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Potent inhibition of Norwalk virus by cyclic sulfamide derivatives

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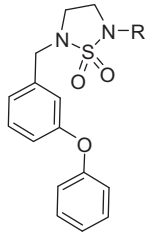
ABSTRACT

A new class of compounds that exhibit anti-norovirus activity in a cell-based system and embody in their structure a cyclosulfamide scaffold has been identified. The structure of the initial hit (compound **2a**, ED_{50} 4 μM, TD_{50} 50 μM) has been prospected by exploiting multiple points of diversity and generating appropriate structure–activity relationships.

1. Introduction

Noroviruses are the most common cause of acute viral gastroenteritis outbreaks in the U.S. and worldwide.[1–3] These outbreaks, which occur primarily in hospitals, cruise ships, army barracks, and schools, are the cause of significant morbidity and mortality, particularly in children, the elderly, and immunocompromised patients. There is currently an urgent and unmet need for the discovery and development of effective therapeutics for the treatment of norovirus infections.

As part of an ongoing program aimed at discovering novel norovirus inhibitors, a subset of compounds from a pharmacologically-rich in-house library of compounds (~2000 compounds) encompassing an array of peptidomimetics characterized by high structural diversity, drug-like characteristics, and high synthetic tractability was screened using a cell-based replicon system (HG23 cells containing Norwalk virus [NV] replication unit),[4–7] leading to the identification of several hits[8] whose structures shared in common the cyclosulfamide scaffold (I), a robust and versatile core structure that embodies multiple points of diversity (Fig. 1). The structural motif embodied in the sulfamide moiety is known to promote enhanced binding, increased aqueous solubility, and better bioavailability.[9] The sulfamide moiety (–$NHSO_2NH$–) can also serve as a bioisosteric replacement of the sulfonamide moiety (–SO_2NH–)[10] and is well-suited to the design of therapeutic agents.[9] Consequently, a hit-to-lead optimization campaign was launched by initiating structure–activity relationships (SARs) aimed at increasing the potency of the identified hit and to understand the SAR



(I) (R=H, ED_{50}: 4 μM
TD_{50}: 50 μM)

Figure 1. General structure of cyclosulfamide inhibitors (I) and structure of initial hit **2a** (R = H).

landscape around the cyclosulfamide scaffold.[11] We report herein the results of studies related to the optimization of this series of compounds.

2. Chemistry

The general strategy undergirding the hit-to-lead optimization campaign entailed probing the effect of making sequential changes in structure (I) (Fig. 1) on anti-norovirus activity. Specifically, the (*m*-phenoxy)phenyl moiety in (I) was probed via the initial synthesis of derivatives **2b–t** (Scheme 1). These compounds were readily synthesized by reductive amination of an appropriate aldehyde with excess ethylediamine in the presence of sodium borohydride in methanol[12,13] to yield the corresponding N-substituted ethylene diamine which, without isolation, was refluxed with sulfamide in pyridine to form the corresponding N-substituted cyclosulfamide

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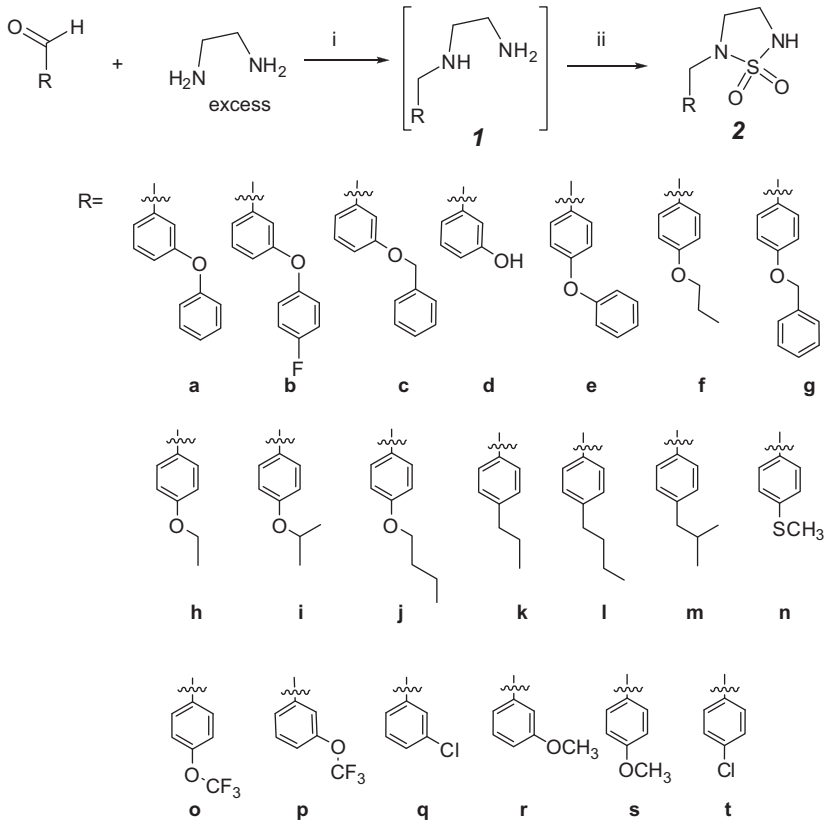
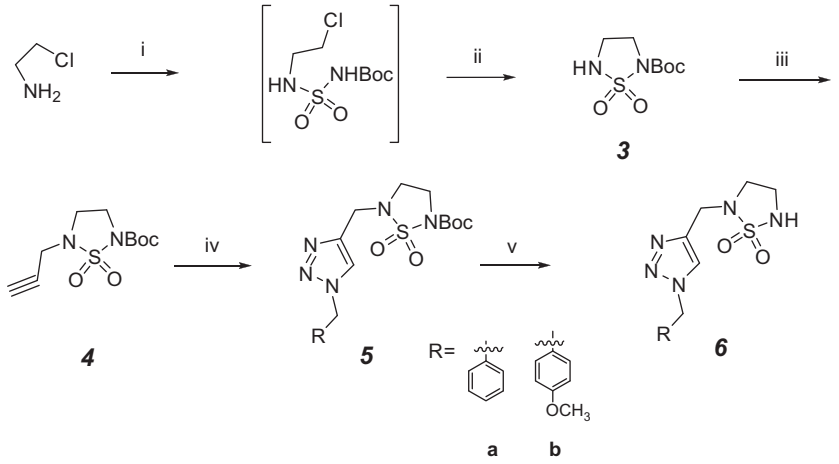


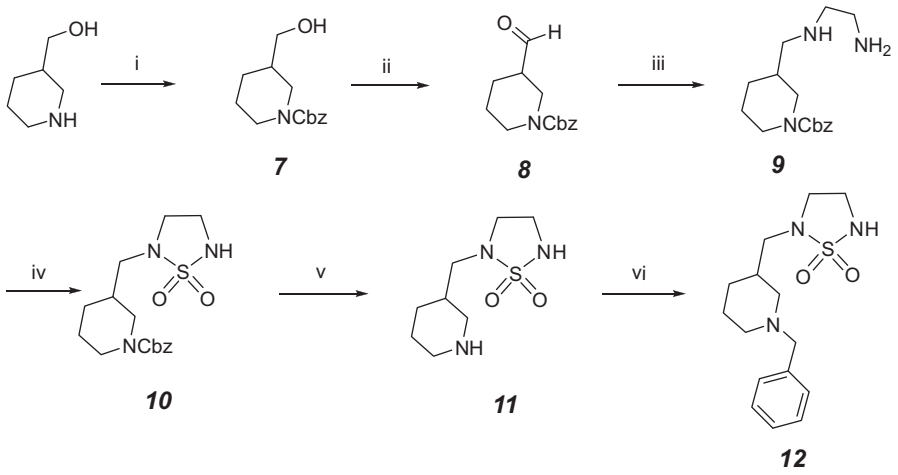
Scheme 1. Reagents and condition: (i) $NaBH_4$/MeOH; (ii) $NH_2SO_2NH_2$/pyridine/reflux 16 h.



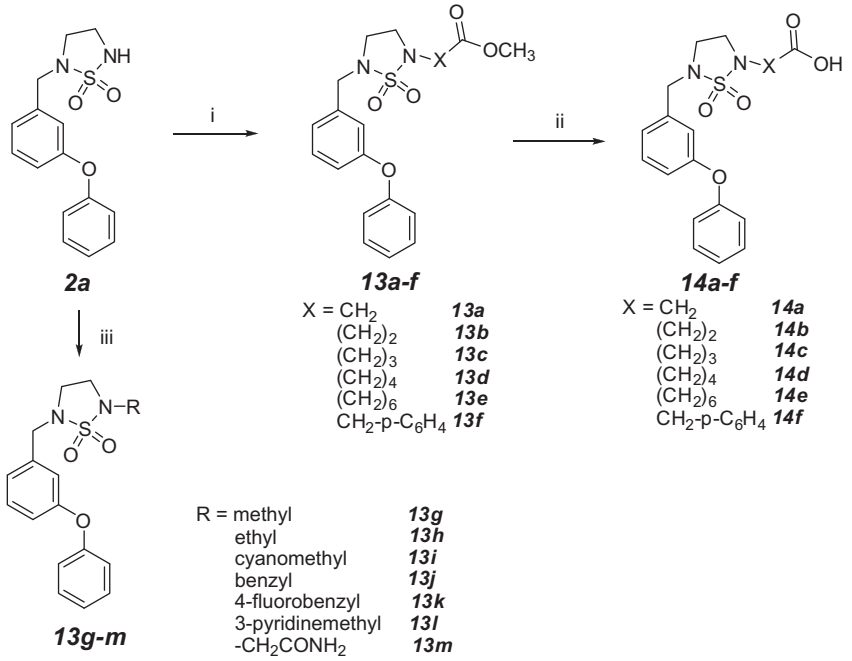
Scheme 2. Reagents and condition: (i) $ClSO_2NCO$/*t*-BuOH/TEA/CH_2Cl_2; (ii) K_2CO_3/DMSO; (iii) NaH/propargyl bromide/DMF; (iv) RCH_2N_3/sodium ascorbate/$CuSO_4$/*t*-BuOH/H_2O; (v) 4 M HCl in 1,4-dioxane.

2. Further structural variations in this segment of (I) included the synthesis of derivatives **6a–b** (Scheme 2) and **10–12** (Scheme 3).

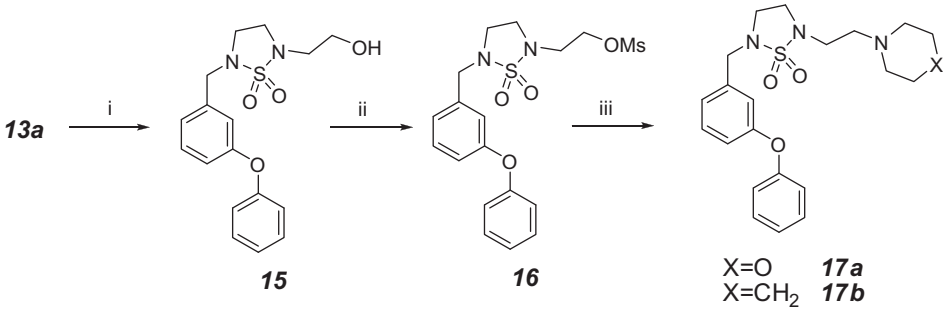
In the case of compounds **6a–b**, this involved the synthesis of Boc-protected cyclosulfamide **3**[13] followed by N-alkylation with propargyl bromide. Subsequent Click chemistry[14–16] with an array of azides and deprotection of the resulting compounds with TFA, yielded the desired compounds. Compounds **10–12** were readily synthesized starting with the commercially available 3-(hydroxymethyl)piperidine. Treatment with benzylchlorofomate afforded the protected alcohol **7** which was oxidized to the corresponding aldehyde **8** with pyridinium chlorochromate.[17] Reductive amination using excess ethylene diamine and sodium borohydride yielded **9** which was cyclized to form **10** by refluxing with sulfamide in pyridine. Subsequent catalytic hydrogenation gave compound **11** which was alkylated with benzyl bromide by refluxing in ethanol in the presence of sodium bicarbonate. The effect of the nature of R (Fig. 1) was probed by generating a series of derivatives of (I), as illustrated in Scheme 4. Thus, treatment of **2a** with sodium hydride in acetonitrile, followed by the addition of $Br(CH_2)_nCOOCH_3$ yielded esters **13a–f** which were hydrolyzed with LiOH/aqueous dioxane to yield the corresponding acids **14a–f**. Derivatives **13g–m** were readily obtained by alkylating compound **2a** (Scheme 4). Treatment of cyclosulfamide derivative **13a** with lithium borohydride yielded the corresponding alcohol which



Scheme 3. Reagents and condition: (i) Benzyl chloroformate/TEA/THF; (ii) PCC/CH_2Cl_2; (iii) excess ethylenediamine/$NaBH_4$/MeOH; (iv) $NH_2SO_2NH_2$/pyridine/reflux 16 h; (v) H_2/Pd-C; (vi) benzyl bromide/$NaHCO_3$/EtOH, reflux.



Scheme 4. Reagents: (i) NaH/ACN/$BrXCOOCH_3$; (ii) LiOH/1,4-dioxane; (iii) NaH/ACN/RBr or RI.



Scheme 5. Reagents and condition: (i) $LiBH_4$/THF/EtOH; (ii) MsCl/TEA/CH_2Cl_2; (iii) RH/$NaHCO_3$/95% EtOH/reflux.

was treated with CH_3SO_2Cl/TEA to yield the mesylate. Subsequent refluxing of the mesylate with morpholine or piperidine in the presence of sodium bicarbonate in 95% ethanol, gave compounds **17a–b** (Scheme 5).

Table 1

Compound	ED_{50} (μM)	TD_{50} (μM)	Compound	ED_{50} (μM)	TD_{50} (μM)
2a	4.1 ± 1.2[a]	50 ± 9.2	**12**	>10	N/D
2b	>10	98 ± 6.4	**13a**	>10	N/D
2c	5.2 ± 1.5	18 ± 3.6	**13b**	>10	N/D
2d	> 10	N/D[b]	**13c**	>10	N/D
2e	5.8 ± 2.1	57 ± 4.2	**13d**	9.7 ± 2.2	46 ± 7.9
2f	5.2 ± 1.7	96 ± 4.9	**13e**	>10	N/D
2g	9.8 ± 3.2	159 ± 11.6	**13f**	>10	N/D
2h	>10	N/D	**14a**	7.8 ± 2.2	48 ± 6.2
2i	>10	N/D	**14b**	>10	N/D
2j	9.5 ± 1.5	N/D	**14c**	>10	N/D
2k	>10	N/D	**14d**	6.1 ± 1.7	100
2l	>10	N/D	**14e**	>10	N/D
2m	9.7 ± 1.9	N/D	**14f**	>10	N/D
2n	> 10	N/D	**13g**	>10	N/D
2o	>10	N/D	**13h**	>10	N/D
2p	>10	N/D	**13i**	>10	N/D
2q	>10	N/D	**13j**	>10	N/D
2r	> 10	N/D	**13k**	>10	N/D
2s	>10	N/D	**13l**	8.1 ± 2.1	53 ± 6.7
2t	>10	N/D	**13m**	>10	N/D
5a	>10	N/D	**17a**	4.2 ± 1.8	51 ± 3.2
5b	9.8 ± 3.2	N/D	**17a**	5.4 ± 1.7	49 ± 7.7
6a	>10	N/D	**17b**	4.3 ± 1.3	9.8 ± 4.1
6b	>10	N/D			

[a] Mean value ± standard deviation with at least two independent experiments.
[b] N/D: not determined due to high ED_{50} value.

3. Biochemical studies

The antiviral effects of the synthesized compounds were determined following previously described procedures using NV replicon-harboring cells (HG23 cells)[4–7] and the results are summarized in Table 1. Detailed procedures for studying the antiviral effects using HG23 cells have been reported elsewhere[4–7] (see also Section 5).

4. Results and discussion

4.1. General strategy and structure–activity relationships

The structure of the initial hit (Fig. 1, structure (I), R = H) was used as a launching pad for the design and synthesis of structural variants displaying improved pharmacological activity. We envisioned accomplishing this goal by exploiting the multiple points of diversity present in structure (I). Thus, structure (I) was systematically probed via the construction of focused libraries, an endeavor that was greatly facilitated by the synthetic tractability of this series of compounds. Furthermore, a minimal number of chemical modifications were initially carried out to prospect the entire structure. Overall, an iterative approach involving the use of medicinal chemistry and cell-based screening was utilized to attain our objectives.

The import of the (*m*-phenoxy)phenyl moiety was probed by using an array of structurally-diverse aldehydes to construct compounds **2a–t** (Scheme 1). It is clearly evident from Table 1 that replacement of the *m*-phenoxy substituent has a profound and, mostly, adverse effect on anti-norovirus activity. While there was a modest improvement in the therapeutic index (TI) of some of the compounds (e.g., compound **2f** vs **2a**, Table 1), in the majority of cases activity was reduced or completely abolished. Replacement of one of the aromatic rings in (I) by either a 1,2,3-triazole ring or a piperidine ring yielded compounds that were devoid of anti-norovirus activity (Table 1, compounds **6a–b,** 12). The nature of the R group in structure (I) was then investigated (Schemes 4 and 5). With respect to compounds **14a–f** and **17a–b**, in addition to optimizing pharmacological activity, a secondary but important goal was to increase the aqueous solubility of the generated compounds. Inspection of the data shown in Table 1 indicates that the methyl esters were inactive, however, the corresponding carboxylic acids were either active or inactive depending on the length of the methylene chain (compare compounds **14a** and **14d** vs compounds **14b–c** and **14e–f**, Table 1). With the exception of compound **13l**, the rest of the alkyl or arylalkyl-substituted compounds (Table 1 compounds **13g–k** and **13m**) also lacked activity. The morpholine and piperidine derivatives (Table 1 compounds **17a**–**b**) were active, however, their therapeutic indices were lower than that of compound **2a** (Fig. 1, structure (I), R = H). Taken together, the SAR studies indicate that structural variations in multiple segments of structure (I) impact pharmacological activity and toxicity. The optimization process was gravely hampered by the lack of information about the target of this class of compounds. It should be noted that the anti-norovirus activity of compound **2a** does not arise from the inhibition of Norwalk virus 3C protease (unpublished data).[18] Ongoing studies aimed at identifying the viral or cellular target of this class of compounds are currently in progress.

In summary, a new class of anti-norovirus agents based on the cyclosulfamide scaffold has been reported. The salient features responsible for the pharmacological activity of these compounds have been delineated via SAR studies.

5. Experimental section

5.1. General

The ^1H spectra were recorded on a Varian XL-300 or XL-400 NMR spectrometer. Melting points were determined on a Mel-Temp apparatus and are uncorrected. High resolution mass spectra (HRMS) were performed at University of Kansas Mass Spectrometry Lab. Reagents and solvents were purchased from various chemical suppliers (Aldrich, Acros Organics, TCI America, and Bachem). Silica gel (230–450 mesh) used for flash chromatography was purchased from Sorbent Technologies (Atlanta, GA). Thin layer chromatography was performed using Analtech silica gel plates to determine the compound purity. The TLC plates for all the compounds were eluted using two different solvent systems and visualized using iodine and/or UV light. Each individual compound was identified as a single spot on TLC plate (purity greater than 95%).

5.1.1. Synthesis of compounds 2a–t

5.1.1.1. Representative synthesis. 2-(3-Phenoxybenzyl)-1,2,5-thiadiazolidine 1,1-dioxide (2a). To a solution of ethylenediamine (6.0 g; 100 mmol) in 65 mL methanol was added 3-(phenoxy)benzaldehyde (4.95 g; 25 mmol) in small portions under an ice-bath. After the addition, sodium borohydride (0.94 g; 25 mmol) was added slowly in small portions at 0 °C. The reaction was allowed to warm to room temperature overnight. The solvent was removed and the residue was taken up in ethyl acetate (100 mL) and water (40 mL). The layers were separated and the organic layer was washed with water (40 mL). The organic layer was dried over anhydrous sodium sulfate. The drying agent was filtered and the solvent was removed using a rotary evaporator to give pure compound **1a** as a colorless oil (6.0 g; 24.8 mmol; 99% yield). To a refluxing solution of sulfamide (2.38 g; 24.8 mmol) in anhydrous pyridine (60 mL) was slowly added compound **1a** (6.0 g; 24.8 mmol) over 1 h. The resulting reaction mixture was refluxed for an additional 16 h. Pyridine was removed under vacuum and the residue was taken up in ethyl acetate (100 mL). The organic layer was washed with 5% HCl (3 × 50 mL), brine (50 mL) and then dried over anhydrous sodium sulfate. The drying agent was filtered

off and the solvent was evaporated, leaving a crude product which was purified using flash chromatography (silica gel/ethyl acetate/hexanes) to give pure compound **2a** as a yellow oil (6.3 g; 83% yield). ^{1}H NMR ($CDCl_3$): δ 3.29 (t, J = 6.2 Hz, 2H), 3.47 (q, J = 7.2 Hz, 2H), 4.16 (s, 2H), 4.44 (s, 1H), 6.90–7.40 (m, 9H). HRMS (ESI): calculated m/z for $C_{15}H_{16}N_2O_3S$ $[M+Na]^+$ 327.0779; found 327.0779.

5.1.1.2. 2-[3-(4-Fluorophenoxy)benzyl]-1,2,5-thiadiazolidine 1,1-dioxide (2b). Yellow oil (74% yield). ^{1}H NMR ($CDCl_3$): δ 3.29 (t, J = 6.3 Hz, 2H), 3.50 (q, J = 6.0 Hz, 2H), 4.15 (s, 2H), 4.37 (t, J = 5.7 Hz, 1H), 6.87–7.13 (m, 6H), 7.25–7.34 (m, 2H). HRMS (ESI): calculated m/z for $C_{15}H_{15}FN_2O_3S$ $[M+Na]^+$ 345.3444; found 345.0685.

5.1.1.3. 2-[3-(Benzyloxy)benzyl]-1,2,5-thiadiazolidine 1,1-dioxide (2c). Colorless oil (85% yield). ^{1}H NMR ($CDCl_3$): δ 3.23 (t, J = 7.0 Hz, 2H), 3.44 (q, J = 7.0 Hz, 2H), 4.13 (s, 2H), 4.42 (t, J = 6.0 Hz, 1H), 6.82–7.03 (m, 3H), 7.20–7.44 (m, 6H). HRMS (ESI): calculated m/z for $C_{16}H_{18}N_2O_3S$ $[M+Na]^+$ 341.3805; found 341.0936.

5.1.1.4. 2-[3-(Hydroxy)benzyl]-1,2,5-thiadiazolidine 1,1-dioxide (2d). To a solution of compound **2c** (0.23 g; 0.72 mmol) in methanol (20 mL) was added Pd-C (10% w/w; 0.05 g) and applied 20 psi hydrogen gas on a Parr hydrogenator for 12 h. The catalyst was filtered off and the solvent was removed, leaving pure compound **2d** as a colorless oil (100% yield). ^{1}H NMR ($CDCl_3$): δ 3.29 (t, J = 6.6 Hz, 2H), 3.50 (q, J = 6.5 Hz, 2H), 4.13 (s, 2H), 4.42 (s, 1H), 5.27 (s, 1H), 6.77–6.94 (m, 3H), 7.20–7.26 (m, 1H). HRMS (ESI): calculated m/z for $C_9H_{12}N_2O_3S$ $[M+Na]^+$ 251.2579; found 251.0466.

5.1.1.5. 2-(4-Phenoxybenzyl)-1,2,5-thiadiazolidine 1,1-dioxide (2e). White solid (59% yield), mp 110–112 °C. ^{1}H NMR ($CDCl_3$): δ 3.30 (t, J = 7.2 Hz, 2H), 3.49 (q, J = 7.8 Hz, 2H), 4.15 (s, 2H), 4.34 (s, 1H), 6.94–7.41 (m, 9H). HRMS (ESI) calculated m/z for $C_{15}H_{16}N_2O_3S$ $[M+Na]^+$ 327.0779; found 327.0764.

5.1.1.6. 2-(4-Propoxybenzyl)-1,2,5-thiadiazolidine 1,1-dioxide (2f). Yellow oil (22% yield). ^{1}H NMR ($CDCl_3$): δ 1.02 (t, J = 18.2 Hz, 3H), 1.72–1.88 (m, 2H), 3.25 (t, J = 18.2 Hz, 2H), 3.34 (q, J = 27.3 Hz, 2H), 3.91 (t, J = 18.2 Hz, 2H), 4.10 (s, 2H), 4.41 (t, J = 27.3 Hz, 1H), 6.87 (d, 2H), 7.26 (d, 2H). HRMS (ESI) calculated m/z for $C_{12}H_{18}N_2O_3S$ $[M+Na]^+$ 293.0936; found 293.0935.

5.1.1.7. 2-[4-(Benzyloxy)benzyl]-1,2,5-thiadiazolidine 1,1-dioxide (2g). Brown solid (52% yield), mp 85–87 °C. ^{1}H NMR ($CDCl_3$): δ 3.25(t, J = 18.2 Hz, 2H), 3.44 (q, J = 27.3 Hz, 2H), 4.10 (s, 2H), 5.05 (s, 2H), 6.95 (d, 2H), 7.28–7.48 (m, 7H). HRMS (ESI) calculated m/z for $C_{16}H_{18}N_2O_3S$ $[M+Na]^+$ 341.0936; found 341.0924.

5.1.1.8. 2-(4-Ethoxybenzyl)-1,2,5-thiadiazolidine 1,1-dioxide (2h). Yellow oil (89% yield). ^{1}H NMR ($CDCl_3$): δ 1.43 (t, J = 6.8 Hz, 3H), 3.29 (t, J = 6.2 Hz, 2H), 3.48 (q, J = 6.8 Hz, 2H), 4.05 (q, J = 7.2 Hz, 2H), 4.14 (s, 2H), 4.40 (s, 1H), 6.80–6.94 (m, 3H), 7.22–7.28 (m, 1H). HRMS (ESI) calculated m/z for $C_{11}H_{16}N_2O_3S$ $[M+Na]^+$ 279.0779; found 279.0804.

5.1.1.9. 2-[4-(Propan-2-yloxy)benzyl]-1,2,5-thiadiazolidine 1,1-dioxide (2i). Yellow oil (76% yield). ^{1}H NMR ($CDCl_3$): δ 1.33 (d, J = 5.9 Hz, 6H), 3.26 (t, J = 6.4 Hz, 2H), 3.45 (q, J = 6.7 Hz, 2H), 4.11 (s, 2H), 4.37 (s, 1H), 4.51–4.60 (m, 1H), 6.86 (d, J = 9.0 Hz, 2H), 7.24 (d, J = 9.0 Hz, 2H). HRMS (ESI) calculated m/z for $C_{12}H_{18}N_2O_3S$ $[M+Na]^+$ 293.0936; found 293.0926.

5.1.1.10. 2-(4-Butoxybenzyl)-1,2,5-thiadiazolidine 1,1-dioxide (2j). Yellow solid (75% yield), mp 49–50 °C. ^{1}H NMR ($CDCl_3$): δ 0.97 (t, J = 7.3 Hz, 3H), 1.43–1.56 (m, 2H), 1.72–1.81 (m, 2H), 3.25 (t, J = 6.2 Hz, 2H), 3.46 (q, J = 6.7 Hz, 2H), 3.95 (t, J = 5.5 Hz, 2H), 4.12 (s, 2H), 4.29 (s, 1H), 6.87 (d, J = 9.1 Hz, 2H), 7.27 (d, J = 9.1 Hz, 2H). HRMS (ESI) calculated m/z for $C_{13}H_{20}N_2O_3S$ $[M+Na]^+$ 307.1092; found 307.1094.

5.1.1.11. 2-(4-Propylbenzyl)-1,2,5-thiadiazolidine 1,1-dioxide (2k). White solid (60% yield), mp 52–53 °C. ^{1}H NMR ($CDCl_3$): δ 0.94 (t, J = 6.7 Hz, 3H), 1.57–1.70 (m, 2H), 2.58 (t, J = 7.8 Hz, 2H), 3.38 (t, J = 6.1 Hz, 2H), 3.49 (q, J = 6.7 Hz, 2H), 4.15 (s, 2H), 4.36 (s, 1H), 7.17 (d, J = 7.4 Hz, 2H), 7.28 (d, J = 7.4 Hz, 2H). HRMS (ESI) calculated m/z for $C_{12}H_{18}N_2O_2S$ $[M+Na]^+$ 277.0987; found 277.0991.

5.1.1.12. 2-(4-Butylbenzyl)-1,2,5-thiadiazolidine 1,1-dioxide (2l). White solid (67% yield), mp 40–41 °C. ^{1}H NMR ($CDCl_3$): δ 0.92 (t, J = 7.1 Hz, 3H), 1.25–1.42 (m, 2H), 1.52–1.65 (m, 2H), 2.62 (t, J = 6.8 Hz, 2H), 3.27 (t, J = 6.0 Hz, 2H), 3.48 (q, J = 6.9 Hz, 2H), 4.15 (s, 2H), 4.39 (s, 1H), 7.16 (d, J = 7.1 Hz, 2H), 7.27 (d. J = 7.1 Hz, 2H). HRMS (ESI) calculated m/z for $C_{13}H_{20}N_2O_2S$ $[M+Na]^+$ 291.1143; found 291.1152.

5.1.1.13. 2-[4-(2-Methylpropyl)benzyl]-1,2,5-thiadiazolidine 1,1-dioxide (2m). White solid (66% yield), mp 62–63 °C. ^{1}H NMR ($CDCl_3$): δ 0.91 (d, J = 7.5 Hz, 6H), 1.80–1.92 (m, 1H), 2.48 (d, J = 6.7 Hz, 2H), 3.26 (t, J = 5.9 Hz, 2H), 3.44 (q, J = 6.8 Hz, 2H), 4.15 (s, 2H), 4.26 (s, 1H), 7.16 (d, J = 8.6 Hz, 2H), 7.26 (d, J = 8.6 Hz, 2H). HRMS (ESI) calculated m/z for $C_{13}H_{20}N_2O_2S$ $[M+Na]^+$ 291.1143; found 291.1143.

5.1.1.14. 2-[4-(Methylsulfanyl)benzyl]-1,2,5-thiadiazolidine 1,1-dioxide (2n). Yellow solid (78% yield), mp 133–135 °C, ^{1}H NMR ($CDCl_3$): δ 2.48 (s, 3H), 3.26 (t, J = 18.8 Hz, 2H), 3.45 (q, J = 28.1 Hz, 2H), 4.16 (s, 2H), 4.29 (t, J = 28.1 Hz, 1H), 7.21–7.34 (m, 4H). HRMS (ESI) calculated m/z for $C_{10}H_{14}N_2O_2S_2$ $[M+Na]^+$ 281.0394; found 281.0396.

5.1.1.15. 2-[4-(Trifluoromethoxy)benzyl]-1,2,5-thiadiazolidine 1,1-dioxide (2o). Colorless oil (92% yield). ^{1}H NMR ($CDCl_3$): δ 3.30 (t, J = 6.6 Hz, 2H), 3.52 (s, 2H), 4.20 (s, 2H), 4.55 (s, 2H), 7.22 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H).

5.1.1.16. 2-[3-(Trifluoromethoxy)benzyl]-1,2,5-thiadiazolidine 1,1-dioxide (2p). Yellow oil (22% yield). ^{1}H NMR ($CDCl_3$): δ 3.30 (t, J = 5.9 Hz, 2H), 3.51 (q, J = 6.8 Hz, 2H), 4.20 (s, 2H), 4.63 (s, 1H), 7.17–7.43 (m, 4H). HRMS (ESI) calculated m/z for $C_{10}H_{11}F_3N_2O_3S$ $[M+Na]^+$ 319.0340; found 319.0344.

5.1.1.17. 2-(3-Chlorobenzyl)-1,2,5-thiadiazolidine 1,1-dioxide (2q). Yellow oil (83% yield). ^{1}H NMR ($CDCl_3$): δ 3.29 (t, J = 6.4 Hz, 2H), 3.52 (q, J = 6.9 Hz, 2H), 4.16 (s, 2H), 4.43 (s, 1H), 7.23–7.41 (m, 4H). HRMS (ESI) calculated m/z for $C_9H_{11}ClN_2O_2S$ $[M+Na]^+$ 269.0127; found 269.0143.

5.1.1.18. 2-(3-Methoxybenzyl)-1,2,5-thiadiazolidine 1,1-dioxide (2r). Yellow oil (36% yield), ^{1}H NMR ($CDCl_3$): δ 3.28 (t, J = 18.2 Hz, 2H), 3.48 (q, J = 27.3 Hz, 2H), 3.81 (s, 3H), 4.15 (s, 3H), 6.82–6.97 (m, 3H), 7.29–7.32 (m, 1H). HRMS (ESI) calculated m/z for $C_{10}H_{14}N_2O_3S$ $[M+H]^+$ 243.0803; found 243.0811.

5.1.1.19. 2-(4-Methoxybenzyl)-1,2,5-thiadiazolidine 1,1-dioxide (2s). Colorless oil (87% yield). ^{1}H NMR ($CDCl_3$): δ 3.25 (t, J = 5.7 Hz,

2H), 3.45 (q, J = 6.5 Hz, 2H), 3.80 (s, 3H), 4.12 (s, 2H), 4.36 (s, 1H), 6.88 (d, J = 9.7 Hz, 2H), 7.37 (d, J = 9.7 Hz, 2H). HRMS (ESI) calculated m/z for $C_{10}H_{14}N_2O_3S$ $[M+Na]^+$ 265.0623; found 265.0615.

5.1.1.20. 2-(4-Chlorobenzyl)-1,2,5-thiadiazolidine 1,1-dioxide (2t). White solid (52% yield), mp 90–91 °C. ^{1}H NMR ($CDCl_3$): δ 3.28 (t, J = 5.7 Hz, 2H), 3.50 (q, J = 6.9 Hz, 2H), 4.17 (s, 2H), 3.55 (s, 1H), 7.23–7.40 (m, 4H). HRMS (ESI) calculated m/z for $C_9H_{11}ClN_2O_2S$ $[M+Na]^+$ 269.0127; found 269.0147.

5.1.1.21. *tert*-Butyl 1,2,5-thiadiazolidine-2-carboxylate 1,1-dioxide (3). To a stirred solution of *N*-chlorosulfonyl isocyanate (10.00 g; 70 mmol) in 200 mL dry methylene chloride was added dropwise a solution of *t*-butanol (6.11 g; 82.5 mmol) in 20 mL methylene chloride at 0 °C. The resulting reaction mixture was stirred for an additional 30 min. The above solution and triethylamine (35.46 g; 350 mmol) were added dropwise to a suspension of 2-chloroethylamine hydrochloride (9.57 g; 82.5 mmol) in 75 mL dry methylene chloride at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. Methylene chloride (250 mL) was added to the reaction mixture and the resulting mixture was washed with 5% HCl until pH neutral, and then washed with brine (150 ml). The organic layer was dried over anhydrous sodium sulfate. The drying agent was filtered off and the solvent was removed under vacuum, leaving a colorless oil (17.0 g). The oil was dissolved in dry DMSO (80 mL) and anhydrous K_2CO_3 (55.20 g; 400 mmol) was added. The mixture was stirred at room temperature overnight. Water (400 mL) was added and the product was extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous sodium sulfate. The drying agent was filtered off and the solvent was removed to give compound **3** as a white solid (6.5 g; 42% yield), mp 140–141 °C. ^{1}H NMR ($CDCl_3$): δ 1.53 (s, 9H), 3.46 (t, J = 7.1 Hz, 2H), 3.83 (t, J = 7.1 Hz, 2H).

5.1.1.22. *tert*-Butyl 5-(prop-2-yn-1-yl)-1,2,5-thiadiazolidine-2-carboxylate 1,1-dioxide (4). To a chilled solution of compound **3** (2.22 g; 10 mmol) in dry DMF (10 mL) was added NaH (60% w/w; 0.4 g; 10 mmol) portion wise. The reaction mixture was stirred for 0.5 h before adding propargyl bromide (1.18 g; 10 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was removed and the residue was taken up in ethyl acetate (30 mL). The ethyl acetate solution was washed with 5% HCl (3 × 20 mL), saturated $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over anhydrous sodium sulfate. The drying agent was filtered and the solvent was removed, yielding compound **4** as a brown oil (2.46 g; 95% yield). ^{1}H NMR ($CDCl_3$): δ 1.55 (s, 9H), 2.40 (t, J = 2.7 Hz, 1H), 3.45–3.56 (m, 2H), 3.83–3.94 (m, 4H).

5.1.2. Synthesis of compounds 5a–b

5.1.2.1. Representative synthesis. *tert*-Butyl 5-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-1,2,5-thiadiazolidine-2-carboxylate 1,1-dioxide (5a). To a solution of compound **4** (0.52 g; 2 mmol) and benzyl azide (0.27 g; 2 mmol) in 6 mL 1:1 *t*-butanol and water was added sodium ascorbate (0.10 g; 1 mmol) and a catalytic amount of $CuSO_4$. The reaction was stirred at room temperature overnight. The solvent was removed and the residue was taken up in ethyl acetate (30 mL). The organic layer was washed with brine (2 × 20 mL) and dried over anhydrous sodium sulfate. The drying agent was filtered off and the solvent was removed. The crude product was purified using flash chromatography (silica gel/ethyl acetate/hexanes) to give compound **5a** as a white solid (41% yield), mp 149–151 °C. ^{1}H NMR ($CDCl_3$): δ 1.53 (s, 9H), 3.44 (t, J = 11.9 Hz, 2H), 3.69 (t, J = 11.9 Hz, 2H), 4.38 (s, 2H), 5.53 (s, 2H), 7.23–7.40 (m, 5H), 7.62 (s, 1H). HRMS (ESI) calculated m/z for $C_{17}H_{23}N_5O_4S$ $[M+Na]^+$ 416.1368; found 416.1353.

5.1.2.2. *tert*-Butyl 5-[(1-(4-methoxybenzyl)-1*H*-1,2,3-triazol-4-yl)methyl]-1,2,5-thiadiazoli-dine-2-carboxylate 1,1-dioxide (5b). White solid (23% yield), mp 129–131 °C. ^{1}H NMR ($CDCl_3$): δ 1.55 (s, 9H), 3.43 (t, J = 11.8 Hz, 2H), 3.71 (t, J = 11.8 Hz, 2H), 4.40 (s, 2H), 5.58 (s, 2H), 7.26–7.38 (m, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.69 (s, 1H), 8.60 (s, 2H). HRMS (ESI) calculated m/z for $C_{18}H_{25}N_5O_5S$ $[M+Na]^+$ 446.1474; found 446.1458.

5.1.2.3. 2-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-1,2,5-thiadiazolidine 1,1-dioxide (6a). Compound **5a** (0.16 g; 0.4 mmol) was added 10 ml 4 M HCl in 1,4-dioxane, and the reaction was at room temperature for 30 min. Solvent was removed, leaving a colorless oil, which was purified by flash chromatography (silica gel/ethyl acetate/hexanes) to give compound **6a** as white solid (100% yield) mp 88–90 °C ^{1}H NMR ($CDCl_3$): δ 3.38–3.52 (m, 4H), 4.3 (s, 2H), 4.8 (t, J = 10.2 Hz, 1H), 5.54 (s, 2H), 7.22–7.41 (m, 5H), 7.6 (s, 1H). HRMS (ESI) calculated m/z for $C_{12}H_{15}N_5O_2S$ $[M+Na]^+$ 316.0844; found 316.0829.

Compound **6b** was prepared using the same procedure as that used in the synthesis of compound **6a**.

5.1.2.4. 2-{[1-(4-Methoxybenzyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1,2,5-thiadiazolidine 1,1-dioxide (6b). White solid (0.21 g; 100% yield), mp 126–128 °C ^{1}H NMR ($CDCl_3$): δ 3.4 (s, 4H), 3.82 (s, 3H), 4.3 (d, J = 8.6 Hz, 2H), 5.45 (s, 2H), 6.92 (d, J = 9.0 Hz, 2H), 7.26 (d, J = 9.0 Hz, 2H), 7.68 (s, 1H). HRMS (ESI) calculated m/z for $C_{13}H_{17}N_5O_3S$ $[M+Na]^+$ 346.0950; found 346.0934.

5.1.2.5. Benzyl 3-(hydroxymethyl)piperidine-1-carboxylate (7). To a chilled solution of 3-(hydroxymethyl)piperidine (0.61 g; 5 mmol) in methylene chloride (10 mL) was added triethylamine (0.51 g; 5 mmol), followed by the dropwise addition of benzyl chloroformate (0.88 g; 5 mmol). The resulting reaction mixture was allowed to warm to room temperature and stirred overnight. Methylene chloride (50 mL) was added to the reaction and the organic layer was washed with 5% HCl (2 × 20 mL), saturated $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over anhydrous sodium sulfate. The drying agent was filtered off and the solvent was removed. The crude product was purified using flash chromatography (silica gel/ethyl acetate/hexanes) to give compound **7** as a colorless oil (1.21 g; 96% yield). ^{1}H NMR ($CDCl_3$): δ 1.20–1.83 (m, 5H), 2.78–3.20 (m, 2H), 3.50 (s, 2H), 3.69–4.05 (m, 2H), 5.14 (s, 2H), 7.25–7.40 (m, 5H).

5.1.2.6. Benzyl 3-formylpiperidine-1-carboxylate (8). To a suspension of pyridinium chlorochromate (0.65 g; 3 mmol) in 10 ml methylene chloride was added compound **7** (0.50 g; 2 mmol) in methylene chloride (5 mL). The reaction was stirred at room temperature for 2 h and filtered. The filtrate was evaporated and the residue was treated with diethyl ether (25 mL). The precipitate was filtered off again and the filtrate was evaporated, leaving pure product **8** as a pink oil (0.50 g; 90% yield). ^{1}H NMR ($CDCl_3$): δ 1.42–1.78 (m, 3H), 2.00 (br s, 1H), 2.43 (br s, 1H), 3.08–3.20 (m, 1H), 3.33–3.41 (m, 1H), 3.71–3.82 (m, 1H), 3.92–4.10 (m, 1H), 5.13 (s, 2H), 7.27–7.42 (m, 5H), 9.68 (s, 1H).

Compounds **9** and **10** were prepared using the same procedure as that used in the synthesis of compounds **1a** and **2a**.

5.1.2.7. Benzyl 3-{[(2-aminoethyl)amino]methyl}piperidine-1-carboxylate (9). Colorless oil (52% yield). ^{1}H NMR ($CDCl_3$): δ 1.40–1.90 (m, 5H), 2.42–2.80 (m, 7H), 2.87–2.98 (m, 1H), 3.90–4.10 (m, 2H), 5.14 (s, 2H), 7.28–7.39 (m, 5H).

5.1.2.8. Benzyl 3-[(1,1-dioxido-1,2,5-thiadiazolidin-2-yl)methyl] piperidine-1-carboxylate (10). Brown oil (70% yield). ^{1}H NMR ($CDCl_3$): δ 1.12–1.33 (m, 1H), 1.36–1.57 (m, 1H), 1.60–1.92 (m, 3H), 2.58–3.02 (m, 4H), 3.18–3.54 (m, 4H), 3.88–4.20 (2H), 5.12 (s, 2H), 7.36 (s, 5H).

5.1.2.9. 3-[(1,1-Dioxido-1,2,5-thiadiazolidin-2-yl)methyl]piperidine (11). To a stirred solution of compound **10** (0.71 g; 2 mmol) in methanol (20 mL) was added Pd-C (10% w/w; 0.13 g) and applied 20 psi hydrogen gas on a Parr hydrogenator overnight. The reaction mixture was filtered through a pad of Celite and the filtrate was evaporated to give pure compound **11** as a colorless oil (0.45 g; 100% yield). ^{1}H NMR ($CDCl_3$): δ 1.04–1.18 (m, 1H), 1.40–1.56 (m, 1H), 1.66–1.90 (m, 3H), 2.28–2.37 (m, 1H), 2.52–2.62 (m, 1H), 2.78–2.95 (m, 2H), 2.97–3.06 (m, 1H), 3.26–3.33 (m, 1H), 3.30–3.53 (m, 4H).

5.1.2.10. 1-Benzyl-3-[(1,1-dioxido-1,2,5-thiadiazolidin-2-yl)methyl]piperidine (12). A mixture of compound **11** (0.33 g; 1.5 mmol), benzyl bromide (0.26 g; 1.5 mmol) and $NaHCO_3$ (0.38 g; 4.5 mmol) in dry DMF (5 mL) was stirred for 2 days. DMF was removed in vacuo and the residue was treated with 5% HCl (20 mL). The solution was extracted with ethyl acetate (2 × 20 mL) to remove impurities. The aqueous layer was adjusted to pH 9 with 1 N NaOH, whereupon a precipitate formed. The precipitate was collected by vacuum filtration and air dried to give compound **12** as a white solid (0.47 g; 49% yield), mp 100–101 °C. ^{1}H NMR ($CDCl_3$): δ 0.49–2.07 (m, 5H), 2.64–2.75 (m, 1H), 2.83 (d, J = 8.7 Hz, 1H), 2.92 (d, J = 7.6 Hz, 2H), 3.29–3.58 (m, 8H), 4.23 (s, 1H), 7.20–7.34 (m, 5H). HRMS (ESI) calculated m/z for $C_{15}H_{23}N_3O_2S$ $[M+Na]^+$ 332.1409; found 332.1408.

5.1.3. Synthesis of compounds 13a–m

5.1.3.1. Representative synthesis. Methyl [5-(3-phenoxybenzyl)-1,1-dioxido-1,2,5-thiadiazolidin-2-yl]acetate (13a). To a solution of compound **2a** (7.3 g; 24 mmol) in dry DMF (50 mL) was added sodium hydride (1.28 g; 60% w/w; 31.2 mmol) at 0 °C. After stirring the reaction mixture for 0.5 h, methyl bromoacetate (4.03 g; 326.4 mmol) was added and the reaction mixture was stirred at room temperature overnight. DMF was removed under vacuum and the residue was taken up in ethyl acetate (200 mL). The organic layer was washed with 5% HCl (2 × 100 mL), brine (100 mL) and then dried over anhydrous sodium sulfate. The drying agent was filtered off and the solvent was removed to give product **13a** as a light yellow solid (8.3 g; 92% yield), mp 69–71 °C. ^{1}H NMR ($CDCl_3$): δ 3.26 (t, J = 5.4 Hz, 2H), 3.54 (t, J = 5.4 Hz, 2H), 3.78 (s, 3H), 3.89 (s, 2H), 4.19 (s, 2H), 6.92–7.40 (m, 9H). HRMS (ESI) calculated m/z for $C_{18}H_{20}N_2O_5S$ $[M+Na]^+$ 399.0991; found 399.0984.

5.1.3.2. Methyl 3-[5-(3-phenoxybenzyl)-1,1-dioxido-1,2,5-thiadiazolidin-2-yl]propanoate (13b). Yellow oil (80% yield). ^{1}H NMR ($CDCl_3$): δ 2.71 (t, J = 5.7 Hz, 2H), 3.18 (t, J = 5.7 Hz, 2H), 2.23–3.53 (m, 4H), 3.72 (s, 3H), 4.17 (s, 2H), 6.92–7.40 (m, 9H). HRMS (ESI) calculated m/z for $C_{19}H_{22}N_2O_5S$ $[M+H]^+$ 391.1328; found 391.1338.

5.1.3.3. Methyl 4-[5-(3-phenoxybenzyl)-1,1-dioxido-1,2,5-thiadiazolidin-2-yl]butyrate (13c). Yellow oil (76% yield). ^{1}H NMR ($CDCl_3$): δ 1.95 (t, J = 6.5 Hz, 2H), 2.44 (t, J = 7.0 Hz, 2H), 3.07–3.32 (m, 6H), 3.68 (s, 2H), 4.15 (s, 2H), 6.88–7.38 (m, 9H). HRMS (ESI) calculated m/z for $C_{20}H_{24}N_2O_5S$ $[M+H]^+$ 405.1484; found 405.1469.

5.1.3.4. Methyl 5-[5-(3-phenoxybenzyl)-1,1-dioxido-1,2,5-thiadiazolidin-2-yl]pentanoate (13d). Yellow oil (100% yield). ^{1}H NMR ($CDCl_3$): δ 1.64–1.78 (m, 4H), 2.38 (t, J = 6.2 Hz, 2H), 3.07 (t, J = 6.2 Hz, 2H), 3.17–3.32 (m, 4H), 3.67 (s, 3H), 4.18 (s, 2H), 6.92–7.40 (m, 9H). HRMS (ESI) calculated m/z for $C_{21}H_{26}N_2O_5S$ $[M+H]^+$ 419.1641; found 419.1658.

5.1.3.5. Methyl 7-[5-(3-phenoxybenzyl)-1,1-dioxido-1,2,5-thiadiazolidin-2-yl]heptanoate (13e). Colorless oil (36% yield). ^{1}H NMR (CDOD): δ 1.24 (t, J = 6.7 Hz, 3H), 1.31–1.46 (m, 4H), 1.55–1.67 (m, 4H), 2.30 (t, J = 7.7 Hz, 2H), 3.04 (t, J = 7.7 Hz, 2H), 3.17–3.28 (m, 4H), 4.07–4.18 (m, 4H), 6.89–7.37 (m, 9H). HRMS (ESI) calculated m/z for $C_{23}H_{30}N_2O_5S$ $[M+H]^+$ 447.1954; found 447.1964.

5.1.3.6. Methyl 4-[(5-(3-phenoxybenzyl)-1,1-dioxido-1,2,5-thiadiazolidin-2-yl)methyl]-benzoate 13f. White solid (63% yield), mp 72–73 °C. ^{1}H NMR ($CDCl_3$): δ 3.18 (s, 4H), 3.90 (s, 3H), 4.20 (s, 2H), 4.25 (s, 2H), 6.89–7.37 (m, 9H), 7.43 (d, J = 8.7 Hz, 2H), 8.02 (d, J = 8.7 Hz, 2H). HRMS (ESI) calculated m/z for $C_{24}H_{24}N_2O_5S$ $[M+Na]^+$ 475.1304; found 475.1305.

5.1.3.7. 2-Methyl-5-(3-phenoxybenzyl)-1,2,5-thiadiazolidine 1,1-dioxide (13g). Colorless oil (80% yield). ^{1}H NMR ($CDCl_3$): δ 2.77 (s, 3H), 3.17–3.30 (m, 4H), 4.19 (s, 2H), 6.90–7.40 (m, 9H). HRMS (ESI) calculated m/z for $C_{16}H_{18}N_2O_3S$ $[M+Na]^+$ 341.0936; found 341.0937.

5.1.3.8. 2-Ethyl-5-(3-phenoxybenzyl)-1,2,5-thiadiazolidine 1,1-dioxide (13h). Colorless oil (51% yield). ^{1}H NMR ($CDCl_3$): δ 1.26 (t, J = 6.4 Hz, 3H), 3.08–3.29 (m, 6H), 4.17 (s, 2H), 6.89–7.39 (m, 9H). HRMS (ESI) calculated m/z for $C_{17}H_{20}N_2O_3S$ $[M+Na]^+$ 355.1092; found 355.1085.

5.1.3.9. [5-(3-Phenoxybenzyl)-1,1-dioxido-1,2,5-thiadiazolidin-2-yl]acetonitrile (13i). White solid (85% yield), mp 80–81 °C. ^{1}H NMR ($CDCl_3$): δ 3.30 (t, J = 6.3 Hz, 2H), 3.49 (t, J = 6.3 Hz, 2H), 4.04 (s, 2H), 4.19 (s, 2H), 6.92–7.40 (m, 9H). HRMS (ESI) calculated m/z for $C_{17}H_{17}N_3O_3S$ $[M+H]^+$ 344.1069; found 344.1072.

5.1.3.10. 2-Benzyl-5-(3-phenoxybenzyl)-1,2,5-thiadiazolidine 1,1-dioxide (13j). Yellow oil (79% yield). ^{1}H NMR ($CDCl_3$): δ 3.17 (s, 4H), 4.20 (s, 2H), 4.21 (s, 2H), 6.91–7.40 (m, 14H). HRMS (ESI) calculated m/z for $C_{22}H_{22}N_2O_3S$ $[M+Na]^+$ 417.1249; 417.1231.

5.1.3.11. 2-(4-Fluorobenzyl)-5-(3-phenoxybenzyl)-1,2,5-thiadiazolidine 1,1-dioxide (13k). Yellow oil (61% yield). ^{1}H NMR ($CDCl_3$): δ 3.17 (s, 4H), 4.18 (s, 2H), 4.19 (s, 2H), 6.89–7.38 (m, 13H). HRMS (ESI) calculated m/z for $C_{22}H_{21}FN_2O_3S$ $[M+H]^+$ 413.1335; found 413.1338.

5.1.3.12. 3-{[5-(3-Phenoxybenzyl)-1,1-dioxido-1,2,5-thiadiazolidin-2-yl]methyl}pyridine (13l). White solid (75% yield), mp 60–61 °C. ^{1}H NMR ($CDCl_3$): δ 3.09 (s, 4H), 4.20 (s, 2H), 4.24 (s, 2H), 6.93–7.40 (m, 10H), 7.76–7.80 (m, 1H), 8.58–8.62 (m, 2H). HRMS (ESI) calculated m/z for $C_{21}H_{21}N_3O_3S$ $[M+H]^+$ 396.1382; found 396.1378.

5.1.3.13. 2-[5-(3-Phenoxybenzyl)-1,1-dioxido-1,2,5-thiadiazolidin-2-yl]acetamide (13m). White solid (80% yield), mp 122–123 °C. ^{1}H NMR ($CDCl_3$): δ 3.26 (t, J = 6.3 Hz, 2H), 3.44 (t, J = 6.3 Hz, 2H), 3.80 (s, 2H), 4.18 (s, 2H), 5.60 (s, 1H), 6.60 (s, 1H), 6.94–7.40 (m, 9H). HRMS (ESI) calculated m/z for $C_{17}H_{19}N_3O_4S$ $[M+H]^+$ 362.1175; found 362.1179.

5.1.4. Synthesis of compounds 14a–f

5.1.4.1. Representative synthesis. [5-(3-Phenoxybenzyl)-1,1-dioxido-1,2,5-thiadiazolidin-2-yl]acetic acid (14a). Compound **13a** (0.30 g; 0.8 mmol) was dissolved in dry 1,4-dioxane (8 mL) and 6 mL 1 M LiOH and the reaction was stirred at room temperature for 1 h. TLC indicated the completion of hydrolysis. The

solvent was removed and the residue was taken up in water (20 mL). The aqueous solution was extracted with ethyl acetate (2 × 15 mL) to remove any remaining starting material. The aqueous layer was adjusted to pH 1 and extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were dried over anhydrous sodium sulfate. The drying agent was filtered off and the solvent was removed to give pure compound **14a** as a colorless oil (0.19 g; 63% yield). ^{1}H NMR ($CDCl_3$): δ 3.26 (t, J = 6.1 Hz, 2H), 3.52 (t, J = 6.1 Hz, 2H), 3.96 (s, 2H), 4.17 (s, 2H), 6.89–7.38 (m, 9H), 9.75 (br s, 1H). HRMS (ESI) calculated m/z for $C_{17}H_{18}N_2O_5S$ $[M-H]^+$ 361.0858; found 361.0871.

5.1.4.2. 3-[5-(3-Phenoxybenzyl)-1,1-dioxido-1,2,5-thiadiazolidin-2-yl]propionic acid (14b). Colorless oil (82% yield). ^{1}H NMR ($CDCl_3$): δ 2.77 (t, J = 6.8 Hz, 2H), 3.20 (t, J = 6.8 Hz, 2H), 3.32–3.45 (m, 4H), 4.16 (s, 2H), 6.92–7.38 (m, 9H). HRMS (ESI) calculated m/z for $C_{18}H_{20}N_2O_5S$ $[M+Na]^+$ 399.0991; found 399.0977.

5.1.4.3. 4-[5-(3-Phenoxybenzyl)-1,1-dioxido-1,2,5-thiadiazolidin-2-yl]butyric acid (14c). Colorless oil (100% yield). ^{1}H NMR ($CDCl_3$): δ 1.92–2.01 (m, 2H), 2.52 (t, J = 7.3 Hz, 2H), 3.15 (t, J = 7.3 Hz, 2H), 3.19–3.34 (m, 4H), 4.17 (s, 2H), 6.90–7.40 (m, 9H). HRMS (ESI) calculated m/z for $C_{19}H_{22}N_2O_5S$ $[M+H]^+$ 391.1328; found 391.1332.

5.1.4.4. 5-[5-(3-Phenoxybenzyl)-1,1-dioxido-1,2,5-thiadiazolidin-2-yl]pentanoic acid (14d). Yellow oil (70% yield). ^{1}H NMR ($CDCl_3$): δ 1.65–1.80 (m, 4H), 2.42 (t, J = 5.9 Hz, 2H), 3.07 (t, J = 5.9 Hz, 2H), 3.17–3.30 (m, 4H), 4.17 (s, 2H), 6.91–7.40 (m, 9H). HRMS (ESI) calculated m/z for $C_{20}H_{24}N_2O_5S$ $[M+Na]^+$ 427.1304; found 427.1283.

5.1.4.5. 7-[5-(3-Phenoxybenzyl)-1,1-dioxido-1,2,5-thiadiazolidin-2-yl]heptanoic acid (14e). Colorless oil (99% yield). ^{1}H NMR ($CDCl_3$): δ 1.32–1.49 (m, 4H), 1.53–1.72 (m, 4H), 2.36 (t, J = 6.7 Hz, 2H), 3.04 (t, J = 6.7 Hz, 2H), 3.16–3.30 (m, 4H), 4.17 (s, 2H), 6.90–7.39 (m, 9H). HRMS (ESI) calculated m/z for $C_{22}H_{28}N_2O_5S$ $[M+H]^+$ $C_{22}H_{28}N_2O_5S$ $[M+H]^+$ 433.1797; found 433.1790.

5.1.4.6. 4-[(5-(3-Phenoxybenzyl)-1,1-dioxido-1,2,5-thiadiazolidin-2-yl)methyl]benzoic acid (14f). White solid (51% yield), mp 144–145 °C. ^{1}H NMR (DMSO-d_6): δ 3.23 (s, 4H), 4.17 (s, 2H), 4.23 (s, 2H), 6.92–7.43 (m, 9H), 7.49 (d, J = 8.7 Hz, 2H), 7.95 (d, J = 8.7 Hz, 2H). HRMS (ESI) calculated m/z for $C_{23}H_{22}N_2O_5S$ $[M+Na]^+$ 461.1147; found 461.1159.

5.1.4.7. 2-[5-(3-Phenoxybenzyl)-1,1-dioxido-1,2,5-thiadiazolidin-2-yl]ethanol (15). To a solution of compound **13a** (1.88 g; 5 mmol) in dry THF (8 mL) was added dropwise a solution of 2 M $LiBH_4$ (2.5 ml; 5 mmol), followed by the dropwise addition of absolute ethanol (15 mL). The reaction mixture was stirred at room temperature overnight and then acidified with cold 5% HCl to pH 4. The solvent was removed under vacuum and the residue was taken up in ethyl acetate (85 mL) and washed with brine (25 mL). The organic layer was dried over anhydrous sodium sulfate. The drying agent was filtered off and the solvent was removed under vacuum to give compound **15** as a colorless oil (1.62 g; 89.6% yield). ^{1}H NMR ($CDCl_3$): δ 2.48 (t, J = 5.0 Hz, 1H), 3.20–3.29 (m, 4H), 3.40 (t, J = 3.40 Hz, 2H), 3.83 (q, J = 6.0 Hz, 2H), 4.18 (s, 2H), 6.92–7.38 (m, 9H).

5.1.4.8. 2-[5-(3-Phenoxybenzyl)-1,1-dioxido-1,2,5-thiadiazolidin-2-yl]ethyl methanesulfonate (16). To a solution of compound **15** (1.36 g; 4 mmol) and triethylamine (0.41 g; 4 mmol) in methylene chloride (10 mL) was added methanesulfonyl chloride (0.50 g; 4.3 mmol) at 0 °C. The reaction was allowed to warm to room temperature and stirred overnight. Additional methylene chloride (10 mL) was added to the reaction and the solution was washed with saturated sodium bicarbonate (2 × 20 mL). The organic layer was separated and dried over anhydrous sodium sulfate. The drying agent was filtered off and the solvent was removed to give compound **16** as a colorless oil (1.58 g; 100% yield). ^{1}H NMR ($CDCl_3$): δ 3.07 (s, 3H), 3.23 (t, J = 6.0 Hz, 2H), 3.40–3.46 (m, 4H), 4.17 (s, 2H), 4.44 (t, J = 4.5 Hz, 2H), 6.92–7.39 (m, 9H).

5.1.4.9. 4-{2-[5-(3-Phenoxybenzyl)-1,1-dioxido-1,2,5-thiadiazolidin-2-yl]ethyl}morpholine (17a). A mixture of compound **16** (0.92 g; 2.2 mmol), morpholine (0.19 g; 2.2 mmol) and anhydrous sodium bicarbonate (1.0 g; 12 mmol) in 95% ethanol (10 mL) was refluxed overnight. The solvent was removed and the residue was taken up with ethyl acetate (30 mL) and water (30 mL). The organic layer was separated and washed with brine (30 mL). The organic layer was dried over anhydrous sodium sulfate. The drying agent was filtered off and the solvent was removed to give pure compound **17a** as a colorless oil (0.92 g; 100% yield). ^{1}H NMR ($CDCl_3$): δ 2.51 (t, J = 5.0 Hz, 4H), 2.63 (t, J = 5.8 Hz, 2H), 3.20 (q, J = 6.5 Hz, 4H), 3.39 (t, J = 6.3 Hz, 2H), 3.71 (t, J = 4.3 Hz, 2H), 4.19 (s, 2H), 6.92–7.39 (m, 9H). HRMS (ESI) calculated m/z for $C_{21}H_{27}N_3O_4S$ $[M+Na]^+$ 440.1620; found 440.1631.

5.1.4.10. 2-[5-(3-Phenoxybenzyl)-1,1-dioxido-1,2,5-thiadiazolidin-2-yl]ethylpiperidine (17b). Yellow oil (75% yield). ^{1}H NMR ($CDCl_3$): δ 1.39–1.60 (m, 6H), 2.35–2.50 (m, 4H), 2.58 (t, J = 7.0 Hz, 2H), 3.20 (q, J = 6.7 Hz, 4H), 3.39 (t, J = 5.5 Hz, 2H), 4.16 (s, 2H), 6.89–7.38 (m, 9H). HRMS (ESI) calculated m/z for $C_{22}H_{29}N_3O_3S$ $[M+Na]^+$ 438.1827; found 438.1815.

5.2. Biochemical studies

The antiviral effects of compounds were determined following previously described procedures using NV replicon-harboring cells.[4–7] Briefly, one-day old, 80–90% confluent HG23 cells were treated with varying concentrations of each compound (0 [mock-DMSO]-10 μM) to examine its effects on the replication of NV. At 24 or 48 h of treatment, the NV genome was analyzed with qRT-PCR. The ED_{50}s of the compounds for NV genome levels were determined at 24 h post-treatment. The ED_{50}s of the compounds listed in Table are the average of at least two independent experiments. The cytotoxic effects of the compounds on HG23 cells were determined with varying concentrations of each compound (0 [mock-DMSO]-320 μM) using a cell cytotoxicity assay kit (Promega, Madison, WI) to calculate the median toxic dose (TD_{50}) at 48 h of treatment.

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