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(4-Substituted-phenyl)-(5*H*-10,11-dihydro-pyrrolo [2,1-*c*][1,4] benzodiazepin-10-yl)-methanone derivatives as vasopressin receptor modulators

Aranapakam M. Venkatesan,[a,*] George T. Grosu,[a] Amedeo A. Failli,[b] Peter S. Chan,[c] Joseph Coupet,[c] Trina Saunders,[c] Hussain Mazandarani[c] and Xun Ru[c]

[a]*Chemical and Screening Sciences, Wyeth Research, Pearl River, NY 10965, USA*
[b]*Chemical and Screening Sciences, Wyeth Research, 567 Ridge Road, Princeton, NJ 08543-8000, USA*
[c]*Cardiovascular and Metabolic Diseases, Wyeth Research, 567 Ridge Road, Princeton, NJ 08543-8000, USA*

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Abstract—Synthesis and structure–activity relationships (SAR) of arginine vasopressin (AVP) receptor modulators are described. Potent and selective compounds are prepared when the amide linkage connecting rings A and B of VPA-985 is replaced with a bond, C═O, –O–, –S–, or –SO_2– bond.

The cyclic peptide hormone, arginine vasopressin (AVP), an anti-diuretic hormone released from the posterior pituitary gland, plays an important role in water balance in the body.[1–4] This hormone is released in response to increased plasma osmolality detected by the brain osmoreceptor, decreased blood volume or decrease in blood pressure sensed by low-pressure volume receptors and arterial baroreceptors. The hormone exerts its action through well-defined receptor subtypes: vascular V_{1a} and renal epithelial V_2 receptors. One of the key roles of AVP is the control of salt (NaCl) balance. The blockade of V_2 receptors may correct the fluid retention in congestive heart failure, liver cirrhosis, nephritic syndrome, CNS injuries, lung disease and hyponatremia. Thus, antagonizing AVP action at the V_2 receptor level with an orally active, non-peptide agent may be the treatment of choice for the above-mentioned disease states.

In the past, several benzazepine derivatives have been reported by Otsuka chemists as V_{1a} and V_2 receptor AVP antagonists.[5,6] As part of the efforts to develop non-peptide vasopressin antagonists, we previously reported on the design and synthesis of the selective V_2 antagonist VPA-985 **1** and closely related analogues, such as **2a**.[7–11] In all these compounds, an amide bond connected rings A and B (Fig. 1). We have shown in the past[4] that a compound such as **2b**, where the rings A and B are directly connected, exhibits excellent V_2 agonist activity. The therapeutic utilities of vasopressin V_2 receptor agonists include diabetes insipidus, nocturnal enuresis, nocturia and urinary incontinence. Hence, it is the objective of this paper to investigate the SAR of compounds, where the amide linkage between these two rings has been replaced with a bond, C═O, –O–, –S–, or –SO_2– bond.

Compounds **3a**–**3p** (Table 1) required for the present investigation were prepared, as indicated in Scheme 1. The tricyclic 10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine **4** was synthesized, according to the literature procedures.[12,13] Derivatives **3a**, **3f**–**g** and **3i**–**3m** were prepared by reacting their respective acid chlorides with **4** in the presence of triethylamine in methylene chloride solution (Scheme 1).[14] The acetylene derivative, **3h**, was synthesized by reacting **7** with phenyl acetylene in the presence of Pd(II)chloride in refluxing acetonitrile. Intermediate **7** was used to prepare compounds **3b**–**3e** by a two-step process. Compound **7** was reacted with bis(tributyl)tin, lithium chloride and tetrakis(triphenylphosphine)palladium(0) in refluxing dioxane to yield the stannyl derivative **8**, which was coupled with the

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* Corresponding author. Tel.: +84 56 02 40 23; fax: +84 56 02 55 61; e-mail: venkata@wyeth.com

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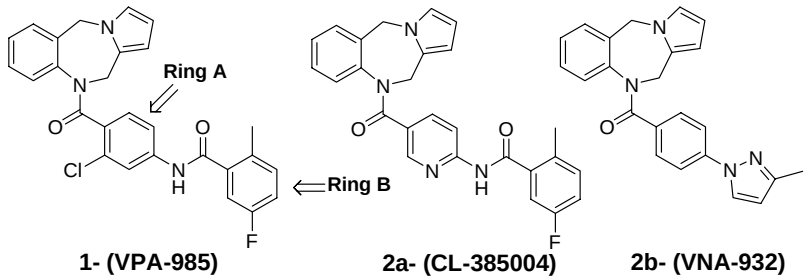
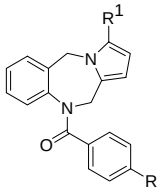


Figure 1. Previously reported AVP modulators.

Table 1. In vitro and in vivo data for compounds **3a**–**3p**

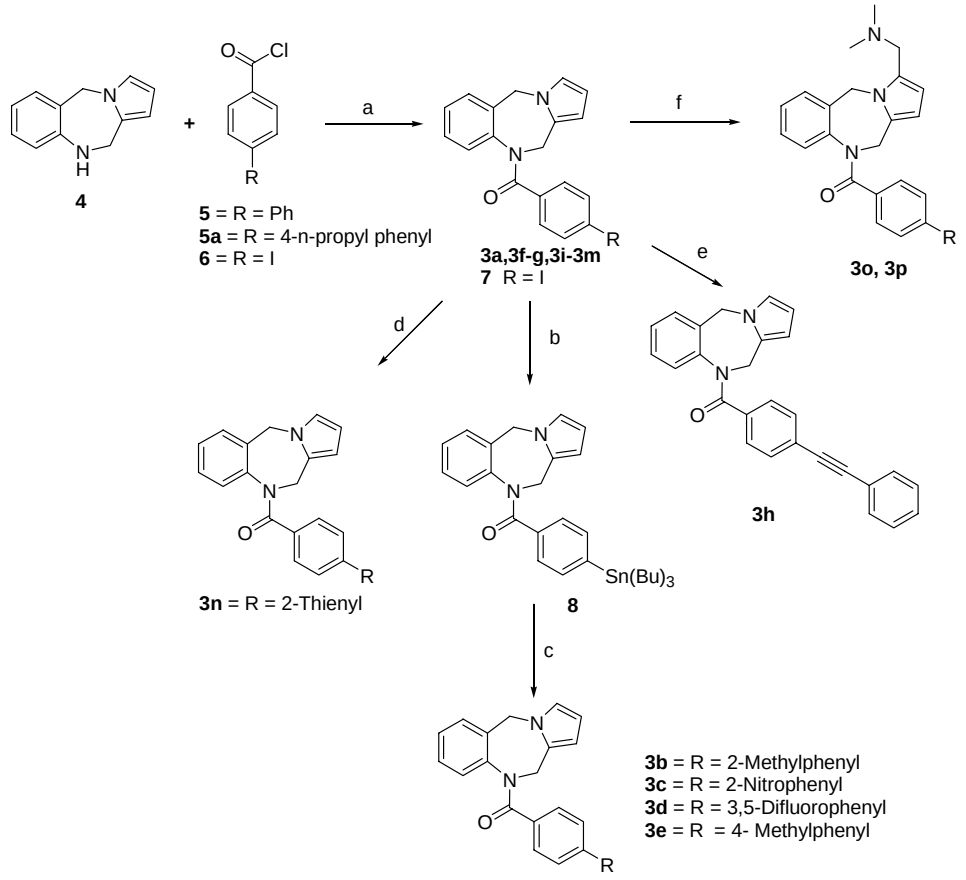


Compound	R	R^1	IC_{50} human nM (% inhibition)		Urine volume[d] (mL)
			V_1[a]	V_2[b]	
	AVP treated control				5.0
	VPA-985		180	1.0	37
3a	Phenyl	H	3	390	3.5
3b	2-Methylphenyl	H	88	2000	7.8
3c	2-Nitrophenyl	H	64	96	5.5
3d	3,5-Difluorophenyl	H	85	2500	5.9
3e	4-CH_3-phenyl	H	2	300	NA
3f	4-Allyloxyphenyl	H	(9% at 10 μM)	NA[c]	4
3g	4-Propyl phenyl	H	12	58	4.5
3h	Phenyl-acetynyl-	H	(35% at 1 μM)	(63% at 1 μM)	6.3
3i	-O-4-Methylphenyl	H	280	(50% at 1 μM)	5.3
3j	-S-Phenyl	H	(47% at 1 μM)	(42% at 1 μM)	4
3k	-S-4-Methylphenyl	H	(15% at 1 μM)	(32% at 1 μM)	11
3l	-SO_2-4-Methylphenyl	H	21	NA[c]	5.5
3m	-CO-Phenyl	H	(82% at 10 μM)	(42% at 1 μM)	6
3n	2-Thienyl	H	13	510	5
3o	Phenyl	-$CH_2N(Me)_2$	13	(78% at 10 μM)	3.5
3p	2-Thienyl	-$CH_2N(Me)_2$	63	15,000	3

[a] V_1 receptor binding in human platelets.
[b] Binding to murine fibroblast LV2 cell line membranes transfected with the human V_2 receptor; urine volume in water-loaded control animals = 13 mL/4 h.
[c] NA = examples **3f** and **3l** have only the rat data for V_2 binding affinity and they show 63% and 51% inhibition at 1 μM concentration.
[d] Urine volume in AVP treated animals = 5 mL/4h.

appropriately substituted aryl bromides in the presence of $(PPh_3)_4Pd(0)$ in boiling toluene to yield **3b**–**3e**. Similarly, compound **3n** was synthesized starting from the iodo intermediate **7**. Stille coupling of **7** with 2-stannyl substituted thiophene yielded **3n** in good yield. To improve water solubility, compounds **3o** and **3p** were prepared with an appended polar functionality. Incorporation of $-CH_2N(CH_3)_2$ functionality was achieved by treating **3a** and **3n** with formaline and dimethylamine in the presence of acetic acid at room temperature.

The initial in vitro radio ligand binding studies were carried out with rat receptors. Binding affinities were determined by measuring the inhibition of (Phe-3,4,5^{3}H) AVP binding to isolated rat hepatic V_{1a} receptors or inhibition of binding of ^{3}H-AVP to isolated kidney medullary V_2 receptors. However, the possibility of species differences with respect to the binding affinities at the V_{1a} receptors[16] prompted us to consider binding studies with human receptors. Thus, the newly synthesized compounds were evaluated for inhibition of binding to membrane preparations from a murine fibroblast cell line (LV2) expressing human V_2 receptors and to V_{1a} receptors from human platelet membranes measuring the displacement of ^{3}H-AVP or ^{3}H-[d$(CH_2)_5^1$, Tyr(Me),^{2}Arg^8]-AVP by the test compound. The in vitro binding affinities for a series of 10,11-dihydro-10-[(biaryl and aryl-heteroaryl)carbonyl]-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine derivatives **3a**–**3p** are shown in Table 1. VPA-985 was used as comparator. It is interesting to note that, when the amide linkage



Scheme 1. Reagents and conditions: (a) CH_2Cl_2/Et_3N; (b) **7**/LiCl/Sn_2 (n-$Bu_3)_2$/$Pd(PPh_3)_4$/dioxane/reflux; (c) arylbromide/$Pd(PPh_3)_4$/toluene/reflux; (d) **7**/2-stannyl derivatives of thiophene/$Pd(PPh_3)_4$/toluene/reflux; (e) **7**/phenyl acetylene/$PdCl_2/CH_3CN$/reflux; (f) **3a** or **3o**/formaline/$(CH_3)_2NH/H^+$/THF/rt.

in VPA-985 is replaced with a direct C–C bond, it appears as though the affinity for the human V_2 receptor decreases and the V_{1a} human receptor affinity increases compared to VPA-985. Thus, when compared to VPA-985, the unsubstituted compound **3a** exhibits very potent affinity for V_{1a} receptor and poor V_2 affinity. Among the newly synthesized molecules, introduction of a methyl substituent at the 2 position of ring B, (compound **3b**) led to decrease in the affinity of both V_{1a} and V_2 receptors. However, switching the methyl group to the 4 position (compound **3e**) restored the potency. Similarly, a *n*-propyl substituent at the 4 position of ring B (compound **3g**) also showed good affinity for both V_{1a} and V_2 receptors. When ring A is linked to ring B via an acetylene (e.g., **3h**), V_{1a} and V_2 affinities decrease drastically. However, when connecting rings A and B via an ether linkage (**3i**), both V_{1a} and V_2 affinities are retained, albeit reduced. The presence of a thioether linkage (**3j** and **3k**), between ring A and ring B or C=O (**3m**), leads to decreased affinity towards both receptors. The fully oxidized sulfone derivative **3l** exhibited good V_{1a} affinity. Replacement of ring B in **3a** with a heterocycle, such as 2-thienyl (**3n**), leads to retention of affinity at both V_{1a} and V_2 receptors. Introduction of basic groups, such as $-CH_2N(Me)_2$ (**3o** and **3p**), leads to a decrease in affinities for both V_{1a} and V_2 receptors, when compared to their respective unsubstituted analogues **3a** and **3n**.

In vivo studies were conducted in conscious AVP-treated (0.4 μg/kg, ip), water-loaded (30 mL/kg, po) rats. The synthesized compounds **3a**–**3p** were given orally at 10 mg/kg (mixed with starch and DMSO). The urine volume was measured during the period of 4 h and compared with AVP-treated controls,which is shown in Table 1. Simultaneously, osmolality was analyzed.[15] It is evident from Table 1 that most of the compounds reported here, when given orally, did not show diuretic effect when compared to water-loaded control animals and AVP-treated controls. In control animals, the urine output was found to be 13 mL/4h and in the AVP-treated animals it was found to be 5 mL/4h. Among the newly synthesized molecules, the unsubstituted derivative **3a** and other derivatives, such as **3f**, **3j**, **3o** and **3p**, exhibit a slight anti-diuretic activity. Compound **3b** in vitro is about 20 times less active than compound **3c** against V_2 receptor, yet slightly more active in vivo. Surprisingly, compound **3k**, which exhibits a poor affinity for the human V_2 receptor, has the most diuretic effect among the newly synthesized derivatives. It almost reversed the effect of AVP on the water-loaded control. This may be due to several factors, such as species differences[16] or a higher blood level concentration of **3k**, although we have no data to put forward to support this aspect. However, none of the other newly synthesized compounds completely reversed the effect of AVP on the water-loaded control (13 mL/4h).

As mentioned earlier, a direct linking of ring A and ring B in VPA-985 through a C–C or a C–N bond can lead to molecules, such as VNA-932 **2b**, which has been shown to exhibit AVP-mimetic properties.[17] To be consistent with these latter findings, the compounds reported here could potentially be partial agonists that cannot be distinguished from weak antagonists using the reported in vivo protocol. Further work is in progress to fully elucidate the structural requirements leading from antagonism to agonism, which will be reported separately.

In summary, this paper describes a series of compounds, where ring A and ring B in VPA-985 have been replaced by a bond, C=O, –O–, –S– or $–SO_2–$. This modification in VPA-985 gave derivatives **3a**–**3p** with binding affinity for the AVP $V1_a$ and V_2 receptors.

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