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Discovery of potential antidepressant agents: Novel 3-arylpyrrolidines with dual mechanism of action on neurotransmission

Fatima Z. Basha,*[1] and John F. DeBernardis[2]

Pharmaceutical Discovery D-4NB Abbott Laboratories, Abbott Park, Illinois 60064 - 3500

Abstract: *A series of 3-arylpyrrolidines **4** and related compounds were synthesized and examined for antidepressant-like activity. Our hypothesis was that the dual action of these agents, namely inhibition of the uptake of biogenic amines and blockade of presynaptic α_2 receptors, should increase CNS levels of the respective biogenic amines in the synaptic cleft. This would enhance the potential utility of these agents as antidepressants. These compounds are inhibitors of the reuptake of norepinephrine in the nerve terminus of rat hypothalamus and are also potent antagonists of α_2 receptors measured both in vitro and in vivo. The rational design and the methodology developed for synthesis of these compounds is presented.*

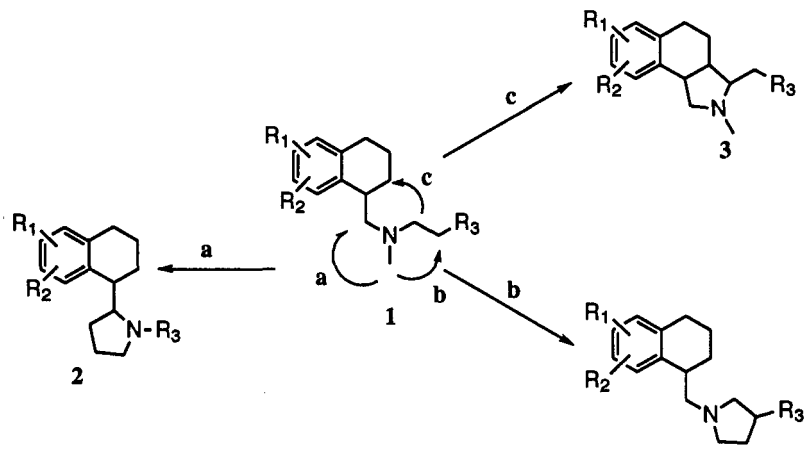

Fig. 1

Antidepressant drugs were introduced in 1950 but a credible theory explaining their action was not introduced until 1967 when Schildkraut (3) proposed the biogenic amine uptake theory postulating a regional deficiency in release of the sympathetic neurotransmitter norepinephrine (NE). Indeed, most currently used antidepressant drugs increase NE in the synapse by inhibiting reuptake phenomenon (4-5). Acting in opposition to this elevation of NE is a presynaptic inhibition of NE release which follows occupation of certain brain α_2 adrenoceptors. Selective antagonists of these presynaptic receptors may demonstrate some antidepressant efficacy (6-7). We set out to identify an improved antidepressant agent which would act by combination of α_2 blockade with NE uptake inhibition. This profile was expected to prevent the feedback inhibition of NE release and thereby result in improved antidepressant efficacy. To achieve this end we designed and synthesized conformationally restricted NE analogs.

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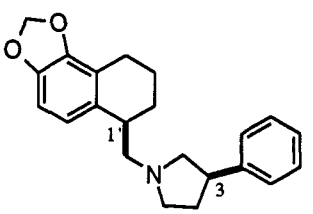
1. *Dedicated to my father on the occasion of his 80th birthday. He taught me the fun of learning, and the virtues of hard work and persistence.*

Consequently, the *t*-amine series **1** was developed. These compounds possess potent and selective α_2 binding activity but weak NE uptake inhibition. Our goal then was to improve NE uptake inhibition while maintaining the α_2 antagonism. We decided to modify the t-amine **1** structure in several ways, three of which are shown in Fig 1.

The pyrrolidine **2** (8, 11) resulted in compounds with no appreciable α_2 antagonism or NE uptake inhibition. Additional rigidity was achieved by synthesizing a series of 3-arylalkyl-benz[e]isoindolines **3**. Most of the compounds inhibit NE uptake more potently than DA uptake, and their activity at inhibiting 5HT uptake is even weaker still. As inhibitors of NE uptake, some of these compounds have similar potency to desimipramine (a tricyclic antidepressant known to inhibit NE uptake potently) but lack activity at adrenergic receptors *in vitro*. Two main synthetic approaches were used to obtain all of the type **3** series compounds: the 1,4-addition of a dithiane anion to unsaturated nitriles (9) and nitronate anion addition to the unsaturated ester. The *cis* diastereoisomers of **3** were more active NE uptake inhibitors but, also disappointingly, lacked α_2 antagonism (10-13).

Utilizing information derived from these two series we designed a novel set of compounds exemplified by ABT-200 in which the structural features of the aminomethyl tetralin are essentially maintained with more rigidity built into the molecule by virtue of the pyrrolidine ring. This enforced conformation eliminates the flexibility of the phenethyl side chain. ABT-200 (**5**) met the desired profile (14). Compound **5** shows comparable affinity and functional activity to the prototypical α_2 antagonist idazoxan and in addition shows moderate NE uptake inhibitory activity. This unique combination presents a theoretically attractive and novel approach to the treatment of depression. These two activities reside in the racemate **5**, with the α_2 antagonist activity in the R,R enantiomer **9** and the NE uptake activity in the S,S enantiomer **11**. Therefore, racemate **5** possesses the desired profile for a clinical antidepressant. The compound **5** is currently undergoing clinical evaluation.



ABT-200 (5)

ABT-200 (**5**), mixed with the R,S/S,R diastereomer **8** was prepared from the alkylation of the amine **6** with the bismesylate **7**. ABT-200 (**5**) was separated by flash chromatography to give the desired R,R/S,S diastereomer **5** as the first eluting product followed by the R,S/S,R diastereomer **6** (15-16). The optically pure enantiomers **9**, **10**, **11**, and **12** were prepared as described above using enantiomerically pure (-)-(R)- or (+)-(S)-phenylsuccinic acid as starting materials. Absolute configurations were established by X-ray crystallography of **9** and **10** as their HCl salts.

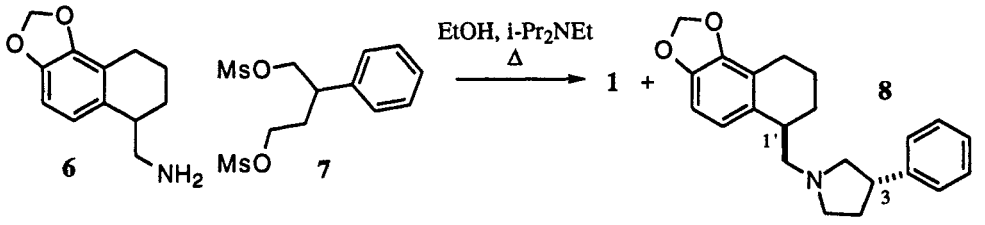
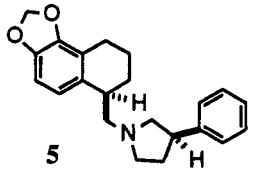
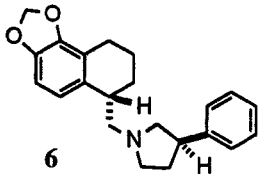


Table 1. *In Vitro* Pharmacology

Compound	Radioligand Binding, Ki (nM)		Functional Characterization		
	α_1	α_2	Presynaptic α_2 pA2	Postsynaptic α_2 pA2	NE Uptake IC_{50} (nM)
 5	112	1.23	7.68	8.17	841
R,R 9	106	0.428	7.78	8.25	3110
S,S 11	104	2.08	6.78	6.80	636
 6	76	0.708	7.84	8.15	1320
S,R 10	189	4.56	6.65	6.68	1450
R,S 12	48	0.500	7.91	8.15	1700
Imipramine	46	255	5.48	6.26	105
Idazoxan	403	1.72	7.93	7.28	>10,000

The biological results are summarized in Table **1**. Compound **5** showed 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 α_2 functional models, DSV and RVD (14). Idazoxan, a prototypical α_2 antagonist, is included for comparision. Compound **5** inhibited NE uptake with an IC_{50} of 840 nM, approximately 8-fold weaker than the imipramine, a prototypical NE uptake inhibitor. Pharmacological

characterization of the enantiomers of **5** showed that the majority of the α_2 antagonist activity resided in the R,R enantiomer **9**, whereas the preponderance of the NE uptake inhibitory activity resided in the S,S enantiomer **11**. The racemate **8** and its pure enantiomers **10** (1S,3R) and **12** (1R,3S) possessed somewhat lower affinity for the NE uptake site, but were of comparable activity at the prototypical NE uptake inhibitor site.

In summary, a novel pyrrolidine series with modest NE uptake inhibition and potent α_2 antagonism was identified and the best of this series ABT-200 (**5**), has entered clinical trials as an antidepressant.

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