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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

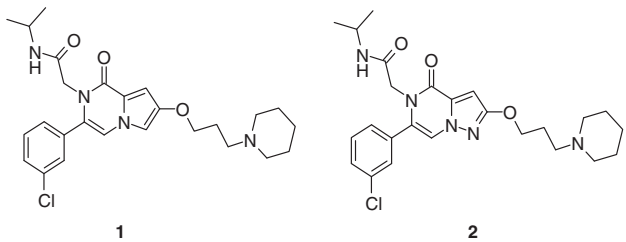

Figure 1. Structures of compounds **1** and **2**.

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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

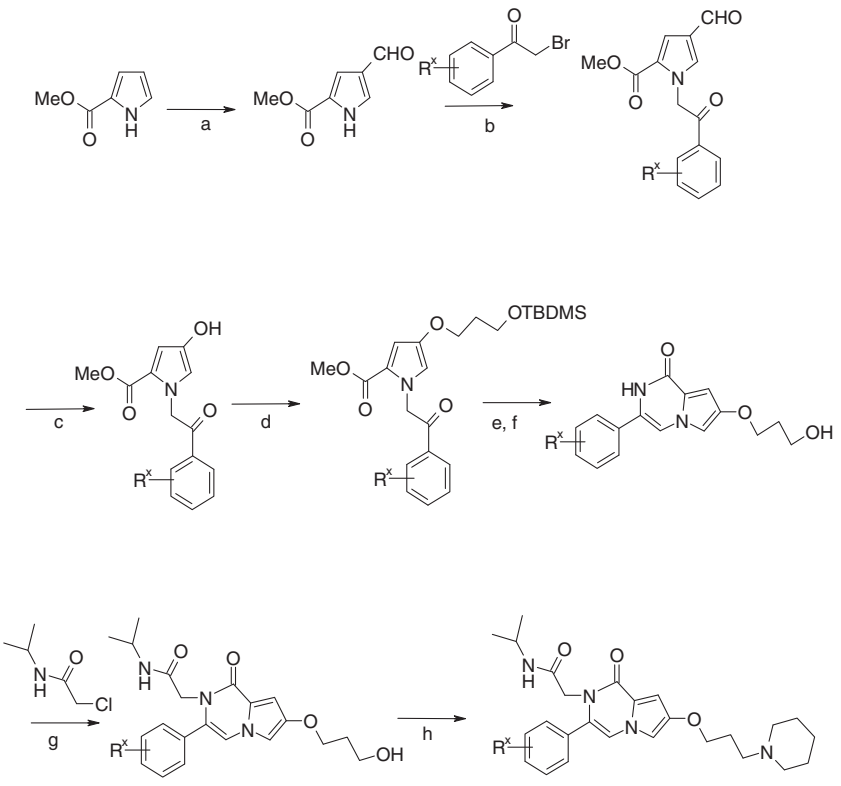
[a] Data are expressed as means of 2–9 experiments, standard error of the mean (SEM) is <0.1.

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}.

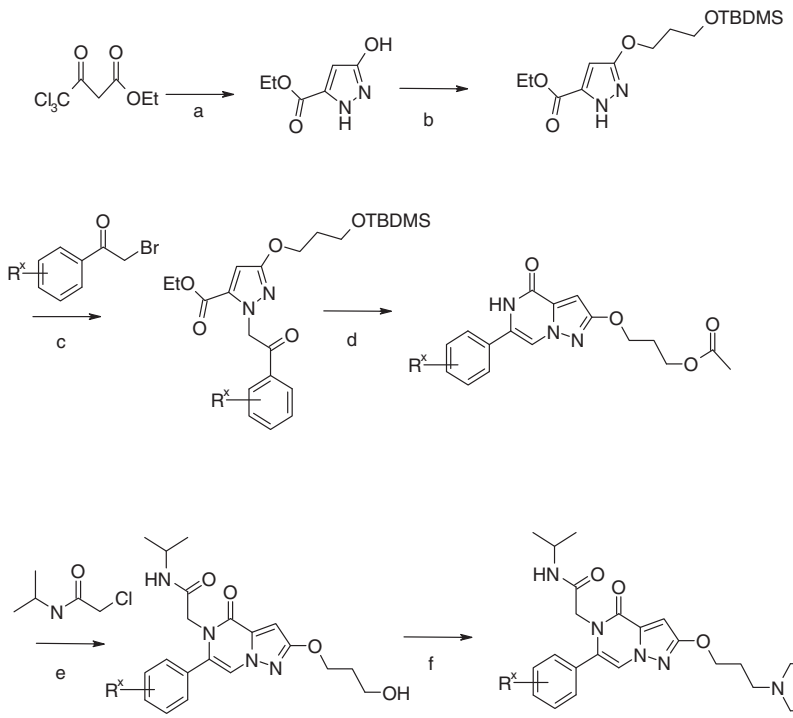
The discovery of compounds **1** and **2** prompted the synthesis of a series of 2-(1-oxo-3-phenylpyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)acetamide and 2-(4-oxo-6-phenylpyrazolo[1,5-*a*]pyrazin-5(4*H*)-yl)acetamide derivatives which were prepared following the synthetic routes outlined in Schemes 1 and 2, 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.



Scheme 2. Reagents and conditions: (a) EtOH, $NH_2NH_2 \cdot HCl$, 85 °C, 48–60 h; (b) Na_2CO_3, $BrCH_2CH_2CH_2OTBDMS$, DMF, 60 °C, 18 h; (c) Na_2CO_3, DMF, 60 °C, 1.5 h; (d) NH_4OAc, AcOH, 100 °C, 24 h; (e) 1—NaH, NaI, DMF, 70 °C, 6 h; 2—LiOH, THF, rt, 3 h; (f) 1—methanesulfonyl chloride, TEA, DMAP, $CHCl_3$, rt, overnight; 2—K_2CO_3, piperidine, DMF, 65 °C, 8 h.

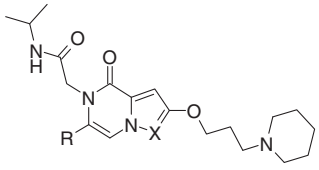


Figure 2. SAR for alternative aryl substitutions.

Table 2
Profiling results for aryl substitutions SAR, compounds **3**–**14**

Compound	X	R	V_{1b} pIC_{50}[a]
3	C	2-Chlorophenyl	6.1
4	C	3-Methoxyphenyl	7.9
5	C	3-Fluorophenyl	7.1
6	C	3-Chloro-4-fluorophenyl	8.4
7	C	3-Trifluoromethyl-4-fluorophenyl	8.3
8	C	3-Chloro-6-fluorophenyl	7.0
9	C	3-Chloro-6-methylphenyl	7.1
10	N	3-Methoxyphenyl	7.8
11	N	3-Trifluoromethyl-4-fluorophenyl	8.4
12	N	3-Chloro-4-fluorophenyl	8.3
13	N	3-Trifluoromethoxyphenyl	6.4
14	N	3-Chloro-2-fluorophenyl	6.8

[a] Data are expressed as means of 3–10 experiments, SEM is <0.2.

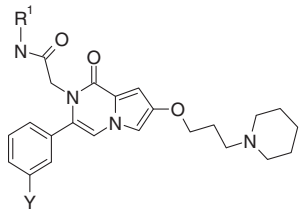
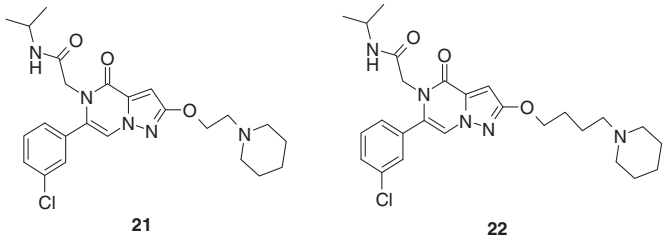


Figure 3. Exploration of substituents in the amide side chain.

Table 3
Profiling results for amide SAR, compounds **15**–**20**

Compound	Y	R^1	V_{1b} pIC_{50}[a]
15	Cl	1,1-Dimethylethyl	8.6
16	Cl	Cyclopropylmethyl	7.2
17	Cl	Cyclobutyl	7.2
18	OMe	Ethyl	6.1
19	OMe	Cyclopropyl	6.7
20	OMe	2,2,2-Trifluoroethyl	6.4

[a] Data are expressed as means of 3–10 experiments, SEM is <0.2.



21 **22**

Figure 4. Variation in alkyl chain length on the RHS.

Table 4
Profiling results for alkyl chain variation, compounds **21**–**22**

Compound	V_{1b} pIC_{50}[a]
21	6.5
22	6.0

[a] Data are expressed as means of 4 experiments, SEM is <0.2.

duction of a fluorine in the C-2 position when a chlorine was present in the C-3 position (compounds **13** and **14**).

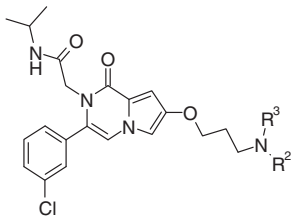


Figure 5. SAR exploration of alternative amines.

Table 5
Profiling results for amine SAR, compounds **23**–**27**

Compound	NR^2R^3	V_{1b} pIC_{50}[a]
23	3-Fluoro-1-piperidinyl	8.0
24	3-(Trifluoromethyl)-1-pyrrolidinyl	8.2
25	4-(Trifluoromethyl)-1-piperidinyl	8.2
26	(8a*S*)-Hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl	7.2
27	(8a*R*)-Hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl	6.7

[a] Data are expressed as means of 3–4 experiments, SEM is <0.2.

Based on their similar in vitro profiles compounds **1** and **4** were used as starting points to explore the SAR of the amide portion on the left upper region of the molecule (Fig. 3 and Table 3). Dealing with the substitution pattern when the isopropyl was replaced with the 1,1-dimethylethyl group an increase of inhibitory potency at the V_{1b} receptor (compound **15**) was observed, whereas cyclopropyl methyl and cyclobutyl groups as well as the cyclopropyl moiety led to a reduction of the pIC_{50} value (compounds **16**, **17**, and **19**). In addition linear substituents (compounds **18** and **20**) were not very well tolerated.

Variation in the length of the alkyl chain on the right hand side (RHS) of compound **2** negatively impacted inhibitory potency at the V_{1b} receptor (Fig. 4 and Table 4).

As far as the SAR exploration of the RHS was concerned, an exploration of alternative amines was carried out starting from compound **1**. Retaining the O-linked linear side chain, the piperidine was replaced with amines with reduced basicity due to the presence of an electron withdrawing group in the beta or gamma position relative to the nitrogen, affording compounds with similar inhibitory potency at V_{1b} receptors to compound **1** (Fig. 5 and Table 5, compounds **23**–**25**). However, when the piperidine was replaced with piperazine derivatives a 10-fold drop in potency was observed (compounds **26** and **27**).

Further chemistry efforts were devoted to the RHS SAR expansion synthesizing derivatives of compound **1** where alternative spacers between the oxygen and the terminal nitrogen were explored.

Table 6
Profiling results for alternative RHS SAR, compounds **28**–**35**

Compound	R^4	V_{1b} pIC_{50}[a]
28	4-Piperidinyl	6.7
29	1-Methyl-4-piperidinyl	7.2
30	1-(1-Methylethyl)-4-piperidinyl	7.2
31	1-Cyclopentyl-4-piperidinyl	8.3
32	(1-Methyl-4-piperidinyl)methyl	5.9
33	2-(1-Methyl-4-piperidinyl)ethyl	5.9
34	2-(1-Methyl-2-piperidinyl)ethyl	6.2
35	(1-Methyl-3-piperidinyl)methyl	6.3

[a] Data are expressed as means of 2–5 experiments, SEM is <0.2.

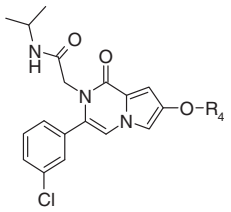


Figure 6. SAR for alternative RHS chains.

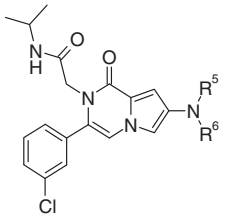
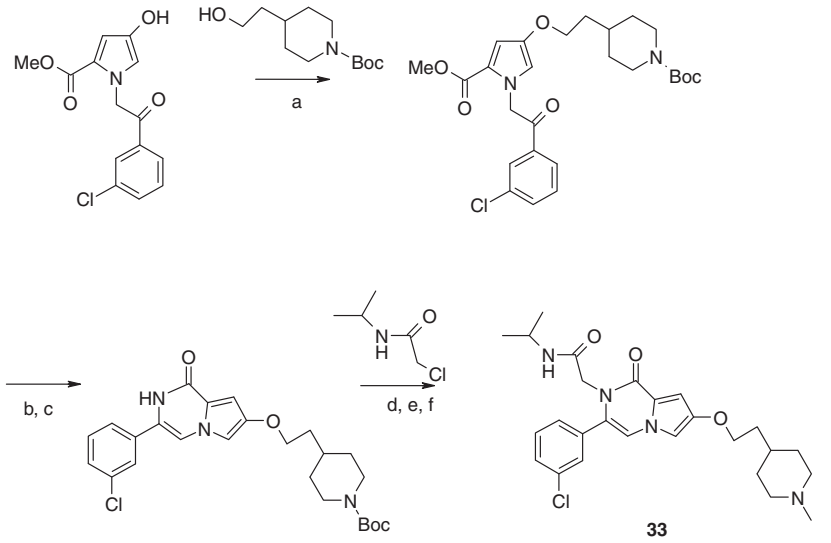
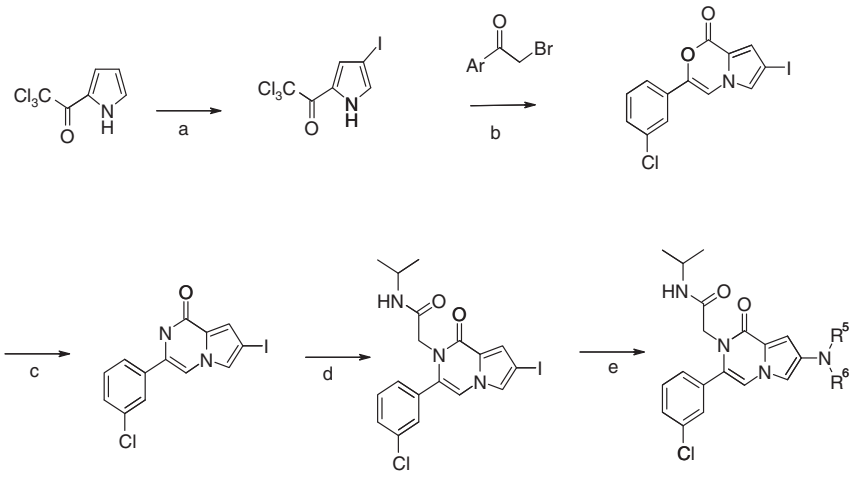


Figure 7. SAR exploration of N-linked chain derivatives.



Scheme 3. Reagents and conditions: (a) PPh_3, diethyl azodicarboxylate, THF, rt, 5 h; (b) NH_4OAc, AcOH, 110 °C, 24 h; (c) $(Boc)_2O$, DCM, rt, 12 h; (d) NaH, NaI, DMF, 65 °C, 16 h; (e) TFA, DCM, rt, 30 min; (f) formaldehyde, $NaCNBH_3$, THF/MeOH (1:1), rt, 30 min.



Scheme 4. Reagents and conditions: (a) I_2, CF_3COOAg, rt, 4 h; (b) K_2CO_3, DMF, rt, 6 h; (c) NH_4OAc, AcOH, 110 °C, 24–36 h; (d) NaH, NaI, $ClCH_2C(O)NH^iPr$, DMF, 65 °C, 16 h; (e) K_2CO_3, CuI, DL-proline, DMSO, amine, 80 °C, 24 h.

Table 7
Profiling results for N-linked chain SAR, compounds **36–49**

Compound	NR^5R^6	V_{1b} pIC_{50}[a]
36	4-Methyl-1-piperazinyl	6.6
37	4-Methylhexahydro-1*H*-1,4-diazepin-1-yl	7.9
38	4-(Dimethylamino)-1-piperidinyl	7.2
39	3-(Dimethylamino)-1-piperidinyl	5.9
40	3-(Dimethylamino)-1-pyrrolidinyl	6.3
41	4-[2-(Dimethylamino)ethyl]-1-piperidinyl	5.4
42	1,4′-Bipiperidin-1′-yl	8.3
43	4-(1-Pyrrolidinyl)-1-piperidinyl	8.2
44	Methyl(1-methyl-4-piperidinyl)amino	7.3
45	1-Methyl-1,7-diazaspiro[4.4]non-7-yl	6.3
46	9-Methyl-2,9-diazaspiro[5.5]undec-2-yl	5.9
47	2-Methyl-2,8-diazaspiro[4.5]dec-8-yl	6.7
48	2,7-Diazaspiro[3.5]non-7-yl	6.2
49	2-Methyl-2,7-diazaspiro[3.5]non-7-yl	6.9

[a] Data are expressed as means of 2–7 experiments, SEM is <0.3.

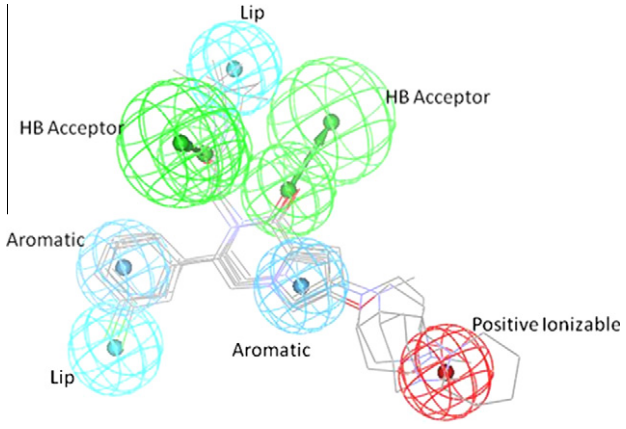


Figure 8. V_{1b} antagonist seven points pharmacophore with superimposed structures **15**, **29**, **37**, **43**, and **44**. The pharmacophore contains the key features that are common to some of the more active pyrrolo pyrazines. The RHS of the pharmacophore contains two pharmacophoric points (aromatic and positive ionizable) and there is a certain level of tolerance in the way those two points are aligned. On the other hand the LHS seems to be much more strictly defined and constrained. Of the five most relevant pharmacophoric points two (the hydrogen bonds acceptors) have also a precise spatial directionality.

The majority of the compounds bearing these alternative RHS chains, were prepared following the route outlined in Scheme 3 for compound **33**. Starting from methyl 1-[2-(3-chlorophenyl)-2-oxoethyl]-4-hydroxy-1*H*-pyrrole-2-carboxylate, prepared as described in Scheme 1, the side chain was introduced via Mitsunobu reaction using the appropriate alcohol. Cyclization with ammonium acetate under reflux afforded the desired pyrrolo[1,2-*a*]pyrazine with untimely deprotection of the amine functionality. Before introduction of the amide chain by alkylation of the pyrrolo[1,2-*a*]pyrazine core with 2-chloro-*N*-isopropylacetamide, the amine group was re-protected with Boc-anhydride. The desired products were obtained after deprotection and methylation of the amine moiety by reductive amination with formaldehyde.[13]

Table 8
Pharmacokinetic parameters in rat for compound **11** (iv dose: 1 mg/kg; po dose: 3 mg/kg)

Clb (mL/min/kg)	43
$t_{1/2}$ (h)	2.9
V_d (l/kg)	9.6
F (%)	69
AUC (h ng/mL)	774
C_{max} (ng/mL)	78
Brain/blood ratio	0.95

Table 6 shows potency data collected for the aforementioned compounds. Good inhibitory potency at the V_{1b} receptor was observed only when replacing the linear chain with a *O*-4-piperidine-N-substituted moiety (Fig. 6 and Table 6, compounds **29**–**31**).

With the aim to further explore the RHS SAR of compound **1**, the O-linked alkyl chain was replaced with a variety of N-linked alkyl chains (Fig. 7).

The desired N-linked derivates were prepared according to the route outlined in Scheme 4. This involved preparation of 2,2,2-trichloro-1-(4-iodo-1*H*-pyrrol-2-yl)ethanone by iodination of a commercially available starting material. One pot alkylation of the nitrogen and cyclization gave the 3-chlorophenyl-7-iodo-1*H*-pyrrolo[2,1-c][1,4]oxazin-1-one derivative, that was converted into the required 3-chloro-phenyl-7-iodopyrrolo[1,2-*a*]pyrazin-1(2*H*)-one by heating at reflux in presence of ammonium acetate in acetic acid. The amide side chain was readily introduced by alkylation with 2-chloro-*N*-isopropylacetamide. Copper iodide catalyzed cross-coupling, in the presence of DL-proline as ligand, afforded the desired products.[13]

The results of this exploration are reported in Table 7. Nitrogen as well as oxygen was tolerated as the linker. The highest potency values at the V_{1b} receptor were observed for compounds **42**, **43**, and **37**, while spiro derivatives **45**–**49** showed low to moderate inhibitory potency. In order to rationalize the SAR for this series

of molecules, a pharmacophoric model[16] was built using molecules **15**, **29**, **37**, **43**, and **44** (Fig. 8). In fact, it was quite evident that the position of the terminal nitrogen on the RHS in compounds **43** and **37**, was superimposable with the position of the terminal nitrogen in the linear chain of compound **15**.

The in vitro pharmacology profile of many exemplars of both series proved to be very attractive. In addition, the developability profile of both series was encouraging; both metabolic stability (Intrinsic Clearance, Cli) and CyP450 inhibition profiles for many compounds appeared promising. Based on the in vitro pharmacology of the different compounds, compound **11** was selected for in vivo pharmacokinetic studies in the rat.[17] Compound **11** as lead exemplar of the pyrazolo[1,5-*a*]pyrazine series proved to be selective towards V_{1a}, V_2, and OT receptor subtypes (pIC_{50} $V_{1a} < 4.3$, pIC_{50} $V_2 < 4.5$, and pIC_{50} OT < 4.7). In addition compound **11** was submitted to the Cerep 'Comprehensive Pharmacological Profile' panel, including 154 biological targets (GPCRs, ion channels, transporters and enzymes), where it produced less than 50% displacement of binding or inhibition at 1 μM in the full panel.

Furthermore, the PK profile of compound **11** proved to be acceptable with moderate blood clearance and high volume of distribution, high oral bioavailability and good brain penetration (Table 8).

In summary, we identified a novel series of potent vasopressin V_{1b} receptor antagonists within which key exemplars showed high selectivity with respect to V_{1a}, V_2, and OT receptor subtypes. The best example selected from the series herein described, showed high selectivity over an extensive range of GPCRs, ion channels, transporters and enzymes. Moreover, this selected compound exhibited a promising pharmacokinetic profile, including good CNS penetration. Compounds from these series therefore deserve to be further explored in vivo to exploit the therapeutic potential of selective V_{1b} receptor antagonists for human diseases.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.07.037.

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16. The common feature pharmacophore was built using Catalyst (2009) as implemented into the Discovery Studio platform. Conformers were generated using the FAST algorithm and defaults settings. The best hypothesis is the one depicted in the paper.
17. All the works involving animals were carried out in accordance with European directive 86/609/EEC governing animal welfare and protection, which is acknowledged by Italian Legislative Decree No. 116, 27 January 1992, and according to internal review performed by the GlaxoSmithKline Committee on Animal Research & Ethics (CARE) and to the company Policy on the Care and Use of Laboratory Animals.