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Synthesis and activity of novel 1- or 3-(3-amino-1-phenyl propyl)-1,3-dihydro-2*H*-benzimidazol-2-ones as selective norepinephrine reuptake inhibitors

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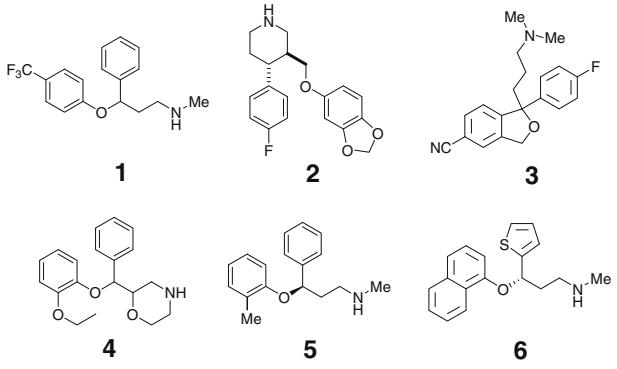
ABSTRACT

A series of novel 1- or 3-(3-amino-1-phenyl propyl)-1,3-dihydro-2*H*-benzimidazol-2-ones as selective norepinephrine reuptake inhibitors was discovered. Several compounds such as **15** and **20** showed good hNET potency. Compounds **15** and **20** also displayed excellent selectivity at hNET that appeared superior to those of reboxetine and atomoxetine (**4** and **5**).

The serotonin (SERT), norepinephrine (NET), and dopamine transporters (DAT) are integral membrane proteins that uptake 5-hydroxytryptamine (5-HT, serotonin), norepinephrine (NE), and dopamine (DA), respectively, 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 thus making transporters an important target for drug development. In the last two decades, numerous selective serotonin reuptake inhibitors (SRIs) and norepinephrine reuptake inhibitors (NRIs) have been developed for the treatment of psychiatric disorders.[3,4] For example, selective SRIs such as fluoxetine (**1**), paroxetine (**2**), and citalopram (**3**) have been used extensively to treat symptoms including depression and panic disorders. Whereas fewer selective NRIs have been approved for CNS diseases. Reboxetine (**4**), a racemic mixture, has been developed for the treatment of major depressive disorder (MDD).[5,6] Clinical evidences also suggested that reboxetine may have efficacy in the treatment of chronic pain such as fibromyalgia and chronic low back pain.[7] Atomoxetine (**5**), another selective NRI, has been approved for attention deficit hyperactivity disorder (ADHD).[8] In addition, considerable research has focused on development of compounds that include both the inhibition of 5-HT and NE reuptake.[2,3] These efforts have led to the development of compounds such as venlafaxine,[9] desvenlafaxine,[10] and duloxetine (**6**)[11] that are dual 5-HT and NE reuptake inhibitors (SNRI). Venlafaxine, desvenlafaxine, and duloxetine are marketed for treatment of MDD.[12–15] Duloxetine has also been approved for diabetic neuropathy,[16] fibromyalgia,[17] and stress urinary incontinence (SUI).[18]



Although numerous monoamine transporter inhibitors are clinically available, there is still considerable interest[19–27] in developing novel compounds with improved metabolic and pharmacological (treatment onset and response rate or efficacy) properties.

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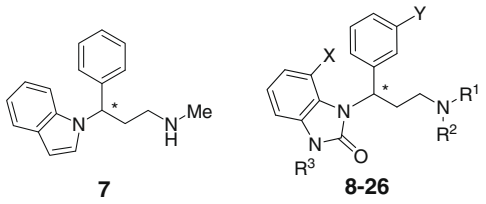
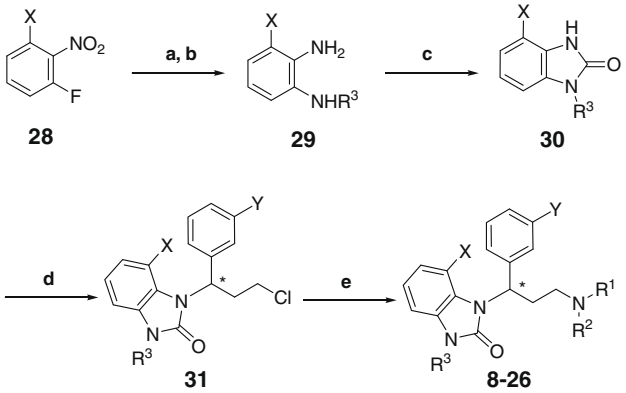
Our interest in understanding the role of NE in CNS disorders and its therapeutic potentials[7,28] led us to undertake a program to develop selective NRIs. In a previous report, we disclosed a series of 3-(1*H*-indol-1-yl)-3-arylpropan-1-amines (e.g., **7**) that was designed to capture the NRI pharmacophore of the aryloxypropanamines (e.g., atomoxetine **4**). To our surprise, these compounds displayed dual acting NE and 5-HT reuptake inhibition.[29,30] In an effort to expand the SAR of this series and identify new compounds selective for NET we further elaborated the indole ring and designed oxindole and benzimidazolone based propanamines. Interestingly, replacement of the indole moiety by oxindoles and benzimidazolones had a marked effect on the NET selectivity over SERT and led to two new series of selective NRIs. Results of oxindole analogs were recently disclosed.[31] Herein we report the synthesis and in vitro activities of benzimidazolone based propanamines and their analog (**8–27**).



7 **8-26**

The preparation of 1- or 3-(3-amino-1-phenylpropyl)-benzimidazol-2-ones is illustrated in Scheme 1. Substituted 1-fluoro-2-nitrobenzenes **28** were treated with an appropriate alkylamine or aniline followed by a palladium-mediated reduction of the nitro moiety to afford benzene-1,2-diamines **29**. Ring closure of compounds **29** to generate benzimidazolones **30** was achieved using 1,1′-carbonyldiimidazole (CDI). With the key headpiece **30** in hand, it was attached to 3-chloro-1-phenylpropane to deliver **31** via Mitsnobu's coupling protocol by replacing the hydroxyl group of (*R*)- or (*S*)-3-chloro-1-phenylpropan-1-ol. (*S*)-3-Chloro-1-(3-fluorophenyl)propan-1-ol was not commercially available and was prepared by reducing 3-chloro-1-(3-fluorophenyl)propan-1-one with BH_3 in the presence of catalytic (*R*)-2-methyl-CBS-oxazaborolidine following Corey's conditions.[32] Compounds **31** were subjected to an alcoholic solution of alkyl amines in the presence of potassium iodide to furnish target compounds **8–26**. Compound **27** was prepared in a similar fashion as described for **8–26** starting from commercially available benzo[*d*]thiazol-2(3*H*)-one.



28 **29** **30**

31 **8-26**

Scheme 1. Synthesis of 1- or 3-(3-amino-1-phenylpropyl)-benzimidazol-2-ones. Reagents and conditions: (a) R^3NH_2, THF, rt, sealed tube, 70–95%; when R^3 = Aryl, *n*-BuLi, THF, −78 to 0 °C, 30–60%; (b) $NaBH_4$, Pd/C (10%), THF/MeOH, rt, N_2, 50–90% or H_2, Pd/C (10%), EtOH, rt, >90%; (c) CDI, THF, rt, 60–90%; (d) (*R*)- or (*S*)-3-chloro-1-arylpropan-1-ol, DIAD, Ph_3P, THF, rt, N_2; 30–70%; (e) KI, MeOH, NHR^1R^2, 30–80%.

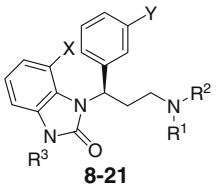
The new 1- or 3-(3-amino-1-phenylpropyl)-benzimidazol-2-ones (**8–26**) and (*R*)-3-(3-(methylamino)-1-phenylpropyl)benzo[*d*]thiazol-2(3*H*)-one (**27**) were evaluated in vitro for their ability to inhibit both the uptake of NE in MDCK-Net6 cells stably transfected with human NET (hNET) and 5-HT in JAR cells stably transfected with the human serotonin transporter (hSERT).[23] Selected compounds were then assayed for inhibition of radioligand binding to the human dopamine transporter (hDAT).[23] The results of these studies are summarized in Tables 1 and 2.

Since a majority of compounds from the indole series did not show a stereochemical preference for NET potency,[30] we decided to start with the (*R*)-enantiomers for the structure–activity relationship of the benzimidazolone-derived propanamines. The inhibitory activities of these compounds at human NET, SERT, and DAT are listed in Table 1. Examining inhibition activities of the analogs with different *N*-substituents (R^3) indicated that the size and nature of the R^3 group had significant impact on hNET potency. The smaller methyl and larger cyclopentyl and cyclohexyl substitutions at the R^3 position resulted in compounds (**8**, **18**, and **19**) with moderate hNET potency (IC_{50} = 201–463 nM). However, the intermediate sized ethyl (**10**), *n*-propyl (**14**), and *i*-propyl (**15**) analogs had increased potency with IC_{50} values ranging from 22–44 nM. The cyclopropyl analog **13** (166 nM) showed moderate hNET potency and was >5-fold less potent than its propyl congeners **14** and **15**. The most potent compounds evaluated at hNET from this series were **20** and **21** (IC_{50} < 10 nM) in which a phenyl moiety was attached to the benzimidazolone at the R^3 position. Fluorination on the benzimidazolone and/or pendent phenyl ring did not significantly change the hNET potency. For example, compounds **10** and **12** had similar hNET potency with IC_{50} values of 44 and 19 nM, respectively, in the hNET functional assay. Fluorinated **21** also had similar hNET potency comparable to its des-fluorine analog **20** (IC_{50} = 6 and 9 nM). Consistent with the previous SAR trend,[30] methylamino compound **16** was more potent at hNET than its dimethylamino analog **17**. In addition, compound **10** was significantly more potent at hNET than its unsubstituted and ethyl analogs (**9** and **11**) indicating methyl substitution is preferred on the propanamine. Benzothiazolone analog **27** showed moderate potency with a hNET IC_{50} value of 121 nM.

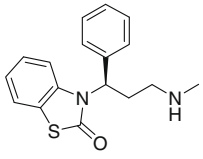
In general, hSERT and hDAT inhibition by benzimidazolone analogs as illustrated in Table 1 were weak. For the hDAT-binding affinity, all compounds that were examined had <50% inhibition of [^{3}H]WIN-35,428 binding to hDAT at a concentration of 10 μM indicating excellent hNET selectivity over hDAT. For the hNET selectivity against hSERT, the ratio derived from the hSERT vs. hNET IC_{50} ranged from 16 to >400 indicating improved selectivity compared to those of the indole leads such as **7**.[30] Among the most potent analogs were compounds **15** and **20** of which their hNET selectivity over hSERT (>300-fold) were superior to those of reboxetine and atomoxetine (16- and 81-fold).

To determine the stereochemical preference of the benzimidazolone series, the selected (*S*)-enantiomers of corresponding potent NRIs from this series were prepared and their inhibition activities at monoamine transporters are listed in Table 2. When compared to their (*R*)-enantiomers, the (*S*)-enantiomers examined were significantly less potent at hNET. For example, (*S*)-**24** (21% inhibition at 1 μM) and **26** (IC_{50} = 215 nM) were over 20-fold less potent than **15** (IC_{50} = 22 nM) and **20** (IC_{50} = 9 nM). In contrast to the hNET potency trend, the (*S*)-enantiomers evaluated had greater or equivalent hSERT potency compared to their (*R*)-enantiomers. For example, compound **16** and **25** had similar hSERT potency with IC_{50} values of 1208 and 1408 nM, respectively while (*S*)-**26** (IC_{50} = 273 nM) was about 10-fold more potent than **20** (IC_{50} = 2995 nM). Finally, three (*S*)-enantiomers tested had similar hDAT-binding affinity compared to their (*R*)-enantiomers suggesting that stereochemistry may not play a major role in their binding to hDAT.

Table 1
Inhibitory activities of (*R*)-1- or 3-(3-amino-1-phenylpropyl)-benzimidazol-2-ones and reference compounds at hNET, hSERT and hDAT



8-21

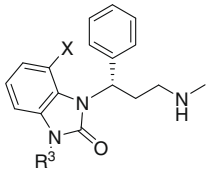


27

Compound	X	Y	R^1	R^2	R^3	hNET IC_{50}[a] (nM)	hSERT IC_{50}[b] (nM)	hSERT IC_{50}/hNET IC_{50}[c]	hDAT% inh. at 10 μM[d] (%)
4						3	242	81	
5						3	48	16	
7						47	327	7	
8	H	H	H	Me	Me	463	10%[e]		12
9	H	H	H	H	Et	51%[e]			
10	H	H	H	Me	Et	44	4311	98	4
11	H	H	H	Et	Et	27%[e]			
12	F	F	H	Me	Et	19	28%[e]		14
13	H	H	H	Me	*c*-Pro	166	4565	28	7
14	H	H	H	Me	*n*-Pro	32	3100	97	3
15	H	H	H	Me	*i*-Pro	22	2%[e,f]	~450[g]	11
16	F	H	H	Me	*i*-Pro	30	1208	40	5
17	F	H	Me	Me	*i*-Pro	27%[e]			
18	H	H	H	Me	*c*-Pent	201	16%[e]		22
19	H	H	H	Me	*c*-Hex	311	20%[e]		24
20	H	H	H	Me	Ph	9	2995	333	33
21	F	H	H	Me	2′-F-Ph	6	483	80	
27						121	1910	16	36

[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 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.
[c] Unitless value as a ratio in which higher numbers represent relatively greater NET selectivity.
[d] Inhibition of [^{3}H]WIN-35,428 binding to membranes from CHO cells expressing recombinant human dopamine transporter (hDAT). Mazindol (22.1 ± 6.5 nM) was used as a standard.
[e] Percent inhibition measured at a concentration of 1 μM.
[f] Fifty-three percent inhibition was observed at a concentration of 10 μM.
[g] Estimated value based on 53% inhibition at 10 μM.

Table 2
Inhibitory activities of (*S*)-1- or 3-(3-amino-1-phenylpropyl)-benzimidazol-2-ones at hNET, hSERT, and hDAT



Compound	X	R^3	hNET IC_{50}[a] (nM)	hSERT IC_{50}[b] (nM)	hDAT% inh. at 10 μM[c] (%)
22	H	*c*-Pro	25%[d]		
23	H	*n*-Pro	627	166	5
24	H	*i*-Pro	21%[d]		
25	F	*i*-Pro	1053	1408	31
26	H	Ph	215	273	23

[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 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.
[c] Inhibition of [^{3}H]WIN-35,428 binding to membranes from CHO cells expressing recombinant human dopamine transporter (hDAT). Mazindol (22.1 ± 6.5 nM) was used as a standard.
[d] Percent inhibition measured at a concentration of 1 μM.

In summary, a new series of 1- or 3-(3-amino-1-phenylpropyl)benzimidazol-2-ones were evaluated for activities of monoamine transporter inhibition. In contrast to indole analogs, the (*R*)-enantiomers from this series were more potent at hNET than their (*S*)-analogs. (*R*)-enantiomers also demonstrated improved hNET selectivity against hSERT. Several compounds such as **15** and **20** showed good hNET potency and excellent selectivity against hSERT and hDAT.

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References and notes

1. Gether, U.; Andersen, P. H.; Larsson, O. M.; Schousboe, A. *Trends Pharmacol. Sci.* **2006**, *27*, 375.
2. Liu, S.; Molino, B. F. *Ann. Reports Med. Chem.* **2007**, *42*, 13.
3. Chen, Z.; Skolnick, P. *Expert Opin. Investig. Drugs* **2007**, *16*, 1365.
4. Iversen, L. *Br. J. Pharmacol.* **2006**, *147*, S82.
5. Scates, A. C.; Doraiswamy, P. M. *Ann. Pharmacother.* **2000**, *34*, 1302.
6. Kasper, S.; El Giamal, N.; Hilger, E. *Expert Opin. Pharmacother.* **2000**, *1*, 771.
7. Krell, H. V.; Leuchter, A. F.; Cook, I. A.; Abrams, M. *Psychosomatics* **2005**, *46*, 379.
8. Christman, A. K.; Fermo, J. D.; Markowitz, J. S. *Pharmacotherapy* **2004**, *24*, 1020.
9. Bolden-Watson, C.; Richelson, E. *Life Sci.* **1993**, *52*, 1023.
10. Deecher, D. C.; Beyer, C. E.; Johnston, G.; Bray, J.; Shah, S.; Abou-Gharbia, M.; Andree, T. H. *J. Pharmacol. Exp. Ther.* **2006**, *318*, 657.
11. Bymaster, F. P.; Dreshfield-Ahmad, L. J.; Threlkeld, P. G.; Shaw, J. L.; Thompson, L.; Nelson, D. L.; Hemrick-Luecke, S. K.; Wong, D. T. *Neuropsychopharmacology* **2001**, *25*, 871.
12. Lieberman, D. Z.; Montgomery, S. A.; Tourian, K. A.; Brisard, C.; Rosas, G.; Padmanabhan, K.; Germain, J.-M.; Pitrosky, B. *Int. Clin. Psychopharmacol.* **2008**, *23*, 188.
13. Morton, W. A.; Sonne, S. C.; Verga, M. A. *Ann. Pharmacother.* **1995**, *29*, 387.
14. Thase, M. E.; Pritchett, Y. L.; Ossanna, M. J.; Swindle, R. W.; Xu, J.; Detke, M. J. *J. Clin. Psychopharmacol.* **2007**, *27*, 672.

15. Wellington, K.; Perry, C. M. *CNS Drugs* **2001**, *15*, 643.
16. Smith, T.; Nicholson, R. A. *Vasc. Health Risk Manage.* **2007**, *3*, 833.
17. Russell, I. J.; Mease, P. J.; Smith, T. R.; Kajdasz, D. K.; Wohlreich, M. M.; Detke, M. J.; Walker, D. J.; Chappell, A. S.; Arnold, L. M. *Pain* **2008**, *136*, 432.
18. Thor, K. B.; Kirby, M.; Viktrup, L. *Int. J. Clin. Pract.* **2007**, *61*, 1349.
19. Chen, C.; Dyck, B.; Fleck, B. A.; Foster, A. C.; Grey, J.; Jovic, F.; Mesleh, M.; Phan, K.; Tamiya, J.; Vickers, T.; Zhang, M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1346.
20. Eildal Jonas, N. N.; Andersen, J.; Kristensen Anders, S.; Jorgensen Anne, M.; Bang-Andersen, B.; Jorgensen, M.; Stromgaard, K. *J. Med. Chem.* **2008**, *51*, 3045.
21. Fish, P. V.; Ryckmans, T.; Stobie, A.; Wakenhut, F. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1795.
22. Fish, P. V.; Deur, C.; Gan, X.; Greene, K.; Hoople, D.; Mackenny, M.; Para, K. S.; Reeves, K.; Ryckmans, T.; Stiff, C.; Stobie, A.; Wakenhut, F.; Whitlock, G. A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2562.
23. 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. *J. Med. Chem.* **2008**, *51*, 4038.
24. Whitlock, G. A.; Blagg, J.; Fish, P. V. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 596.
25. Whitlock, G. A.; Fish, P. V.; Fray, M. J.; Stobie, A.; Wakenhut, F. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2896.
26. Wu, D.; Pontillo, J.; Ching, B.; Hudson, S.; Gao, Y.; Fleck, B. A.; Gogas, K.; Wade, W. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4224.
27. Zhang, M.; Jovic, F.; Vickers, T.; Dyck, B.; Tamiya, J.; Grey, J.; Tran, J. A.; Fleck, B. A.; Pick, R.; Foster, A. C.; Chen, C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3682.
28. Zhou, J. *Drugs Future* **2004**, *29*, 1235.
29. Greenhouse, R.; Jaime-Figueroa, S.; Raptova, L.; Reuter, D. C.; Stein, K. A.; Weikert, R. J. 2005, WO 2005118539.
30. Mahaney, P. E.; Vu, A. T.; McComas, C. C.; Zhang, P.; Nogle, L. M.; Watts, W. L.; Sarkahian, A.; Leventhal, L.; Sullivan, N. R.; Uveges, A. J.; Trybulski, E. J. *Bioorg. Med. Chem.* **2006**, *14*, 8455.
31. McComas, C. C.; Vu, A. T.; Mahaney, P. E.; Cohn, S. T.; Fensome, A.; Marella, M. A.; Nogle, L.; Trybulski, E. J.; Ye, F.; Zhang, P.; Alfinito, P.; Bray, J.; Johnston, G.; Koury, E.; Deecher, D. C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4929.
32. Corey, E. J.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5207.