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SYNTHESIS AND PHARMACOLOGICAL CHARACTERIZATION OF ABT-200: A PUTATIVE NOVEL ANTIDEPRESSANT COMBINING POTENT α-2 ANTAGONISM WITH MODERATE NE UPTAKE INHIBITION

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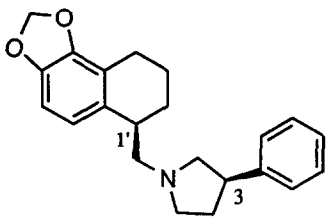
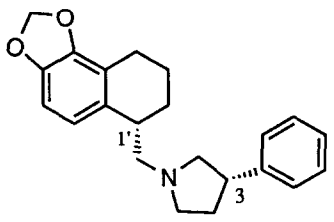
Abstract: ABT-200, (±)-(1'R*, 3R*)-3-phenyl-1-[(1',2',3',4'-tetrahydro-5',6'-methylenedioxy-1'-naphthalenyl)methyl]pyrrolidine, (**1a/b**) represents the first example of a new structural class of potent α-2 antagonists which possess the additional property of norepinephrine (NE) uptake inhibition. This profile of combined activities is expected to have utility in the treatment of depression.

A wide array of clinically effective antidepressants have in common the ability to inhibit the reuptake of the neurotransmitter norepinephrine (NE).[3] However, synaptic release of NE is under the control of presynaptic inhibitory α-2 receptors.[4,5] Consequently, the increased synaptic availability of NE resulting from uptake blockade is counteracted by the inhibitory effect of NE at presynaptic α-2 receptors on neurotransmitter release. Additionally, in order for NE uptake inhibition treatment to be useful, the existing neurons must be tonically active and capable of releasing sufficient neurotransmitter for uptake inhibition to have a significant effect.[6]

Alpha-2 antagonists can act both pre- and post-synaptically to increase adrenergic tone. It has been amply demonstrated that presynaptic α-2 blockade reverses the feedback inhibition of neurotransmitter release.[4,5] Postsynaptic blockade of α-2 receptors located on noradrenergic neuron cell bodies (such as those found in the locus ceruleus) has been demonstrated to increase the firing rate of these neurons.[6,7] By combining α-2 pre- and post-synaptic blockade with NE uptake inhibition, the expectation would be that 1) an increased firing rate for noradrenergic neurons would be observed; 2) deactivation via the NE uptake system would be effectively blocked; and 3) feedback inhibition of further NE release would be antagonized. A combination of potent α-2 antagonism with moderate NE uptake inhibitory activity has been achieved with the racemate **1a/b**.



1a

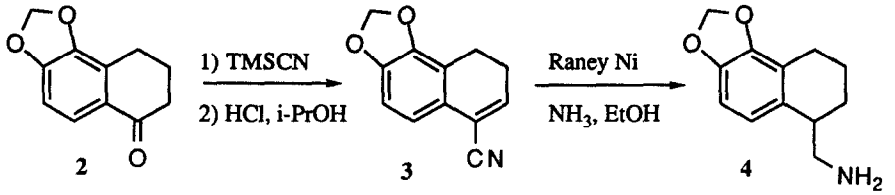


1b

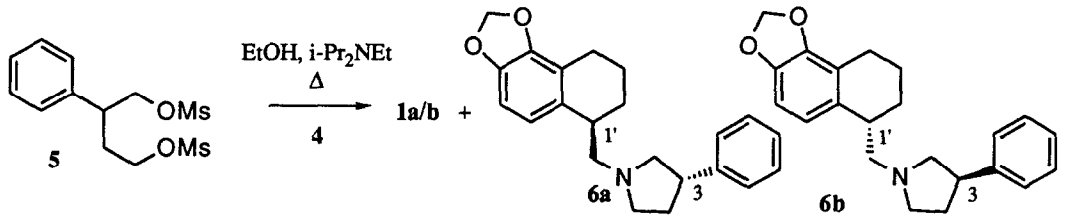
Synthesis

The title compound **1a/b** was prepared in four steps from the known 5,6-methylenedioxytetralone (**2**). The tetralone **2** was treated with trimethylsilylcyanide (1.1 equiv) and LiCN (cat.) in THF to yield an intermediate trimethylsilyl cyanohydrin. Elimination by treatment with HCl in isopropanol yielded the unsaturated nitrile **3** in

80% yield. Raney Nickel hydrogenation of the unsaturated nitrile yielded the racemic aminomethyl tetralin derivative **4** in 95% yield.



The bis-mesylate **5** was prepared in two steps from phenylsuccinic acid in 75% overall yield via BH_3 reduction followed by treatment of the intermediate diol with methanesulfonyl chloride in CH_2Cl_2 containing 2.5 equivalents of triethyl amine. Alkylation of the amine **4** with the bismesylate **5** was conducted in refluxing absolute ethanol in the presence of diisopropylethylamine to yield **1a/b** plus the RS/SR diastereomer **6a/b.**



The diastereomers were separated by flash chromatography (15% Et_2O in hexanes, saturated with NH_3) to give the desired RR/SS diastereomer **1a/b** as the first eluting product followed by the RS/SR diastereomer **6a/b**. The optically pure enantiomers **1a**, **1b**, **6a**, and **6b** were prepared as described above using enantiomerically pure (-)-(R)- or (+)-(S)-phenylsuccinic acid as starting materials[8] for the right-hand fragment of the molecule. Absolute configurations were established by X-ray crystallography of **1a** and **6a** as their HCl salts. Physical properties are summarized in Table 1.

Table 1. Physical Properties of ABT-200 (**1a/b**) and related compounds.

Compound	Molecular Formula	mp, °C	Recrystallization Solvent	$[\alpha]_d^{25}$(c, MeOH)
1a/b	$C_{22}H_{25}NO_2 \cdot CH_3SO_3H$	166-168	EtOH/Et_2O	-
1a (1'R,3R)	$C_{22}H_{25}NO_2 \cdot CH_3SO_3H$	143-144	EtOH/Et_2O	+29.7° (0.56)
1b (1'S,3S)	$C_{22}H_{25}NO_2 \cdot CH_3SO_3H$	141-142	EtOH/Et_2O	-29.4° (0.56)
6a/b	$C_{22}H_{25}NO_2 \cdot CH_3SO_3H$	161-2	EtOH/Et_2O	-
6a (1'R,3S)	$C_{22}H_{25}NO_2 \cdot HCl$	246-7	EtOH/Et_2O	+20.3° (0.97)
6b (1'S,3R)	$C_{22}H_{25}NO_2 \cdot HCl$	246-7	EtOH/Et_2O	-19.9° (1.00)

Pharmacology

Compounds reported in this study were characterized for affinity at α-1 (rat liver) and α-2 (rat cortex) receptors in radioligand binding assays using [^{3}H]-prazosin and [^{3}H]-rauwolscine as radioligands, respectively.[9] The functional pre- and postsynaptic α-2 antagonist activity of these compounds was characterized in peripheral tissue models; the phenoxybenzamine pretreated dog saphenous vein model[10] using norepinephrine as the control agonist was used to assess postsynaptic activity and the rat vas deferens model[11] using clonidine as the control agonist was used to assess presynaptic activity. The biogenic amine reuptake inhibitory activity of these compounds was assessed in synaptosomal rat hypothalamic preparations.[12] Results are summarized in Table 2. Compound **1a/b** showed high potency at the α-2 binding site and approximately 90-fold selectivity for the α-2 vs. α-1 receptor. The high affinity for the α-2 receptor was confirmed in the two α-2 functional models. Idazoxan, a prototypical α-2 antagonist, showed comparable activity in both the binding assays and the functional models. In the NE uptake assay, **1a/b** demonstrated moderate activity, with an IC_{50} of 840 nM, approximately 8-fold weaker than the prototypical NE uptake inhibitor imipramine, but greater than ten-fold more active than the prototypical α-2 antagonist idazoxan. Pharmacological characterization of the enantiomers **1a** and **1b** showed that the preponderance of the α-2 antagonist activity resided in the 1'R,3R enantiomer **1a**, whereas the preponderance of the NE uptake inhibitory activity resided in the 1'S,3S enantiomer **1b**. The racemic RS/SR diastereomer **6a/b** and its pure enantiomers **6a** (1'R,3S) and **6b** (1'S,3R) showed somewhat lower affinity for the NE uptake site, but were of comparable activity at the α-2 site.

Table 2. *In Vitro* Pharmacology

Compound	Radioligand Binding (nM) Ki (95% Confidence Limit)		Functional Characterization pA2 (slope)		NE Uptake (nM) IC_{50} (95% Conf. Limit)
	α-1	α-2	Presynaptic α-2 (Rat Vas Deferens)	Postsynaptic α-2 (Dog Saphenous Vein)	
1a/b	112 (84.3-149)	1.23 (0.524-2.91)	7.68 (1.17)	8.17 (0.85)	841 (480-1470)
1a (1'R,3R)	106 (76.3-146)	0.428 (0.166-1.10)	7.78 (1.21)	8.25 (0.96)	3110 (2110-4580)
1b (1'S,3S)	104 (74.9-145)	2.08 (0.684-6.34)	6.78 (1.23)	6.80 (1.12)	636 (373-1080)
6a/b	75.9 (61.9-93.1)	0.708 (0.310-1.62)	7.84 (0.88)	8.15 (0.83)	1320 (1130-1540)
6a (1'R,3S)	47.4 (38.4-58.5)	0.500 (0.236-1.06)	7.91 (1.25)	8.15 (0.83)	1700 (1040-2800)
6b (1'S,3R)	189 (159-226)	4.56 (2.58-8.08)	6.65 (1.15)	6.68 (1.04)	1450 (974-2140)
Imipramine	46.0 (19.5-108)	255 (66.7-973)	5.48 (est.)	6.26 (est.)	105 (60.3-184)
Idazoxan	403 (267-610)	1.72 (1.22-2.42)	7.93 (1.19)	7.28 (0.81)	>10,000 (est.)

Conclusion

ABT-200 (**1a/b**) is the first representative of a novel structural class which combines α-2 antagonism with moderate NE uptake inhibitory activity. Compound **1a/b** exhibits comparable radioligand binding affinity and *in vitro* functional activity to the prototypical α-2 antagonist idazoxan; and in addition demonstrates moderate *in vitro* activity (approximate 1/8 that of imipramine) as an inhibitor on NE uptake. Despite only moderate *in vitro* activity at the NE uptake site, **1a/b** shows a greater than expected *in vivo* activity (comparable to nomifensine) in inhibiting the cerebellar uptake of NE in the whole rat[13]. These data suggest that the radioligand concentration dependence of IC_{50} values may affect predictions of absoute potency (i.e. imipramine IC_{50} of 105 nM at NE uptake site vs. α-1 Ki of 46 nM is an inaccurate predictor of imipramine's pharmacology). The *in vitro* α-2 antagonist activity of **1a/b** has been confirmed as well in a whole animal model of a centrally mediated α-2 effect - reversal of clonidine induced mydriasis in the rat[14]. This unique combination represents a theoretically attractive and novel approach to the treatment of depression. Evidence exists that the slow onset of clinical efficacy for NE uptake inhibitor-based antidepressants correlates with adaptive changes in the α-2 receptor necessary to overcome the compensatory α-2 mediated inhibition of neurotransmitter release.[15,16] Consequently, an agent which combines α-2 antagonism with NE uptake inhibition may obviate the need for receptor desensitization to exhibit clinical efficacy, and therefore may exhibit more rapid onset of antidepressant action.

The two activities of NE uptake inhibition and α-2 antagonism are clearly demonstrable for the racemate **1a/b**, with the α-2 antagonist activity residing primarily in the 1'R,3R enantiomer **1a** and the NE uptake activity primarily in the 1'S,3S enantiomer **1b**. Therefore, the racemate **1a/b** posseses the desired profile for a clinically effective antidepressant which may exhibit a more rapid onset of therapeutic effect. ABT-200 (**1a/b**) is currently undergoing clinical evaluation.

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