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The Design, Synthesis and Physical Chemical Properties of Novel Human Vasopressin V_2-Receptor Antagonists Optimized for Parenteral Delivery

M. A. Ashwell,* J. F. Bagli, T. J. Caggiano, P. S. Chan, A. J. Molinari, C. Palka, C. H. Park, J. F. Rogers, M. Sherman, E. J. Trybulski and D. K. Williams

Wyeth-Ayerst Research, Princeton, NJ 08543, USA

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Abstract—Ionizable groups were introduced onto the 10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine scaffold of the vasopressin V_2-antagonist WAY-VPA-985 in the search for molecules optimized for parenteral formulation. The synthesis and structure–activity relationships (SAR) are presented together with solubility data in a model parenteral system. The amine, WAY-140288 (**4f**), was chosen for further development.

Arginine vasopressin (AVP, anti-diuretic hormone) critically regulates water reabsorption by interaction with the vasopressin V_2-receptors found in the collecting ducts (aquaporin-2 water channels) of the kidney and as a result extracellular osmolality is critically maintained.[1] A vasopressin V_2-antagonist would therefore be expected to normalize plasma osmolality, control excessive water retention and dilutional hyponatremia in such conditions as congestive heart failure, liver cirrhosis and renal failure.

Several small molecule vasopressin antagonists have been described.[2] One potent human vasopressin V_2-antagonist, *N*-4-[3-chloro-4-(5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-10(11*H*)-ylcarbonyl)phenyl]-5-fluoro-2-methylbenzamide (WAY-VPA-985; **1**, $R_1 = Cl$, $R_2 = H$, $R_3 = Me$, $R_4 = F$)[3] is undergoing phase II clinical trials.

The goal of the work described here was to discover new potent, selective, orally active, non-peptide antagonists of the vasopressin V_2-receptor which had the additional feature of being optimized for parenteral administration.[4] This report describes the manipulation of the 10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine tricyclic scaffold, which is common to this class of vasopressin receptor agents in ways designed to increase aqueous solubility yet maintain the desirable in vitro and in vivo characteristics. The synthesis, structure–activity relationships (SAR) and solubility of these new molecules is described.

Synthesis

The synthetic approach used in elaboration of the 10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine tricyclic scaffold and the SAR of a number of related vasopressin V_2-receptor antagonists has been published previously.[3,5,6]

Utilizing the previous methodology gave access to a wide variety of 10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepine tricyclic scaffolds. The chemical strategy employed in this study involved functionalization of the pyrrole ring leading to acids, acylamines[7] and Mannich derived alkylamines[8] as shown in Scheme 1. Acylamines were prepared from the acid derivatives **2**. Initial reaction of **1** with trichloroacetylchloride[9] was followed by treatment with sodium hydroxide in aqueous THF to furnish acids **2** in overall yields of 60–70%. Amine coupling of the acids led directly to **3** (typically 80–90% yield).

Mannich reactions were performed directly on the pyrrole scaffold.[10] Generally, the corresponding secondary amines were utilized with paraformaldehyde in good yield (60–80%), however, for the introduction of the 3-dimethylaminomethyl group (**4a**, **4f**, **4g** where $R = NMe_2$)

*Corresponding author. Tel.: +1-732-274-4416; fax: +1-732-274-4505; e-mail: ashwellm@war.wyeth.com

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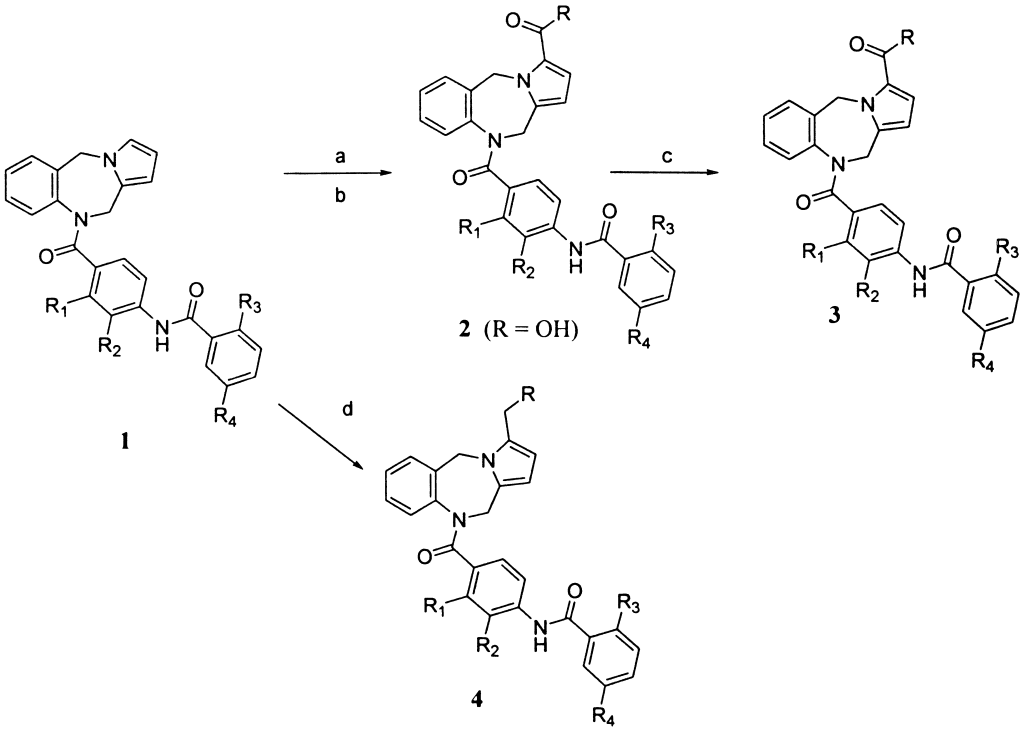


Scheme 1. (a) CCl_3COCl, CH_2Cl_2; (b) NaOH (aq), THF; (c) EDC, CH_2Cl_2, amine; (d) MeOH, AcOH, $(CH_2O)n$, amine.

tetramethyldiaminomethane was employed in a similar yield. In the case of **4g** demethylation of **1** (R_1 = OMe, R_2 = H, R_3 = Ph, R_4 = H) with BBr_3, preceded the Mannich reaction (yield 75%).

Results and Discussion

Acids

The introduction of an acid group to form 10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-3-carboxylic acids maintains in vitro vasopressin V_2-antagonism. However, these compounds were not active orally (**2a**, **2b** in Table 1). The lack of oral activity was attributed to poor absorption presumably from limited dissolution. This assumption was supported by the observation that iv dosing restored in vivo activity (**2a**: urine volume ratio of 5: @ dose 10 mg/kg).

Acylamines

Utilization of the 10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepine-3-carboxylic acids to form amides was a useful synthetic strategy for further modification of the scaffold. It was not until amides containing a basic center were incorporated, however, that significant increases in solubility were achieved.

A series of such acylamines was prepared (**3a**–**c** in Table 1). They were characterized by good in vitro binding and in some cases extremely potent in vivo activity (e.g., **3a**). The incorporation of two basic centers was also tolerated in vivo (e.g., **3b**). The pharmacological results for the acylamines encouraged us to determine their solubility.

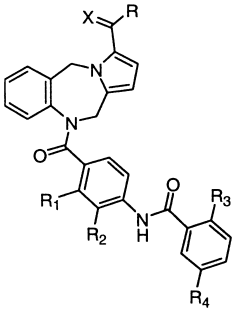
A target solubility equal to or greater than 1 mg/mL in a model parenteral system consisting of 30% polyethylene glycol 200 (PEG-200)/water was set based on the expected volume of delivery and pharmacological profile of the drug candidate. These criteria necessitated having crystalline material as measured by differential scanning calorimetry. However, in general these acylamines proved difficult to crystallize. Measurements on amophorus material of both free bases and salts were promising and a study was initiated to investigate alternative salts[11] as a means to alter the physical characteristics of the parent acylamines.

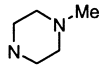
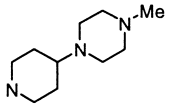
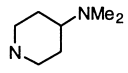
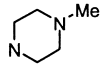
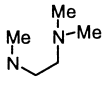
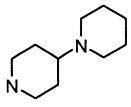
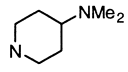
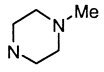
Amines

The Mannich procedure allowed the synthesis and elaboration of a second series of basic molecules. In general these compounds were shown to have good in vitro potency. However, examples containing a 2-phenylbenzoyl derived secondary amide such as **4a** were found to be orally superior to those containing the 2-methyl-5-fluorobenzoyl group present in VPA-985 (e.g., **4i** in Table 2) the former being active at doses well below 10 mg/kg. A similar effect is described for the related precursor pyrrolobenzodiazepine scaffold.[12] The successful combination of a 2-phenylbenzoyl derived amide and a basic center on the pyrrole ring led to the development of a series of amines (**4a**–**h**).

The pharmacological profile of the amines having either one or two basic centers was comparable. In general

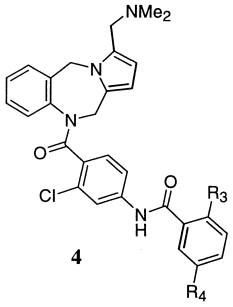
Table 1. In vitro[a] and in vivo[b] antagonist activity



No.	R	X	R_1	R_2	R_3	R_4	Urine volume V_2 ratio[c]	Urine volume V_2 IC_{50} nM
2a	OH	O	Cl	H	Me	F	NE[e]	14
2b	OH	O	Cl	H	Ph	H	NE	4
3a		O	Cl	H	Ph	H	3.6[i]	11.5
3b		O	Cl	H	Ph	H	2.7[h]	NT[f]
3c		O	Cl	H	Ph	H	2	8.8
4a	NMe_2	H_2	Cl	H	Ph	H	6.6	7.5
4b		H_2	Cl	H	Ph	H	3.75	1.3
4c		H_2	Cl	H	Ph	H	4.2	2.6
4d		H_2	Cl	H	Ph	H	1.5	2.1
4e		H_2	Cl	H	Ph	H	2.3	2
4f	NMe_2	H_2	H	OMe	Ph	H	5	5.2
4g	NMe_2	H_2	OH	H	Ph	H	3.8	14.8
4h		H_2	OMe	H	Ph	H	7.8[d]	7
1	WAY-VPA-985		Cl	H	Me	F	7.4[g]	1.2

[a]Compounds were tested as the free bases (or acids) except as noted. Compounds were tested in vitro for their ability to displace ^{3}H AVP in membrane preparations from a murine fibroblast cell line (LV2) expressing the humna vasopressin V_2-receptor.
[b]In vivo studies were conducted in conscious normotensive Sprague–Dawley rats with free access to water before the experiment. The compounds under test were dosed orally (po) at 10 mg/kg (20% dimethyl sulfoxide and 2.5% pre-boiled starch preparation.
[c]Data reported as a ratio of urine volume collected from treatment group after 4 h versus control group.
[d]No dimethyl sulfoxide in vehicle.
[e]NE = no effect.
[f]NT = not tested.
[g]Concious rats dosed (ip) with 0.4 μg/kg of AVP (in peanut oil); 20 min later given orally (by gavage) 30 mL/kg of deionized water followed by WAY-VPA-985 20 min later.[3]
[h]HCl salt.
[i]Citrate salt.

Table 2. Low dose in vivo[a] antagonist activity



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No.	R_3	R_4	Urine volume ratio[b] @ 3 mg/kg	@ 1 mg/kg
4i	Me	F	1.4	1.4
4a	Ph	H	5.6	2.3

[a]In vivo studies were conducted in conscious normotensive Sprague–Dawley rats with free access to water. The compounds under test were dosed orally (po) at stated doses (20% dimethyl sulfoxide and 2.5% pre-boiled starch preparation).
[b]Data reported as a ratio of urine volume collected from treatment group after 4 h versus control group.

Table 3. Model parenteral system solubility[a]

No.	Aq solution 30% PEG mg/mL
4a	0.72[b]
4h	0.3
3a	1.7[c]
4f	2.2
4g	1.9[b]

[a]Values reported for free bases unless noted. The samples were prepared by dissolution of the material in an appropriate solvent system on a wrist action stirrer for ca. 24–36 h. Each solution was filtered through a 0.2 micro Nylon 66 filter disc and appropriate dilutions made before injections were made on the HPLC system. Data reported for crystalline materials as determined by differential scanning calorimetry (DSC).
[b]Mixture of amophorus and crystalline material.
[c]Citrate salt.

they display low nanomolar binding and good oral activity. It was disappointing, however, to again find that the physical properties of these [((1′-biphenyl)-2-ylcarbonyl)amino]-2-chlorobenzoic derived scaffolds hampered their crystallization and hence solubility determination. An approximate upper limit for the solubility of **4a** was established with partially crystalline material (entry **4a** in Table 3) and as this was below the target value it indicated that further increases in solubility would be needed. It was postulated that this increase in solubility could be achieved by the introduction of additional hydrogen bonding groups. A series of substituent modifications were investigated at R_1 and R_2, and, indeed the required increase in solubility occurred when oxygen replacements were incorporated (**4f–h**). These molecules had the desired pharmacological profile and were reproducibly crystalline. Potent oral activity was seen in the absence of dimethyl sulfoxide in the test vehicle (e.g. **4h**) although this initial example failed to meet the solubility cut-off (see entry **4h** in Table 3).

The strategy proved effective, however, with other examples (**4f** and **4g**). Thus these amines met the design needs of the program.

Summary and Conclusion

The utilization of the chemical reactivity of the pyrrole nucleus present in the tricyclic 10,11-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine scaffold led to the discovery of two series of amines and acylamines with potent in vitro and in vivo vasopressin V_2-antagonism. In the case of the Mannich derived amines the target level of solubility was only achieved when further hydrogen bonding groups were added to the scaffold. These materials were also reproducibly crystallized. In the case of the acylamines the target solubility was achieved (**3a**) through an appropriate salt choice (citrate). Of these molecules WAY-140288 (*N*-(4-{[3-[(dimethylamino)methyl]-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-10(11*H*)-yl]carbonyl}-2-methoxyphenyl)[1,1′-biphenyl]-2-carboxamide) (**4f**) was chosen as a development candidate based on both solubility measurements and a promising pharmacologic profile.

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