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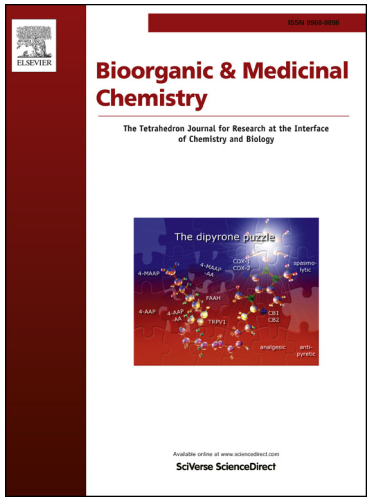

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Discovery of (2-Benzoylethen-1-ol)-Containing 1, 2-Benzothiazine Derivatives as Novel 4-Hydroxyphenylpyruvate Dioxygenase (HPPD) Inhibiting-Based Herbicide Lead Compounds

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Abstract: A series of (2-benzoylethen-1-ol)-containing benzothiazine derivatives was synthesized, and their herbicidal activities were first evaluated. The bioassay results indicated that some of 3-benzoyl-4-hydroxy-2-methyl-2*H*-1, 2-benzothiazine-1, 1-dioxide derivatives displayed good herbicidal activity in greenhouse testing, especially, compound **4w** had good pre-emergent herbicidal activities against *Brassica campestris*, *Amaranthus retroflexus* and *Echinochloa crusgalli* even at a dosage of 187.5 g ha^{-1}. More importantly, compound **4w** displayed significant inhibitory activity against *Arabidopsis thaliana* HPPD and was identified as the most potent candidate with IC_{50} value of 0.48 μM, which is better than the commercial herbicide sulctrione (IC_{50} = 0.53 μM) and comparable with the commercial herbicide mesotrione (IC_{50} = 0.25 μM). The structure-activity relationships was studied and provided some useful information for improving herbicidal activity. The present work indicated that (2-benzoylethen-1-ol)-containing 1, 2-benzothiazine motif could be a potential lead structure for further development of novel HPPD inhibiting-based herbicides.

Keywords: Synthesis; Benzothiazine; Herbicide activity; 4-Hydroxyphenylpyruvate dioxygenase; Structure-activity relationships

1. Introduction

4-Hydroxyphenylpyruvate dioxygenase (HPPD) is a member of the class of non-heme iron oxygenase enzymes.[1–3] It catalyzes the conversion of 4-hydroxyphenylpyruvate (HPP) to homogentisate (HGA) and carbon dioxide in the presence of oxygen and ferrous ion.[4–7] In plants, HGA formed by the action of HPPD is utilized as the aromatic precursor for tocopherols and plastoquinone.[8] Plastoquinone is the redox cofactor for phytoene desaturase, a key enzyme in the biosynthesis of photoprotectant carotenoids. Thus, the inhibition of HPPD prevents the normal functioning of phytoene desaturase in the synthesis of carotenoids, which will result in unique bleaching symptom in sunlight and finally caused necrosis and death of plants.[7, 9–11]

For many years, HPPD has been an important target of interest in the agrochemical industry, and many efforts have been made in the screening and synthesis of HPPD inhibitors, which have lead to a considerable number of HPPD inhibiting-based herbicides. [12–18] Thus far, some of HPPD inhibiting-based herbicides (**Fig. 1**), such as mesotrione, sulcotrione, tefuryltrione, tembotrione, topramezone and pyrasulfotole, have reached the market place. HPPD inhibiting-based herbicides show many advantages, such as low application rate, low toxicity, broad-spectrum weed control, excellent crop selectivity and safety towards the environment.[13,15,17] A survey of the known HPPD inhibiting-based herbicides revealed that most of them have the same structural characteristic, i.e., the common chemical motif of them is the presence of (2-benzoylethen-1-ol) (**Fig. 1**) as the minimum substructure, which can bind to the iron(II) of HPPD.[19] An extensive review of the literature on HPPD inhibiting-based herbicides indicated that modification of the benzoyl group is an effective way to obtain new derivatives with improved herbicidal activity.[13,20,21] Based on the above fact, we become interesting in synthesizing and evaluating the herbicidal activities of various compounds that contains (2-benzoylethen-1-ol) substructure to find novel HPPD inhibiting-based herbicides.

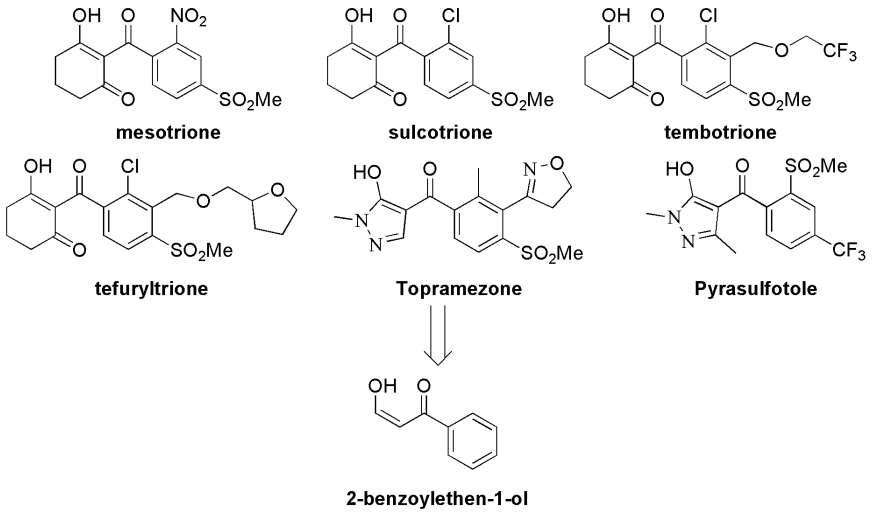


Figure 1. Chemical structures of the commercially HPPD inhibiting-based herbicides and their common substructure

1, 2-Benzothiazines is a heterocyclic scaffold of paramount importance in drug chemistry. During last decades, many 1, 2-benzothiazine derivatives had been successfully synthesized and patented for a wide range of biological activities, including anti-inflammatory,[22–27] antimicrobial,[28] antiallergic[29], antidepressant[30] and antithrombotic[31] properties. Recently, pyrazolo-containing 1, 2-benzothiazine derivatives were reported as potent hepatitis C virus (HCV)

replication inhibitors and anti-HIV-1 agents.[32,33] Although the derivatives of 1, 2-benzothiazine have been extensively studied in medical chemistry, examinations of them as agrochemicals are still very scarce, especially with respect to their herbicidal activities. As a continuation of our work on synthesizing and evaluating the herbicidal activities of compounds that contain (2-benzoylethen-1-ol) substructure,[34] we have synthesized a series of (2-benzoylethen-1-ol)-containing 1, 2-benzothiazine derivatives. Herein, we wish to report the detailed synthesis, herbicidal activities and *in vitro* HPPD inhibitory activity of a series of 3-benzoyl-4-hydroxy-2-methyl-2*H*-1, 2-benzothiazine-1, 1-dioxide derivatives (**Fig. 2 I**).[35] For comparison, a series of 3-benzoyl-4-hydroxy-1-methyl-1*H*-2, 1-benzothiazine-2, 2-dioxide derivatives (**Fig. 2 II**) were also synthesized and their herbicidal activities were evaluated to discuss the structure–activity relationships (SARs). To the best of our knowledge, this is the first report on the herbicidal activities of (2-benzoylethen-1-ol)-containing benzothiazine derivatives.

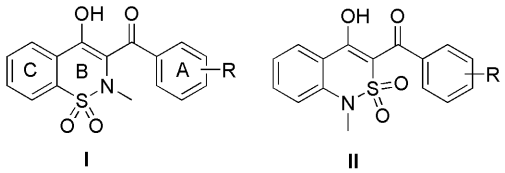


Figure 2. Chemical structures of **I** and **II**

2. Methods and materials

Unless otherwise stated, all reactions were carried out under an argon atmosphere, and all commercially available reagents were used without further purification. ^{1}H NMR and ^{13}C NMR were obtained at 400 MHz and 100 MHz, respectively, using Bruker AV400 spectrometer in $CDCl_3$ or DMSO-d_6 solution with TMS as the internal standard. Chemical shifts are given in δ values. Coupling constants were reported in Hertz (Hz). High-resolution mass spectra were conducted using an Ionspec 7.0T spectrometer by ESI-FTICR technique. The single-crystal structure of compounds **4o** and **15a** were determined on a Rigaku Saturn 724 CCD area-detector diffractometer. The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and were uncorrected.

2.1. X-ray diffraction

Compounds **4o** and **15a** were recrystallised from a mixture of chloroform and methanol to afford a suitable single crystal. Crystallographic data for compounds **4o** and **15a** had been deposited with the Cambridge Crystallographic Data Centre as supplementary publications with the deposition numbers 1425395 and 1425396, respectively. The data can be obtained free of charge from http://www.ccdc.cam.ac.uk/.

2.2. Herbicidal activities

2.2.1. Inhibition of the root growth of rape (*Brassicacampestris L.*)[36-38]

Emulsions of target compounds and mesotrione were prepared by dissolving them in 100 μL of DMF adding a few drops of Tween-80 and dispersing in water. A mixture of the same amount of water, DMF and Tween-80 was used as control. Rape seeds were soaked in distilled water for 4 h before being placed on a filter paper in a 6 cm petri plate, to which 2 mL of inhibitor solution had been added in advance. Usually, 15 seeds were used on each plate. The plate was placed in a dark room and allowed to germinate for 65 h at 28 ± 1 °C. The lengths of ten rape roots randomly selected from each plate were measured, and the means were calculated. The percentage of inhibition was used to describe the control efficiency of the compounds. Each treatment was

performed triplicate.

2.2.2. Inhibition of the seedling growth of Barnyard Grass [*Echinochloa crusgalli (L.) Beauv.*][36-38]

Emulsions of target compounds and mesotrione were prepared according to above method. A mixture of the same amount of water, DMF and Tween-80 was used as control. Ten *Echinochloa crusgalli* seeds were placed into a 50 mL cup covered with a layer of glass beads and a piece of filter paper at the bottom, to which 5 mL of inhibitor solution had been added in advance. The cup was placed in a bright room, and the seeds were allowed to germinate for 65 h at 28 ± 1 °C. The heights of the above-ground parts of the seedlings in each cup were measured, and the means were calculated. The percentage inhibition was used to describe the control efficiency of the compounds. Each test was performed in triplicate.

2.2.3. Greenhouse Tests[37,38]

Emulsions of the test compounds and mesotrione were prepared according to above method. The emulsions were sprayed using a laboratory belt sprayer at 750 L ha^{-1}. All the experiments were performed under natural light conditions at 18 – 28 °C. Additionally, adverse weather lighting was provided using sodium vapour lamps with a 12 : 12 h light : dark photoperiod.

2.3. Preparation of HPPD and the Evaluation of HPPD Inhibitors

Recombinant *Arabidopsis thaliana* HPPD (*At*HPPD) was prepared and purified according the reported method.[39-44] Our coupled enzyme assays for the *in vitro* activity and inhibition of HPPD were measured by a modification of methods previously reported in the literature.[45] Assays were performed in 96-well plates at 30 °C using a UV/Vis plate reader to monitor the formation of maleylacetoacetate at 318nm (ε_{330}=13500 M^{-1} cm^{-1}). Before assays were conducted, all reaction components were pre-equilibrated at 30 °C for at least 10 min. The inhibitor and HPPD were preincubated for 20 min to reach a steady state in practical kinetic measurement, followed by the addition of a mixture of appropriate amounts of HPPA, 100 μM of $FeCl_2$, 2 mM of sodium ascorbate, 50 mM of HEPES buffer (pH 7.0) and HGD (150 nM). The amount of HGD activity was predetermined to be in large excess of the HPPD activity to ensure that the reaction was tightly coupled. Each experiment was repeated at least 3 times and the values were averaged. HPPD inhibitors were dissolved in dimethyl sulfoxide (DMSO) for stock solution and diluted to various concentrations with reaction buffer just before use. The IC_{50} values were then calculated based on the plot of plotting the residue activity against the concentration of inhibitor at certain concentrations of substrate.

2.4. Computational Methods

Molecular modeling was performed using SYBYL 6.91 software, and the comparative molecular field analysis (CoMFA) method has been performed according to our previous papers.[46,47] The herbicidal activities of 23 compounds (compounds **4a**-**4w**, for training sets compounds) against *Brassica campestris* at 1500 g ha^{-1} under post-emergence condition used to derive the CoMFA analyses model were listed in **Table 5**. The activity was expressed in terms of ED by the formula ED=log [I/(100 - I)×MW], where I is the percent control efficacy and MW is the molecular weight of the tested compounds. The compound **4o**, owing to the determination of the crystal structure, was used as a template to build the other molecular structures. Each structure was fully geometry-optimized using a conjugate gradient procedure based on the TRIPOS force field and Gasteiger and Hückel charges. Because these compounds share a common skeleton, 23 atoms marked with an asterisk were used for root-mean-square (RMS) fitting onto the

corresponding atoms of the template structure. CoMFA steric and electrostatic interaction fields were calculated at each lattice intersection on a regularly spaced grid of 2.0 Å. The grid pattern was generated automatically by the SYBYL/CoMFA routine, and an sp^3 carbon atom with a van der Waals radius of 1.52 Å and a +1.0 charge was used as the probe to calculate the steric (Lennard-Jones 6-12 potential) field energies and electrostatic (Coulombic potential) fields with a distance-dependent dielectric at each lattice point. Values of the steric and electrostatic fields were truncated at 30.0 kcal/mol. The CoMFA steric and electrostatic fields generated were scaled by the CoMFA-STD method in SYBYL. The electrostatic fields were ignored at the lattice points with maximal steric interactions. A partial least-squares approach was used to derive the 3D QSAR, in which the CoMFA descriptors were used as independent variables and ED values were used as dependent variables. The cross-validation with the leave-one-out option and the SAMPLS program, rather than column filtering, was carried out to obtain the optimal number of components to be used in the final analysis. After the optimal number of components was determined, a non-cross-validated analysis was performed without column filtering. The modeling capability (goodness of fit) was judged by the correlation coefficient squared, r^2, and the prediction capability (goodness of prediction) was indicated by the cross-validated r^2 (q^2).

3. Results and discussion

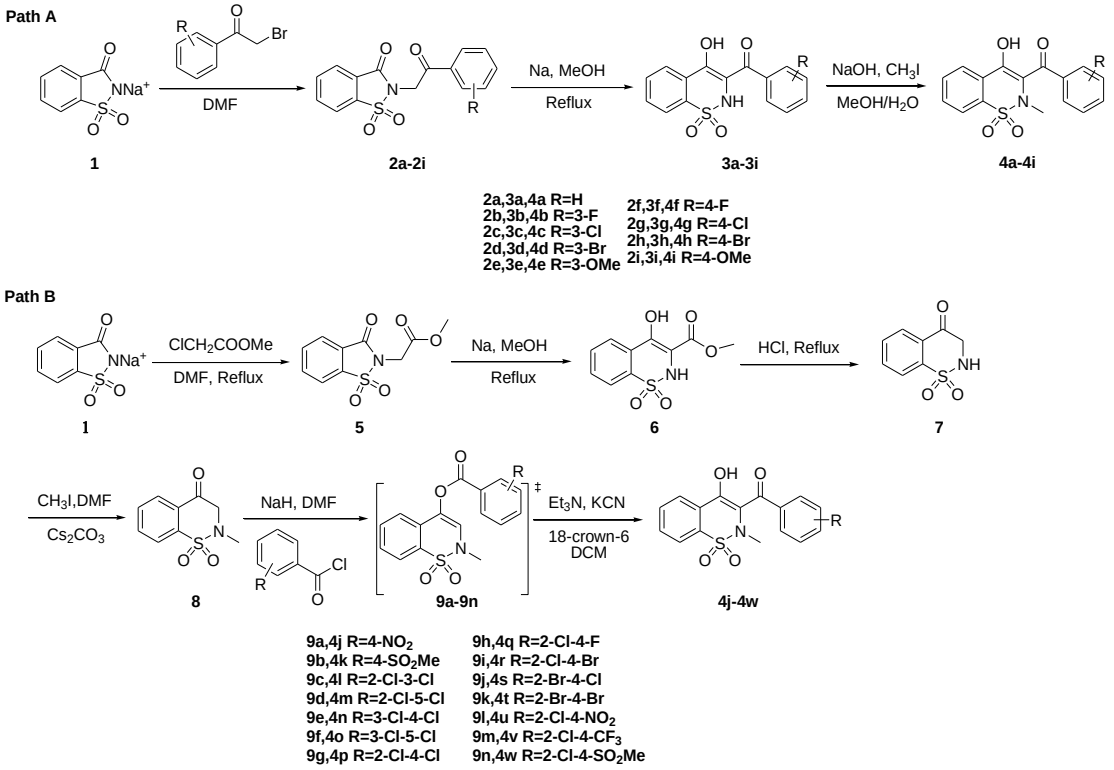
3.1. Chemistry

As shown in **Scheme 1** (Path A), compounds **4a**–**4i** were synthesized according to the reported methods.[33,35,48] Saccharin sodium salt **1** was reacted with α-bromo ketone in *N*, *N*-dimethylformamide (DMF) to provide the alkylated products **2a**–**2i** in excellent yield. Gabriele-Colman type ring expansion of the five-membered isothiazole ring of compounds **2a**–**2i** to the six-membered thiazine ring yielded compounds **3a**–**3i**, which were further reacted with methyl iodide under base condition to result in the target products **4a**–**4i**. Target compounds **4j**–**4w** were synthesized according to our developed method (**Scheme 1** Path B). The key mediate compound **8** was first synthesized according to the reported method,[49] with slight modification. By reacting saccharin sodium salt **1** with methyl chloroacetate in DMF under reflux conditions, methyl [1, 1-dioxido-3-oxo-1, 2-benzisothiazol-2(3*H*)-yl]acetate **5** was obtained in excellent yield. Gabriele-Colman type ring expansion of compound **5** yielded methyl 4-hydroxy-2*H*-1, 2-benzothiazine-3-carboxylate 1, 1-dioxide **6**. Compound **6** was refluxed with concentrated hydrochloric acid to get 2*H*-1, 2-benzothiazin-4(3*H*)-one 1, 1-dioxide **7**, which were further reacted with methyl iodide and cesium carbonate under mild condition to result in 2-methyl-2*H*-1, 2-benzothiazin-4(3*H*)-one 1, 1-dioxide **8**. Subsequently, intermediate compounds **9a**–**9n** were synthesized by the reaction of compound **8** with a series of benzoic acid derivatives in the presence of sodium hydride (NaH) in DMF, which was treated with potassium cyanide (KCN) and 18-crown-6 at ambient temperature to give the target compounds **4j**–**4w**.

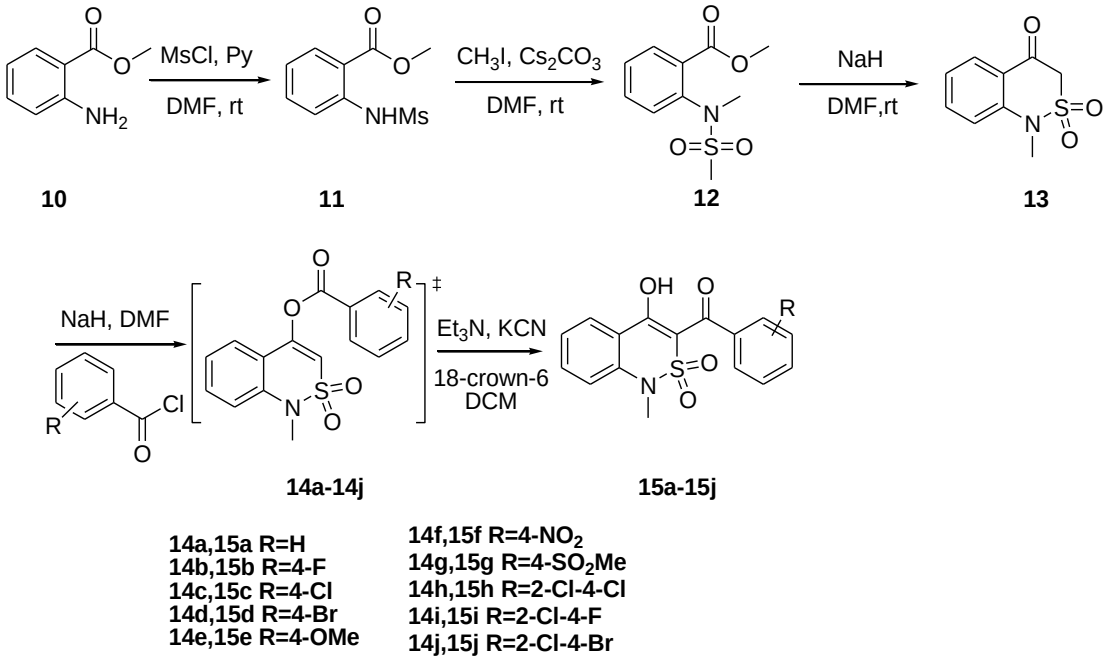
As shown in **Scheme 2**, target compounds **15a**–**15j** were synthesized according to the reported methods.[50-52] 1-Methyl-1*H*-2, 1-benzothiazin-4(3*H*)-one 2, 2-dioxide **13** was synthesized by condensation of methane sulfonyl chloride with methyl anthranilate followed by N-methylation and base catalyzed cyclization. Subsequently, compounds **14a**–**14j** were synthesized by the reaction of compound **13** with a series of benzoyl chloride derivatives in the presence of NaH in DMF, which was treated with KCN and 18-crown-6 at ambient temperature to give the target compounds **15a**–**15j**.

The structures of all target compounds were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS

spectral data. In addition, the crystal structures of **4o** and **15a** were further determined by X-ray diffraction analysis (CCDC 1425395 and CCDC 1425396; **Fig. 3**).



Scheme 1. The synthetic route of target compounds **4a**–**4w**



Scheme 2. The synthetic route of target compounds **15a**–**15l**

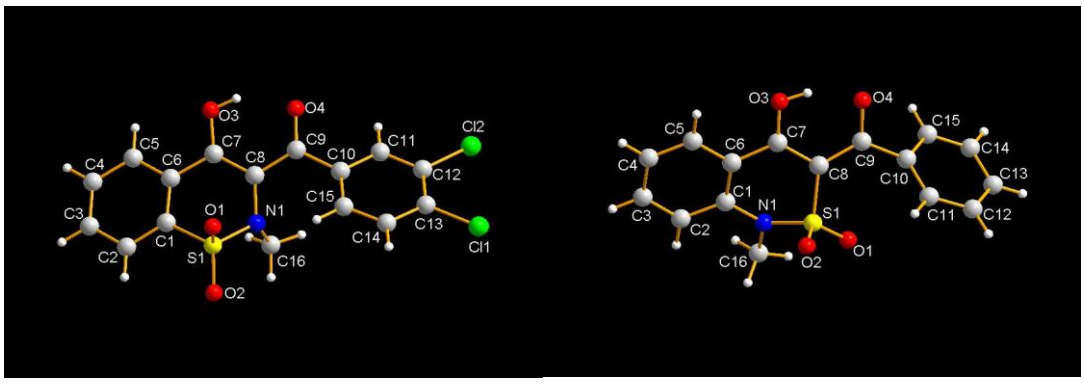
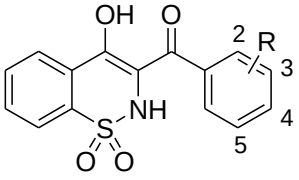


Figure 3. Crystal structures of **4o** (left) and **15a** (right)

3.2. Herbicidal activity *in vitro* and preliminary SARs study

The herbicidal activities of compounds **4a**–**4w** and **15a**–**15j** were preliminary determined with *Brassica campestris* root test and *Echinochloa crusgalli* cup test. Also, the herbicidal activities of intermediate compounds **3a**–**3i** were evaluated. Mesotrione was selected as a positive control. The bioassay results were shown in **Table 1**. It was found that most of the target compounds **4a**–**4w** showed good herbicidal activities against *Brassica campestris* and *Echinochloa crusgalli* at 100 μg mL^{-1}, especially, compound **4p** was the most active compound with 90.0% and 100% inhibition against *Brassica campestris* and *Echinochloa crusgalli* at 100 μg mL^{-1}, respectively, superior even to mesotrione. Compounds **3a**–**3i** and **15a**–**15j** showed moderate herbicidal activities against *Brassica campestris* at 100 μg mL^{-1}, but showed very low or even no herbicidal activities against *Echinochloa crusgalli*. Parallel activity contrasting between compounds **3a**–**3i** and **4a**–**4i** against *Brassica campestris* and *Echinochloa crusgalli* at 100 μg mL^{-1} were performed. As shown in (**Fig. 4A**), series **4** always displayed better herbicidal activities against *Brassica campestris* and *Echinochloa crusgalli* at 100 μg mL^{-1} than that of series **3** in a whole, indicating that the methyl group at the N-2 position of the ring B would be essential for herbicidal activity. Subsequently, parallel activity contrasting between compounds **4a**, **4f**–**4k**, **4p**–**4r** and compounds **15a**–**15j** was performed. (**Fig. 4B**) It was found that that series **4** had better herbicidal activities against *Brassica campestris* and *Echinochloa crusgalli* at 100 μg mL^{-1} than that of series **15** in a whole, indicating that the position between NCH_3 group and O=S=O group was very important for herbicidal activity.

Table 1. Herbicidal Activity of Compounds **3a**–**3e**, **4a**–**4l** and **15a**–**15j** (Percent Inhibition) [a]



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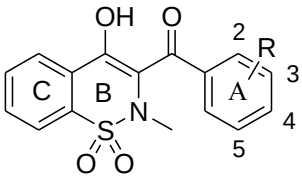

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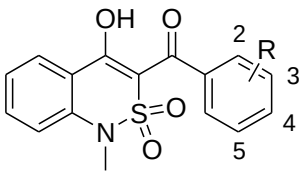

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Comp.	R	*Brassica campestris* root test		*Echinochloa crusgalli* cup test	
		10 μg mL^{-1}	100 μg mL^{-1}	10 μg mL^{-1}	100 μg mL^{-1}
3a	H	0	0	8.8±0.4	15.4±1.1
3b	3-F	0	53.4±0.6	13.9±0.7	30.4±0.4
3c	3-Cl	0	76.8±0.8	19.6±0.4	23.6±1.0
3d	3-Br	0	61.7±1.2	5.0±0.3	21.4±1.3

3e	3-OMe	39.1±0.7	73.0±1.8	0	0
3f	4-F	0	33.1±1.4	8.2±0.7	15.3±1.8
3g	4-Cl	0	60.5±0.7	8.2±0.4	29.3±1.0
3h	4-Br	0	44.7±0.2	7.7±0.6	22.6±0.7
3i	4-OMe	0	12.6±0.5	0	13.2±1.0
4a	H	9.0±0.5	67.9±0.7	12.5±1.1	28.3±1.6
4b	3-F	36.2±0.8	87.3±2.1	29.0±0.9	81.2±0.8
4c	3-Cl	18.7±0.9	87.4±1.0	16.9±0.4	84.9±0.9
4d	3-Br	20.7±0.4	86.6±0.6	13.6±0.3	71.5±1.9
4e	3-OMe	0	75.9±0.9	0	49.5±0.8*
4f	4-F	55.3±2.0	72.4±1.3	14.0±1.1	58.5±1.3
4g	4-Cl	47.3±1.5	93.4±0.8	25.2±1.6	88.6±1.8
4h	4-Br	0	70.2±0.6	9.1±0.7	59.3±0.6
4i	4-OMe	0	0	0	18.6±1.2
4j	4-NO_2	40.2±0.7	95.6±1.1	11.6±0.9	39.8±0.9*
4k	4-SO_2Me	43.4±0.5	94.8±0.7	19.7±0.7	37.6±1.5*
4l	2-Cl-3-Cl	0	79.6±0.9	17.8±0.7	26.4±0.4*
4m	2-Cl-5-Cl	0	78.8±1.7	16.9±1.4	40.7±1.2*
4n	3-Cl-4-Cl	0	0	0	13.5±1.6
4o	3-Cl-5-Cl	0	23.3±1.8	22.3±1.1	29.3±0.5
4p	2-Cl-4-Cl	42.8±0.9	90.0±1.3	37.7±0.8*	100
4q	2-Cl-4-F	26.9±1.1	84.3±1.5	17.4±0.9*	79.3±0.6**
4r	2-Cl-4-Br	0	88.4±2.1	34.3±1.6*	80.2±2.4**
4s	2-Br-4-Cl	0	76.4±0.6	26.3±0.8*	81.7±1.3**
4t	2-Br-4-Br	12.8±1.8	74.0±1.2	30.8±1.2*	100
4u	2-Cl-4-NO_2	18.0±0.6	71.6±1.4	21.1±1.1*	69.5±0.6**
4v	2-Cl-4-CF_3	43.7±2.3	87.3±0.3	50.7±0.9*	80.7±0.2**
4w	2-Cl-4-SO_2Me	16.4±1.7	82.1±0.9	54.8±1.0*	85.6±0.8**
15a	H	0	31.0±0.6	0	0
15b	4-F	0	51.9±0.8	0	0
15c	4-Cl	0	68.5±1.3	0	0
15d	4-Br	0	65.6±1.5	0	0
15e	4-OMe	0	85.2±2.0	0	0
15f	4-NO_2	0	34.9±1.9	0	0
15g	4-SO_2Me	0	23.0±0.9	0	0
15h	2-Cl-4-Cl	23.4±0.9	78.7±0.7	0	12.0±0.4
15i	2-Cl-4-F	10.6±0.5	65.6±1.4	0	10.7±0.7
15j	2-Cl-4-Br	7.4±0.8	71.3±0.5	0	13.1±1.1
Mesotrione	/	80.3±0.4	89.7±1.2	85.8±0.6**	90.5±2.1**

[a] Each value represents the average of three experiments; * Partial bleaching symptom; ** Complete bleaching symptom

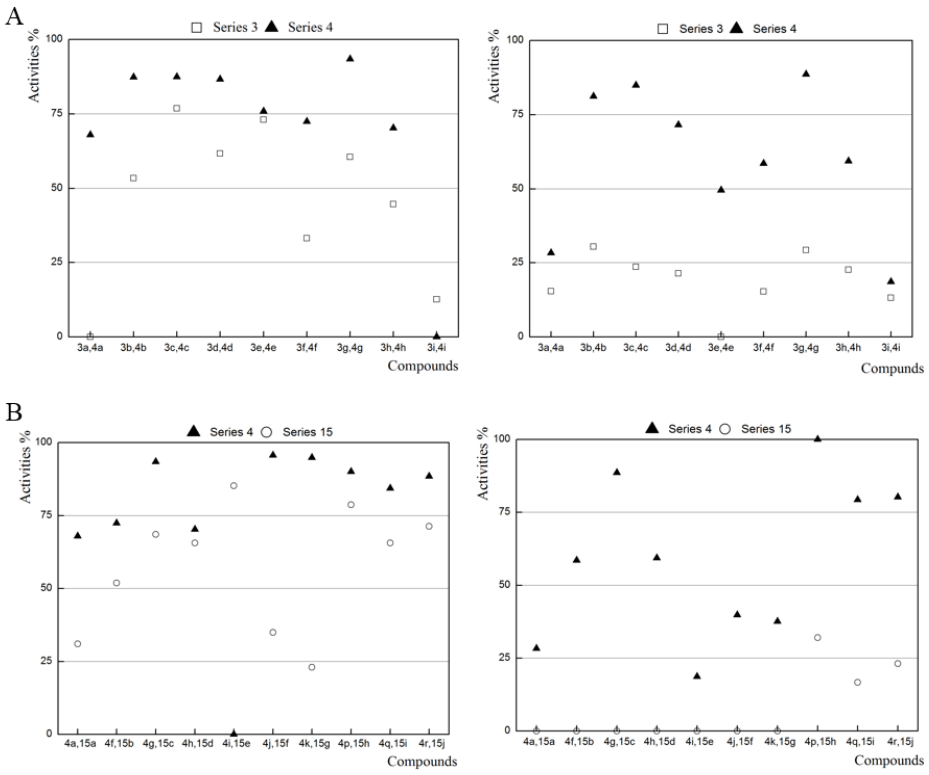

Figure 4. Parallel activity contrasts between compounds **3a**–**3i** and compounds **4a**–**4i**, between compounds**4a**, **4f**–**4k**, **4p**–**4r** and compounds **15a**–**15j** against *Brassica campestris* (left) *and Echinochloa crusgalli* (right). The inhibition activity was tested at 100 μg mL^{-1} and expressed in ordinate

It was very interesting that the treated *Echinochloa crusgalli* by some compounds developed bleaching symptom, especially, compounds **4q**–**4s** and **4u**–**4w** had made *Echinochloa crusgalli* bleached completely, which possibly implying these compounds had the similar herbicide mechanism with mesotrione. Noteworthy, the treated *Echinochloa crusgalli* by compounds **15h**–**15j** did not develop the bleaching symptom as the corresponding isomers **4p**–**4r**, possibly implying the position between NCH_3 group and O=S=O group had important impact on the herbicide mechanism.

3.3. Herbicidal activity in greenhouse tests and further SARs study

Based on the above bioassay results, compounds **4a**–**4w** were chosen to test on four species representative of monocotyledonous and dicotyledonous plants at a dosage of 1500 g ha^{-1} in the glasshouse. As the bioassay data shown in **Table 2**, some of the target compounds, such as compounds **4p**, **4r**, **4s** and **4t**–**4w**, were found to display good herbicidal activities. We were encouraged to observe that compound **4w** displayed 100 % inhibition activities against all weeds tested under the pre-emergence condition, equal to the commercial herbicide mesotrione; compounds **4v** also exhibited 100 % control against *Brassica campestris*, *Amaranthus retroflexus* and *Echinochloa crusgalli* under the pre-emergence condition. It was very interesting that the treated monocotyledonous plants *Echinochloa crusgalli* and *Digitaria sanguinalis* by compound **4w** developed bleaching symptom, followed by necrosis, which indicated the typical characteristics of HPPD-inhibiting based herbicides.

Subsequently, the most activity compound **4w** against all weeds tested under pre-emergence condition were further measured using dose reduction with serial two-fold dilution. As the results

shown in **Table 3**, the herbicidal activities of compound **4w** became progressively lower against *Echinochloa crusgalli* and *Digitaria sanguinalis* at concentrations of 750 g ha^{-1}, 375 g ha^{-1} and 187.5 g ha^{-1}, whereas the control compound mesotrione still showed 100 % inhibition at these concentrations. The results indicated that compound **4w** had lower herbicidal activity than the commercial herbicide mesotrione. The present compound showed good herbicidal activities with 92.0 %, 89.8 % and 80.4 % inhibition against *Brassica campestris*, *Amaranthus retroflexus* and *Echinochloa crusgalli* even at a dose of 187.5 g ha^{-1}, respectively, which comparable with mesotrione, indicating that compound **4w** had certain herbicidal activity and could be served as a lead compound for further optimization.

Table 2. Herbicidal Activity of Compounds (Percent Inhibition) (Rate=1500 g ha^{-1})[a]

Comp.	*Brassica campestris*		*Amaranthus retroflexus*		*Echinochloa crusgalli*		*Digitaria sanguinalis*	
	pre	post	pre	post	pre	post	pre	post
4a	0	18.1±0.7	0	31.2±1.7	0	0	0	0
4b	13.3±1.4	44.9±1.0	47.6±0.8	28.8±0.6	0	0	0	0
4c	5.0±0.5	46.7±1.1	0	55.2±1.0	0	27.5±1.3	18.0±0.6	6.8±0.5
4d	5.0±0.7	30.3±1.7	55.1±1.2	70.7±1.9	0	0	20.2±1.3	59.6±0.9
4e	0	39.6±0.9	28.3±1.4	36.8±2.0	0	38.0±0.8	0	29.9±1.6
4f	10.0±0.6	37.3±1.4	0	45.6±0.7	0	5.1±1.0	21.9±1.1	35.9±1.7
4g	19.7±1.3	37.7±1.5	19.0±0.6	55.4±1.1	0	9.6±1.5	33.3±1.2	69.1±0.9
4h	0	71.8±1.0	10.0±0.5	27.7±1.0	0	0	18.5±1.4	59.6±0.8
4i	0	0	0	0	0	0	0	0
4j	0	46.4±0.9	20.7±1.3	44.0±0.8	0	5.0±0.5	0	0
4k	7.0±0.9	50.2±1.3	16.9±0.7	41.4±1.4	7.1±0.9	27.4±0.8	0	11.6±1.6
4l	12.9±1.7	85.5±0.8	56.9±1.2	44.8±1.5	0	0	0	20.0±0.4
4m	57.0±1.4	78.6±1.7	95.9±1.0	39.2±0.9	0	24.0±1.6	0	22.5±0.6
4n	0	0	0	0	0	0	0	0
4o	0	0	0	0	0	0	0	0
4p	100	100	96.1±0.7	58.6±1.0	78.8±1.0*	26.6±1.1**	81.8±0.9*	51.3±1.1*
4q	38.4±2.2	53.8±2.0	47.6±1.4	48.8±1.1	73.7±0.8	13.4±1.0*	47.3±1.4	20.0±0.5
4r	77.4±1.1	91.4±0.6	85.8±0.5	28.8±1.4	94.1±1.1	67.7±1.4*	71.4±1.9	0
4s	81.7±1.3	93.3±1.2	77.2±2.0	31.4±1.3	61.0±1.0	17.3±0.8*	77.1±0.9	11.4±0.7
4t	100	87.4±1.0	94.0±0.9	54.0±1.6	44.8±1.2*	6.6±1.2**	61.8±1.1*	41.8±0.9*
4u	100	96.8±0.7	82.2±1.5	38.4±2.0	100	47.6±2.3*	0*	37.5±1.8
4v	100	100	100	85.6±1.2	100	81.0±0.6*	31.7±2.1	13.3±1.7*
4w	100	100	100	90.4±0.6	100	93.0±1.4**	100	58.0±1.3*
Mesotrione	100	100	100	100	100	100	100	100

[a] Each value represents the average of three experiments; * Partial bleaching symptom; ** Complete bleaching symptom

Table 3. Further herbicidal testing of compound **4w** (pre-emergence)

Comp.	Rate (g ha^{-1})	*Brassica campestris*	*Amaranthus retroflexus*	*Echinochloa crusgalli*	*Digitaria sanguinalis*
4w	750	100	100	100	74.6±1.6**
	375	100	100	94.7±0.6**	29.4±0.7*

	187.5	92.0±1.7	89.8±1.4	80.4±1.0**	20.0±1.1
	750	100	100	100	100
mesotrione	375	100	100	100	100
	187.5	100	100	100	100

[a] Each value represents the average of three experiments; * Partial bleaching symptom; ** Complete bleaching symptom

Based on the bioassay data in greenhouse tests, SARs was discussed. It was found that the changes of substituent on the benzene ring A affected the herbicidal activity. To better understand the SARs for herbicidal activity, CoMFA was performed. *Brassica campestris* data of compounds **4a**–**4w** at 1500 g ha^{-1} under post-emergence condition was used to derive the CoMFA analyses model. As listed in **Table 4**, a predictive CoMFA model was established with the conventional correlation coefficient $r^2 = 0.963$ and the cross-validated coefficient $q^2 = 0.798$. The contributions of steric and electrostatic fields are 68.1 % and 31.9 % as shown in **Figure 5**, respectively. The observed and calculated activity values are listed in **Table 5**. The models showed a good predictability on these compounds.

Table 4. Summary of CoMFA analysis

	r^2	q^2	Compound	Contribution	
				steric	electrostatic
CoMFA	0.963	0.798	**4s**	68.1 %	31.9 %

Table 5. Experimental and calculated activity of compounds in training set and test set

Compounds	ED	PD_{CoMFA}	Compounds	ED	PD_{CoMFA}
4a	18.10	20.44	**4m**	78.60	65.16
4b	44.90	44.07	**4n**	0	0
4c	46.70	42.38	**4o**	0	0
4d	30.30	29.21	**4p**	99.90	83.52
4e[a]	39.60	39.10	**4q**	53.80	67.22
4f	37.30	33.54	**4r**[a]	91.40	94.27
4g	52.70	50.05	**4s**	93.30	90.01
4h	37.70	45.72	**4t**	87.40	96.07
4i	0	0	**4u**[a]	96.80	98.23
4j[a]	46.40	45.23	**4v**	99.90	97.18
4k	50.20	56.21	**4w**	99.90	92.47
4l	85.50	88.13			

ED: experimental value; PD_{CoMFA}: predictive value by CoMFA; [a] Represent the compounds in test set

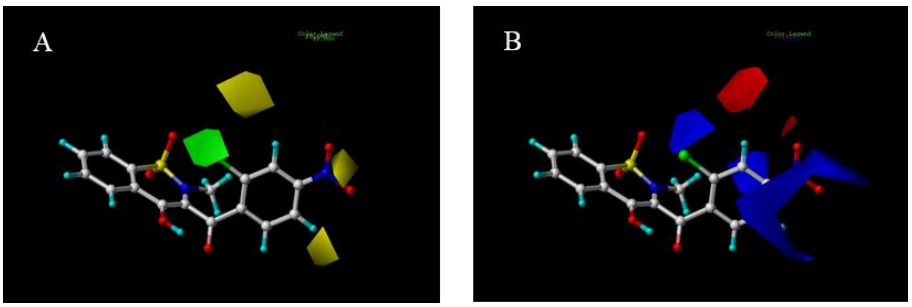

Figure 5. (A) Steric maps from the CoMFA model. (B) Electrostatic maps from the CoMFA

model

The steric field contour map is plotted in **Figure 5A**. The green displays a position where a bulky group would be favorable for higher herbicidal activity. As shown in **Figure 5**A, the CoMFA steric contour plots obviously indicated that a green region is located around the 2-positions of the benzene ring. This means that the bulky substituents at 2-positions will increase the herbicidal activity. The electrostatic contour plot is shown in **Figure 5B**. The blue contour defines a region where an increase in the positive charge will result in an increase in the activity, whereas the red contour defines a region of space where increasing electron density is favorable. As shown in **Figure 5B**, the target compounds bearing an electron-withdrawing group at the 2- or 4-position of the benzene ring and an electron-donating group at the 3-position displayed higher activity. These results provide useful information for improving herbicidal activity.

3.4. *In Vitro* HPPD Inhibitory Activity

As mentioned above, the treated *Echinochloa crusgalli* and *Digitaria sanguinalis* by some compounds, such as compounds **4p**–**4w**, caused significant bleaching symptom. Thus, it was speculated that these compounds would be served as potential HPPD inhibitors. In order to prove this conjecture, the *in vitro* HPPD inhibitory activities of compounds **4p**–**4w** were evaluated subsequently. As shown in **Table 6**, most of compounds **4p**–**4w** displayed significant inhibitory activity against the *At*HPPD. For example, compounds **4p**, **4t** and **4w** showed good potency with IC_{50} value of 0.69 μM, 0.86 μM and 0.48 μM, respectively. Compound **4w** was identified as the most potent candidate with IC_{50} value of 0.48 μM against *At*HPPD, which is better than the commercial herbicide sulctrione and comparable with mesotrione. These results indicated that compound **4w** could be a potential lead compound for further development of novel HPPD inhibiting-based herbicide.

Table 6. Biological activity of compounds **4p**–**4w** against *At*HPPD

Compounds	IC_{50} (μM)	Compounds	IC_{50} (μM)
4p	0.69 ± 0.031	**4t**	0.86 ± 0.045
4q	1.44 ± 0.087	**4u**	1.13 ± 0.069
4r	1.66 ± 0.087	**4v**	1.57 ± 0.090
4s	1.37 ± 0.045	**4w**	0.48 ± 0.024
Mesotrione	0.25 ± 0.012	Sulctrione	0.53 ± 0.055

4. Conclusion

In conclusion, a series of 3-benzoyl-4-hydroxy-2-methyl-2*H*-1, 2-benzothiazine-1, 1-dioxide and 3-benzoyl-4-hydroxy-1-methyl-1*H*-2, 1-benzothiazine-2, 2-dioxide derivatives were synthesized, and their herbicidal activities were firstly evaluated. The preliminary herbicidal results indicated that most of 3-benzoyl-4-hydroxy-2-methyl-2*H*-1, 2-benzothiazine-1, 1-dioxide derivatives showed good herbicidal activities against *Brassica campestris* and *Echinochloa crusgalli* at a concentration of 100 μg mL^{-1}. The preliminary study of structure–activity relationships indicated that the methyl group at the N-2 position of the ring B, and the position between NCH_3 group and SO_2 group played an important role on the herbicidal activity. The results of greenhouse experiments showed that compounds **4w** displayed good pre-emergent herbicidal activities against *Brassica campestris*, *Amaranthus retroflexus* and *Echinochloa crusgalli* even at a dosage of 187.5 g ha^{-1}, which is comparable with the commercial herbicide mesotrione. Most surprisingly, compounds **4w** showed the best HPPD inhibition activity with an IC_{50} value of 0.47 μM, which is better than the commercial herbicide sulctrione (IC_{50} = 0.53 μM)

and comparable with mesotrione (IC_{50} = 0.25 μM). The promising results suggested that compound **4w** is well worth further optimization as a potential HPPD inhibiting-based herbicide lead compound. Further structural optimization of compound **4w** is still ongoing.

5. Experiment

5.1. General procedure for compounds (2a-2i):

A mixture of **1** (2.0 g, 10 mmol) and α-bromoacetophenone (2.0 g, 10 mmol) in *N*, *N*-dimethylformamide (DMF) (20 mL) was taken in a round bottom flask and was heated at 100 °C for 1 h. Contents were then cooled to room temperature and poured over ice cooled water (100 ml) resulting in the formation of a light yellow solid, which was filtered to give desired product **2a** (2.5 g, yield: 83 %). The rest of compounds were prepared by the similar procedure to **2a**.

5.2. General procedure for compounds (3a-3i):

Sodium metal (0.5 g, 21 mmol) and dry methanol (20 ml) was allowed to reflux until all the metal dissolved. To this solution, **2a** (2.5 g, 8.4 mmol) was added in a single portion. Temperature of the mixture was maintained at 55 °C for 30 min till the completion of reaction. The contents were then cooled to 5 °C and poured over an ice-water mixture. Hydrochloric acid (2 N) was added to the mixture till the pH became approximately 3. The precipitates formed were filtered and dried to get the product **3a** as a yellow solid (2.0 g, yield: 80 %). The rest of compounds were prepared by the similar procedure to **3a**.

5.3. General procedure for compounds (4a-4i):

Compound **3a** (2.0 g, 6.7 mmol) was dissolved in ethanol (10 mL) and was treated with aqueous sodium hydroxide (1 M, 7.4 mL) followed by iodomethane (1.0 g, 6.7 mmol) and was stirred at room temperature for 12 h. Hydrochloric acid (2 N) was added to the mixture till the pH became approximately 3. The resulting suspension was filtered, and the solid was washed with water and dried to give desired product **4a** as a yellow solid (1.7 g, yield: 79 %). The rest of compounds were prepared by the similar procedure to **4a**.

Data for (4a): yield 79 %; yellow solid; m.p. 160–162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 15.83 (s, 1H), 8.26 – 8.21 (m, 1H), 8.20 – 8.16 (m, 2H), 7.97 – 7.92 (m, 1H), 7.86 – 7.79 (m, 2H), 7.66 – 7.60 (m, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 2.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.9, 169.3, 136.3, 134.9, 133.7, 132.9, 129.4, 128.8, 128.6, 127.8, 124.3, 118.8, 40.0; HRMS: calcd for $C_{16}H_{13}NO_4S$ $[M+H]^+$ 316.0565, found 316.0640.

Data for (4b): yield 82 %; yellow solid; m.p. 142–143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 15.69 (s, 1H), 8.24 – 8.22 (m, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.97 – 7.95 (m, 1H), 7.85 – 7.81 (m, 3H), 7.56 – 7.50 (m, 1H), 7.35 – 7.28 (m, 1H), 2.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 188.3, 168.7, 161.4 (d, *J* = 247.9 Hz), 135.8 (d, *J* = 7.1 Hz), 135.3, 132.9, 131.9, 129.3 (d, *J* = 7.6 Hz), 127.6, 126.82, 124.34 (d, *J* = 3.2 Hz), 123.39, 118.90 (d, *J* = 21.1 Hz), 117.80, 115.19 (d, *J* = 23.3 Hz), 39.15; HRMS: calcd for $C_{16}H_{12}FNO_4S$ $[M+H]^+$ 334.0471, found 334.0545.

Data for (4c): yield 81 %; light yellow solid; m.p. 131–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 15.64 (s, 1H), 8.27 – 8.21 (m, 1H), 8.17 (d, *J* = 7.7 Hz, 1H), 8.05 (s, 1H), 8.00 – 7.92 (m, 1H), 7.87 – 7.79 (m, 2H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.49 (t, *J* = 7.9 Hz, 1H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 189.4, 169.66, 136.52, 136.31, 134.78, 133.93, 133.03, 132.84, 129.87, 129.08, 128.56, 127.86, 127.76, 124.44, 118.84, 40.21; HRMS: calcd for $C_{16}H_{12}ClNO_4S$ $[M+H]^+$ 350.0176, found 350.0249.

Data for (4d): yield 78 %; light yellow solid; m.p. 149–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ:

15.62 (s, 1H), 8.24 – 8.21 (m, 2H), 8.19 (s, 1H), 7.99 – 7.93 (m, 1H), 7.88 – 7.79 (m, 2H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 1H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 189.3, 169.6, 136.7, 136.3, 135.7, 133.9, 133.0, 131.9, 130.1, 128.6, 128.2, 127.9, 124.4, 122.7, 118.8, 40.2; HRMS: calcd for $C_{16}H_{12}BrNO_4S$ $[M+H]^+$ 393.9670, found 393.9743.

Data for (4e): yield 72 %; light yellow solid; m.p. 143–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 15.64 (s, 1H), 8.18 – 8.08 (m, 1H), 7.86 – 7.83 (m, 1H), 7.74 – 7.69 (m, 3H), 7.59 (s, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.07 (dd, *J* = 8.3, 2.5 Hz, 1H), 3.82 (s, 3H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.9, 169.0, 159.5, 136.4, 136.2, 133.7, 132.9, 129.7, 128.7, 127.7, 124.3, 121.9, 119.6, 118.8, 113.6, 55.5, 40.0; HRMS: calcd for $C_{17}H_{15}NO_5S$ $[M+H]^+$ 346.0671, found 346.0745.

Data for (4f): yield 74 %; yellow solid; m.p. 183–184 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 15.75 (s, 1H), 8.27 – 8.16 (m, 3H), 7.97 – 7.88 (m, 1H), 7.84 – 7.78 (m, 2H), 7.24 – 7.16 (m, 2H), 2.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 189.5, 169.2, 165.6 (d, *J* = 255.5 Hz), 136.2, 133.8, 133.0, 132.2 (d, *J* = 9.2 Hz), 131.2 (d, *J* = 3.1 Hz), 128.7, 127.8, 124.4, 118.7, 115.8 (d, *J* = 21.8 Hz), 99.9, 40.1; HRMS: calcd for $C_{16}H_{12}FNO_4S$ $[M+H]^+$ 334.0471, found 334.0545.

Data for (4g): yield 86 %; yellow solid; m.p. 165–167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 15.72 (s, 1H), 8.25 – 8.20 (m, 1H), 8.16 (d, *J* = 8.6 Hz, 2H), 7.98 – 7.93 (m, 1H), 7.87 – 7.79 (m, 2H), 7.52 (d, *J* = 8.6 Hz, 2H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 188.4, 168.6, 138.4, 135.2, 132.8, 132.2, 131.9, 129.9, 127.9, 127.6, 126.8, 123.4, 117.8, 39.1; HRMS: calcd for $C_{16}H_{12}ClNO_4S$ $[M+H]^+$ 350.0176, found 350.0249.

Data for (4h): yield 82 %; yellow solid; m.p. 205–207 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 15.69 (s, 1H), 8.24 – 8.17 (m, 1H), 8.05 (d, *J* = 8.5 Hz, 2H), 7.96 – 7.90 (m, 1H), 7.84 – 7.78 (m, 2H), 7.67 (d, *J* = 8.5 Hz, 2H), 2.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 189.6, 169.6, 136.3, 133.9, 133.7, 133.0, 131.9, 130.9, 128.6, 128.1, 127.8, 124.4, 118.8, 40.2; HRMS: calcd for $C_{16}H_{12}BrNO_4S$ $[M+H]^+$ 393.9670, found 393.9743.

Data for (4i): yield 78 %; yellow solid; m.p. 164–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 16.05 (s, 1H), 8.28 – 8.22 (m, 2H), 8.22 – 8.16 (m, 1H), 7.93-7.92 (m, 1H), 7.83 – 7.74 (m, 2H), 7.03 – 6.94 (m, 2H), 3.91 (s, 3H), 2.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 189.4, 168.7, 163.6, 136.1, 133.4, 132.9, 132.0, 129.0, 127.7, 127.5, 124.2, 118.6, 113.9, 55.6, 40.0; HRMS: calcd for $C_{17}H_{15}NO_5S$ $[M+H]^+$ 346.0671, found 346.0745.

5.4. Methyl (1, 1-dioxido-3-oxo-1, 2-benzisothiazol-2(3H)-yl) acetate (5):

A mixture of **1** (41.0 g, 0.2 mol) and methyl chloroformate (21.6 g, 0.2 mol) in DMF (300 ml) was taken in a round bottom flask and was heated at 138 °C for 2 h. Contents were then cooled to room temperature and poured over ice cooled water (1000 ml) resulting in the formation of a white solid, which was filtered and washed with cold water. The solid was dried and recrystallized from methanol to get the product **5** as a white solid (48.1 g, yield: 94.3%).

5.5. Methyl 4-hydroxy-2H-1, 2-benzothiazine-3-carboxylate 1, 1-dioxide (6):

Sodium metal (6.9 g; 300 mmol) and dry methanol (400 ml) was allowed to reflux until all the metal dissolved. To this solution, **5** (30.2 g; 118.4 mmol) was added in a single portion. Temperature of the mixture was maintained at 55 °C for 30 min till the completion of reaction. The contents were then cooled to 5 °C and poured over an ice-water mixture. Hydrochloric acid (2 N) was added to the mixture till the pH became approximately 3. The precipitates formed were filtered and dried at 70 °C to get the product **6** as a white solid (26.4 g, yield: 87 %).

5.6. 2H-1, 2-benzothiazin-4(3H)-one 1, 1-dioxide (7):

Compound **6** (25.5 g, 0.1 mol) was added to concentrated hydrochloric acid (300 mL) and

refluxed for 8 h. The crude material was then poured into ice-water mixture and the precipitate was collected by suction filtration, washed with cold water and dried to give the desired product **7** as a white solid (9.4 g, yield: 48 %).

5.7. 2-Methyl-2H-1, 2-Benzothiazin-4(3H)-one 1, 1-dioxide (8):

A mixture of **7** (2.0 g, 10 mmol), cesium carbonate (3.6 g, 11 mmol) and iodomethane (1.4 g, 10 mmol) in DMF (20 ml) was taken in a round bottom flask and was stirred at room temperature until the starting material had disappeared. The mixture was poured into water and extracted with ethyl acetate. The combined organic phase was dried with anhydrous sodium sulfate, filtered and removed by rotary evaporation to yield brown viscous oil. The oil was scratched from ethyl acetate and petroleum ether (1/10 by volumn) to give desired product **8** as a light yellow solid (1.4 g, yield: 66 %).

5.8. General procedure for compounds (4j-4w):

A solution of compound **8** (1.1 g, 5 mmol) in DMF (10 mL) was added to sodium hydride (0.26 g, 7.5 mmol of a 60 % suspension in mineral oil which had been washed with benzene by decantation) at 0 °C. After stirring for 10 min, 4-nitrobenzoyl chloride was added during 20 min. The solution was stirred at 25 °C for 1 h and then evaporated. The residue was suspended in water and extracted with ethyl acetate. The combined organic phase was dried with anhydrous sodium sulfate, filtered and removed by rotary evaporation to yield **9a** as brown viscous oil, which was used in the next step without further purification.

A solution of compound **9a** (1.0 g, 2.7 mmol) in dichloromethane (10 mL) was added to triethylamine (0.4 g, 4 mmol), 18-Crown-6 (71 mg, 0.3 mmol) and potassium cyanide (91 mg, 1.4mmol). The mixture was stirred at 25 °C for 48 h. The mixture was poured into water and extracted with dichloromethane. The combined organic phase was dried with anhydrous sodium sulfate, filtered and removed by rotary evaporation. The residue was scratched from ethyl acetate and ethanol (1/1 by volumn) to give desired product to **4j** as a yellow solid (734 mg, yield: 41 %). The rest of compounds were prepared by the similar procedure to **4j**.

Data for (4j): yield 41 %; yellow solid; m.p. 196–197 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 15.45 (s, 1H), 8.42 – 8.36 (m, 2H), 8.35 – 8.29 (m, 2H), 8.27 – 8.18 (m, 1H), 7.98–7.95 (m, 1H), 7.91 – 7.82 (m, 2H), 2.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 188.3, 170.8, 149.9, 140.2, 136.3, 134.3, 133.2, 130.5, 128.3, 128.0, 124.6, 123.7, 119.1, 40.4; HRMS: calcd for $C_{16}H_{12}N_2O_6S$ $[M+H]^+$ 361.0416, found 361.0492.

Data for (4k): yield 32 %; light yellow solid; m.p. 223–225 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 15.47 (s, 1H), 8.38 – 8.30 (m, 2H), 8.27 – 8.20 (m, 1H), 8.16 – 8.10 (m, 2H), 8.00 – 7.94 (m, 1H), 7.89 – 7.82 (m, 2H), 3.15 (s, 3H), 2.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 187.7, 169.6, 142.7, 138.5, 135.3, 133.3, 132.2, 129.2, 127.3, 126.9, 126.5, 123.6, 118.0, 43.3, 39.4; HRMS: calcd for $C_{17}H_{15}NO_6S_2$ $[M+H]^+$ 394.0341, found 394.0416.

Data for (4l): yield 43 %; light yellow solid; m.p. 209–210 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 14.89 (s, 1H), 8.25 – 8.20 (m, 1H), 7.95 – 7.90 (m, 1H), 7.87 – 7.82 (m, 2H), 7.64 (d, J = 7.9 Hz, 2H), 7.39 (t, J = 7.9 Hz, 1H), 2.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.8, 168.7, 136.4, 136.4, 134.1, 133.0, 132.5, 129.6, 128.4, 128.2, 127.8, 127.5, 125.2, 124.5, 119.2, 40.0; HRMS: calcd for $C_{16}H_{11}C_{l2}NO_4S$ $[M+H]^+$ 383.9786, found 383.9861.

Data for (4m): yield 41 %; light yellow solid; m.p. 184–185 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 14.88 (s, 1H), 8.22 (dd, J = 5.9, 3.2 Hz, 1H), 7.94 (dd, J = 5.9, 3.0 Hz, 1H), 7.88 – 7.80 (m, 2H), 7.69 (s, 1H), 7.46 (s, 2H), 2.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.1, 168.9, 136.5, 135.8,

134.2, 133.0, 132.8, 131.9, 131.4, 129.9, 129.5, 128.2, 127.8, 124.6, 119.3, 40.1; HRMS: calcd for $C_{16}H_{11}C_{l2}NO_4S$ $[M+H]^+$ 383.9786, found 383.9861.

Data for (4n): yield 38 %; yellow solid; m.p. 212–214 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 15.55 (s, 1H), 8.22 – 8.18 (m, 1H), 8.17 (d, *J* = 2.0 Hz, 1H), 8.12 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.93 (dt, *J* = 5.3, 3.0 Hz, 1H), 7.84 – 7.79 (m, 2H), 7.60 (d, *J* = 8.4 Hz, 1H), 2.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 188.1, 169.9, 137.5, 136.2, 134.6, 134.1, 133.3, 133.1, 131.1, 130.7, 128.8, 128.5, 127.9, 124.5, 118.8, 40.3; HRMS: calcd for $C_{16}H_{11}C_{l2}NO_4S$ $[M+H]^+$ 383.9786, found 383.9861.

Data for (4o): yield 43 %; yellow solid; m.p. 221–222 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 15.47 (s, 1H), 8.25 – 8.19 (m, 1H), 8.03 (d, *J* = 1.8 Hz, 2H), 7.99 – 7.94 (m, 1H), 7.90 – 7.81 (m, 2H), 7.60 (t, *J* = 1.8 Hz, 1H), 2.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 186.9, 169.0, 136.4, 135.3, 134.4, 133.1, 132.1, 131.5, 127.3, 126.9, 126.6, 123.6, 117.8, 39.3; HRMS: calcd for $C_{16}H_{11}C_{l2}NO_4S$ $[M+H]^+$ 383.9786, found 383.9861.

Data for (4p): yield 32 %; light yellow solid; m.p. 158–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 14.92 (s, 1H), 8.23 (dd, *J* = 5.9, 3.1 Hz, 1H), 7.96 – 7.90 (m, 1H), 7.88 – 7.81 (m, 2H), 7.73 (d, *J* = 8.3 Hz, 1H), 7.56 (d, *J* = 1.9 Hz, 1H), 7.43 (dd, *J* = 8.3, 2.0 Hz, 1H), 2.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.4, 168.7, 137.6, 136.4, 134.1, 133.0, 132.7, 132.4, 131.5, 130.3, 128.3, 127.8, 127.1, 124.5, 119.3, 40.0; HRMS: calcd for $C_{16}H_{11}C_{l2}NO_4S$ $[M+H]^+$ 383.9786, found 383.9861.

Data for (4q): yield 33 %; light yellow solid; m.p. 174–175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 14.97 (s, 1H), 8.27 – 8.18 (m, 1H), 7.97 – 7.91 (m, 1H), 7.88 – 7.78 (m, 3H), 7.29 – 7.26 (m, 1H), 7.16 (td, *J* = 8.4, 2.3 Hz, 1H), 2.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.5, 168.5, 163.6 (d, *J* = 255.5 Hz), 136.4, 134.0, 133.0, 133.0 (d, *J* = 10.5 Hz), 132.4 (d, *J* = 9.5 Hz), 130.5 (d, *J* = 3.3 Hz), 128.3, 127.8, 124.5, 119.3, 118.0 (d, *J* = 25.0 Hz), 114.2 (d, *J* = 21.4 Hz), 39.9; HRMS: calcd for $C_{16}H_{11}ClFNO_4S$ $[M+H]^+$ 368.0081, found 368.0157.

Data for (4r): yield 27 %; light yellow solid; m.p. 171–172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 14.89 (s, 1H), 8.20 (dd, *J* = 5.8, 3.2 Hz, 1H), 7.91 (dd, *J* = 5.8, 3.2 Hz, 1H), 7.84 – 7.79 (m, 2H), 7.69 (d, *J* = 1.7 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.55 (dd, *J* = 8.3, 1.7 Hz, 1H), 2.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.4, 167.6, 135.4, 133.1, 132.1, 131.9, 131.3, 130.5, 128.9, 127.2, 126.8, 124.5, 123.5, 118.2, 38.9; HRMS: calcd for $C_{16}H_{11}BrClNO_4S$ $[M+H]^+$ 427.9281, found 427.9355.

Data for (4s): yield 21 %; light yellow solid; m.p. 159–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 14.86 (s, 1H), 8.23 – 8.16 (m, 1H), 7.92 – 7.89 (m, 1H), 7.85 – 7.78 (m, 2H), 7.71 (d, *J* = 1.9 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 1H), 7.45 (dd, *J* = 8.3, 2.0 Hz, 1H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 192.2, 168.7, 137.6, 136.5, 134.7, 134.1, 133.3, 133.0, 131.5, 128.2, 127.8, 127.6, 124.5, 120.2, 119.1, 39.9; HRMS: calcd for $C_{16}H_{11}BrClNO_4S$ $[M+H]^+$ 427.9281, found 427.9355.

Data for (4t): yield 29 %; light yellow solid; m.p. 134–136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 14.87 (s, 1H), 8.26 – 8.18 (m, 1H), 7.96 – 7.88 (m, 2H), 7.87 – 7.80 (m, 2H), 7.63 (s, 2H), 2.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 192.3, 168.6, 136.4, 136.0, 135.1, 134.1, 133.0, 131.6, 130.5, 128.2, 127.8, 125.6, 125.2, 124.5, 119.0, 40.0; HRMS: calcd for $C_{16}H_{11}Br_2NO_4S$ $[M+H]^+$ 471.8776, found 471.8849.

Data for (4u): yield 36 %; light yellow solid; m.p. 202–203 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 14.69 (s, 1H), 8.39 (d, *J* = 2.0 Hz, 1H), 8.27 (dd, *J* = 8.5, 2.1 Hz, 1H), 8.24 – 8.18 (m, 1H), 7.95 – 7.88 (m, 2H), 7.87 – 7.80 (m, 2H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.4, 169.3, 149.2, 140.0, 136.4, 134.5, 133.2, 132.7, 131.3, 127.9, 125.5, 124.8, 121.8, 119.2, 40.3; HRMS: calcd for $C_{16}H_{11}ClN_2O_6S$ $[M+H]^+$ 395.0026, found 395.0100.

Data for (4v): yield 32 %; light yellow solid; m.p. 175–177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 14.81 (s, 1H), 8.27 – 8.19 (m, 1H), 7.98 – 7.91 (m, 1H), 7.91 – 7.83 (m, 3H), 7.80 (s, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 2.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.1, 169.1, 137.7, 136.5, 134.3, 133.1, 132.0, 130.9, 128.1, 127.9, 127.4 (q, *J* = 4.2 Hz), 124.6 (s), 123.7 (dd, *J* = 7.2, 3.6 Hz), 119.3, 40.1; HRMS: calcd for $C_{17}H_{11}ClF_3NO_4S$ $[M+H]^+$ 418.0049, found 418.0123.

Data for (4w): yield 40 %; light yellow solid; m.p. 224–226 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 14.65 (s, 1H), 8.19 – 8.11 (m, 1H), 8.04 (s, 1H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.85 (t, *J* = 7.3 Hz, 2H), 7.78 (dd, *J* = 8.8, 5.0 Hz, 2H), 3.08 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 189.7, 168.2, 142.6, 138.3, 135.3, 133.4, 132.2, 131.6, 130.4, 128.3, 126.9, 126.9, 124.5, 123.7, 118.2, 43.4, 39.3; HRMS: calcd for $C_{17}H_{14}ClNO_6S_2$ $[M+H]^+$ 427.9951, found 428.0027.

5.9. Methyl 2-(methylsulfonamido)benzoate(11):

To a stirred solution of methyl 2-aminobenzoate (25.0 g, 165.6 mmol) in pyridine (200 mL) at 0 °C, methane sulfonyl chloride (13 mL, 168 mmol) was added drop wise and the mixture stirred at 25 °C for 3 h. After completion, the reaction was quenched with ice cold water and extracted with ethyl acetate (3 x 200 mL). The organic layer was washed with water (50 mL), brine (50 mL), dried with anhydrous sodium sulfate and concentrated. The resulting crude product eluted at ethyl acetate in hexane (1/4 by volumn). The fractions with product were concentrated to obtain methyl 2-(methylsulfonamido) benzoate as white solid (37.0 g, yield: 98 %).

5.10. Methyl 2-(N-methylmethylsulfonamido)benzoate (12):

To a solution of methyl 2-(methylsulfonamido) benzoate (37.0 g, 162 mmol) in DMF (300 mL), cesium carbonate (79.0 g, 242.4 mmol) was added slowly and stirred for 12 h. To this mixture, excess methyl iodide (12 mL, 193.9 mmol) was added and the mixture stirred at 25 °C for 16 h. After completion, the mixture was quenched with saturated ammonium chloride solution (100 mL). The aqueous layer was extracted with ethyl acetate (3 x 300 mL) and the combined organic layer was washed with water (100 mL), brine (50 mL), dried over anhydrous sodium sulfate and concentrated to obtain methyl 2-(N-methylmethylsulfonamido)benzoate as white solid (28.0 g, 71 %).

5.11. 2, 2-Dioxo-1-methyl-2, 1-benzothiazin-4(3H)-one (13):

To a suspension of benzene washed sodium hydride (2.3 g; 96 mmol) in dry DMF (30 mL), a solution of 2-(N-methylmethylsulfonamido) benzoate (11.7 g; 48 mmol) in dry DMF (70 mL) was added and stirred at room temperature for 1.5 h. After completion of the reaction (as indicated by TLC), the contents were poured into cold hydrochloric acid (2 N) to get the precipitates, which were dried at room temperature to get 2, 2-dioxo-1-methyl-2, 1-benzothiazin-4(3H)-one as white solid (9.1 g, 90 %).

5.12. General procedure for compounds (15a-15j):

A solution of compound **13** (1.1 g, 5 mmol) in DMF (10 mL) was added to sodium hydride (0.3 g, 7.5 mmol of a 60% suspension in mineral oil which had been washed with benzene by decantation) at 0 °C. After stirring for 10 min, benzoyl chloride (1.4 g, 10 mmol) was added during 20 min. The solution was stirred at 25 °C for 1 h and then evaporated. The residue was suspended in water and extracted with ethyl acetate. The combined organic phase was dried with anhydrous sodium sulfate, filtered and removed by rotary evaporation to yield **14a** as brown viscous oil, which was used in the next step without further purification.

A solution of compound **14a** (0.9 g, 2.8 mmol) in dichloromethane (10 mL) was added to triethylamine (0.4 g, 4 mmol), 18-Crown-6 (71 mg, 0.3 mmol) and potassium cyanide (91 mg,

1.4mmol). The mixture was stirred at 25 ℃ for 48 h. The mixture was poured into water and extracted with dichloromethane. The combined organic phase was dried with anhydrous sodium sulfate, filtered and removed by rotary evaporation. The residue was scratched from ethyl acetate and ethanol (1/1 by volumn) to give desired product **15a** as yellow solid (572 mg, yield: 36 %). The rest of compounds were prepared by the similar procedure to **15a**.

Data for (15a): yield 36 %; light yellow solid; m.p. 208–210 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.19 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.86 (dd, *J* = 5.2, 3.3 Hz, 2H), 7.73 – 7.67 (m, 1H), 7.65 – 7.59 (m, 1H), 7.53 (dd, *J* = 10.4, 4.7 Hz, 2H), 7.38 – 7.31 (m, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 3.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.2, 177.4, 142.1, 137.2, 135.6, 132.5, 128.2, 128.1, 128.1, 123.9 , 120.3, 117.9, 115.2, 32.1; HRMS: calcd for $C_{16}H_{13}NO_4S$ $[M+H]^+$ 316.0565, found 316.0640.

Data for (15b): yield 33 %; light yellow solid; m.p. 138–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.19 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.96 – 7.88 (m, 2H), 7.76 – 7.68 (m, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.22 (dd, *J* = 17.8, 8.9 Hz, 3H), 3.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.8, 177.2, 165.4 (d, *J* = 254.1 Hz), 141.9, 135.7, 133.4 (d, *J* = 3.0 Hz), 131.1 (d, *J* = 9.4 Hz), 128.1, 124.1, 120.2, 117.9, 115.4 (d, *J* = 22.0 Hz), 115.1, 32.2; HRMS: calcd for $C_{16}H_{12}FNO_4S$ $[M+H]^+$ 334.0471, found 334.0545.

Data for (15c): yield 38 %; light yellow solid; m.p. 170–172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.19 (d, *J* = 7.4 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.72 (t, *J* = 7.3 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 8.3 Hz, 1H), 3.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.9, 177.2, 142.0, 138.9, 135.8, 135.6, 129.8, 128.5, 128.2, 124.1, 120.1, 117.9, 115.1, 32.2; HRMS: calcd for $C_{16}H_{12}ClNO_4S$ $[M+H]^+$ 350.0176, found 350.0249.

Data for (15d): yield 30 %; light yellow solid; m.p. 178–180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.73 (t, *J* = 6.4 Hz, 3H), 7.65 (d, *J* = 8.6 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 3.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.1, 176.2, 141.0, 134.9, 134.8, 130.4, 128.8, 127.1, 126.5, 123.0, 119.0, 116.9, 114.1, 31.1; HRMS: calcd for $C_{16}H_{12}BrNO_4S$ $[M+H]^+$ 393.9670, found 393.9743.

Data for (15e): yield 24 %; light yellow solid; m.p. 135–136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.92 (d, *J* = 8.8 Hz, 2H), 7.72 – 7.63 (m, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H), 3.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.5, 177.4, 163.5, 141.9, 135.3, 131.2, 129.2, 128.0, 124.1, 120.8, 118.1, 114.9, 113.5, 55.5, 32.5; HRMS: calcd for $C_{17}H_{15}NO_5S$ $[M+H]^+$ 346.0671, found 346.0745.

Data for (15f): yield 39 %; yellow solid; m.p. 162–164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.36 (d, *J* = 8.6 Hz, 2H), 8.22 (d, *J* = 7.9 Hz, 1H), 7.96 (d, *J* = 8.6 Hz, 2H), 7.76 (t, *J* = 7.3 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.26 (d, *J* = 8.3 Hz, 1H), 3.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.6, 176.9, 149.6, 142.9, 142.2, 136.3, 129.0, 128.3, 124.2, 123.4, 119.4, 117.9, 115.1, 31.9; HRMS: calcd for $C_{16}H_{12}N_2O_6S$ $[M+H]^+$ 361.0416, found 361.0492.

Data for (15g): yield 27 %; light yellow solid; m.p. 195–197 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.19 (d, *J* = 7.9 Hz, 1H), 8.07 (d, *J* = 8.3 Hz, 2H), 7.97 (d, *J* = 8.3 Hz, 2H), 7.76 – 7.69 (m, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 3.38 (s, 3H), 3.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.9, 177.1, 143.3, 142.2, 136.2, 128.9, 128.3, 127.2, 124.2, 119.5, 117.9, 115.1, 44.4, 32.0; HRMS: calcd for $C_{17}H_{15}NO_6S_2$ $[M+H]^+$ 394.0341, found 394.0416.

Data for (15h): yield 31 %; light yellow solid; m.p. 161–163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.75 – 7.66 (m, 1H), 7.50 (d, *J* = 1.7 Hz, 1H), 7.43 (d, *J* = 8.2 Hz,

1H), 7.39 – 7.29 (m, 2H), 7.20 (d, *J* = 8.3 Hz, 1H), 3.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.9, 176.6, 142.6, 137.1, 136.3, 135.1, 131.5, 129.8, 128.8, 128.3, 127.0, 123.8, 118.9, 117.6, 115.1, 31.7; HRMS: calcd for $C_{16}H_{11}C_{l2}NO_4S$ $[M+H]^+$ 383.9786, found 383.9861.

Data for (15i): yield 32 %; light yellow solid; m.p. 209–211 °C; ^{1}H NMR (400 MHz, DMSO) δ: 8.03 (d, *J* = 7.9 Hz, 1H), 7.78 (t, *J* = 7.2 Hz, 1H), 7.64 – 7.54 (m, 2H), 7.44 (d, *J* = 8.3 Hz, 1H), 7.38 – 7.31 (m, 2H), 3.33 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ: 187.3, 172.8, 162.9 (d, *J* = 250.4 Hz), 142.5, 136.0, 135.4 (d, *J* = 2.6 Hz), 131.6 (d, *J* = 11.2 Hz), 131.0 (d, *J* = 9.6 Hz), 127.9, 124.1, 120.2, 118.9, 117.5 (d, *J* = 25.4 Hz), 115.5, 114.8 (d, *J* = 21.7 Hz), 32.1; HRMS: calcd for $C_{16}H_{11}ClFNO_4S$ $[M+H]^+$ 368.0081, found 368.0157.

Data for (15j): yield 34 %; light yellow solid; m.p. 190–192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.24 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.78 – 7.71 (m, 1H), 7.69 (d, *J* = 1.7 Hz, 1H), 7.56 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.42 – 7.32 (m, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 3.43 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 189.9, 175.6, 141.5, 135.3, 134.5, 131.5, 130.5, 128.9, 127.8, 127.3, 123.9, 122.8, 117.9, 116.5, 113.9, 30.6; HRMS: calcd for $C_{16}H_{11}BrClNO_4S$ $[M+H]^+$ 427.9281, found 427.9355.

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