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Synthesis and evaluation of spirobenzazepines as potent vasopressin receptor antagonists

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Abstract—A novel series of spirobenzazepines was synthesized and evaluated for V_{1a} and V_2 receptor antagonist activity. Compounds **8b**, **8i**, and **8k** have shown selective V_{1a} receptor antagonist activity. Compounds **8p** and **8q** were shown to be dual V_{1a}/V_2 receptor antagonists.

Arginine vasopressin (AVP) is a cyclic nonapeptide secreted from the posterior pituitary and is known to exert a variety of biological effects. Upon release it is known to interact with AVP receptor subtypes V_{1a}, V_{1b}, and V_2. Interaction at the V_{1a} receptor results in vasoconstriction, vascular smooth muscle proliferation among other responses, whereas interaction at the V_2 receptor results predominantly in the regulation of osmotic water channels in the kidneys.[1] As a result, the development of AVP receptor antagonists could prove to be therapeutically useful in the treatment of congestive heart failure, liver cirrhosis, hyponatremia, and nephrotic syndrome.[2]

Mozavaptan, Conivaptan, and Lixivaptan are known AVP antagonists undergoing clinical trials.[3] Mozavaptan and Lixivaptan are both selective vasopressin V_2 receptor antagonists, whereas Conivaptan is a dual V_{1a}/V_2 receptor antagonist. All three compounds are based on the same benzazepine scaffold bearing a lower aryl chain. Additionally, all compounds have a basic nitrogen either in the form of a fused heterocycle or as a substituent on the seven-membered ring (Fig. 1).

We had previously demonstrated the effective design and use of highly constrained quaternary systems as peptide receptor antagonists.[4] Based on this earlier work, we sought to explore spirobenzazepines as V_{1a}/V_2 receptor antagonists. Toward that end, commercially available 3-ethoxycyclohexene-1-one **1** with treated with benzyl magnesium bromide followed by reduction with lithium

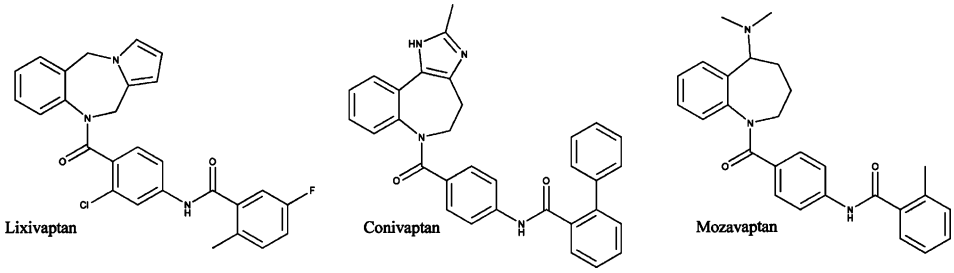

Figure 1. Known AVP antagonists.

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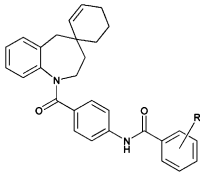
aluminum hydride (LAH) to afford allyl alcohol **2** in a two-step process in 80% yield. Alcohol **2** was treated with sodium hydride and phenyl vinyl sulfoxide to provide (in Michael type addition) the corresponding allyloxy ethyl aryl sulfoxide. Upon heating in decalin, the crude sulfoxide underwent a Claisen rearrangement to provide aldehyde **3** in a 70% yield over two steps.[5] Oxidation of aldehyde **3** with sodium chlorite to carboxylic acid (**4**) proceeded in 65% yield, and was followed by an intramolecular Friedel Craft's acylation with trifluoroacetic anhydride (TFAA) and trifluoroacetic acid (TFA) to afford spiroketone **5** as a racemic mixture. Schmidt rearrangement of spiroketone **5** with sodium azide and TFA provided spirolactam **6**. Reduction of the amide to the corresponding amine (**7**) with LAH was followed by acylation with an appropriately substituted acid chloride to afford spirobenzazepine **8** (Scheme 1).[6]

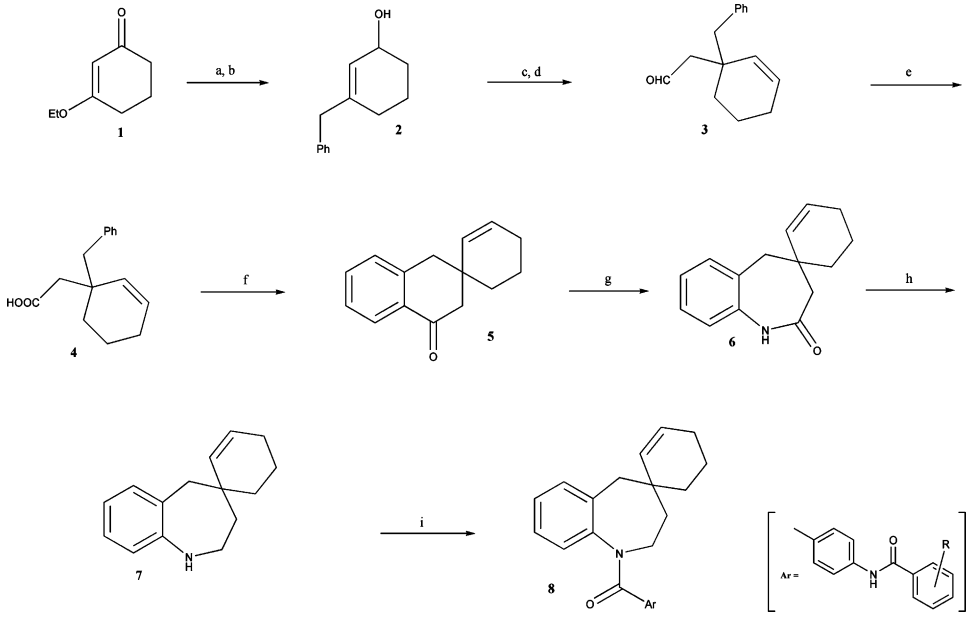
Table 1 summarizes the in vitro potency of the racemic benzazepines. Compound **8a** bearing no substitutions on the phenyl ring was found to be a potent V_{1a} antagonist with moderate V_2 antagonist activity. The introduction of a methyl group at positions 2, 3, or 4 of the phenyl ring resulted in compounds **8b**, **8c**, and **8d**, respectively. Compound **8b** bearing a methyl group at the 2 position was clearly the most potent compound of the set with an IC_{50} of 10 nM in the V_{1a} binding assay and an IC_{50} of 70 nM in the V_2 binding assay. The 3,4-dimethyl substituted compound **8d** showed a loss of potency in the V_{1a} binding assay and is a poor V_2 receptor antagonist. Compound **8f** bearing a 2-methoxy substituent on the phenyl ring was a potent V_{1a} antagonist with moderate V_2 antagonist activity, but still less potent than the 2-methyl compound **8b**. The 2,6-dimethoxy substituted compound **8g** showed a moderate loss in potency in the V_{1a} binding assay and had negligible V_2 receptor antagonist activity, whereas compound **8h** bearing a 3,4-dimethoxy substitution pattern resulted in a loss of potency in both V_{1a} and V_2 binding assays. The 4-thiomethyl substituted compound **8i** was a potent V_{1a} receptor antagonist with an IC_{50} value of 15 nM with very poor potency in the V_2 receptor binding assay. Compound **8i** is a selective V_{1a} receptor antagonist. Oxidation of the thiomethyl group to the corresponding

Table 1. In vitro activity of spirobenzoxazines



Compound	R[a]	V_{1a} Binding[7] IC_{50} (nM)	V_2 Binding[7] IC_{50} (nM)
8a	H	20	390
8b	2-CH_3	10	70
8c	3-CH_3	50	380
8d	4-CH_3	74	>1000
8e	3,4-diCH_3	140	>1000
8f	2-OCH_3	30	0.20
8g	2,6-diOCH_3	41	>1000
8h	3,4-diOCH_3	>1000	>1000
8i	4-SCH_3	15	>1000
8j	4-$SOCH_3$	>1000	>1000
8k	4-NH_2	10	>1000
8l	2-F	10	550
8m	2-Cl	12	180
8n	2,6-diCl	46	159
8o	2,4-diCl	16	274
8p	2-CH_3, 5-F	8	67
8q	2-Ph	26	29

[a] All compounds are racemic.



Scheme 1. Reagents and conditions: (a) BnMgCl, THF; (b) LAH, THF, 80% over two steps; (c) phenyl vinyl sulfoxide, NaH, THF; (d) decalin, NaH, sodium bicarbonate, 70% over two steps; (e) sodium chlorite, sodium phosphate, 65%; (f) trifluoroacetic anhydride, trifluoroacetic acid, 90%; (g) sodium azide, trifluoroacetic acid, 65%; (h) LAH, THF, 97%; (i) ArCOCl, TEA, DCM, 65–90%.

sulfone moiety (**8j**) resulted in an inactive compound in both V_{1a} and V_2 binding assays. The 2-amino substituted compound **8k** was also a V_{1a} selective compound with an IC_{50} of 10 nM and negligible potency in the V_2 binding assay. Introduction of halogens on the phenyl ring in the form of 2-fluoro (**8l**) and 2-chloro (**8m**) substituted phenyl compounds, resulted in potent V_{1a} antagonists with moderate (180–550 nM) V_2 antagonist activity. The introduction of the dihalo substituted phenyl ring compounds such as 2,6-dichloro (**8n**) and 2,4-dichloro (**8o**) did not alter the V_{1a}/V_2 potency profile with respect to that observed for the monohalo substituted compounds (**8l** and **8m**). Compound **8p** bearing a 2-methyl,5-fluoro substituent provided a potent V_{1a} and V_2 dual antagonist with IC_{50} values of 8 and 67 nM, respectively. The introduction of a 2-phenyl group resulted in compound **8q**, bearing an excellent V_{1a} and V_2 dual antagonist activity profile with IC_{50} values of 26 and 29 nM, respectively. Next, we sought to examine the metabolic stability and solubility profiles of the compounds of interest. We were disappointed to discover that the metabolic profiles for the potent compounds of this series were rather poor with half-lives in the human microsomal stability assay consistently being less than 10 min. Solubilities of compounds of interest were determined to be below detectable levels at both pH 2 and 7.4.

In summary, although we were able to identify novel compounds that were both selective V_{1a} receptor antagonists in compounds **8b**, **8g**, **8i**, and **8k** as well as dual V_{1a}/V_2 receptor antagonists in compounds **8p** and **8q**, lack of metabolic stability and a poor solubility profile precluded further development of this series of compounds. The spiro substituent does not appear to regulate selectivity in this template, and could be a probable cause of the poor metabolic stability and solubility profiles. Additional alterations in the scaffold are underway and will be reported in due course.

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