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5-FLUORO-2-METHYL-N-[5-(5*H*-PYRROLO[2,1-*c*][1,4]BENZODIAZEPINE-10(11*H*)-YL CARBONYL)-2-PYRIDINYL]BENZAMIDE (CL-385004) AND ANALOGS AS ORALLY ACTIVE ARGININE VASOPRESSIN RECEPTOR ANTAGONISTS

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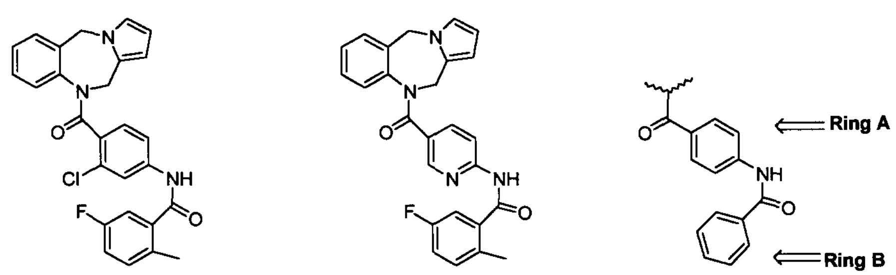
Abstract: Synthesis and structure–activity relationships (SAR) of orally active arginine vasopressin (AVP) receptor antagonists are discussed. Potent and orally active AVP receptor antagonists are produced when ring A of VPA-985 **(1)** is replaced with a 3-pyridinyl unit **(2b)**.

Vasopressin is an antidiuretic hormone, released from the posterior pituitary gland.[1-3] The hormone exerts its action through two receptor subtypes: vascular V_{1a} and renal epithilial V_2 receptors. One of the key roles of arginine vasopressin (AVP) is the control of salt (NaCl) balances. The blockade of V_2 receptors may be useful in treating diseases characterized by excess renal absorption of free water. Thus V_2 antagonists may correct the fluid retention in congestive heart failure, liver cirrhosis, nephrotic syndrome, CNS injuries, lung disease and hyponatremia. Thus antagonizing AVP actions at the receptor level with orally active, nonpeptidic agents may be the treatment of choice for edematous states associated with hyponatremia.

Figure 1



1: VPA-985 **2b: CL-385004**

Otsuka chemists[4,5] reported 2,3,4,5-tetrahydro1,5-benzazepines as V_{1a} and V_2 receptor AVP antagonists, while Albright, et al.[6,7] reported on the design and synthesis of VPA-985 **1**, which is currently undergoing phase II clinical trials. This paper presents the SAR of derivatives where the phenyl ring A (Figure 1) is replaced with a 3-pyridinyl moiety. These compounds were prepared to increase the polarity and potentially to increase the water solubility of VPA-985. The compounds required for the present investigation were prepared as indicated in Scheme 1.

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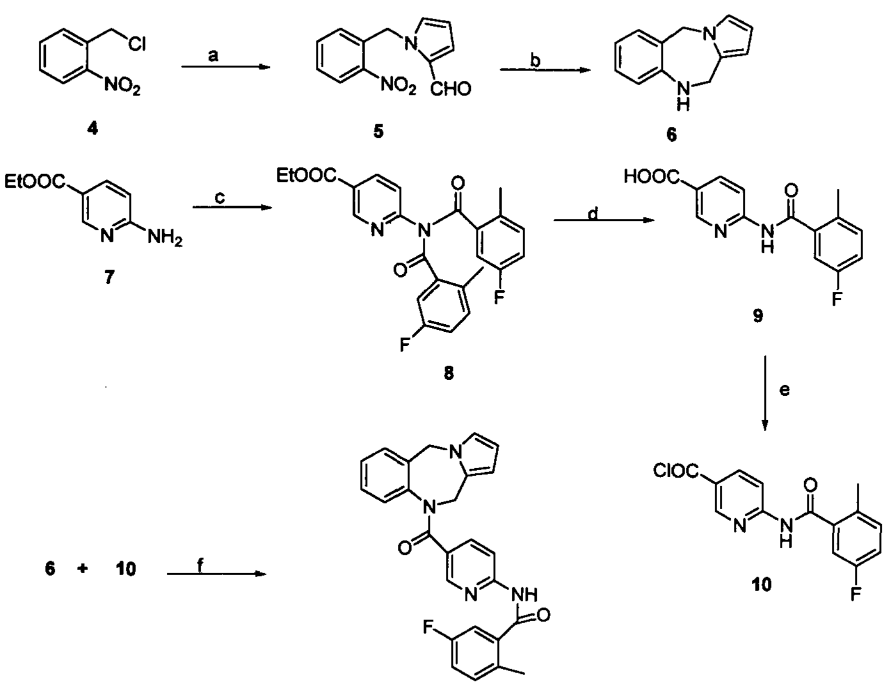
SCHEME 1



(a) 2-pyrrole carboxaldehyde/NaH/THF/0 °C; (b) H_2/Pd/C/EtOH/rt; (c) 5-fluoro-2-methylbenzoyl chloride/Et_3N/CH_2Cl_2 rt; (d) THF/NaOH/rt/24 h; (e) $(COCl)_2$/DMF/CH_2Cl_2 /0 °C; (f) Et_3N/CH_2Cl_2 rt.

The tricyclic 10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine **6** was synthesized according to the literature procedure[8,9] by reductive ring closure of 1-(2-nitrobenzyl)-2-pyrrole carboxyaldehyde **5** (Scheme 1). The appropriately substituted acid chlorides **10,** as exemplified for the preparation of **2b**, were prepared starting from the commercially available 6-aminonicotinic acid. Esterification with ethanolic hydrogen chloride gave the ethyl ester **7**. This ester was reacted with 2 equiv of 5-fluoro-2-methylbenzoyl chloride to give bis derivative **8**, which was hydrolyzed to acid **9** with 2 N NaOH/THF at room temperature. The acid **9** was converted to the acid chloride using oxalyl chloride/DMF. Reaction of acid chloride **10** with compound **6** (CH_2Cl_2/Et_3N at room temperature) gave derivative **2b**. Compounds (**2a**–**2r**) prepared via Scheme 1 are listed in Table 1.

The in vitro binding studies were carried out with receptors isolated from rat liver (V_{1a}) and rat kindney (V_2).[10] Binding assays 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. In vivo studies were conducted in conscious AVP-treated (0.4 ug/kg, ip) and water-loaded (30 mL/kg; po) rats. The compounds **2a**–**2r** were given orally 10 mg/kg (mixed with starch and DMSO). The amount of urine output was measured and compared.

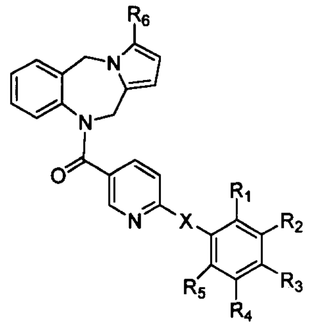
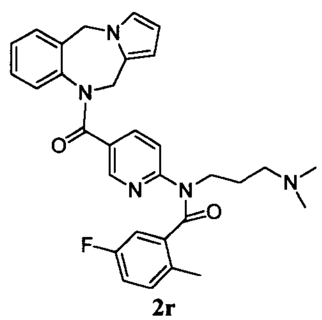


Table 1

								IC$_{50}$ nm		ML/4 h
No	**X**	**R$_1$**	**R$_2$**	**R$_3$**	**R$_4$**	**R$_5$**	**R$_6$**	**V$_{1a}$**	**V$_2$**	**Urine Vol[a]**
2a	-NHCO-	CH_3	H	H	H	H	H	21	3	5.3
2b	-NHCO-	CH_3	H	H	F	H	H	33	4	20[b]
2c	-NHCO-	H	OMe	OMe	OMe	H	H	51%[c]	41%[c]	NT
2d	-NHCO-	CH_3	F	H	H	H	H	9	1	34
2e	-NHCO-	CH_3	H	H	F	H	Y[d]	99	33	12.5
2f	-NHCO-	F	H	F	H	H	H	37%[c]	58%[c]	NT
2g	-NHCO-	Cl	H	H	H	H	H	11	1.8	4
2h	-NHCO-	Br	H	H	H	H	H	7	1.6	NT
2i	-NHCO-	Cl	H	F	H	H	H	6	1.1	30.5
2j	-NHCO-	Ph	H	H	H	H	H	30	8.3	16.5
2k	-NHCO-	Cl	H	H	X[e]	H	H	260	480	NT
2l	-NHCO-	Cl	H	H	Br	H	H	82	7.3	16.5
2m	-NHCO-	NO_2	H	H	H	H	H	920	160	NT
2n	-NHCO-	NH_2	H	H	H	H	H	29%[c]	210	NT
2o	-NHCO-	Cl	H	H	Cl	H	H	100	4.3	19.3
2p	-NHCO-	Cl	H	H	H	F	H	40	4	15.8
2q	-NHCO-	F	H	H	F	H	H	310	240	11.8



2r

V_{1a} = 68% (10 uM); V_2 = 290 nM

1				VPA-985				82	0.5	35

[a]Rat dose 10 mg/kg/po, urine volume of control 5 mL; [b]1 mg/kg/po; [c]% Inhibition at 10 μM; [d]Y = $CH_2N(CH_3)_2$; [e]X =2-pyridinyl.

The IC_{50} values of different compounds and their in vivo activities are enlisted in Table 1. These values indicate that a bulky R_1 substituent is essential for the activity. When R_1 = H or F (example **2c** and **2f**) there is a loss in the activity. Introduction of polar functional groups such as $-NO_2$ (example **2m**) and $-NH_2$ (example **2n**) leads to a decrease in the V_{1a} and V_2 binding affinities. When R_1 is CH_3 and R_4 is fluorine (example **2b**), R_1 is CH_3 and R_2 is fluorine (example **2d**) and R_1 is chlorine and R_3 is fluorine (example **2i**) both the in vivo and in vitro potency increases. (Compared to other compounds enlisted in Table 1). But both compounds (example **2d** and **2i**) are not efficacious at lower dosage, at 1mg/kg/po. Compound **2b** when administered at 1 mg/kg/po the output of urine was found to be 20 mL/4h. (Control 5 mL). Thus example **2b** (CL-385004) is the most potent orally active compound in this series. Introduction of a $-CH_2N(CH_3)_2$ moiety at R_6 (example **2e**) decreased the in vitro activity (eightfold, compared to example **2b**, V_2 affinity). Replacement of hydrogen present in the amide linkage, connecting the A-ring and the B-ring with $-(CH_2)_3N(CH_3)_2$ (example **2t**) led to loss of V_{1a} and V_2 activity.

In conclusion, replacement of the phenyl unit in ring-A of VPA-985 with a 3-pyridinyl unit give potent V_{1a} and V_2 active compounds . The compounds **2b**, **2d**, and **2i** exhibit potent in vitro activity and show good oral activity in rats. But among these three compounds, derivative **2b**, (CL-385004) is the most potent orally active compound in this series.

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