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An Efficient Method for the Synthesis of Benzofused Five-Membered Cyclic Sulfamates

Abstract

An efficient and scalable method for the synthesis of 1,2,3-benzoxathiazole 2,2-dioxides and related five-membered cyclic sulfamates employing gaseous sulfuryl fluoride (SO_2F_2) in the presence of Et_3N is described. The one-pot cyclization of 2-aminophenol derivatives proceeds at rt and tolerates a variety of substituents on the aromatic ring, including electron-withdrawing groups, as well as *N*-substituted substrates. The method provides the target heterocycles in improved yields compared to classical SO_2Cl_2-based protocols and is readily scalable to 50 g without the loss of efficiency. A virtual library of 49 cyclic sulfamate derivatives was generated and evaluated using the LLAMA approach. The library members demonstrate favorable lead-like physicochemical profiles with 100 % compliance with the Lipinski, Veber, Muegge, and GSK 4/400 filters, supporting the utility of the chemotypes proposed for medicinal chemistry applications.

***Keywords*:** heterocycles; organosulfur compounds; sulfamates; building blocks

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Ефективний метод синтезу бензоконденсованих п’ятичленних циклічних сульфаматів

Анотація

Описано ефективний і масштабований метод синтезу 1,2,3-бензоксатіазол-2,2-діоксидів та споріднених п’ятичленних циклічних сульфаматів з використанням газоподібного сульфурилфториду (SO_2F_2) у присутності Et_3N. Одностадійна циклізація похідних 2-амінофенолу з різноманітними замісниками на ароматичному кільці, разом із електроноакцепторними групами, а також *N*-заміщеними субстратами, відбувається за кімнатної температури. Метод забезпечує одержання цільових гетероциклів з покращеними виходами, якщо порівнювати з класичними методами, які полягали у використанні SO_2Cl_2, і, на відміну від останніх, дозволяє масштабувати спосіб синтезу цільових сульфаматів. Було створено віртуальну бібліотеку з 49 циклічних похідних сульфаматів та оцінено її за допомогою підходу LLAMA. Представники бібліотеки демонструють сприятливі лідер-подібні фізико-хімічні характеристики зі 100 % відповідністю фільтрам Ліпінського, Вебера, Мюгге та GSK 4/400, що підтверджує корисність запропонованих хемотипів для застосування в медичній хімії.

***Ключові слова*:** гетероцикли; сульфурорганічні сполуки; сульфамати; будівельні блоки

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Introduction

The pioneering synthesis of 1,2,3-benzoxathiazole 2,2-dioxides was reported by *Andersen et al.* in 1991 [1] by the treatment of *N*-(2-hydroxyphenyl)-*p*-toluenesulfonamides (the parent heterocycle and a NO_2-substituted derivative) with sulfuryl chloride and triethylamine. The *N*-unsubstituted (NH) cyclic sulfamates were subsequently obtained by the removal of the *N*-tosyl group using potassium fluoride or sodium azide [2]. An alternative approach to five-membered cyclic sulfamidates from 1,2-amino alcohols was developed through the sequential treatment with thionyl chloride followed by the ruthenium-catalyzed oxidation ($RuCl_3/NaIO_4$) [3–6]. Another synthetic strategy involves the use of the Burgess reagent (*N*-(triethylammoniumsulfonyl)-carbamates) for the construction of spiro-sulfamidate glycosides from *exo*-glycals [7].

Cyclic sulfamates have found significant applications as enzyme inhibitors in medicinal chemistry. Hanson, Whalen, and Wong evaluated five-membered cyclic sulfamates (CySAs) as mechanism-based inhibitors of sulfatases [8] (**Figure 1**). In the context of the steroid sulfatase (STS) inhibition, Lawrence Woo et al. prepared cyclic sulfamate derivatives of estrone (EMATE) by fusing the 1,2,3-benzoxathiazole 2,2-dioxide ring in 2,3- or 3,4-positions of the steroidal A-ring [9]. *Kok et al.* reported that a 1,6-*epi*-cyclophellitol cyclosulfamidate acts as a selective, reversible α-glucosidase inhibitor that mimics the $^4C_1$ Michaelis complex conformation [6]. Critically, this cyclosulfamidate stabilized recombinant human GAA *in vitro*, *in cellulo* (Pompe disease fibroblasts), and *in vivo* (zebrafish), outperforming *N*-butyldeoxynojirimycin (Miglustat) as a pharmacological chaperone for Pompe disease. *Benltifa et al.* demonstrated that deprotected spiro-sulfamidate glycosides act as selective, competitive inhibitors of α-glucosidase from yeast (K_i = 190 μM) and amyloglucosidase from *Aspergillus niger* (K_i = 258 μM) [7].

Kim et al. incorporated five-membered cyclic sulfamidate motifs into the side chains of 1ß-methylcarbapenems [3] and oxazolidinones [4]. In the carbapenem series, derivatives bearing cyclic sulfonamide moieties demonstrated the broad-spectrum antibacterial activity comparable to or superior to meropenem and imipenem against a panel of Gram-positive and Gram-negative bacteria.

Clarke et al. described BACE-1 hydroxyethylamine inhibitors, in which a cyclic sulfamate-containing fragment was evaluated as part of the non-prime side substituent interacting with Arg-296 via an edge-to-face aromatic interaction [10]. Yan et al. designed a 1,2,3-benzoxathiazole 2,2-dioxide derivative as a phosphotyrosine mimetic for the inhibition of protein tyrosine phosphatases [11]. In the area of GPCR ligands, Saitoh et al. constructed a cyclic sulfamate by bridging the 14-hydroxyl and 17-amino groups

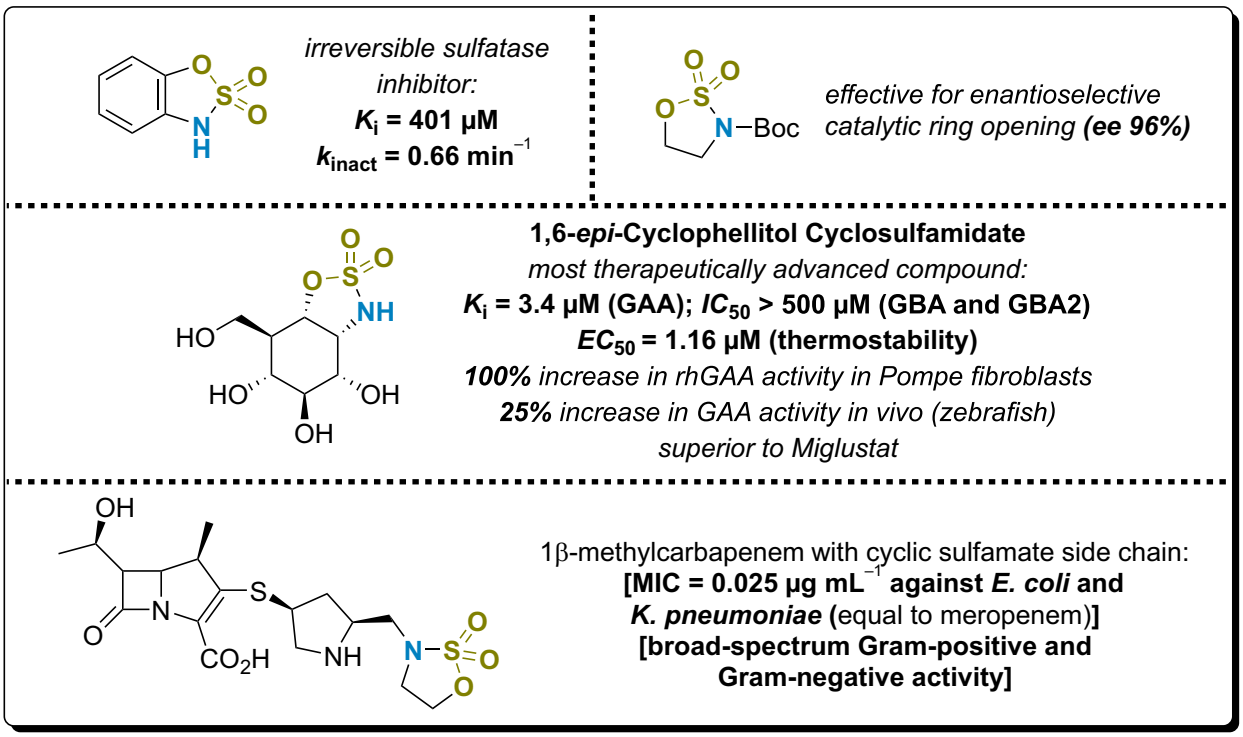


Figure 1. Important examples of cyclic 5-membered sulfamates in organic and medicinal chemistry

of a simplified morphinan scaffold as part of the structure–activity relationship studies toward orexin 1 receptor antagonists [12].

Herein, we report an improved, scalable synthesis of five-membered cyclic sulfamates using gaseous sulfuryl fluoride (SO_2F_2) in the presence of a base as a readily available, bench-stable alternative to sulfuryl chloride (**Figure 2**). This approach affords the target heterocycles in higher yields than classical methods and is readily amenable to scale-up, as demonstrated by the preparation of up to 50 g of the final product. Furthermore, to evaluate the drug discovery potential of the resulting cyclic sulfamate scaffolds, a virtual compound library was generated from the compounds synthesized. It was analyzed using the Lead-Likeness and Molecular Analysis (LLAMA) approach. Key physicochemical descriptors were calculated, and a set of established molecular property filters was applied to assess the lead-likeness of the library members.

Results and discussion

The synthesis of five-membered cyclic sulfamates is outlined in **Scheme 1**. The treatment of 2-amino-4-substituted phenols **1a–e** with SO_2F_2 in the presence of triethylamine in acetonitrile at rt and 1 atm for 16 h afforded the corresponding 1,2,3-benzoxathiazole 2,2-dioxides **3a–e** in a one-pot fashion. The reaction is presumed to proceed *via* the intermediacy of *O*-sulfamoyl fluorides **2a–c**, which undergo the spontaneous intramolecular cyclization through the nucleophilic substitution of fluoride. This protocol proved applicable to substrates bearing electron-withdrawing substituents on the aromatic ring, including bromo (**3a–c**), nitro (**3d**), and methyl carboxylate (**3e**) groups (**Scheme 1**).

The methodology was also extended to *N*-substituted 2-aminophenol derivatives **4a** and **4b**, which furnished the *N*-substituted cyclic sulfamates **5a** and **5b** under the same conditions, demonstrating that secondary amines and amides

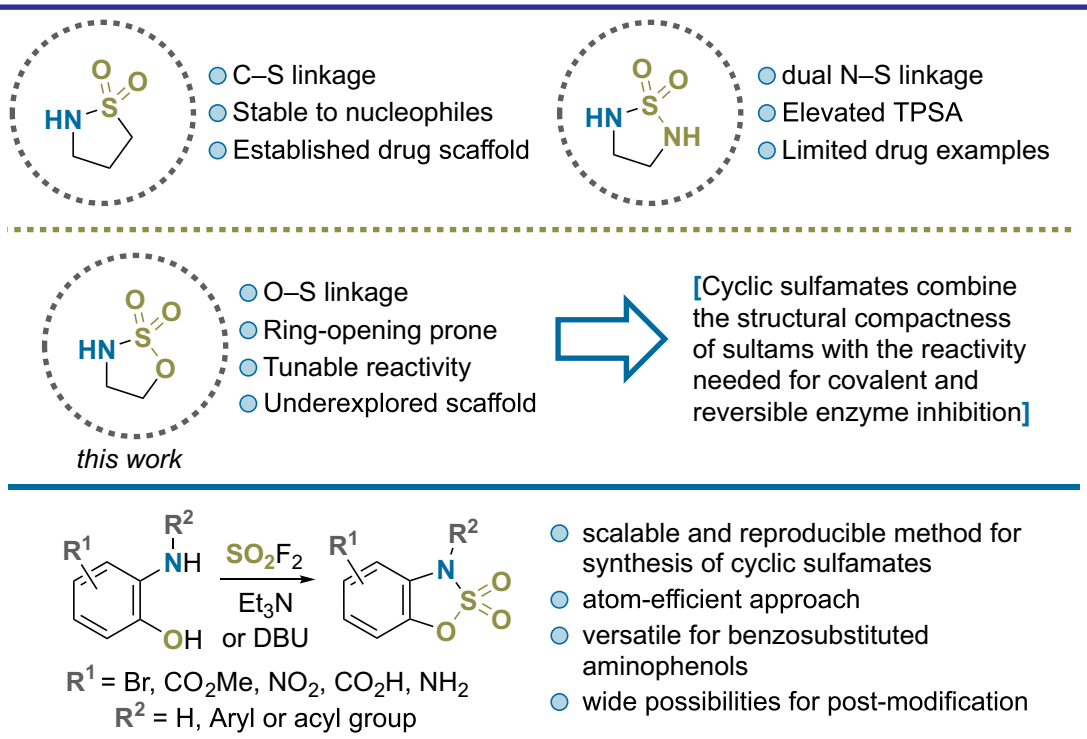
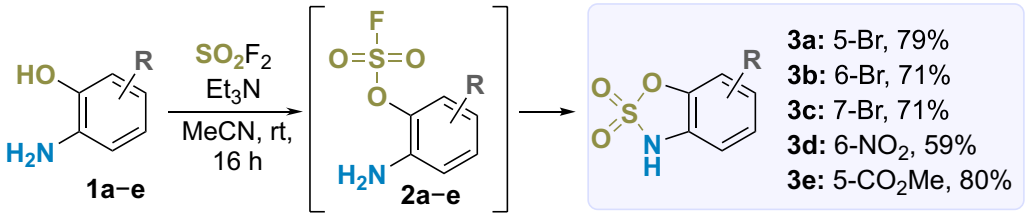


Figure 2. Five-membered cyclic sulfamates as a reactive and underexplored class of S–N heterocycles: the scaffold comparison and a scalable synthetic approach



Scheme 1. The synthesis of substituted cyclic sulfamates **3a–e**

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were competent nucleophiles for the ring closure (**Scheme 2**). It is worth noting that steric hindrance from the second *N*-substituent led to a mixture of closed- and open-ring products, resulting in a lower reaction yield. The target compounds were isolated from the mixtures by flash chromatography.

The versatility of the products was further demonstrated by straightforward functional group interconversions: the nitro group reduction in **3d** gave amine **3f**, while the hydrolysis of ester **3e** provided carboxylic acid **3g**, both of which offered handles for further diversification (**Scheme 3**).

To evaluate the drug discovery potential of the cyclic sulfamate building blocks synthesized, a virtual compound library of 49 derivatives was generated and analyzed using the Lead-Likeness and Molecular Analysis (LLAMA) approach, as previously described by Nelson and co-workers [13] (**Figure 3**). Key physicochemical descriptors were computed for each library member. The molecular weight (MW) of the compounds ranged from 228.3 to 343.4 Da (mean 290.6 ± 28.2), with cLog*P* values spanning from –1.85 to 1.99 (mean 0.45 ± 0.93), indicating that the library occupied a predominantly hydrophilic chemical space. The topological polar surface area (TPSA) ranged from 67.4 to 127.6 Å^2 (mean 93.7 ± 15.8), and the number of hydrogen-bond acceptors (estimated as the sum of nitrogen and oxygen atoms) was between 5 and 9, reflecting the polar character of the cyclic sulfamate moiety.

The library was then subjected to a series of established molecular property filters (**Figure 4**). All 49 compounds (100%) satisfied Lipinski Ro5, the Veber filter (rotatable bonds ≤ 10, TPSA ≤ 140 Å^2), and the Muegge filter, confirming an excellent overall drug-likeness of the scaffold. The GSK 4/400 rule (MW ≤ 400, cLog*P* ≤ 4) was also met by all 49 members (100%), consistent with the cyclic sulfamate core compact, polar nature. The Ghose filter was satisfied by 41 out of 49 compounds (84%); the eight failures were attributed exclusively to cLog*P* values falling below the lower Ghose threshold (cLog*P* ≥ –0.4), highlighting the high polarity imparted by the sulfamate ring (**Figure 4**).

More stringent lead-likeness criteria yielded predictably lower pass rates. The Oprea lead-like filter (150 < MW ≤ 350, –1 ≤ cLog*P* ≤ 3) was satisfied by 46 compounds (94%), with the three failures caused by cLog*P* values below –1.0. Churcher's criteria (MW < 350, cLog*P* < 3, 60 ≤ TPSA ≤ 100 Å^2) were met by 32 compounds (65%); here, the sole limiting parameter was TPSA, with 17 compounds exceeding the upper bound of 100 Å^2 due to the cumulative contribution of sulfonyl oxygens and additional heteroatoms. All compounds satisfied the MW and cLog*P* requirements of the Churcher's filter individually (49/49, 100%) (**Figure 4**).

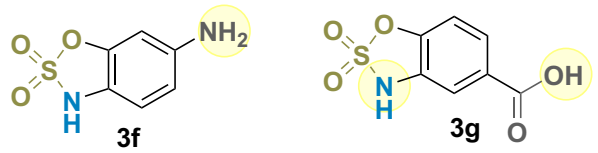
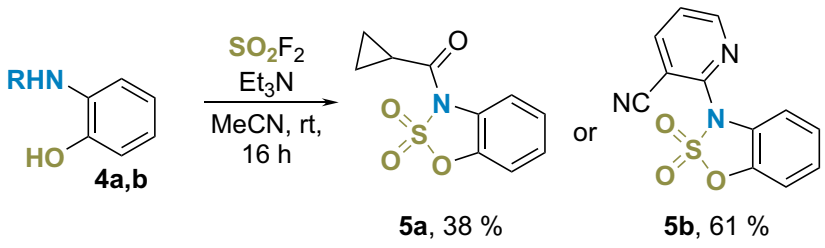
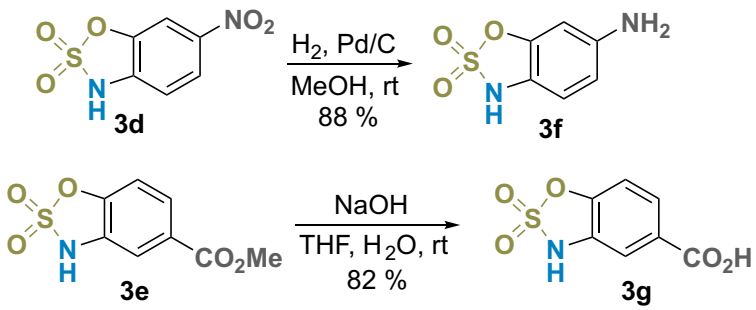


Figure 3. Building blocks used as scaffolds to generate the virtual library



Scheme 2. The synthesis of *N*-substituted cyclic sulfamates **5a** and **5b**



Scheme 3. The synthesis of sulfamates **3f** and **3g** via the functional group transformations of **3d** and **3e**

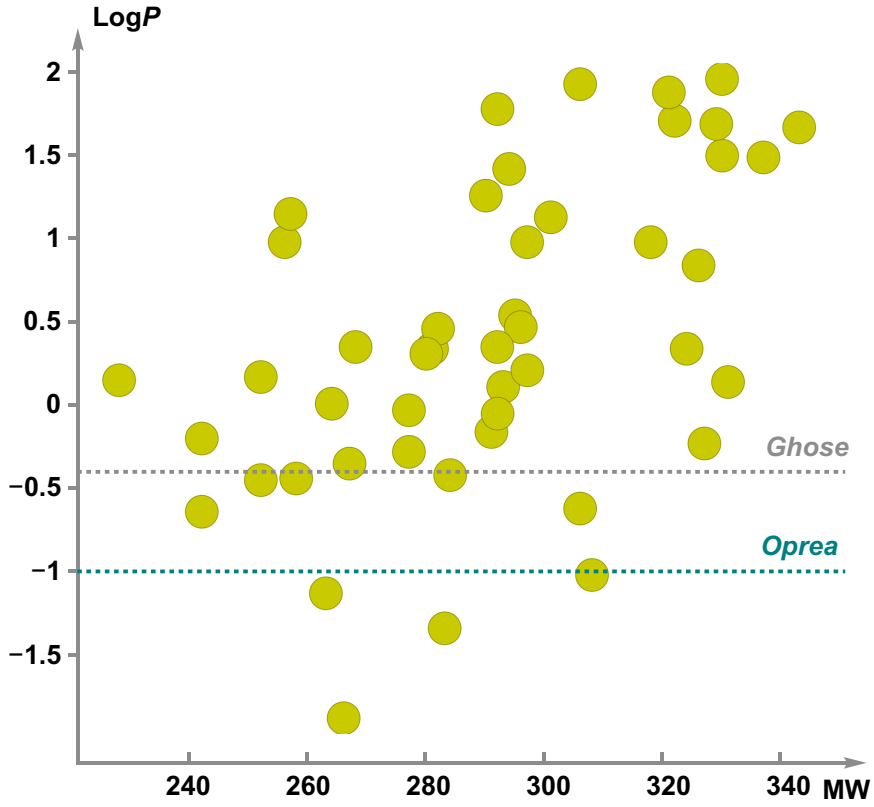


Figure 4. The log*P*–MW plot for the generated compound library

These results demonstrate that five-membered cyclic sulfamate derivatives occupy a favorable lead-like physicochemical space characterized by the low molecular weight, moderate-to-low lipophilicity, and adequate polar surface area. The principal limitation, e.g., elevated TPSA in a subset of compounds, is an inherent consequence of the sulfamate pharmacophore and the nitrogen-rich heterocyclic substituents, but it does not preclude oral bioavailability as TPSA values remain well below the 140 Å^2 threshold commonly associated with poor absorption. The high pass rates across multiple orthogonal drug-likeness filters support the utility of this scaffold class as starting points for lead optimization campaigns.

■ Conclusions

We have developed an expedient synthesis of five-membered cyclic sulfamates using sulfuryl fluoride at atmospheric pressure as a readily available, bench-stable, and less aggressive alternative to the classically employed sulfuryl chloride. The key advantages of the present method include high yields, mild reaction conditions (rt, 16 h), and the straightforward scalability, as demonstrated by the preparation of up to 50 g of the final product. The generality of the approach was determined across substrates bearing diverse ring substituents and *N*-acyl/aryl groups, with further diversification achievable through post-cyclization functional group manipulations, such as the nitro group reduction and the ester hydrolysis.

The lead-likeness assessment of a 49-member virtual library conducted using the LLAMA platform revealed an exceptionally favorable physicochemical profile for the cyclic sulfamate scaffold. All library members satisfied the Lipinski Rule of Five, Veber, Muegge, and GSK 4/400 filters (100%), while the Ghose filter was passed by 41 compounds (84%), and the Oprea lead-like criteria by 46 (94%). The more stringent Churcher's criteria were met by 32 compounds (65%), with the sole limiting factor being elevated TPSA values (>100 Å^2) in a subset of derivatives – an inherent feature of the polar sulfamate pharmacophore that nonetheless remained well within the acceptable range for oral bioavailability. The library is characterized by low molecular weights (mean MW 290.6 Da), moderate lipophilicity (mean cLog*P* 0.45), and the high polar surface area (mean TPSA 93.7 Å^2), collectively positioning these compounds in a physicochemical space that is well-suited for the lead optimization.

■ Experimental part

The solvents were purified according to the standard procedures.[14] All starting compounds

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were available from Enamine Ltd. or purchased from other commercial sources. Operations with SO_2F_2 were performed at atmospheric pressure using a balloon. Melting points were measured on the MPA100 OptiMelt automated melting point system. ^{1}H and ^{13}C{H} spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR, and 126 MHz for ^{13}C{H} NMR) and a Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H NMR, and 101 MHz for ^{13}C{H} NMR). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 2.50 and 39.52 ppm for ^{1}H and ^{13}C{^{1}H}, respectively. Coupling constants (*J*) are given in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, and coupling constants (Hz). Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)). High-resolution mass spectra (HRMS) were obtained on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer.

The general procedure for the synthesis of 3a–e, 5a, and 5b

5-Bromo-3*H*-benzo[*d*][1,2,3]oxathiazole 2,2-dioxide (3a)

Compound **1a** (30.0 g, 0.159 mol) was dissolved in MeCN (500 mL), and Et_3N (48.4 g, 0.479 mol, 66.7 mL) was added. The reaction mixture was then cooled to 0–5 °C and was degassed three times with SO_2F_2. The mixture was stirred at rt and 1 atm of SO_2F_2 (in a balloon) for 16 h. After the completion, the solvent was evaporated in *vacuo*, and the residue was dissolved in a saturated aq. $NaHSO_4$ solution and extracted three times with EtOAc (3 × 300 mL). The ethyl acetate solution was washed with a saturated aq. $NaHSO_4$ solution and brine, dried over Na_2SO_4, and evaporated in *vacuo*.

A pink powder. Yield – 31.7 g (79%). M. p. 153–155°C. ^{1}H NMR (500 MHz, DMSO-d_6), *δ*, ppm: 6.89 (1H, s), 7.06 (1H, dd, *J* = 8.5, 2.2 Hz), 7.09–7.21 (2H, m). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 112.6, 114.8, 116.5, 124.4, 133.4, 142.2. LC-MS, *m*/*z* (ESI): 248/250 [M–H]$^-$.

6-Bromo-3*H*-benzo[*d*][1,2,3]oxathiazole 2,2-dioxide (3b)

A brownish powder. Yield – 47.3 g (71%) from 50.0 g, 0.266 mol of **1b**. M. p. 174–175°C (lit. [2] 178–181°C). ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 6.58 (1H, br. s), 6.91 (1H, d, *J* = 8.4 Hz), 7.24 (1H, dd, *J* = 8.4, 2.1 Hz), 7.51 (1H, d, *J* = 2.1 Hz). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 112.7, 113.9, 114.2, 127.8, 131.3, 143.5. HRMS, *m*/*z* (ESI–TOF): [M–H]$^-$ calcd. for $C_6H_3BrNO_3S$ 247.9022/249.9002, found 247.9029/249.9007.

7-Bromo-3*H*-benzo[*d*][1,2,3]oxathiazole 2,2-dioxide (3c)

A brownish powder. Yield – 38.0 g (71%) from 40.0 g, 0.213 mol of **1c**. M. p. 125–127°C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 5.91 (1H, br. s), 6.88 (1H, d, *J* = 8.0 Hz), 6.96 (1H, t, *J* = 8.0 Hz), 7.06 (1H, d, *J* = 8.0 Hz). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 102.3, 111.5, 124.4, 126.1, 133.4, 141.1. LC-MS, *m*/*z* (ESI): 248/250 [M–H]$^-$.

6-Nitro-3*H*-benzo[*d*][1,2,3]oxathiazole 2,2-dioxide (3d)

A yellow solid. Yield – 2.49 g (59%) from 3.00 g, 19.5 mmol of **1d**. M. p. 194–196°C (lit. [2] 200–202°C). ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 6.59 (1H, d, *J* = 8.8 Hz), 7.63 (1H, d, *J* = 2.5 Hz), 7.82 (1H, dd, *J* = 8.8, 2.5 Hz). ^{13}C NMR (101 MHz, DMSO-d_6), δ, ppm: 102.9, 108.3, 122.1, 135.1, 144.3, 149.9. HRMS, *m*/*z* (ESI–TOF): [M–H]$^-$ calcd. for $C_6H_3N_2O_5S$ 214.9768, found 213.9777.

Methyl 3*H*-benzo[*d*][1,2,3]oxathiazole-5-carboxylate 2,2-dioxide (3e)

A colorless solid. Yield – 21.9 g (80%) from 20.0 g, 0.120 mol of **1e**. M. p. 53–56°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.76 (3H, s), 6.79 (1H, d, *J* = 8.0 Hz), 6.99 (1H, d, *J* = 2.0 Hz), 7.08 (1H, dd, *J* = 8.0, 2.0 Hz). LC-MS, *m*/*z* (ESI): 228 [M–H]$^-$.

Cyclopropyl(2,2-dioxido-3*H*-benzo[*d*][1,2,3]oxathiazol-3-yl)methanone (5a)

A colorless powder. Yield – 0.102 g (38%) from 200 mg, 1.13 mmol of **4a**. The compound was purified by flash chromatography (gradient: $CHCl_3$ – MeCN, 95:5 to 85:15). M. p. 75–76°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.17–1.31 (4H, m), 2.31 (1H, tt, *J* = 7.5, 4.4 Hz), 7.36 (2H, dd, *J* = 6.4, 3.3 Hz), 7.54 (1H, dd, *J* = 6.4, 3.3 Hz), 7.88 (1H, dd, *J* = 6.4, 3.3 Hz). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 8.1, 11.5, 15.0, 112.4, 116.7, 126.4, 126.4, 126.6, 139.8, 169.7. HRMS, *m*/*z* (ESI–TOF): [M+H]$^+$ calcd. for $C_{10}H_{10}NO_4S$ 240.0331, found 240.0323.

2-(2,2-Dioxido-3*H*-benzo[*d*][1,2,3]oxathiazol-3-yl)nicotinonitrile (5b)

A yellow crystalline powder. Yield – 0.235 g (61%) from 300 mg, 1.42 mmol of **4a**. The compound was purified by flash chromatography (gradient: hexanes – EtOAc, 80:20 to 0:100). M. p. 175–176°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 7.29–7.43 (3H, m), 7.57–7.66 (1H, m), 7.79 (1H, dd, *J* = 7.9, 4.9 Hz), 8.68 (1H, dd, *J* = 7.9, 1.9 Hz),

8.83 (1H, dd, J = 4.9, 1.9 Hz). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 106.8, 112.7, 114.8, 117.4, 125.2, 126.3, 126.8, 129.5, 142.8, 145.2, 149.6, 154.1. HRMS, m/z (ESI–TOF): $[M+H]^+$ calcd. for $C_{12}H_8N_3O_3S$ 274.0286, found 274.0281.

6-Amino-3*H*-benzo[*d*][1,2,3]oxathiazole 2,2-dioxide (3f)

10% Pd/C (50.0 mg) was added to the solution of **3d** (*ca.* 2.50 g) in MeOH (25 mL). The solution was carefully degassed and vigorously stirred under 50 atm of H_2 at rt. Upon the completion of the reaction, the catalyst was filtered off, and the mixture was concentrated in *vacuo*.

A purple solid. Yield – 1.89 g (88%). M. p. 185–188°C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 6.48–6.62 (2H, m), 6.67 (1H, s), 9.00 (3H, br. s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 101.4, 110.5, 115.2, 145.8. LC-MS, m/z (ESI): 187 $[M+H]^+$.

3*H*-Benzo[*d*][1,2,3]oxathiazole-5-carboxylic acid 2,2-dioxide (3g)

Compound **3e** (*ca.* 22.0 g, 96.0 mmol) was dissolved in THF (300 mL) and cooled to 0–5 °C. An aqueous solution of NaOH (9.60 g, 240 mmol) in water (100 mL) was added to the reaction mixture. The mixture was stirred at rt for 16 h. After the completion, the solvent was evaporated to leave an aqueous residue. The aqueous solution was washed with EtOAc (100 mL) and acidified to pH = 2–3 with 6 M aq. HCl. The mixture was then extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated in *vacuo*.

A beige powder. Yield 17.0 g (82%). M. p. 144–145°C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 7.28 (1H, d, J = 8.4 Hz), 7.41 (1H, s), 7.56 (1H, d, J = 8.4 Hz). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 110.9, 112.7, 124.2, 127.7, 131.9, 145.9, 166.8. HRMS, m/z (ESI–TOF): $[M–H]^-$ calcd. for $C_7H_4NO_5S$ 213.9816, found 213.9823.

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