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Structure–Activity Study of Novel Tricyclic Benzazepine Arginine Vasopressin Antagonists

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Abstract—Novel tricyclic benzazepine derivatives were synthesized as arginine vasopressin (AVP) antagonists. Several tricyclic compounds showed potent antagonistic activity in rat AVP receptors V_{1a} and V_2. Derivatives containing pyrrolo-tricyclic amines, **13i–k**, **30**, and **31** also showed selectivity for the V_2 receptor.
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Arginine vasopressin (AVP) is a cyclic nonapeptide hormone released from the posterior pituitary in response to either increased plasma osmolality, or decreased blood volume and blood pressure. AVP binds to three known receptor subtypes: vascular V_{1a}, hormone releasing V_{1b}, and renal V_2 receptors, and regulates osmotic water permeability of water channels in the kidney through the V_2 receptor.[1–3] Antagonists of the V_2 receptor are potentially useful for treating diseases characterized by excess renal reabsorption of free water, such as congestive heart failure, liver cirrhosis, nephrotic syndrome, and hyponatremia.[4]

VPA-985 (Fig. 1), discovered in our laboratories,[5] is an orally active AVP antagonist with selectivity for the V_2 receptor. It is currently in clinical trials for the treatment of congestive heart failure. During the course of developing VPA-985, we have investigated a large number of tricyclic benzazepine derivatives. Herein we report the synthesis and structure–activity relationship of a series of compounds containing different tricyclic 'head-pieces', as well as a series of 10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzdiazepine analogues with modifications at the benzoylamino 'tail-piece'.

We have selected eleven tricyclic amines (Fig. 2) to study the effect of various head-pieces on AVP antagonistic activity. 5,6-Dihydro-phenanthridine (**1a**) was prepared by reduction of the commercially available 6(5*H*)-phenanthridinone (Scheme 1). The 4-nitrobenzoyl derivative of **1b** was synthesized according to Scheme 2. The acid chloride of 2-iodophenylacetic acid was reacted with 2-iodoaniline to give amide **2**, which was reduced to amine **3** with borane-methyl sulfide. The cyclization of **3** through aryl–aryl coupling to form **1b** proved to be problematic. However, the 4-nitrobenzamide **4** cyclized smoothly to **5** under copper catalyzed coupling conditions. Compound **5** was used directly to prepare the final product **13b** through reduction of the nitro group, followed by acylation of the resulting amine with *o*-toluoyl chloride. The synthesis of **1h** is

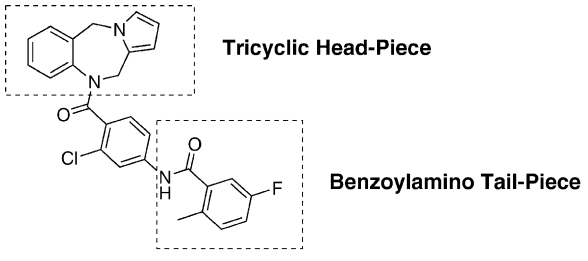

Figure 1.

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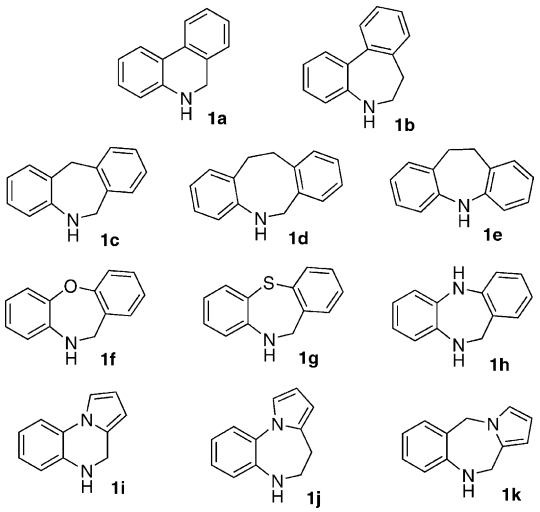
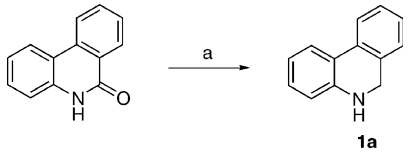
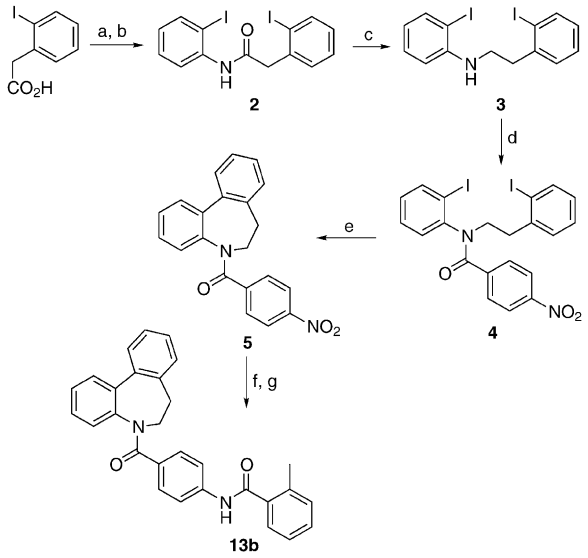


Figure 2.

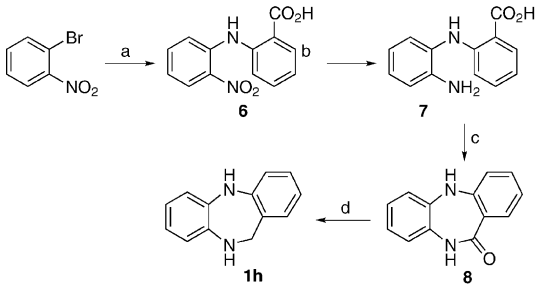


Scheme 1. (a) BH_3–Me_2S, THF, reflux.

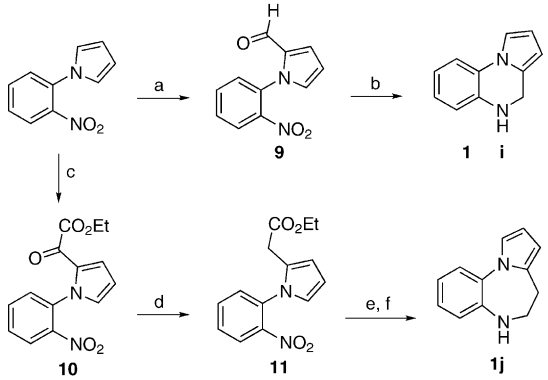


Scheme 2. (a) $SOCl_2$; (b) 2-iodoaniline, Et_3N, CH_2Cl_2; (c) BH_3–Me_2S, THF, reflux; (d) 4-nitrobenzoyl chloride, Et_3N, CH_2Cl_2; (e) Cu, DMF, reflux; (f) H_2, 10% Pd/C, MeOH; (g) *o*-toluoyl chloride, Et_3N, CH_2Cl_2.

shown in Scheme 3. A mixture of 1-bromo-2-nitrobenzene and anthranilic acid was heated neat in the presence of copper and potassium carbonate to give the diarylamine **6**. Hydrogenation of **6**, and subsequent cyclization of the resulting amine **7** gave the lactam **8**, which upon reduction with borane-methyl sulfide yielded the dibenzdiazepine **1h**. Scheme 4 illustrates the synthetic routes to amines **1i** and **1j**. Formylation of 1-(4-nitrophenyl)-1*H*-pyrrole, followed by hydrogenation of the product **9** gave the pyrroloquinoxaline **1i**.



Scheme 3. (a) Cu, K_2CO_3, neat, 200 °C; (b) H_2, 10% Pd/C, MeOH; (c) xylene, reflux; (d) BH_3–Me_2S, THF, reflux.



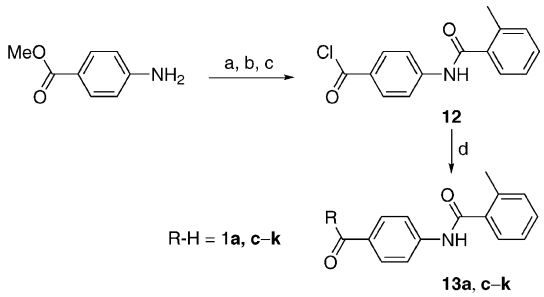
Scheme 4. (a) $POCl_3$, DMF; (b) H_2, 10% Pd/C, MeOH; (c) ethyl oxalyl chloride, BF_3–Et_2O, CH_2Cl_2; (d) ZnI_2, $NaCNBH_3$, 1,2-dichloroethane, reflux; (e) $SnCl_2$, EtOH, reflux; (f) BH_3–Me_2S, THF, reflux.

Similarly, 1-(4-nitrophenyl)-1*H*-pyrrole was first acylated with ethyl oxalyl chloride to give compound **10**, which was selectively reduced to the ester **11** with zinc iodide and sodium cyanoborohydride. Reduction of the nitro group and cyclization to the lactam was accomplished by treatment with stannous chloride in refluxing ethanol. Subsequent reduction with borane-methyl sulfide led to the pyrrolobenzodiazepine **1j**.

5,6-Dihydro-11*H*-dibenz[*b*,*e*]azepine (**1c**),[6] 10,11-dihydrodibenz[*b*,*f*][1,4]oxazepine (**1f**),[7] 10,11-dihydrodibenz[*b*,*f*][1,4]thiazepine (**1g**),[7] and 10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepine (**1k**)[8] were prepared according to procedures reported in the literature. Commercially available 5,6,11,12-tetrahydrodibenz[*b*,*f*]azocine (**1d**) and 10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine (**1e**) were used directly.

In order to study the structure–activity relationship of various tricyclic derivatives, the *o*-toluoyl group was chosen as the common tail-piece. These compounds were prepared in a convergent manner as shown in Scheme 5. Thus, the common acid chloride intermediate **12**, prepared in three steps from methyl 4-aminobenzoate, was treated with the aforementioned tricyclic amines (except **1b**) to give products **13a**, **c**–**k**. The antagonistic activities of these compounds for the rat V_{1a} and V_2 receptors[5c] are summarized in Table 1.

To investigate the effect of modifications of the tail-piece, we synthesized a series of analogues containing



Scheme 5. (a) *o*-Toluoyl chloride, Et_3N, CH_2Cl_2; (b) 1 N NaOH, MeOH; (c) $SOCl_2$; (d) R-H, Et_3N, CH_2Cl_2.

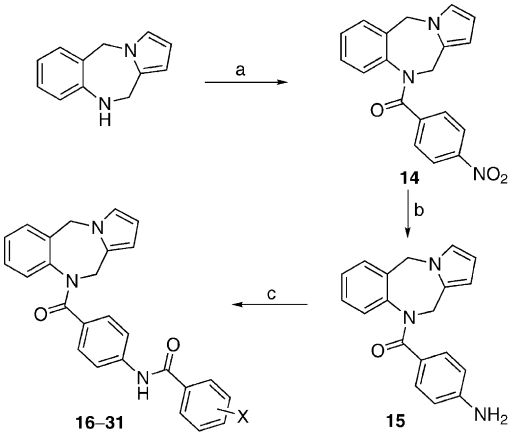
Table 1. Activity of tricyclic derivatives in V_{1a} and V_2 receptors

Compd	R-H	V_{1a} IC_{50}, μM[a]	V_2 IC_{50}, μM[a]
13a	**1a**	0.056	0.029
13b	**1b**	0.098	0.025
13c	**1c**	0.15	0.068
13d	**1d**	60% (50 μM)	80% (50 μM)
13e	**1e**	2.5	0.86
13f	**1f**	1.5	1.7
13g	**1g**	0.40	0.86
13h	**1h**	0.019	0.042
13i	**1i**	0.17	0.066
13j	**1j**	0.27	0.033
13k	**1k**	0.038	0.004

[a]Binding assays were determined by measuring the inhibition of ^{3}H-AVP binding to rat hepatic V_{1a} receptors or rat kidney medullary V_2 receptors.

the head-piece **1k** and different substituted benzoyl groups according to Scheme 6. Acylation of **1k** with 4-nitrobenzoyl chloride gave the amide **14**, which was reduced by either catalytic hydrogenation or stannous chloride to the amine **15**. The common intermediate **15** was then coupled with various aroyl chlorides to give the final products. Examples of these analogues and their V_{1a} and V_2 activities are listed in Table 2.

In vivo studies were conducted on a number of the derivatives in Tables 1 and 2 using water loaded (30 mL/kg) Sprague–Dawley rats treated (ip) with AVP (0.4 μg/kg). The aquaretic effect of these compounds was measured by the amount of urine collected after 4 h compared with control, and results are shown in Table 3.



Scheme 6. (a) 4-Nitrobenzoyl chloride, Et_3N, CH_2Cl_2; (b) H_2, 10% Pd/C, MeOH; or $SnCl_2$, EtOH, reflux; (d) ArCOCl, Et_3N, CH_2Cl_2.

Table 2. Activity of derivatives containing **1k** in V_{1a} and V_2 receptors

Compd	X	V_{1a} IC_{50}, μM[a]	V_2 IC_{50}, μM[a]
13k	2-Methyl	0.038	0.004
16	2-Trifluoromethyl	0.026	0.022
17	2-Methoxy	0.031	0.014
18	2-Methylthio	0.009	0.013
19	2-Ethoxy	0.045	0.077
20	2-Hydroxy	0.085	0.54
21	2-Fluoro	0.056	0.035
22	2-Chloro	0.01	0.005
23	2-Bromo	0.002	0.007
24	2,3-Dimethyl	0.24	0.013
25	2,3-Dichloro	0.027	0.029
26	2,4-Dichloro	0.023	0.003
27	2,5-Dichloro	0.12	0.014
28	2,6-Dichloro	0.094	0.015
29	2-Chloro-4-fluoro	0.007	0.004
30	2-Methyl-3-fluoro	0.026	0.004
31	2-Methyl-5-fluoro	0.02	0.0015
VPA-985		0.41	0.0023

[a]Binding assays were determined by measuring the inhibition of ^{3}H-AVP binding to rat hepatic V_{1a} receptors or rat kidney medullary V_2 receptors.

Majority of these compounds exhibited aquaresis activity in agreement their V_2 antagonistic activity.

It is apparent from the data in Table 1 that the tricyclic head-piece of the examples prepared has a substantial effect on their antagonistic activity for the V_{1a} and V_2 receptors. A few trends are also notable. Within the dibenz-tricyclic amine series of compounds (**13a**–**13e**) the 6,7-dihydro-5H-dibenz[*b*,*d*]azepine derivative **13b** exhibited the best V_2 activity as well as selectivity over V_{1a}. Azepine head-pieces containing another heteroatom (examples **13f**–**13h**) tend to diminish both activity and selectivity. The pyrrolo-tricyclic compounds (**13I**–**13k**) showed higher selectivity for the V_2 receptor. Compound **13k**, with the 10,11-dihydro-5H-pyrrolo[2,1-*c*][1,4]benzdiazepine head-piece **1k**, also showed potent V_2 activity.

Substitutions on the phenyl ring of the benzoyl tail-piece appear to influence selectivity for the V_2 receptor,

Table 3. Aquaretic effect in normal Sprague–Dawley rats

Compd	Dose (ip) (mg/kg)	No. of rats	Urine volume (mL/4 h)
Control (10%DMSO)		6	12.1±1
AVP control		6	2±0.2
13b	10	2	13.5
13c	10	6	15.2±2.4
13g	10	2	7.7
13h	30	2	7.4
13i	10	2	5.2
13j	10	2	7
13k	10	7	15.8±1
16	10	2	12.5
17	10	2	9.3
22	10	2	12.4
24	10	2	18.0
26	10	8	20.4±1
27	10	2	16.9
28	10	2	11.3
30	10	2	14.1
31	10	2	21.8
VPA-985	10	2	22

as data on examples containing the common head-piece **1k** in Table 2 indicate. In general, a methyl group at the 2-position (**13k, 30, and 31**) enhances V_2 over V_{1a} selectivity significantly. Surprisingly, a 2-hydroxy substitution (**20**) reverses the selectivity. Among other 2-substituted analogues, the 2-chloro derivative showed better V_2 activity. However, most of them lost selectivity. The 2,4-dichloro compound **26** seems to be superior to the other dichloro-substituted positional isomers. A 3-fold increase in V_2 activity was achieved with the 5-fluoro substituted compound **31** in comparison with compound **13k**, while V_{1a} activity was relatively unchanged.

In summary, we have discovered a number of novel, potent, as well as selective, AVP antagonists of the V_2 receptor by incorporating tricyclic benzazepines as head-pieces in our designed targets. Further structure–activity study of a series of derivatives containing the most promising head-piece **1k** and modifications at the tail-piece led to the discovery of compound **31**, which showed potent V_2 receptor activity ($IC_{50} = 1.5$ nM) and greater than 10-fold selectivity over the V_{1a} receptor. Results from this investigation provided potential lead candidates in our effort to develop AVP antagonists for the treatment of diseases associated with excess renal reabsorption of free water.

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