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3-(Arylamino)-3-phenylpropan-2-olamines as a new series of dual norepinephrine and serotonin reuptake inhibitors

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ABSTRACT

A series of 3-(arylamino)-3-phenylpropan-2-olamines was prepared and screened for their ability to inhibit monoamine reuptake. A number of analogues displayed significant dual norepinephrine and serotonin reuptake inhibition. Compounds in this class exhibited minimal affinity for the dopamine transporter.

Biogenic monoamine neurotransmitters, specifically serotonin (5-HT), norepinephrine (NE) and dopamine (DA), play a crucial role in various central nervous system (CNS) activities, and monoamine deficiency has been implicated in a variety of CNS disorders.[1] One approach to enhance monoaminergic neurotransmission is to inhibit its reuptake after release into the synaptic cleft. Selective serotonin reuptake inhibitors (SSRI) such as fluoxetine (**1**), paroxetine and sertraline have been widely used for the treatment of depression as well as other neuropsychiatric disorders. In contrast, fewer selective norepinephrine reuptake inhibitors (NRI) are in clinical use.[2] Atomoxetine (**2**), a moderately selective NRI, was approved for the treatment of attention deficit hyperactivity disorder (ADHD);[3] whereas racemic reboxetine (**3**), a selective NRI, is marketed in Europe for the treatment of major depressive disorder (MDD).[4] In addition, some recent data suggest that these compounds also have clinical implications in treating chronic pain disorders such as fibromyalgia and low back pain.[5] The *S,S*-enantiomer of reboxetine, a highly selective NRI, is currently in clinical studies in the US for the treatment of fibromyalgia and diabetic neuropathy. Furthermore, dual acting serotonin and norepinephrine reuptake inhibitors (SNRI) such as venlafaxine (**4**) and duloxetine (**5**) have emerged as another class of antidepressant drugs that offer improved efficacy and/or faster onset of action relative to SSRIs.[6] Duloxetine has also been shown be effective in other therapeutic indications including neuropathic pain[5a,7] and stress urinary incontinence.[8] Accordingly, considerable research efforts continue to focus on the development of pharmaceutical agents that possess norepinephrine reuptake inhibition either selectively[9,10] or in combination with serotonin reuptake inhibition (Fig. 1).[11]

Fluoxetine (**1**), atomoxetine (**2**), reboxetine (**3**), and duloxetine (**5**) all share a common aryloxypropanamine scaffold (Fig. 2). The application of this structural framework has generated a number of potent monoamine reuptake inhibitors. In our continued interest to identify novel NRIs[9] to probe their therapeutic potential, we designed a new series of 3-(arylamino)-3-phenylpropan-2-olamines based on the well-known aryloxypropanamine scaffold (Fig. 2), where the aryloxy domain is replaced by an arylamino moiety, and a hydroxyl group is incorporated into the amino side chain to mimic the β-hydroxyl of NE.[12] These compounds were then tested for their ability to block the biogenic amine

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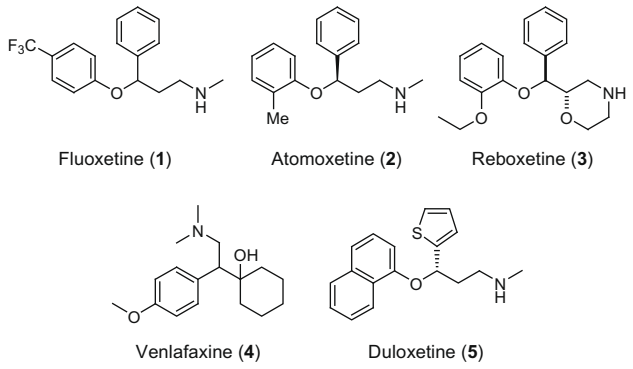


Figure 1.

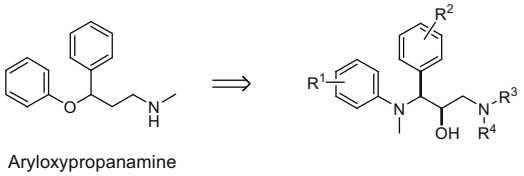


Figure 2. Scaffold evolution.

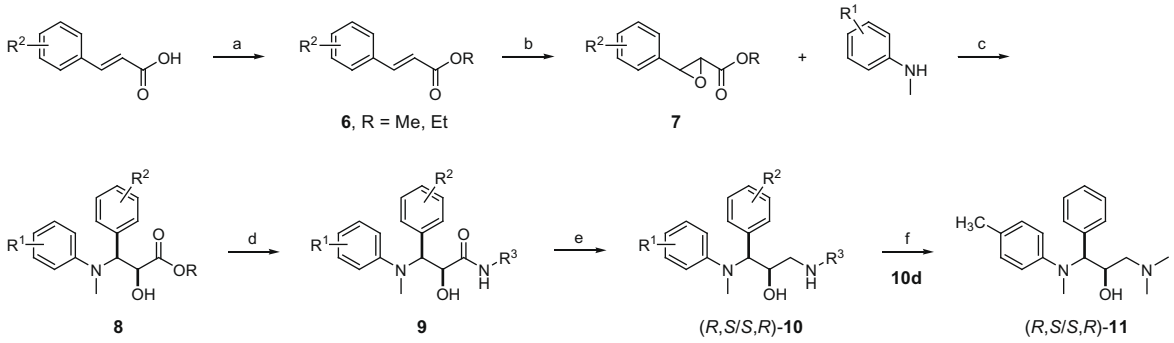
transporters. Herein we describe the synthesis and structure–activity relationship of the 3-(arylamino)-3-phenylpropan-2-olamine series.

The synthesis of the 3-(arylamino)-3-phenylpropan-2-olamines is illustrated in Scheme 1, which follows an existing route reported by Melloni.[13] All target compounds in Table 1 were prepared as racemic, single diastereomers.[14] The synthesis started from *trans*-3-phenylglycidates **7** which were obtained either from commercial sources (for R^2 = H, 4-OMe), or were prepared by a two-step reaction sequence shown in Scheme 1. Thus commercially available *trans*-cinnamic acids (R^2 = 3-F, 3-Cl, and 4-Cl) were converted to *trans*-cinnamate esters **6** either by O-methylation of the carboxylic acid group mediated by cesium carbonate, or by Fischer esterification in ethanol. Subsequent epoxidation using methyl(trifluoromethyl)dioxirane,[15] which was generated in situ from trifluoroacetone and oxone, provided *trans*-3-phenylglycidates **7**. Thermally induced epoxide ring-opening of **7** with various *N*-methylanilines afforded *syn*-esters **8** regioselectively and stereospecifically. Direct amidation of **8** by heating with excess amines (ammonia, methylamine, and ethylamine), followed by borane reduction furnished target compounds (*R,S*/*S,R*)-*syn*-**10**. Eschweiler–Clarke methylation of **10d** (R^1 = 4-Me, R^2 = H, R^3 = Me) was accomplished by heating with formaldehyde in formic acid to give compound (*R,S*/*S,R*)-**11**. Analogue (*R,R*/*S,S*)-**10v** is an *anti* diastereomer that was derived from the corresponding *anti* ester **8v** (R = Et, R^1 and R^2 = H).[16] Finally, amines **10** and **11** were converted to hydrochloride salts prior to biological evaluation.

Compounds **10** and **11** were evaluated in vitro for their ability to inhibit both the uptake of norepinephrine in MDCK-Net6 cells stably transfected with human norepinephrine transporter (hNET) and serotonin in JAR cells stably transfected with the human serotonin transporter (hSERT). Selected compounds were also evaluated for their inhibition of [^{3}H]WIN-35428 radioligand binding to the human dopamine transporter (hDAT). Detailed experimental protocols for these inhibitory assays were reported previously.[9c] Results of the in vitro screening are presented in Table 1.[17]

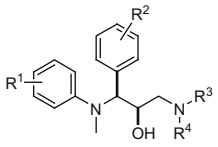
The unsubstituted 3-(arylamino)-3-phenylpropan-2-olamine **10a** displayed significant norepinephrine reuptake inhibition. Incorporating a small R^1 substituent such as methyl, 4-fluoro, chloro or methoxy group (**10b**–**k**) onto the arylamino ring offered essentially no improvement on the hNET potency relative to their unsubstituted congener **10a**. A few analogues **10d**, **10g**, and **10h** however showed comparable norepinephrine reuptake inhibition to that of **10a**. Methoxy substitution (**10i**–**k**) or substitution at the *ortho* position of this ring (**10b**, **10f** and **10i**) caused a decrease in the hNET potency compared to **10a**. For phenyl ring substitution, among several small R^2 groups investigated (**10m**–**p**), the 3-fluoro substituent (**10m**) provided an enhancement on the hNET potency relative to **10a**. Compound **10m** was the most potent NRI (hNET IC_{50} = 12 nM) among the target compounds presented. Examining the effect of the pendant amino group substitution (**10q**–**u**) revealed that this region of the molecule was rather sensitive to modification, and that there was an intrinsic preference for secondary methylamines. For example, primary amines **10q**, **10s**, and **10u** showed weaker hNET potencies compared to their corresponding secondary methylamines **10a**, **10m**, and **10p**; whereas slightly larger secondary ethylamines **10r** and **10t**, and dimethyl tertiary amine **11** resulted in a poor norepinephrine inhibitory activity. The *anti* diastereomer **10v** was substantially less potent at hNET than its *syn* diastereomer **10a**.

A number of 3-(arylamino)-3-phenylpropan-2-olamines also displayed substantial serotonin reuptake inhibition. However certain substitution on the arylamino ring exerted considerable effects on the hSERT potency. For example, the 2-methyl (**10b**) and 2-methoxy (**10i**) groups caused a more significant decrease in the inhibitory activity for serotonin than for norepinephrine, thus resulting in overall selectivity of 7–12-fold of hNET over hSERT. A similar effect was observed for compound **10l** where the phenyla-

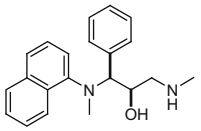


Scheme 1. Reagents and conditions: (a) MeI, Cs_2CO_3, acetone, 65 °C, 1.5 h, or EtOH, cat. H_2SO_4, 70 °C, 85–99%; (b) CF_3COCH_3, Na_2·EDTA, then oxone/$NaHCO_3$, CH_3CN/H_2O, 0 °C–rt, 12 h, 93–99%; (c) 135 °C, neat, 3 h, 75–97%; (d) For R^3 = H: NH_4OH, EtOH, 80 °C, sealed tube, 12 h, or 7 N NH_3 in MeOH, 100 °C, sealed tube, 5 h, 31–54%; For R^3 = Me: 33 wt % CH_3NH_2 in EtOH, 80 °C, sealed tube, 5 h, 80–99%; For R^3 = Et:2M $EtNH_2$ in MeOH, 120 °C, sealed tube, 48 h, 46–57%; (e) BH_3·THF, 70 °C, 1 h, 58–97%; (f) H_2C = O, HCO_2H, H_2O, 70 °C, 1 h, 86%.

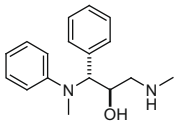
Table 1
Inhibitory activity of 3-(arylamino)-3-phenylpropan-2-olamines and reference compounds at hNET, hSERT and hDAT[a]



(*R*,*S*/*S*,*R*)-*syn*-**10a-k, 10m-u, 11**



(*R*,*S*/*S*,*R*)-*syn*-**10l**



(*R*,*R*/*S*,*S*)-*anti*-**10v**

Compound	R^1	R^2	R^3	R^4	hNET IC_{50}[b] (nM)	hSERT IC_{50}[c] (nM)	hSERT IC50/hNET IC_{50}[d]	hDAT % inh.@ 1 μM[e]
Fluoxetine (**1**)					563	10	0.02	
Atomoxetine (**2**)					3	48	16	
Reboxetine (**3**)					3	242	81	
Duloxetine (**5**)					4	3	0.75	
10a	H	H	Me	H	30	76	2.6	9
10b	2-Me	H	Me	H	217	2607	12	6
10c	3-Me	H	Me	H	61	32	0.5	8
10d	4-Me	H	Me	H	29	73	2.5	8
10e	4-F	H	Me	H	62	33	0.5	6
10f	2-Cl	H	Me	H	240	286	1.2	7
10g	3-Cl	H	Me	H	20	41	2.1	33
10h	4-Cl	H	Me	H	23	22	1	4
10i	2-OMe	H	Me	H	300	2105	7	4
10j	3-OMe	H	Me	H	400	17	0.04	1
10k	4-OMe	H	Me	H	99	3	0.03	4
10l					120	836	7	10
10m	H	3-F	Me	H	12	112	9.3	33
10n	H	3-Cl	Me	H	73	237	3.3	4
10o	H	4-Cl	Me	H	110	167	1.5	
10p	H	4-OMe	Me	H	34	55	1.6	0
10q	H	H	H	H	68	196	2.9	
10r	4-Me	H	Et	H	32%[f]			
11	4-Me	H	Me	Me	32%[f]			
10s	H	3-F	H	H	550	439	0.8	
10t	H	3-Cl	Et	H	31%[f]			
10u	H	4-OMe	H	H	156	183	1.2	10
10v[g]					1100	416	0.4	

[a] All 3-(arylamino)-3-phenylpropan-2-olamines are racemic, single diastereomers. Compounds **10a**–**u** and **11** are *syn* diastereomers with *R*,*S*/*S*,*R* stereochemistry.
[b] Inhibition of norepinephrine uptake in MDCK-Net6 cells, stably transfected with human NET. Desipramine (IC_{50} = 3.4 ± 1.6 nM) was used as a standard.
[c] Inhibition of serotonin uptake in JAR cells, stably transfected with human SERT. Fluoxetine (IC_{50} = 10 ± 3.1 nM) was used as a standard.
[d] Unitless value as a ratio in which higher values represent greater NET selectivity, a value of 1 represents no selectivity, and values approaching 0 represent SERT selectivity.
[e] Inhibition of [^{3}H]WIN-35,428 binding to membranes from CHO cells expressing recombinant hDAT. Mazindol (IC_{50} = 22 ± 6.5 nM) was used as a standard.
[f] Percent inhibition measured at a concentration of 1 μM.
[g] Compound **10v** is an *anti* diastereomer of **10a** with *R*,*R*/*S*,*S* stereochemistry.

mino moiety was replaced by a 1-naphthylamino group. In contrast, the 3-methoxy (**10j**) and 4-methoxy (**10k**) groups significantly increased the hSERT potencies while weakening the hNET inhibition (vs **10a**), thus engendering substantial selectivity for hSERT. Compound **10k** was the most potent serotonin reuptake inhibitor (hSERT IC_{50} = 3 nM) among the target molecules reported. Compound **10m** bearing a 3-fluoro substituent on phenyl ring exhibited a modest hNET selectivity of ninefold, which was due to its enhanced hNET potency and slightly reduced hSERT potency relative to **10a**.

A number of compounds were further evaluated for their dopamine transporter binding affinity and were found to be very weak ligands for hDAT (⩽33% inh. @ 1 μM).

In summary, we have designed and investigated a new series of 3-(arylamino)-3-phenylpropan-2-olamines. A number of analogues were found to be potent SNRIs. The compounds in this class displayed a wide range selectivity for either hNET or hSERT depending on the substituents on both the arylamino and phenyl rings. Moreover, the weak dopamine binding affinity of this series indicated good selectivity over the dopamine transporter. Additionally, most 3-(arylamino)-3-phenylpropan-2-olamines including **10m** and **10k** have low TPSA (35–44 Å^2), and are therefore anticipated to cross the blood-brain barrier.[18] Further exploration of this scaffold to maximize norepinephrine inhibitory activity and selectivity will be reported in future publications.

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References and notes

1. (a) Walter, M. W. *Drug. Dev. Res.* **2005**, *65*, 97–118; (b) Bymaster, F. P.; McNamara, R. K.; Tran, P. V. *Exp. Opin. Invest. Drugs* **2003**, *12*, 531–543.
2. For a recent review on norepinephrine reuptake inhibitors, see: Babu, R. P. K.; Maiti, S. N. *Heterocycles* **2006**, *69*, 539–567.
3. Christman, A. K.; Fermo, D. J.; Markowitz, J. S. *Pharmacotherapy* **2004**, *24*, 1020–1026.
4. Hajos, M.; Fleishaker, J. C.; Filipiak-Reisner, J. K.; Brown, M. T.; Wong, E. H. F. *CNS Drug Rev.* **2004**, *10*, 23–44.
5. (a) Krell, H. V.; Leuchter, A. F.; Cook, I. A.; Abrams, M. *Psychosomatics* **2005**, *46*, 379–384; (b) Berigan, T. *Can. J. Psychiatry* **2004**, *49*, 499–500.
6. Tran, P. V.; Bymaster, F. P.; McNamara, R. K.; Potter, W. Z. *J. Clin. Psychopharmacol.* **2003**, *23*, 78–86.
7. Collins, S. D.; Chessell, I. P. *Exp. Opin. Emerg. Drugs* **2005**, *10*, 95–108.
8. McCormack, P. L.; Keating, G. M. *Drugs* **2004**, *64*, 2567–2573.
9. (a) Zhang, P.; Terefenko, E. A.; McComas, C. C.; Mahaney, P.; Vu, A.; Trybulski, E.; Koury, E.; Johnston, G.; Bray, J.; Deecher, D. *Bioorg. Med. Chem. Lett.* **2008**, *18*,

6067–6070; (b) McComas, C. C.; Vu, A. T.; Mahaney, P. E.; Cohn, S. T.; Fensome, A.; Marella, M. A.; Nogel, L.; Trybulski, E. J.; Ye, F.; Zhang, P.; Alfinito, P.; Bray, J. A.; Johnston, G. H.; Koury, E. J.; Deecher, D. C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4929–4931; (c) 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*, 4038–4049; (d) 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*, 8455–8466.

10. (a) Xu, W.; Gray, D. L.; Glase, S. A.; Barta, N. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5550–5553; (b) Hudson, S.; Kiankarimi, M.; Eccles, W.; Mostofi, Y. S.; Genicot, M. J.; Dwight, W.; Fleck, B. A.; Gogas, K.; Wade, W. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4495–4498; (c) Hudson, S.; Kiankarimi, M.; Eccles, W.; Dwight, W.; Mostofi, Y. S.; Genicot, M. J.; Fleck, B. A.; Gogas, K.; Aparicio, A.; Wang, H.; Wen, J.; Wade, W. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4491–4494; (d) Wu, D.; Pontillo, J.; Ching, B.; Hudson, S.; Gao, Y.; Fleck, B. A.; Gogas, K.; Wade, W. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4224–4227; (e) Cases-Thomas, M. J.; Masters, J. J.; Walter, M. W.; Campbell, G.; Haughton, L.; Gallagher, P. T.; Dobson, D. R.; Mancuso, V.; Bonnier, B.; Giard, T.; Defrance, T.; Vanmarsenille, M.; Ledgard, A.; White, C.; Ouwerkerk-Mahadevan, S.; Brunelle, F. J.; Dezutter, N. A.; Herbots, C. A.; Lienard, J. Y.; Findlay, J.; Hayhurst, L.; Boot, J.; Thompson, L. K.; Hemrick-Luecke, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2022–2025; (f) Beadle, C. D.; Boot, J.; Camp, N. P.; Dezutter, N.; Findlay, J.; Hayhurst, L.; Masters, J. J.; Penariol, R.; Walter, M. W. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4432–4437.

11. (a) Wakenhut, F.; Fish, P. V.; Fray, M. J.; Gurrell, I.; Mills, J. E.; Stobie, A.; Whitlock, G. A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4308–4311; (b) Whitlock, G. A.; Fish, P. V.; Fray, M. J.; Stobie, A.; Wakenhut, F. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2896–2899; (c) 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*, 2562–2566; (d) Whitlock, G. A.; Blagg, J.; Fish, P. V. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 596–599.

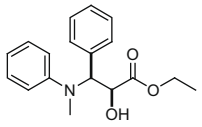
12. Introduction of a β-hydroxyl group into the aryloxypropanamine framework was described previously by Melloni and co-workers. See Ref. 13.

13. Melloni, P.; Carniel, G.; Torre, A. D.; Bonsignori, A.; Buonamici, M.; Pozzi, O.; Ricciardi, S.; Rossi, A. C. *Eur. J. Med. Chem.* **1984**, *19*, 235–242.

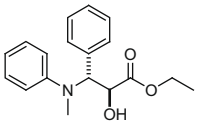
14. For detailed synthetic procedures, see: *US 2008085938 A1*.

15. Yang, D.; Wong, M.-K.; Yip, Y.-C. *J. Org. Chem.* **1995**, *60*, 3887–3889.

16. The epoxide ring-opening reaction of *trans*-ethyl 3-phenylglycidate (commercially available from Aldrich, which also contains a minor amount of the *cis* epoxide) by *N*-methylaniline gave *syn* ester **8a** as a major product and *anti* ester **8v** as a minor product. The structure determination and relative stereochemistry assignment of **8a** and **8v** were supported by one-dimensional proton NMR spectra as well as by two-dimensional NMR experiments including ^{1}H–^{1}H gCOSY (gradient Correlation Spectroscopy) and NOESY, ^{1}H–^{13}C gHSQC, gHMBC and 1,1-ADEQUATE.



8a



8v

17. Since the in vitro data in Table 1 are for racemic compounds, it is possible that the contributing effects from each enantiomer may be unequal. See Ref. 11c.

18. Hitchcock, S. A.; Pennington, L. D. *J. Med. Chem.* **2006**, *49*, 7559–7583.