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Structure–activity relationships of norepinephrine reuptake inhibitors with benzothiadiazine dioxide or dihydrosulfostyril cores

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ABSTRACT

Two related series of selective norepinephrine reuptake inhibitors were synthesized based on 3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxide or 3,4-dihydrosulfostyril cores, and screened for monoamine reuptake inhibition. Structure–activity relationships were determined for the series' in vitro potency and selectivity versus serotonin or dopamine transporter inhibition, and analogs based on both cores were identified as potent and selective NRIs. The 3,4-dihydrosulfostyril series was further tested for microsome stability, and compound **16j**, which was optimized for both potency and stability, showed efficacy in an in vivo model of thermoregulatory dysfunction.

Norepinephrine (noradrenalin), serotonin (5-HT) and dopamine are monoamine neurotransmitters involved in the regulation of a variety of physiological processes. A deficit in monoaminergic signaling has been implicated in a number of neurological disorders, making modulation of the level of these neurotransmitters an important objective in drug discovery. Norepinephrine reuptake inhibitors (NRIs) enhance neuron signaling by increasing norepinephrine concentration in the synaptic cleft through inhibition of its reuptake by the norepinephrine transporter (NET). Similarly, serotonin- or dopamine-mediated neurotransmission can be upregulated by inhibiting the serotonin or dopamine transporters (SERT or DAT).[1]

Many of the known monoamine transporter inhibitors share common structural features: two closely situated aromatic rings and a basic amino group on a flexible chain 3–5 atoms away (Fig. 1).[2,3] Fluoxetine (**1**) and citalopram (**2**) are serotonin reuptake inhibitors (SRIs) used for the treatment of depression and panic disorders.[4] Duloxetine (**3**) is an example of a dual NRI and SRI used for the treatment of neurological conditions including depression and pain.[5] Atomoxetine (**4**) is a selective NRI which was recently approved for attention-deficit hyperactivity disorder.[6] Although a variety of monoamine transporter inhibitors have been developed, there remains considerable demand for new agents with improved efficacy and pharmacological properties, fueling significant ongoing research.[7–10]

Our interest in further understanding the potential for NRIs in treating neurological disorders led us to explore and develop new scaffolds which could provide such benefits. One aspect of these efforts was the investigation into 3,4-dihydro-1*H*-2,1,3-benzothiadiazine-2,2-dioxide (**5**) or 3,4-dihydro-1*H*-2,1-benzothiazine-2,2-dioxide (3,4-dihydrosulfostyril, **6**) as potential cores for two new series of inhibitors (Fig. 2). These scaffolds can be readily synthesized and functionalized with a second aromatic ring and appropriate amino side-chain. Furthermore, such fused ring systems impose constraints on the molecules' conformational freedom, which could be beneficial to the properties and selectivity

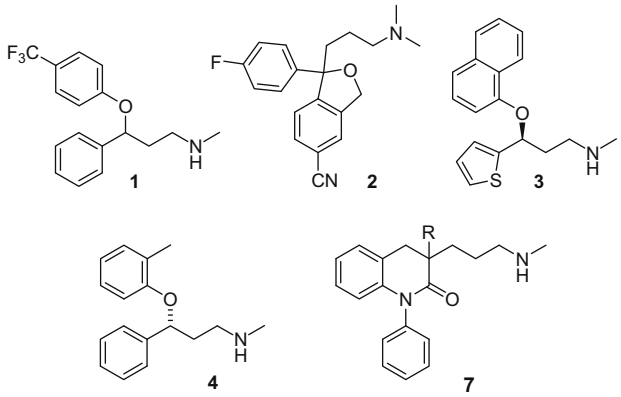

Figure 1. Examples of structurally related monoamine reuptake inhibitors.

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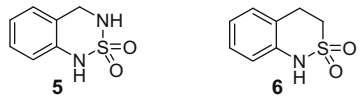


Figure 2. Core scaffolds 3,4-dihydro-1*H*-2,1,3-benzothiadiazine-2,2-dioxide (**5**) and 3,4-dihydro-1*H*-2,1-benzothiazine-2,2-dioxide (3,4-dihydrosulfostyril, **6**).

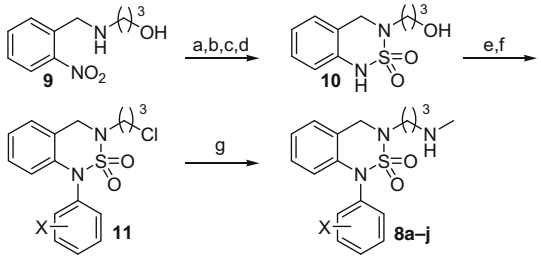
of the series. A related approach was recently demonstrated using a different core in a report from Beadle et al.,[7] where compounds of general structure **7** (Fig. 1) were found to be potent and selective NRIs.

The investigation of the benzothiadiazine dioxide scaffold (**5**) began with the parallel synthesis of target compounds **8a–j** starting from (2-nitrobenzyl)aminopropanol, **9** (Scheme 1).[11] Introduction of a sulfonyl group and cyclization generated the bicyclic core in **10**. After chlorination, diversity in the pendant aryl ring was achieved through Chan–Lam couplings[12] to the free sulfamide amino group using phenylboronic acids with differing *meta* and *para* substituents,[13] providing penultimate intermediate **11**. The terminal methylamino group was then introduced onto the side-chain by a substitution reaction (Scheme 1, step g) to complete the synthesis.

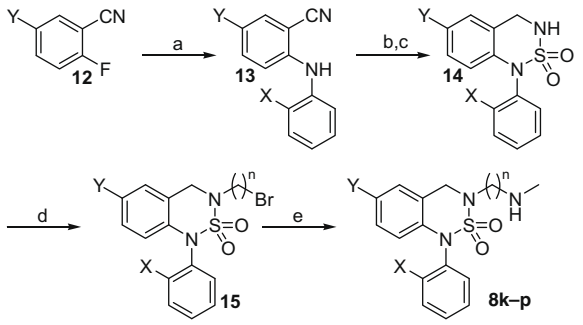
A follow-up series of compounds (**8k–p**) was prepared by an alternative route starting from *ortho*-fluorobenzonitrile **12**, as shown in Scheme 2. In the revised synthesis, the initial coupling of the two aryl groups provided intermediate **13** (Scheme 2, step a) which allowed the introduction of substituents at the *ortho* position of the pendant phenyl ring as well as at the core's 6-position. Additionally, after reduction and cyclization to form the benzothiadiazine dioxide core in intermediate **14**, the late attachment of the side-chain (Scheme 2, step d), allowed straightforward modification of its length. Introduction of the methylamino group onto bromide **15** again completed the sequence.

In the case of the 3,4-dihydrosulfostyril scaffold (**6**), functionalized agents **16a–l** were prepared[14] beginning with the synthesis of intermediate **17** by one of two methods as depicted in Scheme 3. (1) Starting with the assembled 3,4-dihydrosulfostyril[15] core **6**, the pendant phenyl group was attached by Chan–Lam coupling (Scheme 3, step a). (2) Starting with acyclic sulfonyl chloride **18**,[14] substituted anilines were coupled followed by copper-catalyzed cyclization (Scheme 3, steps b and c). Both syntheses were completed by racemic introduction of the side-chain onto **17** by alkylation followed by amination (Scheme 3, steps d and e). The final target compounds (**16a–l**) were resolved by chiral supercritical fluid chromatography (SFC) and assigned stereoisomers i or ii based on their order of column elution.

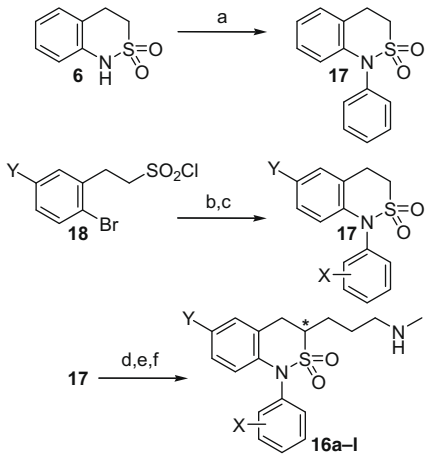
The benzothiadiazine dioxide series was designed to provide compounds with calculated properties, for example, topological polar surface area (TPSA),[16] appropriate for neuroscience drugs



Scheme 1. Synthesis of 3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxides.[11] Reagents and conditions: (a) TBDPSCl, imidazole, 80%; (b) Zn, NH_4Cl, 94%; (c) $NH_2SO_2NH_2$, diglyme, reflux, 70–95%; (d) TBAF, AcOH, 90%; (e) $SOCl_2$, DMF, 79%; (f) arylboronic acid, $Cu(OAc)_2$, pyridine, 9–21%; (g) methylamine, ethanol, 50 °C, 28–96%.



Scheme 2. Alternative synthesis of 3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxides.[11] Reagents and conditions: (a) aniline, KO*t*Bu, DMSO, 55–62%; (b) BH_3–THF, 66–83%; (c) $NH_2SO_2NH_2$, diglyme, reflux, 70–95%; (d) bromoalkanol, PPh_3, DIAD, 59–74%; (e) methylamine, ethanol, 50 °C, 28–96%.



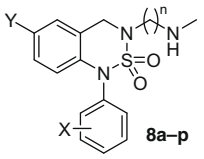
Scheme 3. Synthesis of functionalized 3,4-dihydrosulfostyrils.[14] Reagents and conditions: (a) phenylboronic acid, $Cu(OAc)_2$, pyridine 40%; (b) aniline, pyridine, CH_2Cl_2, 15–52%; (c) CuI, CsOAc, DMSO, 82–96%; (d) LiHMDS, $Br(CH_2)_3Cl$ or $Br(CH_2)_3Br$, THF, 43–84%; (e) methylamine, ethanol, 50 °C, 74–82%; (f) chiral SFC.

(Table 1). Screening results of **8a–p** for inhibition of norepinephrine reuptake are presented in Table 1. All tested compounds with *meta* and *para* substitutions on the pendant ring (**8b–j**) had significantly decreased NET inhibition levels (IC_{50}'s 0.49–3.55 μM) relative to the parent compound, **8a** (IC_{50} = 0.13 μM), aside from *para*-methyl **8f** (IC_{50} = 0.14 μM). The most detrimental substituent was the electron-donating methoxy group, particularly in the *para* position (**8g**). Introduction of an *ortho*-fluoro group on the pendant ring, however, caused a fourfold increase in NET inhibition potency (**8l** vs **8a**).

Shortening the amino side-chain length to two methylene units caused a 7–12-fold drop in NET inhibition potency (**8l** vs **8k**, **8o** vs **8n**), whereas lengthening the chain to four methylene units on the unsubstituted core had a lesser effect (**8l** vs **8m**, **8o** vs **8p**). Introduction of a fluorine atom onto the 6-position of the benzothiadiazine dioxide core lowered NET inhibition potency in the case of the analogs with short or medium-length side chains (**8k,l** vs **8n,o**), but had no significant impact in combination with the longer four-atom chain (**8m** vs **8p**).

Selectivity data was obtained for a group of the most potent agents (**8a,l–p**) and included in Table 1. The compounds were found to be highly selective overall for NET versus both SERT and DAT inhibition, however, it was observed that NET/SERT inhibition selectivity was significantly lowered by introduction of the 6-fluoro substitution (e.g., **8l** = 190-fold NRI/SRI selective; **8o** = 13-fold). In the case of the introduction of the 6-fluoro substituent in

Table 1
Monoamine reuptake inhibition by compounds **8a–p**

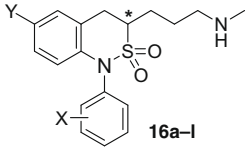


8a–p

	X	*n*	Y	TPSA[a]	NET IC_{50}[b] (μM)	SERT IC_{50}[c] (μM)	DAT %I[d] (1 μM)
4				21.3	0.003	—[e]	—[e]
8a	H	3	H	52.7	0.13	6	17
8b	3-F	3	H	52.7	0.63	—	—
8c	3-CH_3	3	H	52.7	1.03	—	—
8d	3-MeO	3	H	61.9	0.79	—	—
8e	4-F	3	H	52.7	0.49	—	—
8f	4-CH_3	3	H	52.7	0.14	—	—
8g	4-MeO	3	H	61.9	3.55	—	—
8h	4-Cl	3	H	52.7	0.91	—	—
8i	3-F,4-F	3	H	52.7	0.97	—	—
8j	3-Cl,4-F	3	H	52.7	1.50	—	—
8k	2-F	2	H	52.7	0.20	24%[f]	24
8l	2-F	3	H	52.7	0.029	5.5	−7
8m	2-F	4	H	52.7	0.038	2.0	18
8n	2-F	2	F	52.7	1.4	13.3	−5
8o	2-F	3	F	52.7	0.12	1.5	2.5
8p	2-F	4	F	52.7	0.030	0.11	25

[a] Topological polar surface area (TPSA).[16]
[b] Inhibition of norepinephrine uptake in MDCK-Net6 cells transfected with the human norepinephrine transporter (NET). Desipramine (IC_{50} = 3.4 ± 1.6 nM) was used as a standard.
[c] Inhibition of serotonin uptake in JAR cells natively expressing human serotonin transporter (SERT). Fluoxetine (**1**, IC_{50} = 9.4 ± 3.1 nM) was used as a standard.
[d] %Inhibition at 1 μM of [^{3}H]WIN-35,428 binding to membranes from CHO cells expressing recombinant human dopamine transporter (DAT). Mazindol (IC_{50} = 22.1 ± 6.5 nM) was used as a standard.
[e] Assay results not available.
[f] IC_{50} not available; %inhibition at 1 μM.

Table 2
Monoamine reuptake inhibition and microsome stability for compounds **16a–l**



16a–l

Compound	X	Y	Stereoisomer [a]	NET IC_{50}[b] (μM)	SERT IC_{50}[c] (μM)	DAT IC_{50}[d] (μM)	Microsome $t_{1/2}$[e] (min)
16a	H	H	i	0.088	6.9	—[h]	3
16b	H	H	ii	0.012	2.5	6.6	<1
16c	2-F	H	i	0.055	11%[f]	21%[g]	<1
16d	2-F	H	ii	0.003	74%[f]	23%[g]	<1
16e	2,6-DiF	H	i	0.052	40%[f]	—	3
16f	2,6-DiF	H	ii	0.005	8.0	3.8%[g]	4
16g	H	F	i	0.17	85%[f]	—	<1
16h	H	F	ii	0.026	0.24	4.0	>30
16i	2-F	F	i	0.093	0.72	—	>30
16j	2-F	F	ii	0.011	0.34	50%[g]	>30
16k	2,6-DiF	F	i	0.025	82%[f]	—	>30
16l	2,6-DiF	F	ii	0.027	0.60	—	>30

[a] Racemic compounds were resolved by chiral SFC; enantiomers were labeled i or ii based on their order of column elution.
[b] Inhibition of norepinephrine uptake in MDCK-Net6 cells transfected with the human norepinephrine transporter (NET). Desipramine (IC_{50} = 3.4 ± 1.6 nM) was used as a standard.
[c] Inhibition of serotonin uptake in JAR cells natively expressing the human serotonin transporter (SERT). 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 (DAT). Mazindol (IC_{50} = 22.1 ± 6.5 nM) was used as a standard.
[e] Half-life of compounds treated with rat liver microsomes at 1 μM concentration.
[f] IC_{50} not available; listed values are the percent inhibition of serotonin uptake at a compound concentration of 6 μM.
[g] IC_{50} not available; listed values are the percent inhibition of dopamine uptake at a compound concentration of 10 μM.
[h] Assay results not available.

combination with the longer side-chain (**8l** vs **8p**), the observed decrease in NRI/SRI selectivity can be attributed solely to improved SERT inhibition potency (SERT IC_{50} = 5.5 vs 0.11 μM).

Key SAR findings from the benzothiadiazine dioxide series—that is, the advantage of the *ortho*-fluorine substituent and the generally preferred side-chain length of three methylene units (vide

Table 3
In vivo efficacy of compounds **16f** and **16j** in a thermoregulatory dysfunction model[a]

Compound	Maximum temperature reduction (°C)	Mean temperature reduction (°C)	Duration of action (h)	Onset of activity (h)
16f	0	0	–	–
16j	2.4	1.5	6	Immediate

[a] Compounds were dosed po at 3 mg/kg; see Refs. 10 and 18 for details.

supra)—were applied to the 3,4-dihydrosulfostyril ring system, a slightly less polar scaffold (TPSA[16] for **16a–l** = 49.4). Incorporation of these features afforded a new series of potent NRIs (Table 2). For most analog pairs, a clear stereochemical preference was observed for NET inhibition (eudismic ratios 6–18), except for trifluorinated compounds **16k** and **16l**, where the enantiomers were equipotent. Introduction of an *ortho*-fluoro group on the pendant phenyl ring had a modest effect, but did provide up to a fourfold increase in NET inhibition potency in the case of the unsubstituted core (**16a**,**b** vs **16c**,**d**); difluorination had a similar effect (**16a**,**b** vs **16e**,**f**).

The metabolic stability of the dihydrosulfostyril series was evaluated by measuring compound half-lives in rat liver microsomes. Compounds **16a–f** were found to be quickly metabolized (Table 2), however, fluorination at the 6-position of the dihydrosulfostyril core provided compounds (**16g–l**) that were generally highly stable under the same assay conditions. This was consistent with a computational prediction that the 6-position was the preferred site of CYP-mediated oxidation.[17] A consequence of the 6-fluoro substitution, however, was a decrease in NRI/SRI selectivity. The 6-hydro compounds **16a–f** were highly selective for NET inhibition (~100-fold selectivity versus SERT inhibition for available data), whereas the 6-fluoro analogs **16g–l** showed more modest NRI/SRI selectivity. The series as a whole was also found to be highly selective for NET versus DAT inhibition.

The in vivo efficacy of compound **16j**, which combines NET inhibition potency and microsome stability (IC_{50} = 0.011 μM, microsome $t_{1/2}$ >30 min, Table 2), was studied in a thermoregulatory dysfunction model. Norepinephrine stimulates areas of the hypothalamus believed to regulate temperature, and NRIs have previously been reported to lower tail skin temperature (TST) in ovariectomized rats.[10,18] As is summarized in Table 3, the TST of treated rats was lowered by up to 2.4 °C following oral administration of 3 mg/kg of **16j**. Oral dosing of **16f**, which has comparable in vitro NET inhibition potency, produced no observed effect on TST, potentially due to poor metabolic stability (microsome $t_{1/2}$ = 4 min, Table 2).

In summary, two related series of norepinephrine reuptake inhibitors were synthesized based on 3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxide or 3,4-dihydrosulfostyril cores and screened for inhibition of monoamine reuptake. Structure–activity relationships were determined for the series' in vitro potency and selectivity versus inhibition of serotonin and dopamine. Lead compounds based on both cores were identified as potent and selective NRIs, and 3,4-dihydrosulfostyril analog **16j**, which was optimized for both potency and stability, showed efficacy in a rat model of thermoregulatory dysfunction.

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