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Discovery of Novel Selective Norepinephrine Reuptake Inhibitors: 4-[3-Aryl-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-1-(methylamino)butan-2-ols (WYE-103231)

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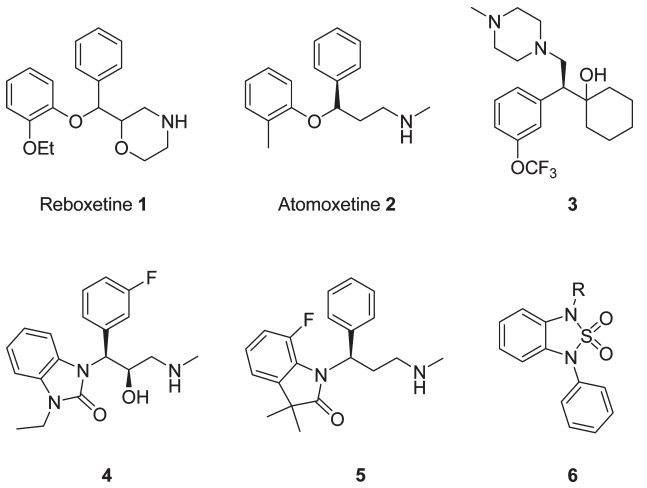
Structural modification of a virtual screening hit led to the identification of a new series of 4-[3-aryl-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-1-(methylamino)butan-2-ols which are potent and selective inhibitors of the norepinephrine transporter over both the serotonin and dopamine transporters. One representative compound ***S*-17b** (WYE-103231) had low nanomolar hNET potency (IC_{50} = 1.2 nM) and excellent selectivity for hNET over hSERT (> 1600-fold) and hDAT (> 600-fold). ***S*-17b** additionally had a good pharmacokinetic profile and demonstrated oral efficacy in rat models of ovariectomized-induced thermoregulatory dysfunction and morphine dependent flush as well as the hot plate and spinal nerve ligation (SNL) models of acute and neuropathic pain.

Introduction

The norepinephrine transporter (NET[a]) is a membrane bound protein which regulates the uptake of the neurotransmitter norepinephrine (NE) from the presynaptic cleft of noradrenergic neurons during synaptic transmission.[1,2] It therefore plays an important role in regulating the physiological functions of NE, the deficiency of which has been implicated in a number of neurological disorders. NE reuptake inhibitors (NRIs) block the return of NE to the axon terminal, thereby maintaining its synaptic concentration resulting in a treatment for a range of CNS disorders.[3] In the last 20 years, a number of monoamine neurotransmitter reuptake inhibitors have been approved for the treatment of neurological disorders such as depression and pain.[4] More recently, selective NRIs such as reboxetine **1** and atomoxetine **2** have been used clinically for the alleviation of major depressive disorder and attention deficit hyperactivity disorder (ADHD), respectively.[5,6] There is also evidence that these compounds may have efficacy in the treatment of chronic pain including fibromyalgia and lower back pain.[7,8]



Our previous reports have detailed efforts which resulted in the discovery of selective NRIs including cycloalkanol ethylamines,[9] e.g. **3**, benzimidazol-2-ones,[10] e.g. **4**, and indolin-2-ones **5**.[11] In our continuing effort to search for novel and selective NRIs, we have identified the *N*-aryl 2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl core, **6**, via virtual screening and rational drug design approaches.[12] Extensive SAR studies of this core have led to potent and selective NRI series. This report will cover the 4-[3-aryl-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-1-(methylamino)butan-2-ols, their synthesis, in vitro SAR, and the in vivo efficacy of lead compound ***S*-17b**. Additional

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[a] Abbreviations: NE, norepinephrine; NET, norephinephrine transporter; NRI, norepinephrine reuptake inhibitor; CNS, central nervous system; SERT, serotonin transporter; DAT, dopamine transporter; hNET, human norepinephrine transporter; hSERT, human serotonin transporter; hDAT, human dopamine transporter; SAR, structure–activity relationship; LMS, liver microsomal stability; CYP450, cytochrome P450; hERG, human ether-a-go-go related gene; QTc, heartrate-corrected QT interval; pk, pharmacokinetics; Clp, clearance; Vss, steady state volume of distribution; C_{max}, maximum concentration; T_{max}, time to maximum concentration; *F*%, percent bioavailability; AUC, area under the curve; OVX, ovariectomized; TST, tail-skin temperature; SNL, spinal nerve ligation.

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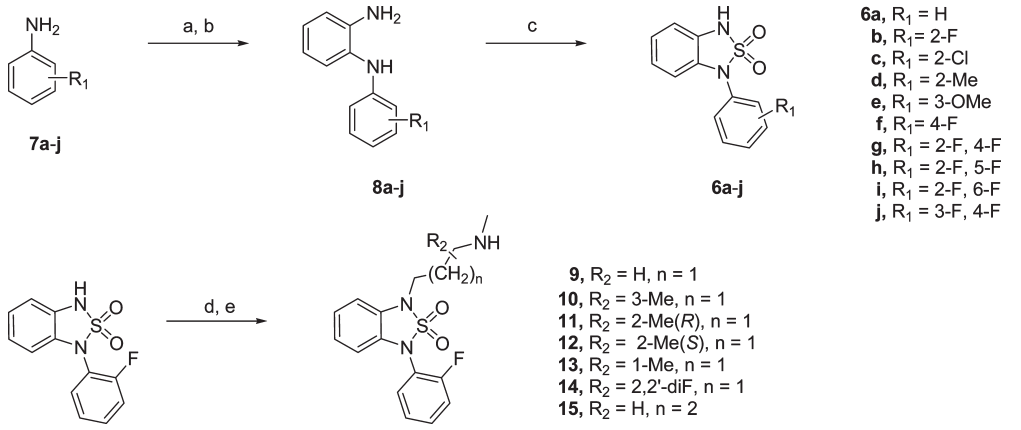
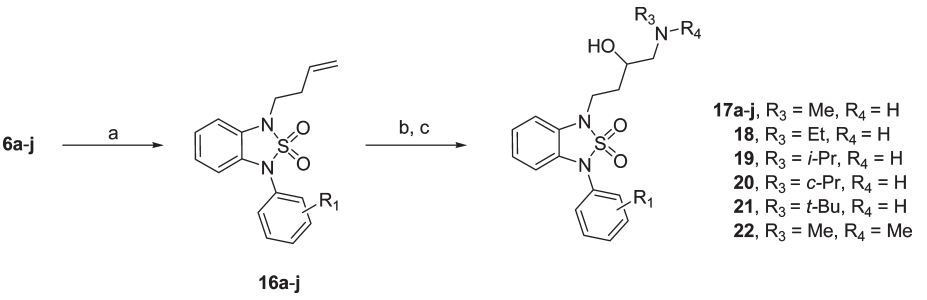
Scheme 1. Synthesis of *N*-Aryl-2,2-Dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl Cores and Targets **9**−**15**[a]



[a] Reagents and conditions: (a) 2-fluoronitrobenzene, NaH, DMF; (b) H_2, Pd/C, EtOAc; (c) sulfamide, sulfamic acid, diglyme, 190 °C; (d) HO-R_2alkyl-Br, DIAD, PPh_3, THF; (e) $MeNH_2$, EtOH, sealed tube, rt.

Scheme 2. Synthesis of 4-[3-Aryl-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-1-(alkylamino)butan-2-ols **17**−**22**[a]



[a] Reagents and conditions: (a) but-3-en-1-ol, DIAD, PPh_3, THF, rt; (b) *m*-CPBA, DCM, rt; (c) R_3R_4NH, EtOH, 100 °C, 3 min, microwave.

work incorporating this core to produce other chemical series will be disclosed in due course.

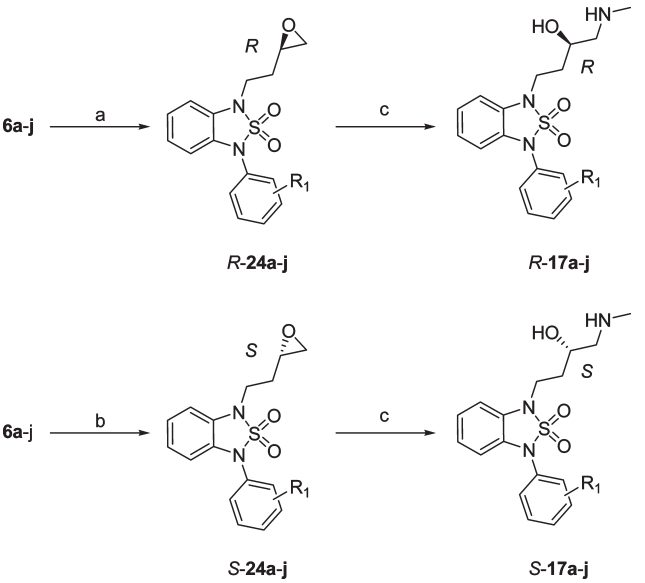
Chemistry

A synthetic route toward the preparation of the *N*-aryl 2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl cores and targets **9**−**15** is described in Scheme 1. Amine deprotonation of the substituted anilines **7a**−**j** followed by addition of 2-fluoronitrobenzene resulted in nucleophilic substitution of the fluorine. Hydrogenation of the nitrobenzene intermediates resulted in dianilines **8a**−**j**. Ring closure of **8a**−**j** with sulfamide furnished cyclic 2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yls **6a**−**j**. With these key cores in hand, target compounds **9**−**15** were easily accessible employing a Mitsonobu *N*-alkylation. This was exemplified with the *N*-2-fluorophenyl 2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl core **6b**, which can be treated with a variety of substituted bromoalkyl alcohols. Subsequent halogen-amine substitution with methylamine furnished target compounds **9**−**15**.

Mitsonobu *N*-alkylation of cores **6a**−**j** with but-3-en-1-ol, Scheme 2, provided the intermediate alkenes **16a**−**j**, which were epoxidized with *m*-CPBA, then typically used without isolation and ring-opened with alkylamines to provide targets **17**−**22**.

Compounds **17a**−**b** were separated into the *R*- and *S*-enantiomers utilizing chiral preparative HPLC. The absolute configuration of each enantiomer was determined by asymmetric synthesis utilizing intermediates of known chirality, Scheme 3. This route was also used to prepare additional

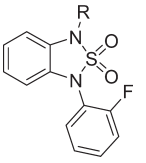
Scheme 3. Asymmetric Synthesis of 4-[3-Aryl-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-1- (methylamino)butan-2-ols ***R*-17a**−**j** and ***S*-17a**−**j**[a]

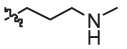
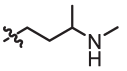
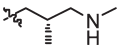
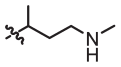
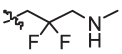
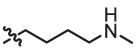
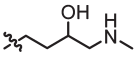
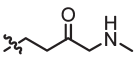


[a] Reagents and conditions: (a) (*R*)-4-tosyloxy-1,2-epoxybutane, K_2CO_3, acetone, rt; (b) (*S*)-4-bromo-1,2-epoxybutane, K_2CO_3, acetone, rt; (c) $MeNH_2$, EtOH, 100 °C, 3 min, microwave.

analogues. Mitsonobu *N*-alkylation of a 2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl core with either the *R* or the *S* chiral epoxide provided ***R*-24a**−**j** and ***S*-24a**−**j**. Ring-opening with

Table 1. Monoamine Reuptake Inhibition and Rat Metabolic Stability of *N*-2-Fluorophenyl-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yls **9**−**23**



Compd.	R	hNET IC_{50} (nM)[a]	hNET Binding IC_{50} (nM)[b]	hSERT %inh. @ 6 μM[c,e]	hDAT %inh. @ 10 μM[d,e]	Rat LMS t1/2 (min)[f]
9		**1±0.2**	**2.7±0.7**	**39**	**(512±51)**	**2**
10		**72±46**	**5**	**72**	**95**	**<1**
11		**305±144**	**57**	**63**	**91**	**<1**
12		**602±248**	**441**	**67**	**88**	**<1**
13		**7±1.3**	**2**	**15**	**74**	**<1**
14		**238±170**	**94±30**	**0**	**85**	**2**
15		**4.5±0.6**	**1.1±0.3**	**(2042±909)**	**40**	**3**
17b		**10±1.6**	**2**	**(4589±1486)**	**78**	**9**
23		**5.1±0.1**	**2**	**33**	**(1475±382)**	**<1**

[a] Inhibition of norepinephrine uptake in MDCK-Net6 cells, stably transfected with human norepinephrine transporter (hNET). Desipramine (IC_{50} = 3.4 ± 1.6 nM) was used as a standard. [b] Inhibition of [^{3}H] nisoxetine binding to MDCK-Net6 cells stably transfected with hNET. Desipramine (K_i = 2.1 ± 0.6 nM) was used as a standard. Compounds without standard errors are reported as an *n* of 1. [c] Inhibition of serotonin uptake in JAR cells, natively expressing human serotonin transporter (hSERT). Fluoxetine (IC_{50} = 9.4 ± 3.1 nM) was used as a standard. [d] Inhibition of [^{3}H]WIN-35,428 binding to membranes from CHO cells expressing recombinant human dopamine transporter (hDAT). Mazindol (K_i = 22.1 ± 6.5 nM) was used as a standard. [e] Values in the parentheses are IC_{50} (nM). [f] LMS, liver microsomal stability.[15]

methylamine provided the desired targets ***R*-17a**−**j** and ***S*-17a**−**j**, respectively.

Final compounds were converted to their hydrochloride salt prior to in vitro and in vivo testing.

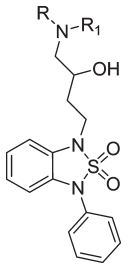
Results and Discussion

In Vitro Characterization. Initial optimization of the *N*-aryl 2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl scaffold led to the identification of **9**. This initial lead had excellent potency for hNET (IC_{50} = 1 nM) and good selectivity over hDAT and hSERT, Table 1, however **9** also displayed a low rodent metabolic half-life. The primary sites of metabolism were predicted[13] and confirmed experimentally as demethylation of the amine as well as oxidation of the benzo and pendant phenyl rings. To address the metabolic instability in rodents, various structural modifications were made to block these sites of metabolism. Modification of the electronic and steric character of the amine side chain aimed at reducing dealkylation while maintaining or improving the hNET potency and selectivity was the focus of the work described in this report. Detailed experimental protocols for all assays discussed were reported previously.[9,14]

Analogues incorporating a methyl group along the propyl side chain, **10**−**13**, resulted in an overall 7−600-fold drop in hNET functional potency with no increase in rat liver microsomal stability (LMS). While substitution proximal to the amine, **10**, gave a 70-fold drop in hNET potency (IC_{50} = 72 nM), incorporation of the methyl group at the center carbon of the propyl chain resulted in the greatest drop in potency (**12**, hNET IC_{50} = 602 nM). The distal methyl analogue **13** caused the smallest reduction in hNET functional potency (IC_{50} = 7 nM). Incorporation of electronegative groups in the side chain, such as the β-fluoro analogue **14**, reduced hNET potency (IC_{50} = 238 nM) without any improvement in rat metabolic stability. Extending the propyl side chain to four carbons provided compound **15** (IC_{50} = 4 nM), which had comparable in vitro potency and reduced hDAT selectivity when compared to **9**. Interestingly, compound **17b**, a four-carbon chain analogue with a β-hydroxy group had improved rat LMS ($t_{1/2}$ = 9 min) while maintaining good hNET potency (IC_{50} = 10 nM) and excellent selectivity. Attempted introduction of the β-hydroxy substitution into the propyl chain led to degradation of the target compound. Oxidation of the alcohol, **17b**, to the ketone, **23**, led to an equally potent NRI with reduced metabolic stability.

Compound **17b** demonstrated improved metabolic stability while maintaining good hNET potency and selectivity versus hSERT and hDAT. In addition, introduction of the β-hydroxy group had a significant impact on clogP and tPSA values, which improved the drug-like properties of the series.[16] A variety of β-hydroxy substituted analogues were synthesized on the *N*-phenyl-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl core (Tables 2 and 3). As shown in Table 2, increasing the

Table 2. NE Reuptake Inhibition and Rat Metabolic Stability of 4-[3-Phenyl-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-1-(alkylamino)butan-2-ols



compd	R	R_1	hNET IC_{50} (nM)[a]	rat LMS $t_{1/2}$ (min) [b]
17a	Me	H	2 ± 0.2	12
18	Et	H	196 ± 76	9
19	*i*-Pr	H	2255 ± 1489	6
20	*c*-Pr	H	9 ± 1.8	6
21	*t*-Bu	H	853 ± 298	6
22	Me	Me	481 ± 161	3

[a] Inhibition of norepinephrine uptake in MDCK-Net6 cells, stably transfected with human norepinephrine transporter (hNET). Desipramine ($IC_{50} = 3.4 \pm 1.6$ nM) was used as a standard. [b] LMS, liver microsomal stability.

size of the *N*-alkyl group reduced hNET potency as well as rat LMS. The dimethylamino compound **22** showed minimal rat microsomal stability as might be expected. Interestingly, the cyclopropylamino derivative **20** demonstrated the smallest drop in hNET potency with an IC_{50} of 9 nM in the hNET functional assay while its isopropyl analogue **19** was over 100-fold less potent.

The SAR of substitution around the pendant aryl ring was examined (Table 3). Compounds in this series were tested as single enantiomers. In general, the *R*-enantiomers were 2−9-fold less potent in the hNET assays than the corresponding *S*-enantiomers. While both enantiomers showed comparable hSERT selectivity, the *R*-enantiomers were less selective for hDAT. Compound ***S*-17b** was the most potent of the *S*-enantiomers tested ($IC_{50} = 1$ nM) with excellent hNET selectivity versus hSERT (> 1300-fold) and hDAT (> 600-fold). Analogues ***S*-17h** and ***S*-17i** displayed similar profiles to ***S*-17b** (hNET $IC_{50} < 5$ nM), and all three compounds had rat LMS half-lives that were improved over **9b** ($t_{1/2} = 9, 6, 6$ min respectively vs 2 min). Incorporation of a 4-F group hindered metabolism and further increased the rat metabolic stability, exemplified by ***S*-17f**, ***S*-17g**, and ***S*-17j**, which display half-lives greater than 30 min. Incorporation of the 4-fluorophenyl substituent impacted hNET activity, with a 15−122-fold drop in potency, and for ***S*-17f** and **g** a drop of 7-fold and 167-fold, respectively, in hDAT selectivity. Alternate substitution at the 2-phenyl position such as chlorine and methyl, ***S*-17c** and **d**, showed decreased hNET potency ($IC_{50} = 28$ and 64 nM) and rat LMS ($t_{1/2} = 6$ and 5 min.). Incorporating an electron-donating group such as methoxy to the phenyl 3-position, ***S*-17e**, led to decreased metabolism ($t_{1/2} = 14$ min.) relative to **9b** but decreased hNET potency ($IC_{50} = 25$ nM) and selectivity over hDAT (~135-fold). Several lead compounds, ***S*-17a**, ***S*-17b**, ***S*-17h**, and ***S*-17i**, demonstrated the desired in vitro profile and improved rat LMS relative to **9b** and were profiled further. In general, each compound showed a low potential for drug−drug interaction with low CYP450 inhibition against multiple isozymes (generally < 15% inhibition @ 3 μM). Compound ***S*-17b** demonstrated low hERG inhibition ($IC_{50} = > 30$ μM), which suggests a low potential for QTc prolongation.[17] Compounds ***S*-17a**, ***S*-17h**, and ***S*-17i**, however were not as selective at hERG with IC_{50}'s of 8, 13, and 20 μM, respectively.

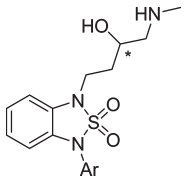
In Vivo Characterization. Compound ***S*-17b** was selected based on its in vitro profile for complete in vivo characterization.[18] Table 4 highlights the male, intact female, and ovariectomized female (OVX) rat pharmacokinetic parameters of ***S*-17b** using both intravenous and oral administration. In general, ***S*-17b** showed high to moderate clearance, high volume of distribution, and long terminal half-life. Overall, the compound exhibited an acceptable p*K* profile with bioavailability ranging from 41% to 100%. In addition, ***S*-17b** had good brain penetration, with a brain/plasma ratio of 3.6 in OVX rats.

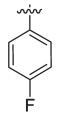
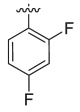
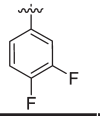
Compound ***S*-17b** was profiled in a series of in vivo models to assess its effects on norepinephrine neurobiology. It is widely believed that fluctuations in estrogen levels due to menopause result in corresponding changes to norepinephrine levels in the brain.[19] In particular, norepinephrine has been reported to regulate temperature control via stimulation of areas of the hypothalamus.[20,21] Hormone depletion causes thermoregulatory dysfunction (hot flush), which has been shown to be alleviated by NRIs.[22,23] Compound ***S*-17b** was therefore characterized in several predictive disease models for vasomotor symptoms (VMS).[22] We have previously shown that selective NRIs can significantly reduce the tail-skin temperature (TST) in a telemetric rat model of ovariectomized-induced thermoregulatory dysfunction.[9,10] The effect of ***S*-17b** on temperature homeostasis was evaluated in this telemetric rat model over a 12 h period (Figure 1). When administered orally, compound ***S*-17b** significantly reduced TST, with an immediate onset and a maximum temperature reduction of 4.5° at a dose of 30 mg/kg. The compound lowered the TST in a dose-dependent manner with a minimum efficacious dose of 0.1 mg/kg.

The regulation of TST was further confirmed in a second in vivo thermoregulatory efficacy model where the effect of acute oral doses of ***S*-17b** on the abatement of morphine dependent flush was evaluated in OVX rats (Figure 2).[22] In this model, morphine dependent OVX rats were treated sequentially with a single oral dose of the test compound followed by a 1 mg/kg of the nonselective opioid antagonist naloxone 90 min later, resulting in an immediate rise in TST. Dose-dependently, ***S*-17b** abated the increase in TST caused by naloxone treatment. At 30 mg/kg, compound ***S*-17b** abated the flush by 90% and had an ED_{50} of 1 mg/kg.

NE has also been implicated in the modulation of nociceptive processing,[24] which is a component of the endogenous descending pain inhibitory system. Reduced levels of NE may in part contribute to the establishment and/or maintenance of chronic pain states.[25−27] It was reported that by blocking reuptake of NE, NRIs increase NE levels which subsequently activate descending inhibitory pathways.[24] The rat hot plate assay of acute analgesia was used to investigate the efficacy of ***S*-17b** on alleviating pain.[28,29] In this assay, rats are placed on a metal plate maintained at a temperature of 52 °C. The latency to exhibit a response to this thermal stimulus, such as hind paw lift, flutter, licking, or escape behavior, was measured with a cutoff of 30 s to avoid tissue damage. Upon oral administration, ***S*-17b** significantly increased latency at both 3 and 10 mg/kg 1 and 3 h postdosing (Figure 3). These data suggest that compound ***S*-17b** was efficacious in treating acute pain.

Table 3. Monoamine Reuptake Inhibition and Rat Metabolic Stability of 4-[3-Aryl-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-1-(methylamino)butan-2-ols



Compd	Ar	hNET IC_{50} (nM)[a]	hNET Binding IC_{50} (nM)[b]	hSERT %inh. @ 6 μM[c]	hDAT %inh. @ 10 μM[d,e,f]	Rat LMS t1/2 (min)[g]
R-**17a**		**3±1.2**	**9**	**28**	**ND**	**19**
S-**17a**		**4±0.7**	**2±0.2**	**68**	**(2113±349)**	**9**
R-**17b**		**3±1**	**4±0.6**	**21**	**(2409±347)**	**10**
S-**17b**		**1±0.2**	**6±0.2**	**48**	**(3617±670)**	**9**
R-**17c**		**61±26**	**48±8**	**67**	**ND**	**5**
S-**17c**		**28±4**	**8**	**31**	**ND**	**6**
R-**17d**		**294±86**	**155±4**	**35**	**(1872±483)**	**6**
S-**17d**		**64±16**	**22**	**11**	**(2326±228)**	**5**
R-**17e**		**143±39**	**80±20**	**65**	**(267±63)**	**29**
S-**17e**		**25±4**	**19**	**56**	**(2570±)**	**14**
R-**17f**		**328±34**	**244±57**	**52**	**(262±56)**	**>30**
S-**17f**		**146±28**	**51**	**31**	**(386±90)**	**>30**
R-**17g**		**100±53**	**109±5**	**43**	**(998±279)**	**30**
S-**17g**		**18±8**	**19**	**24**	**(3185±338)**	**30**
R-**17h**		**10±1.1**	**34**	**48**	**(509±155)**	**8**
S-**17h**		**3±0.1**	**2±0.4**	**58**	**(2086±369)**	**6**
R-**17i**		**9±1.2**	**6±3**	**40**	**(5500±2247)**	**8**
S-**17i**		**4±0.2**	**2±0.2**	**38**	**(2618±235)**	**6**
R-**17j**		**394±68**	**277±125**	**33**	**(291±27)**	**>30**
S-**17j**		**43±10**	**36**	**23**	**ND**	**>30**

[a] Inhibition of norepinephrine uptake in MDCK-Net6 cells, stably transfected with human norepinephrine transporter (hNET). Desipramine (IC_{50} = 3.4 ± 1.6 nM) was used as a standard. [b] Inhibition of [^{3}H] nisoxetine binding to MDCK-Net6 cells stably transfected with hNET. Desipramine (K_i = 2.1 ± 0.6 nM) was used as a standard. Compounds without standard errors are reported as an *n* of 1. [c] Inhibition of serotonin uptake in JAR cells, natively expressing human serotonin transporter (hSERT). Fluoxetine (IC_{50} = 9.4 ± 3.1 nM) was used as a standard. [d] Inhibition of [^{3}H]WIN-35,428 binding to membranes from CHO cells expressing recombinant human dopamine transporter (hDAT). Mazindol (K_i = 22.1 ± 6.5 nM) was used as a standard. [e] Values in the parentheses are IC_{50} (nM). [f] ND: not determined. [g] LMS: liver microsomal stability.

The activity of compound ***S*-17b** was also evaluated in a rat spinal nerve ligation (SNL) model of neuropathic pain. In this model,[30,31] surgery was performed to tightly ligate the left L5 spinal nerve. Assessment of mechanical thresholds was then measured as the hind paw withdrawal threshold to a noxious mechanical stimulus as determined using the paw pressure technique (Randall−Selitto). The cutoff was set at 250 g of pressure, and the end point was complete paw withdrawal. Thresholds were evaluated prior to surgery to act as an internal control and reassessed three to four weeks after recovery from SNL surgery. Compound ***S*-17b** was administered orally in 0.5% methylcellulose plus 2% Tween in water, and the ability to reverse SNL-induced mechanical hyperalgesia with this agent was assessed. Compound ***S*-17b** significantly and dose-dependently reversed mechanical hyperalgesia at 5, 7, 10, and 30 mg/kg, suggesting efficacy in treating neuropathic pain (Figure 4).

Table 4. Pharmacokinetic Parameters of Compound ***S*-17b** in the Male, Intact Female, and OVX Rats after Intravenous and Oral Administrations[a]

rat	dose (mg/kg)	Clp (mL/min/kg)	Vss (L/kg)	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)	AUC_{0-inf} (h·ng/mL)	*F*%
M	2 (iv)	170	36.3			2.9	199	
F	2 (iv)	36	11.3			4.7	929	
OVX	2 (iv)	66	25.3			6.3	505	
M	10 (po)			154	1.38	3.2	1038	100
F	5 (po)			135	0.56	4.4	959	41.3
OVX	5 (po)			125	1.63	4.7	1200	95.2

[a] 2% Tween-80/0.5% methylcellulose in water and DMSO/80%PEG200 were used as vehicles for oral and intravenous administrations, respectively. Three rats were used in each study.

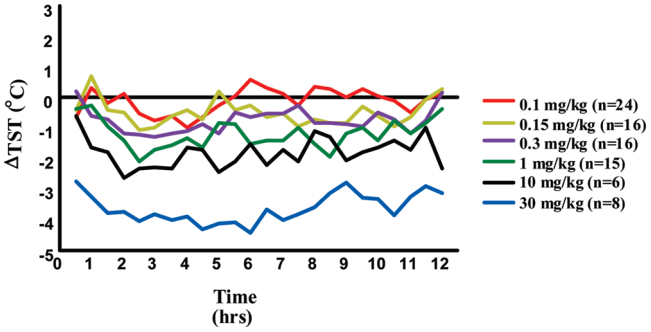


Figure 1. Oral activity of compound ***S*-17b** in a telemetric rat model of ovariectomized-induced thermoregulatory dysfunction. Compound was dosed in 2% Tween-80/0.5% methylcellulose in water. The onset of an effect was defined as the first half-hour interval of two consecutive significant ($p < 0.05$) half-hour intervals following any number of nonsignificant half-hour intervals. The treatment effect was considered to have ended when two consecutive nonsignificant half-hour intervals followed any number of significant half-hour intervals. Mean temperature change was calculated from half-hour TST averages obtained over the treatment duration.

Conclusion

The lead optimization efforts toward the improvement of compound **9b** resulted in the discovery of a new series of *N*-aryl-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-1-(methylamino)butan-2-ols, which are potent and selective for the inhibition of norepinephrine transport without effects on both serotonin and dopamine transport. The lead compound demonstrated good pharmacokinetic and pharmaceutical profiles. Compound ***S*-17b** was orally efficacious toward alleviating behavioral symptoms associated with NE deficiency in four in vivo models. In the telemetric rat model and in the morphine dependent flush model, ***S*-17b** dose-dependently reduced tail skin temperature in OVX rats and was the most potent NRI seen in these models to date. This compound also showed good activity in both the rat hot plate and spinal nerve ligation models, demonstrating an additional potential to treat acute and neuropathic pain. On the basis of this profile, ***S*-17b** (WYE-103231) advanced into development for the treatment of vasomotor symptoms and pain.

Experimental Section

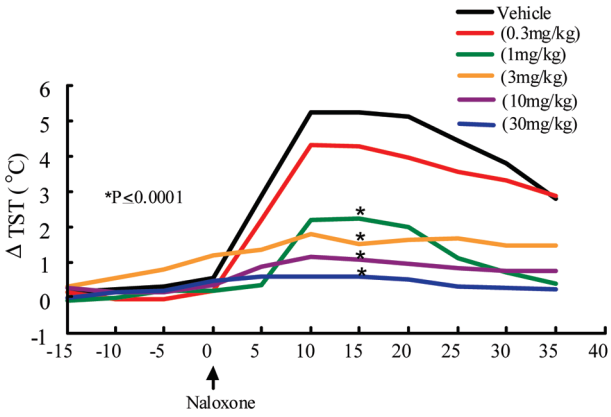
^{1}H NMR spectra were recorded on a Varian INOVA 400 or Bruker AVANCE II 400 instrument. Chemical shifts are reported in δ values (parts per million, ppm) relative to an internal standard of tetramethylsilane in $CDCl_3$ or DMSO-d_6. Electrospray (ESI) mass spectra were recorded using a Hewlett-Packard 5989B MS engine or Waters Alliance-ZMD mass spectrometer. Electron impact ionization (EI, EE = 70 eV) mass spectra were recorded on a Finnigan Trace mass spectrometer. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel, 60 F-254), and spots were visualized with UV light and stained in iodine. Solvents were purchased as anhydrous grade and were used without further purification. Crude reaction products were purified using the ISCO Rf purification system. Preparative HPLC purifications were performed on a preparative Gilson HPLC system using a CombiPrep Pro C18 column with acetonitrile (0.1% TFA) and water (0.1% TFA) as solvents at a flow rate of 20 mL/min. Chiral HPLC separations were carried out using supercritical fluid chromatography conditions using a 250 mm × 4.6 mm i.d. column at 2.0 mL/min flow rate using Chiralpak AS-H 5 analytical supercritical fluid chromatography (Berger Instruments, Inc. Newark, DE). Compound purity was assessed by ^{1}H NMR and analytical HPLC as described in the Supporting Information. Biological results were obtained on compounds of >95% chemical purity as determined by the above methods.

1-Phenyl-1,3-dihydro-2,1,3-benzothiadiazole 2,2-dioxide (6a). Compound **6a** was prepared following the general procedure for **6b** with *N*-(2-fluorophenyl)benzene-1,2-diamine being replaced with *N*-phenyl-*o*-phenylenediamine.

MS (ES) *m*/*z* 245.2 ([M − H]$^+$). HRMS: calcd for $C_{12}H_{10}N_2O_2S + H^+$, 247.0536; found (ESI, [M + H]$^+$), 247.0541. ^{1}H NMR (DMSO-d_6) δ 11.62 (br s, 1H), 7.49 (m, 5H), 6.91 (m, 3H), 6.57 (d, J = 7.54 Hz, 1H).

General Procedure for the Synthesis of the Sulfamide Cores. 1-(2-Fluorophenyl)-1,3-dihydro-2,1,3-benzothiadiazole 2,2-Dioxide (6b). 2-Fluoroaniline (1.45 mL, 15 mmol) was dissolved in DMF (10 mL), and sodium hydride (0.58 g, 15 mmol) was added and the mixture was stirred for 30 min. 2-Fluoronitrobenzene (1.05 mL, 10 mmol) was added, and the mixture was stirred for 16 h. The mixture was quenched with saturated NH_4Cl and diluted with ether. The mixture was washed with water, brine, dried over anhydrous magnesium sulfate, and concentrated. The crude product was purified via chromatography (Redisep, silica, gradient 5−30% ethyl acetate in hexane) to afford 1.4 g of 2-fluoro-*N*-(2-nitrophenyl)aniline (MS (ES) *m*/*z* 232.9), which was dissolved in ethyl acetate (20 mL), and 10% palladium on activated carbon (150 mg) was added. The mixture was shaken under a hydrogen atmosphere (40 psi) for 2 h. The mixture was filtered through a pad of celite and concentrated to give 1.2 g of *N*-(2-fluorophenyl)benzene-1,2-diamine (MS (ES) *m*/*z* 203.0) that was carried on directly to the next step. Dry diglyme (10 mL) was added to a flask equipped with a dropping funnel under a nitrogen atmosphere and brought to a vigorous reflux. *N*-(2-Fluorophenyl)benzene-1,2-diamine (1.2 g, 5.9 mmol) and sulfamide (0.68 g, 7.1 mmol) were dissolved in 5 mL of diglyme and placed in the dropping funnel. The mixture was added dropwise to the flask over 15 min, and then refluxing was continued for an additional 15 min. The mixture was cooled to ambient temperature and diluted with ether, washed with water, 2N HCl, water, and brine, dried over anhydrous magnesium sulfate, and concentrated. The crude product was purified via chromatography (Redisep, silica, gradient 5−50% (ethyl acetate containing 2% formic acid) in hexane) to afford 0.37 g of 1-(2-fluorophenyl)-1,3-dihydro-2,1,3-benzothiadiazole 2,2-dioxide **6b** (28%).

MS (ES) *m*/*z* 262.9 ([M − H]$^+$); HRMS: calcd for $C_{12}H_9FN_2O_2S + H^+$, 265.0442; found (ESI, [M + H]$^+$), 265.0444;



27b (mg/kg,po)	% Abatement
0.3	18
1	58
3	72
10	79
30	90

Figure 2. Abatement of compound ***S*-17b** on morphine dependent flush in OVX Rats. Compound was dosed in accordance with the previously published protocol.[22] $N = 10$ rats per dose.

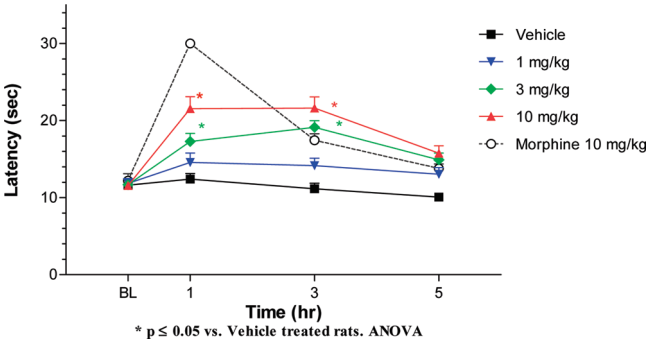


Figure 3. Oral activity of compound ***S*-17b** on hot plate latency. Male, Sprague−Dawley rats, wt = 181−215 g, (n = 10/group). The hot plate was set at 52 °C and cut off was set at 30 s. Latency to nocifensive response was measured. ***S*-17b** was administered (po) as a solution in 2% Tween/0.5% methylcellulose (vehicle). Morphine was administered (sc) as a solution in 0.9% saline. Data shown are means ± SEM.

^{1}H NMR (DMSO-d_6) δ 7.54 (m, 3H), 7.40−7.35 (m, 1H), 6.90 (m, 3H), 6.44 (d, J = 7.81 Hz, 1H).

1-(2-Chlorophenyl)-1,3-dihydro-2,1,3-benzothiadiazole 2,2-Dioxide (6c). Compound **6c** was prepared following the general procedure for sulfamide synthesis with 2-fluoroaniline being replaced with 2-chloroaniline.

MS (ES) m/z 278.8 ([M − H]$^+$). HRMS: calcd for $C_{12}H_9ClN_2O_2S$ − H$^+$, 279.0000; found (ESI, [M − H]$^+$), 279.0002. ^{1}H NMR (DMSO-d_6) δ 7.72 (m, 1H), 7.56 (m, 3H), 6.90 (m, 3H), 6.28 (d, J = 7.55 Hz, 1H).

1-(2-Methylphenyl)-1,3-dihydro-2,1,3-benzothiadiazole 2,2-Dioxide (6d). Compound **6d** was prepared following the general procedure for sulfamide synthesis with 2-fluoroaniline being replaced with 2-methylaniline.

MS (ES) m/z 261.0 ([M + H]$^+$). HRMS: calcd for $C_{13}H_{12}N_2O_2S$ − H$^+$, 259.0547; found (ESI, [M − H]$^+$), 259.0546. ^{1}H NMR (DMSO-d_6) δ 11.62 (br s, 1H), 7.51 (m, 2H), 7.42 (m, 2H), 6.92 (m, 3H), 6.25 (d, J = 7.54 Hz, 1H), 2.21 (s, 3H).

1-(3-Methoxyphenyl)-1,3-dihydro-2,1,3-benzothiadiazole 2,2-Dioxide (6e). Compound **6e** was prepared following the general procedure for sulfamide synthesis with 2-fluoroaniline being replaced with 3-methoxyaniline.

MS (ES) m/z 276.9 ([M + H]$^+$). HRMS: calcd for $C_{13}H_{12}N_2O_3S$ − H$^+$, 275.0496; found (ESI, [M − H]$^+$), 275.0494. ^{1}H NMR (DMSO-d_6) δ 11.64 (br s, 1H), 7.44 (m, 1H), 7.02 (m, 2H), 6.90 (m, 4H), 6.63 (m, 1H), 3.75 (s, 3H).

1-(4-Fluorophenyl)-1,3-dihydro-2,1,3-benzothiadiazole 2,2-Dioxide (6f). Compound **6f** was prepared following the general procedure for sulfamide synthesis with 2-fluoroaniline being replaced with 4-fluoroaniline.

MS (ES) m/z 263.0 ([M − H]$^+$). HRMS: calcd for $C_{12}H_9FN_2O_2S$ − H$^+$, 263.0296; found (ESI, [M − H]$^+$), 263.0295. ^{1}H NMR (DMSO-d_6) δ 11.65 (br s, 1H), 7.48 (m, 2H), 7.39 (m, 2H), 6.91 (m, 3H), 6.54 (d, J = 7.69 Hz, 1H).

1-(2,4-Difluorophenyl)-1,3-dihydro-2,1,3-benzothiadiazole 2,2-Dioxide (6g). Compound **6g** was prepared following the general procedure for sulfamide synthesis with 2-fluoroaniline being replaced with 2,4-difluoroaniline.

MS (ES) m/z 281.0 ([M − H]$^+$). HRMS: calcd for $C_{12}H_8F_2N_2O_2S$ − H$^+$, 281.0202; found (ESI, [M − H]$^+$), 281.0207. ^{1}H NMR (DMSO-d_6) δ 11.80 (br s, 1H), 7.65 (m, 2H), 7.33 (m, 1H), 6.50 (m, 3H), 6.53 (d, J = 7.66 Hz, 1H).

1-(2,5-Difluorophenyl)-1,3-dihydro-2,1,3-benzothiadiazole 2,2-Dioxide (6h). Compound **6h** was prepared following the general procedure for sulfamide synthesis with 2-fluoroaniline being replaced with 2,5-difluoroaniline.

MS (ES) m/z 280.9 ([M − H]$^+$). HRMS: calcd for $C_{12}H_8F_2N_2O_2S$ − H$^+$, 281.0202; found (ESI, [M − H]$^+$), 281.0204. ^{1}H NMR (DMSO-d_6) δ 11.82 (br s, 1H), 7.61 (m, 1H), 7.52 (m, 2H), 6.98 (m, 3H), 6.60 (d, J = 7.80 Hz, 1H).

1-(2,6-Difluorophenyl)-1,3-dihydro-2,1,3-benzothiadiazole 2,2-Dioxide (6i). Compound **6i** was prepared following the general procedure for sulfamide synthesis with 2-fluoroaniline being replaced with 2,6-difluoroaniline.

MS (ES) m/z 281.3 ([M − H]$^+$). HRMS: calcd for $C_{12}H_8F_2N_2O_2S$ + H$^+$, 283.0347; found (ESI, [M + H]$^+$), 283.0347.; ^{1}H NMR (DMSO-d_6) δ 11.88 (br s, 1H), 7.73 (m, 1H), 7.42 (m, 2H), 6.98 (m, 3H), 6.56 (d, J = 7.80 Hz, 1H).

1-(3,4-Difluorophenyl)-1,3-dihydro-2,1,3-benzothiadiazole 2,2-Dioxide (6j). Compound **6j** was prepared following the general procedure for sulfamide synthesis with 2-fluoroaniline being replaced with 3,4-difluoroaniline.

MS (ES) m/z 280.8 ([M − H]$^+$). HRMS: calcd for $C_{12}H_8F_2N_2O_2S$ − H$^+$, 281.0202; found (ESI, [M + H]$^+$), 281.0203. ^{1}H NMR (DMSO-d_6) δ 11.78 (br s, 1H), 7.63 (m, 2H), 7.34 (m, 1H), 6.92(m, 3H), 6.65 (d, J = 7.95 Hz, 1H).

3-[3-(2-Fluorophenyl)-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-*N*-methylpropan-1-amine (9). 6b (0.37 g, 1.4 mmol) was dissolved in THF (10 mL). Triphenylphosphine (440 mg, 1.68 mmol) and 3-bromopropanol (0.12 mL, 1.4 mmol) were added, followed by diisopropylazodicarboxylate (0.33 mL, 1.68 mmol). The mixture was stirred for 16 h and then concentrated. Purification via chromatography (Redisep, silica, gradient 5−50% ethyl acetate in hexane) afforded 0.41 g of 1-(3-bromopropyl)-3-(2-fluorophenyl)-1,3-dihydro-2,1,3-benzothiadiazole 2,2-dioxide, which was immediately carried on to the next step. 1-(3-Bromopropyl)-3-(2-fluorophenyl)-1,3-dihydro-2,1,3-benzothiadiazole 2,2-dioxide (0.4 g, 1.04 mmol) was dissolved in 8N methylamine in methanol (20 mL) and stirred for 16 h in a sealed flask. The mixture was concentrated in vacuo to give the crude product. The crude product was purified via chromatography (silica, 5% methanol

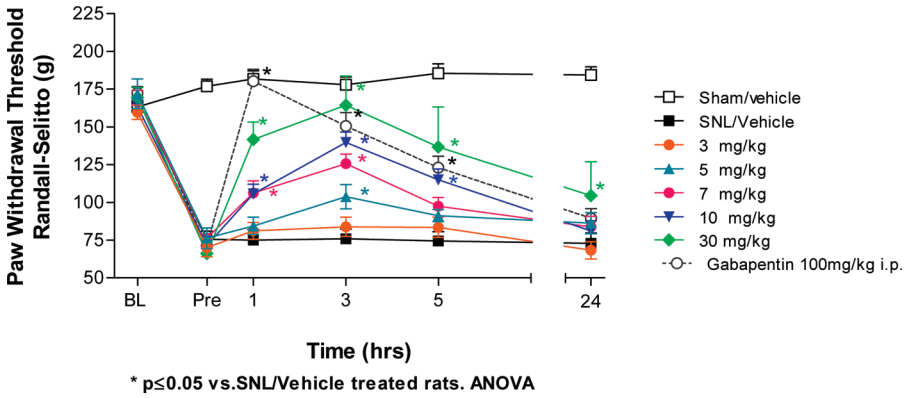


Figure 4. Oral activity of compound ***S*-17b** on SNL-induced mechanical hyperalgesia. Male, Sprague−Dawley rats (238−304 g, 9−10/group), 3 weeks postsurgery. Threshold to paw withdrawal was measured. ***S*-17b** was administered orally as a suspension of 0.5% methylcellulose plus 2% Tween in water. Gabapentin was used as a positive control and administered (ip) as a solution in 0.9% saline. Data shown are means ± SEM. * indicates a p value of ≤0.05 vs SNL/vehicle (ANOVA).

saturated with ammonia in chloroform) to give 350 mg of 3-[3-(2-fluorophenyl)-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-*N*-methylpropan-1-amine. The free base was dissolved in ether (10 mL) and treated with 1N hydrochloric acid in ether (1 equiv). The white precipitate was collected and dried under vacuum to provide **9**.

MS (ES) m/z 335.9 ($[M + H]^+$). HRMS: calcd for $C_{16}H_{18}FN_3O_2S + H^+$, 336.1177; found (ESI, $[M + H]^+$), 336.1177. ^{1}H NMR (DMSO-d_6) δ 8.85 (br s, 2H), 7.57 (m, 2H), 7.41 (m, 1H), 7.20 (m, 1H), 7.06 (m, 1H), 6.93 (m, 1H), 6.52 (d, J = 7.82 Hz, 1H), 3.95 (m, 2H), 2.99 (m, 2H), 2.5 (s, 3H), 2.09 (m, 2H).

3-[3-(2-Fluorophenyl)-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-*N*-methylbutan-2-amine (10). Compound **10** was prepared following the procedure for compound **9** with 3-bromopropanol being replaced with 3-bromobutan-1-ol.

MS (ES) m/z 350.0 ($[M + H]^+$). HRMS: calcd for $C_{17}H_{15}FN_2O + H^+$, 350.1339; found (ESI, $[M + H]^+$), 350.1338. ^{1}H NMR (DMSO-d_6) δ 8.82 (br s, 2H), 7.64 (m, 3H), 7.46 (m, 1H), 7.26 (m, 1H), 7.12 (m, 1H), 6.99 (m, 1H), 6.58 (d, J = 7.82 Hz, 1H), 3.38 (m, 1H), 2.55 (m, 3H), 2.26 (m, 2H), 1.98 (m, 2H), 1.33 (d, J = 6.54 Hz, 3H).

(2*R*)-3-[3-(2-Fluorophenyl)-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-N,2-dimethylpropan-1-amine (11). Compound **11** was prepared following the procedure for compound **9** with 3-bromopropanol being replaced with (*S*)-3-bromo-2-methylpropan-1-ol.

MS (ES) m/z 350.0 ($[M + H]^+$). HRMS: calcd for $C_{17}H_{15}FN_2O + H^+$, 350.1339; found (ESI, $[M + H]^+$), 350.1335. ^{1}H NMR (DMSO-d_6) δ 8.79 (br s, 2H), 7.57 (m, 3H), 7.43 (m, 1H), 7.21 (m, 1H), 7.04 (m, 1H), 6.94 (m, 1H), 6.52 (d, J = 7.81 Hz, 1H), 3.88 (m, 1H), 3.72 (m, 1H), 3.02 (m, 1H), 2.89 (m, 1H), 2.52 (m, 3H), 1.06 (d, J = 6.67 Hz, 3H).

(2*S*)-3-[3-(2-Fluorophenyl)-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-*N*,2-dimethylpropan-1-amine (12). Compound **12** was prepared following the procedure for compound **9** with 3-bromopropanol being replaced with (*R*)-3-bromo-2-methylpropan-1-ol.

MS (ES) m/z 350.0 ($[M + H]^+$). HRMS: calcd for $C_{17}H_{15}FN_2O + H^+$, 350.1339; found (ESI, $[M + H]^+$), 350.1337. ^{1}H NMR (DMSO-d_6) δ 8.79 (br s, 2H), 7.57 (m, 3H), 7.43 (m, 1H), 7.21 (m, 1H), 7.04 (m, 1H), 6.94 (m, 1H), 6.52 (d, J = 7.81 Hz, 1H), 3.88 (m, 1H), 3.72 (m, 1H), 3.02 (m, 1H), 2.89 (m, 1H), 2.52 (m, 3H), 1.06 (d, J = 6.67 Hz, 3H).

(2*S*)-3-[3-(2-Fluorophenyl)-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-*N*,2-dimethylpropan-1-amine (13). Compound **13** was prepared following the procedure for compound **9** with 3-bromopropanol being replaced with 4-bromobutan-2-ol.

MS (ES) m/z 350.0 ($[M + H]^+$). HRMS: calcd for $C_{17}H_{15}FN_2O + H^+$, 350.1339; found (ESI, $[M + H]^+$), 350.1335. ^{1}H NMR (DMSO-d_6) δ 8.47 (br s, 2H), 7.64 (m, 1H), 7.52 (m, 1H), 7.41 (m, 1H), 7.20 (m, 1H), 7.05 (m, 1H), 6.92 (m, 1H), 6.53 (d, J = 7.82 Hz, 1H), 3.02 (m, 2H), 2.53 (m, 3H), 2.31 (m, 2H), 2.11 (m, 1H), 1.48 (d, J = 6.92 Hz, 3H).

2,2-Difluoro-3-[3-(2-fluorophenyl)-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-*N*-methylpropan-1-amine (14). Compound **14** was prepared following the procedure for compound **9** with 3-bromopropanol being replaced with 2,2-difluoro-3-hydroxy-*N*-methylpropanamide. The resulting impure solid was treated with borane-tetrahyrofuran complex (1 M in THF, 3 equiv) at 0 °C and then stirred for 2 h, quenched with dilute hydrochloric acid, basified (NaOH), and extracted with ethyl acetate. The organic layer was washed with water, dried ($MgSO_4$), and evaporated. The residue was purified first via chromatography (Redisep, silica, gradient 0−100% ethyl acetate in hexane) and then by reverse phase HPLC.

MS (ES) m/z 372.0 ($[M + H]^+$). HRMS: calcd for $C_{16}H_{16}F_3N_3O_2S + H^+$, 372.09881; found (ESI, $[M + H]^+$), 372.0982. ^{1}H NMR (DMSO-d_6) δ 9.45 (br s, 2H), 7.59 (m, 3H), 7.42 (m, 1H), 7.18 (m, 1H), 7.08 (m, 1H), 7.99 (m, 1H), 6.55 (d, J = 7.95 Hz, 1H), 4.58 (t, J = 5.89 Hz, 2H), 3.82 (t, J = 7.82 Hz, 2H), 2.31 (s, 3H).

4-[3-(2-Fluorophenyl)-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-*N*-methylbutan-1-amine (15). Compound **15** was prepared following the procedure for compound **9** with 3-bromopropanol being replaced with 4-bromobutan-1-ol.

MS (ESI) m/z 350.1 ($[M + H]^+$). HRMS: calcd for $C_{17}H_{20}FN_3O_2S + H^+$, 350.13330; found (ESI-FTMS, $[M + H]^+$), 350.13369. ^{1}H NMR (DMSO-d_6) δ 8.26 (br s, 2H), 7.53 (m, 4H), 7.14 (m, 1H), 7.05 (m, 1H), 6.92 (m, 1H), 6.51 (d, J = 6.92 Hz, 1H), 3.86 (t, J = 6.92 Hz, 2H), 2.90 (t, J = 7.56 Hz, 2H), 2.49 (s, 3H), 1.79 (m, 2H), 1.66 (m, 2H).

Achiral Route toward 17a and b. 1-(But-3-enyl)-3-(2-fluorophenyl)-1,3-dihydro-2,1,3-benzothiadiazole 2,2-Dioxide (16b). 6b (0.45 g, 1.7 mmol) was dissolved in tetrahydrofuran (20 mL), and triphenylphosphine (0.54 g, 2 mmol) was added followed by 3-buten-1-ol (0.16 mL, 1.87 mmol) and diisopropyl azodicarboxylate (0.39 g, 2 mmol). The mixture was stirred for 18 h at 23 °C. The mixture was concentrated and purified via chromatography (Redisep, silica, gradient 0−50% ethyl acetate in hexane) to afford 0.44 g of 1-(but-3-enyl)-3-(2-fluorophenyl)-1,3-dihydro-2,1,3-benzothiadiazole 2,2- dioxide.

MS (ESI) m/z 318.8 ($[M + H]^+$). HRMS: calcd for $C_{16}H_{15}FN_2O_2S + Na^+$, 341.07304; found (ESI, $[M + Na]^+$), 341.0727. ^{1}H NMR (DMSO-d_6) δ 7.56 (m, 3H), 7.41 (m, 1H), 7.15 (m, 1H), 7.03 (m, 1H), 6.91 (m, 1H), 6.51 (d, J = 7.82 Hz, 1H), 5.87 (m, 1H), 5.16 (m, 1H), 5.06 (m, 1H), 3.88 (m, 2H), 2.51 (m, 2H).

4-(2,2-Dioxido-3-phenyl-2,1,3-benzothiadiazol-1(3*H*)-yl)-1-(methylamino)butan-2-ol (17a). Compound **17a** was prepared following the procedure for compound **17b**.

MS (ESI) m/z 348.1 ($[M + H]^+$). HRMS: calcd for $C_{17}H_{21}N_3O_3S + H^+$, 348.1376; found (ESI, $[M + H]^+$), 348.1381.

^{1}H NMR (DMSO-d_6) δ 8.69 (br s, 2H), 7.61 (m, 3H), 7.51 (m, 2H), 7.18 (m, 1H), 7.09 (m, 1H), 6.98 (m, 1H), 6.66 (d, J = 6.91 Hz, 1H), 5.69 (m, 1H), 3.96 (m, 3H), 3.05 (m, 1H), 2.90 (m, 1H), 2.55 (m, 3H), 2.00 (m, 1H), 1.85 (m, 1H).

4-[3-(2-Fluorophenyl)-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-1-(methylamino)butan-2-ol (17b). 16b (0.44 g, 1.64 mmol) was dissolved in CH_2Cl_2 (10 mL) at 23 °C. 3-Chlorobenzoperoxoic acid (1.02 g, 3.9 mmol) was added and the mixture allowed to stir for 18 h and then filtered and concentrated. The residue was diluted with EtOAc and washed with 10% $NaHCO_3$ solution then brine. After drying with Na_2SO_4, the solution was concentrated and then 300 mg of the residue was dissolved in 10 mL of $MeNH_2$ solution (8 M in EtOH). The solution was irradiated in a microwave cuvette at 100 °C for 3 min. The reaction mixture was concentrated and then loaded directly onto silica gel and purified via chromatography (Redisep, silica, gradient 0−10% 7 M ammonia/MeOH solution in dichloromethane) to afford 300 mg of racemic **17b**.

MS (ESI) m/z 366.6 ([M + H]$^+$). HRMS: calcd for $C_{17}H_{20}FN_3O_3S + H^+$, 366.1288; found (ESI, [M + H]$^+$), 366.1269. ^{1}H NMR (DMSO-d_6) δ 8.51 (br s, 2H), 7.53 (m, 4H), 7.12 (m, 1H), 7.07 (m, 1H), 6.91 (m, 1H), 6.51 (d, J = 7.82 Hz, 1H), 5.60 (m, 1H), 3.91 (m, 3H), 3.00 (m, 1H), 2.85 (m, 1H), 2.51 (s, 3H), 1.95 (m, 1H), 1.80 (m, 1H).

(2*R*)-4-(2,2-Dioxido-3-phenyl-2,1,3-benzothiadiazol-1(3*H*)-yl)-1-(methylamino)butan-2-ol (*R*-17a) and (2*S*)-4-(2,2-Dioxido-3-phenyl-2,1,3-benzothiadiazol-1(3*H*)-yl)-1-(methylamino)butan-2-ol (*S*-17a). Compounds ***R*-17a** and ***S*-17a** were prepared following the procedure for compounds ***R*-17b** and ***S*-17b**.

***R*-17a:** MS (ESI) m/z 348.1 ([M + H]$^+$). HRMS: calcd for $C_{17}H_{21}N_3O_3S + H^+$, 348.1376; found (ESI, [M + H]$^+$), 348.1381. ^{1}H NMR (DMSO-d_6) δ 8.65 (br s, 2H), 7.66 − 7.56 (m, 3H), 7.51 (m, 2H), 7.18 (m, 1H), 7.09 (m, 1H), 6.98 (m, 1H), 6.67 (d, J = 7.81 Hz, 1H), 5.68 (m, 1H), 3.96 (m, 3H), 3.05 (m, 1H), 2.90 (m, 1H), 2.55 (m, 3H), 2.00 (m, 1H), 1.85 (m, 1H).

***S*-17a:** MS (ESI) m/z 348.1 ([M + H]$^+$). HRMS: calcd for $C_{17}H_{21}N_3O_3S + H^+$, 348.1376; found (ESI, [M + H]$^+$), 348.1381. ^{1}H NMR (DMSO-d_6) δ 8.65 (br s, 2H), 7.66 − 7.56 (m, 3H), 7.51 (m, 2H), 7.18 (m, 1H), 7.09 (m, 1H), 6.98 (m, 1H), 6.67 (d, J = 7.81 Hz, 1H), 5.68 (m, 1H), 3.96 (m, 3H), 3.05 (m, 1H), 2.90 (m, 1H), 2.55 (m, 3H), 2.00 (m, 1H), 1.85 (m, 1H).

(2*R*)-(4-[3-(2-Fluorophenyl)-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-1-(methylamino)butan-2-ol (*R*-17b) and (2*S*)-(4-[3-(2-Fluorophenyl)-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-1-(methylamino)butan-2-ol (*S*-17b). Approximately 300 mg of racemic **17b** was dissolved in 4 mL of methanol. Then 200 μL of the resulting solution was repetitively injected onto the supercritical fluid chromatography instrument, and the baseline resolved enantiomers were separately collected using the conditions described below. The chiral purity of each enantiomer was determined under the same supercritical fluid chromatography conditions using a 250 mm × 4.6 mm i.d. column at 2.0 mL/min flow rate using Chiralpak AS-H 5 analytical supercritical fluid chromatography (Berger Instruments, Inc. Newark, DE). Both enantiomers were found to be > 99.9% enantiomerically pure.

***R*-17b:** MS (ESI) m/z 366.1 ([M + H]$^+$). HRMS: calcd for $C_{17}H_{20}FN_3O_3S + H^+$, 366.1288; found (ESI, [M + H]$^+$), 366.1289. ^{1}H NMR (DMSO-d_6) δ 8.47 (br s, 2H), 7.63 (m, 1H), 7.54 (m, 2H), 7. 42 (m, 1H), 7.14 (m, 1H), 7.07 (m, 1H), 6.93 (m, 1H), 6.52 (d, J = 7.95 Hz, 1H), 5.60 (d, J = 6.02 Hz, 1H), 3.91 (m, 3H), 3.00 (m, 1H), 2.85 (m, 1H), 2.51 (s, 3H), 1.95 (m, 1H), 1.80 (m, 1H).

***S*-17b:** MS (ESI) m/z 365.9 ([M + H]$^+$). HRMS: calcd for $C_{17}H_{20}FN_3O_3S$ + H$^+$, 366.1288; found (ESI, [M + H]$^+$), 366.1290. ^{1}H NMR (DMSO-d_6) δ 8.47 (br s, 2H), 7.63 (m, 1H), 7.54 (m, 2H), 7. 42 (m, 1H), 7.14 (m, 1H), 7.07 (m, 1H), 6.93 (m, 1H), 6.52 (d, J = 7.95 Hz, 1H), 5.60 (d, J = 6.02 Hz, 1H), 3.91 (m, 3H), 3.00 (m, 1H), 2.85 (m, 1H), 2.51 (s, 3H), 1.95 (m, 1H), 1.80 (m, 1H).

Asymmetric Route to Compounds *R*-17c−j. (2*R*)-(4-[3-(2-Chlorophenyl)-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-1-(methylamino)butan-2-ol (*R*-17c). Compound ***R*-17c** was prepared following the procedure for compound ***R*-17i**.

MS (ESI) m/z 381.6 ([M + H]$^+$). HRMS: calcd for $C_{17}H_{20}ClN_3O_3S + H^+$, 382.0987; found (ESI, [M + H]$^+$), 382.0990. ^{1}H NMR (DMSO-d_6) δ 8.61 (br s, 2H), 7.80 (m, 1H), 7.67 (m, 1H), 7.60 (m, 1H), 7.18 (m, 1H), 7.08 (m, 1H), 6.93 (m, 1H), 6.41 (d, J = 7.55 Hz, 1H), 5.68 (m, 1H), 3.96 (m, 3H), 3.03 (m, 1H), 2.88 (m, 1H), 2.55 (m, 3H), 1.99 (m, 1H), 1.86 (m, 1H).

(2*R*)-(4-[3-(2-Methylphenyl)-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-1-(methylamino)butan-2-ol (*R*-17d). Compound ***R*-17d** was prepared following the procedure for compound ***R*-17i**.

MS (ESI) m/z 361.7 ([M + H]$^+$). HRMS: calcd for $C_{18}H_{23}N_3O_3S + H^+$, 362.1533; found (ESI, [M + H]$^+$), 362.1538. ^{1}H NMR (DMSO-d_6) δ 8.63 (br s, 2H), 7.54 (m, 2H), 7.44 (m, 1H), 7.38 (m, 1H), 7.18 (m, 1H), 7.08 (m, 1H), 6.92 (m, 1H), 6.31 (d, J = 7.82 Hz, 1H), 5.67 (m, 1H), 3.97 (m, 3H), 3.03 (m, 1H), 2.88 (m, 1H), 2.55 (m, 3H), 2.21 (s, 3H), 2.01 (m, 1H), 1.86 (m, 1H).

(2*R*)-(4-[3-(3-Methoxyphenyl)-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-1-(methylamino)butan-2-ol (*R*-17e). Compound ***R*-17e** was prepared following the procedure for compound ***R*-17i**.

MS (ESI) m/z 377.7 ([M + H]$^+$). HRMS: calcd for $C_{18}H_{23}N_3O_4S + H^+$, 378.1482; found (ESI, [M + H]$^+$), 378.1490. ^{1}H NMR (DMSO-d_6) δ 8.54 (br s, 2H), 7.54 (m, 1H), 7.18 (m, 2H), 7.09 (m, 2H), 6.99 (m, 2H), 6.73 (d, J = 7.80 Hz, 1H), 5.66 (d, J = 5.97 Hz, 1H), 3.96 (m, 3H), 3.8 (s, 3H), 3.03 (m, 1H), 2.88 (m, 1H), 2.55 (s, 3H), 1.99 (m, 1H), 1.85 (m, 1H).

(2*R*)-(4-[3-(4-Fluorophenyl)-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-1-(methylamino)butan-2-ol (*R*-17f). Compound ***R*-17f** was prepared following the procedure for compound ***R*-17i**.

MS (ESI) m/z 365.6 ([M + H]$^+$). HRMS: calcd for $C_{17}H_{20}FN_3O_3S + H^+$, 366.1282; found (ESI, [M + H]$^+$), 378.1291. ^{1}H NMR (DMSO-d_6) δ 8.62 (br s, 2H), 7.57 (m, 2H), 7.48 (m, 2H), 7.18 (m, 1H), 7.09 (m, 1H), 6.98 (m, 1H), 6.62 (m, 1H), 5.68 (m, 1H), 3.96 (m, 3H), 3.8 (s, 3H), 3.03 (m, 1H), 2.88 (m, 1H), 2.55 (m, 3H), 1.99 (m, 1H), 1.85 (m, 1H).

(2*R*)-(4-[3-(2,4-Difluorophenyl)-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-1-(methylamino)butan-2-ol (*R*-17g). Compound ***R*-17g** was prepared following the procedure for compound ***R*-17i**.

MS (ESI) m/z 383.6 ([M + H]$^+$). HRMS: calcd for $C_{17}H_{19}F_2N_3O_3S + H^+$, 384.1188; found (ESI, [M + H]$^+$), 384.1193. ^{1}H NMR (DMSO-d_6) δ 8.62 (br s, 2H), 7.69 (m, 2H), 7.37 (m, 1H), 7.18 (m, 1H), 7.11 (m, 1H), 6.98 (m, 1H), 6.61 (d, J = 7.84 Hz, 1H), 5.68 (d, J = 5.84 Hz, 1H), 3.96 (m, 3H), 3.8 (s, 3H), 3.03 (m, 1H), 2.88 (m, 1H), 2.55 (m, 3H), 1.99 (m, 1H), 1.85 (m, 1H).

(2*R*)-(4-[3-(2,5-Difluorophenyl)-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-1-(methylamino)butan-2-ol (*R*-17h). Compound ***R*-17h** was prepared following the procedure for compound ***R*-17i**.

MS (ESI) m/z 383.6 ([M + H]$^+$). HRMS: calcd for $C_{17}H_{19}F_2N_3O_3S + H^+$, 384.1188; found (ESI, [M + H]$^+$), 384.1189. ^{1}H NMR (DMSO-d_6) δ 8.59 (br s, 2H), 7.60 (m, 3H), 7.18 (m, 1H), 7.12 (m, 1H), 6.98 (m, 1H), 6.68 (d, J = 7.87 Hz, 1H), 5.67 (d, J = 6 Hz, 1H), 3.96 (m, 3H), 3.8 (s, 3H), 3.03 (m, 1H), 2.88 (m, 1H), 2.55 (m, 3H), 1.99 (m, 1H), 1.85 (m, 1H).

(2*R*)-(4-[3-(2,6-Difluorophenyl)-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-1-(methylamino)butan-2-ol (*R*-17i). 6i (0.15 g, 0.5 mmol) was dissolved in acetone (5 mL), and potassium carbonate (0.14 g, 1.0 mmol) was added followed by (*R*)-2-(oxiran-2-yl)ethyl 4-tosylate (0.24 g, 1.0 mmol). The mixture was stirred for 18 h at 50 °C in a sealed vial and then diluted with EtOAc (100 mL) and washed with water (2×) and brine and then dried (Na_2SO_4). After concentration, the residue was dissolved in 10 mL of $MeNH_2$ solution (8 M in EtOH). The solution was irradiated in a microwave cuvette at 100 °C for 3 min. The reaction mixture was concentrated and then loaded directly onto silica gel and purified via chromatography (Redisep, silica, gradient 0−100% of 10% 7 M ammonia in MeOH/dichloromethane) to afford 59 mg of ***R*-17i**.

MS (ESI) m/z 383.6 ([M + H]$^+$). HRMS: calcd for $C_{17}H_{19}F_2N_3O_3S + H^+$, 384.1188; found (ESI, [M + H]$^+$), 384.1191. ^{1}H NMR (DMSO-d_6) δ 8.65 (br s, 2H), 7.77 (m, 1H), 7.45 (m, 2H), 7.21 (m, 1H), 7.12 (m, 1H), 6.99 (m, 1H), 6.64 (d, J = 7.80 Hz, 1H), 5.69 (d, J = 5.97 Hz, 1H), 3.96 (m, 3H), 3.05 (m, 1H), 2.90 (m, 1H), 2.55 (m, 3H), 2.00 (m, 1H), 1.85 (m, 1H).

(2*R*)-(4-[3-(3,4-Difluorophenyl)-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-1-(methylamino)butan-2-ol (*R*-17j). Compound ***R*-17j** was prepared following the procedure for compound ***R*-17i**.

MS (ESI) *m*/*z* 383.6 ([M + H]$^+$). HRMS: calcd for $C_{17}H_{19}F_2N_3O_3S + H^+$, 384.1188; found (ESI, [M + H]$^+$), 384.1190. ^{1}H NMR (DMSO-d_6) δ 8.61 (br s, 2H), 7.70 (m, 2H), 7.41 (m, 1H), 7.18 (m, 1H), 7.12 (m, 1H), 7.00 (m, 1H), 6.75 (d, J = 7.85 Hz, 1H), 5.68 (d, J = 5.99 Hz, 1H), 3.96 (m, 3H), 3.8 (s, 3H), 3.03 (m, 1H), 2.88 (m, 1H), 2.55 (m, 3H), 1.99 (m, 1H), 1.85 (m, 1H).

Asymmetric Route to Compounds *S*-17c−j. (2*S*)-(4-[3-(2-Chlorophenyl)-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-1-(methylamino)butan-2-ol (*S*-17c). Compound ***S*-17c** was prepared following the procedure for compound ***S*-17i**.

MS (ESI) *m*/*z* 381.6 ([M + H]$^+$). HRMS: calcd for $C_{17}H_{20}ClN_3O_3S + H^+$, 382.0987; found (ESI, [M + H]$^+$), 382.0993. ^{1}H NMR (DMSO-d_6) δ 8.61 (br s, 2H), 7.80 (m, 1H), 7.67 (m, 1H), 7.60 (m, 1H), 7.18 (m, 1H), 7.08 (m, 1H), 6.93 (m, 1H), 6.41 (d, J = 7.55 Hz, 1H), 5.68 (m, 1H), 3.96 (m, 3H), 3.03 (m, 1H), 2.88 (m, 1H), 2.55 (m, 3H), 1.99 (m, 1H), 1.86 (m, 1H).

(2*S*)-(4-[3-(2-Methylphenyl)-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-1-(methylamino)butan-2-ol (*S*-17d). Compound ***S*-17d** was prepared following the procedure for compound ***S*-17i**.

MS (ESI) *m*/*z* 361.8 ([M + H]$^+$). HRMS: calcd for $C_{18}H_{23}N_3O_3S + H^+$, 362.1533; found (ESI, [M + H]$^+$), 362.1538. ^{1}H NMR (DMSO-d_6) δ 8.63 (br s, 2H), 7.54 (m, 2H), 7.44 (m, 1H), 7.38 (m, 1H), 7.18 (m, 1H), 7.08 (m, 1H), 6.92 (m, 1H), 6.31 (d, J = 7.82 Hz, 1H), 5.67 (m, 1H), 3.97 (m, 3H), 3.03 (m, 1H), 2.88 (m, 1H), 2.55 (m, 3H), 2.21 (s, 3H), 2.01 (m, 1H), 1.86 (m, 1H).

(2*S*)-(4-[3-(3-Methoxyphenyl)-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-1-(methylamino)butan-2-ol (*R*-17e). Compound ***R*-17e** was prepared following the procedure for compound ***R*-17i**.

MS (ESI) *m*/*z* 378.1 ([M + H]$^+$). HRMS: calcd for $C_{18}H_{23}N_3O_4S + H^+$, 378.1482; found (ESI, [M + H]$^+$), 378.1484. ^{1}H NMR (DMSO-d_6) δ 8.54 (br s, 2H), 7.54 (m, 1H), 7.18 (m, 2H), 7.09 (m, 2H), 6.99 (m, 2H), 6.73 (d, J = 7.80 Hz, 1H), 5.66 (d, J = 5.97 Hz, 1H), 3.96 (m, 3H), 3.8 (s, 3H), 3.03 (m, 1H), 2.88 (m, 1H), 2.55 (s, 3H), 1.99 (m, 1H), 1.85 (m, 1H).

(2*S*)-(4-[3-(4-Fluorophenyl)-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-1-(methylamino)butan-2-ol (*S*-17f). Compound ***S*-17f** was prepared following the procedure for compound ***S*-17i**.

MS (ESI) *m*/*z* 365.7 ([M + H]$^+$). HRMS: calcd for $C_{17}H_{20}FN_3O_3S + H^+$, 366.1282; found (ESI, [M + H]$^+$), 378.1287. ^{1}H NMR (DMSO-d_6) δ 8.62 (br s, 2H), 7.57 (m, 2H), 7.48 (m, 2H), 7.18 (m, 1H), 7.09 (m, 1H), 6.98 (m, 1H), 6.62 (m, 1H), 5.68 (m, 1H), 3.96 (m, 3H), 3.8 (s, 3H), 3.03 (m, 1H), 2.88 (m, 1H), 2.55 (m, 3H), 1.99 (m, 1H), 1.85 (m, 1H).

(2*S*)-(4-[3-(2,4-Difluorophenyl)-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-1-(methylamino)butan-2-ol (*S*-17g). Compound ***S*-17g** was prepared following the procedure for compound ***S*-17i**.

MS (ESI) *m*/*z* 383.6 ([M + H]$^+$). HRMS: calcd for $C_{17}H_{19}F_2N_3O_3S + H^+$, 384.1188; found (ESI, [M + H]$^+$), 384.1194. ^{1}H NMR (DMSO-d_6) δ 8.62 (br s, 2H), 7.69 (m, 2H), 7.37 (m, 1H), 7.18 (m, 1H), 7.11 (m, 1H), 6.98 (m, 1H), 6.61 (d, J = 7.84 Hz, 1H), 5.68 (d, J = 5.84 Hz, 1H), 3.96 (m, 3H), 3.8 (s, 3H), 3.03 (m, 1H), 2.88 (m, 1H), 2.55 (m, 3H), 1.99 (m, 1H), 1.85 (m, 1H).

(2*S*)-(4-[3-(2,5-Difluorophenyl)-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-1-(methylamino)butan-2-ol (*S*-17h). Compound ***S*-17h** was prepared following the procedure for compound ***S*-17i**.

MS (ESI) *m*/*z* 383.6 ([M + H]$^+$). HRMS: calcd for $C_{17}H_{19}F_2N_3O_3S + H^+$, 384.1188; found (ESI, [M + H]$^+$), 384.1194. ^{1}H NMR (DMSO-d_6) δ 8.59 (br s, 2H), 7.60 (m, 3H), 7.18 (m, 1H), 7.12 (m, 1H), 6.98 (m, 1H), 6.68 (d, J = 7.87 Hz, 1H), 5.67 (d, J = 6 Hz, 1H), 3.96 (m, 3H), 3.8 (s, 3H), 3.03 (m, 1H), 2.88 (m, 1H), 2.55 (m, 3H), 1.99 (m, 1H), 1.85 (m, 1H).

(2*S*)-(4-[3-(2,6-Difluorophenyl)-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-1-(methylamino)butan-2-ol (*S*-17i). 6i (0.15 g, 0.5 mmol) was dissolved in acetone (5 mL), and potassium carbonate (0.14 g, 1 mmol) was added followed by *S*(−)-4-bromo-1,2-epoxybutane (0.15 g, 1 mmol). The mixture was stirred for 18 h at 50 °C in a sealed vial and then diluted with EtOAc (100 mL) and washed with water (2×) and brine and then dried (Na_2SO_4). After concentration, the residue was dissolved in 10 mL of $MeNH_2$ solution (8 M in EtOH). The solution was irradiated in a microwave cuvette at 100 °C for 3 min. The reaction mixture was concentrated and then loaded directly onto silica gel and purified via chromatography (Redisep, silica, gradient 0−100% of 10% 7 M ammonia in MeOH/dichloromethane) to afford 69 mg of ***S*-17i**.

MS (ESI) *m*/*z* 383.6 ([M + H]$^+$). HRMS: calcd for $C_{17}H_{19}F_2N_3O_3S + H^+$, 384.1188; found (ESI, [M + H]$^+$), 384.1194. ^{1}H NMR (DMSO-d_6) δ 8.65 (br s, 2H), 7.77 (m, 1H), 7.45 (m, 2H), 7.21 (m, 1H), 7.12 (m, 1H), 6.99 (m, 1H), 6.64 (d, J = 7.80 Hz, 1H), 5.69 (d, J = 5.97 Hz, 1H), 3.96 (m, 3H), 3.05 (m, 1H), 2.90 (m, 1H), 2.55 (m, 3H), 2.00 (m, 1H), 1.85 (m, 1H).

(2*S*)-(4-[3-(3,4-Difluorophenyl)-2,2-dioxido-2,1,3-benzothiadiazol-1(3*H*)-yl]-1-(methylamino)butan-2-ol (*S*-17j). Compound ***S*-17j** was prepared following the procedure for compound ***S*-17j**.

MS (ESI) *m*/*z* 384.2 ([M + H]$^+$). HRMS: calcd for $C_{17}H_{19}F_2N_3O_3S + H^+$, 384.1188; found (ESI, [M + H]$^+$), 384.1192. ^{1}H NMR (DMSO-d_6) δ 8.61 (br s, 2H), 7.70 (m, 2H), 7.41 (m, 1H), 7.18 (m, 1H), 7.12 (m, 1H), 7.00 (m, 1H), 6.75 (d, J = 7.85 Hz, 1H), 5.68 (d, J = 5.99 Hz, 1H), 3.96 (m, 3H), 3.8 (s, 3H), 3.03 (m, 1H), 2.88 (m, 1H), 2.55 (m, 3H), 1.99 (m, 1H), 1.85 (m, 1H).

4-(2,2-Dioxido-3-phenyl-2,1,3-benzothiadiazol-1(3*H*)-yl)-1-(ethylamino)butan-2-ol (18). Compound **18** was prepared following the procedure for compound **17b**, replacing $MeNH_2$ with $EtNH_2$.

MS (ESI) *m*/*z* 362.1 ([M + H]$^+$). HRMS: calcd for $C_{18}H_{23}N_3O_3S + H^+$, 362.1533; found (ESI, [M + H]$^+$), 362.1540. ^{1}H NMR (DMSO-d_6) δ 8.51 (br s, 2H), 7.61 (m, 3H), 7.50 (m, 2H), 7.18 (m, 1H), 7.10 (m, 1H), 6.98 (m, 1H), 6.67 (d, J = 6.92 Hz, 1H), 5.64 (d, J = 6.02 Hz, 1H), 3.97 (m, 3H), 3.05 (m, 1H), 2.94 (m, 2H), 2.89 (m, 1H), 2.01 (m, 1H), 1.78 (m, 1H), 1.20(t, J = 7.31 Hz, 3H).

4-(2,2-Dioxido-3-phenyl-2,1,3-benzothiadiazol-1(3*H*)-yl)-1-(isopropylamino)butan-2-ol (19). Compound **19** was prepared following the procedure for compound **17b**, replacing $MeNH_2$ with $^iPrNH_2$.

MS (ESI) *m*/*z* 376.1 ([M + H]$^+$). HRMS: calcd for $C_{19}H_{25}N_3O_3S + H^+$, 376.1689; found (ESI, [M + H]$^+$), 376.1695. ^{1}H NMR (DMSO-d_6) δ 8.41 (br s, 2H), 7.62 (m, 3H), 7.50 (m, 2H), 7.18 (m, 1H), 7.10 (m, 1H), 6.98 (m, 1H), 6.67 (d, J = 7.82 Hz, 1H), 5.62 (d, J = 6.02 Hz, 1H), 3.97 (m, 3H), 3.29 (m, 1H), 3.05 (m, 1H), 2.88 (m, 1H), 2.03 (m, 1H), 1.89 (m, 1H), 1.22 (m, 6H).

1-(Cyclopropylamino)-4-(2,2-dioxido-3-phenyl-2,1,3-benzothiadiazol-1(3*H*)-yl)butan-2-ol (20). Compound **20** was prepared following the procedure for compound **17b**, replacing $MeNH_2$ with $^cPrNH_2$.

MS (ESI) *m*/*z* 374.1 ([M + H]$^+$). HRMS: calcd for $C_{19}H_{23}N_3O_3S + H^+$, 374.1533; found (ESI, [M + H]$^+$), 374.1537. ^{1}H NMR (DMSO-d_6) δ 8.82 (br s, 2H), 7.62 (m, 3H), 7.50 (m, 2H), 7.19 (m, 1H), 7.10 (m, 1H), 6.98 (m, 1H), 6.67 (d, J = 7.81 Hz, 1H), 5.62 (m, 1H), 3.97 (m, 3H), 3.18 (m, 1H), 2.99 (m, 1H), 2.69 (m, 1H), 2.02 (m, 1H), 1.89 (m, 1H), 0.86 (m, 2H), 0.71(m, 2H).

1-(*tert*-Butylamino)-4-(2,2-dioxido-3-phenyl-2,1,3-benzothiadiazol-1(3*H*)-yl)butan-2-ol (21). Compound **21** was prepared following the procedure for compound **17b**, replacing $MeNH_2$ with $^tBuNH_2$.

MS (ESI) *m*/*z* 390.2 ([M + H]$^+$). HRMS: calcd for $C_{20}H_{27}N_3O_3S + H^+$, 390.1846; found (ESI, [M + H]$^+$), 390.1850. ^{1}H NMR (DMSO-d_6) δ 8.60 (br s, 1H), 8.40 (br s, 1H), 7.62 (m, 3H), 7.50 (m, 2H), 7.20 (m, 1H), 7.10 (m, 1H), 6.99 (m, 1H), 6.67 (d, J = 7.94 Hz, 1H), 5.62 (m, J = 5.90 Hz, 1H), 3.97 (m, 3H), 3.05 (m, 1H), 2.83 (m, 1H), 2.07 (m, 1H), 1.90 (m, 1H), 1.29 (s, 9H).

1-(Dimethylamino)-4-(2,2-dioxido-3-phenyl-2,1,3-benzothiadiazol-1(3*H*)-yl)butan-2-ol (22). Compound **22** was prepared following the procedure for compound **17b**, replacing $MeNH_2$ with Me_2NH.

MS (ESI) *m*/*z* 362.1 ([M + H]$^+$). HRMS: calcd for $C_{18}H_{23}N_3O_3S + H^+$, 362.1533; found (ESI, [M + H]$^+$), 362.1536. ^{1}H NMR (DMSO-d_6) δ 9.41 (br s, 1H), 7.62 (m, 3H), 7.50 (m, 2H), 7.18 (m, 1H), 7.10 (m, 1H), 6.99 (m, 1H), 6.67 (d, J = 7.95 Hz,

1H), 5.78 (m, J = 6.15 Hz, 1H), 4.08 (m, 1H), 3.95 (m, 2H), 3.13 (m, 2H), 2.79(s, 6H), 1.96 (m, 1H), 1.86 (m, 1H).

4-(2,2-Dioxido-3-phenyl-2,1,3-benzothiadiazol-1(3*H*)-yl)-1-(methylamino)butan-2-one (23). 17b (90 mg, 0.25 mmol) and di-*tert*-butyl dicarbonate (59 mg, 0.26 mmol) were stirred in dichloromethane (5 mL) in a sealed vial at room temperature for 18 h. The reaction mixture was concentrated and then loaded directly onto silica gel and purified via chromatography, providing a clear oil of which 50 mg (0.11 mmol) was stirred with Dess−Martin periodinane (68 mg, 0.16 mmol) in dichloromethane (5 mL) in a sealed vial at room temperature for 18 h. The reaction mixture was concentrated and then loaded directly onto silica gel and purified via chromatography to afford a clear oil, which was dissolved in diethyl ether/methanol. 4N HCl in dioxane was added and a precipitate slowly formed. The reaction was filtered to afford 23 mg of **23** as a white solid.

MS (ESI) m/z 346.0 ($[M + H]^+$). HRMS: calcd for $C_{17}H_{19}N_3O_3S + H^+$, 346.1220; found (ESI, $[M + H]^+$), 346.1223. ^{1}H NMR (DMSO-d_6) δ 8.91 (br s, 2H), 7.61 (m, 3H), 7.50 (m, 2H), 7.20 (m, 1H), 7.10 (m, 1H), 6.99 (m, 1H), 6.67 (d, J = 7.94 Hz, 1H), 4.12 (m, 4H), 3.10 (m, 2H), 2.52(s, 3H).

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Supporting Information Available: Analytical HPLC purity data is provided for all tested compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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