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Design, synthesis and biological evaluation of benzo[1.3.2]dithiazolium ylide 1,1-dioxide derivatives as potential dual cyclooxygenase-2/5-lipoxygenase inhibitors

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ABSTRACT

3-(4-Bromophenyl)-6-nitrobenzo[1.3.2]dithiazolium ylide 1,1-dioxide (**5**) was discovered as a new prototype for dual inhibitors of cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX). Thus, the structure–activity relationships of benzo[1.3.2]dithiazolium ylide 1,1-dioxide skeleton were carried out. The 6-NO_2 group played an essential role in the inhibitory activity. In addition, moderate-sized lipophilic substituents at the *para*-position of the 3-aryl moiety were required for dual COX-2/5-LOX inhibitory activity. Among the identified potent dual inhibitors, 3-(4-*t*butylphenyl) derivative **30c** (IC_{50} values of 0.27 μM and 0.30 μM against COX-2 and 5-LOX, respectively) and 3-(4-biphenyl) derivative **30f** (IC_{50} values of 0.50 μM and 0.15 μM against COX-2 and 5-LOX, respectively) were the most potent dual COX-2/5-LOX inhibitors. Intraperitoneal administration of **30c** at 100 mg/kg demonstrated potent acute anti-inflammatory activity. As a result, benzo[1.3.2]dithiazolium ylide 1,1-dioxide represented a novel scaffold for the exploitation in developing dual COX-2/5-LOX inhibitors.

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of pain and inflammation. NSAIDs inhibit the cyclooxygenase (COX) enzymes to block arachidonic acid metabolism. There are two isoforms of COX enzyme. COX-1 is a constitutive isoform responsible for cytoprotective effects while COX-2 is an inducible isoform for inflammatory effects.[1] Classical NSAIDs may cause gastroinstinal (GI) side effects due to the nonselective inhibition of both COX-1 and COX-2 isoforms.[2] Selective COX-2 inhibitors such as celecoxib (**1**)[3,4] and rofecoxib (**2**)[5] (Fig. 1) represent a new generation of NSAIDs. However, rofecoxib was withdrawn from the market due to increased cardiovascular risks such as myocardial infarction and stroke.[6,7] The adverse cardiovascular effects might result from the inhibition of prostacyclin production by selective COX-2 inhibitors.[8] In addition to the COX enzymes, lipoxygenase (LOX) is also responsible for the metabolism of arachidonic acid. Thus, 5-LOX inhibitors are considered as potential therapeutic anti-inflammatory agents as well.[9] It is believed[12] that dual inhibition of COX-2 and 5-LOX mechanistic pathways might be more effective in anti-inflammation with less adverse effects. Dual COX-2/5-LOX inhibitors such as compounds **3**[10] and **4**[11] (Fig. 1) have drawn attention. Dual COX-2/5-LOX inhibitors have been validated for the treatment of inflammation[13] and inflammation-related diseases such as acute pancreatitis,[14] arthritis, and bronchospasm resulted from physiological inflammation processes.[15,16]

6-Nitrobenzo[1.3.2]dithiazolium ylide 1,1-dioxide **5** was discovered as dual COX-2/5-LOX inhibitor in our previous study.[17] Compound **5** possessed inhibitory activity with IC_{50} values of 1.7 μM and 1.22 μM (Table 1) against COX-2 and 5-LOX, respectively. Interestingly, 5-nitro derivative **6** displayed high potency against 5-LOX enzyme with an IC_{50} value of 0.47 μM but it was inactive against COX-2 enzyme. Replacement of the 5-NO_2 group by 5-SO_2NH_2 group did not improve the COX-2 inhibitory activity but defeated the potency against 5-LOX (Table 1).[17]

Compound **5** exists in a racemic mixture, and docking model revealed that (*S*)-enantiomer could fit into the active site of COX-2 enzyme.[17] The (*S*)-**5** was predicted to have two hydrogen bonds via the SO_2 group with Arg120 and Tyr355 and two hydrogen bonds via the 6-NO_2 group with His90 and Arg513 in the active site of COX-2 (Fig. 2). Docking model[17] showed that the SO_2 group of compound **6** had two hydrogen bonds with Tyr355 but the 5-NO_2 group was not hydrogen bonded to His90. Indeed, compound **5** possessed moderate inhibitory potency against COX-2 enzyme (IC_{50} = 1.70 μM) while compound **6** exhibited very weak inhibition against COX-2 enzyme (23% at 10 μM). Apparently, the 6-NO_2 group

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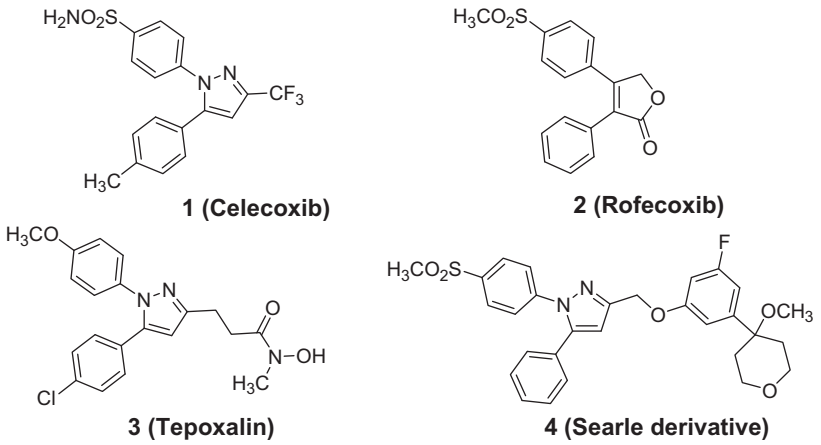
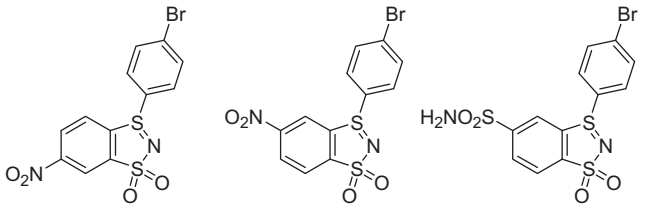


Figure 1. COX-2 inhibitors (**1** and **2**) and dual COX-2/5-LOX inhibitors (**3** and **4**).

Table 1
Inhibitory activity of compounds **5–7** on human recombinant COX-2 and 5-LOX[a]



Compd	COX-2	5-LOX
5	IC_{50} = 1.70 μM	IC_{50} = 1.22 μM
6	23% at 10 μM	IC_{50} = 0.47 μM
7	27% at 10 μM	14% at 10 μM

[a] Data from Ref. 13.

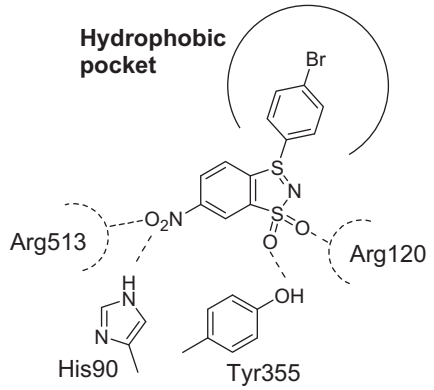
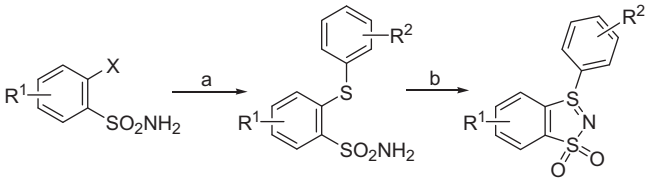


Figure 2. Docking mode of compound **5** in the active site of COX-2 enzyme.

of (*S*)-**5** played an important role in inhibiting COX-2 enzyme. Furthermore, the aryl moiety at the 3-position of benzo[1.3.2]dithiazolium ylide 1,1-dioxide derivatives was predicted to fit into the hydrophobic pocket.[17] The substitution at the 5- and 6-position might associate with the inhibitory activity on COX-2 and 5-LOX, and the aryl group on the sulfur atom at the 3-position may also play roles in the inhibition. In the present study, we carried out the structure-activity relationship of a series of benzo[1.3.2]dithiazolium ylide 1,1-dioxide derivatives, and the in vivo anti-inflammatory activity of potent dual COX-2/5-LOX inhibitor **30c** was evaluated.



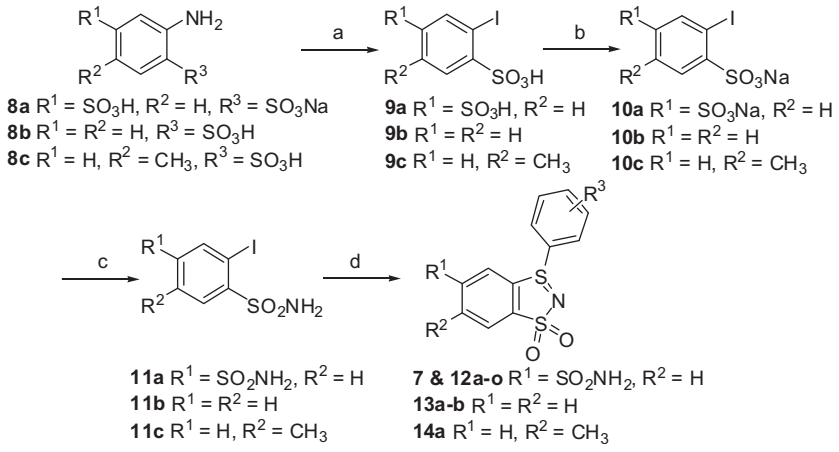
Scheme 1. General synthesis of benzo[1.3.2]dithiazolium ylide 1,1-dioxidederivatives. Reagents and conditions: (a) For X = I: aryl thiol, CuI (10 mol %), neocuproine (10 mol %), K_3PO_4 (1.5 equiv), toluene, reflux; For X = Br: aryl thiol, K_2CO_3, ethanol, reflux; (b) Br_2, MeOH, rt.

2. Results and discussion

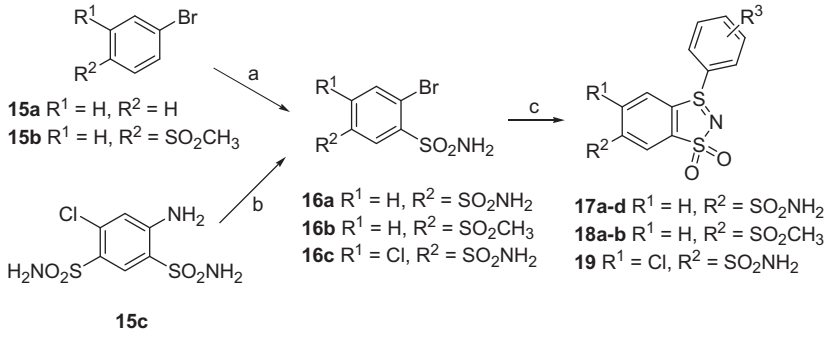
2.1. Chemistry

The construction of benzo[1.3.2]dithiazolium ylide 1,1-dioxide skeleton consists of cross-coupling reaction by 2-halobenzenesulfonamides with aryl thiols and followed oxidative intramolecular cyclization reaction (Scheme 1).[17,18] The key intermediates 2-arylsulfanylbenzenesulfonamides were prepared by 2-bromo- or 2-iodobenzenesulfonamides with thiols in different reaction conditions. The cross-coupling of aryl iodides and thiols was accomplished by the catalyst of 10 mol % copper iodide, the ligand of 10 mol % neocuproine, and the base of K_3PO_4 at moderate temperature.[19] This coupling reaction condition is selective for aryl iodides. For 2-bromobenzenesulfonamide derivatives, the bromo substituent was easily substituted by thiols in the presence of K_2CO_3 as the base (Scheme 1).

Diazotization of aniline-2,5-disulfonic acid (**8a**) and followed iodide substitution afforded 2-iodobenzene-1,4-disulfonic acid (**9a**), which was then converted to sulfonate **10a** (Scheme 2). Chlorination of **10a** with PCl_5 and then a treatment with ammonium hydroxide provided the desired 2-iodobenzenesulfonamide **11a**, which was applied for the preparation of 5-sulfonamidobenzo[1.3.2]dithiazolium ylide 1,1-dioxide derivatives **7** and **12a**–**o** as shown in Scheme 1. Compounds **13a**,**b** without substitution at the 5- or 6-position, and compound **14a** with 6-CH_3 group were synthesized from **8b** and **8c**, respectively, by the same reaction procedures as outlined in Scheme 2.



Scheme 2. Preparation of 5-SO_2NH_2 and 6-CH_3 substituted derivatives **7**, **12a–o**, **13a**,**b**, and **14a**. Reagents and conditions: (a) (i) Na_2CO_3, $NaNO_2$; (ii) concd HCl, 0 °C; (iii) KI, 0–80 °C; (b) 10 *N* NaOH; (c) (i) PCl_5, 80 °C; (ii) concd NH_4OH, 0 °C; (d) (i) aryl thiol, CuI (10 mol %), neocuproine (10 mol %), K_3PO_4 (1.5 equiv), toluene, reflux; (ii) Br_2, MeOH, rt.



Scheme 3. Preparation of 6-SO_2NH_2 and 6-SO_2CH_3 substituted derivatives **17a–d**, **18a**,**b**, and **19**. Reagents and conditions: (a) (i) $ClSO_3H$, 150 °C; (ii) concd NH_4OH, 0 °C; (b) (i) $NaNO_2$; (ii) concd H_2SO_4, 0 °C; (iii) $CuBr_2$, 0–80 °C; (c) (i) aryl thiol, K_2CO_3, ethanol, reflux; (ii) Br_2, MeOH, rt.

The preparations of 6-SO_2NH_2 and 6-SO_2CH_3 derivatives **17a–d**, **18a**,**b**, and **19** are illustrated in Scheme 3. Sulfonation and the successive chlorination of **15a,b** in the presence of chlorosulfonic acid at reflux in a one-pot system afforded the corresponding sulfonyl chlorides. The resulted sulfonyl chloride was treated with concentrated ammonium hydroxide to give 2-bromobenzenesulfonamides **16a–c**, which were converted to benzo[1.3.2]dithiazolium ylide 1,1-dioxide derivatives according to the method in Scheme 1.

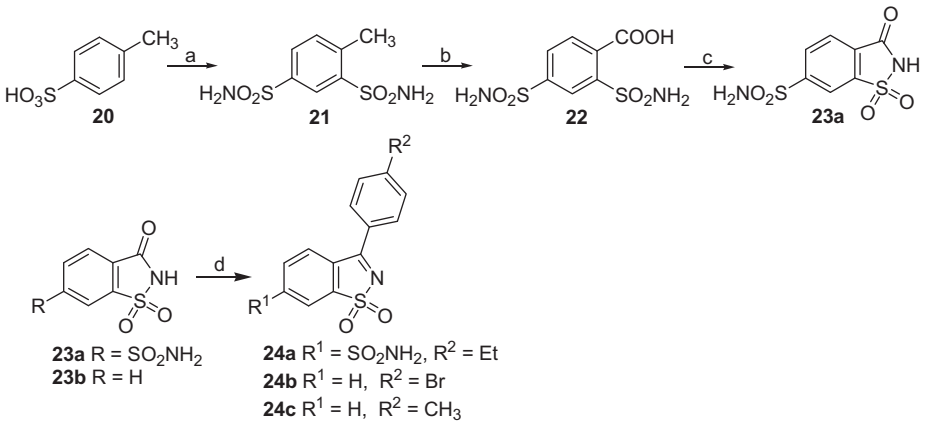
Benzo[1.2]isothiazole 1,1-dioxides **24a–c**, bioisosteric analogs of benzo[1.3.2]dithiazolium ylide 1,1-dioxides, were prepared as shown in Scheme 4. *p*-Toluenesulfonic acid (**20**) underwent sulfonation, chlorination, and amidation to give 2,4-disulfamyltoluene (**21**). Compound **21** was oxidized to **22**, which was then converted to saccharin **23a** in concentrated sulfuric acid. Treatment of compound **23a** and commercially available saccharin **23b** with Grignard reagents gave the expected benzo[1.2]isothiazole 1,1-dioxides **24a** and **24b–c**, respectively.

2-(4-Bromophenylsulfanyl)-5-methylbenzenesulfonamide (**25**) was used for the preparation of benzo[1.3.2]dithiazolium ylide 1,1-dioxides **14b–d** with carboxylic acid derivatives substituted at the 6-potition (Scheme 5). It is found that oxidation condition ($KMnO_4$ in 5% NaOH at reflux) caused the ring-opening of dithiazolium ylide 1,1-dioxide. Thus, 5-methylbenzenesulfonamide **25** was firstly oxidized to benzoic acid **26**, which was then cyclized to benzo[1.3.2]dithiazolium ylide 1,1-dioxide **14b**. Subsequently, carboxylic acid **14b** was converted to methyl ester **14c** and amide **14d.**

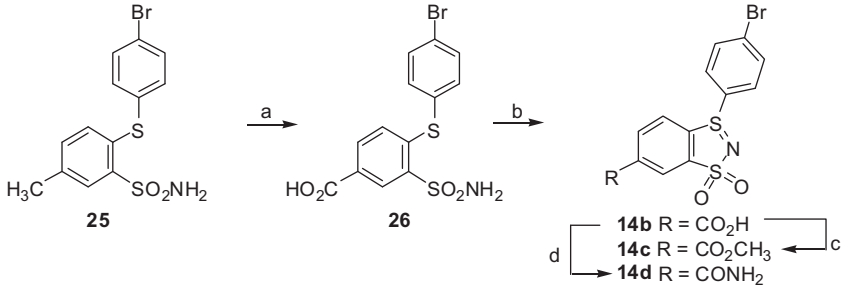
6-Nitro derivatives **5** and **30a–j** were obtained by 2-iodo-5-nitrobenzenesulfonamide (**29**) (Scheme 6) according to our previously described method.[17,20] Compounds **30i** and **30j** with a phenoxyethyl character were prepared from thiols **33a** and **33b**, respectively, which were obtained according to the reported method[21] for the preparation of alkanethiol as illustrated in Scheme 7. Phenol **31b** containing methoxytetrahydropyran[16] was prepared according to the reported method.[22] Then, commercially available **31a** and prepared **31b** underwent nucleophilic substitution with ethylene dibromide to afford phenoxyethyl bromides **32a** and **32b**, respectively. Treatments of **32a** and **32b** with thiourea, NaOH, and HCl in sequence gave the corresponding mercaptoethoxy derivatives **33a** and **33b**, respectively.

2.2. Biological evaluation

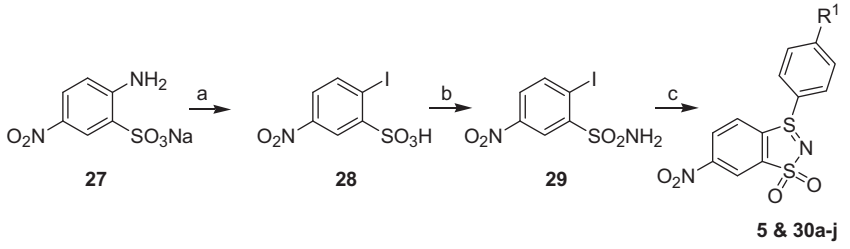
In addition to nitro group, hydrogen bond acceptors SO_2NH_2, SO_2CH_3, and carboxylic acid derivatives were introduced to benzo[1.3.2]dithiazolium ylide 1,1-dioxide for hydrogen bonding to His90, Initially, 5-SO_2NH_2 derivatives **12a–o** were evaluated at a concentration of 10 μM but they showed very weak or no inhibition against both COX-2 and 5-LOX (Table 2). Compounds **13a** and **13b**, without 5- or 6-substitution, showed no inhibition on COX-2 and 5-LOX (Table 3). Then, 6-SO_2NH_2 derivatives **17a–d** were investigated. Still, the 6-SO_2NH_2 group did not improve the inhibitory activity against COX-2 and 5-LOX as compared to the 6-NO_2 derivative **5** (Table 3). Additional 5-chloro substituent (**19**) improved the inhibitory activity on COX-2 (IC_{50} = 2.30 μM) as compared to **17a**. In comparison of **18a–17a**, 6-SO_2CH_3 group was favored in the inhibitory activity against COX-2 and 5-LOX with IC_{50} = 1.80 μM and 13.5 μM, respectively. 6-Methyl derivative **14a** had no inhibition on COX-2, as expected. However, compound



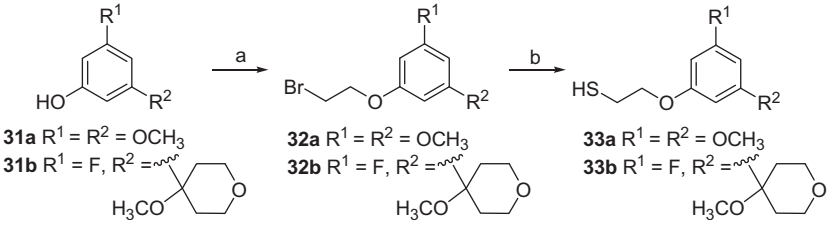
Scheme 4. Preparation of benzo[1.2]isothiazole 1,1-dioxides **24a–c**. Reagents and conditions: (a) (i) $ClSO_3H$, 150 °C; (ii) concd NH_4OH, 0 °C; (b) $KMnO_4$, 5% $NaOH_{aq}$, reflux; (c) concd H_2SO_4, rt; (d) Grignard reagents (1–3 equiv).



Scheme 5. Preparation of benzo[1.3.2]dithiazolium ylide 1,1-dioxide derivatives with carboxylic acid derivative substituents **14b–d**. Reagents and conditions: (a) $KMnO_4$, 5% NaOH, reflux; (b) Br_2, MeOH, rt; (c) (i) $SOCl_2$; (ii) MeOH, 0 °C to rt; (d) (i) $SOCl_2$; (ii) concd NH_4OH, 0 °C to rt.



Scheme 6. Preparation of 6-nitrobenzo[1.3.2]dithiazolium ylide 1,1-dioxide derivatives **5** and **30a–j**. Reagents and conditions: (a) (i) HCl, $NaNO_2$, H_2O, 0 °C; (ii) KI, rt; (b) (i) $SOCl_2$, DMF, reflux; (ii) NH_4OH, rt; (c) (i) aryl thiol, CuI, neocuproine, *t*-BuONa or K_3PO4, toluene, reflux; (ii) Br_2, MeOH, rt.

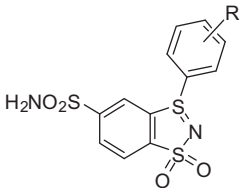


Scheme 7. Preparation of mercaptoethoxy derivatives **33a** and **33b**. Reagents and conditions: (a) $BrCH_2CH_2Br$, reflux; (b) (i) thiourea, EtOH, reflux; (ii) 2.5 *N* NaOH, reflux; (iii) 1 *N* HCl.

14a somewhat inhibited 5-LOX (IC_{50} = 6.05 μM, Table 3). Carboxylic acid derivatives **14b–d** exhibited very weak or no inhibitory activity against COX-2 and 5-LOX. Replacing the 3-sulfur atom of benzo[1.3.2]dithiazolium ylide 1,1-dioxides by a carbon atom led to benzo[1.2]isothiazole 1,1-dioxides **24a–c**, which have planar structure different from the chiral structure in benzo[1.3.2]dithiazolium ylide 1,1-dioxide. The results showed that compounds **24a–c** had no or very weak inhibition against both COX-2 and 5-LOX enzymes (Table 4).

The 6-NO_2 group on benzo[1.3.2]dithiazolium ylide 1,1-dioxide is essential for the inhibitory activity against COX-2 and 5-LOX. From the docking model,[17] the 3-(4-bromophenyl) group of compound **5** entered the hydrophobic pocket. Thus, miscellaneous groups eligible for the hydrophobic pocket were introduced onto

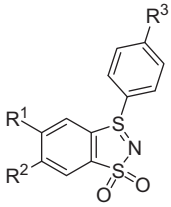
Table 2
Inhibitory activity of 5-SO_2NH_2 derivatives on human recombinant COX-2 and 5-LOX



Compd	R	%Inhibition at 10 μM	
		COX-2	5-LOX
7	4-Br	27%	14%
12a	3-Br	7%	28%
12b	4-F	2%	9%
12c	4-Cl	NI[a]	19%
12d	4-Me	2%	9%
12e	4-Et	NI[a]	7%
12f	4-*i*Pr	10%	19%
12g	4-*t*Bu	NI[a]	25%
12h	4-CF_3	NI[a]	37%
12i	4-OMe	NI[a]	21%
12j	2,4-F	NI[a]	NI[a]
12k	2,4-Cl	9%	NI[a]
12l	2,4-Me	NI[a]	NI[a]
12m	3,4-Cl	14%	NI[a]
12n	3,4-Me	15%	NI[a]
12o	3,4-OMe	6%	NI[a]

[a] NI: no inhibition.

Table 3
Inhibitory activity of **13a**,**b** and 6-substituted derivatives on human recombinant COX-2 and 5-LOX

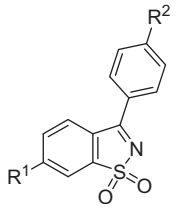


Compd	R^1	R^2	R^3	IC_{50} (μM) or %inhibition at 10 μM	
				COX-2	5-LOX
13a	H	H	H	0%	14%
13b	H	H	Br	2%	33%
17a	H	SO_2NH_2	Br	0%	91.1
17b	H	SO_2NH_2	*i*Pr	44%	42%
17c	H	SO_2NH_2	*t*Bu	21%	23%
17d	H	SO_2NH_2	Ph	31%	3.45
19	Cl	SO_2NH_2	Br	2.30	25.8
18a	H	SO_2Me	Br	1.80	13.5
18b	H	SO_2Me	Et	43%	35%
14a	H	Me	Br	14%	6.05
14b	H	CO_2H	Br	7%	2%
14c	H	CO_2Me	Br	33%	4.10
14d	H	$CONH_2$	Br	0%	15%
Rofecoxib				0.17	—
NDGA[a]				—	0.025

[a] NDGA, nordihydroguaiaretic acid.

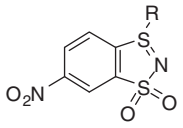
the 3-phenyl moiety of 6-nitrobenzo[1.3.2]dithiazolium ylide 1, 1-dioxide. It was found that compounds **30a–d** and **30f** containing substituents Et, *i*Pr, *t*Bu, OMe, and Ph were all potent dual COX-2/5-LOX inhibitors and more potent than compound **5** (Table 5). Among them, compound **30c** with 3-(4-*t*butylphenyl) substituent was the most potent COX-2 inhibitor (IC_{50} = 0.27 μM) and compound **30f** with 3-(4-biphenyl) substituent was the most potent 5-LOX inhibitor (IC_{50} = 0.15 μM). Apparently, bulky group

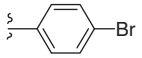
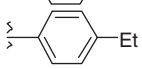
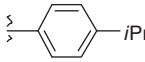
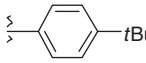
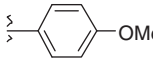
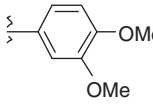
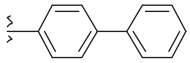
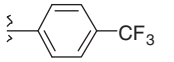
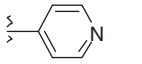
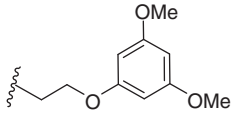
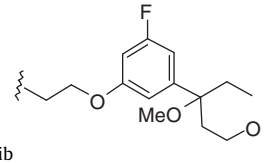
Table 4
Inhibitory activity of benzo[1.2]isothiazole 1,1-dioxides **24a–c** on human recombinant COX-2 and 5-LOX



Compd	R^1	R^2	%Inhibition at 10 μM	
			COX-2 (%)	5-LOX (%)
24a	SO_2NH_2	Et	0	8
24b	H	Br	0	11
24c	H	Me	16	9

Table 5
Inhibitory activity of 6-NO_2 derivatives on human recombinant COX-2 and 5-LOX



Compd	R	IC_{50} (μM) or %inhibition at 10 μM	
		COX-2	5-LOX
5		1.7	1.22
30a		1.70	0.18
30b		0.73	0.36
30c		0.27	0.30
30d		0.88	0.35
30e		15%	0.68
30f		0.50	0.15
30g		2.99	3.09
30h		15%	17%
30i		35%	3.70
30j		25%	25%
Rofecoxib		0.17	—
NDGA[a]		—	0.025

[a] NDGA, nordihydroguaiaretic acid.

like *t*-butyl and phenyl groups interacted with the hydrophobic pocket better than other smaller alkyl groups. In the comparison of **30d** and **30e**, an extra methoxy group on the *meta*-position of phenyl ring caused a decrease activity. The CF_3 group (**30g**) led

Table 6
Anti-inflammatory activity of compound **30c** in a carrageenan-induced rat paw edema assay

Compd	Route[a]	Dose	%Inhibition[b]
Vehicle[c]	IP	—	—
30c	IP	10 mg/kg	14%
	IP	30 mg/kg	27%
	IP	100 mg/kg	65%
Aspirin	PO	150 mg/kg	38%

[a] IP, intraperitoneal administration; PO, oral administration.
[b] Compound **30c** was administered intraperitoneally 30 min before the right hind paw received intraplantar injection of carrageenan (0.1 mL of 1% suspension). The hind paw edema was measured 3 h later. Reduction of hind paw edema by 30% or greater ($\geqslant$30%) relative to the vehicle control group indicates significant acute anti-inflammatory activity.
[c] Vehicle: 1% Tween 80/0.9% NaCl.

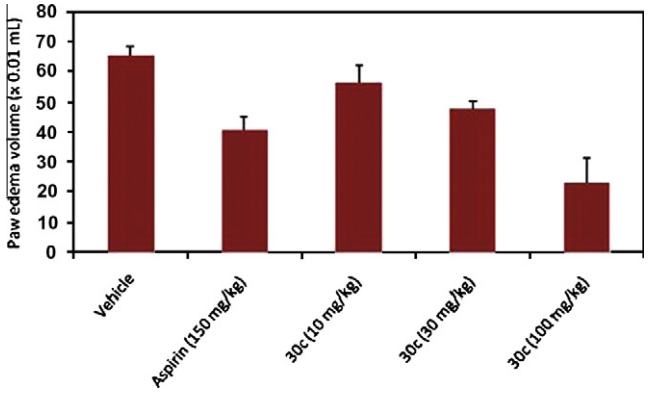


Figure 3. Effect of compound **30c** on carrageenan-induced paw edema. The vehicle, 1% Tween 80/0.9% NaCl, was tested at 5 mg/kg, associated with the net increase of paw volume of 0.65 mL. Data represent the mean ± SEM of duplicate determinations.

to a reduced inhibition on COX-2/5-LOX. Compound **30h** having 4-pyridinyl moiety at the 3-position was inactive, probably due to its polar property and the insufficiency in bulkiness.

It was reported that introduction of methoxytetrahydropyran onto a selective COX-2 inhibitors resulted in benefit on dual COX-2/5-LOX inhibitors such as **4**.[16,23] Initially, the simpler side chain was prepared from commercially available 3,5-dimethoxyphenol for the replacement of the 4-bromophenyl group on the sulfur atom by 3,5-dimethoxyphenoxyethyl group. However, **30i** exhibited decreased inhibitory activity on both COX-2 and 5-LOX. Concurrently, methoxytetrahydropyran[16] was introduced onto the phenoxyethyl group at the 3-position of 6-nitrobenzo[1.3.2]dithiazolium ylide 1,1-dioxide as compound **30j**. Compounds **30i** and **30j** were inactive to COX-2 and 5-LOX, probably resulted from the oversized side chain.

The potent dual COX-2/5-LOX inhibitor **30c** was evaluated for anti-inflammatory activity in the carrageenan-induced paw edema assay in male Wistar rats. Compound **30c** was administered intraperitoneally (IP) 30 min before carrageenan challenge. At doses of 10, 30, and 100 mg/kg, compound **30c** exhibited a dose-dependent inhibition of 14%, 27%, and 65%, respectively, relative to the vehicle group (Table 6 and Fig. 3). Compound **30c** at 100 mg/kg (IP) was associated with significant activity of 65% inhibition of the carrageenan-induced paw swelling in rats, an inhibitory activity more potent than aspirin with 35% inhibition at 150 mg/kg administered orally. This result demonstrates that benzo[1.3.2]dithiazolium ylide 1,1-dioxide **30c** was a potential lead for further development as anti-inflammatory drugs.

3. Conclusions

A series of benzo[1.3.2]dithiazolium ylide 1,1-dioxide derivatives were prepared and evaluated for the COX-2 and 5-LOX inhibitory activity. 6-Nitro substituted derivatives **30a–d** and **30f** were potent dual COX-2/5-LOX inhibitors. Compound **30c** exhibited potent in vivo anti-inflammatory activity. Our results demonstrated that benzo[1.3.2]dithiazolium ylide 1,1-dioxide derivatives represented a novel prototype for dual COX-2/5-LOX inhibitors.

4. Experimental

4.1. Chemistry

4.1.1. 2-Iodobenzene-1,4-disulfonic acid (9a)

A mixture of aniline-2,5-disulfonic acid monosodium salt (**8a**, 13.76 g, 50 mmol) and sodium carbonate (2.8 g, 26.4 mmol) in 60 mL water was stirred to a homogeneous solution, to which was added sodium nitrite (4.0 g, 56 mmol) with vigorous stirring. The solution was stirred at 0 °C for 30 min, to which was added concd HCl (10 mL) dropwise. After the precipitate of diazonium salts had appeared for 30 min, a solution of KI (10 g, 60 mmol) in H_2O (10 mL) was added to the reaction mixture. After stirring for 1 h, the reaction was warmed to room temperature and then heated to 80 °C to evolve nitrogen gas. When no further gas was generated, the solution was evaporated in reduced pressure to give a yellowish-orange solid **9a** in 72% yield. Mp 185–186 °C. ^{1}H NMR (200 MHz, D_2O) δ 8.30 (d, J = 1.8 Hz, 1H; ArH), 7.93 (d, J = 8.4 Hz, 1H; ArH), 7.72 (dd, J = 1.8, 8.4 Hz, 1H; ArH). ^{13}C NMR (50 MHz, acetone-d_6) δ 150.9, 149.9, 138.7, 128.5, 125.3, 93.3. MS (EI) m/z = 364 $[M]^+$. Anal. ($C_6H_5IO_6S_2$): C, 19.79; H, 1.38. Found: C, 19.65; H, 1.30.

4.1.2. 2-Iodobenzene-1,4-disulfonamide (11a)

To a solution of **9a** (5 g) in water (20 mL) at 0 °C was added 10 N NaOH dropwise, and then the filtrate was collected and evaporated in reduced pressure to afford **10a** (90%). Without further purification, **10a** was mixed with excessive PCl_5 (3 g) and heated to 80 °C till complete liquefaction. The resulting mixture was added portionwise to crushed ices (25 g), and the precipitate was collected and washed with ice water (10 mL). To the solid in an ice bath was then added concd NH_4OH (6 mL) dropwise, and the mixture was stirred at 0 °C to room temperature. After 3 h, the reaction mixture was partitioned with ethyl acetate (5 mL × 3), and the organic part was collected, evaporated and purified by column chromatography (silica gel; hexane/EtOAc 1:1) to afford **11a** in 54% yield. Mp 167–169 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.54 (s, 1H; ArH), 8.27 (d, J = 8.0 Hz, 1H; ArH), 8.05 (d, J = 8.0 Hz, 1H; ArH), 6.88 (br, 4H; $2SO_2NH_2$). ^{13}C NMR (100 MHz, acetone-d_6) δ 149.3, 148.0, 140.9, 140.8, 131.0, 92.3. MS (EI) m/z = 362 $[M]^+$. Anal. ($C_6H_7IN_2O_4S_2$): C, 19.90; H, 1.95; N, 7.73. Found: C, 19.84; H, 1.58; N, 7.82.

4.1.3. 2-Iodo-benzenesulfonamide (11b)

To a homogeneous solution of aniline-2-sulfonic acid (**8b**, 12.63 g, 70 mmol) and sodium carbonate (3.5 g, 33.0 mmol) in water (75 mL) was added sodium nitrite (5 g, 70 mmol). The solution was stirred at 0 °C for 30 min, to which was added concd HCl (12.5 mL) and crushed ice (25 g) portionwise. After the precipitate of diazonium salts had appeared for 30 min, to the reaction was added a solution of KI (12.5 g, 75 mmol) in H_2O (12.5 mL). After 1 h, the reaction was warmed to room temperature and then heated to 80 °C to evolve nitrogen gas. When no further gas was generated, the solution was evaporated to give a yellowish solid **9b**. To a solution of **9b** (4.7 g) in water (22 mL) at 0 °C was added

10 N NaOH (8 mL) dropwise, and then the filtrate was collected and evaporated. Without further purification, the residue was mixed with excess PCl_5 (3 g) and heated to 80 °C till complete liquidized. Subsequent reaction with concd NH_4OH (12 mL) at 0 °C for 3 h and followed by the evaporation of water afforded **11b**[24] in 68% yield. Mp 174 °C. ^{1}H NMR (200 MHz, acetone-d_6) δ 8.15–8.11 (m, 2H; ArH), 7.59–7.55 (m, 1H; ArH), 7.31–7.26 (m, 2H; ArH), 6.75 (s, 2H; SO_2NH_2). ^{13}C NMR (100 MHz, acetone-d_6) δ 145.8, 142.4, 133.1, 129.0, 128.6, 91.7. MS (EI) m/z = 283 $[M]^+$. Anal. ($C_6H_6INO_2S$): C, 25.46; H, 2.14; N, 4.95. Found: C, 25.44; H, 2.25; N, 4.74.

4.1.4. 2-Iodo-5-methylbenzenesulfonamide (11c)

To a homogeneous solution of 2-amino-5-methylbenzenesulfonic acid (**8c**, 20 g, 107 mmol) and sodium carbonate (5.98 g, 56 mmol) in water (120 mL) was added sodium nitrite (8.27 g, 119.8 mmol). The solution was stirred at 0 °C for 30 min, to which was added concd HCl (21.7 mL) and crushed ice (32 g) portionwise. After the precipitate of diazonium salts had appeared for 30 min, to the reaction was added a solution of KI (21.4 g, 128 mmol) in H_2O (25 mL). After 1 h, the reaction was warmed to room temperature and then gradually heated to 80 °C to evolve nitrogen gas. When no further gas was generated, the solution was concentrated to give a yellow solid **9c**. To a solution of **9c** in water (27 mL) at 0 °C was added 10 N NaOH (15 mL) dropwise, and then the filtrate was collected and then evaporated. Without further purification, the residue was mixed with excess PCl_5 (7.2 g) and heated to 80 °C till complete liquefaction. Subsequent reaction with concd NH_4OH (25 mL) at 0 °C for 3 h and followed by the evaporation of water afforded a pale yellow solid **11c** in 72% yield. Mp 169–170 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 7.98 (d, J = 8.0 Hz, 1H; ArH), 7.94 (d, J = 2.0 Hz, 1H; ArH), 7.12 (dd, J = 8.0, 2.0 Hz, 1H; ArH), 6.58 (s, 2H; SO_2NH_2), 2.36 (s, 3H; CH_3). ^{13}C NMR (100 MHz, acetone-d_6) δ 146.4, 142.8, 139.6, 134.4, 130.3, 88.1, 20.7. MS (EI) m/z = 297 $[M]^+$. Anal. ($C_7H_8INO_2S$): C, 28.30; H, 2.71; N, 4.71. Found: C, 28.42; H, 2.56; N, 4.78.

4.1.5. 4-Bromobenzene-1,3-disulfonamide (16a)

Bromobenzene (**15a**, 5 mL, 47.8 mmol) in chlorosulfonic acid (15 mL) was heated to 150 °C and the reaction was stirred for 3 h. The resulting mixture was cooled in ice bath and then added to ice/water (30 g/5 mL) dropwise. Afterward, the solid was filtered, washed with cold water (6 mL), and dried in reduced pressure. Subsequent treatment of the solid with concd NH_4OH (15 mL) at 0 °C for 3 h and followed by the evaporation of water afforded **16a** in 75% yield. Mp 243 °C (lit:[25] 243–245 °C). ^{1}H NMR (200 MHz, acetone-d_6) δ 8.53 (d, J = 2.0 Hz, 1H; ArH), 8.06–7.92 (m, 2H; ArH), 6.96 (br, 2H; SO_2NH_2), 6.93 (br, 2H; SO_2NH_2). ^{13}C NMR (50 MHz, acetone-d_6) δ 143.4, 143.0, 135.8, 130.1, 126.9, 123.0.

4.1.6. 2-Bromo-5-methylsulfonylbenzenesulfonamide (16b)

4-Bromophenyl methyl sulfone (**15b**, 2.5 g) in chlorosulfonic acid (5 mL) was heated to 150 °C and stirred for 3 h. The resulting solution was cooled to 0 °C, which was then added to ice/water (10 g/4 mL) dropwise. The precipitate was washed with cold water (3 mL), and dried. Subsequent treatment of the solid with concd NH_4OH (11 mL) at 0 °C for 3 h afforded the product, which was purified by flash column chromatography on a silica gel column with hexane/EtOAc (1:2) to provide a pale yellowish solid **16b** in 82% yield. Mp 238–240 °C. ^{1}H NMR (200 MHz, acetone-d_6) δ 8.56–8.52 (m, 1H; ArH), 8.15–7.92 (m, 2H; ArH), 7.04 (br, 2H; SO_2NH_2), 3.25 (s, 3H; SO_2CH_3). ^{13}C NMR (50 MHz, acetone-d_6) δ 144.2, 141.5, 136.9, 132.1, 128.8, 125.7, 43.7. MS (EI) m/z = 313 $[M]^+$. Anal. ($C_7H_8BrNO_4S_2$): C, 26.76; H, 2.57; N, 4.46. Found: C, 26.85; H, 2.58; N, 4.26.

4.1.7. 2-Bromo-4-chlorobenzene-1,5-disulfonamide (16c)

To a solution of 2,4-disulfamyl-5-chloroaniline (**15c**, 3 g, 10 mmol) in acetonitrile (120 mL) at 40 °C was slowly added concd sulfuric acid (13.5 mL). After 30 min, to the solution was added sodium nitrite (1.32 g, 19.1 mmol) portionwise. The solution was stirred at 0 °C for 1 h, to which was then added a solution of $CuBr_2$ (2.46 g, 11 mmol) in water (2 mL) in portions. After 1.5 h, the reaction mixture was warmed to room temperature and then heated to 80 °C to evolve nitrogen gas. When no further gas was generated, the solution was concentrated. Purification by flash column chromatography on a silica gel column with hexane/EtOAc (1:1) provided a pale yellowish solid **16c** in 62% yield. Mp 291–292 °C (lit:[25] 290 °C). ^{1}H NMR (400 MHz, acetone-d_6) δ 8.67 (s, 1H; ArH), 8.36 (s, 1H; ArH), 7.03 (br, 4 H; SO_2NH_2). ^{13}C NMR (100 MHz, acetone-d_6) δ 145.0, 144.1, 140.7, 134.0, 128.8, 96.7.

4.1.8. 2,4-Disulfamyltoluene (21)

A solution of *p*-toluene sulfonic acid (**20**, 1 g) in chlorosulfonic acid (5 mL) was heated to 150 °C for 6 h. The solution was then poured into ice/water (6 g/3 mL) portionwise, and the precipitate was filtered, washed with cold water (3 mL), and evaporated. Subsequent treatment of the solid with concd NH_4OH (13 mL) at 0 °C for 3 h afforded the product, which was then purified by flash column chromatography on a silica gel column with hexane/EtOAc (1:3) to provide **21** as an off-white solid in 58% yield. Mp 198 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.42 (d, J = 2.0 Hz, 1H; ArH), 7.95 (dd, J = 8.0, 2.0 Hz, 1H; ArH), 7.57 (d, J = 8.0 Hz, 1H; ArH), 6.79 (s, 2H; SO_2NH_2), 6.72 (s, 2H; SO_2NH_2), 2.74 (s, 3H; CH_3).^{13}C NMR (100 MHz, acetone-d_6) δ 143.1, 142.8, 141.4, 133.6, 129.7, 126.1, 19.9. MS (EI) m/z = 250 $[M]^+$. Anal. ($C_7H_{10}N_2O_4S_2$): C, 33.59; H, 4.03; N, 11.19. Found: C, 33.48; H, 4.18; N, 11.35.

4.1.9. 2-(4-Bromophenylsulfanyl)-5-(hydroxycarbony) benzenesulfonamide (26)

A mixture of **25** (5 g, 14.2 mmol) and $KMnO_4$ (7.34 g, 46.5 mmol) in 5% NaOH (123 mL) was heated at reflux for 30 min. The resulting mixture was filtered, and the filtrate was acidified to pH 2 with concd HCl. After partition with CH_2Cl_2/MeOH (18 mL/2 mL), the organic layer was evaporated to give **26** as a pale yellow solid in 66% yield. Mp 272–274 °C. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.74 (d, J = 1.6 Hz, 1H; ArH), 8.41 (d, J = 8.0 Hz, 1H; ArH), 8.31 (dd, J = 8.0, 1.6 Hz, 1H; ArH), 7.84 (dd, J = 7.0, 1.9 Hz, 2H; ArH), 7.64–7.67 (m, 2H; ArH). ^{13}C NMR (100 MHz, methanol-d_4) δ 173.0, 170.8, 144.8, 142.9, 141.1, 139.6, 134.2, 133.1, 132.0, 130.9, 129.5. MS (EI) m/z = 387 $[M]^+$. Anal. ($C_{13}H_{10}BrNO_4S_2$): C, 40.22; H, 2.60; N, 3.61. Found: C, 40.54; H, 2.52; N, 3.87.

4.1.10. Synthesis of 4-(3-Fluoro-5-hydroxyphenyl)-4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (31b)

4.1.10.1. (3-Benzyloxy-5-fluorophenyl) bromide. NaH (60% dispersion in oil, 1.5 mmol) was added portionwise to a stirred solution of benzyl alcohol (7.09 g, 65.6 mmol) in dry THF (50 mL). After 1 h, 1-bromo-3,5-difluorobenzene (10.55 g, 54.67 mmol) was added at a slow rate to maintain the temperature below 40 °C. The reaction mixture was stirred at room temperature for 4 h, added to water (25 mL), and extracted with EtOAc (7.5 mL × 2). The combined organic phase was evaporated, and the residue was purified by flash column chromatography over silica gel (hexane as the eluent) to give the desired bromide as colorless oil in 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.45 (m, 5H; ArH), 6.99 (s, 1H; ArH), 6.91 (d, J = 8.0 Hz, 1H; ArH), 6.67 (d, J = 8.0 Hz, 1H; ArH), 5.02 (s, 2H; CH_2), consistent with the reported data;[19] ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 128.6, 128.3, 127.4, 114.29, 114.26, 111.8, 111.6, 101.9, 101.7, 70.4.

4.1.10.2. 4-(3-Benzyloxy-5-fluorophenyl)-4-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran. To a stirred solution of (3-benzyloxy-5-fluorophenyl) bromide (3.94 g, 14 mmol) in dry THF (20 mL) was added butyl lithium (5.6 mL, 2.5 M solution in hexanes, 14 mmol) dropwise over 1 h to maintain the reaction temperature below −70 °C. After stirring for an additional 1 hr at −70 °C, a clear solution of 3,4,5,6-tetrahydro-2*H*-pyran-4-one (1.3 mL, 14 mmol) in dry THF (3 mL) was added dropwise over 10 min. The reaction mixture was maintained at −70 °C for 1 h and then allowed to warm to 0 °C over 2 h. To the mixture was added saturated NH_4C1 (10 mL), and the mixture was then partitioned with ethyl acetate (15 mL). The organic phase was collected, evaporated, and purified by flash column chromatography over silica gel with hexane/EtOAc (3:1) to give the desired product as oil in 52% yield. ^{1}H NMR (400 MHz, acetone-d_6) δ 7.46–7.48 (m, 2H; ArH), 7.30–7.40 (m, 3H; ArH), 7.04 (d, J = 0.8 Hz, 1H; ArH), 6.89 (dd, J = 8.4, 0.8 Hz, 1H; ArH), 6.67 (s, 1H; ArH), 5.13 (s, 2H; CH_2), 4.18 (s, 1H; OH), 4.01–4.07 (m, 2H; CH_2), 3.84–3.89 (m, 2H; CH_2), 3.72–3.76 (m, 2H; CH_2), 1.56–1.60 (m, 2H; CH_2), consistent with the reported data;[19] ^{13}C NMR (100 MHz, acetone-d_6) δ 137.7, 129.0, 128.5, 128.2, 108.4, 104.8, 104.6, 100.9, 100.6, 70.5, 63.9, 60.3, 39.2, 20.6.

4.1.10.3. 4-(3-Benzyloxy-5-fluorophenyl)-4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran. To a solution of 4-(3-benzyloxy-5-fluorophenyl)-4-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran (0.66 g, 2.18 mm ol) in THF (40 mL) at 5 °C was added NaH (60% dispersion in oil, 0.11 g, 4.41 mmol) portionwise. After 1 h, to the reaction was added methyl iodide (0.41 mL, 6.54 mmol) over 10 min. The reaction mixture was allowed to warm to room temperature for 4 h, poured into water (10 mL), and extracted with EtOAc (15 mL × 3). The combined organic layer was washed with water (5 mL × 2) and brine (3 mL), and then evaporated to give the product as a yellowish solid, which was used without further purification.

4.1.10.4. 4-(3-Fluoro-5-hydroxyphenyl)-4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (31b). To a solution of 4-(3-benzyloxy-5-fluorophenyl)-4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (0.5 g, 1.58 mmol) in methanol (6 mL) was added 10% palladium on charcoal (0.05 g) in a closed system, followed by the duplicate degassing and refilling of hydrogen. After stirring under hydrogen for 1 h, the reaction mixture was filtered through Celite, and the filtrate was concentrated and then purified by flash column chromatography over silica gel with hexane/EtOAc (2:1) to give **31b** as a white solid in 85% yield. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.77 (s, 1H; OH), 6.73–6.72 (m, 1H; ArH), 6.65–6.62 (m, 1H; ArH), 6.52–6.48 (m, 1H; ArH), 3.758–3.68 (m, 4H; CH_2), 2.96 (s, 3H; CH_3), 1.91–1.88 (m, 4H; CH_2), consistent with the reported data;[19] ^{13}C NMR (100 MHz, acetone-d_6) δ 163.3, 109.8, 104.6, 104.4, 102.2, 101.9, 75.4, 63.7, 49.8, 35.8.

4.1.11. 2-(3,5-Dimethoxyphenoxy)ethyl bromide (32a)

A mixture of **31a** (8 g, 51.9 mmol), 1,2-dibromoethane (32.17 g, 171.2 mmol) and potassium carbonate (14.34 g, 103.8 mmol) in acetone (50 mL) was brought to reflux for 24 h. The resulting mixture was evaporated, washed with water, and partitioned with ethyl acetate (60 mL). The organic phase was then collected and concentrated to give **32a** as a yellowish liquid, which was used without further purification.

4.1.12. 4-(3-(2-Bromoethoxy)-5-fluorophenyl)-4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (32b)

A mixture of **31b** (2.3 g, 10.2 mmol), 1,2-dibromoethane (6.3 g, 33.5 mmol) and potassium carbonate (2.81 g, 20.3 mmol) in acetone (15 mL) was heated at reflux for 24 h. The resulting mixture was evaporated and then purified by flash column chromatography over silica gel with hexane/EtOAc (3:1) to give **32b** as a yellowish liquid in 38% yield. ^{1}H NMR (400 MHz, acetone-d_6) δ 6.84 (d, J = 2.0 Hz, 1H; ArH), 6.80–6.77 (m, 1H; ArH), 6.71–6.67 (m, 1H; ArH), 4.41 (t, J = 5.6 Hz, 2H; CH_2), 3.78 (t, J = 5.6 Hz, 2H; CH_2), 3.75–3.71 (m, 4H; CH_2), 2.97 (s, 3H; CH_3), 2.05–1.91 (m, 4H; CH_2); ^{13}C NMR (100 MHz, acetone-d_6) δ 165.7, 163.3, 149.8, 149.7, 109.5, 106.2, 101.7, 75.6, 69.1, 63.8, 50.0, 35.8.MS (EI) m/z = 332 $[M]^+$. Anal. Calcd ($C_{14}H_{18}BrFO_3$): C, 50.47; H, 5.45. Found: C, 50.73; H, 5.25.

4.1.13. 2-(3,5-Dimethoxyphenoxy)ethanethiol (33a)

According to the reported procedure,[17] to a solution of **32a** (5.43 g, 20.8 mmol) in 95% ethanol (15 mL) was added thiourea (1.9 g, 25 mmol), and the reaction was heated at reflux for 3 h. Then, 2.5 N NaOH (12.5 mL, 1.5 equiv) was added into the mixture at reflux for 2 h. The resulting mixture was concentrated to a small volume and then acidified to pH 1 by 10% HCl. The mixture was partitioned with ether (45 mL), and the organic phase was then concentrated to give **33a** as a yellowish liquid with an irritant odor in 57% yield, which was used without further purification.

4.1.14. 4-(3-Fluoro-5-(2-mercaptoethoxy)phenyl)-4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (33b)

To a solution of **32b** (1.61 g, 4.83 mmol) in 95% ethanol (10 mL) was added thiourea (0.44 g, 5.8 mmol), and the reaction was heated at reflux for 3 h. Sodium hydroxide solution (2.5 *N*, 1.5 equiv) was then added into the reaction mixture, and the reaction was heated at reflux for additional 2 h. The resulting mixture was evaporated to a small volume and acidified to pH 1 by 10% HCl. The mixture was partitioned with ether (20 mL), and the organic phase was concentrated to give **33b** as a yellowish liquid with an irritant odor in 42% yield, which was used without further purification.

4.2. General procedures for cross-coupling aryl iodide/bromide with thiols: from aryl iodide

Treatment of aryl iodide (1 mmol) with various aryl thiol (1.1 mmol) in the presence of copper iodide (0.1 mmol), neocuproine (0.1 mmol), and potassium phosphate (1.5 mmol) in toluene (10 mL) at reflux under N_2 for 8 h resulted in a sticky mixture. The resulting mixture was neutralized by 1 N HCl (1.5 mL) and then evaporated. The residue was extracted with ethyl acetate (15 mL × 3), and the organic layers were concentrated to give 2-aryl- or 2-alkylsulfanylbenzenesulfonamide. *From aryl bromide:* A mixture of aryl bromide (1 mmol), aryl thiol (1.1 mmol), and K_2CO_3 (2 mmol) in ethanol (15 mL) was heated to reflux. After 24 h, the resulting mixture was neutralized to pH 7 with saturated NH_4Cl and then evaporated. The residue was extracted with ethyl acetate (15 mL × 3), and the organic layers were concentrated to give 2-aryl- or 2-alkylsulfanylbenzenesulfonamide.

4.3. General procedures for intramolecular cyclization 2-aryl- or 2-alkylsulfanylbenzenesulfonamide

To 2-alkyl- or 2-arylsulfanylbenzenesulfonamide in methanol/water (15 mL/5 mL) was added a solution of bromine (1 mmol) in methanol (1 mL), and the reaction mixture was stirred at ambient temperature for 30 min. The precipitate was collected and washed with H_2O to give the cyclized product. Otherwise the resulting solution was neutralized with saturated $NaHCO_3$ (3 mL), evaporated, and extracted with ethyl acetate (10 mL × 3), and the organic phase was concentrated. Purification by flash chromatography on a silica gel column with hexane/EtOAc (1:1) provided the desired product. After recrystallization in acetone/hexane, desired products were obtained in 51–65% yields (two steps from iodo/bromobenzenesulfonamides).

4.3.1. 5-Aminosulfonyl-3-(4-bromophenyl)benzo[1.3.2] dithiazolium ylide 1,1-dioxide (7)

A white solid in 62% yield. Mp 301 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.61 (d, J = 1.1 Hz, 1H; ArH), 8.40 (dd, J = 8.0, 1.1 Hz, 1H; ArH), 8.24 (d, J = 8.0 Hz, 1H; ArH), 7.96 (dd, J = 6.8, 2.0 Hz, 2H; ArH), 7.82 (dd, J = 6.8, 2.0 Hz, 2H; ArH), 6.97 (s, 2H; SO_2NH_2). ^{13}C NMR (100 MHz, acetone-d_6) δ 150.0, 139.7, 138.3, 136.7, 134.2, 132.8 130.3, 128.4, 124.8, 124.6. MS (FAB) m/z = 421 $[M+H]^+$. Anal. ($C_{12}H_9BrN_2O_4S_3$): C, 34.21; H, 2.15; N, 6.65. Found: C, 34.05; H, 2.51; N, 6.55.

4.3.2. 5-Aminosulfonyl-3-(3-bromophenyl)benzo[1.3.2] dithiazolium ylide 1,1-dioxide (12a)

A yellow-brown solid in 53% yield. Mp 144 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.19 (d, J = 8.4 Hz, 1H; ArH), 7.89–7.86 (m, 1H; ArH), 7.72–7.69 (m, 2H; ArH), 7.58–7.57 (m, 1H; ArH), 7.53–7.52 (m, 1H; ArH), 7.44–7.41 (m, 1H; ArH), 6.77 (s, 2H; SO_2NH_2). ^{13}C NMR (100 MHz, acetone-d_6) δ 147.9, 137.4, 135.7, 132.5, 132.3, 131.9, 129.8, 129.4, 129.3, 126.3, 124.5, 123.2. MS (EI) m/z = 420 $[M]^+$. Anal. ($C_{12}H_9BrN_2O_4S_3$): C, 34.21; H, 2.15; N, 6.65. Found: C, 33.96; H, 2.09; N, 6.66.

4.3.3. 5-Aminosulfonyl-3-(4-fluorophenyl)benzo[1.3.2] dithiazolium ylide 1,1-dioxide (12b)

A pale brown solid in 60% yield. Mp 279–281 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.57 (d, J = 1.2 Hz, 1H; ArH), 8.40 (dd, J = 8.0, 1.4 Hz, 1H; ArH), 8.25 (d, J = 8.0 Hz, 1H; ArH), 8.11–8.06 (m, 2H; ArH), 7.44–7.38 (m, 2H; ArH), 6.97 (s, 2H; SO_2NH_2). ^{13}C NMR (100 MHz, acetone-d_6) δ 149.9, 139.7, 136.9, 132.6, 131.7, 131.5, 124.7, 124.5, 118.5, 118.0. MS (EI) m/z = 360 $[M]^+$. Anal. ($C_{12}H_9FN_2O_4S_3$): C, 39.99; H, 2.52; N, 7.77. Found: C, 39.90; H, 2.63; N, 7.47.

4.3.4. 5-Aminosulfonyl-3-(4-chlorophenyl)benzo[1.3.2] dithiazolium ylide 1,1-dioxide (12c)

A white solid in 59% yield. Mp 278 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.63 (d, J = 1.5 Hz, 1H; ArH), 8.41 (dd, J = 8.0, 1.5 Hz, 1H; ArH), 8.25 (d, J = 8.0 Hz, 1H; ArH), 8.04 (dd, J = 6.7, 1.9 Hz, 2H; ArH), 7.67 (dd, J = 6.7, 1.9 Hz, 2H; ArH), 7.04 (s, 2H; SO_2NH_2). ^{13}C NMR (100 MHz, acetone-d_6) δ 139.8, 139.5, 137.6, 136.7, 132.6, 131.1, 130.1, 125.7, 124.7, 124.5. MS (FAB) m/z = 377 $[M+H]^+$. Anal. ($C_{12}H_9ClN_2O_4S_3$): C, 38.24; H, 2.41; N, 7.43. Found: C, 37.90; H, 2.13; N, 7.46.

4.3.5. 5-Aminosulfonyl-3-(4-methylphenyl)benzo[1.3.2] dithiazolium ylide 1,1-dioxide (12d)

A pale yellow solid in 65% yield. Mp 269 °C. ^{1}H NMR (200 MHz, acetone-d_6) δ 8.53–8.21 (m, 3H; ArH), 7.87 (dd, J = 8.0, 6.0 Hz, 2H; ArH), 7.42 (d, J = 8.0 Hz, 2H; ArH), 7.09 (s, 2H; SO_2NH_2), 2.38 (s, 1H; CH_3). ^{13}C NMR (100 MHz, acetone-d_6) δ 167.1, 131.1, 130.5, 129.7, 129.3, 126.5, 126.3, 124.4, 124.2, 116.1, 21.1. MS (EI) m/z = 356 $[M]^+$. Anal. ($C_{13}H_{12}N_2O_4S_3$): C, 43.80; H, 3.39; N, 7.86. Found: C, 43.46; H, 3.56; N, 8.18.

4.3.6. 5-Aminosulfonyl-3-(4-ethylphenyl)benzo[1.3.2] dithiazolium ylide 1,1-dioxide (12e)

A white solid in 60% yield. Mp 277 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.52 (s, 1H; ArH), 8.39 (dd, J = 8.0, 1.2 Hz, 1H; ArH), 8.23 (d, J = 8.0 Hz, 1H; ArH), 7.91–7.88 (m, 2H; ArH), 7.46 (d, J = 8.4 Hz, 2H; ArH), 6.98 (s, 2H; SO_2NH_2), 2.70 (q, J = 7.6 Hz, 2H; CH_2), 1.20 (d, J = 7.6 Hz, 3H; CH_3). ^{13}C NMR (100 MHz, acetone-d_6) δ 151.4, 149.8, 140.0, 137.2, 135.6, 132.5, 130.6, 128.8, 124.7, 124.5, 28.8, 15.3. MS (EI) m/z = 370. $[M]^+$. Anal. ($C_{14}H_{14}N_2O_4S_3$): C, 45.39; H, 3.81; N, 7.56. Found: C, 45.19; H, 4.06; N, 7.53.

4.3.7. 5-Aminosulfonyl-3-(4-isopropylphenyl)benzo[1.3.2] dithiazolium ylide 1,1-dioxide (12f)

A pale yellow solid in 55% yield. Mp 245 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.53 (s, 1H; ArH), 8.40 (dd, J = 8.0, 1.0 Hz, 1H; ArH), 8.23 (d, J = 8.0 Hz, 1H; ArH), 7.91–7.88 (m, 2H; ArH), 7.50 (d, J = 8.4 Hz, 2H; ArH), 7.01 (s, 2H; SO_2NH_2), 2.99 (septet, J = 6.9 Hz, 1H; CH), 1.25 (d, J = 6.9 Hz, 6H; CH_3). ^{13}C NMR (100 MHz, acetone-d_6) δ 155.7, 149.8, 139.9, 137.0, 135.5, 132.4, 129.1, 128.8, 124.6, 124.4, 34.6, 23.6. MS (EI) m/z = 384 $[M]^+$. Anal. ($C_{15}H_{16}N_2O_4S_3$): C, 46.86; H, 4.19; N, 7.29. Found: C, 46.77; H, 4.21; N, 7.30.

4.3.8. 5-Aminosulfonyl-3-(4-*tert*-butylphenyl)benzo[1.3.2] dithiazolium ylide 1,1-dioxide (12g)

A brown solid in 52% yield. Mp 229–230 °C. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.36 (d, J = 1.2 Hz, 1H; ArH), 8.31 (dd, J = 8.0, 1.2 Hz, 1H; ArH), 8.17 (d, J = 1.2 Hz, 1H; ArH), 7.74 (dd, J = 6.8, 2.0 Hz, 2H; ArH), 7.58 (dd, J = 6.8, 2.0 Hz, 2H; ArH), 1.25 (s, 9H; CH_3). ^{13}C NMR (100 MHz, acetone-d_6) δ 157.7, 149.6, 139.6, 136.7, 134.9, 132.3, 128.3, 127.9, 124.4, 124.3, 35.4, 30.8. MS (EI) m/z = 398 $[M]^+$. Anal. ($C_{16}H_{18}N_2O_4S_3$): C, 48.22; H, 4.55; N, 7.03. Found: C, 47.99; H, 4.60; N, 7.15.

4.3.9. 5-Aminosulfonyl-3-(4-trifluoromethylphenyl)benzo [1.3.2]dithiazo-lium ylide 1,1-dioxide (12h)

A white solid in 64% yield. Mp 277–278 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.71 (d, J = 1.2 Hz, 1H; ArH), 8.42 (dd, J = 8.0, 1.1 Hz, 1H; ArH), 8.29–7.99 (m, 3H; ArH), 7.98 (d, J = 8.4 Hz, 2H; ArH), 6.98 (s, 2H; SO_2NH_2). ^{13}C NMR (100 MHz, acetone-d_6) δ 136.3, 132.9, 132.8, 128.9, 127.9, 127.9, 125.7, 124.9, 124.7, 106.4, 98.1. MS (EI) m/z = 410 $[M]^+$. Anal. ($C_{13}H_9F_3N_2O_4S_3$): C, 38.04; H, 2.21; N, 6.83. Found: C, 37.93; H, 2.10; N, 6.47.

4.3.10. 5-Aminosulfonyl-3-(4-methoxyphenyl)benzo[1.3.2] dithiazolium ylide 1,1-dioxide (12i)

A white solid in 62% yield. Mp 265 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.45 (d, J = 1.1 Hz, 1H; ArH), 8.40 (dd, J = 8.0, 1.1 Hz, 1H; ArH), 8.24 (d, J = 8.0 Hz, 1H; ArH), 7.91–7.87 (m, 2H; ArH), 7.15–7.10 (m, 2H; ArH), 6.96 (s, 2H; SO_2NH_2), 3.86 (s, 3H; OCH_3). ^{13}C NMR (100 MHz, acetone-d_6) δ 164.7, 149.7, 140.1, 137.5, 132.4, 131.4, 128.8, 124.5, 124.4, 116.5, 56.2. MS (EI) m/z = 372 $[M]^+$. Anal. ($C_{13}H_{12}N_2O_5S_3$): C, 41.92; H, 3.25; N, 7.52. Found: C, 41.73; H, 3.32; N, 7.33.

4.3.11. 5-Aminosulfonyl-3-(2,3-difluorophenyl)benzo[1.3.2] dithiazolium ylide 1,1-dioxide (12j)

A white solid in 52% yield. Mp 196 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.84 (s, 1H; ArH), 8.26–8.20 (m, 2H; ArH), 7.36 (m, 1H; ArH), 7.17–7.05 (m, 4H; ArH and SO_2NH_2). ^{13}C NMR (100 MHz, acetone-d_6) δ 148.9, 144.8, 131.3, 131.2, 130.4, 130.0, 125.2, 124.8, 113.4, 113.2, 105.6, 105.3. MS (EI) m/z = 378 $[M]^+$. Anal. ($C_{12}H_8F_2N_2O_4S_3$): C, 38.09; H, 2.13; N, 7.40. Found: C, 37.97; H, 2.10; N, 7.37.

4.3.12. 5-Aminosulfonyl-3-(2,3-dichlorophenyl)benzo[1.3.2] dithiazolium ylide 1,1-dioxide (12k)

A brownish solid in 52% yield. Mp 193 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.75 (d, J = 1.2 Hz, 1H; ArH), 8.48 (dd, J = 8.0, 1.2 Hz, 1H; ArH), 8.26 (d, J = 8.0 Hz, 1H; ArH), 7.82 (d, J = 2.0 Hz, 1H; ArH), 7.70 (d, J = 8.8 Hz, 1H; ArH), 7.56 (dd, J = 8.8, 2.0 Hz, 1H; ArH), 7.13 (s, 2H; SO_2NH_2). ^{13}C NMR (100 MHz, acetone-d_6) δ 149.9, 140.2, 140.0, 136.0, 135.3, 134.7, 133.1, 131.3, 130.9, 130.0, 124.9, 124.7. MS (EI) m/z = 410 $[M]^+$. Anal. ($C_{12}H_8Cl_2N_2O_4S_3$): C, 35.04; H, 1.96; N, 6.81. Found: C, 35.01; H, 1.93; N, 6.76.

4.3.13. 5-Aminosulfonyl-3-(2,3-dimethylphenyl)benzo[1.3.2] dithiazolium ylide 1,1-dioxide (12l)

A a pale yellow solid in 64% yield. Mp 230 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.73 (d, J = 1.2 Hz, 1H; ArH), 8.23–8.18 (m, 2H; ArH), 7.15 (s, 1H; ArH), 7.05–7.03 (m, 2H; ArH), 6.76 (s, 2H; SO_2NH_2), 2.64 (s, 3H; CH_3), 2.30 (s, 3H; CH_3). ^{13}C NMR (100 MHz, acetone-d_6) δ 171.8, 142.0, 135.1, 132.6, 130.4, 129.6, 129.5, 128.5, 127.4, 125.5, 106.5, 98.2, 21.1, 19.2. MS (EI) m/z = 370 $[M]^+$. Anal. ($C_{14}H_{14}N_2O_4S_3$): C, 45.39; H, 3.81; N, 7.56. Found: C, 45.75; H, 3.90; N, 7.33.

4.3.14. 5-Aminosulfonyl-3-(3,4-dichlorophenyl)benzo[1.3.2] dithiazolium ylide 1,1-dioxide (12m)

A pale yellow solid in 59% yield. Mp 198–200 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.68–8.65 (m, 1H; ArH), 8.41 (d, J = 9.6 Hz, 1H; ArH), 8.28–8.26 (m, 1H; ArH), 8.26–8.17 (m, 1H; ArH), 8.00–7.99 (m, 1H; ArH), 7.84–7.72 (m, 1H; ArH), 6.99 (s, 2H; SO_2NH_2). ^{13}C NMR (100 MHz, acetone-d_6) δ 136.3, 133.0, 132.8, 132.2, 130.0, 129.9, 127.91, 127.88, 126.0, 124.8, 124.6, 123.9. MS (EI) m/z = 410 $[M]^+$. Anal. ($C_{12}H_8Cl_2N_2O_4S_3$): C, 35.04; H, 1.96; N, 6.81. Found: C, 34.81; H, 2.29; N, 6.49.

4.3.15. 5-Aminosulfonyl-3-(3,4-dimethylphenyl)benzo[1.3.2] dithiazolium ylide 1,1-dioxide (12n)

A yellow-brown solid in 55% yield. Mp 184 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.54 (d, J = 1.2 Hz, 1H; ArH), 8.39 (dd, J = 8.0, 1.2 Hz, 1H; ArH), 8.21 (d, J = 8.0 Hz, 1H; ArH), 7.79 (d, J = 1.6 Hz, 1H; ArH), 7.70 (dd, J = 8.4, 1.6 Hz, 1H; ArH), 7.35 (d, J = 8.4 Hz, 1H; ArH), 7.01 (s, 2H; SO_2NH_2), 2.29 (s, 3H; CH_3), 2.24 (s, 3H; CH_3). ^{13}C NMR (100 MHz, acetone-d_6) δ 144.0, 140.1, 137.2, 135.4, 132.3, 132.0, 129.2, 126.0, 125.7, 124.5, 124.4, 123.9, 19.7, 19.6. MS (EI) m/z = 370 $[M]^+$. Anal. ($C_{14}H_{14}N_2O_4S_3$): C, 45.39; H, 3.81; N, 7.56. Found: C, 45.16; H, 3.77; N, 7.66.

4.3.16. 5-Aminosulfonyl-3-(3,4-dimethoxyphenyl)benzo[1.3.2] dithiazolium ylide 1,1-dioxide (12o)

A pale yellow solid in 53% yield. Mp 261 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.12 (d, J = 9.6 Hz, 1H; ArH), 7.80 (dd, J = 8.0, 2.0 Hz, 1H; ArH), 7.48 (d, J = 2.0 Hz, 1H; ArH), 7.33 (s, 1H; ArH), 7.29 (s, 1H; ArH), 6.81 (s, 1H; ArH), 6.71 (s, 2H; SO_2NH_2), 3.92 (s, 3H; OCH_3), 3.81 (s, 3H; OCH_3). ^{13}C NMR (100 MHz, acetone-d_6) δ 152.6, 150.5, 148.4, 139.3, 129.9, 126.8, 125.8, 123.9, 123.0, 121.4, 120.3, 117.6, 56.6, 56.5. MS (EI) m/z = 338 [M-2×MeOH]$^+$. Anal. ($C_{14}H_{14}N_2O_6S_3$): C, 41.78; H, 3.51; N, 6.96. Found: C, 41.81; H, 3.45; N, 6.86.

4.3.17. 3-Phenylbenzo[1.3.2]dithiazolium ylide 1,1-dioxide (13a)

A white solid in 64% yield. Mp 196 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.09–8.03 (m, 1H; ArH), 7.97–7.86 (m, 4H; ArH), 7.64–7.58 (m, 3H; ArH). ^{13}C NMR (100 MHz, acetone-d_6) δ 139.6, 137.1, 135.6, 134.4, 134.1, 133.7, 130.9, 127.9, 126.3, 123.7. MS (EI) m/z = 263 $[M]^+$. Anal. ($C_{12}H_9NO_2S_2$): C, 54.73; H, 3.44; N, 5.32. Found: C, 54.52; H, 3.63; N, 5.33.

4.3.18. 3-(4-Bromophenyl)benzo[1.3.2]dithiazolium ylide 1,1-dioxide (13b)

A pale yellow solid in 61% yield. Mp 170–173 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.13 (d, J = 8.0 Hz, 1H; ArH), 8.04 (d, J = 8.0 Hz, 1H; ArH), 7.95–7.88 (m, 4H; ArH), 7.80–7.77 (m, 2H; ArH). ^{13}C NMR (100 MHz, acetone-d_6) δ 137.0, 135.2, 134.5, 134.3, 134.0, 129.8, 127.9, 126.4, 124.8, 123.8. MS (EI) m/z = 341 $[M]^+$. Anal. ($C_{12}H_8BrNO_2S_2$): C, 42.11; H, 2.36; N, 4.09. Found: C, 42.32; H, 2.73; N, 4.10.

4.3.19. 6-Aminosulfonyl-3-(4-bromophenyl)benzo[1.3.2] dithiazolium ylide 1,1-dioxide (17a)

A pale yellow solid in 62% yield. Mp 299 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.40 (d, J = 1.2 Hz, 1H; ArH), 8.37–8.32 (m, 2H; ArH), 7.93 (dd, J = 6.8, 2.0 Hz, 2H; ArH), 7.84–7.80 (m, 2H; ArH), 7.03 (s, 2H; SO_2NH_2). ^{13}C NMR (100 MHz, acetone-d_6) δ 143.7, 138.6, 138.3, 137.9, 134.2, 132.0, 130.0, 128.4, 127.8, 121.5. MS (EI) m/z = 420 $[M]^+$. Anal. ($C_{12}H_9BrN_2O_4S_3$): C, 34.21; H, 2.15; N, 6.65. Found: C, 33.87; H, 2.40; N, 6.44.

4.3.20. 6-Aminosulfonyl-3-(4-isopropylphenyl)benzo[1.3.2] dithiazolium ylide 1,1-dioxide (17b)

A white solid in 61% yield. Mp 241–242 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.40 (d, J = 0.8 Hz, 1H; ArH), 8.32–8.25 (m, 2H; ArH), 7.88 (d, J = 8.4 Hz, 2H; ArH), 7.50 (d, J = 8.4 Hz, 2H; ArH), 7.02 (br, 2H; SO_2NH_2), 2.89 (septet, J = 6.8 Hz, 1H; CH), 1.22 (d, J = 6.8 Hz, 6H; CH_3). ^{13}C NMR (100 MHz, acetone-d_6) δ 155.8, 152.7, 152.2, 149.1, 131.8, 129.2, 128.6, 127.6, 121.4, 109.7, 34.7, 23.7. MS (ESI) m/z = 383 $[M-H]^+$. Anal. ($C_{15}H_{16}N_2O_4S_3$): C, 46.86; H, 4.19; N, 7.29. Found: C, 46.77; H, 3.97; N, 7.23.

4.3.21. 6-Aminosulfonyl-3-(4-*tert*-butylphenyl)benzo[1.3.2] dithiazolium ylide 1,1-dioxide (17c)

A yellowish solid in 62% yield. Mp 173–175 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.39 (s, 1H; ArH), 8.28–8.20 (m, 2 Hz; ArH), 7.86–7.72 (m, 2H; ArH), 7.63–7.49 (m, 2H; ArH), 7.02 (br, 2H; SO_2NH_2), 1.92 (s, 9H; CH_3). ^{13}C NMR (100 MHz, acetone-d_6) δ 157.8, 150.0, 131.6, 128.1, 128.0, 127.4, 126.9, 126.3, 125.8, 121.2, 35.5, 30.3. MS (ESI) m/z = 397 $[M-H]^+$. Anal. ($C_{16}H_{18}N_2O_4S_3$): C, 48.22; H, 4.55; N, 7.03. Found, C, 48.43; H, 4.81; N, 7.25.

4.3.22. 6-Aminosulfonyl-3-(4-biphenyl)benzo[1.3.2] dithiazolium ylide 1,1-dioxide (17d)

A white solid in 56% yield. Mp 295 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.43 (d, J = 0.8 Hz, 1H; ArH), 8.33 (m, 2 Hz; ArH), 8.06 (d, J = 8.4 Hz, 2H; ArH), 7.89 (d, J = 8.8 Hz, 2H; ArH), 7.70 (dd, J = 6.8, 1.6 Hz, 2H; ArH), 7.51–7.41 (m, 5H; ArH and SO_2NH_2). ^{13}C NMR (100 MHz, acetone-d_6) δ 150.2, 139.1, 137.3, 134.9, 132.3, 131.9, 130.5, 129.9, 129.5, 128.9, 128.0, 127.7, 121.5, 114.6. MS (ESI) m/z = 418 $[M+H]^+$. Anal. ($C_{18}H_{14}N_2O_4S_3$): C, 51.66; H, 3.37; N, 6.69. Found, C, 51.83; H, 3.60; N, 6.45.

4.3.23. 3-(4-Bromophenyl)-6-methanesulfonylbenzo[1.3.2] dithiazolium ylide 1,1-dioxide (18a)

A white solid in 59% yield. Mp 251 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.50 (s, 1H; ArH), 8.43 (m, 2H; ArH), 7.94 (d, J = 8.4 Hz, 2H; ArH), 7.82 (d, J = 8.4 Hz, 2H; ArH), 3.35 (s, 3H; SO_2CH_3). ^{13}C NMR (100 MHz, acetone-d_6) δ 147.7, 140.3, 138.1, 138.0, 134.2, 133.3, 130.1, 128.4, 128.1, 123.0, 43.8. MS (EI) m/z = 419 $[M]^+$. Anal. ($C_{13}H_{10}BrNO_4S_3$): C, 37.15; H, 2.40; N, 3.33. Found: C, 37.35; H, 2.62; N, 3.27.

4.3.24. 3-(4-Ethylphenyl)-6-methanesulfonylbenzo[1.3.2] dithiazolium ylide 1,1-dioxide (18b)

A white solid in 63% yield. Mp 221–223 °C. ^{1}H NMR (200 MHz, acetone-d_6) δ 8.49 (s, 1H; ArH), 8.38 (s, 2H; ArH), 7.88 (d, J = 8.4 Hz, 2H; ArH), 7.46 (d, J = 8.4 Hz, 2H; ArH), 3.36 (s, 3H; SO_2CH_3), 2.70 (q, J = 7.6 Hz, 2H; CH_2), 1.19 (t, J = 7.6 Hz, 3H; CH_3). ^{13}C NMR (50 MHz, acetone-d_6) δ 151.4, 147.4, 140.8, 138.3, 133.0, 130.6, 128.6, 127.9, 124.8, 122.9, 43.7, 28.9, 15.3. MS (FAB) m/z = 370 $[M+H]^+$. Anal. ($C_{15}H_{15}NO_4S_3$): C, 48.76; H, 4.09; N, 3.79. Found, C, 49.06; H, 3.95; N, 3.52.

4.3.25. 6-Aminosulfonyl-3-(4-bromophenyl)-5-chlorobenzo [1.3.2]-dithiazolium ylide 1,1-dioxide (19)

A white solid in 54% yield. Mp 279 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.55–8.50 (m, 2H; ArH), 7.95 (d, J = 8.4 Hz,2H; ArH), 7.82 (d, J = 8.4 Hz, 2H; ArH), 7.25 (s, 2H; SO_2NH_2). ^{13}C NMR (100 MHz, acetone-d_6) δ 146.9, 139.9, 137.7, 137.1, 135.9, 134.2, 130.2, 129.7, 128.5, 124.0. MS (EI) m/z = 454 $[M]^+$. Anal.

($C_{12}H_8BrClN_2O_4S_3$): C, 31.62; H, 1.77; N, 6.15. Found: C, 31.44; H, 2.06; N, 6.11.

4.3.26. 3-(4-Bromophenyl)-6-methylbenzo[1.3.2]dithiazolium ylide 1,1-dioxide (14a)

This compound was obtained according to the general procedure as a pale pink solid in 64% yield. Mp 128–130 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 7.98 (d, J = 8.0 Hz, 1H; ArH), 7.90–7.87 (m, 2H; ArH), 7.83 (s, 1H; ArH), 7.78 (dd, J = 9.4, 2.4 Hz, 2H; ArH), 7.69–7.68 (m, 1H; ArH), 2.56 (s, 3H; CH_3). ^{13}C NMR (100 MHz, acetone-d_6) δ 146.2, 139.4, 137.5, 135.2, 134.0, 132.2, 129.7, 127.9, 125.9, 123.9, 21.1. MS (EI) m/z = 355 $[M]^+$. Anal. ($C_{13}H_{10}BrNO_2S_2$): C, 43.83; H, 2.83; N, 3.93. Found: C, 43.81; H, 3.08; N, 3.97.

4.3.27. 3-(4-Bromophenyl)-6-(hydroxycarbonyl)benzo[1.3.2] dithiazolium ylide 1,1-dioxide (14b)

This compound was obtained according to the general procedure as a white solid in 65% yield. Mp 291 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.77 (d, J = 2.0 Hz, 1H; ArH), 8.66 (d, J = 8.0 Hz, 1H; ArH), 8.48 (dd, J = 8.0, 2.0 Hz, 1H; ArH), 7.95 (dt, J = 9.1, 2.3 Hz, 2H; ArH), 7.82–7.78 (m, 2H; ArH). ^{13}C NMR (100 MHz, acetone-d_6) δ 165.0, 143.6, 141.8, 140.6, 136.8, 134.6, 134.6, 132.9, 131.9, 130.9, 129.1. MS (EI) m/z = 368 $[M-OH]^+$. Anal. ($C_{13}H_8BrNO_4S_2$): C, 40.43; H, 2.09; N, 3.63. Found: C, 40.31; H, 2.49; N, 3.36.

4.3.28. 3-(4-Bromophenyl)-6-(methoxycarbonyl)benzo[1.3.2] dithiazolium ylide 1,1-dioxide (14c)

A solution of **14b** (3 g) in thionyl chloride (8 mL) was heated at reflux for 8 h. The resulting mixture was evaporated to a small volume. To the residue was added methanol (12 mL) at 0 °C, and the reaction was gradually warmed to room temperature in 3 h. The resulting mixture was evaporated in reduced pressure and then extracted with ethyl acetate (5 mL × 3). The organic layer was evaporated in reduced pressure to give **14c** as a pale yellow solid in 53% yield. Mp 142 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.46 (d, J = 8.4 Hz, 1H; ArH), 8.17 (dd, J = 8.4, 1.4 Hz, 1H; ArH), 8.02 (d, J = 1.4 Hz, 1H; ArH), 7.92 (d, J = 8.8 Hz, 2H; ArH), 7.83 (d, J = 8.8 Hz, 2H; ArH), 3.93 (s, 3H; OCH_3). ^{13}C NMR (100 MHz, acetone-d_6) δ 160.7, 142.4, 139.7, 137.1, 133.24, 133.20, 132.2, 131.2, 129.4, 129.2. MS (EI) m/z = 399 $[M]^+$. Anal. ($C_{14}H_{10}BrNO_4S_2$): C, 42.01; H, 2.52; N, 3.50. Found: C, 42.30; H, 2.57; N, 3.51.

4.3.29. 3-(4-Bromophenyl)-6-carbamoylbenzo[1.3.2] dithiazolium ylide 1,1-dioxide (14d)

A solution of **14b** (3 g) in thionyl chloride (8 mL) was heated at reflux for 8 h. The resulting mixture was evaporated to a small volume. To the residue was added 35% NH_4OH solution (18 mL) at 0 °C, and the reaction was gradually warmed to room temperature in 3 h. The resulting mixture was evaporated and then extracted with ethyl acetate (5 mL × 3). The organic layer was evaporated in reduced pressure to give **14d** as a pale yellowish solid in 52% yield. Mp 245–246 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.64 (d, J = 2.0 Hz, 1H; ArH), 8.61 (d, J = 8.4 Hz, 1H; ArH), 8.02 (dd, J = 8.4, 2.0 Hz, 1H; ArH), 7.96–7.92 (m, 2H; ArH), 7.81–7.77 (m, 2H; ArH), 6.79 (s, 2H; CO_2NH_2). ^{13}C NMR (100 MHz, acetone-d_6) δ 171.8, 162.6, 140.9, 140.8, 134.5, 132.9, 132.5, 130.9, 130.4, 125.8, 106.5. MS (EI) m/z = 384 $[M]^+$. Anal. ($C_{13}H_9BrN_2O_3S_2$): C, 40.53; H, 2.35; N, 7.27. Found: C, 40.27; H, 2.67; N, 6.97.

4.3.30. 6-Aminosulfonyl-3-(4-ethylphenyl)benzo[1.2] isothiazole 1,1-dioxide (24a)

A solution of **21** (0.2 g) and $KMnO_4$ (0.42 g) in 5% NaOH (7 mL) was heated to reflux for 30 min. The mixture was then filtered, and the filtrate was acidified to pH 4 with 10% $HCl_{(aq)}$, and concentrated to give **22**. To **22** was added concd sulfuric acid (4 mL), and the reaction mixture was stirred at room temperature for 1 h. The solution was neutralized with 10% $NaOH_{(aq)}$, partitioned with CH_2Cl_2/MeOH (18 mL/2 mL), and evaporated to give **23a**. To **23a** in THF (20 mL) was added a solution of ethylbenzene magnesium bromide (3.2 equiv) in THF (9.5 mL) dropwise, and the reaction mixture was stirred at room temperature for 1 h, and then heated to reflux for 2 h. The resulting mixture was poured into cold water (28 mL), and the precipitate was washed with ethyl acetate (10 mL) and then purified by gel chromatography (silica gel, 6 cm in height, 2 cm in diameter) with hexane/ethyl acetate (1:1) to provide **24a** as a white solid in 45% yield. Mp 297 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.51–8.49 (m, 1H; ArH), 8.36 (d, J = 1.0 Hz, 2H; ArH), 8.07 (dd, J = 6.5, 1.8 Hz, 2H; ArH), 7.57 (d, J = 8.4 Hz, 2H; ArH), 7.08 (s, 2H; ArH), 2.79 (q, J = 7.6 Hz, 2H; CH_2), 1.29 (t, J = 7.6 Hz, 3H; CH_3). ^{13}C NMR (100 MHz, acetone-d_6) δ 170.6, 151.8, 149.7, 142.5, 133.5, 132.5, 130.8, 129.6, 129.1, 128.5, 120.8, 29.4, 15.4. MS (EI) m/z = 350 $[M]^+$. Anal. ($C_{15}H_{14}N_2O_4S_2$): C, 51.41; H, 4.03; N, 7.99. Found: C, 51.56; H, 4.36; N, 7.65.

4.3.31. 3-(4-Methylphenyl)benzo[1.2]isothiazole 1,1-dioxide(24c)

To saccharin (0.5 g) in THF (25 mL) was added *p*-tolyl magnesium bromide (1.1 equiv) in THF (10 mL) dropwise, and the reaction was stirred at room temperature for 1 h and then heated to reflux for 2 h. The resulting mixture was poured into cold water (30 mL), and the precipitate was washed with ethyl acetate (15 mL) and then purified by gel chromatography with hexane/ethyl acetate (3:1) to provide **24c** as a pale yellow solid in 70% yield. Mp 156 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 7.80 (d, J = 2.0 Hz, 1H; ArH), 7.63–7.60 (m, 2H; ArH), 7.37–7.34 (m, 2H; ArH), 7.28–7.27 (m, 1H; ArH), 7.19 (d, J = 7.8 Hz, 2H; ArH), 2.31 (s, 3H; CH_3). ^{13}C NMR (100 MHz, acetone-d_6) δ 141.3, 138.7, 138.2, 136.4, 133.6, 130.1, 130.0, 128.1, 126.3, 121.2, 20.9. MS (EI) m/z = 257 $[M]^+$. Anal. ($C_{14}H_{11}NO_2S$): C, 65.35; H, 4.31; N, 5.44. Found: C, 65.07; H, 4.61; N, 5.76.

4.3.32. 3-(4-Bromophenyl)benzo[1.2]isothiazole 1,1-dioxide (24b)

According to the above coupling reaction by *p*-bromophenyl magnesium bromide (1.1 equiv), compound **24b** was obtained as a pale yellow solid in 65% yield. Mp 109–111 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.13–8.07 (m, 1H; ArH), 7.99–7.90 (m, 1H; ArH), 7.83–7.81 (m, 1H; ArH), 7.71–7.56 (m, 3H; ArH), 7.45–7.47 (m, 1H; ArH), 7.35–7.32 (m, 1H; ArH). ^{13}C NMR (100 MHz, acetone-d_6) δ 134.6, 133.8, 132.6, 130.7, 130.3, 130.1, 130.0, 128.0, 126.3, 123.4, 121.3. MS (EI) m/z = 321 $[M]^+$. Anal. ($C_{13}H_8BrNO_2S$): C, 48.46; H, 2.50; N, 4.35. Found: C, 48.33; H, 2.62; N, 3.99.

4.3.33. 3-(4-Ethylphenyl)-6-nitrobenzo[1.3.2]dithiazolium ylide 1,1-dioxide (30a)

A pale yellow solid in 60% yield. Mp 205 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.74 (d, J = 2.0 Hz, 1H; ArH), 8.68 (dd, J = 8.6, 2.0 Hz, 1H; ArH), 8.40 (d, J = 8.6 Hz, 1H; ArH), 7.88 (d, J = 8.4 Hz, 2H; ArH), 7.47 (d, J = 8.8 Hz, 2H; ArH), 2.70 (q, J = 7.6 Hz, 2H; CH_2), 1.18 (t, J = 7.6 Hz, 3H; CH_3). ^{13}C NMR (100 MHz, acetone-d_6) δ 152.3, 151.5, 141.3, 138.9, 135.0, 130.6, 129.2, 128.7, 128.1, 118.9, 29.0, 15.3. MS (EI) m/z = 336 $[M]^+$. Anal. ($C_{14}H_{12}N_2O_4S_2$): C, 49.99; H, 3.60; N, 8.33. Found: C, 49.74; H, 3.80; N, 8.25.

4.3.34. 3-(4-Isopropylphenyl)-6-nitrobenzo[1.3.2]dithiazolium ylide 1,1-dioxide (30b)

A pale yellow solid in 55% yield. Mp 184 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.73 (d, J = 2.0 Hz, 1H; ArH), 8.69–8.65 (m, 1H; ArH), 8.39 (d, J = 8.4 Hz, 1H; ArH), 7.91–7.88 (m, 2H; ArH), 7.50 (d, J = 8.4 Hz, 2H; ArH), 2.80 (septet, J = 6.9 Hz, 1H; CH), 1.22 (d, J = 6.9 Hz, 6H; CH_3). ^{13}C NMR (100 MHz, acetone-d_6) δ 156.0,

152.5, 141.4, 139.1, 135.2, 129.3, 129.2, 128.8, 128.2, 119.0, 34.7, 23.6. MS (ESI) m/z = 351 $[M+H]^+$. Anal. ($C_{15}H_{14}N_2O_4S_2$): C, 51.41; H, 4.03; N, 7.99. Found: C, 51.74; H, 3.83; N, 8.15.

4.3.35. 3-(4-*tert*-Butylphenyl)-6-nitrobenzo[1.3.2]dithiazolium ylide 1,1-dioxide (30c)

A yellow-brown solid in 59% yield. Mp 214 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.73 (d, J = 2.0 Hz, 1H; ArH), 8.67 (dd, J = 8.8, 2.0 Hz, 1H; ArH), 8.40 (d, J = 8.8 Hz, 1H; ArH), 7.92–7.88 (m, 2H; ArH), 7.66 (dd, J = 6.8, 2 Hz, 2H; ArH), 12.9 (s, 9H; CH_3). ^{13}C NMR (100 MHz, acetone-d_6) δ 158.1, 152.4, 141.3, 139.0, 134.8, 129.2, 128.5, 128.2, 128.1, 119.0, 35.7, 31.0. MS (ESI) m/z = 365 $[M+H]^+$. Anal. ($C_{16}H_{16}N_2O_4S_2$): C, 52.73; H, 4.43; N, 7.69. Found: C, 52.45; H, 4.80; N, 7.55.

4.3.36. 3-(4-Methoxyphenyl)-6-nitrobenzo[1.3.2]dithiazolium ylide 1,1-dioxide (30d)

A yellow solid in 62% yield. Mp 222–223 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.74 (d, J = 2.0 Hz, 1H; ArH), 8.66 (dd, J = 8.4, 2.0 Hz, 1H; ArH), 8.31 (d, J = 8.4 Hz, 1H; ArH), 7.88 (d, J = 6.8 Hz, 2H; ArH), 7.13 (d, J = 6.8 Hz, 2H; ArH), 3.88 (s, 3H; OCH_3). ^{13}C NMR (100 MHz, acetone-d_6) δ 164.9, 152.3, 141.7, 139.3, 131.4, 129.1, 128.2, 128.1, 118.9, 116.5, 56.2. MS (ESI) m/z = 339 $[M+H]^+$. Anal. ($C_{13}H_{10}N_2O_5S_2$): C, 46.15; H, 2.98; N, 8.28. Found: C, 46.37; H, 3.10; N, 8.26.

4.3.37. 3-(3,4-Dimethoxyphenyl)-6-nitrobenzo[1.3.2] dithiazolium ylide 1,1-dioxide (30e)

A pale yellow solid in 60% yield. Mp 238–240 °C. ^{1}H NMR (400 MHz, methanol-*d4*) δ 8.81 (d, J = 2.1 Hz, 1H; ArH), 8.60 (dd, J = 8.6, 2.1 Hz, 1H; ArH), 8.36 (d, J = 8.6 Hz, 1H; ArH), 7.48 (s, 1H; ArH), 7.30 (s, 1H; ArH), 7.17–7.11 (m, 1H; ArH), 3.84 (s, 3H; OCH_3), 3.67 (s, 3H; OCH_3). ^{13}C NMR (100 MHz, CD_3OD) δ 154.9, 151.2, 141.7, 138.5, 129.6, 128.4, 127.7, 127.6, 119.4, 117.2, 113.4, 111.6, 57.0, 56.5. MS (ESI) m/z = 369 $[M+H]^+$. Anal. ($C_{14}H_{12}N_2O_6S_2$): C, 45.65; H, 3.28; N, 7.60. Found: C, 45.77; H, 3.50; N, 7.72.

4.3.38. 3-(4-Biphenyl)-6-nitrobenzo[1.3.2]dithiazolium ylide 1,1-dioxide (30f)

A pale yellow solid in 53% yield. Mp 277–278 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.76 (d, J = 2.0 Hz, 1H; ArH), 8.70 (dd, J = 8.4, 2.0 Hz, 1H; ArH), 8.47 (d, J = 8.4 Hz, 1H; ArH), 8.08 (d, J = 8.8 Hz, 2H; ArH), 7.90 (d, J = 8.4 Hz, 2H; ArH), 7.69 (d, J = 7.2 Hz, 2H; ArH), 7.51–7.41 (m, 3H; ArH). ^{13}C NMR (100 MHz, acetone-d_6) δ 146.9, 141.3, 139.5, 139.1, 136.9, 136.5, 129.9, 129.5, 129.3, 129.2, 129.0, 128.3, 128.0, 119.1. MS (ESI) m/z = 385 $[M+H]^+$. Anal. ($C_{18}H_{12}N_2O_4S_2$): C, 56.24; H, 3.15; N, 7.29. Found: C, 56.37; H, 3.32; N, 7.15.

4.3.39. 3-(4-Trifluoromethylphenyl)-6-nitrobenzo[1.3.2] dithiazolium ylide 1,1-dioxide (30g)

A pale yellow solid in 53% yield. Mp 153–155 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.75 (d, J = 2.0 Hz, 1H; ArH), 8.71 (dd, J = 8.6, 2.0 Hz, 1H; ArH), 8.58 (d, J = 8.6 Hz, 1H; ArH), 8.27 (d, J = 8.0 Hz, 2H; ArH), 7.98 (d, J = 8.0 Hz, 2H; ArH). ^{13}C NMR (100 MHz, acetone-d_6) δ 152.6, 143.1, 140.5, 138.6, 129.5, 128.8, 128.4, 128.0, 127.9, 127.8, 119.2. MS (ESI) m/z = 377 $[M+H]^+$. Anal. ($C_{13}H_7F_3N_2O_4S_2$): C, 41.49; H, 1.87; N, 7.44. Found: C, 41.56; H, 1.80; N, 7.25.

4.3.40. 6-Nitro-3-(4-pyridin)benzo[1.3.2]dithiazolium ylide 1,1-dioxide (30h)

A yellow solid in 51% yield. Mp 185 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 9.10 (dd, J = 4.8, 1.5 Hz, 2H; ArH), 8.99 (d, J = 1.9 Hz, 1H; ArH), 8.82 (dd, J = 8.6, 1.9 Hz, 1H; ArH), 8.59 (d, J = 8.6 Hz, 1H; ArH), 8.10 (dd, J = 4.8, 1.5 Hz, 2H; ArH). ^{13}C NMR (100 MHz, acetone-d_6) δ 153.1, 144.5, 144.4, 139.8, 131.2, 130.4, 128.0, 122.6, 119.4. MS (EI) m/z = 309 $[M]^+$. Anal. ($C_{11}H_7N_3O_4S_2$): C, 42.71; H, 2.28; N, 13.58. Found: C, 43.06; H, 1.99; N, 13.52.

4.3.41. 3-(2-(3,5-Dimethoxyphenoxyl)ethyl)-6-nitrobenzo[1.3.2] dithiazo-lium ylide 1,1-dioxide (30i)

A brown solid in 53% yield. Mp 109–110 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.70–8.67 (m, 1H; ArH), 8.35–8.29 (m, 1H; ArH), 7.93–7.89 (m, 1H; ArH), 6.09–6.06 (m, 3H; ArH), 4.18–4.12 (m, 2H; CH_2), 3.74 (s, 3H; OCH_3), 3.73 (s, 3H; OCH_3), 3.57–3.49 (m, 2H; CH_2). ^{13}C NMR (100 MHz, acetone-d_6) δ 161.7, 160.6, 132.0, 129.2, 124.0, 122.2, 113.9, 94.1, 93.3, 93.1, 70.1, 68.1, 54.7. MS (ESI) m/z = 411 $[M-H]^+$. Anal. ($C_{16}H_{16}N_2O_7S_2$): C, 46.59; H, 3.91; N, 6.79. Found: C, 46.62; H, 3.88; N, 6.53.

4.3.42. 3-(2-(3-Fluoro-5-(4-(4-methoxytetrahydropyranyl)) phenoxy)ethyl)-6-nitro- benzo[1.3.2]dithiazolium ylide 1,1-dioxide (30j)

A pale yellow-brown solid in 51% yield. Mp 166 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.79 (d, J = 2.8 Hz, 1H; ArH), 8.29 (dd, J = 8.8, 2.8 Hz, 1H; ArH), 8.10 (d, J = 8.8 Hz, 1H; ArH), 6.77–6.44 (m, 3H; ArH), 4.03–3.97 (m, 2H; CH_2), 3.71–3.64 (m, 4H; CH_2), 3.04–3.01 (m, 2H; CH_2), 2.92 (s, 3H; CH_3), 1.92–1.83 (m, 4H; CH_2). ^{13}C NMR (100 MHz, acetone-d_6) δ 147.5, 144.7, 137.3, 127.9, 127.1, 124.7, 109.6, 109.1, 104.4, 104.2, 102.0, 101.8, 69.0, 63.5, 60.2, 49.7, 49.6, 35.6. MS (ESI) m/z = 485 $[M+H]^+$. Anal. ($C_{20}H_{21}FN_2O_7S_2$): C, 49.58; H, 4.37; N, 5.78. Found: C, 49.61; H, 4.19; N, 5.68.

4.4. Biology

4.4.1. Assay of human recombinant COX-2 inhibition

The COX-2 inhibition assay was performed by MDS Pharma Services (Taipei, Taiwan) using the test method numbered 118010 for COX-2 with human recombinant COX-2 (expressed in insect Sf21 cells). Test compounds were preincubated for 15 min at 37 °C with COX-2 (0.11 U) in Tris–HCl buffer (pH 7.7) containing glutathione (1 mM), phenol (500 μM), and hematin (1 μM). The enzymatic reaction was initiated by addition of 0.3 μM arachidonic acid. After incubation at 37 °C for 5 min, the reaction was terminated by addition of 1 N HCl. Prostaglandin E_2 (PGE_2) production was quantified to measure COX-2 activity using an enzyme immunoassay (EIA) kit (Amersham).

4.4.2. Assay of human recombinant 5-LOX inhibition

The 5-LOX inhibition assay was performed by MDS Pharma Services (Taipei, Taiwan) with human peripheral blood mononuclear leukocytes (PBML). Test compounds were preincubated at 37 °C for 15 min with human PBML (5×10^6 cells/mL) in HBSS buffer (pH 7.4). The enzymatic reaction was initiated by addition of the calcium ionophore A23187 (30 μM). After incubation at 37 °C for 15 min, the reaction was terminated by addition of 1 N HCl. After neutralization with NaOH and centrifugation, the LTB_4 concentration in the supernatant was measured using an EIA kit.

4.4.3. In vivo inhibition of carrageenan-induced paw swelling

Male Wistar derived rats weighing 160 ± 10 g were provided by BioLasco Taiwan (under Charles River Laboratories Technology Licensee). Space allocation for 5 animals was 45 × 23 × 21 cm. All animals were maintained in a controlled temperature (20–24 °C) and humidity (50–80%) environment with 12 h light/dark cycles for at least three days at Ricerca Taiwan, Ltd laboratory prior to use. Unless animals were fasted for special purpose, free access to standard lab chow [MF-18 (Oriental Yeast Co., Ltd, Japan)] and reverse osmosis (RO) water was granted. All aspects of this work including housing, experimentation and disposal of animals were

performed in general accordance with the Guide for the Care and Use of Laboratory Animals (National Academy Press, Washington, DC, 1996). Aspirin (Sigma, USA), λ-Carrageenan (Fluka, Switzerland), Distilled water (Tai-Yu, Taiwan), Pyrogen free saline (Sintong, Taiwan) and Tween 80 (Sigma, USA). Animal Cage (Allentown, USA), Glass syringes (Mitsuba, Japan), Hypodermic needle 26G × 1″ (Top Corporation, Japan), Plethysmometer (PV-01 Paw volume apparatus, SINGA Technology Co. Taiwan), Rat oral needle (Natsume, Japan) and Rat scale (1–1000 g, TANITA, Japan).

Male Wistar derived rats were fasted overnight prior to use. Compound **30c** was suspended in 1% Tween 80/0.9% NaCl with concentrations of 2, 6, and 20 mg/mL. The reference compound aspirin was suspended in 1% Tween 80/0.9% NaCl with a concentration of 15 mg/mL. The dosing volume was 5 mL/kg. Compound **30c** at 10, 30 and 100 mg/kg were administered intraperitoneally 30 min before the right hind paw received intraplantar injection of carrageenan (0.1 mL of 1% suspension). In the reference group, aspirin (150 mg/kg) was administered orally 1 h before carrageenan injection. Hind paw edema, as a measure of inflammation, was recorded 3 h after carrageenan administration using a plethysmometer. Reduction of hind paw edema by 30% or more relative to the vehicle group indicates acute anti-inflammatory activity.

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