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# Duloxetine (Cymbalta™), a Dual Inhibitor of Serotonin and Norepinephrine Reuptake

F. P. Bymaster,[a] E. E. Beedle,[a] J. Findlay,[b] P. T. Gallagher,[b,*] J. H. Krushinski,[a] S. Mitchell,[b] D. W. Robertson,[a] D. C. Thompson,[a] L. Wallace[b] and D. T. Wong[a]

[a]*Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA*
[b]*Eli Lilly and Company, Ltd, Lilly Research Centre, Windlesham, Surrey GU20 6PH, UK*

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**Abstract**—A series of naphthalenyloxy-arylpropylamines have been prepared and are demonstrated to be inhibitors of both serotonin and norepinephrine reuptake. One member of this series, duloxetine (Cymbalta™) has proven to be effective in clinical trials for the treatment of depression.


Major depressive disorder is currently the fourth leading cause of disease or disability worldwide and is projected to rise to second by 2020.[1] Unfortunately current monotherapy for depression for example, Selective Serotonin Reuptake Inhibitors (SSRI's) provide remission in only approximately one-third of cases in controlled trials.[2] That enhancing both serotonergic and noradrenergic neurotransmission results in antidepressant efficacy is now supported by clinical experience with duloxetine (Cymbalta™).[3]

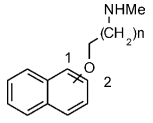
Herein we report the activity of a series of naphthalenyloxy-arylpropylamines one of which, duloxetine (**25**) demonstrates high affinity for the serotonin (5-HT) and norepinephrine (NE) transporters and has proven effective in clinical trials for the treatment of depression.[3]

The synthesis of naphthyl ethers **1**–**6** (Table 1) started from either 1- or 2-naphthol (Scheme 1) followed by alkylation with the appropriate di-halo alkane. The resultant haloalkyl ethers were converted to the methylamino ethers with methylamine in either DMF, THF or methanol in the presence of sodium iodide.

Variations in chain length and naphthalene substitution position did not produce the desired levels of NE uptake activity, however incorporation of a phenyl ring (**7**) into the amino-ether chain resulted in an improvement in both the 5-HT and the NE uptake affinity.

The synthesis of **7** started with the reduction of 3-dimethylamino-1-phenylpropan-1-one with sodium borohydride in ethanol to give 3-dimethylamino-1-phenylpropan-1-ol.[5] The aminopropanol was then arylated with 1-fluoronaphthalene, the resultant amino ether was then mono-demethylated in a two step process. Treatment with trichloroethylchloroformate and conversion of the resultant carbamate with zinc metal

**Table 1.** Binding affinities at the norepinephrine and serotonin transporters for the 1- and 2-linked naphthyl ethers compounds **1**–**6**[4]




| Compd | Naphthyl | *n* | 5-HT | NE |
|---|---|---|---|---|
| **1** | 1 | 1 | 2%[a] | 17%[c] |
| **2** | 1 | 2 | 75[b] | 25%[c] |
| **3** | 1 | 3 | 31[b] | 25.5%[c] |
| **4** | 1 | 4 | 35.5%[a] | 23%[c] |
| **5** | 2 | 2 | 23%[a] | 39%[c] |
| **6** | 2 | 3 | 32%[a] | 17%[c] |

[a]% Inhibition @ 0.1 μM.
[b]$K_i$, nM.
[c]% Inhibition @ 1 μM. Binding affinities and displacement measurements were done in triplicate.

*Corresponding author. Tel.: +44-(0)1276-483536; fax: +44-(0)1276-483525; e-mail: gallagher_p@lilly.com

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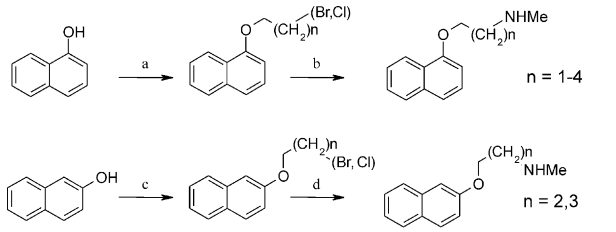
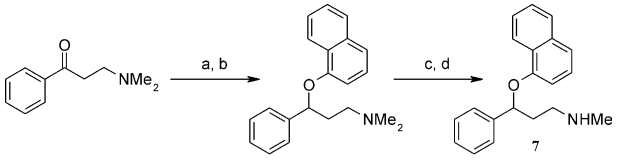



**Scheme 1.** Synthesis of naphthyl ethers **1**–**6**. Reagents and conditions: (a) NaH, DMF, and for $n=1$ $Br(CH_2)_2Br$; for $n=2$ $Br(CH_2)_3Br$; for $n=3$ $Br(CH_2)_4Br$; for $n=4$ $Br(CH_2)_5Cl$; (b) for $n=1$ & 2, $MeNH_2$, THF; for $n=3$ $MeNH_2$, MeOH; for $n=4$ $MeNH_2$, DMF, NaI; (c) NaH, DMF, for $n=2$ $Br(CH_2)_2Br$; for $n=3$ $Br(CH_2)_4Cl$; (d) for $n=2$, $MeNH_2$, THF; for $n=3$ $MeNH_2$, DMF, NaI.




**Scheme 2.** (a) $NaBH_4$, EtOH; (b) 1-fluoronaphthalene, NaH, DMA; (c) $Cl_3CCH_2OCOCl$, benzene; (d) HCOOH, Zn, DMF.

and formic acid in DMF provided the monomethylamine **7** (Scheme 2).

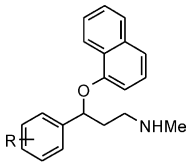
Compounds **8**–**20** in Table 2 were synthesized by the method used for compound **7**. Substitution of the phenyl ring was next attempted but both the introduction of electron donating, electron withdrawing or neutral substituents in either the 2-, 3- or 4-positions of the phenyl ring was not rewarded with improvement of affinity at the NE transporter.

A notable feature is the improvement in 5-HT uptake affinity on introducing a 4-fluoro susbtituent to the phenyl ring (**8**). As substitution of the phenyl ring did not improve the inhibition of NE uptake while maintaining inhibition of 5-HT uptake, isosteric replacement of the phenyl ring was attempted. Thus, heterocyclic alternatives to the phenyl ring of compound **7** were synthesized (Table 3).

Compounds **21**–**23** were synthesized analogously to the thiazole analogue (**24**). Thus 2-acetylthiazole was reacted with dimethylamine hydrochloride and paraformaldehyde under Mannich conditions to give 3-dimethylamino-1-thiazol-2-yl-propan-1-one (Scheme 3). The aminopropanone was reduced with sodium borohydride in methanol and the resultant alcohol was coupled to 1-fluoronaphthalene with sodium hydride in dimethylacetamide. Finally dealkylation of the tertiary amine was achieved in two steps, an intermediate phenyl carbamate was formed with phenylchlorofomate and the carbamate then hydrolyzed with sodium hydroxide in propylene glycol to give methyl-[3-(naphthalen-1-yloxy)-3-thiazol-2-yl-propyl]-amine (**24**).

Of the heterocyclic alternatives synthesized, the thienyl and furan-2-yl analogues **21**–**23** demonstrated improved 5-HT uptake inhibition, with the furan analogue (**23**) having a $K_i$ value of 0.7 nM.

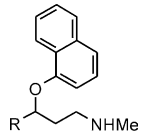
**Table 2.** Binding affinities at the norepinephrine and serotonin transporters for the substituted phenyl naphthyl ethers **7**–**20**




| Compd | R | 5-HT[a] | NE |
|---|---|---|---|
| **7** | H | 2.4 | 20[a] |
| **8** | 4-F | 0.95 | 42[a] |
| **9** | 3-Br | 7.6 | 67[a] |
| **10** | 4-Br | 4.1 | 160[a] |
| **11** | 2-$CF_3$ | 10 | 38%[b] |
| **12** | 3-$CF_3$ | 19 | 70[a] |
| **13** | 4-$CF_3$ | 14.5 | 55%[b] |
| **14** | 4-Cl | 3.8 | 78[a] |
| **15** | 2-Me | 2.0 | 110[a] |
| **16** | 3-Me | 4.0 | 40[a] |
| **17** | 4-Me | 2.1 | 36[a] |
| **18** | 2-MeO | 2.3 | 56%[b] |
| **19** | 3-MeO | 2.2 | 81[a] |
| **20** | 4-MeO | 3.5 | 74[a] |

[a] $K_i$, nM.
[b] % Inhibition @ 1 μM. Binding affinities and displacement measurements were done in triplicate.

**Table 3.** Binding affinities at the norepinephrine and serotonin transporters for the heterocyclic naphthyl ethers **21**–**24**



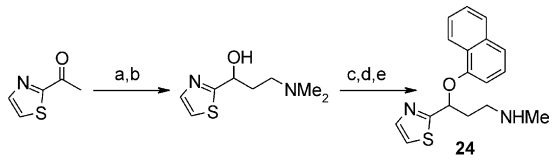

| Compd | R | 5-HT[a] | NE[a] |
|---|---|---|---|
| **7** | Phenyl | 2.4 | 20 |
| **21** | Thien-2-yl | 1.4 | 20 |
| **22** | Thien-3-yl | 1.1 | 21 |
| **23** | Furan-2-yl | 0.7 | 20 |
| **24** | Thiazol-2-yl | 6.4 | 55 |

[a] $K_i$, nM. Binding affinities were done in triplicate.

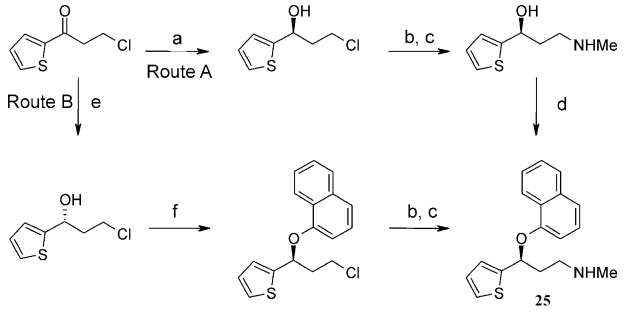
Compound **21** was then chosen for further study. Two chiral routes to the enantiomers of **21** were developed.[6]

Both routes (Scheme 4) started from a common intermediate 2-(3-chloropropionyl)thiophene and are depicted for enantiomer **25**.[7] Route A commenced with an enantioselective reduction using *R*-1-methyl-3,3-diphenyl-tetrahydropyrrolo[1,2-*c*][1,3,2]oxazaborole in the presence of borane in THF.

The resultant chloroalcohol was then transformed via the iodide to *S*-3-methylamino-1-thiophen-2-yl-propan-1-ol. This was then used in a nucleophilic displacement reaction with 1-fluoronaphthalene to give **25**. Route B utilized *S*-1-methyl-3,3-diphenyl-tetrahydropyrrolo[1,2-*c*][1,3,2]oxazaborole to produce *R*-3-chloro-1-thiophen-2-yl-propan-1-ol. This was then subjected to a Mitsunobu reaction with 1-naphthol, diethylazodicarboxylate and triphenylphosphine and the resultant chloroether

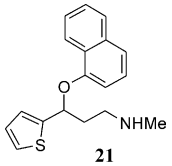



**Scheme 3.** (a) Paraformaldehyde, $(CH_3)_2NH$–HCl, 12N HCl, EtOH; (b) $K_2CO_3$, $H_2O$, $NaBH_4$, MeOH; (c) 1-fluoronaphthalene, NaH, DMA; (d) PhOCOCl, toluene; (e) NaOH, propylene glycol.




**Scheme 4.** Synthesis of **25**. Reagents and conditions: Route A (a) *R*-1-methyl-3,3-diphenyl-tetrahydro-pyrrolo[1,2-*c*][1,3,2]oxazaborole, $BH_3$, THF: (b) NaI, acetone; (c) methylamine, THF; (d) 1-fluoronaphthalene, NaH, DMA; Route B (e) *S*-1-methyl-3,3-diphenyl-tetrahydro-pyrrolo[1,2-*c*][1,3,2]oxazaborole, $BH_3$, THF: (f) 1-naphthol, DEAD, $Ph_3P$.

**Table 4.** Inhibition of norepinephrine and serotonin uptake into rat synaptosomes for the enantiomers of compound **21**[10]




| Compd | Compd | 5-HT[a] | NE[a] | DA[a] |
|---|---|---|---|---|
| **25** | ***S*-21** | 4.6 | 16 | 370 |
| **26** | ***R*-21** | 8.8 | 16 | 660 |
| **27** | Fluoxetine | 48 | 2000 | 6000 |
| **28** | Atomoxetine | 1500 | 4 | 2000 |

[a] $K_i$, nM.

was converted to *S*-methyl-[3-(naphthalen-1-yloxy)-3-thiophen-2-yl-propyl]-amine **25** with methylamine in THF.[6,8,9]

Compounds **25** and **26** were then assessed for their ability to inhibit synaptosomal uptake into rat synaptosomes (Table 4).[10] Inhibition of monoamine uptake into rat synaptosomes has been used to assess the functional ability of a compound to block re-uptake of monoamines. The resolved enantiomers **25** and **26** proved to be equipotent at the NE transporters, however compound **25** was shown to be more active at the 5-HT transporter and was selected for further study.[10]

Compound **25** was also evaluated for its ability to inhibit the reuptake of 5-HT, NE and dopamine at the respective human transporters. Thus compound **25** was shown to inhibit monoamine uptake with $K_i$'s (nM) of 0.8, 7.5 and 240 at the 5-HT, NE and dopamine uptake transporters, respectively.

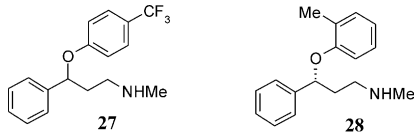



**Figure 1.**

From Table 4 it can also be seen that by comparison to the SSRI fluoxetine (**27**) and the selective NE reuptake inhibitor atomoxetine (**28**) (Fig. 1), that **25** is a potent dual inhibitor of 5-HT and NE.

Further in vivo evaluation of **25** was also made, thus in microdialysis experiments to determine the increase in synaptic concentration of NE and 5-HT in rat, following administration of **25**, at 10 mg/kg po increases in basal levels of NE and 5-HT by $208 \pm 31\%$ and $353 \pm 62\%$, respectively, were found. Full microdialysis results will be published elsewhere.

In summary **25** inhibits binding to human cell lines expressing NE and 5-HT transporters, inhibits the reuptake of NE and 5-HT in rat synaptosomes of 5-HT and NE and increases NE and 5-HT in rat pre-frontal cortex. Compound **25** has been progressed to the clinic (as duloxetine hydrochloride, Cymbalta™) and has been shown to be effective in the treatment of depression.[3]

## Acknowledgements

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The method for determining the $K_i$ is the same for each transporter, thus at the NE transporter the following protocol was followed.
[$^3$H]-Nisoxetine binding assay: Each well of a 96-well microtitre plate was set up to contain the following:
50 μL 2nM-[N-methyl-$^3$H]-Nisoxetine hydrochloride (70–87 Ci/mmol) (NEN)
75 μL Assay buffer (50mM Tris·HCl pH 7.4 containing 300 mM NaCl and 5 mM KCl)

25 μL Test compound, assay buffer (total binding) or 10 μM Desipramine HCl (non-specific binding)
50 μL WGA PVT SPA Beads (10 mg/mL)
50 μL Membrane (0.2 mg protein per mL)
The microtitre plates were incubated at room temperature for 10 h prior to reading in a Trilux scintillation counter. The results were analyzed using an automatic spline fitting programme (Multicalc, Packard, Milton Keynes, UK) to provide $K_i$ values for each of the test compounds.

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