Bioorganic & Medicinal Chemistry Letters 21 (2011) 3603–3607

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Identification and optimisation of novel sulfonamide, selective vasopressin V_{1B} receptor antagonists

James Baker [c], Matilda Bingham [a,*], Ruth Blackburn-Munro [a], Jiaqiang Cai [a], Mark Craighead [b], Robert Gilfillan [a], Kate Goan [b], David Jaap [a], Rachel Milne [b], J. Richard Morphy [a], Susan Napier [a,*], Jeremy Presland [b], Gayle Spinks [a], Fiona Thomson [b]

[a] Department of Medicinal Chemistry, MSD, Newhouse, Motherwell ML1 5SH, United Kingdom
[b] Department of Molecular Pharmacology, MSD, Newhouse, Motherwell ML1 5SH, United Kingdom
[c] Department of Pharmacology, MSD, Newhouse, Motherwell ML1 5SH, United Kingdom

ARTICLE INFO

Article history:
Received 11 March 2011
Revised 20 April 2011
Accepted 22 April 2011
Available online 1 May 2011

Keywords:
Vasopressin antagonist
GPCR antagonist

ABSTRACT

The synthesis and preliminary structure–activity relationships (SAR) of a novel class of vasopressin V_{1B} receptor antagonists are described. Hit compound **5**, identified via high throughput screening of the corporate collection, showed good activity in a V_{1B} binding assay (K_i 63 nM) but did not possess the lead-like physicochemical properties typically required in a hit compound. A 'deletion approach' on the HTS hit **5** was performed, with the focus on improvement of physicochemical properties, yielding the selective V_{1B} antagonist **9f** (K_i 190 nM), with improved druglike characteristics.

The hypothalamic-pituitary-adrenal (HPA) axis is one of the main routes by which humans and other mammals cope with and adapt to stress.[1] A majority of patients suffering from severe depressive disorder exhibit a profound alteration in their ability to regulate the HPA, indeed, hyperactivity of the HPA axis is a neuroendocrine abnormality that has been reported to occur in a number of psychiatric conditions including major depressive disorder.[1] There are strong data to indicate that hyperactivity of the HPA axis during chronic stress and in depression is caused by a shift towards a predominant vasopressin (AVP) regulation of this system via binding and activation of the pituitary V_{1B} receptor.[2] Thus, antagonists of the pituitary V_{1B} receptor are proposed to normalise HPA overactivity and, as such, could provide therapeutic benefit in the treatment of diseases such as major depression and stress-related disorders.[3] Preclinical studies with the literature V_{1B} antagonist **SSR 149415** in animal models predictive of antidepressant and anxiolytic activity further support this hypothesis.[4]

A number of V_{1B} receptor antagonists have been reported in the literature (Fig. 1, Table 1). However, these ligands are often characterised by high molecular weight, non lead-like properties, and with the exception of the recently reported and structurally related **3** and **4**, show off-target activity at the related GPCR receptors in the vasopressin receptor family the V_{1A}, V_2 vasopressin receptors and the oxytocin (OT) receptor. This emphasises the challenges inherent in the identification of small molecule non-peptide antagonists for this neuropeptide GPCR family of receptors and is reflected in the scant reports of selective non-peptide V_{1B} ligands since the discovery of the receptor in 1994.[5] Our programme aim was thus to identify a reasonably potent (K_i <500 nM) and selective lead compound which was structurally distinct from known V_{1B} antagonists with suitable druglike and physicochemical properties to serve as a basis for further lead optimisation efforts.

An in-house HTS campaign identified hit **5** as a potent non-selective V_{1B} antagonist (Fig. 2, Table 2). This compound would not routinely be a selected as a suitable start point for a Hit-to-Lead programme due to its poor physicochemical properties however, with favourable precedent in the vasopressin field, we elected to employ a strategy successfully utilized in our discovery of a novel series of 2-(4-oxo-2-aryl-quinazolin-3(4*H*)-yl)acetamide V_{1B} antagonists,[8] where a similarly high molecular weight hit was optimised via careful monitoring of ligand efficiency and physicochemical properties.

Scheme 1 illustrates a typical synthetic route which was used to prepare analogues of the hit compound **5**. Final compounds were prepared using parallel synthesis technology, either via resin chemistry as illustrated in Scheme 1, or via solution phase chemistry as in Scheme 2. Final products were isolated and purified by preparative LCMS.

The compounds thus prepared were evaluated for their ability to displace the binding of tritium labelled arginine vasopressin ([^{3}H]-AVP) to the human V_{1B} receptor in a whole cell binding assay

* Corresponding authors. Tel.: +44 1698736000; fax: +44 1698736187 (M.B.).
E-mail addresses: matilda.bingham@virginmedia.com (M. Bingham), susannapier67@googlemail.com (S. Napier).

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doi:10.1016/j.bmcl.2011.04.104

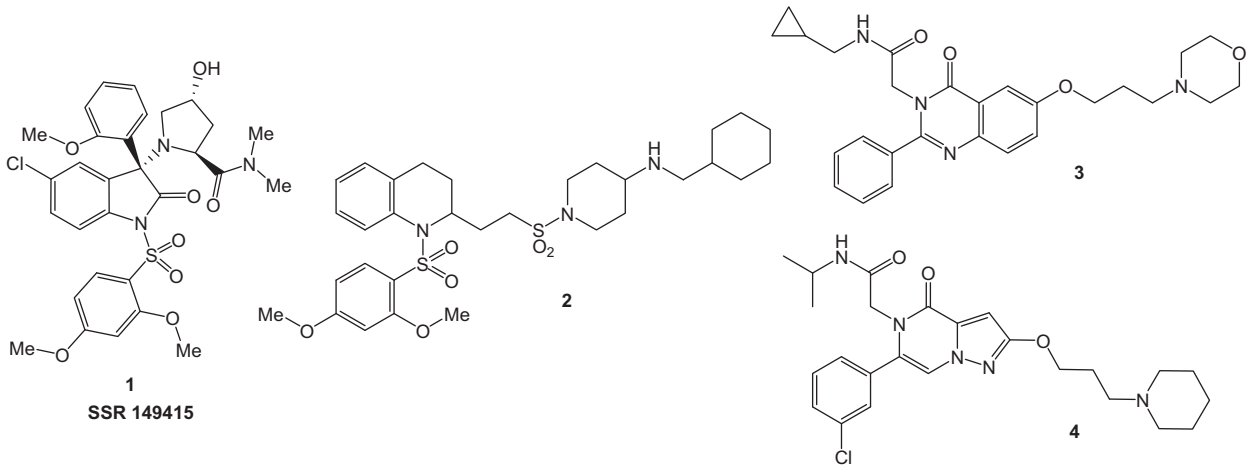


Figure 1.

Table 1
Physicochemical properties of literature V_{1B} antagonists

	MWt	Rotatable bonds	*c* Log *P*	PSA	Donor/ acceptors	Reference
1	630.1	8	3.9	125.9	9/1	6
2	619.8	11	5.1	105.9	7/1	7
3	476.6	10	3.7	83.5	6/1	8
4	486.0	9	4.1	79.7	5/1	9

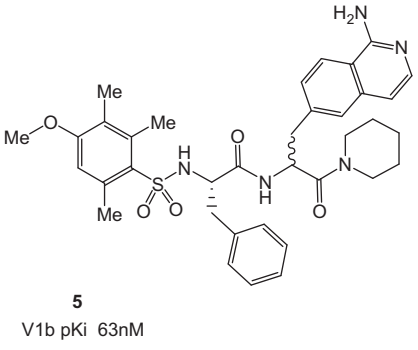


Figure 2.

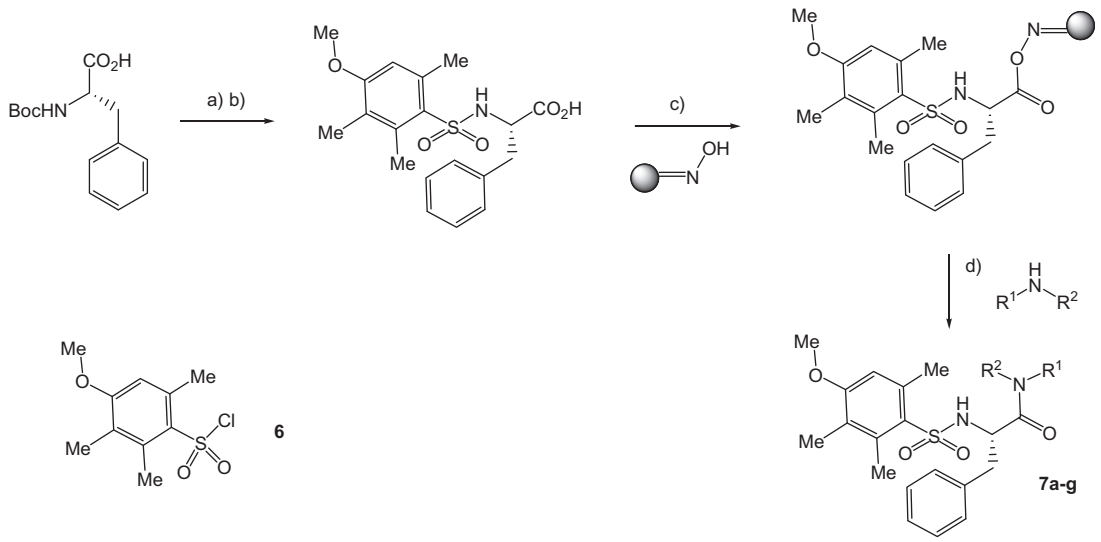
Table 2
Physicochemical properties of hit compound **5**

	MWt	Rotatable bonds	*c* Log *P*	PSA	Ligand efficiency	Donor/ acceptors
5	630.1	8	3.9	125.9	0.21	9/1

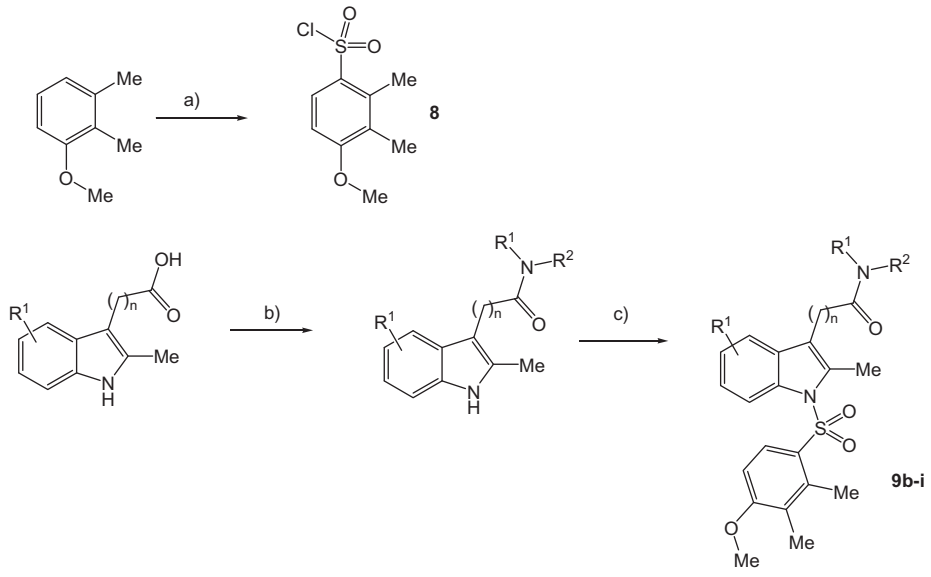
using CHO cells recombinantly expressing the human V_{1B} receptor.[10]

Our initial studies were focused on reducing the molecular weight of compound **5** hence a series of deletion analogues were prepared to determine the minimum pharmacophore required for activity at V_{1B} (Table 3).

These deletion analogues in Table 3 suggested that the (*S*), (*S*)-enantiomer was responsible for the potency at the V_{1B} receptor, however, it was notable that the (*S*)-CH_2(napthalen-2-yl) analogue **10c**, which more closely resembled the steric requirements of hit compound **5**, was not active in contrast to the (*S*)-CH_2Ph analogue **10b**. This led us to hypothesise that the basic group in the (1-aminoisoquinolin-6-yl) side chain of hit **5** was responsible for a key interaction with the V_{1B} receptor. To test this hypothesis, and further reduce the molecular weight of the compounds in line

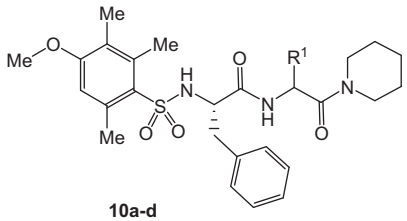


Scheme 1. (a) TFA (b) **6**, DIPEA, DMF:H_2O (2:1) 61% (c) DIC, HOBt, DMAP, DMF (d) R^1R^2NH, DCM, rt 18 h.



Scheme 2. (a) PCl_5, DCM, 0 °C, $ClSO_3H$, 96% (b) EDCI, DIEA, HOBt, DCM (c) KOtBu, THF, **8**, 20–96% after LCMS (2 steps).

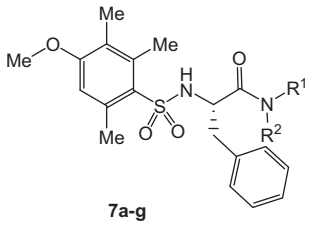
Table 3
V_{1B} binding assay results for deletion analogues **10a-d**

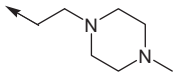
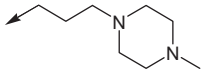
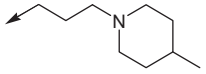
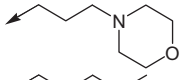
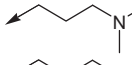
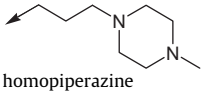


	R^1	V_{1B}[a] K_i (μM)	MWt
10a	(*R*)-CH_2Ph	>10	591.8
10b	(*S*)-CH_2Ph	0.63	591.8
10c	(*S*)-CH_2(naphthalen-2-yl)	>10	641.8
10d	H	>10	501.6

[a] Values are mean of at least 2 independent experiments carried out in duplicate.

Table 4
V_{1B} binding assay results for compounds **7a–7g**



	R^1	R^2	V_{1B}[a] K_i (μM)	MWt
7a	H		0.50	503.7
7b	H		0.25	516.7
7c	H		2.5	515.7
7d	H		10	503.7
7e	H		2.0	461.6
7f	Me		1.0	530.7
7g	*N*-Methyl homopiperazine		3.2	473.6

[a] Values are mean of at least 2 independent experiments carried out in duplicate.

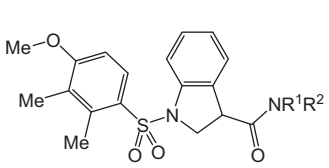
with the stated strategy, a diverse array of compounds where the terminal piperidinyl carboxyamide amino acid was replaced with an amine group were synthesised. In addition to reducing the molecular weight this would also allow removal of one of the amide bonds, improving the predicted oral absorption properties. Selected active compounds from this array are highlighted in Table 4.

Table 4 details a number of amines which successfully replaced the terminal piperidinyl carboxyamide amino acid of hit **5**, whilst maintaining activity at V_{1B}. The distance of the basic centre from the amide bond appears to be key, with the propyl spacer as optimal (**7a** vs **7b**). The distal amino group is most important for activity since both the 4-methylpiperidine and morpholino equivalents of **7b** were less active. The secondary amide is also preferred, although tertiary amides can be tolerated, as both **7f** and the homopiperazine **7g** were less active. Importantly compound **7b** represents a breakthrough since it possesses significantly better properties compared with the hit **5** in terms of molecular weight (516.7 vs 630.1), a reduced number of amide bonds (1 vs 2) and an improved ligand efficiency (0.26 vs 0.21).

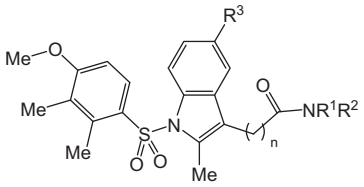
An exploration of the SAR of the aryl-sulfonamide region of the molecule proved less fruitful. A diverse array of sulfonamides were synthesized including alkyl, heterocyclic and aryl sulfonamides (not shown), however only small changes to the electron rich aromatic ring were tolerated with the original sulfonamide present in compounds **7a–g** remaining the best substituent. Removal of the aryl 6-methyl group was tolerated and this sulfonamide was used in subsequent compounds **9a–i** due to the modest improvement it afforded in reduction of MW and *c* Log *P*.

The next focus for optimisation was the number of rotatable bonds. A number of cyclic constraints were investigated in this regard, the two most successful both involved formation of a 6,5-bicycle via cyclisation of the central phenylalanine aryl ring in compounds **7a–g** (Table 4) onto the sulfonamide NH, to afford

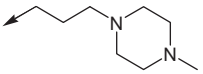
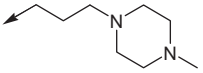
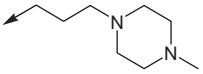
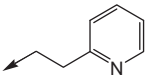
Table 5
V_{1B} binding assay results for compounds **9a–i**



9a

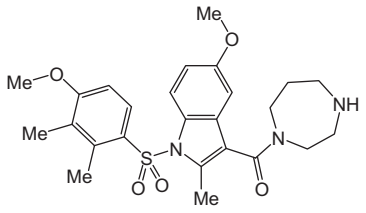


9b-i

	R^1	R^2	R^3	n	V_{1B}[a] K_i (μM)	Rotatable bonds
9a		H	—	—	1.2	8
9b		H	H	0	0.56	8
9c	*N*-Methyl homopiperazine		H	0	0.50	4
9d	Homopiperazine		Me	0	0.79	4
9e	Homopiperazine		F	0	0.31	4
9f	Homopiperazine		OMe	0	0.19	5
9g	Homopiperazine		OMe	1	0.18	6
9h		H	F	1	0.43	9
9i		Me	F	1	0.26	8

[a] Values are mean of at least 2 independent experiments carried out in duplicate.

Table 6
Selectivity profile for compound **9f**



9f

	hV_{1B}[a] K_i (μM)	hV_{1A}[a] K_i (μM)	hV_2[a] K_i (μM)	hOT[a] K_i (μM)
9f	0.19	>10	>10	>10

[a] Values are mean of at least 2 independent experiments carried out in duplicate.

an indoline-3-carboxamide or 2-methyl-indole-3-carboxamide. Examples of active compounds from these series are indoline-3-carboxamide **9a** and the 2-methyl-1*H*-indole-3-carboxamides and (2-methyl-1*H*-indol-3-yl)acetamides **9b–i** (Table 5). Interestingly, carboxamide substitution at the 3-position of the indole and indoline rather than 2-substitution (not shown) afforded the active isosteric replacement, highlighting the importance of testing all the possible regioisomers. The indoline chemotype represented by **9a** was found to have significant off target affinity for $5HT_6$ and was therefore deprioritised in favour of **9b–i** (Table 5).[11]

It was possible to further reduce the rotatable bond count by replacing the (4-methylpiperazin-1-yl)propyl side chain in **9b** with a homopiperizine side chain. The modest potency of these analogues could be improved by substitution in the indole 5-position (compounds **9d–f**) to afford compounds such as **9f** with the target potency and greatly reduced rotatable bond count (4 vs 11 for compound **9b**). The addition of a methylene spacer as in compounds **9g–i** was also tolerated, as was the use of a less basic side chain such as pyridine in **9i**, however these modifications, although interesting from an SAR standpoint did little to improve the physicochemical properties.

Compound **9f** was chosen for further selectivity profiling against the family of related receptors V_{1A}, V_2 and OT (Table 6) and was shown to be a selective V_{1B} ligand which retained selectivity against $5HT_6$. Furthermore functional antagonism was demonstrated in an hV_{1B} luciferase reporter assay linked to AVP-mediated intracellular calcium mobilisation (**9f** IC_{50} 371 nM). Compound **9f** has good solubility (Solkin at $pH_{7.4}$ 72 mg/L), moderate rat and mouse microsomal stability (RLM Cl_{int} 55, MLM Cl_{int} 58, HLM 217) and measured log $D_{7.4}$ 2.0. The addition of the methylene spacer as in **9g** improves the microsomal stability (RLM Cl_{int} 25, MLM Cl_{int} 16, HLM 16), demonstrating there is scope for optimisation within the series however this is at the expense of the hOT selectivity (**9g** hOT K_i 320 nM).

In conclusion, hit optimisation efforts focussing on the improvement of physicochemical properties have lead to the identification of selective V_{1B} antagonist **9f** representing a novel chemotype in the vasopressin field. Significant improvements have been made to the physicochemical properties in comparison with the original hit compound **5** (e.g., compound **5** MW = 630, *c* Log *P* 3.9, PSA 125.9, Rotatable bonds 11, L.E. 0.21 vs **9f** MW = 485, *c* Log *P* 4.1, Log $D_{7.4}$ 2.0, PSA 71.8, Rotatable bonds 5 L.E. 0.28). Compound **9f** thus represents a novel start point, with physicochemical properties suitable for further optimisation.

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10. CHO cells (V_{1B} and OT) or membranes prepared from CHO cells (V_{1A} and V_2) expressing the human versions of the receptors were incubated with tritiated ligand ([^{3}H] AVP for V_{1A}, V_{1B} and V_2; [^{3}H]oxytocin for OT) and increasing concentrations of the compound. Nonspecific binding was determined in the presence of 10 μM lysine vasopressin for V_{1A}, V_{1B} and V_2; 10 μM oxytocin for OT. The concentration of compound was plotted against specific binding and data were analysed by non-linear regression to calculate affinities of the compound for each receptor.
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