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The characterization of a novel V1b antagonist lead series

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ABSTRACT

The SAR around a V1b antagonist HTS hit **3** was explored to produce a series of thiazole sulfonamides as a lead series with selectivity over the related V1 and oxytocin receptors.

Arginine vasopressin (AVP) is a neuropeptide produced in the hypothalamus. It is involved in many biological processes of both the circulatory system and the central nervous system (CNS), including water homeostasis, renal function, mediation of cardiovascular function, non-opioid mediation of tolerance for pain, regulation of temperature in mammals and modulation of corticotropin release from the pituitary.[1–3] AVP acts on three vasopressin receptor subtypes, designated V1a, V2 and V1b (V3) and has also been shown to agonize the closely related oxytocin (OT) receptor.[4] The V1b receptor is expressed mainly in the anterior pituitary and treatment with a Vlb receptor antagonist can inhibit stress-induced corticotropin releasing hormone (CRH) stimulated adrenocorticotropic hormone (ACTH) secretion.[5] Behavioral studies of V1b knockout mice, which are healthy and viable, have shown that the V1b receptor is implicated in anxiety, depression and aggression.[6,7] Therefore selective antagonism of the Vlb receptor may have significant clinical potential as a treatment for certain types of depression and stress-related affective disorders. It is believed that Vlb antagonists that penetrate the CNS may have greater therapeutic potential for stress-related affective disorders. Some V1b receptor antagonists have been described in the literature, among them those by Sanofi **1**[8] and Organon/Schering-Plough **2**[9,10] (Fig. 1). The reported V1b antagonists tend to have high molecular weight and high topological surface area (tPSA) which are molecular properties usually associated with poor CNS penetration.[11] They also generally show poor selectivity over the V1a and OT receptors.[12] Herein we report the development of a novel, selective lead series of V1b antagonists with improved physicochemical properties.

Compound **3** was identified as a V1b antagonist from a high throughput screen performed on the GSK compound collection (Fig. 1).[13] The compound was found to be >10-fold selective over the OT and V1a receptors and had lower molecular weight and tPSA than previously identified V1b antagonists. Compound **3** was therefore an attractive starting point for hit to lead optimization. The SAR was investigated with the aim of increasing the V1b in vitro potency and improving physicochemical properties, especially the high calculated log *D* at pH 7.4 ($c\log D_{7.4}$)[14] whilst maintaining the selectivity profile over the V1a and OT receptors.

Many of the compounds were synthesized from commercially available ethyl 2-bromothiazole-4-carboxylate, **4**, using the route shown (Scheme 1). The key intermediate **5** could be subsequently reacted in Suzuki cross-coupling reactions or in Buchwald amidations.[15] The sulfonylation, Suzuki and Buchwald couplings and the two reductive alkylation steps were all amenable to parallel synthesis, which allowed for rapid SAR exploration.

The SAR of the thiazole-2-position was explored. Substituents in the *ortho* and *meta* positions were found to be generally less potent than *para* substituents (data not shown) so the *para* position was explored in more detail. A series of simple alkyl substitutions, butylamine analogs and benzylic aromatics were prepared (Table 1, compounds **6**–**12**) as alternatives to the terminal butylamine. An increase in target potency was observed with **6**, V1b pK_i = 7.6. It was shown by preparation of **7**, V1b pK_i = 7.0 that the activity could also be retained by formation of the tertiary amine. Compounds **10–12** demonstrated that the potency was not simply driven by

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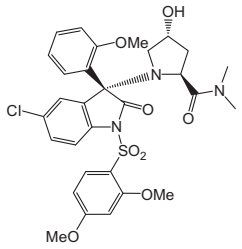
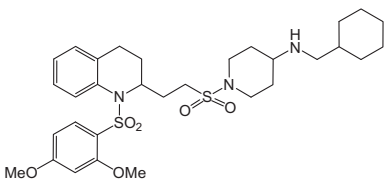
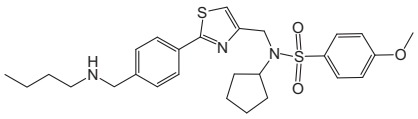


1 SSR149415
V1b pKi = 9.34, V1a pKi = 7.23, OT pKi 8.82
Molecular weight = 630 tPSA = 125.9 Å^2
clogD$_{7.4}$ = -0.2.

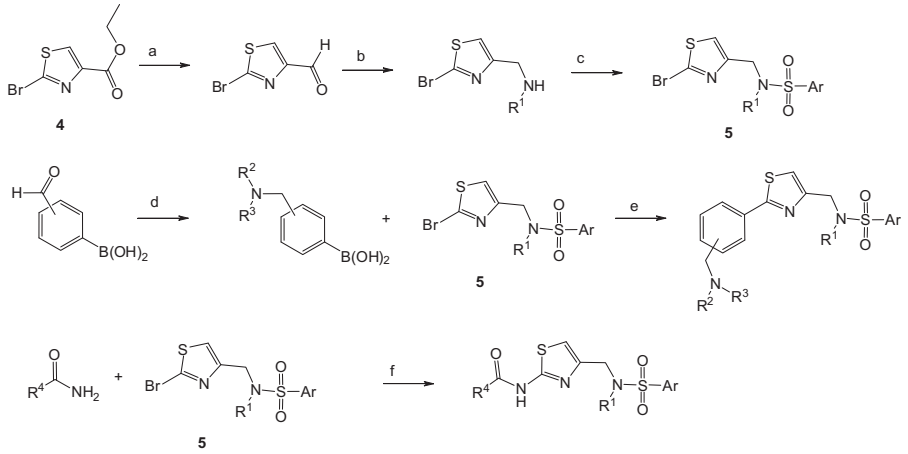


2
V1b pKi =7.36, V1a pKi = 5.25,OT pKi=6.50
Molecular weight = 619, tPSA = 105.3 Å^2,
clogD$_{7.4}$ = 3.0



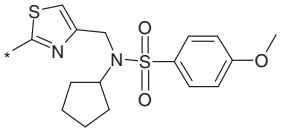
3
V1b pKi=6.8, V1a pIC$_{50}$=5.6, OT pIC$_{50}$=5.3,
Molecular weight = 513, tPSA = 71.5 Å^2,
cLogD$_{7.4}$= 4.3

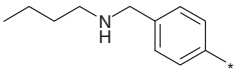
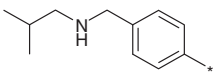
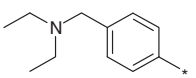
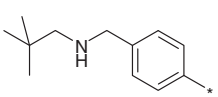
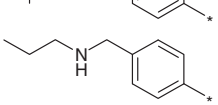
Figure 1. Selected literature V1b antagonists and HTS hit **3**.



Scheme 1. Representative synthesis of compounds. Reagents and conditions: (a) DIBAL-H, THF, CH_2Cl_2, −78 °C; (b) NH_2R^1, $NaBH(OAc)_3$, CH_2Cl_2; (c) Ar-SO_2Cl, solid supported-1,5,7-triazabicyclo[4.4.0]dec-5-ene, DIPEA, CH_2Cl_2, DMA, microwave 60 °C, 20 min; (d) NHR^2R^3, $NaBH_4$, MeOH; (e) $Pd(PPh_3)_2Cl_2$, LiCl, Na_2CO_3, 1:1 toluene, ethanol, microwave, 130 °C, 30 min; (f) $Pd(OAc)_2$, Xantphos, Cs_2CO_3, THF, microwave, 130 °C, 15 min.

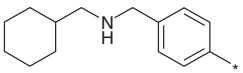
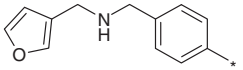
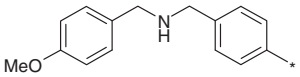
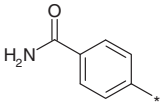
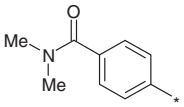
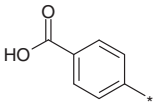
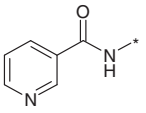
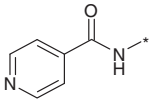
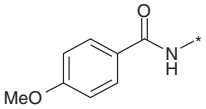
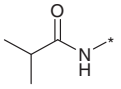
Table 1
Variation of thiazole-2-substituent



	R	V1b pK_i	V1a pK_i	OT pK_i	Molecular weight	tPSA (Å^2)	*c* log $D_{7.4}$
3		6.8	5.6	5.3	513	71.5	4.3
6		7.6	6.0	5.6	513	71.5	4.2
7		7.0	5.7	5.4	513	62.7	3.9
8		7.0	5.1	4.6	527	71.5	4.7
9		7.0	5.7	5.2	499	71.5	3.9

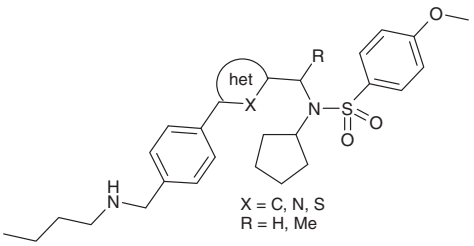
(*continued on next page*)

Table 1 (*continued*)

	R	V1b pK_i	V1a pK_i	OT pK_i	Molecular weight	tPSA (Å^2)	*c* log $D_{7.4}$
10		6.5	5.5	5.2	553	71.5	5.2
11		6.4	5.2	4.7	537	84.7	5.0
12		5.6	4.4	<4.3	577	80.8	5.0
13		6.3	n.d.	n.d.	471	102.6	4.1
14		6.2	n.d.	n.d.	499	79.8	4.3
15		6.1	n.d.	n.d.	472	96.8	1.9
16		7.0	n.d.	n.d.	473	101.5	3.4
17		6.8	n.d.	n.d.	473	101.5	2.9
18		6.4	n.d.	n.d.	502	97.8	5.5
19		6.5	n.d.	n.d.	438	88.6	4.4

Effect on V1b in vitro potency, n.d. = not determined.

Table 2
Variation of thiazole core



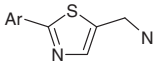
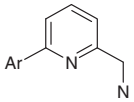
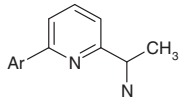
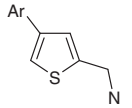
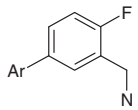
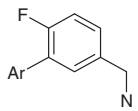
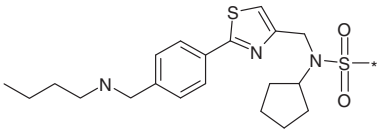
	Core	V1b pK_i	Molecular weight	tPSA (Å^2)	*c* log $D_{7.4}$
3		6.8	513	71.5	4.3
20		6.4	507	71.5	4.7

Table 2 (*continued*)

	Core	V1b pK_i	Molecular weight	tPSA (Å^2)	*c* log $D_{7.4}$
21		5.9	521	71.5	5.2
22		6.1	476	41.5	3.1
23		5.5	524	58.6	5.1
24		6.0	524	58.6	5.2

Effect on V1b in vitro potency.

Table 3
Alteration of sulfonamide



	R	V1b pK_i	Molecular weight	tPSA (Å^2)	*c* log $D_{7.4}$
3	4-MeOPh	6.8	513	71.5	4.3
25	3-MeOPh	6.3	513	71.5	4.8
26	2-MeOPh	5.9	513	71.5	4.2
27	3,4-MeOPh	5.9	543	80.7	4.2
28	4-*i*PrOph	5.9	541	71.5	5.2
29	4-OCF_3Ph	5.7	567	71.5	5.0
30	4-FPh	6.4	501	62.3	4.0
31	Ph	6.2	483	62.3	4.4
32	3-NHAcPh	6.6	540	91.4	3.7

Effect on V1b in vitro potency.

lipophilicity as increasing *c* log $D_{7.4}$ lowered the V1b potency. The selectivity of all of these compounds for V1b over V1a and OT was maintained at 10- to 100-fold.

These results encouraged us to make further changes to the left-hand portion of the molecule, replacing the butylamine with non-basic substituents (compounds **13–19**). The compounds prepared maintained V1b antagonist potency and demonstrated that the *c* log $D_{7.4}$ could be reduced substantially, as demonstrated in the acidic compound **15**, V1b pK_i = 6.1, *c* log $D_{7.4}$ = 1.9. The molecular weight could also be reduced substantially whilst maintaining V1b potency as demonstrated by compounds such as **19**, V1b pK_i = 6.5, molecular weight = 438.

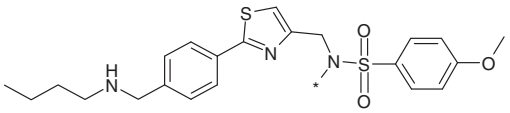
Replacement of the thiazole ring in **3** with alternative aryl rings was investigated using analogous chemistry to that described in Scheme 1. These replacements generally had similar or slightly lower potency than **3** (Table 2) and were not pursued further at this stage.

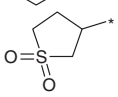
Substitution of the aryl sulfonamide ring was investigated (Table 3). Comparison of compounds **25** and **26** with **3** demonstrates that there is a slight preference in the binding site for 4-substitution. It appears that there is a tight size constraint at the *para* position as replacement of the methoxy group in **3** by trifluoromethoxy **29** or isopropoxy **28** groups resulted in decreased potency, whilst replacement by fluoro or H in compounds **30** and **31** resulted in little or no decrease. The drop-off in potency observed with the disubstituted compound **27** also suggested that there is a strong steric component to binding in this region. No increase in potency from **3** was observed although it was encouraging that in vitro potency could be maintained in **32** with a simultaneous reduction in *c* log $D_{7.4}$ (3.7 compared to 4.3 for **3**).

Compound **3** was studied in a rat DMPK experiment (Table 4)[16] and was found to have good brain penetration which was consistent with predictions based on its relatively low tPSA value. However **3** was also found to have low oral bioavailability, which was attributed to its high clearance (>liver blood flow). A metabolite ID study of **3** (data not shown) was therefore conducted and identified that the cyclopentyl moiety was a key site of metabolism for this compound. We postulated that the introduction of heteroatoms into this ring would stabilise the ring to oxidative metabolism. Several analogs were synthesized and a number of them retained V1b potency. These analogs were progressed to DMPK experiments where, gratifyingly, a reduction in in vitro and in vivo clearance was observed. However, the compounds did not show an improvement in measured oral bioavailability from **3**. Although the high clearance had been addressed the low oral bioavailability suggests that the compounds also have poor absorption which would require further optimization. By introducing additional heteroatoms to reduce clearance, the tPSA of these compounds was increased and a trend for decreasing CNS penetration with increasing tPSA was observed.

In summary, a novel series of selective V1b antagonists has been identified with lower tPSA and molecular weight than previously identified V1b antagonists. The hit to lead effort demonstrated that a number of properties of the HTS hit **3** could be improved. An improvement to in vitro potency at the V1b receptor was achieved with **6**. The physicochemical properties of the hit were improved, for example, *c* log $D_{7.4}$ was substantially reduced in **15** and molecular weight was reduced in **19**. The DMPK profile was partially addressed with whole blood clearance substantially reduced for **33**, **34** and **35**. These molecules represent useful tools for in vivo experimentation. However, further optimization is now

Table 4
Alteration of sulfonamide N-substituent



	R	V1b pK_i	Molecular weight	tPSA (Å^2)	*c* log $D_{7.4}$	Rat Cl_{int} (ml/min/g)	Cl_b (ml/min/kg)	V_{dss} (L/kg)	$T_{1/2}$ (h)	*F*%	Ratio [Brain]:[Blood]
3		6.8	513	71.5	4.3	17.3	129	4.5	0.8	<1%	6.3:1
33		6.2	515	80.7	2.7	6.8	62	4.0	1.1	<1%	0.9:1
34		6.9	529	80.7	3.1	3.5	48	1.5	0.6	<1%	1.1:1
35		5.9	563	105.6	1.9	1.4	33	2.0	1.4	<1%	0.4:1

Effect on V1b in vitro potency and in vivo DMPK. Rat Cl_{int} is intrinsic clearance measured in rat microsomes; Cl_b refers to whole blood clearance; V_{dss} is volume of distribution at steady state; $T_{1/2}$ is the half life of the test compound; *F*% is the oral bioavailability expressed as a percentage; ratio [Brain]:[Blood] is the ratio of test compound concentration in the brain and blood.

required to identify molecules with lower clearance combined with improved physicochemical properties which could result in improved oral bioavailability.

References and notes

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13. All V1b compound screening and profiling activities were conducted using a Chinese Hamster Ovary (CHO) host stably expressing a recombinant V1b receptor cell. A 384 well plate based FLIPR Ca^{2+} assay (Fluorescence Imaging Plate Reader) was also configured to measure compound inhibition of a vasopressin mediated response. 10 K cells per well were plated overnight in culture media before being washed in assay buffer and then loaded with calcium fluorophore, Fluo4-AM for 1 h. Test compounds were equilibrated with cells at 1% DMSO for 10 min before addition of EC_{80} vasopressin. For compound screening, compounds were tested at 10 μM and hits were identified as those compounds capable of giving >50% inhibition of the vasopressin response. For further characterization of hits, concentration response curves were constructed versus EC_{80} of vasopressin, and the concentration at which 50% of the maximal inhibition is achieved was calculated (IC_{50}). All quoted data is for a minimum of $n = 3$ determinations of IC_{50}. pK_i values are calculated from the IC_{50} values by using the Cheng and Prusoff equation.
14. Calculated using log *D* suite version 11. Advanced Chemistry Development, Inc., Toronto, Ontario, Canada (http://www.acdlabs.com/).
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16. Pharmacokinetics measured in male Sprague–Dawley rats following intravenous (iv) and oral (po) administration. Dose was 1 mg/kg iv and 5 mg/kg po for compound **3**. Dose was 1 mg/kg iv and 1 mg/kg po for all other compounds. These studies used at least three animals for each (iv/po) leg.