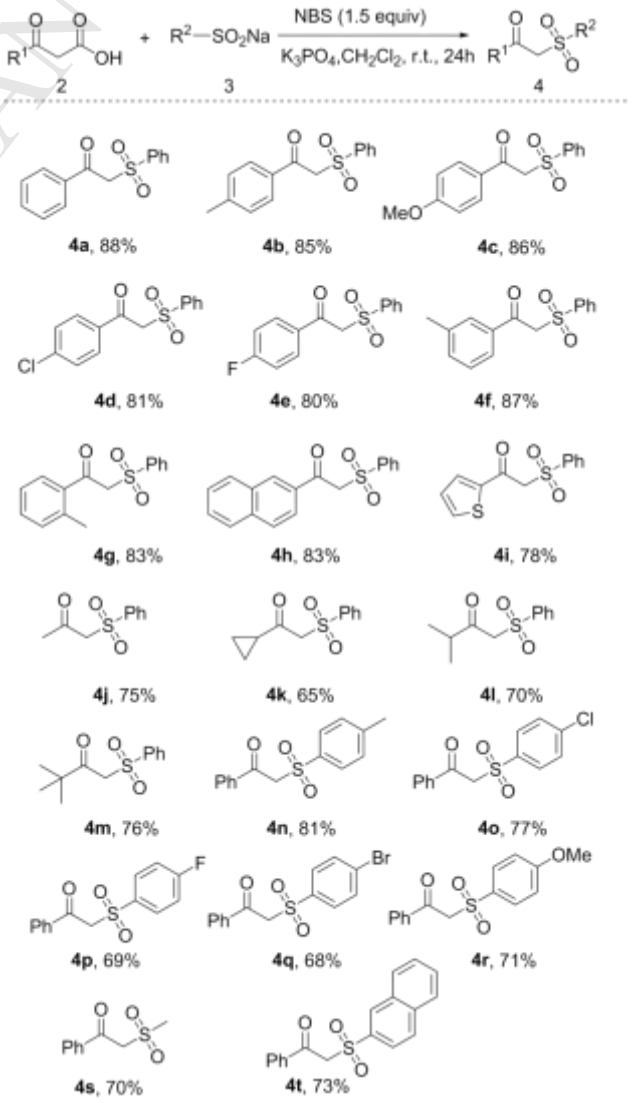
[a] General reaction conditions: **2a** (0.75 mmol), **3a** (0.5 mmol) and base (0.75 mmol) in solvent (3 mL) at room temperature for 24 h.

[b] The yields indicated are the isolated yields by column purification.

2.2. Substrate scope

With the optimal conditions in hands, we examined the substrate scope with respect to *β*-keto acids (Scheme 1). *β*-Keto acids with both the electron-donating groups (4-OMe), electron-neutral (4-H, 4-Me, 3-Me), and halogenated (4-F, 4-Cl) on the aromatic ring were smoothly converted to the corresponding products **4a**-**4f** in excellent yields (80-88%). Moreover, reactions with ortho-substituted substrate also gave the corresponding *β*-keto sulfone **4g** in high yield (83%), indicating the tolerance of steric hindrance. Gratifyingly, 2-Naphthylphenone-derived *β*-keto acid was also viable substrate, and the isolation of **4h** in 83% yield, whereas heteroaryl-substituted *β*-keto acid furnished the desired product **4i** with 78% yield. Notably, aliphatic substituted *β*-keto acids displayed lower reactivity under the standard reaction conditions.

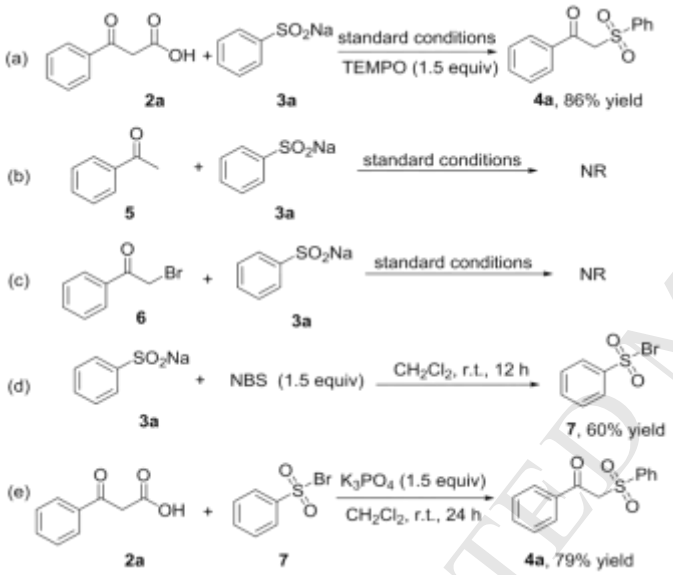
Next, we explored the scope of sodium sulfinates under the optimal reaction conditions, as shown in Scheme 1. It was found that a range of sodium benzenesulfinates bearing various electrondonating, electronwithdrawing, and halogen substituents at the para position of the arene ring were effectively coupled with **2a** and furnished the desired product (**4n**-**4r**) in 68-81% isolated yields. In addition, 2-naphthyl substituted sulfinic acid sodium also proved to be a suitable substrate, delivering the desired product **4t** in 73% yield. In addition to aromatic sodium sulfinates, less reactive sodium methanesulfinate was tolerated in this transformation, affording product **4s** in good yield.



Scheme 1. Reaction conditions: **2** (0.75 mmol), **3** (0.5 mmol) and K_3PO_4 (0.75 mmol) in 3 mL CH_2Cl_2 at room temperature for 24 h. The yields indicated are the isolated yields by column purification.

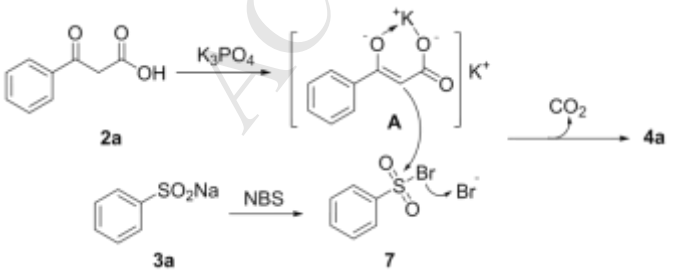
2.3. *Mechanistic studies*

We further carried out a series of control experiments to gain insight into the reaction mechanism (Scheme 2). Firstly, radical inhibition experiment was performed (Scheme 2a). When radical inhibitor 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was employed in the standard reaction, the reaction was not obviously inhibited. The results indicated that the reaction presumably did not undergo a radical pathway. Secondly, using acetophenone **5** and 2-bromoacetophenone **6** under the optimized reaction conditions did not furnish the expected product (Scheme 2b and 2c). This result suggested that the *β*-keto acid is essential for the reaction to proceed efficiently. Treatment of sodium sulfinate **3a** with 1.5 equiv of NBS at room temperature gave benzenesulfonyl bromide **7** in 60% yield (Scheme 2d). The compound **7** further reacted with benzoylacetic acid **2a** to afford *β*-keto sulfone product **4a** in 79% yield (Scheme 2e). These results partially implied that this transformation probably proceeded through a sulfonyl bromide intermediate pathway.



Scheme 2. Control experiments.

On the basis of these experiments and literature precedents, a plausible mechanism for the *β*-keto sulfone synthesis process is proposed in Scheme 3. *β*-keto acid **2a** reacts with K_3PO_4 to give the enolate intermediate **A**. The nucleophilic attack of the enolate intermediate **A** onto benzenesulfonyl bromide **7** generates *β*-keto sulfone product **4a** followed by subsequent decarboxylation.



Scheme 3. Proposed mechanism.

2.4. *Evaluation of inhibitory activities against CES1*

Following the establishment of these *β*-keto sulfones and considering the pharmacophore characters of the *β*-keto sulfone, a further investigation was carried out to evaluate whether these novel compounds possess potential biological activities as expected. Human carboxylesterase 1 (CES1), one of the most important serine hydrolases distributed in liver and adipocytes, plays key roles in endobiotic homeostasis and xenobiotic metabolism.[14] Recent studies have revealed that the activities of CES1 are markedly elevated in obese individuals and patients with type 2 diabetes, and the treatment of CES1 inhibitors displayed multiple beneficial effects in both lipid and glucose homeostasis in genetic and diet-induced mouse models of obesity, insulin resistance and type 2 diabetes.[15] Because of the enzymatic cleaving of triglyceride stores in hepatocytes, CES1 has been recognized as a therapeutic target for hypertriglyceridaemia.[16] Unfortunately, only one CES1 inhibitor termed GR148672X is in preclinical development for the treatment of hypertriglyceridaemia and no CES1 modulators have been approved as medicines to date.[17] It is highly desirable to find CES1 inhibitors for potential remedy of the related diseases.[18] Thus, a further survey was carried out to evaluate the inhibitory effect against CES1 of these novel *β*-keto sulfones using D-Luciferin methyl ester (DME) as specific optical substrate for CES1. As shown in Table 2, we firstly focused our attention on the variation of the benzoyl moiety of *β*-keto sulfones (**4a-4g**). Substitution with a 4-chlorine on the benzoyl unit of the *β*-keto sulfone showed good inhibitory effect against CES1 with IC_{50} value of 6.11 μM (**4d**), but the benzoyl unit with other substitutes (methyl, methoxyl, fluorine) at 4-position displayed poor inhibition toward CES1. The *β*-keto sulfone (**4h**) with 2-naphthoyl unit afforded increased inhibitory effect against CES1 compared with compound **4d**, while the variation of the benzoyl group with 2-thienoyl group (**4i**) and alkanoyl group (**4j-m**) finally resulted in a loss of potency. Further characterizations of compounds **4n-t** with the variation of sulfonyl unit demonstrated that compound **4r** with the 4-methoxyl substitute in sulfonyl unit is more beneficial for compound inhibitory property toward CES1. Primary SAR analysis of all tested *β*-keto sulfones compounds provide insights into the fine relationships linking between the inhibitory effects on CES1 and the substituent-properties of these compounds. 2-naphthoyl and 4-methoxyl sulfonyl moiety were beneficial for *β*-keto sulfones inhibitory property toward CES1, led to the increase of the inhibitory effect on CES1.

Table 2 The inhibition potency of *β*-keto sulfones towards CES1. [a]

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
4a	62.10±10.61	**4l**	＞100
4b	＞100	**4m**	＞100
4c	＞100	**4n**	36.95±5.41
4d	6.11±1.18	**4o**	＞100
4e	＞100	**4p**	＞100
4f	＞100	**4q**	41.42±3.75
4g	＞100	**4r**	21.54±1.61
4h	3.74±0.47	**4s**	＞100
4i	＞100	**4t**	27.55±4.33
4j	＞100	**4u**	1.61±0.33
4k	＞100	**bavachinin**[b]	3.72±0.94

[a] All data presented are averages of at least three separate experiments.

[b] Bavachinin, a positive inhibitor against CES1.

Guided by these SARs results, we next design and synthesize a novel *β*-keto sulfone compound **4u** that may exhibit more potent inhibitory effect on CES1. The synthetic route is described in Scheme 4. Gratifyingly, 2-naphthylphenone-derived *β*-keto acid **2h** was reacted with sodium 4-methoxyl

benzenesulfinate **3f** to harvest the target product **4u** in 86% yield. The novel *β*-keto sulfone compound **4u** showed unusually potent inhibitory activity against CES1 with much lower IC_{50} value of 1.61 μM (Scheme 4 and Fig. S1).

Scheme 4. Synthesis of compound **4u**.

3. Conclusion

In summary, the transient directing strategy was successfully utilized in the decarboxylative sulfonylation of *β*-keto acids with sodium sulfinates. This synthetic protocol featured by mild reaction conditions and good functional group compatibility. Preliminary mechanistic studies showed that this reaction is likely to proceed through a nucleophilic substitution of *β*-keto acid with sulfonyl bromide pathway. All synthesized *β*-keto sulfones were evaluated the inhibitory effect against CES1. The SAR analysis revealed that 2-naphthoyl moiety and 4-methoxyl sulfonyl moiety of *β*-keto sulfones are very essential for CES1 inhibition. In addition, we design and synthesize a novel *β*-keto sulfone **4u**, which demonstrated potent inhibitory activity against CES1. Detailed mechanism for the *β*-keto sulfones synthesis process and other biological activity studies for the *β*-keto sulfones are currently ongoing in our laboratory..

4. Experimental section

4.1. General Information

All reactions were carried out under air. Flash chromatography was performed on silica gel 60 (40-63μm, 60Å). Thin layer chromatography (TLC) was performed on glass plates coated with silica gel 60 with F254 indicator. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker 600 MHz spectrometer. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$ = δ 7.28). Carbon nuclear magnetic resonance (^{13}C NMR) spectra recorded on a Bruker 600 operating at 150 MHz. Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$ = δ 77.07). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz), integration. Electrospray ionization high-resolution mass spectra (ESI-HRMS) were recorded on a Bruke P-SIMS-Gly FT-ICR mass spectrometer. Starting materials: *β*-keto acids[11c] and sodium sulfinates[9k] were prepared according to literature procedures. Commercial available chemicals were purchased from Sigma-Aldrich and used without further purification. Bavachinin was purchased from purchased from Chengdu Pufei De Biotech Co., Ltd. (Chengdu, Sichuan, China). Stock solutions of *β*-keto sulfones were prepared in DMSO and stored at 4°C until use. Phosphate buffer (100 mM, pH 6.5) was prepared by using Millipore water and stored at 4°C until use. Human liver microsomes (HLMs) were obtained from Celsis (Shanghai, China). The specific probes DME was synthesized in our lab as described previously.[13] The Luciferin Detection Reagent (LDR) was obtained from Promega Corporation (USA).

4.2. General Procedure for the decarboxylative sulfonylation reaction.

A 25 mL Schlenk tube was charged with *β*-keto acids **2** (0.75 mmol), sodium sulfinates **3** (0.5 mmol), NBS (0.75 mmol), K_3PO_4 (0.75 mmol) and CH_2Cl_2 (3 mL). The mixture was stirred at room temperature for 24 h. After completion of the reaction, the solvent was evaporated under reduced pressure, and the resulting residue was purified by flash column chromatography on silica gel to provide the desired product.

*4.2.1 1-phenyl-2-(phenylsulfonyl)ethan-1-one (**4a**).*[9d]

White solid; yield: 114.5 mg, 88%; eluent composition petroleum ether/ethyl acetate = 4:1.

*4.2.2 2-(phenylsulfonyl)-1-(p-tolyl)ethan-1-one (**4b**).* [9d]

White solid; yield: 116.6 mg, 85%; eluent composition petroleum ether/ethyl acetate = 4:1.

*4.2.3 1-(4-methoxyphenyl)-2-(phenylsulfonyl)ethan-1-one (**4c**).* [9d]

White solid; yield: 124.8 mg, 86%; eluent composition petroleum ether/ethyl acetate = 4:1.

*4.2.4 1-(4-chlorophenyl)-2-(phenylsulfonyl)ethan-1-one (**4d**).* [9d]

White solid; yield: 119.4 mg, 81%; eluent composition petroleum ether/ethyl acetate = 4:1.

*4.2.5 1-(4-fluorophenyl)-2-(phenylsulfonyl)ethan-1-one (**4e**).* [9d]

White solid; yield: 111.3 mg, 80%; eluent composition petroleum ether/ethyl acetate = 4:1.

*4.2.6 2-(phenylsulfonyl)-1-(m-tolyl)ethan-1-one (**4f**).* [9d]

White solid; yield: 119.3 mg, 87%; eluent composition petroleum ether/ethyl acetate = 4:1.

*4.2.7 2-(phenylsulfonyl)-1-(o-tolyl)ethan-1-one (**4g**).* [9d]

White solid; yield: 113.8 mg, 83%; eluent composition petroleum ether/ethyl acetate = 4:1.

*4.2.8 1-(naphthalen-2-yl)-2-(phenylsulfonyl)ethan-1-one (**4h**).* [9d]

White solid; yield: 128.8 mg, 83%; eluent composition petroleum ether/ethyl acetate = 4:1.

*4.2.9 2-(phenylsulfonyl)-1-(thiophen-2-yl)ethan-1-one (**4i**).* [9e]

White solid; yield: 103.9 mg, 78%; eluent composition petroleum ether/ethyl acetate = 4:1.

*4.2.10 1-(phenylsulfonyl)propan-2-one (**4j**).* [9e]

White solid; yield: 74.3 mg, 75%; eluent composition petroleum ether/ethyl acetate = 4:1.

*4.2.11 1-cyclopropyl-2-(phenylsulfonyl)ethan-1-one (**4k**).*

White solid; yield: 72.9 mg, 65%; eluent composition petroleum ether/ethyl acetate = 4:1; m.p. = 54.2-55.2 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.3 Hz, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.9 Hz, 2H), 4.29 (s, 2H), 2.29-2.26 (m, 1H), 1.10-1.04 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 197.8, 138.2, 133.7, 128.7, 127.8, 67.6, 21.5, 12.8; HRMS calc. for $[M+H]^+$ $C_{11}H_{13}O_3S$: 225.0585, found, 225.0575.

*4.2.12 3-methyl-1-(phenylsulfonyl)butan-2-one (**4l**).*

White solid; yield: 79.2 mg, 70%; eluent composition petroleum ether/ethyl acetate = 4:1; m.p. = 68.3-69.2 °C; ^{1}H

NMR (600 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.71-7.68 (m, 1H), 7.60-7.58 (m, 2H), 4.25 (s, 2H), 2.94-2.89 (m, 1H), 1.11 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 201.3, 138.3, 133.7, 128.7, 127.8, 64.1, 41.4, 17.0; HRMS calc. for $[M+Na]^+$ $C_{11}H_{14}NaO_3S$: 249.0561, found, 249.0551.

*4.2.13 3, 3-dimethyl-1-(phenylsulfonyl)butan-2-one (**4m**).*

White solid; yield: 91.3 mg, 76%; eluent composition petroleum ether/ethyl acetate = 4:1; m.p. = 77.6-78.9 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97-7.96 (m, 2H), 7.70-7.67 (m, 1H), 7.60-7.58 (m, 2H), 4.34 (s, 2H), 1.13 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 202.7, 138.9, 133.4, 128.5, 128.1, 60.2, 44.7, 25.0; HRMS calc. for $[M+H]^+$ $C_{12}H_{17}O_3S$: 241.0898, found, 241.0889.

*4.2.14 1-phenyl-2-tosylethan-1-one (**4n**).* [9d]

White solid; yield: 111.1 mg, 81%; eluent composition petroleum ether/ethyl acetate = 4:1.

*4.2.15 2-((4-chlorophenyl)sulfonyl)-1-phenylethan-1-one (**4o**).* [9d]

White solid; yield: 113.5 mg, 77%; eluent composition petroleum ether/ethyl acetate = 4:1.

*4.2.16 2-((4-fluorophenyl)sulfonyl)-1-phenylethan-1-one (**4p**).* [9d]

White solid; yield: 96.0 mg, 69%; eluent composition petroleum ether/ethyl acetate = 4:1.

*4.2.17 2-((4-bromophenyl)sulfonyl)-1-phenylethan-1-one (**4q**).* [9d]

White solid; yield: 115.3 mg, 68%; eluent composition petroleum ether/ethyl acetate = 4:1.

*4.2.18 2-((4-methoxyphenyl)sulfonyl)-1-phenylethan-1-one (**4r**).* [9d]

White solid; yield: 103.1 mg, 71%; eluent composition petroleum ether/ethyl acetate = 4:1.

*4.2.19 2-(methylsulfonyl)-1-phenylethan-1-one (**4s**).* [9k]

White solid; yield: 69.4 mg, 70%; eluent composition petroleum ether/ethyl acetate = 4:1.

*4.2.20 2-(naphthalen-2-ylsulfonyl)-1-phenylethan-1-one (**4t**).* [9k]

White solid; yield: 113.3 mg, 73%; eluent composition petroleum ether/ethyl acetate = 4:1.

*4.2.21 2-((4-methoxyphenyl)sulfonyl)-1-(naphthalen-2-yl)ethan-1-one (**4u**).*

White solid; yield: 146.4 mg, 86%; eluent composition petroleum ether/ethyl acetate = 4:1; m.p. = 158.6-161.0 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.96 (d, *J* = 8.5 Hz, 2H), 7.93-7.87 (m, 2H), 7.81 (d, *J* = 8.9 Hz, 2H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 8.9 Hz, 2H), 4.84 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 188.2, 164.2, 136.0, 133.2, 132.3, 132.2, 130.9, 130.2, 130.0, 129.4, 128.8, 127.8, 127.1, 124.0, 114.4, 64.0, 55.7; HRMS calc. for $[M+H]^+$ $C_{19}H_{17}O_4S$: 341.0848, found, 341.0840.

4.3 General procedure for inhibition assays of CES1-mediated DME hydrolysis.

The inhibitory effects against human carboxylesterase 1 (CES1) were investigated using D-Luciferin methyl ester (DME) as the probe substrate,[13] while bavachinin were used as positive control.[19] In brief, the incubation mixture with a total volume of 100 μL was consisted of PBS (pH 6.5), HLM (10 μg/mL, final concentration), and each inhibitor. After 10 min pre-incubation at 37 °C, the reaction was started by the addition of DME (3μM, near the K_m value of DME in HLM, final concentration), with the final concentration of DMSO at 1% (v/v, without loss of the catalytic activity). After incubation at 37 °C for 10 min in a shaking bath, LDR (equal volume of incubation mixture, 50 μL) was added to terminate the reaction. The mixture was then taken for luminescence measurements by a Synergy H^1 Multi-Mode Reader (Biotek, USA). The luminescent product of D-Luciferin (the hydrolytic metabolite of DME) was quantified with the excitation wavelength of 600 nm, while the emission wavelength was 662 nm. The gain value was set at 60. The residual activities of CES1 were calculated with the following formula: the residual activity (%) = (the florescence intensity in the presence of inhibitor)/the florescence intensity in negative control (without any inhibitor) × 100%. All assays were conducted in triplicate, and the data were shown as mean ± SD.

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