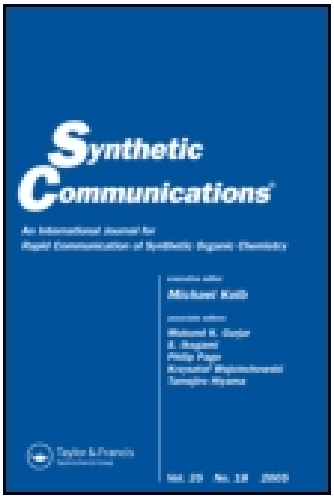


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Facile Synthesis of 4H-1,2,4-Benzothiadiazine-1,1-dioxides

Artem Cherepakha [a], Vladimir O. Kovtunenko [a], Andrey Tolmachev [a b], Oleg Lukin [a b] & Konstantin G. Nazarenko [c]

[a] National Taras Shevchenko University, ChemBioCenter, Kiev, Ukraine

[b] Enamine Ltd., Kiev, Ukraine

[c] Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Kiev, Ukraine

Published online: 02 May 2011.

To cite this article: Artem Cherepakha, Vladimir O. Kovtunenko, Andrey Tolmachev, Oleg Lukin & Konstantin G. Nazarenko (2011) Facile Synthesis of 4H-1,2,4-Benzothiadiazine-1,1-dioxides, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 41:13, 1977-1989, DOI: 10.1080/00397911.2010.494815

To link to this article: http://dx.doi.org/10.1080/00397911.2010.494815

Synthetic Communications®, 41: 1977–1989, 2011

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.494815

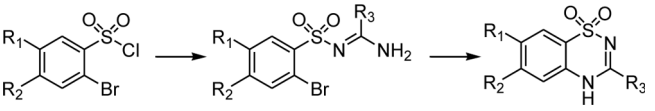
Taylor & Francis
Taylor & Francis Group

FACILE SYNTHESIS OF 4*H*-1,2,4-BENZOTHIADIAZINE-1,1-DIOXIDES

Artem Cherepakha,[1] Vladimir O. Kovtunenko,[1] Andrey Tolmachev,[1,2] Oleg Lukin,[1,2] and Konstantin G. Nazarenko[3]

[1]*National Taras Shevchenko University, ChemBioCenter, Kiev, Ukraine*
[2]*Enamine Ltd., Kiev, Ukraine*
[3]*Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Kiev, Ukraine*

GRAPHICAL ABSTRACT



Abstract o-*Bromoarylsulfonylated amidines prepared either by acylation of amidine with* o-*bromoarylsulfonyl chloride or through the reaction of* o-*bromoarylsulfoamide with lactime ether underwent Cu(I)-catalyzed intramolecular cyclization to give 4*H-*1,2,4-benzothiadiazine-1,1-dioxides in good yield. By varying substituents on arylsulfonyl moieties, amidines, and lactime ethers, a small library of structurally diverse 4*H-*1,2,4-benzothiadiazine-1,1-dioxide derivatives was prepared.*

Keywords Acylation; amidines; 1,2,4-benzothiadiazine-1,1-dioxide; copper-catalyzed cyclization; sulfonyl chlorides

INTRODUCTION

The 1,2,4-benzothiadiazine-1,1-dioxide structural unit is found in compounds possessing antihypertensive,[1,2] antimicrobial,[3] and antiviral[4] (including anti-HIV) activities. In connection with this, a range of synthetic pathways to the benzothiadiazine ring system has been developed. The biologically potent 1,2,4-benzothiadiazine-1,1-dioxide ring is usually assembled through the reaction of *o*-aminoaryl-sulfonamides with either orthoesters[5] or acylating reagents.[6,7] The main disadvantage of this approach is a limited availability of *o*-aminosulfonamides, narrowing the chemical space for drug design. An alternative one-pot approach to the 1,2,4-benzothiadiazine-1,1-dioxide ring is based on the Michael addition of chlorosulfonyl isocyanate to aniline derivatives followed by the ring closure under

Received February 17, 2010.

Address correspondence to Oleg Lukin, National Taras Shevchenko University, ChemBioCenter, Volodymyrska St. 62, 01033 Kiev, Ukraine. E-mail: oleg.lukin@univ.kiev.ua

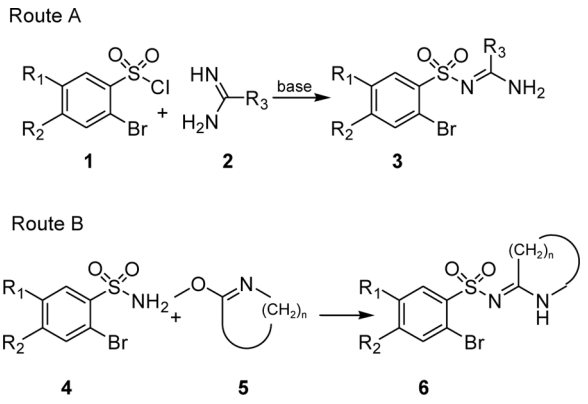
Friedel–Crafts conditions.[8] Despite the ease of the latter procedure, the resulting sulfonylated urea was shown to be hydrolytically unstable under acidic conditions, giving rise to an open-chain aminosulfonamide. Recently, a Cu(I)-catalyzed coupling of *o*-bromobenzylsulfonyl azide with functionalized terminal acetylene and ammonium chloride was used for the synthesis of the 4*H*-1,2,4-benzothiadiazine-1,1-dioxides.[9] However, the diversity of the target compounds is limited by the availability of functionalized terminal acetylenes. The benzothiadiazine-1,1-dioxides were also synthesized through a Fe(III) chloride–mediated cyclization of *o*-bromobenzenesulfonamide with various amidines at 120 °C.[10] Under such harsh conditions, only 4*H*-1,2,4-benzothiadiazine-1,1-dioxide derivatives bearing simple hydrocarbon substituents were synthesized.

We have recently reported that 4*H*-1,2,4-benzothiadiazine-1,1-dioxides can be easily synthesized by reacting *o*-chloroarylsulfonamides with lactime ethers.[11] The reaction proceeds via formation of a sulfonylated amidine intermediate that undergoes intramolecular cyclization at 160 °C. Like in the preceding case, the reaction conditions are quite harsh for many functional groups to survive. In addition, the presence of electron-withdrawing groups such as NO_2 or $COOCH_3$ in the *o*-chloroarylsulfonamide component was a prerequisite for the successful cyclization step. Given the advantages and drawbacks of these synthetic routes to the benzothiadiazine-1,1-dioxide ring system, it becomes clear that further optimization of the synthetic schemes is necessary to access its diversely functionalized derivatives. These points of the published procedures prompted us to the following optimal scheme: First, the cyclization of the sulfonylated amidine should be carried out under mild conditions, tolerating a majority of functional groups. For this purpose, the Cu(I)-catalyzed intramolecular arylation of *o*-bromobenzenesulfonamide intermediates[9] seems to be the best suited cyclization technique. Second, the preparation of the sulfonylated amidine intermediate should be more straightforward. It should involve easily accessible building blocks that bear at least one diversity point each and react under mild conditions.

In this contribution, we describe two efficient approaches to *o*-bromoarylsulfonylated amidines and their copper-catalyzed intramolecular cyclization to the corresponding 4*H*-1,2,4-benzothiadiazine-1,1-dioxides.

RESULTS AND DISCUSSION

As noted, the most common route to sulfonylated amidines is the reaction of an amidine with a sulfonamide. The latter is usually prepared from the corresponding sulfonyl chloride. Therefore, a direct sulfonylation of amidines with sulfonyl chlorides would save one synthetic step.[12] Indeed, as shown in Scheme 1 (route A) the condensation of *o*-bromoarylsulfonyl chlorides **1** with amidines **2** in the presence of a base readily gives the sulfonylated amidines **3** in good yield (Table 1). ^{1}H NMR spectra of compounds **3a**–**3h** recorded in dimethylsulfoxide (DMSO-d_6) contain characteristic signals of the NH_2 group at 8.2–8.8 ppm and those of aromatic proton located in the *ortho*- position to the sulfo- group at 8.5–8.6 ppm (**3b**–**3d**) and 8.1–8.2 (**3e**–**3h**). Notably, the signals pertaining to the NH_2 protons in compounds **3** appear as either a broad singlet or two singlets dependently on the R- groups. Analysis of the literature shows that such spectral manifestations are



Scheme 1. Preparation of the sulfonylated amidine intermediates.

due to a slow on the NMR timescale rotation of the amino group about the C-N bond rather than a prototropic equilibrium that takes place only in amidine dimers, forming themselves in low polar solvents and in the solid state.[13] Additionally, the absence of the terminal C=N double bond in sulfonylated amidines was recently proven by means of single-crystal x-ray diffraction.[14] Amino-group proton signals in the ^{1}H NMR spectra of sulfonylated amidines described in the latter work appear at 8.6 ppm, which is in agreement with our own NMR data for compounds **3**. ^{1}H and ^{13}C NMR, liquid chromatography/mass spectrometry (LC/MS), and elemental analyses of the sulfonylated amidines **3a**–**3h** confirmed their composition and high purity. Given our stock availabilities of many functionalized *o*-bromoarylsulfonyl chlorides and amidines, the method can be employed in parallel syntheses of combinatorial libraries of sulfonylated amidines. To introduce additional structural variations into the sulfonylated amidine structure, a small library of compounds **6** bearing cyclic functionalities was prepared through condensing *o*-bromoarylsulfonamides with lactime ethers (Scheme 1, route B, Table 2) according to our own procedure.[11]

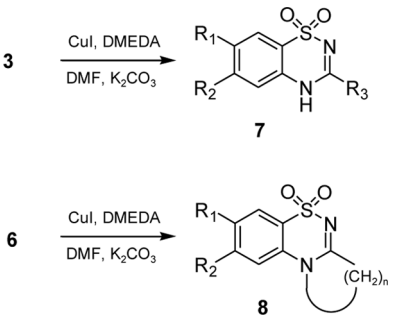
Sulfonylated amidines **3** and **6** underwent the Cu(I)-catalyzed cyclization reaction (Scheme 2) to give the corresponding 4*H*-1,2,4-benzothiadiazine-1,1-dioxides in

Table 1. Sulfonylated amidines obtained via route A

No.	R_1	R_2	R_3	Solvent	Base	Mp (°C)	Yield (%)
3a	H	H	CH_3	benzene	K_2CO_3	178	95
3b	CO_2Me	H	CH_3	dichloromethane	K_2CO_3	194	85
3c	CO_2Me	H	Ph	dichloromethane	KOH	192	92
3d	CO_2Me	H	Pyrrolidin-1-yl	dichloromethane	KOH	197	83
3e	CO_2Me	H	SMe	dichloromethane	KOH	162	84
3f	CO_2Me	H	OMe	dichloromethane	KOH	166	87
3g	Br	H	CH_3	benzene	K_2CO_3	174 (subl.)	92
3h	Br	H	Ph	benzene	KOH	164	89
3i	H	Br	CH_3	benzene	K_2CO_3	158	71
3j	H	Br	Ph	benzene	KOH	137	89

Table 2. Sulfonylated amidines obtained via route B

No.	R_1	R_2	*n*	Mp (°C)	Yield (%)
6a	H	H	3	159	98
6b	CO_2Me	H	3	139 (subl.)	95
6c	CO_2Me	H	5	148	97
6d	Br	H	3	179 (subl.)	94
6e	H	Br	3	184	97



Scheme 2. Cyclization of the sulfonylated amidines obtained via routes **A** and **B**.

good yield (Table 2). Noteworthy, the use of N,N′-dimethylethylenediamine (DMEDA) instead of 1,10-phenanthroline as reported by Chang et al.[9] allowed us to achieve generally better conversions and a clean workup. ^1H and ^{13}C NMR spectra, LC/MS, and elemental analyses of compounds **7** and **8** are fully consistent

Table 3. 4*H*-1,2,4-Benzothiadiazines 1,1-dioxides (**7**)

No.	R_1	R_2	R_3	Mp (°C)	Yield (%)
7a	H	H	CH_3	254	98
7b	CO_2Me	H	CH_3	261	95
7c	CO_2Me	H	Ph	303	97
7d	CO_2Me	H	Pirrolidin-1-yl	322	93
7e	CO_2Me	H	OMe	242	65
7f	Br	H	CH_3	320 (subl.)	95
7g	Br	H	Ph	349	98
7h	H	Br	CH_3	315	95
7i	H	Br	Ph	370 (decomp.)	98

Table 4. 4*H*-1,2,4-Benzothidiazine-1,1-dioxides (**8**)

No.	R1	R2	*n*	Mp (°C)	Yield (%)
8a	H	H	3	296	99
8b	CO_2Me	H	3	163	97
8c	CO_2Me	H	5	163	98
8d	Br	H	3	263	98
8e	H	Br	3	267	98

with their structures. Although this method is not applicable to compound **3d**, the corresponding compound **7** can be synthesized through an alternative solid-phase synthetic route.[7]

CONCLUSIONS

In conclusion, an efficient and flexible approach to various 4*H*-1,2,4-benzothiadiazine-1,1-dioxide derivatives was developed. The structural diversity of the title compounds is achieved by a two-step synthesis proceeding under mild conditions. First, *o*-bromoarylsulfonylated amidines, the key precursors, are obtained by either of two new procedures from readily available building blocks such as functionalized bromoarylsulfonyl chlorides, amidines and lactime ethers. The second step consists of a high-yielding Cu(I)-catalyzed cyclization of the intermediates. The reported approach broadens considerably the scope of the available methods by including optimized reaction conditions, new reagents, and structural subunits, such as cyclic sulfonylated amidines.

EXPERIMENTAL

^{1}H (500-MHz) and ^{13}C (125-MHz) NMR spectra were recorded on a Bruker Avance DRX 500 spectrometer in DMSO-d_6 solution with tetramethylsilane (TMS) as an internal standard. Melting points were measured with a Büchi melting-point apparatus and are uncorrected. High-performance (HP) LC-MS analyses were done on an Agilent 1100 LCMSD SL instrument (APCI mode). The HPLC-MS data for the compounds reported in this work are available from the authors upon request. Infrared (IR) spectra were recorded on a Perkin-Elmer Spectrum BX II Fourier Transform (FT)–IR spectrometer. Elemental analysis was carried out by the Analytical Laboratory of Institute of Organic Chemistry of NAS. 2-Bromobenzenesulfonyl chloride (**1a**) and 2-bromosulfonyl amide (**4a**) were prepared by a procedure of Bahlman.[15] 2,5-Dibromosulfonyl chroride (**1c**), 2,5-dibromobenzenesulfonyl amide (**4c**), and 2,4-dibromobenzenesulfonyl (**4d**) amide were prepared using the procedure of Huntress and Carten,[16] and 2,4-dibromobenzenesulfonyl (**1d**) chloride was prepared by the procedure of Pezold et al.[17]

2-Bromo-4-carbomethoxybenzenesulfonyl Chloride (1b)

The 2-bromo-4-carboxybenzenesulfonyl chloride precursor was prepared according to the published procedure.[18] The precursor (140 g, 0.468 mol) was dissolved in 300 mL of thionyl chloride and refluxed for 4 h. The excess of thionyl chloride was removed under reduced pressure, and the viscous residue was slowly poured into 150 ml of methanol at 0 °C. The 2-bromo-4-carbomethoxybenzenesulfonyl chloride precipitated from the solution in the form of a white crystalline powder. The precipitated product was filtered, washed with cold methanol, and dried in vacuum. Yield of the pure product is 120 g (82%).

^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 3.85$ (s, 3 H, CO_2CH_3), 7.74 (s, 2 H, ArH), 8.47 (s, 1 H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 52.18$, 125.74, 128.71, 129.97, 130.96, 135.08, 147.58, 165.98. Calcd. (%) for $C_8H_6BrClO_4S$: C 30.65, H 1.93. Found: C 30.52, H 1.95.

2-Bromo-4-carbomethoxybenzenesulfonamide (4b)

The 2-bromo-4-carboxybenzenesulfonyl chloride (30 g, 0.1 mol) was slowly added to 100 mL of concentrated water solution of ammonia at 0 °C, and then the reaction mixture was stirred for 15 min. The solvent was removed under reduced pressure, and the residue was dissolved in water. The addition of hydrochloric acid to the latter solution caused precipitation of the 2-bromo-4-carboxybenzenesulfonamide (28 g). The compound was purified by recrystallization from ethanol. The purified substance was dissolved in methanol, and the solution was transferred into a three-neck flask equipped with a dropping funnel, reflux condenser, and a mechanical stirrer. Then to the stirred solution thionyl chloride (14.2 g, 0.12 mol) was added drop wise. Upon addition of the thionyl chloride, the reaction mixture was refluxed for 1 h, and then the solvent was removed under reduced pressure. The residue was triturated with water, and the white precipitate was filtered, washed with water and dried under ambient conditions. The crude product can be additionally purified by recrystallization from methanol/water mixture. Yield 24 g (81.6%); ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 3.90$ (s, 3 H, CO_2CH_3), 7.80 (s, 2 H, NH_2), 8.00 (s, 2 H, ArH), 8.53 (s, 1 H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 53.22$, 124.96, 129.65, 129.85, 133.75, 136.42, 143.77, 165.24. Calcd. (%) for $C_8H_8BrNO_4S$: C, 32.67; H, 2.74; Br, 27.17; N, 4.76. Found: C, 32.58; H, 2.71; Br, 27.05; N, 4.71.

General Procedure for Preparation of Sulfonylated Amidines (Route A)

A concentrated water solution of the base (see Table 1) was slowly added to a stirred solution of equimolar amounts of *o*-bromoarylsulfonyl chloride **1** and amidine hydrochloride **2** in the appropriate solvent at 0 °C. The reaction mixture was allowed to stir overnight at room temperature. The precipitated sulfonylated amidine **3** was filtered, washed with water and dichloromethane, and dried at ambient conditions. If further purification is necessary, the product is recrystallized from ethanol/water.

Selected Data for 3a–3j

N1-(1-Aminoethylidene)-2-bromobenzenesulfonamide (3a). IR: 3409, 3324, 3242 (NH), 1637 (NH_2), 1541 (C=N), 1288, 1146 (SO_2) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 2.12$ (s, 3 H, CH_3), 7.48 (t, $^3J_{HH} = 7$ Hz, 1 H, ArH), 7.55 (t, $^3J_{HH} = 7$ Hz, 1 H, ArH), 7.81 (d, $^3J_{HH} = 7$ Hz, 1 H, ArH), 8.06 (d, $^3J_{HH} = 7$ Hz, 1 H, ArH), 8.13 (b.s., 1 H, NH), 8.56 (b.s., 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 22.17$, 120.24, 128.24, 129.61, 133.64, 135.45, 142.48, 168.77. Calcd. (%) for $C_8H_9BrN_2O_2S$: C, 34.67; H, 3.27; Br, 23.83; N, 10.11. Found: C, 34.62; H, 3.21; Br, 23.75; N, 10.19.

Methyl-3-(1-aminoethylidenesulfamoyl)-4-bromobenzoate (3b). IR: 3331, 3131 (NH), 1590 (NH_2), 1537 (C=N), 1292, 1130 (SO_2) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 2.15$ (s, 3 H, CH_3), 3.90 (s, 3 H, CO_2CH_3), 7.97 (s, 2 H, ArH), 8.54 (s, 1 H, ArH), 9.12 (b.s., 2 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 22.06$, 53.17, 125.82, 129.53, 129.71, 133.61, 136.37, 143.15, 165.30, 169.18.

Calcd. (%) for $C_{10}H_{11}BrN_2O_4S$: C, 35.84; H, 3.31; Br, 23.84; N, 8.36. Found: C, 35.75; H, 3.22; Br, 23.67; N, 8.15.

Methyl-3-(amino(phenyl)methylenesulfamoyl)-4-bromobenzoate (3c). IR: 3335, 3177 (NH), 1586 (NH_2), 1482 (C=N), 1297, 1174 (SO_2) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): $\delta = 3.90$ (s, 3 H, CO_2CH_3), 7.49 (t, $^3J_{HH} = 8$ Hz, 2 H, ArH), 7.60 (t, $^3J_{HH} = 8$ Hz, 1H, ArH), 7.91 (t, $^3J_{HH} = 8$ Hz, 2 H, ArH), 8.00 (s, 2 H, ArH), 8.41 (b.s., 1 H, NH), 8.54 (s, ArH), 9.33 (b.s, 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 52.83$, 125.79, 128.57, 128.64, 128.70, 129.49, 130.00, 130.93, 134.27, 135.08, 147.73, 166.00, 166.10. Calcd. (%) for $C_{15}H_{13}BrN_2O_4S$: C, 45.35; H, 3.30; Br, 20.11; N, 7.05. Found: C, 45.02; H, 3.37; Br 19.89; N, 6.92.

Methyl-3-(amino(tetrahydro-1*H*-pyrrolyl)methylenesulfamoyl)-4-bromobenzoate (3d). IR: 3419, 3326, 3233 (NH), 1586 (NH_2), 1558 (C=N), 1285, 1193 (SO_2) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): $\delta = 1.85$ (m, 4 H, CH_2), 3.36 (m, 4 H, NCH_2), 3.89 (s, 3 H, CO_2CH_3), 7.014 (b.s., 2 H, NH), 7.93 (s, 2 H, ArH), 8.55 (s, 1 H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 24.87$, 25.43, 46.25, 47.88, 53.10, 125.49, 129.33, 129.79, 133.07, 136.36, 144.28, 154.60, 165.42. Calcd. (%) for $C_{13}H_{16}BrN_3O_4S$: C, 40.01; H, 4.13; Br, 20.47; N, 10.77. Found: C, 39.82; H, 4.05; Br, 20.32; N, 10.54.

Methyl-3-(amino(methylthio)methylenesulfamoyl)-4-bromobenzoate (3e). IR: 3433, 3335 (NH), 1588 (NH_2), 1533 (C=N), 1283, 1147 (SO_2) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): $\delta = 2.32$ (s, 3 H, SCH_3), 3.9 (s, 3 H, CO_2CH_3), 8.00 (s, 2 H, ArH), 8.21 (b.s., 1 H, NH), 8.55 (s, 1 H, ArH), 8.93 (b.s., 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 14.24$, 53.18, 125.70, 129.55, 130.18, 133.96, 136.52, 142.46, 165.24, 170.34. Calcd. (%) for $C_{10}H_{11}BrN_2O_4S_2$: C, 32.71; H, 3.02; Br, 21.76; N, 7.63. Found: C, 32.52; H, 3.09; Br, 21.53; N, 7.52.

Methyl-3-(amino(methoxy)methylene)sulfamoyl)-4-bromobenzoate (3f). IR: 3442, 3321 (NH), 1620 (NH_2), 1546 (C=N), 1281, 1149 (SO_2) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): $\delta = 3.7$ (s, 3 H, OCH_3), 3.9 (s, 3 H, CO_2CH_3), 7.43 (b.s., 1 H, NH), 8.00 (s, 2 H, ArH), 8.45 (b.s., 1 H, NH), 8.60 (s, 1 H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 53.17$, 55.53, 125.53, 129.60, 130.10, 133.92, 136.93, 142.53, 160.64, 165.25. Calcd. (%) for $C_{10}H_{11}BrN_2O_5S$: C, 34.20; H, 3.16; Br, 22.75; N, 7.98. Found: C, 34.03; H, 3.24; Br, 22.53; N, 8.02.

N1-(1-Aminoethilidene)-2,5-dibromo-1benzenesulfonamide (3g). IR: 3224, 3140 (NH_2), 1620 (NH_2), 1442 (C=N), 1248, 1151 (SO_2) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): $\delta = 2.14$ (s, 3 H, CH_3), 7.75 (d, $^3J_{HH} = 8$ Hz, 1 H, ArH), 7.69 (d, $^3J_{HH} = 8$ Hz, 1 H, ArH), 8.13 (s, 1 H, ArH), 8.55 (b. s. 2 H, NH). ^{13}C NMR (125 MHz, DMSO–d_6): $\delta = 22.18$, 119.36, 120.98, 131.82, 136.29, 137.48, 144.19, 169.18. Calcd. (%) for $C_8H_8Br_2N_2O_2S$: C, 26.99; H, 2.26; Br, 44.89; N, 7.87. Found: C, 26.77; H, 2.22; Br, 44.68; N, 7.76.

N1-Amino(phenyl)methylene-2,5-dibromo-1-benzenesulfonamide (3h). IR: 3428, 3315, 3247 (NH), 1617 (NH_2), 1512 (C=N), 1282, 1140 (SO_2) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): $\delta = 7.49$ (t, $^3J_{HH} = 7$ Hz, 2 H, ArH), 7.60 (t, $^3J_{HH} = 7$ Hz, 1 H, ArH), 7.72 (d, $^3J_{HH} = 7$ Hz, 1 H, ArH), 7.77 (d, $^3J_{HH} = 7$ Hz, 1 H, ArH), 7.90 (d, $^3J_{HH} = 7$ Hz, 2 H, ArH), 8.28 (s, 1 H, ArH), 8.74 (b.s., 2, H,

NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 119.51, 121.07, 128.60, 128.95, 132.30, 133.01, 133.69, 136.60, 137.56, 143.63, 164.07. Calcd. (%) for $C_{13}H_{10}Br_2N_2O_2S$: C, 37.35; H, 2.41; Br, 38.22; N, 6.70. Found: C, 37.07; H, 2.38; Br, 38.33; N, 6.58.

N1-(1-Iminoethylidene)-2,4-dibromo-1-benzenesulfonamide (3i). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.12 (s, 3 H, CH_3), 7.76 (d, $^3J_{HH}$ = 8 Hz, 1 H, ArH), 7.96 (d, $^3J_{HH}$ = 8 Hz, 1 H, ArH), 8.06 (s, 1 H, ArH), 8.18 (b.s, 1 H, NH), 8.62 (b.s., 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 22.11, 121.43, 126.07, 131.11, 131.30, 137.25, 141.99, 169.03. Calcd. (%) for $C_8H_8Br_2N_2O_2S$: C, 26.99; H, 2.26; Br, 44.89; N, 7.87. Found: C, 27.05; H, 2.23; Br, 44.52; N, 7.72.

N1-Amino(phenyl)methylene-2,4-dibromo-1-benzenesulfonamide (3j). IR: 3405, 3317, 3228 (NH), 1625 (NH_2), 1528 (C=N), 1278, 1153 (SO_2) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.48 (t, $^3J_{HH}$ = 8 Hz, 2 H, ArH), 7.6 (t, $^3J_{HH}$ = 8 Hz, 1 H, ArH), 7.80 (d, $^3J_{HH}$ = 8.5 Hz, 1 H, ArH), 7.88 (d, $^3J_{HH}$ = 8 Hz, 2 H, ArH), 8.05–8.1 (m, 2 H, ArH), 8.29 (b.s., 1 H, NH), 9.27 (b.s., 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 121.59, 126.60, 128.57, 128.89, 131.35, 131.41, 133.05, 133.59, 137.43, 141.30, 163.88. Calcd. (%) for $C_{13}H_{10}Br_2N_2O_2S$: C, 37.35; H, 2.41; Br, 38.22; N, 6.70. Found: C, 37.02; H, 2.38; Br, 38.03; N, 6.59.

General Procedure for Preparation of Sulfonylated Amidines (Route B)

Lactime ether **5** (1.2 eq) was added to a solution of *o*-bromoarylsulfonamide **4** in ethanol. The reaction mixture was refluxed for 8 h, and then the solvent was removed under reduced pressure. The residue was triturated with water, and the resulting precipitate was filtered, thoroughly washed with water, and dried at ambient conditions. If further purification is necessary the product is recrystallized from methanol.

Selected Data for 6a–6e

2-(2-Bromophenylsulfonylimino)pyrrolidine (6a). IR: 3409, 3321, 3205 (NH), 1563 (C=N), 1300, 1148 (SO_2) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.03–1.98 (m, 2 H, CH_2), 2.76 (t, $^3J_{HH}$ = 8.5 Hz, 2 H, CH_2), 3.42 (t, $^3J_{HH}$ = 8.5 Hz, 2 H, CH_2), 7.48 (t, $^3J_{HH}$ = 7.5 Hz, 1H, ArH), 7.55 (t, $^3J_{HH}$ = 7.5 Hz, 1 H, ArH), 7.79 (d, $^3J_{HH}$ = 7.5 Hz, 1 H, ArH), 8.06 (d, $^3J_{HH}$ = 7.5 Hz, 1 H, ArH), 9.12 (b.s., 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.92, 32.25, 46.37, 120.20, 128.25, 129.71, 133.58, 135.44, 142.63, 173.16. Calcd. (%) for $C_{10}H_{11}BrN_2O_2S$: C, 39.62; H, 3.66; Br, 26.36; N, 9.24. Found: C, 39.24; H, 3.71; Br, 26.15; N, 9.17.

Metyl-4-bromo-3-tetrahydro-1*H*-2-pyrrolydensulfamoylbenzoate (6b). IR: 3382, 3275, 3126 (NH), 1588 (C=N), 1281, 1153 (SO_2) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.03 (p, $^3J_{HH}$ = 7 Hz, 2 H, CH_2), 2.79 (t, $^3J_{HH}$ = 7 Hz, 2 H, CH_2), 3.43 (t, $^3J_{HH}$ = 7 Hz, 2 H, CH_2), 3.90 (s, 3 H, CO_2CH_3), 7.97 (s, 2 H, ArH), 8.55 (s, 1 H, ArH), 9.23 (b.s., 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.96, 32.30, 45.38, 53.17, 125.81, 129.55, 129.86, 133.56, 136.36, 143.26,

163.52, 173.47. Calcd. (%) for $C_{12}H_{13}BrN_2O_4S$: C, 39.90; H, 3.63; Br, 22.21; N, 7.76. Found: C, 40.06; H, 3.58; Br, 22.02; N, 7.82.

Methyl-3-(2-azapanylidensulfamoyl)-4-bromobenzoate (6c). IR: 3419, 3326 (NH), 1528 (C=N), 1283, 1149 (SO_2) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): $\delta = 1.36$–1.60 (m, 2 H, CH_2), 1.62–1.70 (m, 2 H, CH_2), 2.72 (m, 2 H, CH_2), 3.90 (s, 3 H, CO_2CH_3), 7.97 (s, 2 H, ArH), 8.55 (s, 1 H, ArH), 8.92 (b.s., 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 23.20$, 28.44, 29.70, 34.54, 43.77, 53.18, 125.88, 129.52, 129.66, 133.64, 136.39, 143.14, 165.27, 173.38. Calcd. (%) for $C_{14}H_{17}BrN_2O_4S$: C, 43.20; H, 4.40; Br, 20.53; N, 7.20. Found: C, 43.05; H, 4.32; Br, 20.37; N, 7.32.

2-(2,5-Dibromophenylsulfonylimino)pyrrolidine (6d). IR: 3224, 3140 (NH), 1618 (C=N), 1301, 1151 (SO_2) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): $\delta = 2.02$ (m, 2 H, CH_2), 2.97 (t, $^3J_{HH} = 7$ Hz, 2 H, CH_2), 3.43 (t, $^3J_{HH} = 7$ Hz, 2 H, CH_2), 7.74 (d, $^3J_{HH} = 8.5$ Hz, 1 H, ArH), 7.69 (dd, $^3J_{HH} = 8.5$ Hz, $^4J_{HH} = 2$ Hz, ArH), 8.13 (d, $^3J_{HH} = 2$ Hz, 1 H, ArH), 9.23 (b.s., 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 20.94$, 32.24, 45.40, 121.43, 126.02, 131.22, 131.31, 137.23, 142.09, 173.41. Calcd. (%) for $C_{10}H_{10}Br_2N_2O_2S$: C, 31.44; H, 2.64; Br, 41.38; N, 7.33. Found: C, 31.21; H, 2.69; Br, 41.39; N, 7.21.

2-(2,4-Dibromophenylsulfonylimino)pyrrolidine (6e). IR: 3205, 3113 (NH) 1563 (C=N), 1299, 1151 (SO2) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): $\delta = 2.01$ (t, $^3J_{HH} = 7$ Hz, 2 H, CH_2), 2.77 (t, $^3J_{HH} = 7$ Hz, 2 H, CH_2), 3.42 (t, $^3J_{HH} = 7$ Hz, 2 H, CH_2), 7.6 (dd, $^3J_{HH} = 8$ Hz, $^4J_{HH} = 2$ Hz, 1 H, ArH), 7.97 (d, $^3J_{HH} = 8$ Hz, 1 H, ArH), 8.04 (d, $^3J_{HH} = 2$ H, 1 H, ArH), 9.18 (b.s., 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 20.94$, 32.24, 45.40, 121.43, 126.02, 131.22, 131.31, 137.23, 142.09, 173.41. Calcd. (%) for $C_{10}H_{10}Br_2N_2O_2S$: C, 31.44; H, 2.64; Br, 41.38; N, 7.33. Found: C, 31.25; H, 2.59; Br, 41.72; N, 7.28.

General Procedure for Preparation of 4*H*-1,2,4-Benzothiadiazine-1,1-dioxides (7)

Potassium carbonate (2 eq), 5 mol% of Cu (I) iodide, and 10 mol% of DMEDA were added to a DMF solution of a sulfonylated amidine (**3**) under argon flow. The reaction mixture was stirred under argon at 70 °C for 8 h. After that, solvent was removed at reduced pressure. The residue was dissolved in water and acidified to pH 1. The precipitate was filtered out, washed with water, and dried at ambient condition.

Selected Data for 7a–7i

3-Methyl-4*H*-1,2,4-benzothiadiazine-1,1-dioxide (7a). Mp 254 °C (previously reported 254–255 °C[9]). ^1H NMR (500 MHz, DMSO-d_6): $\delta = 2.31$ (s, 3 H, CH_3), 7.30 (d, $^3J_{HH} = 8$ Hz, 1 H, ArH), 7.43 (t, $^3J_{HH} = 8$ Hz, 1 H, ArH), 7.67 (t, $^3J_{HH} = 8$ Hz, 1 H, ArH), 7.79 (d, $^3J_{HH} = 8$ Hz, ArH), 12.03 (b.s., 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 23.20$, 120.09, 120.52, 126.18, 126.25, 129.56,

136.97, 158.04. Calcd. (%) for $C_8H_8N_2O_2S$: C, 48.97; H, 4.11; N, 14.28. Found: C, 48.75; H, 4.05; N, 14.53.

Methyl-1,1-dioxo-3-methyl-4*H*-1,2,4-benzothiadiazine-7-carboxylate (7b). IR: 1244, 1133 (SO_2) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): $\delta = 2.34$ (s, 3 H, CH_3), 3.90 (s, 3 H, CO_2CH_3), 7.43 (d, $^3J_{HH} = 9$ Hz, 1 H, ArH), 8.18 (dd, $^3J_{HH} = 9$ Hz, $^4J_{HH} = 2$ Hz, 1 H, ArH), 8.25 (d, $^3J_{HH} = 2$ Hz, ArH), 12.43 (b.s., 1 H, NH). ^{13}C (125 MHz, DMSO-d_6): $\delta = 23.21$, 53.01, 118.48, 121.24, 125.47, 127.42, 133.66, 139.14, 158.49, 164.90. Calcd. (%) for $C_{10}H_{10}N_2O_4S$: C, 47.24; H, 3.96; N, 11.02. Found: C, 47.02; H, 3.92; N, 11.15.

Methyl-1,1-dioxo-3-phenyl-4*H*-1,2,4-benzothiadiazine-7-carboxylate (7c). IR: 1246, 1123 (SO_2) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): $\delta = 3.90$ (s, 3 H, CO_2CH_3), 7.6–7.68 (m, 2 H, ArH), 7.69–7.82 (m, 2 H, ArH), 8.0–8.1 (m, 2 H, ArH), 8.25 (d, $^3J_{HH} = 7.5$ Hz, 1 H, ArH), 8.32 (s, 1 H, ArH) 12.55 (b.s., 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 53.11$, 119.74, 121.62, 125.30, 128.00, 128.87, 129.45, 131.87, 133.80, 133.81, 139.44, 155.96, 164.98. Calcd. (%) for $C_{15}H_{12}N_2O_4S$: C, 56.95; H, 3.82; N, 8.86. Found: C, 56.72; H, 3.85; N, 8.78.

Methyl-1,1-dioxo-3-(tetrahydro-1*H*-1-pyrrolyl)-4*H*-1,2,4-benzothiadiazine-7-carboxylate (7d). IR: 1251, 1121 (SO_2) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): $\delta = 1.8$ (m, 4 H, CH_2), 3.4–3.65 (m, 4 H, CH_2), 3.87 (s, 3 H, CO_2CH_3), 7.61 (d, $^3J_{HH} = 8$ Hz, 1 H, ArH), 8.10 (d, $^3J_{HH} = 8$ Hz, ArH), 8.17 (s, 1 H, ArH), 10.62 (b.s., 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 25.19$, 47.78, 52.80, 118.30, 123.21, 124.57, 125.19, 133.00, 140.35, 149.19, 165.29. Calcd. (%) for $C_{13}H_{15}N_3O_4S$: C, 50.48; H, 4.89; N, 13.58. Found: C, 50.53; H, 4.82; N, 13.62.

Methyl-1,1-dioxo-3-methoxy-4*H*-1,2,4-benzothiadiazine-7-carboxylate (7e). IR: 1251, 1133 (SO_2) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): $\delta = 3.87$ (s, 3 H, CO_2CH_3), 3.93 (s, 3 H, OCH_3), 7.47 (d, $^3J_{HH} = 8$ Hz, 1 H, ArH), 8.14 (d, $^3J_{HH} = 8$ Hz, 1 H, ArH), 8.22 (s, 1 H, ArH), 12.74 (b.s., 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 52.96$, 56.19, 118.21, 121.60, 125.28, 126.41, 133.91, 138.69, 154.67, 164.99. Calcd. (%) for $C_{10}H_{10}N_2O_5S$: C, 44.44; H, 3.73; N, 10.37. Found: C, 44.27; H, 3.68; N, 10.25.

7-Bromo-3-methyl-4*H*-1,2,4-benzothiadiazine-1,1-dioxide (7f). Mp 320 °C (sublimation; previously reported 333–335 °C[20]). IR: 1281, 1133 (SO_2) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): $\delta = 2.31$ (s, 3 H, CH_3), 7.28 (d, $^3J_{HH} = 8.5$ Hz, 1 H, ArH), 7.83 (dd, $^3J_{HH} = 8.5$ Hz, $^4J_{HH} = 2$ Hz, 1 H, ArH), 7.93 (d, $^3J_{HH} = 2$ Hz, ArH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 23.14$, 117.53, 120.30, 122.84, 126.02, 134.92, 136.40, 157.99. Calcd. for $C_8H_7BrN_2O_2S$: C, 34.93; H, 2.56; Br, 29.04; N, 10.18. Found: C, 34.81; H, 2.52; Br, 29.13; N, 10.08.

7-Bromo-3-phenyl-4*H*-1,2,4-benzothiadiazine-1,1-dioxide (7g). Mp 349 °C (formerly reported 348–349 °C[20]). ^1H NMR (500 MHz, DMSO-d_6): $\delta = 7.55$–7.66 (m, 2 H, ArH), 766–7.76 (m, 2 H, ArH), 7.93 (d, $^3J_{HH} = 8$ Hz, 1 H, ArH), 8.02 (s, 1H, ArH), 8.08 (d, $^3J_{HH} = 7$ Hz, 2 H, ArH), 12.47 (b.s., 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 118.24$, 121.58, 125.90, 128.86, 129.36, 132.02, 133.50, 135.30, 136.53, 155.38. Calcd. (%) for $C_{13}H_9BrN_2O_2S$: C, 46.31; H, 2.69; Br, 23.70; N, 8.31. Found: C, 46.23; H, 2.66; Br, 23.54; N, 8.27.

6-Bromo-3-methyl-4*H*-1,2,4-benzothiadiazine-1,1-dioxide (7h). Mp 315 °C (formerly reported 312–316 °C[6]). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.32 (s, 3 H, CH_3), 7.46 (s, 1 H, ArH), 7.61 (d, $^3J_{HH}$ = 8 Hz, 1 H, ArH), 7.76 (d, $^3J_{HH}$ = 8 Hz, 1 H, ArH), 12.12 (b.s., 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 23.20, 120.09, 120.52, 126.18, 126.25, 129.56, 136.97, 158.04. Calcd for $C_8H_7BrN_2O_2S$: C, 34.93; H, 2.56; Br, 29.04; N, 10.18. Found: C, 34.68; H, 2.59; Br, 28.92; N, 10.09.

6-Bromo-3-phenyl-4*H*-1,2,4-bezothiadiazine-1,1-dioxide (7i). IR: 1251, 1147 (SO_2) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.63 (t, $^3J_{HH}$ = 8 Hz, 2 H, ArH), 7.70 (t, $^3J_{HH}$ = 8 Hz, 2 H, ArH), 7.83 (d, $^3J_{HH}$ = 8 Hz, 1 H, ArH), 7.89 (s, 1 H, ArH), 8.05 (d, $^3J_{HH}$ = 8 Hz, 2 H, ArH), 12.35 (b.s., 1 H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 120.98, 121.48, 126.04, 126.35, 128.80, 129.41, 130.06, 132.02, 133.55, 137.32, 155.43. Calcd. (%) for $C_{13}H_9BrN_2O_2S$: C, 46.31; H, 2.69; Br, 23.70; N, 8.31. Found: C, 46.28; H, 2.64; Br, 23.14; N, 8.25.

General Procedure for Preparation of 4*H*-1,2,4-Benzothiadiazine-1,1-dioxides (8)

Potassium carbonate (2 eq), 5 mol % of Cu (I) iodide, and 10 mol. % of DMEDA were added to a DMF solution of a sulfonylated amidine (**6**) under argon flow. The reaction mixture was stirred under argon at 70 °C for 8 hrs. After that precipitate was filtered out and solvent was removed at reduced pressure. Residue diluted with water and filtered out, washed with water and dried at ambient condition.

Selected Data for 8a–8e

5,5-Dioxo-1*H*,2*H*,3*H*-benzo[e]pyrrolo[2,1-c][1,2,4]thiadiazine (8a). Mp 296 °C (formerly reported 297 °C[19]). IR: 1285, 1147 (SO_2) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.13–2.26 (m, 2 H, CH_2), 2.97 (t, $^3J_{HH}$ = 7.5, Hz 2 H, CH_2), 4.15 (t, $^3J_{HH}$ = 7.5 Hz, 2 H, CH_2), 7.39 (d, $^3J_{HH}$ = 8 Hz, 1 H, ArH), 7.52 (t, $^3J_{HH}$ = 8 Hz, 1 H, ArH), 7.76 (t, $^3J_{HH}$ = 8 Hz, 1 H, ArH), 7.87 (d, $^3J_{HH}$ = 8 Hz, 1 H, ArH). ^{13}C NMR (500 MHz, DMSO-d_6): δ = 18.24, 33.76, 50.38, 116.77, 121.64, 124.40, 126.67, 133.64, 135.14, 163.81. Calcd. (%) for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60. Found: C, 54.11; H, 4.48; N, 12.38.

5,5-Dioxo-7-methyloxycarbonyl-1*H*,2*H*,3*H*-benzo[e]pyrrolo[2,1-c][1,2,4]-thiadiazine (8b). IR: 1292, 1153 (SO_2) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.15–2.3 (m, 2 H, CH_2), 2.95–3.1 (m, 2 H, CH_2), 3.9 (s, 3 H, CO_2CH_3), 4.1–4.3 (m, 2 H, CH_2), 7.52 (d, $^3J_{HH}$ = 8 Hz, 1 H, ArH), 8.24 (d, $^3J_{HH}$ = 8 Hz, 1 H, ArH), 8.3 (s, 1 H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 18.28, 33.84, 50.74, 53.09, 117.66, 121.34, 125.62, 127.36, 133.78, 138.46, 164.69, 164.86. Calcd. (%) for $C_{12}H_{12}N_2O_4S$: C, 51.42; H, 4.32; N, 9.99. Found: C, 51.32; H, 4.26; N, 10.01.

5,5-Dioxo-7-methyloxycarbonyl-7*H*,8*H*,9*H*,10*H*,11*H*-benzo[5,6][1,2,4]-thiadiazino[4,3-a]azepin (8c). IR: 1292, 1167 (SO_2) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.74 (m, 4 H, CH_2), 1.82 (m, 2 H, CH_2), 3.00 (m, 2H, CH_2), 3.90 (s, 3 H, CO_2CH_3), 4.30 (m, 2 H, CH_2), 7.80 (d, $^3J_{HH}$ = 8 Hz, 1 H, ArH), 8.25

(d, $^3J_{HH} = 8$ Hz, 1 H, ArH), 8.30 (s, 1 H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 24.37$, 26.19, 28.01, 38.06, 49.24, 53.09, 117.97, 123.14, 125.43, 127.24, 133.89, 141.50, 164.81, 167.03. Calcd. (%) for $C_{14}H_{16}N_2O_4S$: C, 54.53; H, 5.23; N, 9.08. Found: C, 54.39; H, 5.33; N, 9.13.

7-Bromo-5,5-dioxo-1*H*,2*H*,3*H*-benzo[e]pyrrolo[2,1-c][1,2,4]thiadiazine (8d). ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 2.1$–2.25 (m, 2 H, CH_2), 2.96 (t, $^3J_{HH} = 6$ Hz, 2 H, CH_2), 4.14 (t, $^3J_{HH} = 6$ Hz, 2 H, CH_2), 7.38 (d, $^3J_{HH} = 8$ Hz, 1 H, ArH), 7.95 (d, $^3J_{HH} = 8$ Hz, 1 H, ArH), 8.00 (s, 1 H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 18.14$, 33.79, 50.60, 117.96, 119.52, 122.96, 126.50, 134.44, 136.42, 164.10. Calcd. (%) for $C_{10}H_9BrN_2O_2S$: C, 39.88; H, 3.01; Br, 26.53; N, 9.30. Found: C, 39.82; H, 2.97; Br, 26.64; N, 9.23.

6-Bromo-5,5-dioxo-1*H*,2*H*,3*H*-benzo[e]pyrrolo[2,1-c][1,2,4]thiadiazine (8e). IR: 1290, 1156 (SO_2) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 2.12$–2.24 (m, 2 H, CH_2), 2.98 (t, $^3J_{HH} = 8.5$ Hz, 2 H, CH_2), 4.15 (t, $^3J_{HH} = 8.5$ Hz, 2 H, CH_2), 7.66 (s, 1 H, ArH), 7.70 (d, $^3J_{HH} = 8$ Hz, 1 H, ArH), 7.81 (dd, $^3J_{HH} = 8$ Hz, $^4J_{HH} = 2$ Hz, 1 H, ArH). ^{13}C NMR (125 NHz, DMSO-d_6): $\delta = 18.25$, 33.82, 50.66, 119.56, 120.53, 126.46, 126.89, 129.61, 136.41, 164.24. Calcd. (%) for $C_{10}H_9BrN_2O_2S$: C, 39.88; H, 3.01; Br, 26.53; N, 9.30. Found: C, 39.67; H, 3.04; Br, 26.37; N, 9.24.

REFERENCES

1. Topiliss, J. G.; Yudis, M. D. Correlation of antihypertensive activity with structure in a series of 2*H*-1,2,4-benzothiadiazine 1,1-dioxides using the substituent constant approach. *J. Med. Chem.* **1972**, *15*, 394–400.
2. Tait, A.; Luppi, A.; Franchini, S.; Preziosi, E.; Parenti, C.; Buccioni, M.; Marucci, G.; Leonardi, A.; Poggessi, E.; Brasili, L. 1,2,4-Benzothiadiazine derivatives as α1 and 5-HT1A receptor ligands. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1185–1188.
3. Dibella, M.; Rinaldi, M.; Fabio, U.; Manicard, G. Antimicrobial action of 1,2,4-benzothiadiazine-1,1-dioxide derivatives. *Farmaco* **1973**, *28*, 777–783.
4. Zhan, P.; Liu, X. Y.; De Clercq, E. Recent advances in antiviral activity of benzo/heterothiadiazine dioxide derivatives. *Curr. Med. Chem.* **2008**, *15*, 1529–1540.
5. (a) Topiliss, J. G.; Yudis, M. D. π-Substituent constants for the 2*H*-1,2,4-benzothiadiazine 1,1-dioxide system. *J. Med. Chem.* **1972**, *15*, 400–403; (b) Francotte, P.; de Tullio, P.; Goffin, E.; Dinitilhac, G.; Graindorge, E.; Fraikin, P.; Lestage, P.; Danober, L.; Thomas, J.-Y.; Caignard, D.-H.; Pirotte, B. Design, synthesis, and pharmacology of novel 7-substituted 3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxides as positive allosteric modulators of AMPA receptors. *J. Med. Chem.* **2007**, *50*, 3153–3157.
6. Girad, Y.; Atkinson, J. Aminomethyl-1,2,4-benzothiadiazines as potential analogs of γ-aminobutyric acid: Unexpected discovery of a taurine antagonist. *J. Med. Chem.* **1982**, *25*, 113–116.
7. Makino, S.; Okuzumi, T.; Nakanishi, T.; Tsuji, T. Solid-phase synthesis of 2-substituted-3-(substituted sulfanyl)-1,2,4-benzothiadiazine 1,1-dioxide library. *Tetrahedron Lett.* **2002**, *43*, 8401–8403.
8. Girad, Y.; Atkinson, J. G.; Rokach, J. A new synthesis of 1,2,4-benzothiadiazines and a selective preparation of *o*-aminobenzenesulphonamides. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1043–1047.

9. Kim, J.; Lee, S. Y.; Lee, J.; Do, Y.; Chang, S. Synthetic utility of ammonium salts in a Cu-catalyzed three-component reaction as a facile coupling partner. *J. Org. Chem.* **2008**, *73*, 9454–9457.
10. Yang, D.; Fu, H.; Hu, L.; Jiang, Y.; Zhao, Y. Environmentally friendly iron-catalyzed cascade synthesis of 1,2,4-benzothiadiazine-1,1-dioxide and quinazolinone derivatives. *J. Comb. Chem.* **2009**, *11*, 653–657.
11. Nazarenko, K. G.; Shirokaya, T. I.; Tolmachev, A. New derivatives of 3,4-polymethylene-1,2,4-benzothiadiazine-1,1-dioxides. *Khim. Geter. Soed.* **2005**, 225–229.
12. (a) Srivastava, B. K.; Soni, R.; Joharapurkar, A.; Sairam, K. V. V. M.; Patel, J. Z.; Goswami, A.; Shedage, S. A.; Kar, S. S.; Salunke, R. P.; Gugale, S. B.; Dhawas, A.; Kadam, P.; Mishra, B.; Sadhwani, N.; Unadkat, V. B.; Mitra, P.; Jainb, M. R.; Patela, P. R. Bioisosteric replacement of dihydropyrazole of 4*S*-(–)-3-(4-chlorophenyl)-N-methyl-N′-[(4-chlorophenyl)-sulfonyl]-4-phenyl-4,5-dihydro-1H-pyrazole-1-caboxamidine (SLV-319), a potent CB1 receptor antagonist by imidazole and oxazole. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 963–968; (b) Maccallini, C.; Patruno, A.; Bešker, N.; Ali, J. I.; Ammazzalorso, A.; De Filippis, B.; Franceschelli, S.; Giampietro, L.; Pesce, M.; Reale, M.; Tricca, M. L.; Re, N.; Felaco, M.; Amoro, R. Synthesis, biological evaluation, and docking studies of N-substituted acetamidines as selective inhibitors of inducible nitric oxide synthase. *J. Med. Chem.* **2009**, *52*, 1481–1485.
13. (a) Jackman, L. M.; Jen, T. ^{1}H and ^{13}C nuclear magnetic resonance studies on the tautomerism, geometrical isomerism, and conformation of some cyclic amidines, guanidines, and related systems. *J. Am. Chem. Soc.* **1975**, *97*, 2811–2818; (b) Meschede, L.; Limbach, H.-H. Dynamic NMR study of the kinetic HH/HD/DD isotope effects on the double proton transfer in cyclic bis(*p*-fluorophenyl)formamidine dimers. *J. Phys. Chem.* **1991**, *95*, 10267–10280; (c) Anulewicz, R.; Wawer, I.; Krygowski, T. M.; Männle, F.; Limbach, H.-H. Combined x-ray diffraction and ^{15}N CPMAS NMR study of molecular structure and proton order/disorder phenomena in cyclic N,N′-bisarylformamidine dimers. *J. Am. Chem. Soc.* **1997**, *119*, 12223–12230.
14. Bae, I.; Han, H.; Chang, S. Highly efficient one-pot synthesis of N-sulfonylamidines by Cu-catalyzed three-component coupling of sulfonyl azide, alkyne, and amine. *J. Am. Chem. Soc.* **2005**, *127*, 2038–2039.
15. Bahlman, A. Ueber die Orthobromsulfobenzolsäure. *Just. Lieb. Ann. Chem.* **1876**, *181*, 203–208.
16. Huntress, E. H.; Carten, F. H. Identification of organic compounds, I: Chlorosulfonic acid as a reagent for the identification of aryl halides. *J. Am. Chem. Soc.* **1940**, *62*, 511–514.
17. Pezold, M.; Schreiber, R. S.; Shriner, R. L. The hydrolysis of substituted sulfonanilides, II. *J. Am. Chem. Soc.* **1934**, *56*, 696–697.
18. Wrobel, J.; Green, D.; Jetter, J.; Kao, W.; Rogers, J.; Pérez, M. C.; Hardenburg, J.; Deecher, D. C.; López, F. J.; Arey, B. J.; Shen, E. S. Synthesis of (bis)sulfonic acid, (bis)-benzamides as follicle-stimulating hormone (FSH) antagonists. *Bioorg. Med. Chem.* **2002**, *10*, 639–656.
19. Raffa, L.; Pecorarl, P. Research on 1,2,4-benzo-thiadiazines, XXVIII: Preparation of 5,7-dichloro-l,2,4-benzothia-diazine-l,l-dioxide (hypotensive agent). *Farmaco* **1963**, *18*, 957–963.
20. Moehler, H.; Niefenthaler, H.; Schrinke, J. 3,4-Substituierte Hydro-1,2,4-benzothiadiazin-1,1-dioxide. *Archiv Pharm.* **1990**, *323*, 911–913.