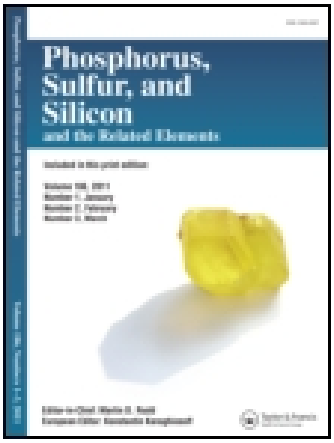


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# Green Approach Toward One Pot Cascade Synthesis of 3-Aryl-3,4-Dihydro-1,2,4 Benzothiadiazine-1,1-Dioxides

Someshwar Dagduappa Dindulkar [a b], Kwon Taek Lim [a], Byung Kwon Cho [a] & Yeon Tae Jeong [a]

[a] Department of Image Science and Engineering, Pukyong National University, Busan, Korea

[b] Mahatma Gandhi Missions Jawaharlal Nehru Engineering College, Aurangabad, 431003, Maharashtra, India

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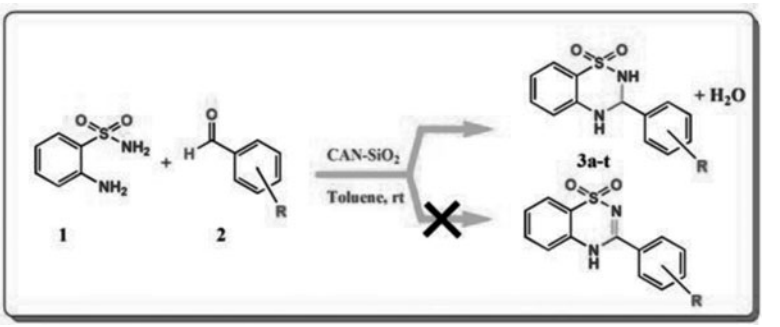
# GREEN APPROACH TOWARD ONE POT CASCADE SYNTHESIS OF 3-ARYL-3,4-DIHYDRO-1,2,4 BENZOTHIADIAZINE-1,1-DIOXIDES

**Someshwar Dagduappa Dindulkar,[1,2] Kwon Taek Lim,[1] Byung Kwon Cho,[1] and Yeon Tae Jeong[1]**

[1]*Department of Image Science and Engineering, Pukyong National University, Busan, Korea*

[2]*Mahatma Gandhi Missions Jawaharlal Nehru Engineering College, Aurangabad, 431003, Maharashtra, India*

## GRAPHICAL ABSTRACT




**Abstract** *A silica-gel-supported ceric ammonium nitrate (CAN-$SiO_2$) was found to be an effective catalyst for the cascade synthesis of functionalized 3-aryl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxides using 2-aminobenzenesulfonamide and benzaldehydes at room temperature. The reaction allows rapid cyclization (10−70 min) with 5 mol% CAN impregnated on silica gel to give the desired products in excellent yield without further column purification. The protocol uses inexpensive and environmentally friendly CAN-$SiO_2$ as the catalyst, and no ligand or additive was required.*

*[Supplementary materials are available for this article. Go to the publisher's online edition of* Phosphorus, Sulfur, and Silicon and the Related Elements *for the following free supplemental files: Additional figures]*

**Keywords:** Supported ceric ammonium nitrate; heterogeneous catalyst; benzothiadiazine-1, 1-dioxides; cascade synthesis

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Address correspondence to Professor Yeon Tae Jeong, Pukyong National University, Image Science and Engg, Gaon Building room 801, Daeon-Dong-3 Nam Gu, Busan 608739 Korea. E-mail: ytjeong@pknu.ac.kr

## INTRODUCTION

Sulfur-nitrogen heterocyclic compounds have retained the interest of organic researchers for several decades. Organosulfur compounds constitute an important class of organic compounds with diverse biological activities, and valuable building blocks for a variety of sulfur containing heterocyclic molecule synthesis.[1] Owing to their biological and physical properties as well as their utility as synthetic intermediates.[2] Organosulfur compounds also have applications in the field of Electron Probe Microanalysis.[3] Specifically, benzothiadiazine-1,1-dioxides are known to show various useful biological and medicinal activities.[4,5] In particular, benzo or pyridothiadiazine dioxides, as well as dihydrobenzopyrans, represent interesting targets to develop in the field of potassium channel openers, potent AMPA receptors, and also the benzothiadiazine groups were found to be a potent selective aldose reductase inhibitors *in vitro* (Figure 1).[6–14] Due to broad application in the field of medicinal chemistry, the benzothiadiazine molecules have raised great interest among chemists, biologists, and pharmacologists. Due to their wide therapeutic use in medicinal chemistry, these adventitious heterocycles encourage us to develop an efficient route for their synthesis.

Although many methods have been developed for the synthesis of different aromatic sulfur heterocyclic compounds, the synthesis of a benzothiadiazine-1,1-dioxide heterocycle, typically involves conventional methods for example $H_2SO_4$ or HCl and $NaHSO_3$ have frequently been used.[15–17] Overall studies indicate that the reported methods possess long reaction times, low yields, costly reagent conditions, and toxic acidic wastes after reaction work up procedure.

Owing to their environmental restrictions on disposal of hazardous toxic acidic waste due to the water-quenching step for neutralization of acidic reagents used in reaction condition, developmental efforts are needed to overcome these drawbacks. Chemists are focusing more on the uses of heterogeneous metal Lewis catalysts instead of traditional homogeneous metal Lewis and Brønsted acid catalysts. This can avoid difficult acidic waste-disposal problems because of easy separation of the heterogeneous catalyst and minimal leaching of catalyst in the solvent. Over the last few years, the number of reports dealing with the preparation, characterization and use of supported catalysts has increased.[18] Many outstanding reviews on supported catalysts have also been reported.[19] Inorganic material-supported catalysts are more efficient due to an increased effective area for the reaction, due

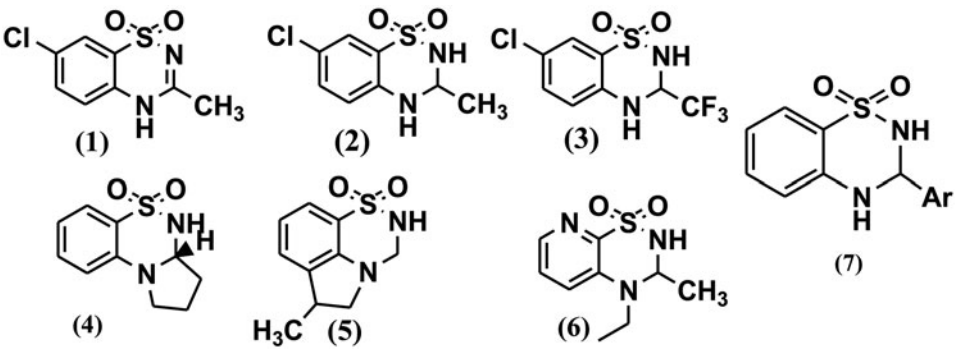
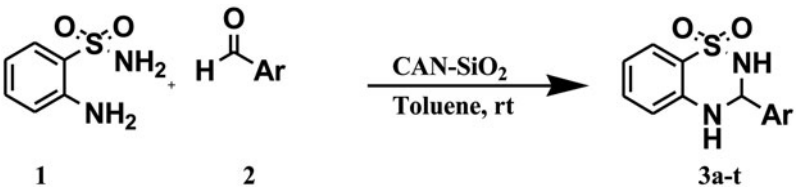



**Figure 1** Chemical structures of some reported biologically active molecule (**1**–**6**) and a general formula of the newly synthesized benzothiadiazine-1,1-dioxides (**7**).

to the presence of pores which force both substrate and catalyst towards a particular course of reaction and thus lower the entropy activation of reaction and accelerate the reaction by constraining both substrate and reagent into proximity.[20–22]

Recently ceric ammonium nitrate (CAN) ($Ce(NH_4)_2(NO_3)_6$) has been used in organic synthesis not only based on its electron-transfer capacity but also with its Lewis acidic property. Due to a dual role as both as oxidant and a Lewis acid,[23–25] it able to catalyze various organic transformations, such as functional-group conversion and promotion of bond-forming reactions.[26,27] It has been reported that silica-gel-supported CAN reagent is an efficient catalyst for selective removal of trityl and silyl groups from protected nucleosides and nucleotides.[28] It is also used in oxidation of aromatic compounds to quinines.[29] Silica-gel-supported CAN proximate the reactant, leading to a faster electron-transfer process between reactants and thus may catalyzes the reaction in shorter time. As a part of our interest on the development of newer environmentally benign methodology for diverse heterocyclic compounds of biological significance, industry and key intermediate for the multistep synthesis, we have implemented a number of green strategies in organic transformations using environmentally friendly catalytic reaction conditions.[30–34] We decided to investigate an efficient catalytic system for the synthesis of biologically active benzothiadiazine-1,1-dioxides. So, herein, we intend to report the tandem synthesis of 3-aryl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxides, from aromatic aldehydes and 2-aminobenzenesulfonamide using CAN-$SiO_2$ as an expeditious catalyst at room temperature. (Scheme 1).




**Scheme 1**

## RESULT AND DISCUSSION

In the present study, we have developed a highly practical and very simple method for synthesis of 3,4-dihydro-1,2,4-benzothiadiazines from 2-aminobenzenesulfonamide and aromatic aldehydes using CAN-$SiO_2$ catalyst at room temperature. After a series of studies, we achieved excellent yields in a very short duration at room temperature. Knowing the reaction is thought to give 2 products,[17] one of which is 3,4-dihydro and another one is 4H-1,2,4-benzothiadiazine-oxidized product, our studies indicated that this reaction proceed selectively with the formation of only 3,4-dihydro-1,2,4-benzothiadiazine using catalytic amount of CAN-$SiO_2$ (containing 0.05 equiv. of CAN) with short reaction time, at ambient temperature. On the other hand, the use of a heterogeneous catalyst makes this methodology more advantageous, because of the easy work-up procedure and recovery of catalyst.

In the beginning, the optimization of the reaction conditions was undertaken by investigating the effect of the various reaction parameters like different catalysts and solvents was carried out (Table 1). In order to establish the real effectiveness of the catalyst for

**Table 1** Optimization of reaction conditions using various solvents and catalysts

| Entry[a] | Catalyst (10 mol%) | Solvent | Time (h) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | Conc. HCl | Ethanol | 12 | 68 |
| 2 | Conc. $H_2SO_4$ | Ethanol | 12 | 75 |
| 3 | PTSA | Toluene | 7 | 74 |
| 4 | Amberlyst-15 | Toluene | 5 | 62 |
| 5[c] | CAN-$SiO_2$ | Toluene | 0.16 | 95 |
| 6 | $Cu(OTf)_2 \cdot SiO_2$ | Toluene | 1 | 90 |
| 7 | CAN | Toluene | 1 | 87 |
| 8 | $SiO_2$ | Toluene | 2 | 56 |
| 9 | — | Toluene | 24 | ≤20 |
| 10 | CAN-$SiO_2$ | Acetonitrile | 1 | 87 |
| 11 | CAN-$SiO_2$ | Ethanol | 1 | 76 |
| 12 | CAN-$SiO_2$ | DCM | 1 | 89 |
| 13 | CAN-$SiO_2$ | THF | 1 | 78 |
| 14 | CAN-$SiO_2$ | Water | 2 | 84 |
| 15[d] | CAN-$SiO_2$ | Toluene | 0.16 | 94 |
| 16[e] | CAN-$SiO_2$ | Toluene | 0.16 | 95 |

[a]Reactions and conditions: all reactions were carried out at room temperature using 2-aminobenzenesulfonamide (0.6 mmol), benzaldehyde (0.6 mmol), and 10%w/v or w/w acid catalyst.
[b]Isolated yields.
[c]CAN-$SiO_2$ containing 10 mol% CAN.
[d]CAN-$SiO_2$ containing 5 mol% CAN.
[e]CAN-$SiO_2$ containing 20 mol% CAN.



the synthesis of 3-phenyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxides, a test reaction was performed without catalyst using equimolar, amounts of 2-aminobenzenesulfonamide (**1**) and benzaldehyde (**2**), at room temperature in air. It was found that less than 20% yield product was obtained in the absence of catalyst even after 24 h (Table 1, entry 9). In order to find a more efficient and eco-friendly catalytic system for this reaction, the same test reaction was performed with different acid catalysts such as PTSA, Amberlyst-15, CAN, CAN-$SiO_2$, and $Cu(OTf)_2 \cdot SiO_2$ (Table 1),which were further compared with traditional reported acid catalysts such as conc. HCl and conc. $H_2SO_4$ (Table 1, entry 1 and 2). The overall study shows that use of traditional acids (mineral acids) reaction takes a long time with lower yield as compared to other acid catalysts; moreover, the work-up of this concentrated acid-catalyzed reaction is tedious and creates a large amount of acid waste.

Among all screened catalysts, CAN-$SiO_2$ gave the best yield in least reaction time (Table 1, entry 5). It noteworthy that when the test reaction was performed using $Cu(OTf)_2 \cdot SiO_2$ catalyst, the reaction was completed with good yield in 1 h. But from the view point of cost, ease of availability, and reaction time, CAN-$SiO_2$ is the best catalyst as compared to $Cu(OTf)_2 \cdot SiO_2$. To study the role of $SiO_2$, the test reaction was also performed with $SiO_2$, and we observed a good yield was obtained as compared to catalyst free reactions (Table 1, entry 8). Also the same test reaction was performed using a CAN, and was found to be less efficient as compared to supported CAN and also provided impurities to the products. Supported CAN is more efficient because of its weak surface Brønsted acidity of OH sites of silica gels. Silica supports improved the performance of heterogeneous metal-containing catalysts, though the mechanism through which it works is not well understood. In additionally, our literature survey on the usage of supported CAN as a catalyst for

the synthesis of 3-aryl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxides are unprecedented and more efficient than conventional methods.

Once we found CAN-$SiO_2$ as the best catalyst for this reaction, solvent and appropriate catalyst-loading optimization was performed. We screened various solvents, such as toluene, EtOH, $CH_3CN$, water, and THF at room temperature. Among the different tested organic solvents, only toluene and acetonitrile were found to give good yields. When we performed reaction in aqueous media, the reaction was completed with moderate yield (Table 1, entry 14). Furthermore, in an attempt to optimize the catalyst, a model reaction was carried out using 5 and 20 mol% of CAN supported on silica at room temperature in toluene (Table 1, entries 15 and 16). It was found that 5 mol% of CAN supported with silica showed the maximum yield in the minimum amount time. A larger amount of the catalyst loading (20 mol%) neither increases the yield nor shortens the conversion time. It was found that, instead of using 1.0 equivalent aldehyde, use of 1.2 equivalent of aldehyde provides a better yield in a short time. Furthermore, CAN-$SiO_2$ was recovered simply by dissolving the reaction mixture in acetone and filtering it to obtain the solid heterogeneous catalyst in excellent yields (about 93%). The crude product was obtained by evaporating the acetone. The crude product was further purified by recrystallization from ethanol or just by giving few washings of chloroform/ethyl acetate (4:1). The recovered catalyst could be further reused in two more consecutive reactions between (**1**) and (**2a**).

Although our aim is to find the best alternative methodology to avoid the formation hazardous acidic waste by a conventional acid mediated method and not toward the reusability of catalyst, we were interested to find determine the reusability of catalyst for two more cycles. Accordingly, after the first fresh run with 94% yield, the recovered catalyst was washed, dried, and used for a second and third time. Yields of 91% and 72%, respectively, were obtained, thus proving the catalyst's reusability (Table 2).

Once the effective catalytic amount of the CAN-$SiO_2$ catalyst (containing 0.05 equiv. of CAN) was proven, to further generalize this, we extended the synthesis to a variety of novel 3-aryl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxides using 2-aminobenzenesulfonamide and various electron-donating, (methoxy, ethoxy, and isopropyl) as well as electron-withdrawing (nitro, bromo-, and chloro-substituted) aromatic aldehydes (Table 3).

Various aromatic aldehydes with different substituents at ortho, meta, or para-positions show equal ease toward product formation in high yields. In contrast, aromatic aldehydes having groups such as Cl, F, Br, MeO, EtO, and nitro showed better reactivity and the reactions were completed in a shorter time. In the of diflurobenzaldehyde and heteroaryl aldehydes such as, nicotinaldehyde, thiophene-2-carbaldehyde the desired product was formed in moderate yields. The overall study concluded that the CAN-$SiO_2$ is best catalytic system for this cascade synthesis, which gives excellent yields in very short duration at room temperature. A possible mechanism for this one pot reaction has

**Table 2** The reusability of CAN-$SiO_2$ in the synthesis of 3-phenyl-3,4-dihydro-1,2,4-benzothiadiazine-1, 1-dioxides

| Entry | Reaction cycle | Yield (%)[a] |
|---|---|---|
| 1 | Ist (Fresh run) | 94 |
| 2 | IInd cycle | 91 |
| 3 | IIIrd cycle | 72 |

[a]Isolated yield.

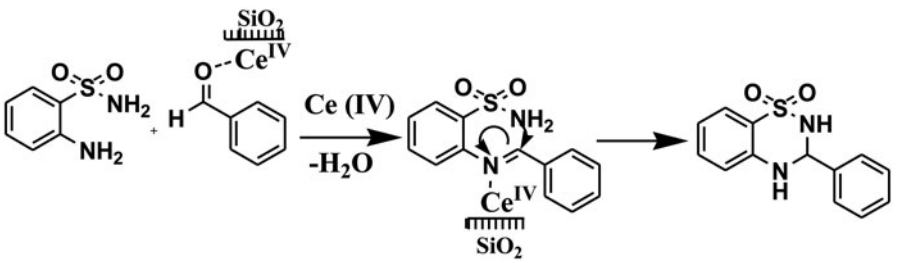
**Table 3** Synthesis of diversified 3-aryl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxides via scheme 1[a]

| Entry[a] | Ar = Aldehydes | Time (min) | Yield (%)[b] | Reference[c] |
|---|---|---|---|---|
| 3a | $C_6H_5$ | 10 | 94 | 37 |
| 3b | 4-iPr-$C_6H_5$ | 35 | 92 | — |
| 3c | 4-MeO-$C_6H_5$ | 50 | 90 | 37 |
| 3d | 2-F-$C_6H_5$ | 70 | 87 | — |
| 3e | 3-MeO-$C_6H_5$ | 50 | 84 | — |
| 3f | 2,3-diF-$C_6H_4$ | 20 | 95 | — |
| 3g | 4-Cl-$C_6H_5$ | 10 | 93 | 37 |
| 3h | 3,4-diF-$C_6H_4$ | 40 | 89 | — |
| 3i | 2,4-diF-$C_6H_4$ | 10 | 93 | — |
| 3j | 4-F-3-$NO_2$-$C_6H_4$ | 50 | 87 | — |
| 3k | 2-F-4-MeO-$C_6H_4$ | 60 | 90 | — |
| 3l | 4-F–$C_6H_5$ | 30 | 92 | 37 |
| 3m | 3-F–$C_6H_5$ | 15 | 85 | — |
| 3n | 4-EtO–$C_6H_5$ | 15 | 92 | — |
| 3o | 4-Br–$C_6H_5$ | 30 | 93 | — |
| 3p | 3,5-diF-$C_6H_4$ | 40 | 94 | — |
| 3q | Thiophene-2-carbaldehyde | 30 | 81 | — |
| 3r | Picolinaldehyde | 60 | 78 | — |
| 3s | 4-$NO_2$−$C_6H_4$ | 20 | 96 | 37 |

[a]Reactions and condition: 2-aminobenzenesulfonamide (0.6 mmol), aldehyde (0.72 mmol), and CAN-$SiO_2$ (containing 5 mol% CAN) in toluene at room temperature.
[b]Isolated yields.
[c]Reported compounds.



been postulated on the basis of similar reaction product 2,3-dihydro-quinazolin-4(1H)-ones from anthranilamide with aldehydes or ketones in the presence of cerium(IV) ammonium nitrate.[35,36] On the basis of the reported literature, the reaction begins with the formation of imine, with an amine of 2-aminobenzenesulfonamide and benzaldehydes and followed by nucleophilic attack of an amide nitrogen to an imine carbon intermediate to give the corresponding benzothiadiazine-1,1-dioxides (Scheme 2). All the new, as well as previously reported compounds, were completely characterized by their spectral properties such as $^1$H, $^{13}$C NMR, and HRMS. Spectral data and melting point of reported compounds coincides with the reported data in literature.[37] Sample $^1$H and $^{13}$C NMR spectra are provided in the Supplemental Materials (Figures S1–S38)




**Scheme 2**

## CONCLUSION

In conclusion, we have proposed a mild, easy, and efficient method for the synthesis of 3-aryl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxides using silica supported CAN as green and expeditious catalyst at ambient temperature. The advantages of performing this cascade synthesis in the presence of CAN-$SiO_2$ catalyst can be summarized as follows: (1) use of a safe, nonvolatile, noncorrosive bifunctional metal-acid catalysts; (2) high yields of recovering of catalyst at the end of the reactions easily; and (3) no base or any additional activator required and the residue was crystallized from ethanol to give the pure product with excellent yield without further column purification. We believe that this novel protocol may useful for the easy generation of new bioactive benzothiadiazine-1,1-dioxides for future medicinal chemistry research.



## EXPERIMENTAL

Chemicals were purchased from Aldrich and Alfa aesar Chemical Companies. NMR spectra were recorded in ppm in DMSO-$d_6$ on a JEOL JNM ECP 400 NMR instrument using TMS as internal standard. HR-MS were recorded on JEOL JMS-700 mass spectrometer, respectively. Melting points are taken in open capillaries and are uncorrected; Electrothermal-9100 (Japan) instrument was used to determine the melting point of the compounds.

### General Procedure for the Synthesis of Silica-Supported Ceric Ammonium Nitrate Catalyst

A supported CAN catalyst was prepared by adopting the literature procedure.[28] Neutral silica gel (9.01 g, Merck Kieselgel 60, particle size 0.063–0.200 mm, 70–230 mesh) was mixed with a solution of CAN (1.02 g) in water (2.0 mL). Evaporation of water under reduced pressure gave a dry yellowish powder, which contained 10% (by weight) of CAN. According to Hwu et al., this reagent was found active for at least six months by storage in a well-capped bottle.[28]

### Typical Procedure for the Synthesis of 3-Aryl-3,4-Dihydro-1,2,4-Benzothiadiazine-1,1-Dioxides (3a–3s)

The standard procedure was followed by use of **1** (1.0 equiv.), **2** (1.2 equiv.), CAN-$SiO_2$ 0.127 mg (containing 31.0 mg of CAN, 0.058 mmol, 0.05 equiv.), and toluene (5.0 mL). After the reaction mixture was stirred for certain period as indicated in Table 3. After completion of the reaction indicated by TLC, the reaction mixture was dissolved in acetone and the catalyst was recovered by filtration. The solvent was then evaporated under vacuum to afford the crude product. This further recrystallised from ethanol or just by giving chloroform: ethyl acetate (4:1). All new compounds were completely characterized by $^{1}H/^{13}C$ NMR and HRMS of few selected compounds is given below. Previously known products (3a. 3c. 3g and 3l) are identical to those reported.[37]

### 3-Phenyl-3,4-Dihydro-2H-Benzo[1,2,4]thiadiazine 1,1-Ddioxide (3a)[37]

Pale white solid; Mp. 129–131°C; Yield 94%. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 7.93 (d, $J$ = 12.0 Hz, 1H), 7.70 (d, $J$ = 6.0 Hz, 2H), 7.56 (d, $J$ = 7.6 Hz, 1H), 7.48–7.42 (m, 4H), 7.33 (t, $J$ = 7.6 Hz, 1H) 6.95 (d, $J$ = 8.4 Hz, 1H), 6.79 (t, $J$ = 7.3 Hz, 1H), 5.82 (d, $J$ = 12.0 Hz, 1H) ppm; $^{13}$C NMR (100.5 MHz, DMSO- $d_6$) $\delta_C$: 143.9, 137.3, 132.8, 129.1, 128.5, 127.5, 123.7, 121.6, 116.5 (d, $J$ = 34.1 Hz), and 68.4 ppm; and HRMS: m/z calculated: 360.0619, found: 360.0619.

### 3-(4-Isopropyl-Phenyl)-3,4-Dihydro-2H Benzo[1,2,4]thiadiazine 1,1-Dioxide (3b)

Pale white solid; Mp. 159–161°C; Yield 81%. $^1$H NMR (400 MHz, DMSO- $d_6$) $\delta$: 7.84 (d, $J$ = 12.1 Hz, 1H), 7.58 (d, $J$ = 8.4 Hz, 2H), 7.53–7.51 (m, 1H), 7.36–7.29 (m, 4H), 6.80 (d, $J$ = 8.0 Hz, 1H), 6.76 (t, $J$ = 7.5 Hz, 1H), 5.74 (d, $J$ = 12.0 Hz, 1H), 2.98–2.88 (m, 1H), 1.22 (d, $J$ = 6.9 Hz, 6H) ppm; $^{13}$C NMR (100.5 MHz, DMSO- $d_6$) $\delta_C$: 149.4, 143.8, 134.8, 132.7, 127.5, 126.3, 123.6, 121.5, 116.5 (d, $J$ = 28.6 Hz), 68.2, and 33.2 ppm; and HRMS: m/z calculated: 302.1089, found: 302.1087.

### 3-(4-Methoxy-Phenyl)-3,4-Dihydro-2H-Benzo[1,2,4]thiadiazine 1,1-Dioxide (3c)[37]

Faint brown solid; Mp. 135–137°C; Yield 87%.$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 7.81 (d, $J$ = 11.7 Hz, 1H), 7.59 (d, $J$ = 7.7 Hz, 1H), 7.32–7.22 (m, 4H), 7.01 (d, $J$ = 7.6 Hz, 1H), 6.91 (d, $J$ = 8.0 Hz, 1H), 6.78 (t, $J$ = 9.2 Hz, 1H), 6.66–6.59 (m, 1H), 5.73 (d, $J$ = 11.7 Hz, 1H), 3.78 (s, 3H) ppm; $^{13}$C NMR (100.5 MHz, DMSO-$d_6$) $\delta_C$: 159.8, 145.5, 143.9, 132.8, 129.5, 128.8, 127.8, 123.7, 121.5, 116.4 (d, $J$ = 29.4 Hz), 67.9, and 55.2 ppm; and HRMS: m/z calculated: 290.0725, found: 290.0727.

### 3-(2-Fluoro-Phenyl)-3,4-Dihydro-2H-Benzo[1,2,4]thiadiazine 1,1-Dioxide (3d)

Pink solid; Mp. 102–104°C; Yield 88%. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.01 (d, $J$ = 11.7 Hz, 1H), 7.83 (br s, 1H), 7.53–7.29 (m, 6H), 6.88 (d, $J$ = 7.6 Hz, 1H), 6.77 (br s, 1H), 6.07 (d, $J$ = 11.7 Hz, 1H) ppm; $^{13}$C NMR (100.5 MHz, DMSO-$d_6$) $\delta_C$: 143.8, 132.9, 131.2, 128.9, 124.6, 122.7, 121.6, 117.0, 116.4, 115.5 (d, $J$ = 21.4 Hz), and 61.4 ppm; and HRMS: m/z calculated: 278.0525, found: 278.0526.

### 3-(3-Mthoxy-Phenyl)-3,4-Dihydro-2H-Benzo[1,2,4]thiadiazine 1,1-Dioxide (3e)

Pale white solid; Mp. 172–174°C; Yield 84%. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 7.88 (d, $J$ = 12.0 Hz, 1H), 7.54 (d, $J$ = 7.7 Hz, 1H), 7.39–7.30 (m, 4H), 7.23 (d, $J$ = 7.3 Hz, 1H), 7.01 (d, $J$ = 8.0 Hz, 1H), 6.93 (d, $J$ = 8.4 Hz, 1H), 6.77 (t, $J$ = 7.5 Hz, 1H) 5.77 (d, $J$ = 12.0 Hz, 1H), 3.80 (s, 3H) ppm; $^{13}$C NMR (100.5 MHz, DMSO-$d_6$) $\delta_C$: 159.3, 143.8, 138.7, 132.8, 129.5, 123.7, 121.6, 119.7, 116.5 (d, $J$ = 34.1 Hz), 114.9, 112.8, 68.3, and 55.2 ppm; and HRMS: m/z calculated: 290.0725, found: 290.0728.

### 3-(2,3-Difluoro-Phenyl)-3,4-Dihydro-2H-benzo[1,2,4]thiadiazine 1,1-Dioxide (3f)

Pale white solid; Mp. 180–182°C; Yield 95%. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.14 (d, $J$ = 12.0 Hz, 1H), 7.62–7.51 (m, 4H), 7.37–7.34 (m, 2H), 6.91 (d, $J$ = 8.0 Hz, 1H), 6.81 (t, $J$ = 7.5 Hz, 1H), 6.12 (d, $J$ = 11.7 Hz, 1H) ppm; $^{13}$C NMR (100.5 MHz, DMSO-$d_6$) $\delta_C$: 143.6, 133.0, 126.7, 125.0, 123.9, 123.7, 121.7, 118.1 (d, $J$ = 16.6), 117.2, 116.4, and 61.3 ppm; and HRMS: m/z calculated: 296.0431, found: 296.0432.

### 3-(4-Chloro-Phenyl)-3,4-Dihydro-2H-Benzo[1,2,4]thiadiazine 1,1-Dioxide (3g)[37]

Pale white solid; Mp. 186–188°C; Yield 93%. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 7.94 (d, $J$ = 12.0 Hz, 1H), 7.70 (d, $J$ = 8.4 Hz, 2H), 7.54 (d, $J$ = 8.4 Hz, 3H), 7.40 (br s, 1H), 7.34–7.30 (m, 1H), 6.90 (d, $J$ = 8.4 Hz, 1H), 6.77 (t, $J$ = 7.5 Hz, 1H), 5.81 (d, $J$ = 12.1 Hz, 1H) ppm; $^{13}$C NMR (100.5 MHz, DMSO-$d_6$) $\delta_C$: 143.7, 136.2, 133.6, 132..8, 129.4, 128.4, 123.7, 121.6, 116.6 (d, $J$ = 49.2 Hz), and 67.5 ppm.

### 3-(3,4-Difluoro-Phenyl)-3,4-Dihydro-2H-Benzo[1,2,4]thiadiazine 1,1-Dioxide (3h)

Pink solid; Mp. 178–180°C; Yield 89%. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 7.97 (d, $J$ = 12.0 Hz, 1H), 7.81 (t, $J$ = 9.7 Hz, 1H), 7.57–7.32 (m, 5H), 6.91 (d, $J$ = 8.4 Hz, 1H), 6.80 (t, $J$ = 7.4 Hz, 1H), 5.86 (d, $J$ = 11.7 Hz, 1H) ppm; $^{13}$C NMR (100.5 MHz, DMSO-$d_6$) $\delta_C$: 143.6, 134.9, 132.9, 124.8, 123.7, 121.7, 117.6, 117.5, 117.0, 116.4 (d, $J$ = 39.7 Hz, 1H), and 67.2 ppm; and HRMS: m/z calculated: 296.0431, found: 296.0432.

### 3-(2,4-Difluoro-Phenyl)-3,4-Dihydro-2H-Benzo[1,2,4]thiadiazine 1,1-Dioxide (3i)

Pale white solid; Mp. 175–177°C; Yield 93%. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.07 (d, $J$ = 11.7 Hz, 1H), 7.92–7.86 (m, 1H), 7.55 (d, $J$ = 8.0 Hz, 1H), 7.45 (br s, 1H), 7.41–7.24 (m, 3H), 6.90 (d, $J$ = 8.4 Hz, 1H), 6.80 (t, $J$ = 7.5 Hz, 1H), 6.07 (d, $J$ = 12.0 Hz, 1H) ppm; $^{13}$C NMR (100.5 MHz, DMSO-$d_6$) $\delta_C$: 143.7, 133.0, 130.4, 123.7, 121.7, 117.1, 116.4, 112.0, and 61.1 ppm; and HRMS: m/z calculated: 296.0431, found: 296.0442.

### 3-(4-Fluoro-3-Nitro-Phenyl)-3,4-Dihydro-2H-Benzo[1,2,4]thiadiazine 1,1-Dioxide (3j)

Pale white solid; Mp. 165–167°C; Yield 87%.$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.56 (d, $J$ = 6.9 Hz, 1H), 8.14 (d, $J$ = 11.7 Hz, 2H), 7.72 (t, $J$ = 9.9 Hz, 1H), 7.58–7.53 (m, 2H), 7.36 (t, $J$ = 7.6 Hz, 1H), 6.93 (d, $J$ = 8.4 Hz, 1H), 6.82 (d, $J$ = 7.5 Hz, 1H), 6.01 (d, $J$ = 12.0 Hz, 1H); $^{13}$C NMR (100.5 MHz, DMSO-$d_6$) $\delta_C$: 156.1, 153.4, 143.6, 136.6, 135.8, 134.8 133.0, 125.4, 123.8, 121.8, 118.7 (d, $J$ = 21.4 Hz), 117.2, and 116.5 ppm; and HRMS: m/z calculated: 323.0376, found: 323.0379.

### 3-(3-Fluoro-4-Methoxy-Phenyl)-3,4-Dihydro-2H-Benzo[1,2,4]thiadiazine 1,1-Dioxide (3k)

Pale white solid; Mp. 187–189°C; Yield 79%. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 7.95 (d, $J$ = 12.0 Hz, 1H), 7.75 (t, $J$ = 8.7 Hz, 1H), 7.54 (d, $J$ = 8.0 Hz, 1H), 7.38–7.31 (m, 2H), 6.95–6.89 (m, 3H), 6.78 (t, $J$ = 7.5 Hz, 1H), 6.00 (d, $J$ = 12.0 Hz, 1H), 3.81 (s, 3H) ppm; $^{13}$C NMR (100.5 MHz, DMSO-$d_6$) $\delta_C$: 161.3, 143.8, 132.9, 129.5, 123.7, 121.5, 116.6 (d, $J$ = 53.2 Hz), 110.6, 101.2 (d, $J$ = 24.6 Hz), 61.2, and 55.8 ppm; and HRMS: m/z calculated: 308.0631, found: 308.0632.

### 3-(4-Fluoro-Phenyl)-3,4-Dihydro-2H-Benzo[1,2,4]thiadiazine 1,1-Dioxide (3l).[37]

Pink solid; Mp. 180–182°C; Yield 92%. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 7.92 (d, $J$ = 12.1 Hz, 1H), 7.75–7.72 (m, 2H), 7.54 (d, $J$ = 7.6 Hz, 1H), 7.39 (br s, 1H), 7.39–7.28 (m, 3H), 6.91 (d, $J$ = 8.4 Hz, 1H), 6.78 (t, $J$ = 7.5 Hz, 1H), 5.82 (d, $J$ = 12.0 Hz, 1H) ppm; $^{13}$C NMR (100.5 MHz, DMSO-$d_6$) $\delta_C$: 1143.8, 133.6, 132.8, 129.8, 129.7, 123.7, 121.6, 116.6 (d, $J$ = 46.1 Hz), 115.3 (d, $J$ = 21.4 Hz), and 67.6 ppm.

### 3-(3-Fluoro-Phenyl)-3,4-Dihydro-2H-Benzo[1,2,4]thiadiazine 1,1-Dioxide (3m)

Brown solid, Mp; 154–156°C, Yield 85%. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 7.96 (d, $J$ = 12.0 Hz, 1H), 7.58–7.27 (m, 7H), 6.93 (d, $J$ = 8.4 Hz, 1H), 6.79 (t, $J$ = 7.5 Hz, 1H), 5.86 (d, $J$ = 11.7 Hz, 1H) ppm; $^{13}$C NMR (100.5 MHz, DMSO-$d_6$) $\delta_C$: 143.7, 139.8 (d, $J$ = 7.1 Hz), 132.9, 130.5 (d, $J$ = 8.7 Hz), 123.8, 121.7, 116.9, 115.9 (d, $J$ = 20.6 Hz), 114.4 (d, $J$ = 22.5 Hz), 67.67, 26.1, and 24.2 ppm; and HRMS: m/z calculated: 278.0525, found: 278.0527.

### 3-(4-Ethoxy-Phenyl)-3,4-Dihydro-2H-Benzo[1,2,4]thiadiazine 1,1-Dioxide (3n)

Yellow solid; Mp. 143–145°C; Yield 92%. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 7.81 (d, $J$ = 12.0 Hz, 1H), 7.58 (d, $J$ = 8.4 Hz, 2H), 7.53 (d, $J$ = 8.0 Hz, 1H), 7.32–7.29 (m, 2H), 7.01 (d, $J$ = 8.4 Hz, 2H), 6.92 (d, $J$ = 8.0 Hz, 1H), 6.76 (t, $J$ = 7.3 Hz, 1H), 5.73 (d, $J$ = 12.1 Hz, 1H), 4.09–4.04 (m, 2H), 1.34 (t, $J$ = 6.7 Hz, 3H) ppm; $^{13}$C NMR (100.5 MHz, DMSO-$d_6$) $\delta_C$: 159.0, 143.9, 132.7, 129.3, 128.8, 123.7, 121.5, 116.4 (d, $J$ = 27.0 Hz), 114.25, 68.0, 63.1, and 14.5 ppm; and HRMS: m/z calculated: 360.0619, found: 360.0619.

### 3-(4-Bromo-Phenyl)-3,4-Dihydro-2H-Benzo[1,2,4]thiadiazine 1,1-Dioxide (3o)

Pink solid; Mp. 186–188°C, Yield 93%. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.16 (d, $J$ = 12.1 Hz, 1H), 7.88–7.83 (m, 4H), 7.74 (d, $J$ = 7.3 Hz, 1H), 7.60 (br s, 1H), 7.52 (t, $J$ = 7.3 Hz, 1H), 7.12 (d, $J$ = 8.0 Hz, 1H), 6.98 (t, $J$ = 7.5 Hz, 1H), 6.02 (d, $J$ = 12.0 Hz, 1H) ppm; $^{13}$C NMR (100.5 MHz, DMSO-$d_6$) $\delta_C$: 143.7, 136.6, 132.8, 131.4, 129.7, 123.7, 122.3, 121.7, 116.6 (d, $J$ = 49.27 Hz), and 67.7 ppm; and HRMS: m/z calculated: 337.9725, found: 337.9727.

### 3-(3,5-Difluoro-Phenyl)-3,4-Dihydro-2H-Benzo[1,2,4]thiadiazine 1,1-Dioxide (3p)

Pink solid; Mp. 154–156°C; Yield 94%. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 7.98 (d, $J = 12.0$ Hz, 1H), 7.55–7.32 (m, 6H), 6.90 (d, $J = 8.4$ Hz, 1H), 6.79 (t, $J = 7.3$ Hz, 1H), 5.87 (d, $J = 11.7$ Hz, 1H) ppm; $^{13}$C NMR (100.5 MHz, DMSO-$d_6$) $\delta_C$: 143.5, 132.9, 123.7, 121.7, 117.1, 116.4, 111.0 (d, $J = 26.2$ Hz), and 67.1 ppm; and HRMS: m/z calculated: 296.0431, found: 296.0442.

### 3-Thiophen-2yl-3,4-Dihydro-2H-Benzo[1,2,4]thiadiazine 1,1-Dioxide (3q)

Yellow solid; Mp. 128–130°C; Yield 81%. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.13 (d, $J = 11.7$ Hz, 1H), 7.13 (d, $J = 5.1$ Hz, 1H), 7.57–7.51 (m, 2H), 7.45 (d, $J = 3.2$ Hz, 1H), 7.37–7.33 (m, 1H), 7.13–7.11 (m, 1H), 6.97 (d, $J = 7.6$ Hz, 1H), 6.81 (t, $J = 7.6$ Hz, 1H) 6.10 (d, $J = 11.3$ Hz, 1H) ppm; $^{13}$C NMR (100.5 MHz, DMSO-$d_6$) $\delta_C$: 143.5, 140.0, 132.9, 126.9, 126.6, 123.6, 121.8, 117.1, 116.5, and 64.1 ppm; and HRMS: m/z calculated: 266.0184, found: 266.0186.

### *3*-Pyridin-2yl-3,4-Dihydro-2H-Benzo[1,2,4]thiadiazine 1,1-Dioxide (3r)

Brown solid; Mp. 158–160°C; Yield 78%. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.66 (d, $J = 4.4$ Hz, 1H), 8.04–7.94 (m, 2H), 7.76 (d, $J = 8.0$ Hz, 1H), 7.56–7.47 (m, 3H), 7.34 (t, $J = 7.6$ Hz, 1H), 7.06 (d, $J = 8.4$ Hz, 1H), 6.79 (t, $J = 7.5$ Hz, 1H), 5.88 (d, $J = 12.0$ Hz, 1H) ppm; $^{13}$C NMR (100.5 MHz, $CDCl_3$) $\delta_C$: 155.1, 148.7, 143.4, 137.4, 132.9, 124.2, 123.7, 121.7, 116.2 (d, $J = 18.2$ Hz), and 68.59 ppm; and HRMS: m/z calculated: 261.0572, found: 261.0574.

### 3-(4-Nitro-Phenyl)-3,4-Dihydro-2H-Benzo[1,2,4]thiadiazine 1,1-Dioxide (3s)

Pale white solid; Mp. 230–232°C; Yield 96%. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.33 (d, $J = 8.8$ Hz, 2H), 8.12 (d, $J = 11.7$ Hz, 1H), 7.96 (d, $J = 8.8$ Hz, 2H), 7.56–7.53 (m, 2H), 7.37–7.33 (m, 1H), 6.94 (d, $J = 8.4$ Hz, 1H), 6.81 (t, $J = 7.3$ Hz, 1H), 5.99 (d, $J = 11.7$ Hz, 1H) ppm; $^{13}$C NMR (100.5 MHz, DMSO-$d_6$) $\delta_C$: 147.8, 144.1, 143.6, 132.9, 129.0, 123.7, 121.8, 117.1, 116.5, and 67.3 ppm.

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