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The Synthesis and Vasopressin (AVP) Antagonist Activity of a Novel Series of *N*-Aroyl-2,4,5,6-tetrahydropyrazolo-[3,4-*d*]thieno[3,2-*b*]azepines

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Abstract—Synthesis and SAR of *N*-[4-[(4,5-dihydropyrazolo[3,4-*d*]thieno[3,2-*b*]azepin-6(2*H*)-yl)carbonyl]phenyl]benzamides as arginine vasopressin (AVP) receptor antagonists are discussed. Potent orally active AVP receptor antagonists are produced when the benzamide moiety contains a phenyl group at the 2-position. Similar analogues of 4,6,7,8-tetrahydro-5*H*-thieno[3,2-*b*]azepine and VPA-985 are reported.

One of the components in the regulation of body fluid is the hormone arginine vasopressin (AVP) which regulates solute free water clearance. Vasopressin (antidiuretic hormone) interacts at the V_2 receptors in the collecting ducts (aquaporin-2 water channels) of the kidney to control water reabsorption and in this manner helps to regulate salt (NaCl) balance via antidiuresis.[1–3] Thus a vasopressin antagonist (as opposed to a conventional diuretic) would be the drug of choice to normalize plasma osmolality and control hyponatremia which occurs in congestive heart failure, liver cirrhosis and renal failure.

The development of peptide and nonpeptide V_{1a} and V_2 vasopressin receptor antagonists has been reviewed[4] and the synthesis and activity of the clinical VPA antagonist, 5-fluoro-2-methyl-*N*-[4-(5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-10(11*H*)-ylcarbonyl)-3-chlorophenyl]benzamide (**21a**) (VPA-985) and analogues have been reported.[5] Derivatives of the tricyclic ring systems, 4,10-dihydro-5*H*-thieno[3,2-*c*][1]benzazepine and 9,10-dihydro-4*H*-thieno[2,3-*c*][1]benzazepine, with a thiophene ring fused to a benzazepine moiety have been reported as potent and orally active AVP antagonists.[6] The nonpeptide bicyclic benzazepine OPC-31260[7–15] and the tricyclic benzazepine YM-087[16–18] have been disclosed as vasopressin antagonists which are orally active aquaretics.

We wish to report on derivatives of the tricyclic heterocycle 2,4,5,6-tetrahydropyrazolo[3,4-*d*]thieno[3,2-*b*]azepine which are potent AVP receptor antagonists. The 4,6,7,8-tetrahydro-5*H*-thieno[3,2-*b*]azepine-5-one **5**[19,20] was synthesized from 4-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene (**1**) (Scheme 1). Reaction with hydroxylamine gave the *syn* and *anti* oximes **2** and **3**[19,20] which were reacted with tosyl chloride to give the oxime-*O*-tosylate (**4**). Rearrangement afforded **5** in 55% overall yield. Reduction of the lactam with borane–dimethylsulfide gave **6** (85%) while reduction with LAH in tetrahydrofuran gave a lower yield of **6** (60%). Reaction of **6** with either 4-nitrobenzoyl chloride or 2-chloro-4-nitrobenzoyl chloride gave **7** and **8**, respectively. Introduction of the 5-oxo group was carried out with $KMnO_4$ in acetone–water (modified literature [21] procedure) to give keto intermediates **9** and **10**.[22]

The derivatives **9** and **10** were reacted with Bredereck's Reagent (*tert*-butoxybis(dimethylamino)methane) to afford the dimethylaminomethylene ketones **11** and **12**. Reaction with either hydrazine or methylhydrazine gave the tricyclic 6-(4-nitrobenzoyl)pyrazolo[3,4-*d*]thieno[3,2-*b*]azepines **13** and **14**, which were reduced to give the intermediate 6-(4-aminobenzoyl)pyrazolo[3,4-*d*]thieno-[3,2-*b*]azepines **15**.[22] The nitro group in compounds without a chloro group was reduced by heating with Pd/C-hydrazine in ethanol. However, nitro derivatives such as **14** with a chlorine atom were reduced with stannous chloride in ethanol in order to avoid partial dechlorination induced with Pd/C-hydrazine in ethanol.

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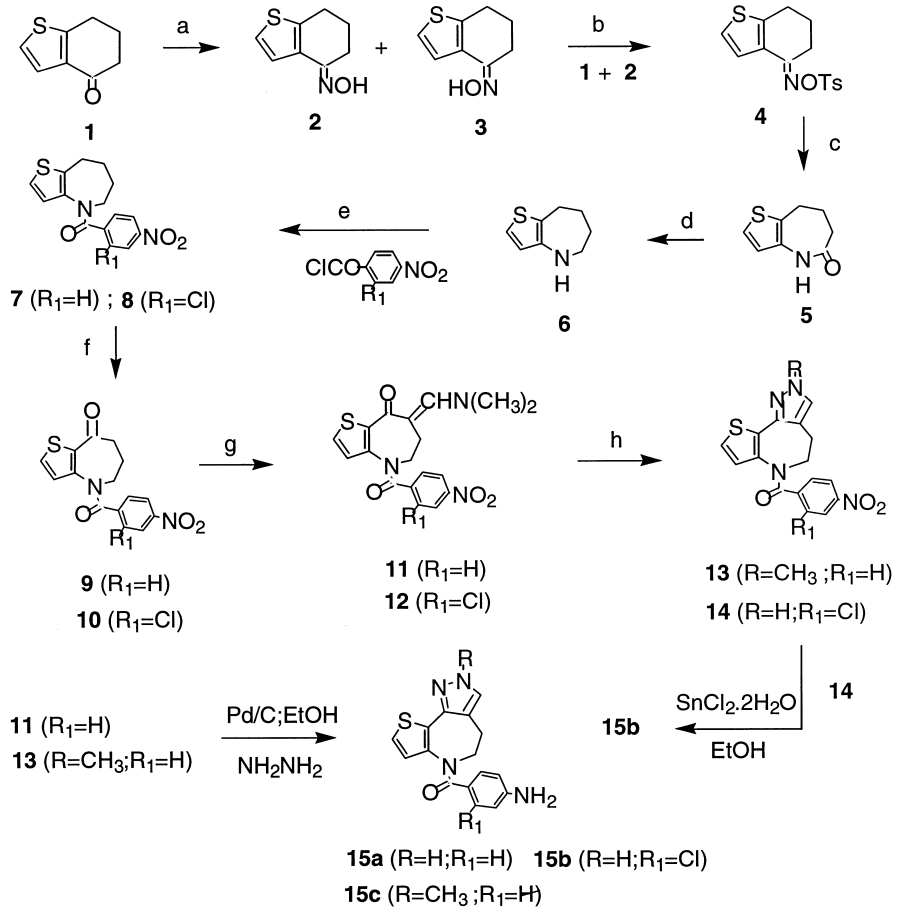
As shown in Scheme 2, the 4-aminobenzoyl derivatives **15** were reacted with acid chlorides (R_2COCl) to obtain analogues **17** and **18**. Diacylation occurs on acylation of the tricyclic pyrazoles with a free NH group to afford intermediates **16** which were deacylated with sodium hydroxide to give the unsubstituted pyrazoles.

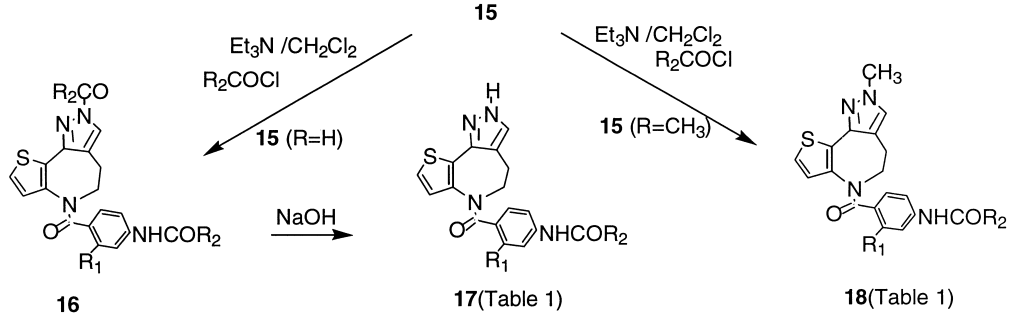
As shown in Table 1, the analogues **17a–e** exhibited moderate binding selectivity for rat V_2 receptors versus rat V_1 receptors and all except **17d** exhibited in vivo (po) aquaretic activity. The analogues **18a–c** with an *N*-methyl group on the pyrazole ring exhibited significant binding activity for rat V_2 receptors; however, they exhibited little or no in vivo (po) aquaretic activity. Notable is the lack of oral activity for **17d** which has the same 2-chloro-4-(2-methyl-5-fluorobenzoylamino)-benzoyl 'tail unit' as **21a** (VPA-985).[5a]

For comparison purposes, derivatives **20a–e** lacking the fused pyrazole ring were synthesized as shown in Scheme 3.[23] The analogue **20a** similar to **17d** with the same 'tail unit' as **21a** (VPA-985) also lacked in vivo activity. A significant finding is the increased binding activity and the potent in vivo (po) activity with derivatives **17f**, **20c–e**, **21c** and **21d**[24] which all have a terminal 2-phenylbenzoyl moiety.

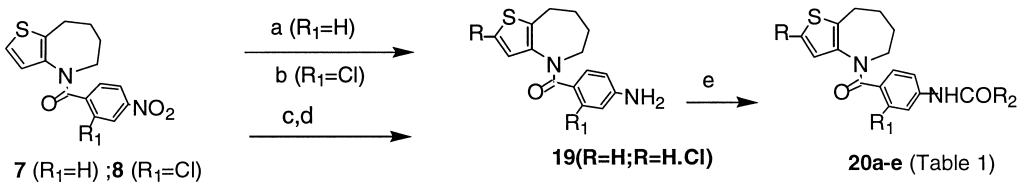
We have shown that potent in vivo activity (aquaresis) is dependent not only on the 'head unit' but also on the substituent groups in the terminal benzoyl moiety. A



Scheme 1. (a) $NH_2OH.HCl/NaOAc[EtOH/H_2O]$ (99%); (b) TsCl/pyridine (92%); (c) $KOAc/EtOH/H_2O$ (60%); (d) $THF/BH_3.S(CH_3)_2$ (91%); (e) Et_3N/CH_2Cl_2; (f) $KMnO_4/MgSO_4$[acetone/H_2O (70 °C]; (g) Brederick's Reagent; (h) NH_2NH_2 or $NH_2NH(CH_3)$.

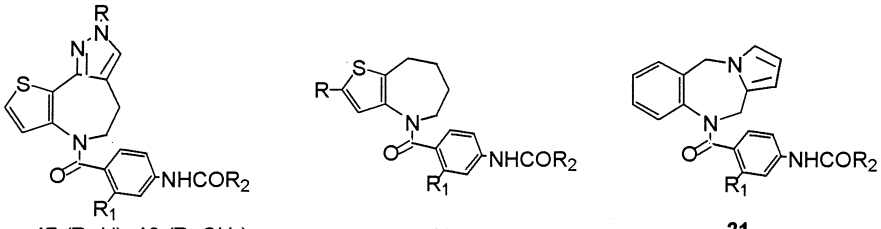


Scheme 2.



Scheme 3. (a) Pd/C-HOAc; H_2; (b) $SnCl_2.2H_2O$/EtOH; (c) NCS; (d) Fe/HOAc; 6N HCl; (e) $R_2COCl/Et_3N/CH_2Cl_2$.

Table 1. In vitro and in vivo antagonist activity



				IC_{50} (nM)[a] (r) = rat (h) = human (receptors)				Urine volume
No.	R	R_1	R_2	V_{1a}		V_2		mL/4 h
17a	H	H	2-CH_3-Ph	(r) 2100	(h) 240	(r) 120	(h) 130	21[e]
17b	H	H	2-Cl-4-F-Ph	(r) 2000	(h) —[b]	(r) 340	(h) 140	15[f]
17c	H	H	2-CH_3-5-F-Ph	(r) 1700	(h) —	(r) 69	(h) 71	18[e]
17d	H	Cl	2-CH_3-5-F-Ph	(r) 12,400	(h) 69%[c]	(r) 6	(h) —	7[f]
17e	H	Cl	2-F-5-Cl-Ph	(r) 18% [c]	(h) —	(r) 36	(h) —	12[f]
17f	H	Cl	2-(Ph)-Ph		—	(r) —	(h) 1.7	27[f] (22)[d]
18a	CH_3	H	2-CH_3-Ph	(r) 2010	(h) 1740	(r) 24	(h) 220	3[f]
18b	CH_3	H	2-Cl-4-Cl-Ph	(r) 2100	(h) 4100	(r) 38	(h) 150	6[e]
18c	CH_3	H	cyclohexyl	(r) 4700	(h) —	(r) 230	(h) —	9[e]
18d	COR_2	H	2-CH_3-Ph	(r) —	(h) 88%[c]	(r) —	(h) 88%[c]	14[e]
20a	H	Cl	2-CH_3-5-F-Ph	(r) —	(h) 110	(r) —	(h) 3.4	4[e]
20b	Cl	H	2-Cl-4-Cl-Ph	(r) 230	(h) —	(r) 19	(h) —	8[e]
20c	H	Cl	2-(Ph)-Ph	(r) —	(h) 86	(r) 1.2	(h) —	19[f]
20d	Cl	H	2-(Ph)-Ph	(r) —	(h) 82	(r) 3.2	(h) —	20[f]
20e	Cl	Cl	2-(Ph)-Ph		—	—	—	22[f]
21a	—	Cl	2-CH_3-5-F-Ph	(r) 340	(h) 230	(r) 2.3	(h) 1.2	22[f] (20)[d]
21b	—	H	2-Cl-4-Cl-Ph	(r) 23	(h) 15	(r) 3.1	(h) 3.2	16[e]
21c	—	Cl	2-(Ph)-Ph	(r) 16	(h) 370	(r) 1.5	(h) 2.7	27[f] (20)[d]
21d	—	H	2-(Ph)-Ph	(r) 3.4	(h) —	(r) 2.6	(h) —	21[f]

[a]See ref 5a for V_{1a}, V_2 receptor binding procedures.
[b]Not tested.
[c]% Inhibition at 10 μM.
[d]Urine volume at a dose of 3 mg/kg.
[e]Water-loaded (30 mL/kg) + 0.4 μg/kg of AVP (ip) (see ref 5a); urine volume of controls 5–6 mL.
[f]Test compounds were given at an oral dose of 10 mg/kg in a volume of 10 mL/kg (20% dimethylsulfoxide in 2.5% preboiled starch). During the test, rats were not provided with water or food. Urine was collected for 4 h after dosing of the compound. At the end of 4 h, urine volume was measured; volume of controls 7–9 mL.

significant finding is the enhanced in vivo (po) activity across three different 'head units' when a 2-phenylbenzoyl group was substituted for a 2-methyl-5-fluorobenzoyl group in the 'tail unit' to give compounds with activity equivalent to or greater than the clinical compound (VPA-985).

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