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Bicyclo[2.2.1]heptanes as Novel Triple Re-uptake Inhibitors for the Treatment of Depression

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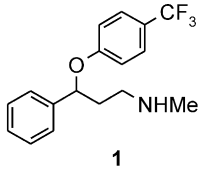
Abstract—A series of substituted naphthyl containing chiral [2.2.1] bicycloheptanes were prepared utilizing asymmetric Diels–Alder chemistry. This paper describes structure–activity relationships in this series. The *N*-methyl 2-naphthyl analogue (**16d**) and its desmethyl analogue (**17d**) are active triple re-uptake inhibitors both in vivo and in vitro.

Introduction

Approaches to antidepressant therapy continue to be a significant area of central nervous system (CNS) research. Over the past 40 years monoamine re-uptake inhibition has been an important neuropharmacological strategy for the treatment of depression and in the modulation of mood.[1,2] The biogenic monoamines serotonin (5HT), norephinephrine (NE) and dopamine (DA) are amongst the most intensely studied of the 200+ chemical entities known to function as neurotransmitters in the mammalian CNS.



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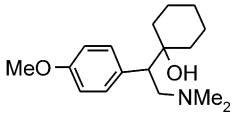

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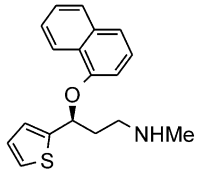

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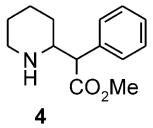
The use of selective serotonin re-uptake inhibitors (SSRIs) in the treatment of depression is well known, for example Prozac (fluoxetine **1**). There are a number of issues with the use of SSRIs: latency of onset (typically 2–3 weeks), lack of efficacy (~30% non-responders) and unwanted side effects such as sexual dysfunction, sleep disturbances, nausea, anxiety and reduced appetite. A newer strategy to address some of these issues has been the development of dual re-uptake inhibitors, a combination of 5HT and NE re-uptake inhibition (SNRIs), for example Efexor (venlafaxine **2**) and Cymbalta (duloxetine **3**).



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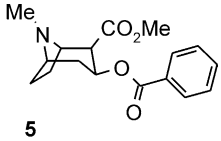

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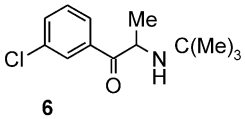

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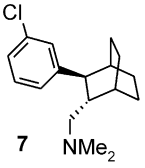

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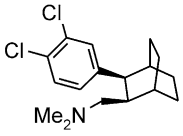

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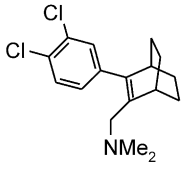

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Although DA dysfunction has been implicated in core depressive symptoms the potential of DA modulation in antidepressant therapy is less certain. A potential concern is the observation that drugs which act largely by blocking uptake of DA, for example Ritalin (methylphenidate **4**) and cocaine **5** have a tendency to produce euphoria or dysphoria and psychomimetic effects.[3] Others have found, for example, that the use of Bromocriptine (2-bromo-α-ergocryptine, an ergopeptine derivative and a DA agonist) and Wellbutrin (bupropion **6**), which has DA re-uptake activity in vitro and in vivo, show antidepressant efficacy. Other combination studies[4–8] have indicated that addition of some affinity at the DA uptake site may have some clinical benefit.

This paper describes our efforts to obtain compounds with equivalent functional activity at 5HT, NE and DA uptake sites, a triple re-uptake inhibitor. Our starting point was a historical series of Lilly compounds, *trans*-(**7**), *cis*-(**8**) and planar-(**9**) bicyclo[2.2.2]octanes. These compounds possess both NE and DA re-uptake inhibitor activity (Table 1).

We used pharmacophore models for each of the three re-uptake binding sites to visualise the relative spatial orientation of an aromatic moiety to a hydrophobe (bicyclo-rings) and to the amine. These models were built using the Catalyst™ modeling package in its common features approach.[10] A training set from a combination of in-house and literature molecules having the basic structures described in Figure 1 and good activity for the appropriate binding site was formed.[2,10] The models predicted that the aryl group could be substituted aryl or bicycloaryl. Indeed, naphthyl had been shown by other workers[11a–c] to increase 5HT activity in a tropane series. The models could not be used to predict the influence of amine substituents. Each bicyclo system has *cis*, *trans* and planar isomers.

Both the bicyclo[2.2.1]heptanes and [3.2.1]octanes have *endo* and *exo* isomers and two stereogenic centres. With this in mind, we chose to focus our early efforts on the bicyclo[2.2.1]heptane series. This paper will describe the synthesis and SAR of a series of naphthyl bicyclo[2.2.1]heptanes. These derivatives were prepared by exploiting recent developments in asymmetric Diels–Alder reactions.

Table 1. In vitro receptor binding affinity and synaptosomal uptake[9]

Compd	Binding K_i (nM)[a]			Synap. Uptake (nM)		
	5-HT	DA	NE	5-HT	DA	NE
7	25	64	51	303 (590)	165 (340)	44 (140)
8	57	7.2	44	270 (3300)	28 (69)	22 (110)
9	N/A	N/A	N/A	(1100)	(40)	(48)

[a]Values are means of three experiments, mimium significant ratio (MSR) < 3. Numbers in brackets are historical values; N/A, no available compound for test.

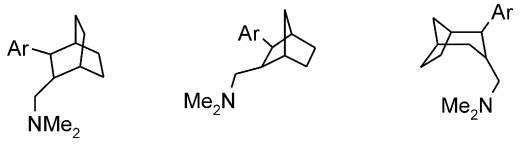
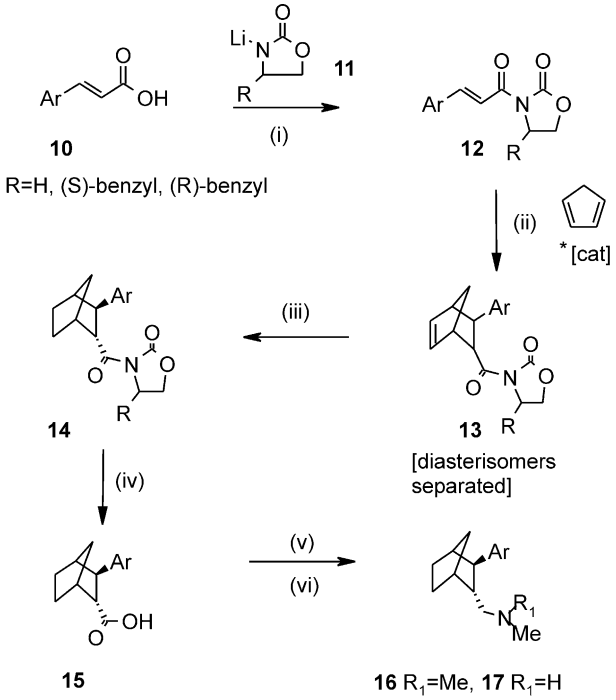


Figure 1. Bicyclo[2.2.2]octane, Bicyclo[2.2.1]heptane, Bicyclo[3.2.1]octane.

Chemistry

Compounds were prepared as described in Scheme 1 and associated catalyst details in Table 2. The requisite dienophiles **12** were prepared by *N*-acylation of oxazolidinones **11**. The lithium salts of **11** were prepared by reaction with *n*BuLi and were then reacted with the mixed anhydride of acid **10,** obtained by reaction with pivaloyl chloride, to afford **12**. Treatment of achiral **12** (R=H, Ar = 3-ClC_6H_4) with cyclopentadiene at low temperature using $Yb(OTf)_3$[12] as Lewis acid gave racemic cycloadducts **13** (*endo*/*exo* ratio 4/1).[13] *endo*/*exo* isomers were separated by preparative HPLC or by recrystallisation. Hydrogenation of the racemic *endo* isomer, followed by basic hydrolysis gave the acid derivative **15** which could be converted to either the dimethyl amino (**16**) or mono methyl amino (**17**) derivatives in two further steps. The racemic *endo* isomer could also be separated into its enantiomers by chiral HPLC[14] and



Scheme 1. Ar = 1-naphthyl, 2-naphthyl, 2-naphthyl-6-OMe, 2-naphthyl-6-OH, 2-naphthyl-6-F. Reagents: (i) pivaloyl chloride, Et_3N, THF, −78 °C (40–60%); (ii) *[cat], DCM, (80–90%); (iii) H_2, Pd/C, EtOAc (80–90%); (iv) LiOH, H_2O_2 (80–90%); (v) oxalyl chloride, Me_2NH or $MeNH_2$ (60–70%); (vi) $LiAlH_4$, Et_2O (80–90%).

Table 2. Catalyst details for Scheme 1

*[Cat] (up to 20 mol%)	Temp (°C)	*endo*/*exo* ratio
$Yb(OTf)_3$	0–20	4/1
[Bis-(oxazoline)copper(II)]$_2SbF_6$	rt	89/11
Et_2AlCl and (*S*) aux	−20	98/2
Et_2AlCl and (*R*) aux	−20	99/1

Table 3. In vitro receptor binding affinity[a] and synaptosomal uptake[b]

2-(*R*),3-(*R*) isomer A 2-(*S*), 3(*S*)-isomer B

Ar	R	Stereo	Binding K_i (nM)[a]			Synaptosomal uptake IC_{50}(nM)		
			5-HT[b]	DA[c]	NE[d]	5-HT	DA	NE
16a 1-Np	Me	rac	52	430	183	93	1514	297
16b 2-Np	Me	rac	2.8	18	111	10	95	45
16c 2-Np	Me	A	5.8	38	149	20	93	34
16d 2-Np	Me	B	2.3	25	152	9	76	25
17b 2-Np	H	rac	4.9	25	266	50	87	45
17d 2-Np	H	B	3.6	41	99	9	86	28
16e 2-Np-6-OMe	Me	B	25	64	68	nd	nd	nd
17e 2-Np-6-OMe	H	B	12	60	120	nd	nd	nd
16f 2-Np-6-F	Me	B	2.6	50	385	nd	nd	nd
17f 2-Np-6-F	H	B	4.4	72	316	nd	nd	nd
16g 2-Np-6-OH	Me	B	47	6	50	nd	nd	nd

nd, not determined; Np, naphthyl.
[a]Values are means of three experiments, MSR < 3.
[b]^{3}H-Citalopram.
[c]^{3}H-Win35,428.
[d]^{3}H-Nisoxetine.

Table 4. In vivo test results

Stereoisomer	R	In Vivo		
		5-HTP ED_{min} (mg/Kg po)	MLA ED_{min} (mg/Kg po)	APO ED_{min} (mg/Kg po)
16c A	Me	> 20	nd	nd
16d B	Me	5	40	25
17d B	H	20	20	25

nd, not determined.

then processed through to final materials for test. Typical overall yields for this seven-step sequence were 10–20%. An alternative approach to obtain chiral bicyclo[2.2.1]-heptanes utilized a chiral Lewis acid catalyst following the work of Evans.[15] The best catalyst for this work was the C_2-symmetric [bis-(oxazoline)copper(II)]SbF_6. This gave the cycloadducts **13** (R=H, Ar = naphthyl) with an *endo*/*exo* ratio of 89/11 and an ee of 97% for the *endo* adduct.[16] Once again, chromatography or recrystallisation was used to separate the *endo*/*exo* Diels–Alder adducts. Finally, we tried Evans chiral auxiliary Diels–Alder methodology as a direct means to access chiral bicyclo[2.2.1]heptanes. Replacement of achiral **11** with chiral 2-oxazolidinone derivatives where R = (*S*)-benzyl and R = (*R*)-benzyl (Ar = Naphthyl)[17,18] gave us chiral **12**. The most appropriate Lewis acid was diethylaluminum chloride and the reaction proceeded at −20 °C in 80% yield to give directly 2-(*S*), 3-(*S*) and 2-(*R*), 3-(*R*) Diels-Alder adducts **13**. With (*S*)-4-benzyl-2-oxazolidinones an *endo*/*exo* ratio of 98/2 was obtained with an ee of 95% (*endo*). The corresponding (*R*)-4-benzyl-2-oxazolidinones gave a ratio of *endo*/*exo* > 99/1 with an ee > 99% (*endo*).[19] All final test compounds were prepared as described. The chiral auxiliary method was applicable to scale-up with no loss of chiral integrity (0.149 mol scale, 80% yield, > 98% ee). Compounds described in Table 3 were prepared using this methodology.

Results and Discussion

Two principal in vitro tests were used to measure re-uptake activity of this series; binding affinity and synaptosomal uptake. The binding affinities were measured as inhibitory binding constants of the test drug against a known radiolabelled re-uptake inhibitor in a similar manner as for a postsynaptic agonist or antagonist. Synaptosomes are 'pinched-off' nerve terminals which contain much of the pre- and post-synaptic machinery intact. The ability of the test drug to inhibit the re-uptake of radiolabelled (^{3}H-tritium) transmitter into synaptosomes were measured. The in vitro potencies of a series of naphthyl bicyclo[2.2.1]heptanes **16, 17** across the three uptake transporters are described in Table 3. Activities are given for the racemate (rac) and the two resolved isomers: 2-(*R*), 3-(*R*) (isomer A), 2-(*S*), 3-(*S*) (isomer B). Synaptosomal data were determined for key compounds only. The inclusion of a bicyclic 2-naphthyl substituent increased activity at the 5-HT transporter. The affinities at both DA and NE transporters were maintained leading to an in vitro triple re-uptake inhibitor. Interestingly, the corresponding 1-naphthyl derivative **16a** was much less active across all three transporters. The enantiomers of the 2-naphthyl analogues **16c**,**d** exhibited different activities across the three transporters.

Microsomal metabolism studies[20] on the tertiary amino 2-naphthyl derivatives **16c**,**d** indicated *N*-demethylation as one of the primary routes of metabolism. The desmethyl analogue **17d** was prepared and found to have in vitro triple re-uptake inhibitor activity. Another route of metabolism was found to be hydroxylation in the 6-position of the naphthyl group. The metabolite (**16g**) was subsequently prepared and shown to be inactive in the 5-HT binding assay. In an attempt to block this route of metabolism, substitution in the 6-position of the 2-naphthyl moiety by F or OMe was attempted.

Whilst 5-HT affinity was maintained in the 2-naphthyl-6-fluoro analogue (**16f**) NE affinity is reduced. The 2-naphthyl-6-methoxy derivative (**16e**) was shown to have reduced activities across all three transporters. Compounds **16c**,**d** and **17d** were then selected for in vivo evaluation (Table 4). Three in vivo models were used: potentiation of 5-hydroxytryptophan-(5-HTP, the precursor of serotonin) induced serotonin syndrome-like behaviour in mouse for 5-HT activity,[21] mouse locomotor activity test (MLA) for DA activity[22] and the mouse apomorphine hypothermia (APO) for NE activity.[23] In vivo triple re-uptake activity was confirmed for **16d** and **17d.** Whilst the in vitro binding profiles for the enantiomeric pair (**16c**,**d**) had only modest differences, in vivo the differences were more pronounced with isomer **16c** weakly active (Table 4).

In conclusion, we have demonstrated potent in vitro triple re-uptake inhibition in a series of bicyclo[2.2.1]-heptanes. Further SAR studies on the related planar [2.2.1]; [2.2.2] and [3.2.1] bicycloalkanes, and their relationship to the *trans endo* series will be the subject of a separate communication.

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10. The training set for each pharmacophore model comprised only active molecules. Six molecules per set with the following in vitro cut offs; K_i (nM): 5HT <5, DA <20 and NE <50. Catalyst™, version 4.5 (Accelerys, San Diego, CA, USA). Common feature approach generated within Catalyst, using BEST with an energy limit at 10 *K*cal/mol, default dictionary definition, feature spacing set to 150 picometer with variable weight and tolerance.
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13. The *endo*/*exo* ratio of model compound 3-{[3-(3-chlorophenyl)bicyclo[2.2.1]hept-5-en-2-yl]carbonyl}-1,3-oxazolidin-2-one was determined by NMR. The *endo* isomer refers to the compound with the oxazolidinone on the opposite side to the one-carbon bridge. ^{1}H, ^{13}C, gHSQC, COSY and gHMBC experiments were used to confirm the proposed structure. *endo*/*exo* isomers can be distinguished using the alkene protons: *endo* ^{1}H (ppm) δ 5.95 (d, 2H), 6.55 (d, 2H); *exo* ^{1}H (ppm) δ 6.05 (d, 2H), 6.50 (d, 2H), ratio 79:21. The major isomer was confirmed as *endo* by nOe: interactions are observed between the bridgehead proton and the aromatic ring; such an interaction is not observed for the *exo* isomer.
14. HPLC separation conditions for *endo*/*exo* isomers of 3-{[3-(3-chlorophenyl)bicyclo[2.2.1]hept-5-en-2-yl] carbonyl}-1,3-oxazolidin-2-one: (KR60-5SIL; 90:10 hexane/DCM (ea. 2% EtOH), 40 °C, 1 mL/min) *exo* t_r 10.3 min, *endo* t_r 11.28 min. Separation of *endo*/*exo* enantiomers by chiral HPLC: (CHIRAPAK-AD; 95:5 hexane/IPA, (ea. 0.2 TEA), 40 °C, 0.5 mL/min) *exo* t_r (E1) 14.85 min, t_r (E2) 19.32 min; *endo* t_r (E1) 15.82 min, t_r (E2) 22.2 min. Analytical column size: 250×4.6 mm 1D and for preparative work: 250×20 mm 1D.
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16. Separation of *endo*/*exo* enantiomers by chiral HPLC: (CHIRACEL-OD; 80:20 hexane/IPA, 40 °C, 0.5 mL/min) *exo* t_r (E1) 10.85 min, t_r (E2) 14.99 min; *endo* t_r (E1) 11.65 min, t_r (E2) 40.89 min. Absolute stereochemistry not assigned. Absolute stereochemistry was assigned later by X-ray crystallographic analysis of Ar = naphthyl, 16 d.
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19. (*S*)-Auxilary: *exo* isomer not evident in NMR spectrum; *endo* isomer alkene protons: *endo* ^{1}H (ppm) δ 6.0 (d, 2H), 6.6 (d, 2H). Separation of *endo*/*exo* enantiomers by chiral HPLC: (CHIRACEL-OD; 90:10 hexane:IPA, 40 °C, 0.5 mL/min) *exo* t_r(E1)$^-$, t_r(E2) 11.62 min; *endo* t_r (E1) 14.69 min, t_r (E2) 19.06 min. (*R*)-Auxiliary: *exo* isomer not evident in NMR spectrum; *endo* isomer alkene protons: *endo* ^{1}H (ppm) δ 6.0 (d, 2H), 6.6 (d, 2H). Separation of *endo*/*exo* enantiomers by chiral HPLC: (CHIRACEL-OD; 90:10 hexane/IPA, 40 °C, 0.5 mL/min) *exo* t_r (E1)$^-$, t_r (E2) 10.57 min; *endo* t_r (E1) 12.23 min, t_r (E2) 15.21 min.
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