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Discovery of WAY-260022, a Potent and Selective Inhibitor of the Norepinephrine Transporter

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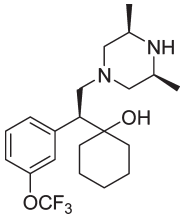
ABSTRACT The potency and selectivity of a series of 1-{(1*S*)-2-[amino]-1-[3-(trifluoromethoxy)phenyl]ethyl}cyclohexanol analogues are described. These compounds were prepared to improve in vitro metabolic stability and achieve brain penetration. Compound **13** (WAY-260022, NRI-022) was found to be a potent inhibitor of norepinephrine reuptake and demonstrated excellent selectivity over the serotonin and dopamine transporters. Additionally, **13** exhibited oral efficacy in a rat model of thermoregulatory dysfunction.

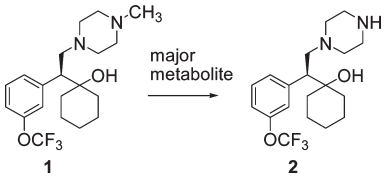
KEYWORDS WAY-260022, norepinephrine reuptake inhibitor, serotonin transporter, dopamine transporter, brain penetration, vasomotor symptoms



Vasomotor symptoms (VMS) consist of hot flushes and night sweats due to hormonal fluctuations associated with menopause, peri-menopause, androgen decline,[1] or hormone deprivation resulting from treatments for prostate cancer.[2] Hot flushes are transient episodes ranging from a warming sensation to intense heat on the upper body and face, redness, and perspiration, often followed by chills. Hot flushes can occur frequently and unpredictably throughout the day and can last up to 30 min per flush. Night sweats are hot flushes with drenching perspiration that occur during the night, often disrupting sleep. VMS in menopausal women can begin as early as age 35 and in some cases can persist past the age of 70.[3]

Patients who experience VMS say these episodes disrupt daily life and impact functional ability. In fact, VMS is the main complaint for which women seek medical treatment during menopause.[4] To date, the most prescribed and effective treatments for alleviating VMS are hormone replacement therapies (HRTs), including estrogens and/or progestins. However, hormone-based drugs are not appropriate for all patients[2] and are not recommended for women or men at risk for hormonally sensitive cancers.[5] The number of postmenopausal women, which is expected to increase from 470 million in 1990 to 1.23 billion by 2030,[6] and the decline in popularity of HRT[7] have intensified the need for new and improved treatments for VMS.

The clear unmet medical need for nonhormonal therapies to relieve VMS has prompted significant research over the past few years.[8] It is widely known that estrogens modulate serotonin (5-HT) and norepinephrine (NE), two neurotransmitters that play a key role in thermoregulation. As fluctuating estrogen levels drop, 5-HT and NE levels become imbalanced and can result in thermoregulatory dysfunction leading to hot flushes and night sweats.[9] These biochemical findings prompted the clinical evaluation of dual 5-HT and NE reuptake inhibitors, such as fluoxetine,[10] venlafaxine,[11] and paroxetine[12] for the treatment of thermoregulatory dysfunction. These agents have shown modest clinical efficacy in reducing the frequency and severity of hot flushes.



1 2

Figure 1. Potent and selective NRI, **1**, and major metabolite, **2**.

Because NE alone has been shown to stimulate the hypothalamus, which plays an important role in temperature regulation,[13] efforts within our laboratories have focused on identifying selective norepinephrine reuptake inhibitors (NRIs) for the treatment of VMS. We have previously reported that the selective NRI, **1** (Figure 1), produced oral efficacy in a telemetric model of thermoregulatory dysfunction using ovariectomized (OVX) rats.[14] This model is based on the fact that intact cycling female rats exhibit a diurnal rhythm in which their tail skin temperature (TST) decreases during their

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Table 1. Efficacy of **1** and **2** in a Telemetric Rat Model of OVX-Induced Thermoregulatory Dysfunction at 30 mg/kg

compd #	route of administration	onset[a] (h)	time of significance[b] (h)	mean ΔTST (°C)	max ΔTST (°C)
1	ip	0.5	6.5	−2.75	−4.87
1	po	1	3	−2.16	−3.15
2	ip	0	0	0	0
2	po	0	0	0	0

[a] The onset of an effect was defined as the first half-hour interval of two consecutive significant ($p < 0.05$) half-hour interval temperature decreases. [b] Significance was measured by a p value of <0.05 vs 2% Tween-80/0.5% methylcellulose in water vehicle. The treatment effect was defined to have ended when there were two consecutive nonsignificant ($p \geq 0.05$) half-hour intervals. Numbers were based on $n = 16$ animals.

dark (active) phase and remains elevated during their light (inactive) phase. Removal of the ovarian hormones through an ovariectomy causes the TST to remain elevated in both the dark and the light phases. Estrogen treatment of OVX rats has been reported to restore the normal temperature pattern as seen in an intact rat.[2] If drug administration to OVX rats, like estrogen, can lower TST, the desired outcome would be achieved, as it is hypothesized that restoration of the diurnal temperature pattern in rats correlates to the alleviation of VMS in patients.[15,16]

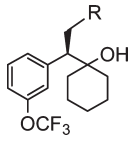
In vitro evaluation of **1** in rat liver microsomes (RLM) showed that it is rapidly metabolized to the des-methyl analogue, **2**, with a half-life of 3.7 min (Figure 1). Compounds **1** and **2** were examined in the model of thermoregulatory dysfunction that was described above. As shown in Table 1, **1** [human norepinephrine transporter (hNET), IC_{50} = 82 nM] was found to be efficacious when dosed intraperitoneally (ip) and orally (po) at 30 mg/kg (% F for **1** = 8% in female rats). Despite the in vitro activity of the des-methyl analogue **2** (hNET IC_{50} = 140 nM), this compound showed no in vivo efficacy at 30 mg/kg via either mode of administration.

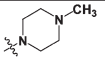
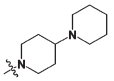
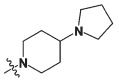
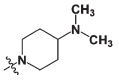
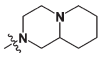
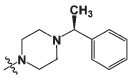
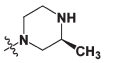
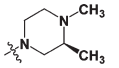
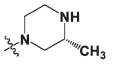
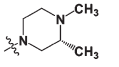
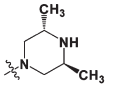
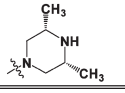
Because of the poor metabolic stability of our lead compound, **1**, our laboratory undertook a systematic optimization of this class to improve the stability of the analogues. Our drug discovery efforts also focused on increasing lipophilicity to enhance brain penetration[17] and oral bioavailability, while maintaining potency against hNET and selectivity versus human serotonin transporter (hSERT) and human dopamine transporter (hDAT).

Toward this end, compounds were prepared, in an analogous fashion to the previously reported synthesis,[14] in an attempt to prevent the formation of nonefficacious compound **2**. N-substituted piperazines, C-substituted piperazines, and 4-aminopiperidines, along with other analogues, were synthesized in this effort. Their structures and biological data are shown in Table 2.

The 4-aminopiperidine derivatives **3**−**5**, acting as piperazine mimetics, maintained hNET potency and selectivity over hDAT. The compounds with increased steric bulk on the piperazine nitrogen (as compared to **1**), such as analogues **6** and **7**, sustained potency at hNET and selectivity over both hSERT and hDAT. Several analogues that had substituents on one or more carbons of the piperazine moiety, **8**−**13**, were prepared. Except for the *trans*-2,6-dimethylpiperazine analogue, **12**, these C-substituted analogues had comparable hNET potency to **1** and were selective over hSERT and hDAT.

Table 2. Characterization of 1-{(1*S*)-2-[amino]-1-[3-(trifluoromethoxy)-phenyl]ethyl}cyclohexanol Analogues at the hDAT, hNET, and hSERT[a]



compd #	R	hNET uptake IC_{50}[b] (StDv) nM	hSERT uptake inhib.[c] % I @ 1 uM	hDAT bind. inhib.[d] % I @ 1 uM	AlogP[f]
1		82 (21)	3 %	6 %	3.6
2		140 (82)	3 %[e]	13 %	3.3
3		126 (76)	56 %	37 %	4.6
4		78 (2)	2 %	30 %	4.9
5		116 (70)	-13 %	-2 %	3.7
6		67 (35)	6 %	1 %	4.5
7		345 (142)	11 %	3 %	5.5
8		115 (67)	17 %	-1 %	3.7
9		351 (219)	5 %	9 %	3.9
10		143 (129)	21 %	-0.5 %	4.7
11		232 (60)	6 %	5 %	3.9
12		44 %[e]	--	--	4.1
13		140 (31)	17 %	-4 %	4.1

[a] IC_{50} data are the average of at least three independent experiments, each run in triplicate. [b] Inhibition of NE uptake in Madin−Darby canine kidney cells (MDCK)-Net6 cells stably tranfected with hNET. Desipramine (IC_{50} = 3.4 ± 1.6 nM) was used as a standard. [c] Inhibition of 5-HT uptake in human choriocarcinoma cell line (JAR) cells natively expressing human SERT. Fluoxetine (IC_{50} = 9.4 ± 3.1 nM) was used as a standard. [d] Inhibition of radioligand [^{3}H]WIN-35428 to membranes of Chinese hamster ovary (CHO) cells expressing recombinant hDAT. Mazindol (K_i = 22.1 ± 6.5 nM) was used as a standard. [e] Percent inhibition measured at a concentration of 1000 nM. [f] AlogP = calculated octanol/water partition coefficient.

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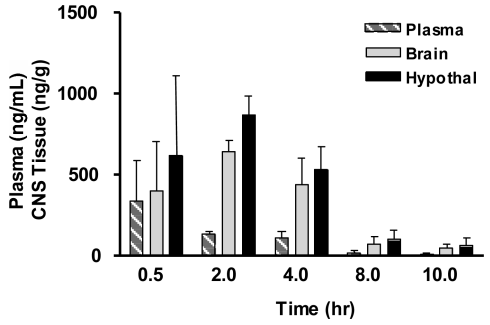

Figure 2. Total exposures of compound **13** in the plasma, brain, and hypothalamus of OVX Sprague−Dawley rats, after a single oral dose of **13** at 10 mg/kg. Data are represented as ng/mL for plasma and ng/g for brain and hypothalamic tissue (mean ± SEM); $n = 3$ rats/data point.

From this work, it is clear that the hNET amine binding region is quite promiscuous and tolerates various amine moieties and substitutions at this position. Additionally, all analogues maintained excellent selectivity over hDAT and, in most cases, complete selectivity over hSERT as well.

Our initial goal was to increase the metabolic stability of the analogues, relative to **1**, when exposed to RLM. Therefore, the amine analogues were examined in an in vitro RLM stability assay, and their $t_{1/2}$ values were calculated. Unfortunately, most of the compounds did not show significantly increased microsomal stability over **1**. However, there was one derivative, **13**, that had notably improved microsomal stability (**13**, $t_{1/2}$ = 11.7 min versus **1**, $t_{1/2}$ = 3.7 min).

Because compound **13** showed a modest increase in in vitro stability and tested positively in our in vitro brain penetration studies,[19] we sought to determine whether **13** had sufficient in vivo brain exposure. As shown in Table 2, all of the analogues prepared were more lipophilic than either the initial lead **1** or the metabolite **2**, as indicated by their calculated octanol/water partition coefficient (AlogP).[18] We hoped that the increased lipophilicity of the analogues would correlate with adequate brain penetration. Monitoring **13** in rat brain would determine if the compound is able to penetrate the blood−brain barrier, and furthermore, evaluating its concentration in the hypothalamus would indicate whether this compound reaches the key region of the brain implicated in temperature regulation.[20] When dosed orally at 10 mg/kg, **13** does indeed have good exposure in both the brain and the hypothalamus, as shown in Figure 2. This in vivo study established that **13** has a brain to plasma ratio of 4 and also has excellent distribution into the hypothalamus. Detailed study protocols, in addition to compound concentrations in plasma, brain, and hypothalamus for each animal at each time point are included in the Supporting Information (S27−S29).

Having verified the acceptable exposure of **13** into the hypothalamus, this compound was then examined in a microdialysis experiment to determine its action in this region of the brain. When **13** was administered orally at 30 mg/kg to an OVX rat, the NE levels in the hypothalamus were significantly increased as compared with that of the control animals. In contrast, the levels of 5-HT and dopamine in the hypothalamus remained the same in both the compound-treated and the control rats. These data confirm that **13** is a potent and selective NRI in vivo; see the Supporting Information for microdialysis details. Compound **13** was further profiled in a broad panel of receptors and enzymes and showed 25−200-fold selectivity for hNET over these targets.

Table 3. Characterization of *S*-(−)-**13** (**13**), *R*-(+)-**13** (**13R**), and Racemic-**13** (**13Rac**) Analogues at hNET, hSERT, and hDAT[a]

compd #	stereo-chemistry	hNET uptake IC_{50} (SD) (nM)	hSERT function inhibition % I at 1 μM	hDAT binding inhibition % I at 1 μM
13	*S*-(−)-	140 (31)	17.5	−4
13R	*R*-(+)-	22% I at 1 μM	8.3	0
13Rac	Rac[b]	203 (105)	−8.5	3.6

[a] See Table 2, footnotes a−d. [b] Rac = racemate.

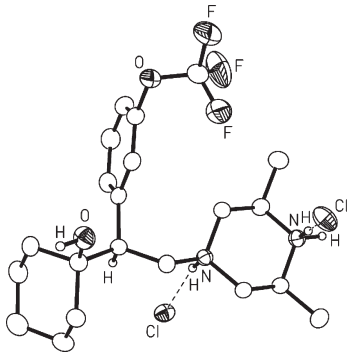

Figure 3. ORTEP view of **13**, 1-{(1*S*)-2-[(*cis*)-3,5-dimethylpiperazin-1-yl]-1-[3-(trifluoromethoxy)phenyl]ethyl} cyclohexanol dihydrochloride.

The *S*-enantiomer of the previously reported cylcoalkanol ethylamine analogues was determined to be the active enantiomer (eutomer).[14] Therefore, it is not surprising that the *S*-configuration was also the eutomer for this structurally related series (Table 3). The absolute stereochemistry of eutomer **13** was confirmed unequivocally by the use of single-crystal X-ray analysis (Figure 3).

The oral pharmacokinetic properties of **13** were explored in Sprague−Dawley female rats, CD-1 female mice, and female dogs. As demonstrated in Table 4, the oral bioavailability of **13** was substantial, between 20 and 49%, in all species examined.

To determine the potential efficacy in treating VMS, compound **13** was examined in the rat telemetry model of thermoregulatory dysfunction. During a time-course study of OVX rats, a dose-dependent decrease in TST within the dark phase was observed, as shown in Table 5. Compound **13** was determined to be a potent NRI with a minimum efficacious dose (MED) of 5 mg/kg in this in vivo model of thermoregulation.[14]

In summary, we have reduced the metabolic liability of our earlier lead candidate **1** by replacing the methyl piperazine moiety with the more sterically demanding (*cis*)-3,5-dimethyl piperazine moiety to afford **13** (WAY-260022, NRI-022). The increased microsomal stability and lipophilicity of **13**

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Table 4. Selected Pharmacokinetic Properties of **13**[a]

	rats[b]	CD mice[c]	dog[d]
	iv (5 mpk)	iv (3 mpk)	iv (2 mpk)
$T_{1/2}$ (h)[e]	1.6	0.72	3.3
VD_{ss} (L/kg)[f]	5.4	12.0	5.93
AUC (ng h/mL)[g]	1999	472	1249
CL_T (L/h/kg)[h]	41	6.36	1.62
	po (30 mpk)	po (5 mpk)	po (5 mpk)
$T_{1/2}$ (h)	2.5	ND[k]	3.3
C_{max} (ng/mL)[i]	944	52.9	247
AUC (ng h/mL)	5998	153	1320
F (%)[j]	49	19.5	43.9

[a] All values are mean values (n = 3). [b] Sprague−Dawley female rats, fasted. [c] CD-1 female mice, fasted. [d] Female beagles, fasted. [e] $T_{1/2}$ = apparent terminal half-life. [f] VD_{ss} = steady-state volume of distribution. [g] AUC = area under the concentration versus time curve. [h] CL_T = total body clearance. [i] C_{max} = peak concentration. [j] F = bioavailability = $[(AUC_{0-24(oral)}dose_{(iv)})/(AUC_{0-24(iv)}dose_{(oral)}] \times 100$. [k] ND = not determined.

Table 5. Oral Doses of **13** in a Telemetric Rat Model of OVX-Induced Thermoregulatory Dysfunction

PO (mg/kg)	N	onset[a] (h)	time of significance[b] (h)	mean ΔTST (°C)	max ΔTST (°C)
3	15	0	0	0	0
5	16	1.5	1	−1.2	−1.2
10	16	1	3	−1.1	−1.7
15	15	1	2	−1.7	−2.2
30	16	immediate	5.5	−1.6	−2.4

[a] See Table 1, footnote [a]. [b] See Table 1, footnote [b].

likely contribute to the good brain to plasma ratio of this compound. Furthermore, **13** has significant bioavailability and excellent efficacy in a model of thermoregulatory dysfunction in rats. On the basis of these and other data, **13** advanced to phase I human clinical trials for the treatment of VMS. The results of these studies will be reported in due course.

SUPPORTING INFORMATION AVAILABLE

Experimental procedures, characterization data, and purity data for all compounds, experimental procedures for biological assays, crystallographic information in cif format, and in vivo dialysis graphs. This material is available free of charge via the Internet at http://pubs.acs.org.

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ABBREVIATIONS

CHO, Chinese hamster ovary; hDAT, human dopamine transporter; hNET, human norepinephrine transporter; hSERT, human serotonin transporter; HRT, hormone replacement therapy; JAR, human choriocarcinoma cell line; MDCK, Madin−Darby canine kidney cells; MED, minimum efficacious dose; NE, norepinephrine; NRI, norepinephrine reuptake inhibitor; OVX, ovariectomized; RLM, rat liver microsomes; TST, tail skin temperature; VMS, vasomotor symptoms; 5-HT, serotonin.

REFERENCES

(1) Katovich, M. J.; Pitman, D. L.; Barney, C. C. Mechanisms mediating the thermal response to morphine withdrawal in rats. *Proc. Soc. Exp. Biol. Med.* **1990,** *193* (2), 129–135.
(2) Berendsen, H. H. G.; Weekers, A. H. J.; Kloosterboer, H. J. Effect of tibolone and raloxifene on the tail temperature of oestrogen-deficient rats. *Eur. J. Pharmacol.* **2001,** *419* (1), 47–54.
(3) Rödström, K.; Bengtsson, C.; Lissner, L.; Milsom, I.; Sundh, V.; Björkelund, C. A longitudinal study of the treatment of hot flushes: The population study of women in Gothenburg during a quarter of a century. *Menopause* **2002,** *9* (3), 156–161.
(4) Groeneveld, F. P. M. J.; Bareman, F. P.; Barentsen, R.; Dokter, H. J.; Drogendijk, A. C.; Hoes, A. W. Vasomotor symptoms and well-being in the climacteric years. *Maturitas* **1996,** *23* (3), 293–299.
(5) LaCroix, A. Z.; Burke, W. Breast cancer and hormone replacement therapy. *Lancet* **1997,** *350* (9084), 1042–1043.
(6) *World Bank*; Oxford University Press: New York, 1993.
(7) Ross, R. K.; Paganini-Hill, A.; Wan, P. C.; Pike, M. C. Effect of Hormone Replacement Therapy on Breast Cancer Risk: Estrogen Versus Estrogen Plus Progestin. *J. Natl. Cancer Inst.* **2000,** *92* (4), 328–332.
(8) Nelson, H. D.; Vesco, K. K.; Haney, E.; Fu, R.; Nedrow, A.; Miller, J.; Nicolaidis, C.; Walker, M.; Humphrey, L. Nonhormonal Therapies for Menopausal Hot Flashes: Systematic Review and Meta-analysis. *J. Am. Med. Assoc.* **2006,** *295*, 2057–2071.
(9) Panek, D. U.; Dixon, W. R. Effect of continuous intraventricular estrogen or catechol estrogen treatment on catecholamine turnover in various brain regions. *J. Pharmacol. Exp. Ther.* **1986,** *236* (3), 646–652.
(10) Loprinzi, C. L.; Sloan, J. A.; Perez, E. A.; Quella, S. K.; Stella, P. J.; Mailliard, J. A.; Halyard, M. Y.; Pruthi, S.; Novotny, P. J.; Rummans, T. A. Phase III Evaluation of Fluoxetine for Treatment of Hot Flashes. *J. Clin. Oncol.* **2002,** *20* (6), 1578–1583.
(11) Loprinzi, C. L.; Kugler, J. W.; Sloan, J. A.; Mailliard, J. A.; LaVasseur, B. I.; Barton, D. L.; Novotny, P. J.; Dakhil, S. R.; Rodger, K.; Rummans, T. A.; Christensen, B. J. Venlafaxine in management of hot flashes in survivors of breast cancer: A randomised controlled trial. *Lancet* **2000,** *356* (9247), 2059–2063.
(12) Stearns, V.; Beebe, K. L.; Iyengar, M.; Dube, E. Paroxetine Controlled Release in the Treatment of Menopausal Hot Flashes: A Randomized Controlled Trial. *J. Am. Med. Assoc.* **2003,** *289* (21), 2827–2834.
(13) Kumar, V. N. Interrelation between thermoregulation and sleep regulation. *Proc. Natl. Acad. Sci., India, Sect. B* **2003,** *69*, 507–524.

DOI: 10.1021/ml100009p | *ACS Med. Chem. Lett.* **2010,** *1*, 91–95

(14) Mahaney, P. E.; Gavrin, L. K.; Trybulski, E. J.; Stack, G. P.; Vu, A. T.; Cohn, S. T.; Ye, F.; Belardi, J. K.; Santilli, A. A.; Sabatucci, J. P.; Leiter, J.; Johnston, G. H.; Bray, J. A.; Burroughs, K. D.; Cosmi, S. A.; Leventhal, L.; Koury, E. J.; Zhang, Y.; Mugford, C. A.; Ho, D. M.; Rosenzweig-Lipson, S. J.; Platt, B.; Smith, V. A.; Deecher, D. C. Structure-activity relationships of the cycloalkanol ethylamine scaffold: Discovery of selective norepinephrine reuptake inhibitors. *J. Med. Chem.* **2008,** *51* (13), 4038–4049.

(15) Deecher, D. C.; Alfinito, P.; Leventhal, L.; Johnston, G. H.; Cosmi, S.; Merchenthaler, I.; Winneker, R. Alleviation of thermoregulatory dysfunction with the new serotonin and norepinephrine reuptake inhibitor desvenlafaxine succinate in ovariectomized rodent models. *Endocrinology* **2007,** *148*, 1376–1383.

(16) Maswood, N.; Alfinito, P. D.; Cosmi, S.; Leventhal, L.; Johnston, G. H.; Deecher, D. C. Evalulation of the selective serotonin reuptake inhibitor, fluoxetine, in ovariectomized (OVX) rat models of temperature regulation. *Neuroendocrinology* **2006,** *85*, 330–338.

(17) Waterhouse, R. N. Determination of lipophilicity and its use as a predictor of blood-brain barrier penetration of molecular imaging agents. *Mol. Imaging Biol.* **2003,** *5* (6), 376–389.

(18) Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. Prediction of Hydrophobic (Lipophilic) Properties of Small Organic Molecules Using Fragment Methods: An Analysis of AlogP and CLogP Methods. *J. Phys. Chem. A* **1998,** *102*, 3762–3772.

(19) Di, L.; Kerns, E. H.; Fan, K.; McConnell, O. J.; Carter, G. T. High throughput artificial membrane permeability assay for blood-brain barrier. *Eur. J. Med. Chem.* **2003,** *38* (3), 223–232.

(20) Mathews, C. K.; van Holde, K. E. Integration and control of metabolic processes. *Biochemistry*; The Benjamin/Cummings Publishing Group: Redwood City, CA, 1990; pp 790−792.

DOI: 10.1021/ml100009p | *ACS Med. Chem. Lett.* **2010,** *1*, 91–95