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Synthesis and SAR studies of novel 2-(4-oxo-2-aryl-quinazolin-3(4*H*)-yl) acetamide vasopressin V_{1b} receptor antagonists

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ABSTRACT

Synthesis and structure–activity relationships (SAR) of a novel series of vasopressin V_{1b} (V_3) antagonists are described. 2-(4-Oxo-2-aryl-quinazolin-3(4*H*)-yl)acetamides have been identified with low nanomolar affinity for the V_{1b} receptor and good selectivity with respect to related receptors V_{1a}, V_2 and oxytocin (OT). Optimised compound **12j** demonstrates a good pharmacokinetic profile and activity in a mechanistic model of HPA dysfunction.

Hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis is a neuroendocrine abnormality that has been reported to occur in a number of psychiatric conditions.[1] Arginine vasopressin (AVP) and corticotrophin releasing hormone (CRH) are the primary driving forces behind activation of the HPA axis. Both hormones are released from the paraventricular nucleus of the hypothalamus and act in synergy to induce adrenocorticotropic hormone (ACTH) release from anterior pituitary corticotrophs. Both AVP and CRH induce ACTH release through binding to specific G-protein coupled receptors located in the pituitary, the vasopressin V_{1b} (V_3) receptor and CRH_1 receptor. 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 AVP/V_{1b} regulation of this system.[2] Antagonists of the pituitary (peripheral) V_{1b} receptor are proposed to normalise HPA overactivity and, as such, could provide therapeutic benefit in the treatment of diseases characterised by an excessive cortisol secretion such as major depression and stress-related disorders.[3] Further support for this hypothesis has come from discovery of the V_{1b} antagonist SSR149415. This compound has been proposed to target specifically V_{1b} receptors, since the reported affinities for the related V_{1a}, V_2 and oxytocin (OT) receptors are in the micromolar or submicromolar range.[4] The selectivity of SSR149415 over the other receptor subtypes is high in rat, however, this compound has recently been shown to display significant antagonism of the human (h) OT receptor.[5] SSR149415 has been demonstrated to inhibit AVP-induced ACTH release in vivo and showed activity in animal models predictive of antidepressant and anxiolytic activity after systemic administration. This compound was advanced to Phase IIb clinical trials but appears to have been discontinued.[6]

We recently reported details of our hit-to-lead optimisation effort around a novel series of 2-(4-oxo-2-aryl-quinazolin-3(4*H*)-yl)acetamides as vasopressin V_{1b} receptor antagonists.[7] This effort gave rise to compounds **1** and **2** with good affinity for the human (h) V_{1b} receptor and significantly lower MW and PSA (e.g., **1**, MW = 475, FPSA = 74.37) than other known ligands (Fig. 1). In addition, **1** and **2** demonstrated comparable affinity at the rat (r) V_{1b} receptor and had excellent selectivity for the hV_{1b} receptor vs. the hV_{1a}, hV_2 and hOT receptors. On the basis of their attractive profiles regarding affinity, physicochemical properties and selectivity we initiated a lead optimisation program utilising compounds **1** and **2** as our starting point.

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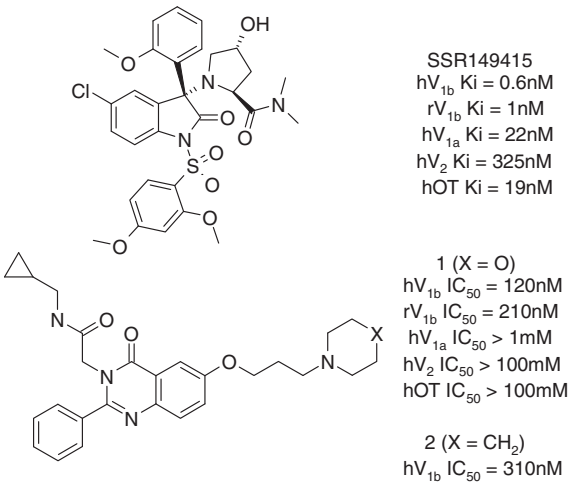
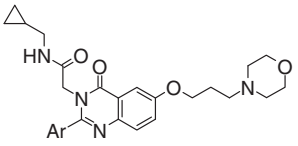


Figure 1. V_{1b} antagonists.

The compounds appearing in Tables 1–3 were synthesised via the general route outlined in Scheme 1. Alternative methods have also been described.[8] 2-Amino-5-hydroxybenzoic acid **3** was reacted with triphosgene to afford the isatoic anhydride **4**. Reaction with glycine amide **5** provided key amide intermediate **6**.[8] Conversion of **6** to intermediate quinazolinones **8** was performed either by condensation of an imidate salt **7** (readily prepared from the corresponding aryl nitrile) or by condensation of **6** with a suitable aldehyde followed by subsequent oxidation of the resultant dihydroquinazolinone intermediate. Finally, the phenol in quinazolinone **8** was alkylated with 1,3-dibromopropane followed by reaction with the appropriate amine to give compounds **9**–**12**.

The compounds in Tables 1–3 were evaluated for their ability to displace the binding of tritium labelled arginine vasopressin ([^{3}H]-AVP) to human V_{1b} receptor in a whole cell binding assay using CHO/human V_{1b}/VIP-Luciferase cells and 5 nM [^{3}H]-AVP.[9] Initially analogues of **1** involving modification to the phenyl substituent at the C(2)-position of the quinazolinone scaffold were explored (Table 1). A systematic scan of the phenyl substituent revealed that substitution was preferred at the 3-position with either electron withdrawing (**9h**) or electron donating (**9g**) groups. Substitution of the phenyl ring at the 4-position was not well tolerated (**9a**–**9d**). Substitution at the 2-position with methyl, to give **9e**, led to a threefold decrease in affinity. Substitution at the 3-position with either a chloro- or methoxy-substituent was favourable for affinity with the 3-chloro analogue **9h** having a fourfold (IC_{50} = 30 nM) and the 3-methoxy analogue **9g** having an eightfold (IC_{50} = 15 nM) higher affinity than **1** (IC_{50} = 120 nM).

Table 1
SAR of phenyl substitution at the C(2)-position of the quinazolinone scaffold

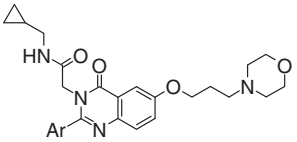


9a-9j

Compds	Ar	hV_{1b} IC_{50}[a] (nM)
1	Ph	120 (±46)
9a	4-Me-phenyl	1450 (±500)
9b	4-MeO-phenyl	1030 (±380)
9c	4-Cl-phenyl	800 (±68)
9d	4-F-phenyl	250 (±180)
9e	2-Me-phenyl	366 (±330)
9f	3-Me-phenyl	125 (±51)
9g	3-MeO-phenyl	15 (±6)
9h	3-Cl-phenyl	30 (±15)
9i	3-F-phenyl	113 (±53)

[a] Values are means of two experiments, standard deviation is given in parentheses.

Table 2
SAR of heteroaryl replacements for phenyl at the C(2)-position of the quinazolinone scaffold



10a-10g

Compds	Ar	hV_{1b} IC_{50}[a] (nM)
1	Ph	120 (±46)
10a	3-Pyridyl	1350 (±780)
10b	4-Pyridyl	3100 (±1600)
10c	2-Thiophenyl	328 (±169)
10d	3-Thiophenyl	470 (±170)
10e	3-Furanyl	644 (±189)
10f	3-Indolyl	387 (±19)
10g	3-Quinolinyl	2400 (±1100)

[a] Values are means of two experiments, standard deviation is given in parentheses.

Replacement of the phenyl moiety with heteroaryl moieties was also investigated (Table 2). Replacement with 3- or 4-pyridyl (**10a** and **10b**) led to a substantial decrease in affinity. Replacement with isosteric 2-thiophenyl, however, gave only a modest decrease with **10c** being only threefold (IC_{50} = 330 nM) less active than **1**. The 3-thiophenyl and 3-furanyl analogues showed similar activity to **10c**. Two analogues (**10f**–**10g**) were prepared in which the phenyl was replaced with bicyclic heteroromatics. Of these **10f** containing a 3-indol-1*H*-yl substituent was the most active, being only three to fourfold less active than **1**.

Next our focus turned to optimisation of the alkyl amide portion of the molecule. Two 2D arrays of twelve compounds each were prepared with the amine substituent fixed as either morpholine (array 1) or piperidine (array 2) since these groups had previously been demonstrated optimal for affinity[7] (Fig. 2). In an effort to

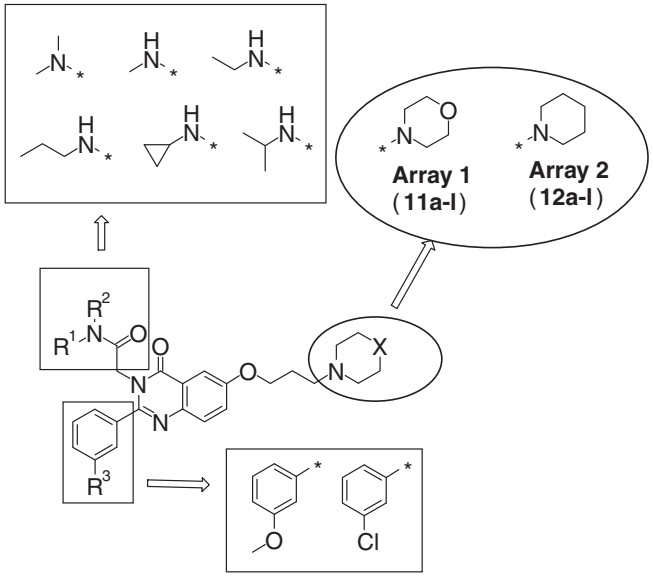


Figure 2. SAR investigation of alkyl amide region in combination with Preferred C(2) aryl and amine substituents.