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4,10-DIHYDRO-5*H*-THIENO[3,2-*c*][1]BENZAZEPINE DERIVATIVES AND 9,10-DIHYDRO-4*H*-THIENO[2,3-*c*][1]BENZAZEPINE DERIVATIVES AS ORALLY ACTIVE ARGININE VASOPRESSIN RECEPTOR ANTAGONISTS

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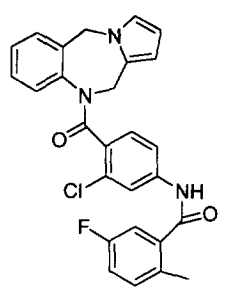
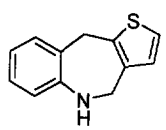
Abstract: Synthesis and structure–activity relationships (SAR) of arginine vasopressin receptor (AVP) antagonists are described. Potent and orally active compounds are prepared when tricyclic 10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine moiety in VPA-985 **1** is replaced with a compound **7** or **12**.

Vasopressin is an antidiuretic hormone, released from the posterior pituitary either in response to increased plasma osmolarity detected by brain osmoreceptors or decreased blood volume and blood pressure sensed by low pressure volume receptors and arterial baroreceptors.[1–3] The hormone exerts its action through well defined 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, nonpeptide agents may be the treatment of choice for edematous states.



VPA-985 1



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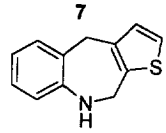

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Otsuka chemists[4,5] reported several benzazepines as V_{1a} and V_2 receptors AVP antagonists. As part of the project to develop nonpeptide vasopressin antagonists, we reported previously[6,7] the discovery and the SAR of 5-fluoro-2-methyl-N-[4-(5*H*-pyrrolo[2,1-*c*][1,4] benzodiazepin-10(11*H*)-ylcarbonyl)-3-chlorophenyl] benzamide

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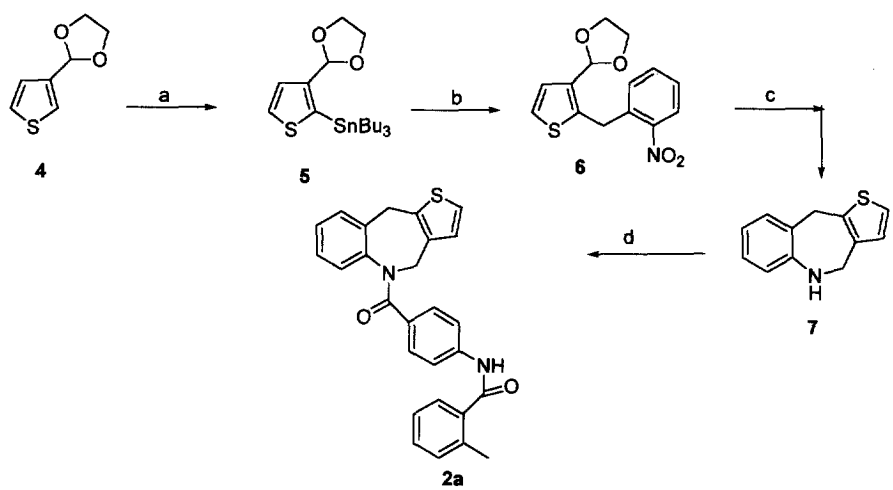
1 (VPA-985), which is currently undergoing clinical trials. In continuation of this project, the tricyclic 10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine moiety in VPA-985 was replaced with the 4,10-dihydro-5*H*-thieno[3,2-*c*][1]benzazepine derivative **7** and 9,10-dihydro-4*H*-thieno[2,3-*c*][1]benzazepine derivative **12**. The ring systems **7** and **12** reported in this paper are prepared by novel routes, and herein we describe the SAR of derivatives of these tricyclic compounds **7** and **12**.

Synthesis of 4,10-dihydro-5*H*-thieno[3,2-*c*][1]benzazepine

2-[(2-Tributylstannyl)-3-thienyl]-1,3-dioxolane **5** was prepared as outlined in Scheme 1, according to the method of Gronowitz et al.[8,9] The stannyl compound **5** was reacted with 2-nitrobenzyl bromide and $[(C_6H_5)_3P]_4Pd$. Deprotection and reductive cyclization was carried out in one step by reacting compound **6** with zinc and aqueous acetic acid. Compound **7** can be reacted with 4-(2-methylbenzoylamino)benzoic acid chloride to give compound **2a**.

SCHEME 1

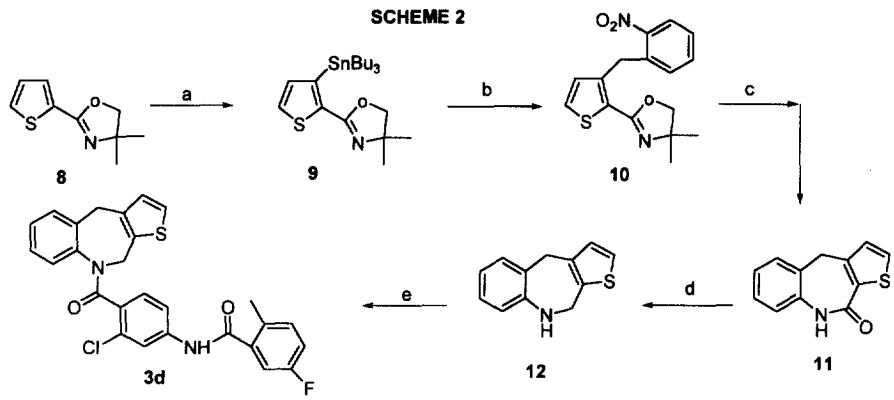


(a) *n*-BuLi/ether/reflux/then –78 °C/$ClSnBu_3$; (b) $[(C_6H_5)_3P]_4Pd$/2-nitrobenzyl bromide/ toluene/reflux/24 h; (c) $Zn/CH_3COOH/H_2O$/80 °C; (d)4-(2-methylbenzoylamino)benzoic acid chloride/Et_3N/CH_2Cl_2/ rt.

Synthesis of 9,10-dihydro-4*H*-thieno[2,3-*c*][1]benzazepine

The other isomer, namely 9,10-dihydro-4*H*-thieno[2,3-*c*][1]benzazepine was prepared as outlined in Scheme 2. 4,5-Dihydro-4,4-dimethyl-2-(2-thienyl)-oxazole **8** was lithiated according to the procedure of Vlattas et al.[10] and the lithio derivative was reacted with tri-*n*-butyltin chloride to give compound **9**. Coupling of **9** with 2-nitrobenzyl bromide in the presence of $[(C_6H_5)_3P]_4Pd$ gave **10**. The oxazolidine was unmasked to afford the carboxylic acid and then reductive cyclization led to the formation of compound **11**. The amide **11** was reduced to amine **12** by reacting it with lithium aluminum hydride in refluxing THF. Compound **12** can be reacted with the appropriately substituted benzoyl chloride to give **3a** to **3d**.

SCHEME 2



(a) *n*-BuLi/Et_2O/–70 °C to 0 °C/$ClSnBu_3$; (b) $[(C_6H_5)_3P]_4Pd$/2-nitrobenzyl bromide/toluene/ reflux/24 h; (c) $Zn/CH_3COOH/H_2O$/80 °C; (d) Li AlH_4/ THF/reflux; (e) 2-chloro-4-(5-fluoro-2-methylbenzoylamino)benzoic acid chloride /Et_3N/CH_2Cl_2/ rt.

The in vitro binding studies were carried out with membrane from murine fibroblast cell line (LV_2) expressing human V_2 receptors or the inhibition of 3H-AVP or ^{3}H-[d(CH_2)$_5$ ^{1}Tyr(Me)^2,Arg^8)-AVP binding to V_{1a} receptors from human platelet membrane.[11] In vivo studies were conducted in conscious AVP-treated (0.4 ug/kg, ip) and water-loaded (30 mL/kg; po) rats. The compounds **3a–3d**, **2a** and **1** were given orally at 10 mg/kg (mixed with starch and DMSO). The amount of urine output was measured and comparative results are listed in Table 1.

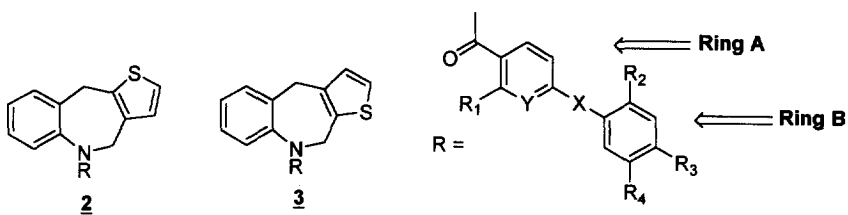


Table 1

No.	Y	X	R_1	R_2	R_3	R_4	IC_{50} (nM) V_{1a}	IC_{50} (nM) V_2	Urine Volume mL/4 h[a]
3a	N	NHCO	H	CH_3	H	F	59[b]	29[b]	16.5
3b	CH	NHCO	H	CH_3	H	H	8.5	0.7	13.5
3c	CH	NHCO	H	Cl	Cl	H	43	19	5.8
3d	CH	NHCO	Cl	CH_3	H	F	59%[c]	6.8	30
2a	CH	NHCO	H	CH_3	H	H	36	9	4.5
VPA-985							230	1.2	35

[a]Dose in rats at 10 mg/kg po. Urine volume of control 5 mL; [b]Rat V_{1a} and Rat V_2 receptor (see ref 7); [c]% inhibition at 10 uM; NT = Not tested;

The receptor binding data (IC_{50} values) for V_{1a} and V_2 receptors for the compounds prepared are also listed in Table 1. When the ring-A phenyl group is replaced by a pyridinyl unit, (example **3a**) the in vitro and in vivo activities are retained. Introduction of chlorine in the ring-A (**3d**) increases the selectivity for V_2 receptors while still retaining the potency for the V_2 receptors. This compound is less active in binding to human receptors than VPA-985 by fivefold, but the in vivo activity is almost identical. The presence of chlorine in ring B, especially adjacent to the carbonyl (**3c**) slightly decreased the potency. Replacing the 9,10-dihydro-4*H*-thieno[2,3-*c*][1]benzazepine unit with 4,10-dihydro-5*H*-thieno[3,2-*c*][1]benzazepine gave derivative **2a**, whose V_2 antagonist activity is more than ten-fold less than the corresponding **3b** analog. This compound also exhibited poor in vivo activity.

In summary, this paper describes the study of 4,10-dihydro-5*H*-thieno[3,2-*c*][1]benzazepine **2** and 9,10-dihydro-4*H*-thieno[2,3-*c*][1]benzazepine **3** derivatives as human vasopressin (V_2) receptor antagonists. Replacing the 10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine unit in VPA-985 with 9,10-dihydro-4*H*-thieno[2,3-*c*][1]benzazepine **3** gave derivatives with potent V_{1a} and V_2 receptor binding activity. The compound **3d** is a potent, orally active and highly selective V_2 antagonist.

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