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Pyrrolo[1,2-*a*]pyrazine and pyrazolo[1,5-*a*]pyrazine: Novel, potent, and selective series of Vasopressin$_{1b}$ receptor antagonists

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ABSTRACT

Novel series of pyrrole-pyrazinone and pyrazole-pyrazinone have been identified as potent and selective Vasopressin$_{1b}$ receptor antagonists. Exploration of the substitution pattern around the core of these templates allowed generation of compounds with high inhibitory potency at the Vasopressin$_{1b}$ receptor, including examples that showed good selectivity with respect to Vasopressin$_{1a}$, Vasopressin$_2$, and Oxytocin receptor subtypes.

Arginine vasopressin (AVP) and Oxytocin (OT) are nonapeptide hormones released from the posterior pituitary into the blood stream and their effects are mediated by four different G-protein coupled receptor subtypes, Vasopressin$_{1a}$ (V_{1a}), Vasopressin$_{1b}$ (V_{1b}), Vasopressin$_2$, and Oxytocin.[1]

In particular, the V_{1b} receptor subtype is involved in the regulation of adrenocorticotropin hormone (ACTH) release from the pituitary gland, in the regulation of social behavior and in the regulation of insulin release from the pancreas.[2] Based on V_{1b} receptor function and distribution, selective V_{1b} receptor antagonists have been suggested as potential therapeutic agents in the treatment of diseases characterized by an excessive cortisol secretion, such as major depression[3] and stress-related disorders.[4] The first nonpeptidic V_{1b} receptor antagonist, SSR149415, was discovered in 2002[5] and its characterization in preclinical models consistently supports the potential therapeutic benefits that may derive from the blockade of V_{1b} receptors in stress-related disorders.[6] However, the selectivity of SSR149415 has been challenged since a remarkable affinity for the human OT receptor has been reported.[7] More recently, a novel selective V_{1b} receptor antagonist has been identified and characterized in vitro and in vivo.[8] Notwithstanding, the role of peripheral versus central V_{1b} receptors in mediating behavioral effects in response to stress needs to be clarified since both peripheral[9] and central sites[10,11] have been proposed to be involved in the anxiolytic and antidepressant-like effects of V_{1b} receptor antagonists. Therefore, the identification of selective, orally bioavailable and brain penetrant V_{1b} receptor antagonists is an essential step to elucidate V_{1b} receptor function and to fully understand the therapeutic potential of molecules acting at this target.

In this paper, we disclose the discovery of two novel series of potent and highly selective vasopressin V_{1b} receptor antagonists. The 2-(1-oxo-3-phenylpyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)acetamide (**1**) and the 2-(4-oxo-6-phenylpyrazolo[1,5-*a*]pyrazin-5(4*H*)-yl)acetamide (**2**) derivatives (Fig. 1) were identified within our proprietary compound collection as potent antagonists at the human V_{1b} receptor, with sub-micromolar potency and high selectivity with respect

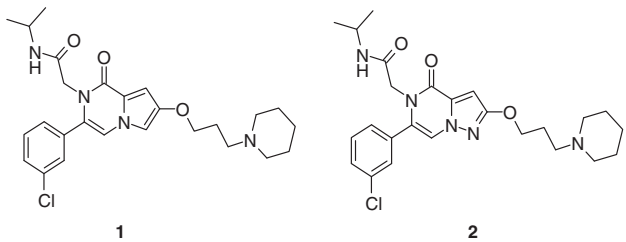

Figure 1. Structures of compounds **1** and **2**.

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Table 1
Profiling results for compounds **1** and **2**

Compound	V_{1b} pIC_{50}[a]	V_{1a} pIC_{50}[a]	V_2 pIC_{50}[a]	OT pIC_{50}[a]
1	8.0	<4.3	<4.5	<4.3
2	7.8	<4.3	<4.5	<4.3

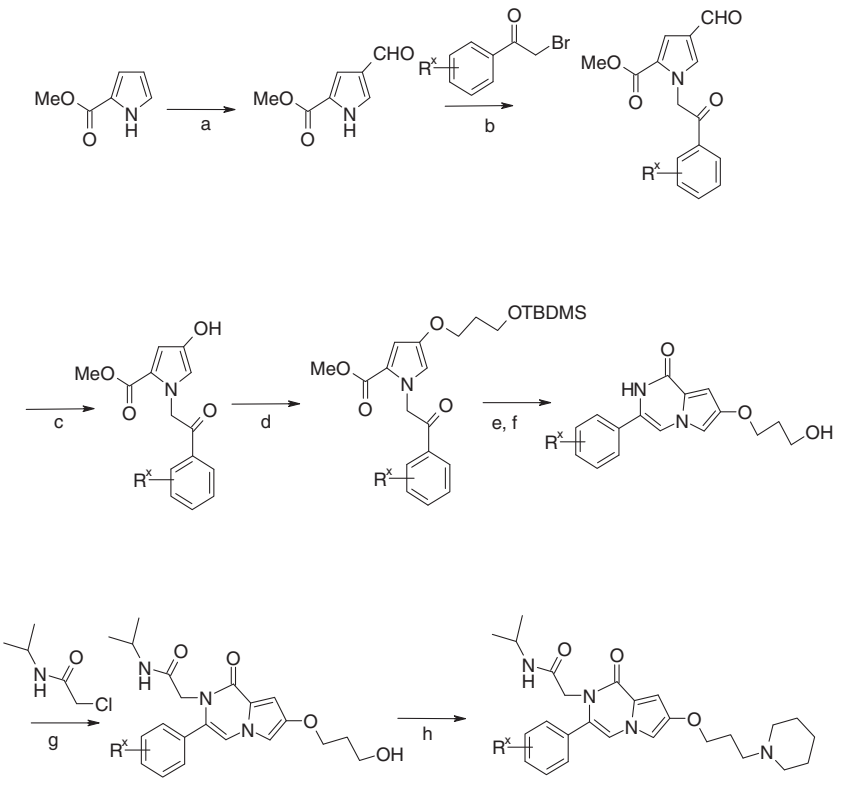
[a] Data are expressed as means of 2–9 experiments, standard error of the mean (SEM) is <0.1.

to V_{1a}, V_2, and OT receptor subtypes (Table 1). Compounds **1** and **2** were tested in a fluorescent imaging plate reader (FLIPR) Ca^{2+} functional assay, measuring inhibition of vasopressin stimulated intracellular calcium mobilization in CHO cells stably transfected with the human V_{1b} receptor; data were analyzed with IDBS Activity Base software and results are expressed as pIC_{50}.

The discovery of compounds **1** and **2** prompted the synthesis of a series of 2-(1-oxo-3-phenylpyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)acetamide and 2-(4-oxo-6-phenylpyrazolo[1,5-*a*]pyrazin-5(4*H*)-yl)acetamide derivatives which were prepared following the synthetic routes outlined in Schemes 1 and 2, respectively. In Scheme 1, methyl 4-formyl-1*H*-pyrrole-2-carboxylate was easily prepared in good yield exposing methyl 1*H*-pyrrole-2-carboxylate to Vilsmeier conditions. Subsequently, the nitrogen of the pyrrole derivative was alkylated with the appropriate 2-bromo-1-aryl-ethanone. The aldehyde group was transformed into a hydroxyl group, following a modified Baeyer–Villiger procedure[12] and then the hydroxyl group was alkylated with [(3-bromopropyl)oxy](1,1-dimethylethyl)dimethylsilane. Cyclization with ammonium acetate under reflux afforded the desired pyrrolo[1,2-*a*]pyrazine derivative, which was treated under basic hydrolysis conditions to remove the protecting group. Alkylation with 2-chloro-*N*-isopropylacetamide readily allowed the introduction of the amide side chain. Reaction with methanesulfonyl chloride followed by amine displacement afforded the desired final product.[13]

In Scheme 2, treatment of the commercially available 4,4,4-trichloroacetoacetate with hydrazine hydrochloride in ethanol under reflux afforded the desired 3-ethoxycarbonyl-5-hydroxypyrazole, with simultaneous transformation of the trichloromethyl group into carboxyl group.[14] The hydroxyl moiety in the C-5 position of the pyrazole intermediate was alkylated with [(3-bromopropyl)oxy](1,1-dimethylethyl)dimethylsilane and, subsequently, the nitrogen of the pyrazole derivative was alkylated with the appropriate 2-bromo-1-aryl-ethanone. Cyclization with ammonium acetate under reflux afforded the required pyrazolo[1,5-*a*]pyrazine derivative, where the *tert*-butyldimethylsilyl protecting group was replaced by the acetate group. Alkylation with 2-chloro-*N*-isopropylacetamide readily allowed the introduction of the amide side chain and the acetate group was removed under basic hydrolysis conditions. Reaction with methanesulfonyl chloride followed by amine displacement afforded the desired final product.[15]

Starting from compounds **1** and **2**, a structure–activity relationship (SAR) exploration was carried out. Initial efforts were focused on analogs of compound **1** in order to investigate the role of the substitution pattern on the aryl moiety in the bottom left portion of the molecule (Fig. 2 and Table 2, compounds **3**–**9**). When the chlorine was moved to the C-2 position a reduction of inhibitory potency at the V_{1b} receptor (compound **3**) was observed, whereas in the C-3 position both a methoxy group and a fluorine (compounds **4** and **5**) were tolerated. 3,4-Disubstitution (compounds **6** and **7**) proved to be beneficial for the inhibitory potency at the V_{1b} receptor, whereas 3,6-substitution (compounds **8** and **9**) proved to be detrimental. SAR exploration of the aromatic portion of compound **2**, exemplified by the synthesis of some key compounds, showed similar results (Fig. 2 and Table 2, compounds **10**–**12**). Additional analogs of compound **2** were prepared and the trifluoromethoxy group in the C-3 position highlighted a reduction of inhibitory potency at the V_{1b} receptor as did the intro-



Scheme 1. Reagents and conditions: (a) Vilsmeier reagent ($POCl_3$, DMF, rt, 30 min), DMF, rt, 16 h; (b) K_2CO_3, CH_3CN, rt, 1 h; (c) 1—*m*-CPBA, DCM, TFA, rt, 6 h; 2—MeOH, Na_2CO_3 (2 N), rt, 5 min; (d) K_2CO_3, NaI, $BrCH_2CH_2CH_2OTBDMS$, CH_3CN, rt, 1 h; (e) NH_4OAc, AcOH, 110 °C, 24–36 h; (f) LiOH, water, rt, 2 h; (g) K_2CO_3, CH_3CN, 85 °C, 16 h; (h) 1—methanesulfonyl chloride, TEA, DMAP, $CHCl_3$, rt, overnight; 2—K_2CO_3, piperidine, DMF, 65 °C, 8 h.