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Synthesis and evaluation of azabicyclo[3.2.1]octane derivatives as potent mixed vasopressin antagonists

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ABSTRACT

A series of biaryl amides containing an azabicyclooctane amine headpiece were synthesized and evaluated as mixed arginine vasopressin (AVP) receptor antagonists. Several analogues, including **8g**, **12g**, **13d**, and **13g**, were shown to have excellent V_{1a}- and good V_2-receptor binding affinities. Compound **13d** was further profiled for drug-like properties and for an in vitro comparison with conivaptan, the program's mixed V_{1a}/V_2-receptor antagonist standard.

Arginine vasopressin (AVP) is a cyclic nonapeptide hormone released from the posterior pituitary in response to either change in plasma tonicity, plasma volume depletion, or blood pressure changes. AVP binds to three known G-protein-coupled receptor subtypes: vascular V_{1a}, hormone releasing V_{1b}, and renal V_2. The V_{1a}-receptors are expressed in several cell types, including vascular smooth muscle cells and cardiomyocytes and mediate vasoconstriction, vascular smooth muscle proliferation, and possibly myocardial function. Interaction of AVP with the V_2-receptor, which is expressed on the basolateral membrane of the renal collecting ducts, promotes free water reabsorption in the kidney.[1,2] AVP receptor antagonists are being investigated for use in the treatment of hyponatremia, hypertension, congestive heart failure, liver cirrhosis, and any state of excessive retention of water.[3]

Tolvaptan,[4,5] lixivaptan, and conivaptan[6,7] are known AVP antagonists either approved or being clinically evaluated for the treatment of hyponatremia and/or heart failure (Fig. 1).[1–3,8–10] Both tolvaptan and lixivaptan are selective V_2-receptor antagonists, while conivaptan has strong affinity for both the V_{1a}- and V_2-receptors. Such dual V_{1a}/V_2-receptor antagonists potentially offer a clinical advantage, especially in the treatment of congestive heart failure, due to the inhibitory effect on both vasoconstriction and water retention.[2,3] Thus recent attention has focused on developing additional dual V_{1a}/V_2-receptor antagonists.[11–14]

The majority of vasopressin receptor antagonists are based on a similar benzazepine headpiece scaffold that is substituted with an optimized bisamide tailpiece. Previous Wyeth programs reported a large number of tricyclic benzodiazepine derivatives with related pharmacology and physical properties.[15–26] Early investigations of a benzodiazepine biphenyl scaffold led to the discovery of a series of compounds with dominant in vitro V_{1a}-receptor antagonist pharmacology.[26] A subsequent investigation of analogues with unsubstituted biphenyl tailpieces and their heterocyclic congeners ultimately led to the discovery of the non-peptide vasopressin mimetic of the V_2-receptor agonist, WAY-151932 (VNA-932).[22] Additional research efforts were directed towards identifying alternative non-benzodiazepine molecular scaffolds for this biological target. In particular, a novel, lower molecular weight scaffold with less aromatic character and potentially improved physical properties that exhibited mixed affinity for the V_{1a}- and V_2-receptors was sought. To this end, a series of biphenyl amides containing a bicyclic amine headpiece were evaluated as novel vasopressin receptor modulators[27] (Fig. 2). Several racemic analogues of this structural series were synthesized and screened in our V_{1a}- and V_2-receptor binding assays.[28] In general, these compounds had significantly reduced molecular weight and retained the high affinity for a V_{1a}-receptor, but produced weak to moderate V_2-receptor binding affinity. The objective of this program was refocused to utilize our

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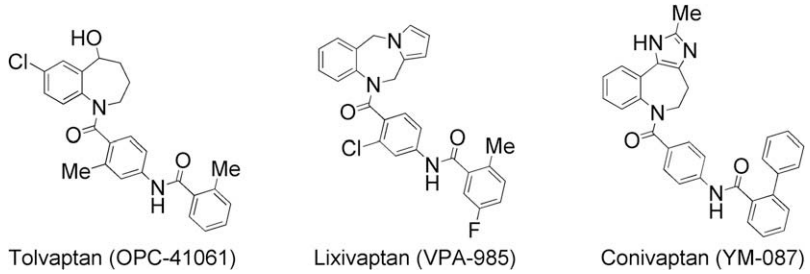


Figure 1. Structures of tolvaptan, lixivaptan, and conivaptan.

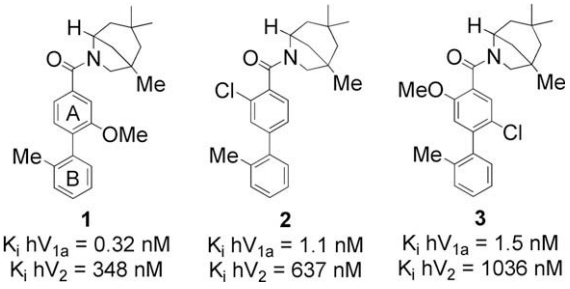


Figure 2. Early biphenyl amide leads.

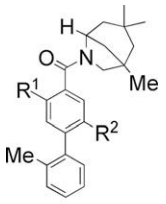
understanding of the biphenyl tailpiece SAR and explore the chirality of the azabicyclooctane headpiece to achieve dual V_{1a}/V_2-receptor activity.

At first the effects of the aryl 'A' ring substitution on the scaffold's activity were systematically investigated while maintaining the 2-methyl phenyl substitution at the aryl 'B' group. Substituents and location of these groups were chosen to examine the affect of both electronics and varying degrees of restricted rotation between the two aryl rings. The results of these efforts to synthesize analogues with varying aryl 'A' groups are shown in Scheme 1. Substituted aryl halides **4** were coupled to 2-methylphenyl boronic acid using a standard Suzuki coupling protocol. The resulting biaryl esters were hydrolyzed and coupled to the bicyclic amine using CDI and DMAP producing racemic mixtures of the desired products **6, 7**. Preliminary receptor binding affinity prompted and encouraged us to separate the stereoisomers using chiral high pressure liquid chromatography.[29,30] This allowed for the identification of potential eutomer/distomer effects.

The binding affinities of a select group of these compounds for the V_{1a}- and V_2-receptors are outlined in Table 1. The data revealed that the (1*S*,5*R*) stereoisomers[30] had significantly higher affinity for both the V_{1a}- and V_2-receptors than their corresponding isomers. In some cases, the eutomer was greater than 1000-fold more active in the V_{1a}-receptor assay than the corresponding distomer. In addition, *o*-chloro and *m*-methoxy substituted phenyl (e.g., **8c** and **8g**, respectively) were identified as optimal aryl 'A' moieties.

The aryl 'B' moiety optimization was then explored utilizing the (1*S*,5*R*) azabicyclooctane headpiece and *m*-methoxy substituted

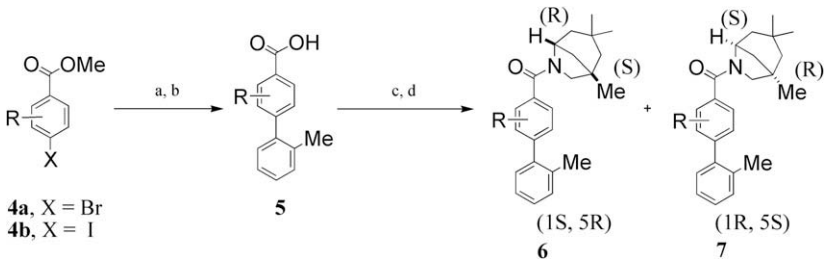
Table 1
Vasopressin receptor binding data for biphenyl amides with varying aryl 'A' groups



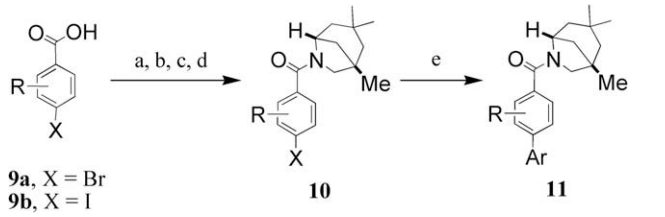
8a-j

Compound	Stereochemistry[a,b]	R^1	R^2	hV_{1a} Binding K_i[c] (nM)	hV_2 Binding K_i[c] (nM)	V_{1a}/V_2 Binding ratio K_i
Conivaptan	—	—	—	0.43	0.36	1.19
8a	(1*S*,5*R*)	H	H	0.05	204	<0.01
8b	(1*R*,5*S*)	H	H	65	3345	0.02
8c	(1*S*,5*R*)	Cl	H	0.31	54	<0.01
8d	(1*R*,5*S*)	Cl	H	11	1032	0.01
8e	(1*S*,5*R*)	H	Me	0.06	478	<0.01
8f	(1*R*,5*S*)	H	Me	36	1057	0.03
8g	(1*S*,5*R*)	H	OMe	20[d]	82[e]	0.24
8h	(1*R*,5*S*)	H	OMe	46	nd[f]	—
8i	(1*S*,5*R*)	OMe	Cl	0.54	107	<0.01
8j	(1*R*,5*S*)	OMe	Cl	25	1205	0.02

[a] >99% enantiomerically pure by chiral HPLC.
[b] Stereochemistry assigned using VCD.[30]
[c] Inhibition of [^{3}H]-Arg-vasopressin binding to recombinant human vasopressin V_{1a} or V_2 receptors ($N = 2$).
[d] Functional measurement of intracellular calcium of hV_{1a} receptor using FLIPR dose–response was obtain to confirm V_{1a} antagonist activity (hV_{1a} IC_{50} = 72.4 nM).
[e] V_2 antagonist activity confirmed by investigating the aquaretic effect in water-load Sprague-Dawley rats (1 mg/kg iv, 50%DMSO/50%PEG400, $N = 2$). 26.7% increase in urine volume and 15.5% decrease in osmolality.
[f] nd = not determined.

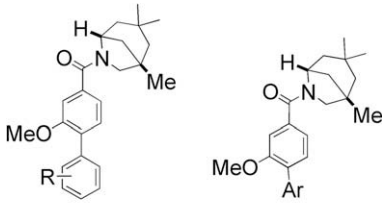


Scheme 1. Reagents and conditions: (a) 5 mol % $Pd(OAc)_2$, 10 mol % (*o*-biphenyl)PCy_2 or (*o*-biphenyl)$P(tBu)_2$, 1.5 equiv 2-methylphenyl boronic acid, 3.0 equiv Cs_2CO_3, THF, rt–60 °C, 16 h–3 d, 43–78%; (b) 2 N NaOH, THF, 65 °C, 3 h, then concd HCl, 59–95%; (c) 2.0 equiv 1,3,3-trimethyl-6-azabicyclo[3.2.1]-octane, 1.5 equiv CDI, 1.5 equiv DMAP, DMF, rt, 16 h–3 d, 66–98%; (d) chiral separation achieved using chiral chromatography,[29] >99% enantiomerically pure, stereochemistry assigned using VCD.[30]



Scheme 2. Reagents and conditions: (a) 2.0 equiv oxalyl chloride, CH_2Cl_2, cat. DMF, rt, 2 h; (b) 1.0 equiv 1,3,3-trimethyl-6-azabicyclo[3.2.1]-octane, 1.1 equiv DIEA, CH_2Cl_2, rt; (c) Chiral separation achieved using chiral chromatography,[29] >99% enantiomerically pure; (d) stereochemistry assigned using VCD;[30] (e) 10 mol % $Pd(PPh_3)_4$, 1.5 equiv boronic acid, 3.0 equiv $Ba(OH)_2$, dioxane–H_2O, 100 °C, 2 h.

Table 2
Vasopressin receptor binding data for biphenyl amides with varying aryl 'B' groups



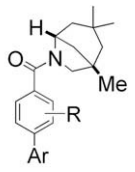
8g, 12a-l **13a-o**

Compound	**8, 12**, R	hV_{1a} Binding K_i[a] (nM)	hV_2 Binding K_i[a] (nM)	V_{1a}/V_2 Binding ratio K_i
Conivaptan	—	0.43	0.36	1.19
8g	2-Me	20	82	0.24
12a	2,6-DiMe	0.60	>2500	—
12b	2-OPh	22.4	846	0.03
12c	2-Ph	2.60	189	0.01
12d	3-Cl-6-Me	2.75	>2500	—
12e	3-Me	3.97	713	<0.01
12f	3-CONHMe	1.03	1170	<0.01
12g	3-NHAc	0.37	30	0.01
12h	3-Ph	13.3	>2500	—
12i	4-Cl	4.42	1810	<0.01
12j	4-Cl-2-Me	2.26	291	<0.01
12k	4-Me	0.80	556	<0.01
12l	4-OPh	58.9	>2500	—
	13, Ar			
13a	Benzofuran-3-yl	3.80	675	<0.01
13b	Benzofuran-3-yl-2-phenyl	5000	>2500	—
13c	Benzothiophen-2-yl	3.78	>2500	—
13d	Benzothiophen-3-yl	0.79	15	0.05
13e	Dibenzofuran-4-yl	38.9	>2500	—
13f	Indol-3-yl	0.10	600	<0.01
13g	Naphthalen-1-yl	5.40	63	0.09
13h	Naphthalen-2-yl	17.0	2380	<0.01
13i	Naphthalen-2-yl, 6-OMe	105	2090	0.05
13j	Pyridin-3-yl, 2-Cl	1.07	2470	<0.01
13k	Quinolin-3-yl	5.79	1890	<0.01
13l	Quinolin-5-yl	23.5	770	0.03
13m	Quinolin-8-yl	0.71	130	<0.01
13n	Styrenyl	51.5	>2500	—
13o	Thiophen-2yl, 5-Ph	92.2	>2500	—

[a] Inhibition of [^{3}H]-Arg-vasopressin binding to recombinant human vasopressin V_{1a} or V_2 receptors ($N = 2$).

phenyl as aryl 'A', based on the V_{1a}- and V_2-receptor binding activity of **8g**. A more efficient synthesis was developed utilizing an enantiomerically pure intermediate **10**, which was prepared on gram scale quantities. This allowed for incorporation of various aryl 'B' moieties as a final step, thereby rapidly producing the desired eutomers in a parallel fashion (Scheme 2, R = 3-OMe).

Table 3
Vasopressin receptor binding data for optimal biphenyl amides



8a,c,e,g,i, 12g, 13d,g,m, 14a-s

Compound	R	Ar	hV_{1a} Binding K_i[a] (nM)	hV_2 Binding K_i[a] (nM)	V_{1a}/V_2 Binding ratio K_i
Conivaptan	—	—	0.43	0.36	1.19
8c	2-Cl	Ph, 2-Me	0.31	54	<0.01
8i	2-OMe-5-Cl	Ph, 2-Me	0.54	107	<0.01
8e	3-Me	Ph, 2-Me	0.06	478	<0.01
8g	3-OMe	Ph, 2-Me	20	82	0.24
8a	H	Ph, 2-Me	0.05	204	<0.01
14a	2,3-diCl	Benzothiophen-3-yl	40.6	124	0.33
14b	2,5-diCl	Benzothiophen-3-yl	315	233	1.35
14c	2-Cl	Benzothiophen-3-yl	52	171	0.30
14d	2-OMe-5-Cl	Benzothiophen-3-yl	86.6	36.5	2.37
13d	3-OMe	Benzothiophen-3-yl	0.79	15	0.05
14e	Naphth-1-yl, 4-	Benzothiophen-3-yl	111	21	5.29
14f	2,3-DiCl	Naphthalen-1-yl	94.6	60.6	1.56
14g	2,5-DiCl	Naphthalen-1-yl	443	133	3.33
14h	2-Cl	Naphthalen-1-yl	95.4	176	0.54
14i	2-OMe-5-Cl	Naphthalen-1-yl	150	39.2	3.83
13g	3-OMe	Naphthalen-1-yl	5.40	63	0.09
14j	2,3-diCl	Ph, 3-NHAc	187	>2550	—
14k	2,5-diCl	Ph, 3-NHAc	5000	>2550	—
14l	2-Cl	Ph, 3-NHAc	116	>2550	—
14m	2-OMe-5-Cl	Ph, 3-NHAc	178	>2550	—
12g	3-OMe	Ph, 3-NHAc	0.37	30	0.01
14n	Naphth-1-yl, 4-	Ph, 3-NHAc	94.4	>2550	—
14o	2,3-diCl	Quinolin-8-yl	33.8	9.2	3.67
14p	2,5-diCl	Quinolin-8-yl	62.5	82	0.76
14q	2-Cl	Quinolin-8-yl	38.6	40	0.97
14r	2-OMe-5-Cl	Quinolin-8-yl	49.7	43.4	1.15
13m	3-OMe	Quinolin-8-yl	0.71	130	<0.01
14s	Naphth-1-yl, 4-	Quinolin-8-yl	7.1	420	0.02

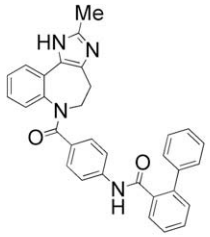
[a] Inhibition of [^{3}H]-Arg-vasopressin binding to recombinant human vasopressin V_{1a} or V_2 receptors ($N = 2$).

A diverse set of targets containing electron rich and poor phenyl, fused aryl, and heteroaryl 'B' groups were synthesized and evaluated for V_{1a}- and V_2-receptor binding affinity (Table 2). Several compounds exhibited more potent V_2-receptor affinity with weakened V_{1a} activity, leading to improved V_{1a}/V_2 ratios. In particular, **8g**, **12g**, **13d**, and **13g** had excellent V_{1a}-receptor binding affinity with the most potent V_2-receptor affinity observed. This data suggested that the described aryl 'B' groups provide guidance as to where the V_2-receptor activity could be optimized.

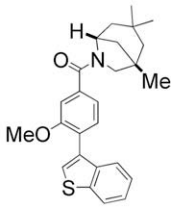
Efforts continued towards improving the V_2-receptor binding affinity while utilizing the optimal aryl 'B' groups. Several additional compounds with excellent V_{1a}-receptor activity and acceptable V_2-receptor binding affinities were identified (Table 3). In addition, these structural modifications led to compounds with varying V_{1a}/V_2 ratios, providing an opportunity to study the effect of varying V_{1a}/V_2 mixed activity in vivo.

One of the targets, **13d,** demonstrated improved V_2-receptor binding and was further profiled for comparison with conivaptan, the program's mixed V_{1a}/V_2 standard (Table 4). Compound **13d** displayed similar V_{1a}-receptor affinity, albeit with a 30-fold weaker V_2-receptor affinity when compared to conivaptan. Significantly weaker inhibitory activity in both the V_{1a} and V_2 functional assays was observed with **13d** vis-à-vis conivaptan, which demonstrated the need to closely monitor the functional activity of this series. This class of compounds, including **13d**, showed a trend toward

Table 4
In vitro profiling of conivaptan and **13d**



conivaptan



13d

Compound	Conivaptan	**13d**
hV_{1a} Binding K_i[a] (nM)	0.43	0.79
hV_2 Binding K_i[a] (nM)	0.36	15
V_{1a}/V_2 Binding ratio K_i	1.19	0.05
hV_{1a} FLIPR Ca^{2+} IC_{50}[b] (nM)	3	41
hV_2 cAMP IC_{50}[c] (nM)	11	838
V_{1a}/V_2 Functional ratio IC_{50}	0.27	0.05
RLM $t_{1/2}$[d] (min)	21	<1
HLM $t_{1/2}$[d] (min)	10	3
Solubility (μg/mL)	<1	<1
Cyp450 3A4, 2D6, 2C9[e] (%)	75, 17, 35	0, 0, 24
MW	498.58	419.59
*c*Log *P*	5	6
tPSA	78	29

[a] Inhibition of [^{3}H]-Arg-vasopressin binding to recombinant human vasopressin V_{1a} or V_2 receptors ($N = 2$).
[b] Functional measurement of intracellular calcium of hV_{1a} receptor using FLIPR dose–response.
[c] Functional measurement of intracellular cAMP of hV_2 receptor using luminescence dose–response.
[d] Profile screening concentration of 1 μM in DMSO.
[e] Profile screening concentration of 3 μM in DMSO.

an improved Cyp450 profile over conivaptan. However, **13d** was identified as having metabolic liabilities, which would need to be addressed with further optimization. Compound **13d** had increased *c*log *P* relative to conivaptan, however this could possibly be improved by incorporating polar moieties, thereby increasing its tPSA and aqueous solubility.

In summary, we have reported several biaryl amides containing a chiral bicyclic amine that possess dual V_{1a}/V_2 vasopressin receptor affinity. Many analogues, including **8g**, **12g**, **13d**, and **13g**, were shown to have excellent V_{1a}- ($K_i \leqslant 5.4$ nM) and good V_2-receptor ($K_i \leqslant 104$ nM) binding affinity. Compound **13d** has undergone further pharmacological and pharmaceutical evaluation and displayed good V_{1a} and moderate V_2 functional activity with an improved Cyp450 profile when compared to conivaptan. However, additional optimization of **13d** will be necessary to address its cellular functional activity, metabolic liability, and limited aqueous solubility.

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27. Compounds with similar structural motifs had been described for modulating the activity of 11 β-hydroxysteroid dehydrogenase type 1 (11βHSDP1); see Andersen, H. S.; Kampen, G. C. T.; Christensen, I. T.; Mogensen, J. P.; Larsen, A. R.; Kilburn, J. P. WO Patent 2004089470, 2004.
28. Inhibition of [^{3}H]-Arg-vasopressin binding to recombinant human vasopressin V_{1a} or V_2 receptors ($N = 2$).
29. Purifications by chiral SFC (CO_2/EtOH or MeOH eluent on ChiralPak AS-H, ChiralPak AD-H or Pirkle Covalent (*R*,*R*) Whelk-01 columns).
30. The VCD spectra were measured using a commercially available VCD instrument ChiralIRTM (BioTools, Inc., Wauconda, IL). Each of the two enantiomers was dissolved in DMSO-d_6 (84 mM) and placed in a BaF_2 cell with a path length of 0.1 mm. The VCD spectrum of each sample and solvent was measured for 8 h with a 4 cm^{-1} resolution and the photo elastic modulators optimized at 1400 cm^{-1}. The VCD baseline was obtained by subtracting the VCD of one enantiomer from that of the other then dividing by two. The IR baseline was obtained by subtracting the IR spectrum of DMSO-d_6 from that of the sample.