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β-Keto sulfones as inhibitors of 11β-hydroxysteroid dehydrogenase type I and the mechanism of action

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Abstract—The design, synthesis, and biological evaluation of β-keto sulfones as 11β-HSD1 inhibitors and the mechanism of inhibition are described here. This class of compounds is not active against 11β-HSD2 and therefore may have therapeutic potential for metabolic syndrome and type 2 diabetes.
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1. Introduction

Metabolic disorders, such as obesity and type 2 diabetes, have assumed epidemic proportions and present major challenges for healthcare systems.[1–3] The dramatic increase in the prevalence of obesity in recent years has led to an increased recognition of 'metabolic syndrome', a collection of metabolic and cardiovascular abnormalities, that is a precursor to type 2 diabetes. Metabolic syndrome is characterized by abdominal obesity, impaired glucose tolerance, dyslipidemia, low levels of high density lipoprotein (HDL) cholesterol, and hypertension.[4,5] Recent investigations have implicated aberrant glucocorticoid receptor (GR) signaling in the development of several phenotypes associated with metabolic syndrome. Glucocorticoid hormones are key metabolic regulators. The major activator of the GR in humans is cortisol, and the adrenal cortex is the major source of circulating cortisol. Recent evidence suggests that GR signaling depends not only on the circulating cortisol levels, but also on the intracellular generation of cortisol through reduction of the inactive glucocorticoid, cortisone.[6] The reduction reaction is catalyzed by 11β-hydroxysteroid dehydrogenase type I (11β-HSD1) with the concomitant oxidation of NADPH, while cortisone itself is generated by the action of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) on cortisol using NAD as a cofactor (Fig. 1).[6]

These two enzymes have very different expression profiles: 11β-HSD1 is highest in liver, adipose, and the central nervous system, whereas 11β-HSD2 is expressed in kidney, colon and other tissues where mineralocorticoid receptor (MR) signaling is important.[6] The MR is activated by aldosterone but it can also bind cortisol with similar affinity. 11β-HSD2 functions to reduce local cortisol concentrations, thereby preventing illicit activation of MR by cortisol. Disruption or mutations in the 11β-HSD2 gene result in sodium retention, hypokalemia, and hypertension because of inappropriate glucocorticoid occupation of the mineralocorticoid receptor in the kidney.[7]

A potential role for 11β-HSD1 inhibitors in metabolic disease in vivo has been demonstrated using a transgenic

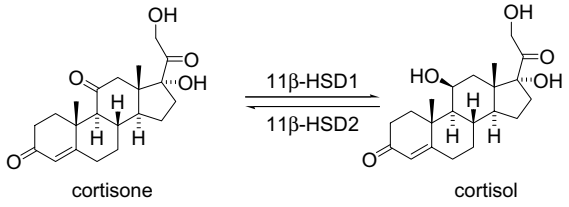

Figure 1. Interconversion of cortisone and cortisol by 11β-HSD type 1 and 2 enzymes.

Keywords: HSD1; 11β-HSD1; Diabetes; Metabolic syndrome; Keto sulfone; Synthesis.
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mouse approach. Over-expression of 11β-HSD1 predominantly in adipose tissue shows several features similar to those observed in patients with metabolic syndrome.[8a] Transgenic mice over-expressing 11β-HSD1 in the liver have also been generated and while they are not obese they do show several features of metabolic syndrome.[8b] Inactivation of the 11β-HSD1 gene in mice confers resistance to diet-induced obesity and improves both insulin sensitivity and lipid profiles.[8c] Administration of specific 11β-HSD1 inhibitors in mouse models of insulin resistance led to improved hyperglycemia and insulin sensitivity.[9,10] Recent studies with the non-specific 11β-HSD1 inhibitor carbenoxolone also show improved hepatic insulin sensitivity and decreased glucose production in humans.[11] However, the 11β-HSD2 inhibitory activity of carbenoxolone was a limiting factor because it induces renal mineralocorticoid excess at higher doses.[11] Thus, while inhibition of 11β-HSD1 is an attractive strategy for the design of therapeutics for metabolic syndrome and type 2 diabetes, it is obvious that an inhibitor against 11β-HSD1 must not affect 11β-HSD2.

Arylsulfonamidothiazole compounds from Biovitrum[9] have been shown to be selective 11β-HSD1 inhibitors. For example, **BVT-14225** (Fig. 2) was reported to have IC_{50} value of 52 nM against 11β-HSD1 in a microsomal enzyme assay and to be 1000-fold less potent against 11β-HSD2. Since then, several publications related to selective 11β-HSD1 inhibition have appeared.[12] We recently published our design, synthesis, and biological evaluation of arylsulfonamidooxazoles as 11β-HSD1 inhibitors.[13] In that paper, we also disclosed our serendipitous discovery of a β-keto sulfone (Fig. 3, compound **2a**) as another class of potent 11β-HSD1 inhibitors.[13] Presented herein is the synthesis and detailed SAR study of β-keto sulfone series. Our screening approach was to use a cell-based assay to evaluate analogs, this ensures that active compounds will also be cell permeable and potentially more drug-like. Our goal is to develop novel, selective, potent, orally bioavailable 11β-HSD1 inhibitors. This β-keto sulfone class of compounds shows no activity against 11β-HSD2 at concentration as high as 100 μM.

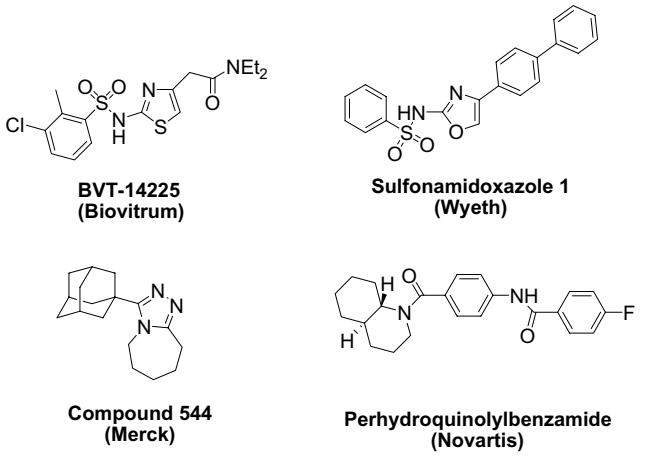


Figure 2. Examples of selective 11β-HSD1 inhibitors.

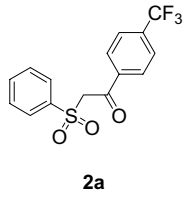


Figure 3. β-Keto sulfone class of selective 11β-HSD1 inhibitors.

2. Chemistry

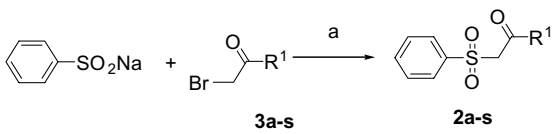
Preparation of β-keto sulfones was carried out through the alkylation of sodium phenylsulfinate with bromomethyl ketones.[14] Using this one-step sequence and microwave radiation, parallel synthetic libraries were quickly prepared to explore the SAR around this lead. Analogs **2a**–**s** were thus isolated in excellent yield (Scheme 1).

Variations to the keto portion of the molecules were next explored. γ-Keto sulfones were prepared through the alkylation of sodium phenylsulfinate with chloroethyl ketones **5a**–**d**. This sequence again proceeded smoothly under microwave heating condition at 100 °C for 40 min. Final products **6a**–**d** were isolated in 70–85% yield after column chromatography (Scheme 2). Alternatively, **2a** was reduced to β-hydroxy sulfone **7** with $NaBH_4$. β-Oxime sulfone **8** was also prepared in high yield by the condensation of β-keto sulfone **2b** and hydroxyamine in ethanol at 100 °C for 20 min (Scheme 3).[15]

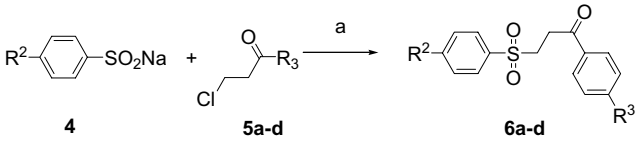
Acylsulfonamides **11a**–**e** were obtained in almost quantitative yield by heating benzenesulfonamides with acetyl chlorides in acetonitrile (Scheme 4). Further alkylation of the acylsulfonamides, nitrogen was carried out with various alkylating agents in the presence of triethylamine to provide **11f** and **g** (Schemes 5 and 6).

3. Results and discussion

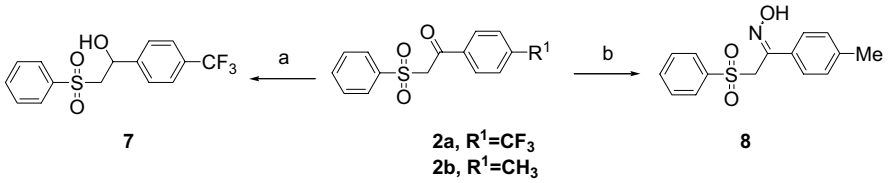
Compound **2a** was found to be a potent hit in the cell-based assay and proved to be a good starting point for further optimization (Table 1). It possessed a phenyl



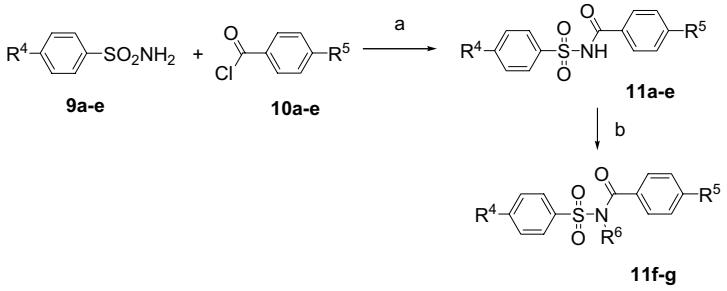
Scheme 1. Reagent and condition: (a) DMF, 120 °C, thermal or microwave irradiation.



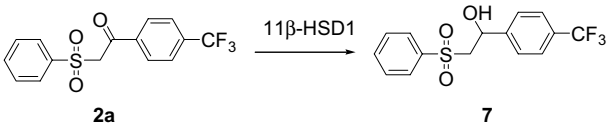
Scheme 2. Reagent and conditions: (a) DMF, 100 °C, 40 min.



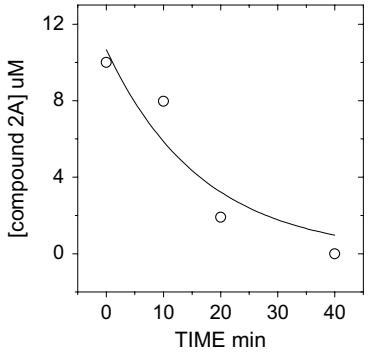
Scheme 3. Reagents and conditions: (a) $NaBH_4$, THF/*i*-PrOH; (b) H_2N–OH, ethanol, 100 °C, 20 min.



Scheme 4. Reagents and conditions: (a) pyridine, CH_3CN, 25–100 °C, 20–120 min; (b) Et_3N, MeI, DMF, 100 °C, 20–60 min.



Scheme 5. β-Keto sulfone **2a** a substrate of 11β-HSD1.



Scheme 6. Concentration of **2a** versus incubation time.

ketone moiety with a strong electron-withdrawing group CF_3 at the *para* position. Variations at this *para* position with methyl, fluoro, chloro (**2b**, **2d**, **2e**) maintained the potency, while **2c** with the electron-donating methoxy showed improved potency. This suggested that both electron-donating groups and electron-withdrawing groups are well tolerated at this position. 3-Methoxyphenyl analog (**2f**) and 3,4-dichlorophenyl analog (**2g**) are very potent indicating that both the *para* position and the *meta* position can be functionalized further. Analogs with polar groups such as nitro or amine decreased the activity dramatically. For example, diethylamino substituted analog **2i** was 23-fold less active than the initial hit **2a**.

The potential reactivity of keto moiety in these inhibitors was a concern to us. The first approach to address this issue was to provide compounds with increased steric hindrance around the keto functionality. Analogs with ortho-substitution at phenyl ring (**2j**, **2k**) decreased activity significantly. Bulky group such as benzhydryl also decreased activity significantly (**2l**). Further SAR study indicated aliphatic keto analogs (**2m**–**o**) all were dramatically less potent. This suggested that the aromatic ring is a key part of the pharmacophore. In silico modeling study of **2a** shows that the benzene ring achieves a strong π-stacking interaction with the enzyme's active site residue tyrosine 177 side chain. The modeling work and HSD1 crystal structure will be disclosed in due course. Potent inhibitors such as **2a**–**f** were

Table 1. Biological activities of β-keto sulfones **2a**–**s** and sulfonamidothiazole **BVT-14225**

Compound	R^1	11β-HSD1 IC_{50}[a] (μM)	11β-HSD2 IC_{50}[a] (μM)
2a	4-CF_3–Ph	0.187	>200
2b	4-Me–Ph	0.102	>200
2c	4-MeO–Ph	0.075	>200
2d	4-F–Ph	0.09	>200
2e	4-Cl–Ph	0.2	>200
2f	3-MeO–Ph	0.06	>200
2g	3,4-DiCl–Ph	0.101	N/A
2h	4-NO_2–Ph	1.31	N/A
2i	4-NEt_2–Ph	4.4	N/A
2j	2,4-DiMe–Ph	1.2	N/A
2k	2,5-DiMeO–Ph	9.3	N/A
2l	Benzhydryl	2.9	N/A
2m	Et	15	N/A
2n	*t*-Bu	90	N/A
2o	$C(CH_3)_2CH_2CO_2Et$	5.0	N/A
2p	3-Thienyl	0.345	N/A
2q	2-(3-Me)Benzothiophene	0.525	N/A
2r	2-(5-Phenyl)thiophene	0.134	N/A
2s	2-(2,4-DiCl-phenyl)-5-furan	0.169	N/A
BVT-14225		1.5	>200

[a] Assay run in duplicate.

tested against 11β-HSD2 in an identical cell-based assay and none were active at concentrations as high as 100 μM. This suggests that β-keto sulfones are 11β-HSD1 specific inhibitors.

The second approach to address potential ketone reactivity was to investigate analogs with electron rich heterocycles conjugated to the ketone. Interestingly, heteroaryl rings such as thienyl and furanyl (**2p–s**) serve as potent phenyl bioisosteres.

The third approach to decrease the electrophilicity of keto moiety was to provide analogs with an extended linker between keto and sulfone. γ-Keto sulfones were prepared in an effort to study this effect. All four γ-keto sulfones (**6a–d**) were weak inhibitors of 11β-HSD1 in this cell-based assay (Table 2). Replacing the methylene carbon linker with nitrogen led to the synthesis of acylsulfonamides **11a–e**. None of these analogs showed any appreciable activity up to 100 μM (Table 3). Alkylation with methyl and benzyl groups at nitrogen position led to compounds **11f** and **11g** with increased lipophilicity. Compounds **11g** showed weak but improved activity compared to analog **11a**. The exact reason for this improvement is not known. It is believed that the enzymatic site is large and quite lipophilic and tends to prefer lipophilic groups. Removing acidic proton **11a** by alkylation forms more lipophilic compounds such as **11f** and **11g**.

To further confirm that the keto and sulfone moieties were essential parts of pharmacophores, a few more analogs were prepared for testing. Examples with variations around the keto moiety are β-hydroxy sulfone **7**, β-oxime sulfone **8**, and β-amido sulfone **19**. Examples with variations around sulfone functionality are β-keto sulfonamides **17**, β-keto amides **18**, and 1,3-diketone **20**. Most of these analogs were weak inhibitors of 11β-HSD1 (Fig. 4). The IC_{50} value of 1,3-diketone **20** was not determined due to its cytotoxicity. However, β-keto sulfonamide **17** did prove to be a potent 11β-HSD1 inhibitor and a detailed SAR for this template will be disclosed in due course.

Table 2. Biological activities of γ-keto sulfones **6a–d**

Compound	R^2	R^3	11β-HSD1 IC_{50}[a] (μM)
6a	H	H	17.4
6b	H	F	19.6
6c	H	Cl	24
6d	H	Br	25

[a] Assay run in duplicate.

Table 3. Biological activities of acylsulfonamides **11a–g**

Compound	R^4	R^5	R^6	11β-HSD1 IC_{50}[a] (μM)
11a	H	H	H	>100
11b	H	3-Cl	H	>100
11c	H	4-CF_3	H	>100
11d	4-Me	H	H	>100
11e	4-Cl	H	H	>100
11f	H	H	Me	35.5
11g	H	H	Bn	5.7

[a] Assay run in duplicate.

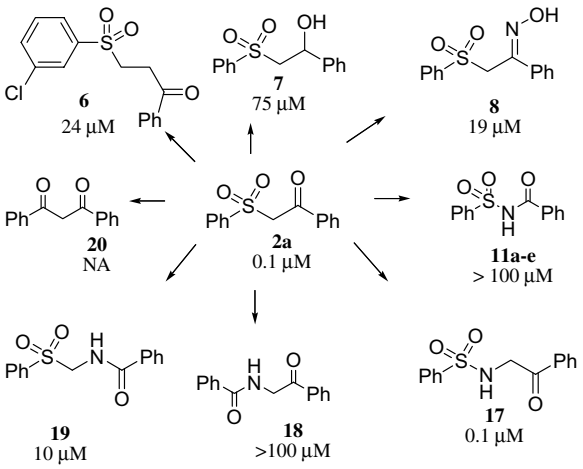


Figure 4. SAR of analogs with β-keto sulfone variations.

The mechanism by which these β-keto sulfones inhibit 11β-HSD1 activity was next examined. These studies were especially interesting for the β-keto sulfone series as the ketone functionality in these compounds could mimic the role of the ketone moiety in the endogenous 11β-HSD1 substrate cortisone. Therefore β-keto sulfone **2a** was incubated with 11β-HSD1 enzyme. Using LC/MS with single ion monitoring (SIM) mode, the starting compound concentration was found to decrease with the incubation time. The half-life of **2a** was found to be 16 min under these conditions. The study supports the conclusion that β-keto sulfone **2a** is substrate of 11β-HSD1 enzyme. Compound **7**, the product of enzymatic reduction, is a very weak inhibitor of 11β-HSD1 with IC_{50} over 100 μM.

4. Conclusions

β-Keto sulfones were shown to be potent and selective 11β-HSD1 inhibitors. The most potent compound from this series, **2f**, has an IC_{50} value in cell-based assay of 60 nM and no activity in an analogous 11β-HSD2 assay at 100 μM. Through a detailed SAR study, it was found that both the keto and sulfone moieties are essential parts of the pharmacophore. Replacement of either the keto or sulfone functionality led to either decreased activity or inactive compounds. A detailed enzymatic study revealed that β-keto sulfones are the substrates of 11β-HSD1 enzyme. They inhibit by competing with substrate for the active site, they are then turned over by the enzyme to products which are not inhibitors.

5. Experimental

All reagents and solvents were of commercial quality and used without further purification. Column chromatography was performed using Merck silica gel 60 (230–400 mesh). Proton nuclear magnetic spectroscopy ^1H NMR spectra (400 MHz) were obtained on a Bruker 400 spectrometer. Chemical shifts are reported in parts per million relative to Me_4Si as internal standard.

Low-resolution mass spectra (MS) were obtained using a Micromass Platform Electrospray Ionization Quadrupole mass spectrometer. High-resolution exact mass measurements (HRMS) were performed on a Bruker ApexIII 7T FT/ICR/MS. All intermediates were characterized by ^{1}H NMR. All new final SAR compounds were determined to be consistent with proposed structure by ^{1}H NMR, MS, HRMS and were greater than 95% pure in two solvent systems (HPLC Method 1: H_2O–CH_3CN and HPLC Method 2: H_2O–MeOH) as determined using an Agilent 1100 HPLC instrument on a C18 column.

5.1. Preparation of β-keto sulfone (2a)

To a solution of 2-bromo-1-(4-(trifluoromethyl)phenyl)-ethanone (2.03 g, 7.59 mmol) in DMF (30 mL) was added benzene sulfonic acid sodium salt (1.25 g, 7.59 mmol). The mixture was heated to 110 °C for 2 h. The mixture was cooled to room temperature and DMF removed via rotavap. The residue thus obtained was partitioned between EtOAc and water. Organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. After silica gel column chromatography (20% EtOAc/hexane), **2a** was obtained as a white solid in 68% yield (1.70 g). Mp 104–106 °C; ^{1}H NMR (400 MHz, acetonitrile-d_3) δ ppm 4.84 (s, 2H), 7.50 (t, J = 7.96 Hz, 2H), 7.62 (t, J = 7.58, 7.56 Hz, 1H), 7.70 (d, J = 8.84 Hz, 2H), 7.78 (d, J = 7.32 Hz, 2H), 7.95 (d, J = 8.84 Hz, 2H); HRMS: calcd for $C_{15}H_{11}F_3O_3S$ + H +, 329.0454; found (ESI-FTMS, $[M+H]^{1+}$), 329.0454; HPLC Method 1: room temperature, 5.76 min, 96.57%. HPLC Method 2: room temperature, 6.28 min, 97.20%; Anal. Calcd for $C_{15}H_{11}F_3O_3S$: C, 54.88; H, 3.38; N, 0. Found: C, 54.90; H, 3.22; N, <0.02.

5.2. General synthetic procedure 2 for compounds 2b–s

To a solution of bromoethylketone **3** (3.00 mmol) in DMF (5 mL) was added benzene sulfonic acid sodium salt (3.00 mmol). The reaction mixture was irradiated under microwave condition at 120 °C for 20 min. The mixture was partitioned between CH_2Cl_2 and water. Organic phase was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was then subjected to column chromatography (10–40% EtOAc/hexanes) to yield compounds **2b**–**s**.

5.2.1. 2-(Phenylsulfonyl)-1-*p*-tolylethanone (2b). Compound **2b** was obtained according to the procedure described in procedure 2 as a white solid in 85% yield (1.50 g). Mp 124–126 °C; ^{1}H NMR (400 MHz, acetonitrile-d_3) δ ppm 2.53 (s, 3H), 4.92–5.02 (m, 2H), 7.44 (d, J = 7.83 Hz, 2H), 7.72 (t, J = 7.71 Hz, 2H), 7.84 (t, J = 7.58 Hz, 1H), 7.94 (d, J = 8.08 Hz, 2H), 8.01 (d, J = 7.33 Hz, 2H); HRMS: calcd for $C_{15}H_{14}O_3S$ + H +, 275.0736; found (ESI-FTMS, $[M+H]^{1+}$), 275.0728; HPLC Method 1: room temperature, 5.28 min, 96.69%. HPLC Method 2: room temperature, 5.46 min, 97.83%; Anal. Calcd for $C_{15}H_{14}O_3S$: C, 65.67; H, 5.14; N, 0. Found: C, 65.79; H, 5.18; N, <0.02.

5.2.2. 1-(4-Methoxyphenyl)-2-(phenylsulfonyl)ethanone (2c). Compound **2c** was obtained as a light yellow solid in 90% yield (0.416 g) according to general procedure 2. Mp 114–116 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.85 (s, 3H), 5.24 (s, 2H), 7.03 (d, J = 8.84 Hz, 2H), 7.63 (t, J = 7.58 Hz, 2H), 7.73 (t, J = 7.45 Hz, 1H), 7.83–7.99 (m, 4H); HRMS: calcd for $C_{15}H_{14}O_4S$ + H +, 291.0686; found (ESI-FTMS, $[M+H]^{1+}$), 291.0687; HPLC Method 1: room temperature, 5.03 min, 99.61%. HPLC Method 2: room temperature, 5.10 min, 100.00%; Anal. Calcd for $C_{15}H_{14}O_4S$: C, 62.05; H, 4.86; N, 0. Found: C, 62.22; H, 4.83; N, <0.02.

5.2.3. 1-(4-Fluorophenyl)-2-(phenylsulfonyl)ethanone (2d). Compound **2d** was obtained as a white solid in 92% yield (0.596 g) according to general procedure 2. Mp 116–118 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.34 (s, 2H), 7.31–7.40 (m, 2H), 7.63 (t, J = 7.58 Hz, 2H), 7.74 (t, J = 7.33 Hz, 1H), 7.90 (m, 2H), 8.05 (d, J = 14.65 Hz, 1H), 8.05 (d, J = 3.54 Hz, 1H); HRMS: calcd for $C_{14}H_{11}FO_3S$ + H +, 279.0486; found (ESI-FTMS, $[M+H]^{1+}$), 279.0486; HPLC Method 1: room temperature, 5.10 min, 98.11%. HPLC Method 2: room temperature, 5.16 min, 98.41%; Anal. Calcd for $C_{14}H_{11}FO_3S$: C, 60.42; H, 3.98; N, 0. Found: C, 60.31; H, 3.85; N, <0.02.

5.2.4. 1-(4-Chlorophenyl)-2-(phenylsulfonyl)ethanone (2e). Compound **2e** was obtained as a white solid in 76% yield (0.551 g) according to general procedure 2. Mp 133–135 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.33–5.36 (m, 2H), 7.61 (m, 4H), 7.73 (m, 1H), 7.89 (m, 2H) 7.97 (m, 2H); HRMS: calcd for $C_{14}H_{11}ClO_3S$ + H +, 295.0190; found (ESI-FTMS, $[M+H]^{1+}$), 295.0194; HPLC Method 1: room temperature, 5.46 min, 99.34%. HPLC Method 2: room temperature, 5.71 min, 99.38%; Anal. Calcd for $C_{14}H_{11}ClO_3S$: C, 57.05; H, 3.76; N, 0. Found: C, 57.06; H, 3.80; N, <0.02.

5.2.5. 1-(3-Methoxyphenyl)-2-(phenylsulfonyl)ethanone (2f). Compound **2f** was obtained as a yellow oil in 90% yield (0.164 g) according to general procedure 2. Mp 96–98 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.81 (s, 3H), 5.37 (s, 2H), 7.24 (dd, J = 8.21, 2.65 Hz, 1H), 7.38–7.47 (m, 2H), 7.56 (d, J = 7.83 Hz, 1H), 7.63 (t, J = 7.58 Hz, 2H), 7.72 (d, J = 7.33 Hz, 1H), 7.90–7.95 (m, 2H); HRMS: calcd for $C_{15}H_{14}O_4S$ + H +, 291.0686; found (ESI-FTMS, $[M+H]^{1+}$), 291.0687; HPLC Method 1: room temperature, 5.12 min, 98.51%. HPLC Method 2: room temperature, 5.22 min, 99.19%; Anal. Calcd for $C_{15}H_{14}O_4S$: C, 62.05; H, 4.86; N, 0. Found: C, 62.22; H, 4.86; N, <0.02.

5.2.6. 1-(3,4-Dichlorophenyl)-2-(phenylsulfonyl)ethanone (2g). Compound **2g** was obtained as a white solid in 88% yield (0.625 g) according to general procedure 2. Mp 149–151 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.40 (s, 2H), 7.64 (t, J = 7.71 Hz, 2H), 7.74 (t, J = 7.58, 7.33 Hz, 1H), 7.80 (d, J = 8.59 Hz, 1H), 7.87–7.92 (m, 3H), 8.18 (d, J = 2.27 Hz, 1H); HRMS: calcd for $C_{14}H_{10}Cl_2O_3S$ + H +, 328.9800; found (ESI-FTMS, $[M+H]^{1+}$), 328.9804; HPLC Method 1: room tempera-

ture, 5.85 min, 99.61%. HPLC Method 2: room temperature, 6.32 min, 99.71%.

5.2.7. 1-(4-Nitrophenyl)-2-(phenylsulfonyl)ethanone (2h). Compound **2h** was obtained as a yellow solid in 53% yield (0.391 g) according to general procedure 2. Mp 137–139 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.47 (s, 2H), 7.65 (t, J = 7.71 Hz, 2H), 7.75 (t, J = 7.45 Hz, 1H), 7.91 (d, J = 7.33 Hz, 2H), 8.19 (d, J = 9.09 Hz, 2H), 8.32 (d, J = 8.84 Hz, 2H); HRMS: calcd for $C_{14}H_{11}NO_5S + NH_4^+$, 323.0696; found (ESI-FTMS, $[M+NH_4]^{1+}$), 323.0694; HPLC Method 1: room temperature, 5.17 min, 97.49%. HPLC Method 2: room temperature, 5.20 min, 97.73%; Anal. Calcd for $C_{14}H_{11}NO_5S$: C, 55.08; H, 3.63; N, 4.59. Found: C, 55.28; H, 3.62; N, 4.46.

5.2.8. 1-(4-(Diethylamino)phenyl)-2-(phenylsulfonyl)ethanone (2i). Compound **2i** was obtained as a light yellow solid in 53% yield (0.426 g) according to general procedure 2. Mp 104–105 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.11 (t, J = 6.95 Hz, 6H), 3.43 (q, J = 7.07 Hz, 4H), 5.04 (s, 2H), 6.65 (d, J = 9.35 Hz, 2H), 7.62 (t, J = 7.71 Hz, 2H), 7.69–7.73 (m, 1H), 7.75 (d, J = 9.09 Hz, 2H), 7.88 (d, J = 7.33 Hz, 2H); HRMS: calcd for $C_{18}H_{21}NO_3S$ + H +, 332.1315; found (ESI-FTMS, $[M+H]^{1+}$), 332.1321; HPLC Method 1: room temperature, 5.60 min, 100.00%. HPLC Method 2: room temperature, 5.89 min, 100.00%; Anal. Calcd for $C_{18}H_{21}NO_3S$: C, 65.23; H, 6.39; N, 4.23. Found: C, 65.41; H, 6.19; N, 4.19.

5.2.9. 1-(3,5-Dimethylphenyl)-2-(phenylsulfonyl)ethanone (2j). Compound **2j** was obtained as a white solid in 95% yield (0.504 g) according to general procedure 2. Mp 106–108 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.28 (s, 3H), 2.31 (s, 3H), 5.21 (s, 2H), 7.04–7.12 (m, 2H), 7.61 (t, J = 7.71 Hz, 2H), 7.72 (t, J = 7.33 Hz, 1H), 7.76 (d, J = 7.83 Hz, 1H), 7.85 (d, J = 7.33 Hz, 2H); HRMS: calcd for $C_{16}H_{16}O_3S$ + H +, 289.0893; found (ESI-FTMS, $[M+H]^{1+}$), 289.0897; HPLC Method 1: room temperature, 5.60 min, 99.52%. HPLC Method 2: room temperature, 5.92 min, 100.00%; Anal. Calcd for $C_{16}H_{16}O_3S$: C, 66.64; H, 5.59; N, 0. Found: C, 66.83; H, 5.54; N, <0.02.

5.2.10. 1-(2,5-Dimethoxyphenyl)-2-(phenylsulfonyl)ethanone (2k). Compound **2k** was obtained as a white solid in 64% yield (0.500 g) according to general procedure 2. Mp 100–102 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.72 (s, 3H), 3.77 (s, 3H), 5.19 (s, 2H), 7.00 (d, J = 3.28 Hz, 1H), 7.04 (d, J = 9.09 Hz, 1H), 7.11–7.18 (m, 1H), 7.60 (t, J = 7.58 Hz, 2H), 7.71 (t, J = 7.45 Hz, 1H), 7.85 (d, J = 7.33 Hz, 2H); HRMS: calcd for $C_{16}H_{16}O_5S$ + H +, 321.0791; found (ESI-FTMS, $[M+H]^{1+}$), 321.0792; HPLC Method 1: room temperature, 5.16 min, 100.00%. HPLC Method 2: room temperature, 5.33 min, 100.00%; Anal. Calcd for $C_{16}H_{16}O_5S$: C, 59.99; H, 5.03; N, 0. Found: C, 59.92; H, 4.82; N, <0.02.

5.2.11. 1,1-Diphenyl-3-(phenylsulfonyl)propan-2-one (2l). Compound **2l** was obtained as a colorless oil in 63% yield (0.534 g) according to general procedure 2. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.81 (s, 2H), 5.45 (s, 1H), 7.13 (d, J = 6.82 Hz, 4H), 7.19–7.37 (m, 6H), 7.63 (t, J = 7.71 Hz, 2H), 7.75 (t, J = 7.45 Hz, 1H), 7.86 (d, J = 7.33 Hz, 2H); HRMS: calcd for $C_{21}H_{18}O_3S + NH_4^+$, 368.1315; found (ESI-FTMS, $[M + NH_4]^{1+}$), 368.1317; HPLC Method 1: room temperature, 5.67 min, 92.59%. HPLC Method 2: room temperature, 6.50 min, 90.29%.

5.2.12. 1-(Phenylsulfonyl)butan-2-one (2m). Compound **2m** was obtained as a white solid in 65% yield (0.338 g) according to general procedure 2. Mp 43–46 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.87 (t, J = 7.07 Hz, 3H), 2.56 (q, J = 7.33 Hz, 2H), 4.69 (s, 2H), 7.66 (t, J = 7.83 Hz, 2H), 7.76 (t, J = 7.33, 7.32 Hz, 1H), 7.89 (d, J = 7.33 Hz, 2H); HRMS: calcd for $C_{10}H_{12}O_3S$ + H +, 213.0580; found (ESI-FTMS, $[M+H]^{1+}$), 213.0583; HPLC Method 1: room temperature, 4.24 min, 100.00%. HPLC Method 2: room temperature, 3.82 min, 100.00%; Anal. Calcd for $C_{10}H_{12}O_3S$: C, 56.58; H, 5.70; N, 0. Found: C, 56.66; H, 5.52; N, <0.02.

5.2.13. 3,3-Dimethyl-1-(phenylsulfonyl)butan-2-one (2n). Compound **2n** was obtained as a white solid in 85% yield (0.413 g) according to general procedure 2. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.00 (s, 9H), 4.94 (s, 2H), 7.64 (t, J = 7.58 Hz, 2H), 7.73 (t, J = 7.33 Hz, 1H), 7.87–7.94 (m, 2H); HRMS: calcd for $C_{12}H_{16}O_3S$ + H +, 241.0893; found (ESI-FTMS, $[M+H]^{1+}$), 241.0894; HPLC Method 1: room temperature, 5.03 min, 99.61%. HPLC Method 2: room temperature, 5.10 min, 100.00%.

5.2.14. Ethyl 3,3-dimethyl-4-oxo-5-(phenylsulfonyl)pentanoate (2o). Compound **2o** was obtained as a white solid in 65% yield (0.494 g) according to general procedure 2. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.05 (s, 6H), 1.10 (t, J = 7.33, 7.07 Hz, 3H), 2.58 (s, 2H), 3.96 (q, J = 7.16 Hz, 2H), 4.91 (s, 2H), 7.63 (t, J = 7.58 Hz, 2H), 7.73 (t, J = 6.82 Hz, 1H), 7.92 (d, J = 7.07 Hz, 2H); HRMS: calcd for $C_{15}H_{20}O_5S$ + H +, 313.1104; found (ESI-FTMS, $[M+H]^{1+}$), 313.1107; HPLC Method 1: room temperature, 5.12 min, 100.00%. HPLC Method 2: room temperature, 5.23 min, 100.00%.

5.2.15. 2-(Phenylsulfonyl)-1-(thiophen-3-yl)ethanone (2p). Compound **2p** was obtained as a light yellow solid in 62% yield (0.405 g) according to general procedure 1. Mp 126–128 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.19 (s, 2H), 7.46 (dd, J = 5.05, 1.26 Hz, 1H), 7.59–7.67 (m, 3H), 7.69–7.77 (m, 1H), 7.87–7.92 (m, 2H), 8.64 (dd, J = 2.78, 1.26 Hz, 1H); HRMS: calcd for $C_{12}H_{10}O_3S_2$ + H +, 267.0144; found (ESI-FTMS, $[M+H]^{1+}$), 267.0144; HPLC Method 1: room temperature, 4.79 min, 99.38%. HPLC Method 2: room temperature, 4.98 min, 99.49%; Anal. Calcd for $C_{12}H_{10}O_3S_2$: C, 54.12; H, 3.78; N, 0. Found: C, 54.08; H, 3.75; N, <0.02.

5.2.16. 1-(3-Methylbenzo[*b*]thiophen-2-yl)-2-(phenylsulfonyl)ethanone (2q). Compound **2q** was obtained as a light yellow solid in 60% yield (0.161 g) according to general procedure 1. Mp 158–159 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.70 (s, 3H), 5.26 (s, 2H), 7.51

(t, J = 7.07 Hz, 1H), 7.59 (t, J = 7.07 Hz, 1H), 7.65 (t, J = 7.58 Hz, 2H), 7.74 (d, J = 7.58 Hz, 1H), 7.93–7.98 (m, 2H), 8.02–8.07 (m, 2H); HRMS: calcd for $C_{17}H_{14}O_3S_2$ + H +, 331.0457; found (ESI-FTMS, $[M+H]^{1+}$), 331.0454; HPLC Method 1: room temperature, 5.93 min, 97.20%. HPLC Method 2: room temperature, 6.53 min, 97.35%.

5.2.17. 2-(Phenylsulfonyl)-1-(5-phenylthiophen-2-yl)ethanone (2r). Compound **2r** was obtained as a light pink solid in 65% yield (0.432 g) according to general procedure 1. Mp 172–174 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.27 (s, 2H), 7.38–7.53 (m, 3H), 7.58–7.83 (m, 6H), 7.92–7.99 (m, 2H), 8.13 (d, J = 4.04 Hz, 1H); HRMS: calcd for $C_{18}H_{14}O_3S_2$ + H +, 343.0457; found (ESI-FTMS, $[M+H]^{1+}$), 343.0452; HPLC Method 1: room temperature, 5.95 min, 100.00%. HPLC Method 2: room temperature, 6.46 min, 100.00%; Anal. Calcd for $C_{18}H_{14}O_3S_2$: C, 63.14; H, 4.12; N, 0. Found: C, 62.90; H, 3.92; N, <0.02.

5.2.18. 1-(5-(2,4-Dichlorophenyl)furan-2-yl)-2-(phenylsulfonyl)ethanone (2s). Compound **2s** was obtained as a light yellow solid in 8% yield (0.019 g) according to general procedure 2. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.14 (s, 2H), 7.35 (d, J = 3.79 Hz, 1H), 7.62 (t, J = 8.21 Hz, 3H), 7.71 (t, J = 7.45 Hz, 1H), 7.78 (d, J = 3.79 Hz, 1H), 7.82 (d, J = 2.02 Hz, 1H), 7.91 (t, J = 7.96 Hz, 3H); HRMS: calcd for $C_{18}H_{12}Cl_2O_4S$ + H +, 394.9906; found (ESI-FTMS, $[M+H]^{1+}$), 394.9908; HPLC Method 1: room temperature, 6.42 min, 100%. HPLC Method 2: room temperature, 7.04 min, 100%.

5.3. General synthetic procedures for γ-keto sulfones (6a–d)

To a solution of chloroethylketone **5** (2.97 mmol) in DMF (5 mL) was added benzene sulfonic acid sodium salt (2.96 mmol). The reaction mixture was irradiated under microwave condition at 100 °C for 30 min. The mixture was cooled to room temperature and poured into cold water. After stirring for 10 min, solid thus precipitated was collected by filtration, washed with water three times, and then air-dried overnight. Purification was done via silica gel column chromatography (EtOAC/hexanes) to yield **6**.

5.3.1. 1-Phenyl-3-(phenylsulfonyl)propan-1-one (6a). Compound **6a** was obtained as an off-white solid in 69% yield (0.562 g) according to general procedure 3. Mp 98–100 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.41 (t, J = 7.07 Hz, 2H), 3.68 (t, J = 7.20 Hz, 2H), 7.49–7.57 (m, 2H), 7.61–7.70 (m, 3H), 7.72–7.80 (m, 1H), 7.89–7.98 (m, 4H); HRMS: calcd for $C_{15}H_{14}O_3S$ + H +, 275.0736; found (ESI-FTMS, $[M+H]^{1+}$), 275.0736; HPLC Method 1: room temperature, 5.22 min, 99.63%. HPLC Method 2: room temperature, 5.70 min, 99.67%; Anal. Calcd for $C_{15}H_{14}O_3S$: C, 65.67; H, 5.14; N, 0. Found: C, 65.57; H, 5.06; N, <0.02.

5.3.2. 1-(4-Fluorophenyl)-3-(phenylsulfonyl)propan-1-one (6b). Compound **6b** was obtained as a white solid in 60% yield (0.516 g) according to general procedure 3. Mp 131–133 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.40 (t, J = 7.20 Hz, 2H), 3.67 (t, J = 7.07 Hz, 2H), 7.34 (t, J = 8.97 Hz, 2H), 7.62–7.70 (m, 2H), 7.72–7.80 (m, 1H), 7.92–7.98 (m, 2H), 7.98–8.06 (m, 2H); HRMS: calcd for $C_{15}H_{13}FO_3S$ + H +, 293.0642; found (ESI-FTMS, $[M+H]^{1+}$), 293.0643; HPLC Method 1: room temperature, 5.33 min, 96.71%. HPLC Method 2: room temperature, 5.88 min, 97.44%; Anal. Calcd for $C_{15}H_{13}FO_3S$: C, 61.63; H, 4.48; N, 0. Found: C, 61.40; H, 4.60; N, <0.02.

5.3.3. 1-(4-Chlorophenyl)-3-(phenylsulfonyl)propan-1-one (6c). Compound **6c** was obtained as a white solid in 58% yield (0.530 g) according to general procedure 2. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.18 (t, J = 7.20 Hz, 2H), 3.44 (t, J = 7.07 Hz, 2H), 7.33–7.39 (m, 2H), 7.40–7.47 (m, 2H), 7.51–7.57 (m, 1H), 7.68–7.75 (m, 4H); HRMS: calcd for $C_{15}H_{13}ClO_3S$ + H +, 309.0348; found (ESI-FTMS, $[M+H]^{1+}$), 309.0344; HPLC Method 1: room temperature, 5.69 min, 95.13%. HPLC Method 2: room temperature, 6.36 min, 95.59%.

5.3.4. 1-(4-Bromophenyl)-3-(phenylsulfonyl)propan-1-one (6d). Compound **6d** was obtained as a white solid in 46% yield (0.456 g) according to general procedure 2. Mp 152–154 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.62 (t, J = 7.07 Hz, 2H), 3.89 (t, J = 7.07 Hz, 2H), 7.84–7.92 (m, 2H), 7.93–8.02 (m, 3H), 8.06–8.12 (m, 2H), 8.14–8.20 (m, 2H); HRMS: calcd for $C_{15}H_{13}BrO_3S$ + H +, 352.9841; found (ESI-FTMS, $[M+H]^{1+}$), 352.9841; HPLC Method 1: room temperature, 5.79 min, 99.39%. HPLC Method 2: room temperature, 6.46 min, 99.37%; Anal. Calcd for $C_{15}H_{13}BrO_3S$: C, 51.00; H, 3.71; N, 0. Found: C, 50.86; H, 3.47; N, <0.02.

5.4. Synthesis of 2-(phenylsulfonyl)-1-(4-(trifluoromethyl)phenyl)ethanol (7)

To a solution of 2-(phenylsulfonyl)-1-(4-(trifluoromethyl)phenyl)ethanone (0.120 g, 0.67 mmol) in THF (10 mL) and isopropanol (1 mL) was added $NaBH_4$ (0.028 g, 0.134 mmol). After stirring for 1 h the reaction mixture was quenched with NH_4Cl (aq), partitioned between EtOAc/H_2O, organic layer dried over $MgSO_4$, concentrated under reduced pressure, and purified via column chromatography (5–30% EtOAC/hexanes). Compound **7** was isolated as a white solid in 25% yield (28 mg). Mp 97–98 °C; ^{1}H NMR (400 MHz, chloroform-d) δ ppm 3.29–3.53 (m, 2H), 3.84 (d, J = 2.27 Hz, 1H), 5.38 (d, J = 9.85 Hz, 1H), 7.44 (d, J = 8.08 Hz, 2H), 7.56–7.65 (m, 4H), 7.67–7.76 (m, 1H), 7.92–8.01 (m, 2H); HRMS: calcd for $C_{15}H_{13}F_3O_3S + NH_4^+$, 348.0876; found (ESI-FTMS, $[M + NH_4]^{1+}$), 348.0871; HPLC Method 1: room temperature, 3.07 min, 99.5%.

5.5. Synthesis of (*E*)-2-(phenylsulfonyl)-1-*p*-tolylethanone oxime (8)

To a solution of 2-(phenylsulfonyl)-1-*p*-tolylethanone (0.150 g, 0.55 mmol) in ethanol (3 mL) was added hydroxylamine HCl salt (0.076 g, 1.09 mmol). The

mixture was irradiated under microwave condition at 100 °C for 40 min. The mixture was cooled to room temperature and solvent removed by rotavap. The residue was dissolved in methanol and purified via column chromatography (5–20% EtOAC/hexanes). Compound **8** was isolated as a white solid in 37% yield (0.108 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.31 (s, 3H), 4.90 (s, 2H), 7.15 (d, J = 8.08 Hz, 2H), 7.46–7.64 (m, 4H), 7.62–7.84 (m, 3H), 11.64 (s, 1H); HRMS: calcd for $C_{15}H_{15}NO_3S$ + H +, 290.0845; found (ESI-FTMS, $[M+H]^{1+}$), 290.0844; HPLC Method 1: room temperature, 5.10 min, 97.95%. HPLC Method 2: room temperature, 5.75 min, 98.06%.

5.6. Synthesis of acylsulfonamides (11a–e)

5.6.1. *N*-(Phenylsulfonyl)benzamide (11a). A solution of benzene sulfonamide (1.6 g, 10.2 mmol) in CH_3CN (50 mL) was cooled to 0 °C then added with benzoyl chloride (1.43 g, 10.2 mmol) and Et_3N (1.52 g, 15.0 mmol). Then the cooling bath was removed and the reaction mixture was allowed to stir at ambient temperature for 2 h. After CH_3CN removal, the residue was subjected to aqueous work up (CH_2Cl_2/H_2O). Then organic layer was dried over $MgSO_4$, concentrated under reduced pressure, and purified via column chromatography (20–80% EtOAC/hexanes) to give **11a** as a white solid in 9% yield (0.23 g). Decomposed at 300 °C; ^{1}H NMR (400 MHz, MeOD) δ ppm 7.40 (dd, J = 4.55, 2.53 Hz, 2H), 7.44–7.66 (m, 4H), 7.93 (s, 2H), 8.06 (d, J = 6.06 Hz, 2H); HRMS: calcd for $C_{13}H_{11}NO_3S$ + H +, 262.0532; found (ESI-FTMS, $[M+H]^{1+}$), 262.0538; HPLC Method 1: room temperature, 4.76 min, 100.00%. HPLC Method 2: room temperature, 5.17 min, 100.00%.

5.6.2. 3-Chloro-*N*-(phenylsulfonyl)benzamide (11b). A solution of benzene sulfonamide (0.501 g, 3.19 mmol) in DMF (5 mL) was added with 3-chlorobenzoyl chloride (0.558 g, 3.19 mmol) and Et_3N (0.376 g, 3.72 mmol). Then the reaction mixture was irradiated under microwave at 60 °C for 20 min, then at 100 °C for another 20 min. The reaction mixture was filtered off through silica gel plug. Liquid phase was diluted with CH_3CN and purified via HPLC to give **11b** as a white solid in 14% yield (0.131 g). Mp 140–143 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.52 (t, J = 7.83 Hz, 1H), 7.59–7.76 (m, 4H), 7.78–7.85 (m, 1H), 7.93 (t, J = 1.77 Hz, 1H), 7.98–8.04 (m, 2H); HRMS: calcd for $C_{13}H_{10}ClNO_3S$ − H +, 293.9997; found (ESI-FTMS, $[M-H]^{1-}$), 293.9991; HPLC Method 1: room temperature, 5.27 min, 100.00%. HPLC Method 2: room temperature, 5.48 min, 100.00%.

5.6.3. *N*-(Phenylsulfonyl)-4-(trifluoromethyl)benzamide (11c). A solution of benzene sulfonamide (0.570 g, 3.63 mmol) in acetonitrile (3.5 mL) was added with 4-trifluoromethylbenzoyl chloride (0.946 g, 4.54 mmol) and pyridine (1.43 g, 18.2 mmol). Then the reaction mixture was irradiated at 75 °C for 20 min. After CH_3CN removal, the residue was subjected to aqueous work up (EtOAc/H_2O), (EtOAc/saturated NaCl). Then organic layer was dried over $MgSO_4$, concentrated under reduced pressure, and purified via column chromatography (3% MeOH/CH_2Cl_2) to give **11c** as a white solid in 5% yield (0.039 g). Mp 365–370 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.43 (s, 3H), 7.69 (d, J = 7.07 Hz, 2H), 7.85 (d, J = 6.32 Hz, 2H), 8.07 (d, J = 6.82 Hz, 2H); HRMS: calcd for $C_{14}H_{10}F_3NO_3S$ + H +, 330.0406; found (ESI-FTMS, $[M+H]^{1+}$), 330.0421; HPLC Method 1: room temperature, 6.15 min, 100.00%. HPLC Method 2: room temperature, 5.48 min, 100.00%.

5.6.4. *N*-[(4-Methylphenyl)sulfonyl]benzamide (11d). Compound **11d** was obtained as a off-white solid in 78% yield using procedures similar to those described for **11a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.40 (s, 3H), 7.35–7.54 (m, 4H), 7.56–7.68 (m, 1H), 7.78–7.94 (m, 4H), 12.48 (s, 1H); HRMS: calcd for $C_{14}H_{13}NO_3S$ + H +, 276.0689; found (ESI-FTMS, $[M+H]^{1+}$), 276.0691; HPLC Method 1: room temperature, 5.09 min, 100.00%. HPLC Method 2: room temperature, 5.74 min, 100.00%.

5.6.5. *N*-(4-Chlorophenylsulfonyl)benzamide (11e). Compound **11e** was obtained as a white solid in 75% yield using procedures similar to those described for **11a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.50 (t, J = 7.83 Hz, 2H), 7.60–7.67 (m, 1H), 7.70–7.77 (m, 2H), 7.84–7.89 (m, 2H), 7.98–8.05 (m, 2H), 12.66 (s, 1H); HRMS: calcd for $C_{13}H_{10}ClNO_3S$ + H +, 296.0143; found (ESI-FTMS, $[M+H]^{1+}$), 296.0143; HPLC Method 1: room temperature, 5.33 min, 98.96%. HPLC Method 2: room temperature, 6.04 min, 100.00%.

5.7. Synthesis of N-alkylated β-keto sulfones (11f and g)

5.7.1. *N*-Methyl-*N*-(phenylsulfonyl)benzamide (11f). *N*-(Phenylsulfonyl)benzamide (0.301 g, 1.15 mmol), iodomethane (0.489 g, 3.45 mmol), triethylamine (0.349 g, 3.49 mmol), and DMF (1 mL) were charged to a microwave vial under argon. The reaction mixture was subjected to microwave irradiation at 100 °C for 40 min. Then more iodomethane (2.27 g, 16.00 mmol) was added and the reaction was repeated for an additional 20 min. The reaction mixture was quenched with water and extracted with EtOAc. Organic layer was washed with saturated sodium chloride, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product thus obtained was purified via column chromatography (20% EtOAC/hexanes). Compound **11f** was obtained as a white solid in 22% yield (0.07 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.31 (s, 3H), 7.48–7.56 (m, 2H), 7.58–7.66 (m, 3H), 7.71 (t, J = 7.58 Hz, 2H), 7.81 (t, J = 6.82 Hz, 1H), 8.03 (dd, J = 8.46, 1.39 Hz, 2H); HRMS: calcd for $C_{14}H_{13}NO_3S$ + H +, 276.0689; found (ESI-FTMS, $[M+H]^{1+}$), 276.0682; HPLC Method 1: room temperature, 5.41 min, 99.56%. HPLC Method 2: room temperature, 5.83 min, 100.00%; Anal. Calcd for $C_{14}H_{13}NO_3S$: C, 61.07; H, 4.76; N, 5.09. Found: C, 61.05; H, 4.54; N, 5.05.

5.7.2. *N*-Benzyl-*N*-(phenylsulfonyl)benzamide (11g). *N*-(Phenylsulfonyl)benzamide (0.3 g, 1.15 mmol) and benzyl bromide (0.589 g, 3.45 mmol), triethylamine

(0.349 g, 3.49 mmol) and DMF (1 mL) were charged to a microwave vial under argon. The reaction mixture was subjected to microwave irradiation at 100 °C for 20 min. The reaction mixture was quenched with water and extracted with EtOAc. Organic layer was washed with saturated sodium chloride, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product thus obtained was purified via column chromatography (20% EtOAC/hexanes) and trituration with hexanes. Compound **11g** was obtained as a white solid in 38% yield (0.153 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.82 (s, 2H), 6.92–6.99 (m, 2H), 7.04–7.13 (m, 3H), 7.19–7.27 (m, 4H), 7.31–7.38 (m, 1H), 7.39–7.46 (m, 2H), 7.51–7.59 (m, 1H), 7.62–7.67 (m, 2H); HRMS: calcd for $C_{20}H_{17}NO_3S + H +$, 352.1002; found (ESI-FTMS, $[M+H]^{1+}$), 352.0989; HPLC Method 1: room temperature, 6.29 min, 100.00%. HPLC Method 2: room temperature, 6.86 min, 100.00%.

5.8. Determination of IC_{50} values in cell-based assay

CHO cells were stably transformed with plasmid containing the full-length sequence of human 11β-HSD1 (Locuslink id. 3290) to generate the CHO–HSD1 cell line. CHO cells were stably transformed with plasmid containing the full-length sequence of human 11β-HSD2 (Locuslink id. 3291) to generate the CHO–HSD2 cell line.

Non-transformed CHO cells do not have detectable 11β-HSD1 or 11β-HSD2 activity. Cell-based assays for 11β-HSD1 were performed using the CHO–HSD1 cell line. The effect of test article on 11β-HSD1 activity was assayed by determination of the conversion of radioactive cortisone to cortisol. In this assay, 50,000 CHO–HSD1 cells were plated in 24-well plates and incubated overnight. The cells were washed once with ethylene glycol dimethyl ether and 197.5 μL ethylene glycol dimethyl ether was added to each well. 2.5 μL of the appropriate drug concentrations was added to each well and the cells were incubated for 30 min at 37 °C/5% CO_2. [1,2-^{3}H]-Cortisone was diluted to a concentration of 200 nM in ethylene glycol dimethyl ether and 50 μL of the 200 nM solution was added to each well. Final cortisone concentration in the assay was 40 nM. Cells were incubated for 2 h at 37 °C/5% CO_2. At the end of the incubation, steroids in media were extracted with three volumes of ethyl acetate. The organic phase was transferred to a fresh tube, dried, resuspended in 5 μL methanol, and spotted on a 60 Å silica TLC plate. The plate was run in 92% chloroform/8% ethanol. The plate was dried and scanned using an AR-2000 TLC Imaging Scanner (BioScan Inc., Washington, DC). IC_{50} values were determined by plotting cortisol formed against inhibitor concentration and fitting the data using Origin 7.0 software (Origin Lab Corporation, Northampton, MA).

Inhibition of 11β-HSD2 was determined using the same assay, except the CHO–HSD2 line was used and [1,2-^{3}H]-hydrocortisone was used as the substrate.

5.9. Enzymatic study of compound 2a

Ten micromolars compound was incubated with 0.7 μM purified 11β-HSD1 enzyme at room temperature in TBS buffer (50 mM Tris, 150 mM NaCl) pH 7.4, containing 0.01% Tween-20. Cofactor of NADPH was at concentration of 400 μM. One hundred microliters reaction sample was quenched by three volumes of acetonitrile at different incubation time (0, 10, 20, 40 min). After a brief centrifugation at 12,000 rpm, the supernatant was air-dried and reconstituted to 200 μL distilled water. SIM was used to monitor the apparent molecular weight for the β-keto sulfone compound. The half-life of the compound is calculated from the integration change of the SIM peak. LC/MS analysis was carried out with an Agilent 1100 LC/MSD. The HPLC gradient went from 98% water and 2% acetonitrile with 0.1% formic acid to 100% acetonitrile with 0.1% formic acid in 10 min. The HPLC column was Thermo Aquasil C18 (2× 50 mm). Flow rate was 0.8 mL/min. Mass spectrometric detection was made using single ion monitoring (SIM). The SIM was set to *m*/*z* 328 ($M+H^+$).

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