Journal of Medicinal Chemistry Article

J. Med. Chem. **2009,** *52,* 5703–5711 **5703**
DOI: 10.1021/jm900888c

1- or 3-(3-Amino-2-hydroxy-1-phenyl propyl)-1,3-dihydro-2*H*-benzimidazol-2-ones: Potent, Selective, and Orally Efficacious Norepinephrine Reuptake Inhibitors[†,‡]

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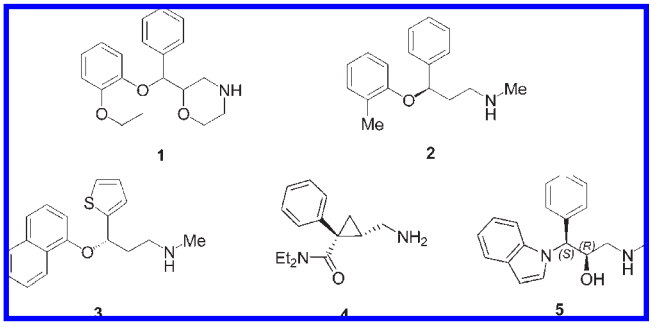
Received June 17, 2009

Sequential structural modifications of the aryloxypropanamine template (e.g., atomoxetine, **2**) led to a novel series of 1-(3-amino-2-hydroxy-1-phenyl propyl)-1,3-dihydro-2*H*-benzimidazol-2-ones as selective norepinephrine reuptake inhibitors (NRIs). In general, this series of compounds potently blocked the human norepinephrine transporter (hNET) while exhibiting selectivity at hNET against both the human serotonin (hSERT) and dopamine transporters (hDAT). Numerous compounds (e.g., **19**−**22**) had low nonamolar hNET potency with IC_{50} values of 7−10 nM and excellent selectivity (>500 fold) at hNET over hSERT and hDAT. Several compounds, such as **20** and **22**, were tested in a telemetric rat model of ovariectomized-induced thermoregulatory dysfunction and were efficacious at oral doses of 3 mg/kg in reducing the tail skin temperature. In addition, compound **20** was also studied in the rat hot plate and spinal nerve ligation (SNL) models of acute and neuropathic pain, respectively, and was orally efficacious at doses of 3−10 mg/kg.

Introduction

The serotonin (SERT[a]), norepinephrine (NET), and dopamine transporters (DAT) are integral membrane proteins that uptake 5-hydroxytryptamine (5-HT, serotonin), norepinephrine (NE), and dopamine (DA), respectively, into presynaptic cells from the synaptic cleft and play a critical role in regulating the physiological functions of these neurotransmitters.[1,2] Monoamine neurotransmitter deficiency has been implicated in a number of neurological disorders making transporter inhibitors potential treatment for a wide range of CNS diseases. Since the early 1980s, numerous monoamine reuptake inhibitors, including selective serotonin reuptake inhibitors (SRIs), norepinephrine reuptake inhibitors (NRIs), and dual serotonin and norepinephrine reuptake inhibitors (SNRIs), have been developed for the treatment of psychiatric disorders.[3,4] Selective SRIs and NRIs such as fluoxetine and reboxetine (**1**) have been used to treat symptoms including major depression and anxiety disorders.[5−7] Additionally, clinical evidence also suggested that reboxetine may have efficacy in the treatment of chronic pain such as fibromyalgia and chronic low back pain.[8] Atomoxetine (**2**), another selective NRI, has been approved for attention deficit hyperactivity disorder (ADHD).[9] Considerable research has also focused on the development of SNRIs.[2,3] These efforts have led to the marketed drugs such as duloxetine (**3**) and milnacipran (**4**), which are both prescribed for treatment of MDD and fibromyalgia.[10−13] Duloxetine has also been approved for diabetic neuropathy[14] and stress urinary incontinence (SUI).[15]



There is still considerable effort[16−27] focused on the development of novel NRIs and SNRIs with improved metabolic and pharmacologic properties (treatment onset, response rate, or efficacy) to address unmet medical needs arising from existing therapy.[28] In our effort to develop selective NRIs, we discovered a novel series of monoamine reuptake

[†]Presented in preliminary form at the 236th ACS National Meeting, Philadelphia, PA, August 17−21, 2008, MEDI-184.

[‡]This manuscript is dedicated to the memory of Dr. Ronald L. Magolda.

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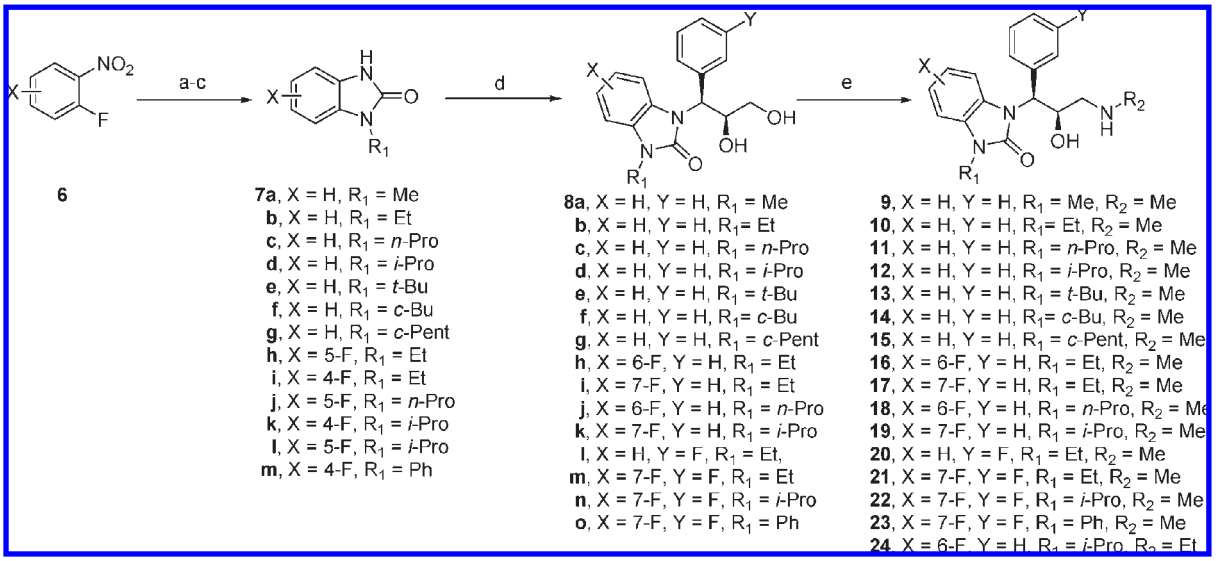
[a]Abbreviations: NE, norepinephrine; NET, norephinephrine transporter; NRI, norepinephrine reuptake inhibitor; 5-HT, serotonin; SERT, serotonin transporter; SRI, serotonin reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; DA, dopamine; DAT, dopamine transporter; hNET, human norepinephrine transporter; hSERT, human serotonin transporter; hDAT, human dopamine transporter; MDD, major depressive disorder; SUI, stress urinary incontinence; ADHD, attention deficit hyperactivity disorder; SAR, structure−activity relationship; AUC, area under the curve; C_{max}, maximum concentration; OVX, ovariectomized; TST, tail-skin temperature; SNL, spinal nerve ligation.

Published on Web 09/01/2009

Scheme 1. Synthesis of 1-(3-Amino-2-hydroxy-1-phenylpropyl)-benzimidazolones[a]



[a] Reagents and conditions: (a) R_1NH_2, DMF, rt, N_2 or $PhNH_2$, KO*t*-Bu, DMF, rt, N_2, 50−80%; (b) $NaBH_4$, MeOH, THF, Pd/C; or H_2 (~30 psi), MeOH, Pd/C, rt, 40−90%; (c) CDI, THF, rt, N_2, 40−80%; (d) ((2*R*,3*R*)-3-phenyloxiran-2-yl)methanol or ((2*R*,3*R*)-3-(3-fluorophenyl)oxiran-2-yl)methanol, NaH, Ti(O*i*-Pr)$_4$, DMF, rt, 60−80%; (e) TsCl, pyridine, rt; then R_2NH_2, EtOH, rt, 4−60% for two steps.

inhibitors, the 1-amino-3-(1*H*-indol-1-yl)-3-phenylpropan-2-ols (e.g., **5**), which were identified by combining virtual and focused screening efforts with a rational drug design approach.[29] Although several compounds from this series demonstrated good hNET potency and selectivity at hNET over hSERT and hDAT, they did not meet our criteria for advancement to development. To further explore the SAR of the propanolamine scaffold, we decided to elaborate the pendent heterocycles by replacing the indole with other benzene-fused heterocycles. Gratifyingly, the substitution of indole for benzimidazolone and oxindole moieties led to two novel series of potent, selective, and orally active NRIs. In this report, we will discuss the synthesis and SAR of benzimidazolone based propanolamines (**9**−**24**) and the in vivo activities of several lead compounds. The oxindole based propanolamines is the subject of a separate report and will be disclosed in the due course.

Chemistry

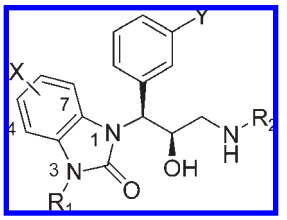
The preparation of 1-(3-amino-2-hydroxy-1-phenylpropyl)-benzimidazolones is illustrated in Scheme 1. Substituted 1-fluoro-2-nitrobenzenes **6** were treated with an appropriate alkylamine or aniline followed by palladium mediated reduction of the nitro moiety using either sodium borohydride or hydrogen to afford benzene-1,2-diamines. The diamines were immediately used in the next step in which they were subjected to a ring closure via 1,1′-carbonyldiimidazole (CDI) to give benzimidazolones **7a**−**l**. With the key headpieces **7** in hand, the epoxide ring-opening of either ((2*R*,3*R*)-3-phenyloxiran-2-yl)methanol or ((2*R*,3*R*)-3-(3-fluorophenyl)oxiran-2-yl)methanol by benzimidazolones **7** was readily achieved in a regio- and stereospecific fashion to furnish the propane-1,2-diols **8a**−**o**. Ring-opening of the epoxide proved to be very sluggish and yielded minimal propane-1,2-diol product in the absence of titanium isopropoxide. The ((2*R*,3*R*)-3-(3-fluorophenyl)oxiran-2-yl)methanol was readily prepared in high enantiomeric excess using a Sharpless epoxidation protocol.[30] The least hindered terminal hydroxyl group in diols **8a**−**o** were selectively activated and converted into their tosylates, which were subsequently treated with an alcoholic solution of alkyl amines to furnish target compounds **9**−**24**. Compounds **9**−**24** were finally converted to their hydrochloride salt prior to in vitro and in vivo testing.

Results and Discussion

Successful discovery of numerous CNS drugs including fluoxetine, duloxetine, and atomoxetine from the aryloxypropanamine scaffold provides a testament that the propanamine scaffold serves as a good drug-like template for CNS drug discovery. However, little has been reported[31] on the introduction of a β-hydroxyl group on the propanamine chain even though it is present in the structure of NE, inferring its significance in the evolution process. In addition, we reasoned that a hydroxyl group reduces the lipophilicity and might have a favorable impact on the ADMET properties of the propanolamines.[32] With these notions, we decided to select the lead compounds that possessed the β-hydroxyl group on the propanamine chain for our NRI program. Our initial effort on the indole and aniline based propanolamine templates led to two new series of selective NRIs or SNRIs,[29,33] and the SAR trends uncovered from these studies have laid a foundation for further SAR expansion. Consequently, our effort on the benzimidazolones was centered on the 3-position of benzimidazolinones while maintaining the preferred stereochemistry and SAR of the pendent phenyl group defined from the previous studies.[29,33] The new 1-(3-amino-2-hydroxy-1-phenylpropyl)-benzimidazol-2-ones (**9**−**24**) were evaluated in vitro for their ability to inhibit both the uptake of NE in MDCK-Net6 cells stably transfected with human NET (hNET) and 5-HT in JAR cells natively expressing the human serotonin transporter (hSERT).[20] Compounds were then assayed for inhibition of radioligand binding to the human dopamine transporter (hDAT).[20] The results of these studies are summarized in Table 1.

Examining the inhibition profiles of the analogues with different *N*-substituents (R_1) indicated that the size of the R_1 group had a significant impact on the hNET potency. The smaller methyl group (R_1 = Me) resulted in compound **9** with

Table 1. Inhibitory Activities of 1-(3-Amino-2-hydroxy-1-phenylpropyl)-benzimidazolones at hNET, hSERT, and hDAT[a]



compd	R_1	R_2	X	Y	hNET IC_{50} (nM)[b]	hNET binding IC_{50} (nM)[b]	hSERT %inh at 1 μM, %[c]	hDAT %inh at 10 μM, %[d]	clogP[h]
1					3.2 ± 0.5		(242)[e]		3.26
(S,S)-1[26]					3.1		(5200)[e]	(> 10000)[e]	3.26
2					3.1 ± 0.3		(48)[e]		3.94
5					28 ± 11.0		(358)[e]	19[f]	2.82
9	Me	Me	H	H	257.0 ± 32.5		15	14	2.03
10	Et	Me	H	H	17.5 ± 1.8	16.8 ± 4.4	4	−19	2.56
11	*n*-Pr	Me	H	H	18.6 ± 2.1		15	6	3.09
12	*i*-Pr	Me	H	H	13.4 ± 1.3	10.8 ± 2.7	19	19	2.87
13	*t*-Bu	Me	H	H	56 ± 4.8		1	3[f]	3.27
14	*c*-Bu	Me	H	H	42.5 ± 5.3	90.0 ± 19.0	5	6	2.95
15	*c*-Pent	Me	H	H	66.7 ± 8.0		46 (2369)[e]	20	3.50
16	Et	Me	6-F	H	36.7 ± 4.5		32	30	2.83
17	Et	Me	7-F	H	13.8 ± 1.6	11.4 ± 5.6	−5	29	2.83
18	*n*-Pr	Me	6-F	H	39.4 ± 5.3		44 (8316)[e]	16	3.36
19	*i*-Pr	Me	7-F	H	7.8 ± 1.2		6 (> 10000)[e]	12	3.14
20	Et	Me	H	F	7.4 ± 1.0	6.4 ± 1.7	15 (> 10000)[e]	−2	2.70
21	Et	Me	7-F	F	10.4 ± 0.8		8 (> 10000)[e]	11	2.97
22	*i*-Pr	Me	7-F	F	6.9 ± 0.8	4.1 ± 1.3	19 (6318)[e]	27	3.28
23	Ph	Me	7-F	F	91.9 ± 18.8		ND[g]	11[f]	4.13
24	*i*-Pr	Et	6-F	H	> 1000		ND[g]	ND[g]	3.67

[a] Inhibition of norepinephrine uptake in MDCK-Net6 cells, natively expressing 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. [c] Inhibition of serotonin uptake in JAR cells, stably transfected with 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_5 (nM). [f] Percent inhibition measured at a concentration of 1 μM. [g] ND: not determined. [h] Calculated logP by Daylight engine V 4.81.

moderate hNET potency (IC_{50} = 257.0 nM). Replacing the methyl group with a larger ethyl or propyl group (**10**−**12**) led to compounds with greater than 10-fold increase in the hNET potency (IC_{50} = 13.4−18.6 nM for **10**−**12** vs 257 nM for **9**). However, further increasing the size of R_1 to *t*-butyl, *c*-butyl, and *c*-pentyl groups caused a slight decrease in hNET potency (**13**−**15**, IC_{50} = 36.7−66.7 nM) compared to their ethyl and propyl analogues. Analogues with a 6-fluorine substitution (**16** and **18**, IC_{50} = 36.7, 39.4 nM)) were marginally less potent at hNET compared to their des-fluorine congeners **10** and **11** (IC_{50} = 17.5, 18.6 nM). However, the 7-fluorine substituted compounds, **17** and **19**, had similar hNET potency as their unsubstituted analogues **10** and **12**. Consistent with previous SAR observation,[33] the *meta*-fluoro analogues, **21**−**22**, were among the most potent analogues from this new series with IC_{50} values of 6.9−10.4 nM. Compound **23**, with a phenyl group at the R_1 position, was significantly less potent at hNET than its alkyl substituted analogues **21** and **22** (IC_{50} = 91.9 vs 6.9−10.4 nM). This finding is quite surprising because phenyl substituted analogues from the corresponding des-hydroxy propanamine series were more potent at hNET than their alkyl substituted analogues.[27] Ethylamino analogue **24** was significantly less potent at hNET, consistent with previous SAR observation on propanamine series.[27,33]

A selected group of compounds were also tested for their inhibition of [^{3}H] nisoxetine binding to whole MDCK-Net6 cells stably transfected with hNET. In general, the binding affinity was consistent with the potency determined from the NE uptake functional assay. For example, compound **20** had similar IC_{50} values from these functional and binding assays (7.4 vs 6.4 nM).

As illustrated in Table 1, inhibition of both hSERT and hDAT by benzimidazolone analogues was marginal. All compounds that were examined exhibited less than 50% inhibition of [^{3}H]WIN-35,428 binding to hDAT at a concentration of 10 μM indicating excellent hNET selectivity over hDAT. For the hNET selectivity versus hSERT, the compounds tested from this series had good to excellent selectivity. Among the most potent analogues, compounds **19**−**22** exhibited excellent hNET selectivity over hSERT (>900 fold) which was similar to that of (*S*,*S*)-reboxetine (**1**) but better than those of atomoxetine (**2**) and lead compounds from aniline and indole-based propanolamines.[29,33] In addition, these compounds possess desirable drug-like molecular properties such as polar surface area (PSA, <70)[34] and clogP (< 4), which are expected to be beneficial to the PK and the in vivo efficacy described below.[32,35]

Neurotransmitters NE and 5-HT have been reported to stimulate areas of the hypothalamus that play an important role in temperature regulation.[36,37] SRIs and SNRIs have been shown preclinically and clinically to restore thermoregulatory dysfunction caused by the hormone depletion.[38−42] More recently, we reported that a selective NRI from a series of cyclohexanol ethylpiperazines significantly reduced the tail skin temperature (TST) in a telemetric rat model of ovariectomized (OVX)-induced thermoregulatory dysfunction.[20]

To examine the effects of benzimidazolone based propanolamines on temperature homeostasis, compounds **10**, **19**, **20**, and **22** were evaluated in the telemetric rat model.[43,44] As illustrated in Table 2, all four compounds significantly reduced TST with maximum temperature reduction between 1.8 and 3.7 °C. It is noteworthy that propanolamine, **22**, at a lower dose was more efficacious in both TST reduction and duration than the ethylpiperazine we previously reported.[20] Also notably, the *meta*-fluorine substituted analogues **20** and **22** were more efficacious in the telemetric rat model than their desfluorine congeners **10** and **19** despite having similar hNET potency (IC_{50} = 7−17 nM). For example, both **20** and **22** had greater mean and maximum reduction in TST as well as longer duration than those of **10** and **19**.

In an effort to establish a pharmacodynamic−pharmacokinetic relationship, the pharmacokinetic properties of compounds **10** and **22** were examined (Table 3). After oral administration, compounds **10** and **22** had good bioavailability, rapid absorption with maximum concentration achieved within 2 h, and a moderate terminal half-life. The pharmacokinetic findings were consistent with the rapid onset and moderate duration of activities observed in the telemetric rat model. However, compound **10** had a higher clearance and consequently lower maximum concentration (C_{max}) and smaller area under the curve (AUC) than those of **22**. These results may in part explain why compound **10** was less efficacious in the telemetric rat model than **22** for both duration and TST reduction.

A number of neurotransmitters have been implicated in the modulation of nociceptive processing. NE is a major component of the endogenous descending pain inhibitory system from the rostral ventral medulla to the spinal cord and a reduced level of endogenous NE activity at both the spine and supra-spine may in part cause chronic pain.[45−48] Consequentially, it is believed that NRIs attenuate pain by blocking reuptake of NE leading to increased postsynaptic NE levels and sustained activation of the descending pain inhibitory pathway. In addition, clinical observations also suggest that drugs with greater NRI versus SRI activity are more effective for the treatment of pain than drugs with only SRI activity.[49,50] To investigate the effect of benzimidazolone based propanolamines on pain, compound **20** was characterized in both acute and neuropathic pain models.

The activity of **20** was evaluated in the rat hot plate assay of acute analgesia. In the hot plate assay,[51,52] rats are placed on a metal plate maintained at a temperature of 52 °C. The latency to exhibit a nocifensive response, defined as hind paw lift, flutter, licking, or escape behavior, was measured with a cutoff of 30 s set to avoid tissue damage. Compound **20** was administered orally in 0.5% methylcellulose plus 2% Tween in water and was observed to significantly increase latency at 10 mg/kg 1, 3, and 5 h postdosing (Figure 1). This data suggests that **20** may be efficacious in treating acute pain at these doses.

The activity of compound **20** was also evaluated in a rat spinal nerve ligation (SNL) model of neuropathic pain. Briefly, in this model,[53,54] 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 and the end point taken is complete paw withdrawal. Thresholds were evaluated prior to surgery and reassessed three to four weeks after SNL surgery. Compound **20** 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 **20** significantly and dose-dependently reversed

Table 2. Oral Activity of **10**, **19**, **20**, and **22** at 3 mg/kg in a Telemetric Rat Model of Ovariectomized-Induced Thermoregulatory Dysfunction[a]

compd	onset of activity, h	duration of action, h	mean reduction in TST, °C	maximum reduction in TST, °C
10	1.0	3.5	−1.57	−1.82
19	1.0	1.0	−1.61	−2.09
20	1.0	5.0	−2.03	−2.62
22	1.0	6.0	−2.44	−3.73

[a] Compound was dosed (po, 3 mg/kg) via % Tween-80 /0.5% methylcellulose in water vehicle. 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 will be considered to have ended when two consecutive nonsignificant half-hour intervals follow any number of significant half-hour intervals. Mean temperature change is calculated from half-hour TST averages obtained over the treatment duration.

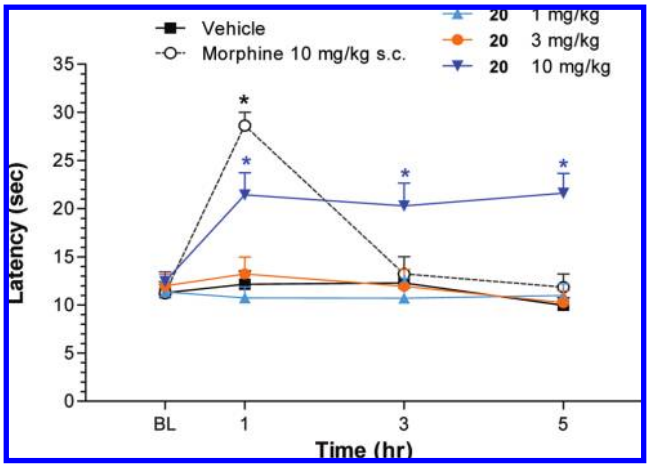


Figure 1. Oral activity of compound **20** on hot plate latency. Male Sprague−Dawley rats (180−210 g, n = 9−10/group). The hot plate was set at 52 °C and cut off was set at 30 s. Latency to nocifensive response was measured. **20** was administered orally as a solution of 0.5% methylcellulose plus 2% Tween in water (vehicle). Morphine as a positive control was administered (sc) as a solution in 0.9% saline. Data shown are means ± SEM * indicates a p value of ≤0.05 vs vehicle (ANOVA).

Table 3. Female Sprague−Dawley (SD) Rat Pharmacokinetic Parameters of Compounds **10** and **22** after Intravenous and Oral Administrations[a]

dose (mg/kg)	compd	Clp (mL/min/kg)	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)	AUC_{0-inf} (h·ng/mL)	F%
5 (iv)	**10**	54 ± 16			3.6 ± 1.4	1645 ± 582	
	22	24 ± 5.7			2.3 ± 0.9	3651 ± 806	
10 (po)	**10**		306 ± 1233	1.1 ± 0.9	3.4 ± 1.0	1845 ± 360	56
	22		1121 ± 527	0.5 ± 0.0	3.9 ± 0.9	7076 ± 3801 3802	97

[a] 2% Tween-80/0.5% methylcellulose in water and 20% of DMSO in PEG200 were used as vehicles for oral and intravenous administrations, respectively. Three rats were used in each study.

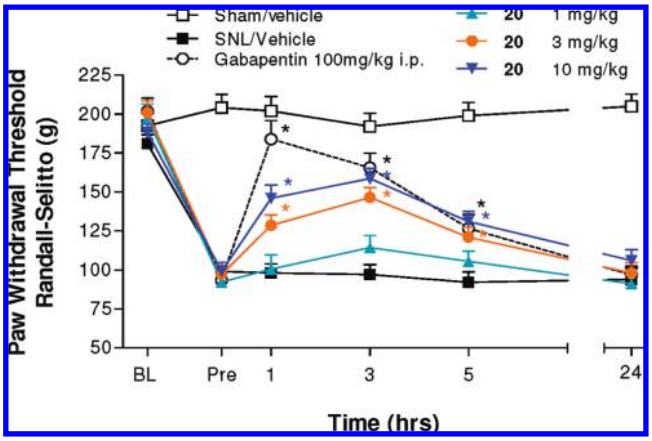


Figure 2. Oral activity of compound **20** on SNL-induced mechanical hyperalgesia. Male Sprague−Dawley rats (238−304 g, 9−10/group), 3 weeks postsurgery. Threshold to paw withdrawal was measured. **20** was administered orally as a suspension of 0.5% methylcellulose plus 2% Tween in water. Gabapentin 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).

mechanical hyperalgesia at 3 and 10 mg/kg, suggesting it may be efficacious in treating neuropathic pain (Figure 2).

Conclusion

A new series of 1-(3-amino-2-hydroxy-1-phenylpropyl)-benzimidazol-2-ones was discovered and evaluated as monoamine reuptake inhibitors and for oral efficacy toward alleviating the dysfunction associated with NE deficiency. Among the most potent analogues, **20** and **22** exhibited similar hNET potency to reboxetine (**1**) and atomoxetine (**2**) and excellent selectivity at hNET versus hSERT and hDAT. Notably, several lead compounds had good pharmacokinetic profiles and exhibited significant efficacy in reducing the tail skin temperature in the telemetric rat model. In addition, compound **20** was also orally efficacious in the rat hot plate and SNL models, suggesting its potential to treat acute and neuropathic pain.

Experimental Section

^{1}H NMR spectra were recorded on a Varian INOVA 400 or Varian INOVA 500 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. 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. Solvents were purchased as anhydrous grade and were used without further purification. Compound purity was assessed by ^{1}H NMR and an analytical HPLC method as described in Supporting Information. Biological results were obtained on compounds of >95% chemical purity as determined by the above methods.

1-*t*-Butyl-1,3-dihydro-benzimidazol-2-one (7e). To a solution of 1-fluoro-2-nitro-benzene (1 g, 7.1 mmol) in DMF (15 mL) was added *t*-butyl amine (0.82 mL, 7.81 mmol) at room temperature, and the reaction mixture stirred at room temperature under nitrogen. After 18 h, the reaction mixture was poured into a saturated aqueous solution of sodium chloride (50 mL) and extracted with ethyl acetate (2 × 50 mL). The organic layer was dried over anhydrous sodium sulfate, concentrated in vacuo, and the residue was purified via flash column chromatography (silica, 1% ethyl acetate in hexane) to give *t*-butyl-(2-nitrophenyl)-amine as an orange oil (1.27 g, 93%). MS (ES) m/z 195.2 ($[M + H]^+$). ^{1}H NMR (DMSO-d_6) δ 8.25 (s, 1H), 8.08 (dd, J = 1.69, 8.71 Hz, 1H), 7.52 (s, 1H), 7.27 (dd, J = 1.30, 8.84 Hz, 1H), 6.68 (ddd, J = 1.17, 6.95, 8.51 Hz, 1H), 1.47 (s, 9H).

To a solution of *t*-butyl-(2-nitrophenyl)-amine (1.27 g, 6.5 mmol), 5% palladium on carbon (0.5 g), and sodium borohydride (0.49 g, 13.1 mmol) in THF (20 mL) was added methanol (10 mL) in a dropwise manner. After addition and stirring for additional 30 min, the reaction mixture was filtered through a pad of celite and the filtrate was poured into a saturated aqueous solution of ammonium chloride (50 mL) and extracted with ethyl acetate (2 × 50 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo to give *N*-*t*-butyl-benzene-1,2-diamine, which was used in the next step without further purification. A solution of *N*-*t*-butyl-benzene-1,2-diamine (1.1 g, 6.7 mmol) and 1,1′-carbonyldiimidazole (1.63 g, 10 mmol) in anhydrous THF (50 mL) was stirred at room temperature for 12 h. The reaction mixture was then poured into a 1N aqueous solution of hydrochloric acid (50 mL) and extracted with ethyl acetate (2 × 50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified via flash column chromatography (silica, 50% ethyl acetate in hexane) to give 1-*t*-butyl-1,3-dihydro-benzimidazol-2-one[55] as an off-white solid (0.66 g, 53% for two steps). MS (ES) m/z 191.1 ($[M + H]^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.71 (s, 1H), 7.39 (d, J = 7.02 Hz, 1H), 6.87−6.95 (m, 3H), 1.69 (s, 9H). Similar procedure was used to prepare other benzimidazolones that were not commercially available.

1-Ethyl-1,3-dihydro-benzimidazol-2-one (7b).[56] MS (ES) m/z 163.2 ($[M + H]^+$). ^{1}H NMR (DMSO-d_6) δ 10.79 (br s, 1H), 7.12 (d, J = 7.02 Hz, 1H), 6.76−7.06 (m, 3H), 3.82 (q, J = 7.28 Hz, 2H), 1.19 (t, J = 7.15 Hz, 3H).

1-Propyl-1,3-dihydro-2*H*-benzimidazol-2-one (7c).[57] MS (ES) m/z 177.1 ($[M + H]^+$). ^{1}H NMR (DMSO-d_6) δ 10.78 (s, 1H), 7.11 (d, J = 5.98 Hz, 1H), 6.91−7.03 (m, 3H), 3.74 (t, J = 7.15 Hz, 2H), 1.55−1.77 (m, 2H), 0.86 (t, J = 7.41 Hz, 3H).

1-Isopropyl-1,3-dihydro-2*H*-benzimidazol-2-one (7d).[58] MS (ES) m/z 176.9 ($[M + H]^+$). ^{1}H NMR (DMSO-d_6) δ 10.77 (s, 1H), 7.13−7.34 (m, 1H), 6.82−7.08 (m, 3H), 4.56 (t, J = 7.02 Hz, 1H), 1.43 (d, J = 7.02 Hz, 6H).

1-Cyclobutyl-1,3-dihydro-2*H*-benzimidazol-2-one (7f). MS (ES) m/z 189 ($[M + H]^+$). ^{1}H NMR (DMSO-d_6) δ 10.75 (s, 1H), 7.22−7.31 (m, 1H), 6.85−6.98 (m, 3H), 4.75 (dd, J = 8.32, 9.36 Hz, 1H), 2.66−2.85 (m, 2H), 2.11−2.28 (m, 2H), 1.64−1.88 (m, 2H).

1-Cyclopentyl-1,3-dihydro-benzimidazol-2-one (7g). MS (ESI) m/z 203 ($[M + H]^+$). ^{1}H NMR (DMSO-d_6) δ 10.80 (s, 1H), 7.08−7.15 (m, 1H), 6.92−7.02 (m, 3H), 4.71 (t, J = 8.58 Hz, 1H), 1.96−2.10 (m, 2H), 1.81−1.96 (m, 4H), 1.58−1.73 (m, 2H).

1-Ethyl-5-fluoro-1,3-dihydro-2*H*-benzimidazol-2-one (7h).[59] MS (ES) m/z 181.2 ($[M + H]^+$). ^{1}H NMR (DMSO-d_6) δ 10.96 (s, 1H), 7.06−7.18 (m, 1H), 6.73−6.89 (m, 2H), 3.81 (q, J = 7.02 Hz, 2H), 1.18 (t, J = 7.15 Hz, 3H).

1-Ethyl-4-fluoro-1,3-dihydro-2*H*-benzimidazol-2-one (7i). MS (ES) m/z 181.2 ($[M + H]^+$). ^{1}H NMR (DMSO-d_6) δ 11.36 (br s, 1H), 7.01 (td, J = 2.21, 3.70 Hz, 2H), 6.78−6.94 (m, 1H), 3.83 (q, J = 7.19 Hz, 2H), 1.19 (t, J = 7.15 Hz, 3H).

5-Fluoro-1-propyl-1,3-dihydro-benzimidazol-2-one (7j).[60] MS (ES) m/z 195.2 ($[M + H]^+$). ^{1}H NMR (DMSO-d_6) δ 10.96 (s, 1H), 7.03−7.16 (m, 1H), 6.75−6.87 (m, 2H), 3.73 (t, J = 7.15 Hz, 2H), 1.54−1.71 (m, 2H), 0.85 (t, J = 7.41 Hz, 3H).

4-Fluoro-1-isopropyl-1,3-dihydro-benzimidazol-2-one (7k). MS (ES) m/z 195.2 ($[M + H]^+$). ^{1}H NMR (DMSO-d_6) δ 11.34 (s, 1H), 7.11 (d, J = 8.06 Hz, 1H), 6.97 (td, J = 5.20, 8.19 Hz, 1H), 6.87 (dd, J = 8.58, 10.40 Hz, 1H), 4.48−4.65 (m, 1H), 1.43 (d, J = 7.02 Hz, 6H).

5-Fluoro-1-isopropyl-1,3-dihydro-2*H*-benzimidazol-2-one (7l).[61] MS (ES) m/z 195.1 ($[M + H]^+$). ^{1}H NMR (DMSO-d_6) δ 10.94 (br s, 1H), 7.22 (dd, J = 4.68, 8.58 Hz, 1H), 6.76−6.84 (m, 2H), 4.40−4.66 (m, 1H), 1.42 (d, J = 7.02 Hz, 6H).

4-Fluoro-1-phenyl-1*H*-benzo[d]imidazol-2(3*H*)-one (7m). To a solution of 2,6-difluoronitrobenzene (2.0 g, 6.28 mmol) and aniline (1.15 mL, 12.6 mmol) in dry DMF (10 mL) was added potassium t-butoxide (1.40 g, 12.5 mmol) in portions. After 16 h at room temperature, the reaction mixture was poured into a saturated aqueous ammonium chloride solution (50 mL) and extracted with dichloromethane (2 × 50 mL). The combined organic layers were washed with water (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to afford crude 3-fluoro-2-nitro-*N*-phenylaniline (1.15 g, 78%), which was used in the next step without further purification. A mixture of 3-fluoro-2-nitro-*N*-phenylaniline (1.15 g, 4.9 mmol) and palladium on charcoal (10%, 200 mg) in methanol (30 mL) was hydrogenated (50 psi H_2) in a Parr shaker apparatus. After 2 h, the catalyst was removed by filtration through a pad of celite and the celite washed with fresh methanol (20 mL). The combined methanol layers were concentrated under reduced pressure and the residue purified by column chromatography (silica, 1:0 to 9:1 hexanes:ethyl acetate) to afford 3-fluoro-*N*-1-phenylbenzene-1,2-diamine (0.47 g, 47%). MS (ES) m/z 203.2 ($[M + H]^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.22 (s, 1H), 7.10 (tt, J = 2.17 and 7.3 Hz, 2H), 6.81 (d, J = 7.94 Hz, 1H), 6.75−6.65 (m, 5H), 6.50−6.44 (m, 1H) and 4.63 (br s, 1H).

To a stirred solution of 3-fluoro-*N*-1-phenylbenzene-1,2-diamine (0.247 g, 1.22 mmol) in dry THF (10 mL) was added carbonyl diimidazole (0.21 g, 1.3 mmol) under nitrogen. After 30 min, 4-dimethylaminopyridine (catalytic amount) was added and the reaction stirred overnight. After 16 h, a further portion of carbonyl diimidazole was added (0.21 g, 1.3 mmol) and stirring continued. After 48 h, the reaction mixture was diluted with ethyl acetate (50 mL) and extracted with sodium hydroxide solution (2N, 2 × 25 mL). The combined basic extracts were washed with ethyl acetate (2 × 20 mL) and then acidified (hydrochloric acid, pH 1). The product was collected by filtration and was then washed with water, hexanes, and air-dried to afford 4-fluoro-1-phenyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one (0.117 g, 42%) as a white solid. MS (ES) m/z 228.9 ($[M + H]^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (br s, 1H), 7.59−7.52 (m, 4H), 7.45 (tt, J = 1.54 and 7.04 Hz, 1H), 7.03−6.95 (m, 2H) and 6.81 (dt, J = 1.66 and 7.18 Hz, 1H).

The intermediates **8a**−**o** were prepared according to the general procedure as described for compound **8e**. Most compounds were not characterized and used in the next step. The selected examples that were characterized are reported herein.

1-*t*-Butyl-3-[(1*S*,2*S*)-2,3-dihydroxy-1-phenyl-propyl]-1,3-dihydro-2*H*-benzimidazol-2-one (8e). A mixture of 1-*t*-butyl-1,3-dihydro-benzimidazol-2-one (0.66 g, 3.5 mmol) and sodium hydride (60% dispersion in mineral oil, 0.15 g, 3.8 mmol) in anhydrous DMF (4 mL) was stirred for 10 min under nitrogen at room temperature. A solution of [(2*R*,3*R*)-3-phenyloxiran-2-yl]methanol (1.07 g, 7.1 mmol) and titanium isopropoxide (2.14 mL, 7.1 mmol) in anhydrous DMF (4 mL) that was aged for 20 min was then added, and the mixture was stirred at room temperature under nitrogen. After 18 h, the mixture was partitioned between a 1N aqueous solution of hydrochloric acid (50 mL) and ethyl acetate (2 × 50 mL). The organic layer was separated, washed with saturated sodium bicarbonate (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified via silica gel column (60% ethyl acetate in hexane) to give 1-*t*-butyl-3-[(1*S*,2*S*)-2,3-dihydroxy-1-phenyl-propyl]-1,3-dihydro-2*H*-benzimidazol-2-one as an oil (0.6 g, 50%). MS (ES) m/z 341.2 ($[M + H]^+$). ^{1}H NMR (, DMSO-d_6) δ 7.52 (d, J = 7.28 Hz, 2H), 7.44−7.48 (m, 1H), 7.27−7.33 (m, 2H), 7.22−7.26 (m, 1H), 7.08−7.15 (m, 1H), 6.89−6.97 (m, 2H), 5.33 (d, J = 8.32 Hz, 1H), 5.21 (d, J = 5.72 Hz, 1H), 4.66−4.75 (m, 1H), 4.60−4.66 (m, 1H), 3.32−3.36 (m, 2H), 1.72 (s, 9H).

1-Cyclobutyl-3-[(1*S*,2*S*)-2,3-dihydroxy-1-phenyl-propyl]-1,3-dihydro-2*H*-benzimidazol-2-one (8f). MS (ES) m/z 339.2 ($[M + H]^+$). ^{1}H NMR (DMSO-d_6) δ 7.51−7.57 (m, 2H), 7.27−7.37 (m, 3H), 7.19−7.26 (m, 2H), 6.95−7.05 (m, 2H), 5.33 (d, J = 8.58 Hz, 1H), 5.20 (d, J = 5.98 Hz, 1H), 4.86 (t, J = 8.97 Hz, 1H), 4.73 (dd, J = 5.59, 8.45 Hz, 1H), 4.63−4.68 (m, 1H), 3.34−3.37 (m, 2H), 2.75−2.89 (m, 2H), 2.23−2.35 (m, 2H), 1.84−1.95 (m, 1H), 1.74−1.84 (m, 1H).

1-Cyclopentyl-3-[(1*S*,2*S*)-2,3-dihydroxy-1-phenylpropyl]-1,3-dihydro-2*H*-benzimidazol-2-one (8g). MS (ES) m/z 352.9 ($[M + H]^+$). ^{1}H NMR (DMSO-d_6) δ 7.55 (d, J = 7.28 Hz, 2H), 7.13−7.36 (m, 5H), 6.99 (dd, J = 6.63, 7.93 Hz, 2H), 5.34 (d, J = 8.06 Hz, 1H), 5.21 (d, J = 5.98 Hz, 1H), 4.69−4.82 (m, 2H), 4.66 (t, J = 5.46 Hz, 1H), 3.33−3.38 (m, 2H), 2.01 (d, J = 7.80 Hz, 2H), 1.90 (br s, 4H), 1.58−1.71 (m, 2H).

3-[(1*S*,2*S*)-2,3-Dihydroxy-1-phenylpropyl]-1-ethyl-5-fluoro-1,3-dihydro-2*H*-benzimidazol-2-one (8h). MS (ES) m/z 331.1 ($[M + H]^+$). ^{1}H NMR (DMSO-d_6) δ 7.53−7.60 (m, 2H), 7.28−7.34 (m, 2H), 7.14−7.27 (m, 3H), 6.81−6.89 (m, 1H), 5.34 (d, J = 8.06 Hz, 1H), 5.20 (d, J = 5.72 Hz, 1H), 4.69−4.76 (m, 1H), 4.66 (t, J = 5.59 Hz, 1H), 3.86 (q, J = 7.28 Hz, 2H), 3.33−3.44 (m, 2H), 1.15−1.22 (m, 3H).

3-[(1*S*,2*S*)-2,3-Dihydroxy-1-phenylpropyl]-1-ethyl-4-fluoro-1,3-dihydro-2*H*-benzimidazol-2-one (8i). MS (ES) m/z 331.1 ($[M + H]^+$). ^{1}H NMR (DMSO-d_6) δ 7.47 (d, J = 7.54 Hz, 2H), 7.28−7.35 (m, 2H), 7.19−7.28 (m, 1H), 6.99−7.09 (m, 2H), 6.82−6.94 (m, 1H), 5.50 (d, J = 8.84 Hz, 1H), 5.16 (d, J = 6.24 Hz, 1H), 4.77 (br s, 1H), 4.65 (t, J = 5.46 Hz, 1H), 3.82−3.94 (m, 2H), 3.34−3.46 (m, 2H), 1.20 (t, J = 7.15 Hz, 3H).

3-[(1*S*,2*S*)-2,3-Dihydroxy-1-(3-fluorophenyl)-propyl]-1-ethyl-4-fluoro-1,3-dihydro-2*H*-benzimidazol-2-one (8m). MS (ES) m/z 349.1 ($[M + H]^+$). ^{1}H NMR (DMSO-d_6) δ 7.23−7.36 (m, 2H), 7.18 (d, J = 7.80 Hz, 1H), 6.92−7.08 (m, 3H), 6.78−6.90 (m, 1H), 5.45 (d, J = 9.36 Hz, 1H), 5.20 (d, J = 6.50 Hz, 1H), 4.65−4.73 (m, 1H), 4.63 (t, J = 5.46 Hz, 1H), 3.75−3.89 (m, 2H), 3.31−3.37 (m, 2H), 1.10−1.17 (m, 3H).

1-*t*-Butyl-3-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride (13). A solution of 1-*t*-butyl-3-[(1*S*,2*S*)-2,3-dihydroxy-1-phenyl-propyl]-1,3-dihydro-2*H*-benzimidazol-2-one (0.55 g, 1.6 mmol) and *p*-toluenesulfonyl chloride (0.37 g, 1.9 mmol) in anhydrous pyridine (5 mL) was stirred at room temperature under nitrogen for 12 h. The reaction was poured into a cold 1N aqueous solution of hydrochloric acid (50 mL) and extracted with ethyl acetate (2 × 50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to give (2*S*,3*S*)-toluene-4-sulfonic acid 3-(3-*t*-butyl-2-oxo-2,3-dihydro-benzimidazol-1-yl)-2-hydroxy-3-phenyl-propyl ester, which was taken up in methanol (10 mL) and added a 2N solution of methylamine in methanol (4 mL, 8 mmol). The reaction mixture was stirred for 12 h at room temperature in a sealed tube and partitioned between a saturated aqueous solution of sodium bicarbonate (50 mL) and ethyl acetate (80 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified via flash column chromatography (silica, 20% MeOH in dichloromethane) to give 1-*t*-butyl-3-[(1*S*,2*R*)-2-hydroxy-3-methylamino-1-phenylpropyl]-1,3-dihydro-2*H*-benzimidazol-2-one as a clear oil. The free base was dissolved in a minimum amount of ethanol and treated with a 2N ethereal solution of hydrochloric acid (1 mL) and stirred for 1 h. The ethanol was removed in vacuo, and the clear oil was triturated with diethyl

ether/dichloromethane to afford 1-*t*-butyl-3-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride as a white solid (0.027 g, 4.7% for two steps). HRMS: calcd for $C_{21}H_{27}N_3O_2 + H^+$, 354.2176; found (ESI, $[M + H]^+$), 354.2179. ^{1}H NMR (DMSO-d_6) δ 8.51 (br s, 2H), 7.52−7.58 (m, 2H), 7.46−7.51 (m, 1H), 7.32−7.39 (m, 2H), 7.24−7.31 (m, 1H), 7.12−7.19 (m, 1H), 6.93−7.00 (m, 2H), 6.05 (d, J = 6.76 Hz, 1H), 5.29 (d, J = 8.84 Hz, 1H), 5.12 (br s, 1H), 2.83−3.04 (m, 2H), 2.54−2.60 (m, 3H), 1.73 (s, 9H). Following this general procedure, analogues **9**−**12** and **14**−**24** were prepared and characterized as follows.

1-[(1*S*,2*R*)-2-Hydroxy-3-(methylamino)-1-phenylpropyl]-3-methyl-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride (9). MS (ES) m/z 312.3 ($[M + H]^+$). HRMS: calcd for $C_{18}H_{21}N_3O_2 + H^+$, 312.17065; found (ESI, $[M + H]^+$), 312.17. ^{1}H NMR (DMSO-d_6) δ 8.69 (br s, 1H), 8.58 (br s, 1H), 7.53−7.58 (m, 2H), 7.31−7.37 (m, 2H), 7.25−7.31 (m, 1H), 7.20−7.24 (m, 1H), 7.13−7.17 (m, 1H), 6.98−7.09 (m, 2H), 6.05 (m, 1H), 5.31 (d, J = 8.84 Hz, 1H), 5.09−5.23 (m, 1H), 3.36 (br s, 3H), 2.99−3.08 (m, 1H), 2.86−2.96 (m, 1H), 2.55 (t, J = 8.00 Hz, 3H).

1-Ethyl-3-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride (10). MS (ES) m/z 326.2 ($[M + H]^+$). HRMS: calcd for $C_{19}H_{23}N_3O_2 + H^+$, 326.18630; found (ESI, $[M + H]^+$), 326.1845. ^{1}H NMR (DMSO-d_6) δ 8.51 (br s, 2H), 7.53−7.58 (m, 2H), 7.33−7.38 (m, 2H), 7.28−7.31 (m, 1H), 7.19−7.24 (m, 2H), 6.96−7.09 (m, 2H), 6.06 (d, J = 7.02 Hz, 1H), 5.30 (d, J = 8.84 Hz, 1H), 5.07−5.18 (m, 1H), 3.81−3.96 (m, 2H), 2.87−3.10 (m, 2H), 2.54−2.59 (m, 3H), 1.22 (t, J = 7.15 Hz, 3H).

1-[(1*S*,2*R*)-2-Hydroxy-3-(methylamino)-1-phenylpropyl]-3-propyl-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride (11). HRMS: calcd for $C_{20}H_{25}N_3O_2 + H^+$, 340.20195; found (ESI, $[M + H]^+$), 340.2007. ^{1}H NMR (DMSO-d_6) δ 8.45−8.68 (m, 2H), 7.50−7.58 (m, 2H), 7.32−7.39 (m, 2H), 7.25−7.32 (m, 1H), 7.21 (d, J = 8.32 Hz, 2H), 6.95−7.10 (m, 2H), 6.08 (d, J = 7.02 Hz, 1H), 5.30 (d, J = 8.58 Hz, 1H), 5.06−5.21 (m, 1H), 3.78−3.87 (m, 2H), 2.99 (d, J = 3.64 Hz, 2H), 2.53−2.60 (m, 3H), 1.61−1.73 (m, 2H), 0.85 (t, J = 7.41 Hz, 3H).

1-[(1*S*,2*R*)-2-Hydroxy-3-(methylamino)-1-phenylpropyl]-3-isopropyl-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride (12). MS (ES) m/z 340.3 ($[M + H]^+$). HRMS: calcd for $C_{20}H_{25}N_3O_2 + H^+$, 340.20195; found (ESI, $[M + H]^+$), 340.2012. ^{1}H NMR (DMSO-d_6) δ 8.57 (br s, 2H), 7.55 (d, J = 7.54 Hz, 2H), 7.25−7.39 (m, 4H), 7.18−7.24 (m, 1H), 6.96−7.06 (m, 2H), 6.07 (d, J = 6.76 Hz, 1H), 5.30 (d, J = 8.58 Hz, 1H), 5.13 (d, J = 8.84 Hz, 1H), 4.65 (quin, J = 6.89 Hz, 1H), 2.85−3.04 (m, 2H), 2.56 (m, 3H), 1.46 (d, J = 7.02 Hz, 6H).

1-Cyclobutyl-3-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride (14). MS (ES) m/z 352.2 ($[M + H]^+$). HRMS: calcd for $C_{21}H_{25}N_3O_2 + H^+$, 352.202; found (ESI, $[M + H]^+$), 352.207. ^{1}H NMR (DMSO-d_6) δ 8.56 (br s, 2H), 7.50−7.63 (m, 2H), 7.31−7.40 (m, 3H), 7.21−7.31 (m, 2H), 6.98−7.08 (m, 2H), 6.04 (d, J = 7.02 Hz, 1H), 5.30 (d, J = 8.84 Hz, 1H), 5.06−5.22 (m, 1H), 4.86 (m, 1H), 3.01 (m, 1H), 2.76−2.91 (m, 3H), 2.56 (s, 3H), 2.22−2.37 (m, 2H), 1.72−1.97 (m, 2H).

1-Cyclopentyl-3-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride (15). MS (ESI) m/z 366 ($[M + H]^+$). ^{1}H NMR (DMSO-d_6) δ 8.68 (br s, 1H), 8.56 (br s, 1H), 7.55 (d, J = 7.28 Hz, 2H), 7.32−7.38 (m, 2H), 7.19−7.31 (m, 3H), 6.98−7.07 (m, 2H), 6.06 (d, J = 8.00 Hz, 1H), 5.31 (d, J = 8.84 Hz, 1H), 4.78 (t, J = 8.45 Hz, 1H), 3.34−3.42 (m, 1H), 2.99 (br s, 2H), 2.56 (t, J = 5.33 Hz, 3H), 1.86−2.10 (m, 6H), 1.60−1.72 (m, 2H).

1-Ethyl-5-fluoro-3-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2*H*-benzimidazol-2-one hydrochloride (16). MS (ES) m/z 344.2 ($[M + H]^+$). HRMS: calcd for $C_{19}H_{22}FN_3O_2 + H^+$, 344.17688; found (ESI, $[M + H]^+$), 344.175. ^{1}H NMR (DMSO-d_6) δ 8.56 (br s, 2H), 7.48−7.61 (m, 2H), 7.28−7.35 (m, 2H), 7.21−7.28 (m, 1H), 7.13−7.20 (m, 2H), 6.85 (ddd, J = 2.47, 8.58, 10.01 Hz, 1H), 6.02 (d, J = 6.50 Hz, 1H), 5.26 (d, J = 8.58 Hz, 1H), 5.01−5.20 (m, 1H), 3.83 (q, J = 7.02 Hz, 2H), 2.83−3.03 (m, 2H), 2.42−2.45 (m, 3H), 1.12−1.20 (m, 3H).

1-Ethyl-4-fluoro-3-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1,3-dihydro-2*H*-benzimidazol-2-one Hydrochloride (17). MS (ES) m/z 344.2 ($[M + H]^+$). HRMS: calcd for $C_{19}H_{22}FN_3O_2 + H^+$, 344.17688; found (ESI, $[M + H]^+$), 344.1768. ^{1}H NMR (DMSO-d_6) δ 8.72 (br s, 1H), 8.60 (br s, 1H), 7.45 (d, J = 7.54 Hz, 2H), 7.32−7.39 (m, 2H), 7.25−7.32 (m, 1H), 7.04−7.13 (m, 2H), 6.91 (ddd, J = 1.43, 7.86, 12.02 Hz, 1H), 6.02 (d, J = 7.54 Hz, 1H), 5.38 (d, J = 9.62 Hz, 1H), 5.06−5.17 (m, 1H), 3.91 (q, J = 7.19 Hz, 2H), 3.08 (br s, 1H), 2.98 (br s, 1H), 2.54−2.60 (m, 3H), 1.22 (t, J = 7.15 Hz, 3H).

5-Fluoro-3-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1-propyl-1,3-dihydro-2*H*-benzimidazol-2-one Hydrochloride (18). MS (ES) m/z 358.2 ($[M + H]^+$). HRMS: calcd for $C_{20}H_{24}FN_3O_2 + H^+$, 358.19253; found (ESI, $[M + H]^+$), 358.1895. ^{1}H NMR (DMSO-d_6) δ 8.53−8.71 (m, 2H), 7.58 (d, J = 8.06 Hz, 2H), 7.33−7.39 (m, 2H), 7.27−7.33 (m, 1H), 7.17−7.23 (m, 2H), 6.85−6.92 (m, 1H), 6.07 (d, J = 6.50 Hz, 1H), 5.31 (d, J = 8.58 Hz, 1H), 5.10−5.20 (m, 1H), 3.81 (t, J = 6.89 Hz, 2H), 2.84−3.08 (m, 2H), 2.56 (t, J = 5.07 Hz, 3H), 1.66 (q, J = 7.02 Hz, 2H), 0.84 (t, J = 7.28 Hz, 3H).

4-Fluoro-3-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-phenylpropyl]-1-isopropyl-1,3-dihydro-2*H*-benzimidazol-2-one Hydrochloride (19). MS (ES) m/z 358.4 ($[M + H]^+$). HRMS: calcd for $C_{20}H_{24}FN_3O_2 + H^+$, 358.19253; found (ESI, $[M + H]^+$), 358.19347. ^{1}H NMR (DMSO-d_6) δ 8.74 (br s, 1H), 8.60 (br s, 1H), 7.42−7.48 (m, 2H), 7.25−7.37 (m, 3H), 7.21 (d, J = 7.28 Hz, 1H), 7.05 (td, J = 4.94, 8.19 Hz, 1H), 6.90 (dd, J = 8.58, 11.96 Hz, 1H), 6.02 (br s, 1H), 5.34−5.43 (m, 1H), 5.06−5.16 (m, 1H), 4.65 (quin, J = 6.95 Hz, 1H), 2.91−3.11 (m, 2H), 2.56 (t, J = 5.46 Hz, 3H), 1.45 (d, J = 4.68 Hz, 6H).

1-Ethyl-3-[1-(3-fluoro-phenyl)-2-hydroxy-3-methylamino-propyl]-1,3-dihydro-benzimidazol-2-one Hydrochloride (20). MS (ES) m/z 344.2 ($[M + H]^+$). HRMS: calcd for $C_{19}H_{22}FN_3O_2 + H^+$, 344.17688; found (ESI, $[M + H]^+$), 344.178. ^{1}H NMR (DMSO-d_6) δ 8.54−8.84 (m, 2H), 7.26−7.47 (m, 4H), 7.19−7.26 (m, 1H), 7.00−7.19 (m, 3H), 6.13 (d, J = 6.76 Hz, 1H), 5.35 (d, J = 8.84 Hz, 1H), 5.05−5.23 (m, 1H), 3.90 (q, J = 7.19 Hz, 2H), 2.99 (br s, 2H), 2.54−2.60 (m, 3H), 1.22 (t, J = 7.15 Hz, 3H).

1-Ethyl-4-fluoro-3-[(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-(3-fluorophenyl)-propyl]-1,3-dihydro-2*H*-benzimidazol-2-one Hydrochloride (21). MS (ES) m/z 362.1 ([M + H]. HRMS: calcd for $C_{19}H_{21}F_2N_3O_2 + H^+$, 362.16746; found (ESI, $[M + H]^+$), 362.1666. ^{1}H NMR (DMSO-d_6) δ 8.57−8.81 (m, 2H), 7.26−7.49 (m, 2H), 7.02−7.25 (m, 4H), 6.87−6.98 (m, 1H), 6.11 (d, J = 7.80 Hz, 1H), 5.40 (d, J = 9.62 Hz, 1H), 5.01−5.16 (m, 1H), 3.91 (q, J = 7.11 Hz, 2H), 2.90−3.12 (m, 2H), 2.54−2.60 (m, 3H), 1.22 (t, J = 7.15 Hz, 3H).

4-Fluoro-3-[(1*S*,2*R*)-1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)-propyl]-1-isopropyl-1,3-dihydro-2*H*-benzimidazol-2-one Hydrochloride (22). MS (ES) m/z 376.2 ($[M + H]^+$). HRMS: calcd for $C_{20}H_{23}F_2N_3O_2 + H^+$, 376.18311; found (ESI, $[M + H]^+$), 376.1845. ^{1}H NMR (DMSO-d_6) δ 8.67 (br s, 1H), 8.55 (br s, 1H), 7.40 (td, J = 6.24, 8.06 Hz, 1H), 7.31 (d, J = 10.40 Hz, 1H), 7.11−7.26 (m, 3H), 7.03−7.10 (m, 1H), 6.93 (dd, J = 8.45, 12.09 Hz, 1H), 6.08 (d, J = 7.80 Hz, 1H), 5.33−5.45 (m, 1H), 5.01−5.16 (m, 1H), 4.57−4.72 (m, 1H), 2.89−3.13 (m, 2H), 2.54−2.61 (m, 3H), 1.46 (d, J = 4.16 Hz, 6H).

4-Fluoro-3-[(1*S*,2*R*)-1-(3-fluorophenyl)-2-hydroxy-3-(methylamino)propyl]-1-phenyl-1,3-dihydro-2*H*-benzimidazol-2-one Hydrochloride (23). HRMS: calculated for $C_{23}H_{21}F_2N_3O_2 + H^+$, 410.16746; found (ESI, $[M + H]^+$), 410.1662. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (br s, 1H), 8.57 (br s, 1H), 7.57−7.52 (m, 4H), 7.47−7.43 (m, 1H), 7.40−7.33 (m, 2H), 7.26 (d, J = 7.82 Hz, 1H), 7.12 (dt, J = 2.18 and 8.58 Hz, 1H), 7.05−6.95 (m, 2H), 6.81 (dd, J = 0.89 and 7.68 Hz, 1H), 6.05 (d, J = 7.94 Hz, 1H), 5.42 (d, J = 9.36 Hz. 1H), 5.09−5.07 (m, 1H), 3.25−3.20 (m, 1H), 3.02−2.98 (m, 1H) and 2.53 (br s, 3H).

3-[(1*S*,2*R*)-3-(Ethylamino)-2-hydroxy-1-phenylpropyl]-5-fluoro-1-isopropyl-1,3-dihydro-2*H*-benzimidazol-2-one Hydrochloride (24). MS (ESI) *m*/*z* 372.21 ([M + H]$^+$). HRMS: calcd for $C_{21}H_{26}FN_3O_2 + H^+$, 372.20818; found (ESI, [M + H]$^+$), 372.2099. ^{1}H NMR (DMSO-d_6) δ 8.42−8.62 (m, 2H), 7.53−7.62 (m, 2H), 7.34−7.41 (m, 2H), 7.27−7.34 (m, 2H), 7.21 (dd, *J* = 2.34, 9.36 Hz, 1H), 6.81−6.91 (m, 1H), 6.04 (d, *J* = 6.50 Hz, 1H), 5.27 (d, *J* = 8.32 Hz, 1H), 5.08−5.19 (m, 1H), 4.62 (quin, *J* = 7.02 Hz, 1H), 2.84−3.07 (m, 4H), 1.44 (d, *J* = 7.02 Hz, 6H), 1.13−1.19 (m, 3H).

Acknowledgment. The authors wish to thank the Discovery Analytical Chemistry group for compound analysis. We also thank our management Drs. Ronald Magolda, Magid Abou-Gharbia, and Menelas Pangalos for their support.

Supporting Information Available: Analytical HPLC purity data of all tested compounds, synthetic procedures for ((2*R*,3*R*)-3-(3-fluorophenyl)oxiran-2-yl)methanol, and ((2*R*,3*R*)-3-phenyloxiran-2-yl)methanol. This material is available free of charge via the Internet at http://pubs.acs.org.

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