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Identification and optimization of novel 2-(4-oxo-2-aryl-quinazolin-3(4*H*)-yl)acetamide vasopressin V3 (V1b) receptor antagonists

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ABSTRACT

The discovery, synthesis, and preliminary structure–activity relationship (SAR) of a novel class of vasopressin V3 (V1b) receptor antagonists is described. Compound **1**, identified by high throughput screening of a diverse, three million-member compound collection, prepared using ECLiPS™ technology, had good activity in a V3 binding assay (IC_{50} = 0.20 μM), but less than desirable physicochemical properties. Optimization of compound **1** yielded potent analogs **19** (IC_{50} = 0.31 μM) and **24** (IC_{50} = 0.12 μM) with improved drug-like characteristics.

A majority of patients suffering from severe depressive disorder exhibit a profound alteration in their ability to regulate the hypothalamic–pituitary–adrenal (HPA) axis—the major route via which humans (and other mammals) cope with, and adapt to stress.[1] Arginine vasopressin (AVP) is thought to play a pivotal role in HPA axis regulation, particularly in situations of chronic stress.[2] AVP mediates its effects via binding to the V3 (V1b) receptor expressed upon pituitary corticotropes. Through this mechanism, AVP acts synergistically with corticotropin releasing hormone (CRH) to elicit release of adrenocorticotropic hormone (ACTH), thus positively driving the HPA axis. Much evidence indicates that while CRH may be relevant in orchestrating HPA responsivity to acute stress,[3] AVP-induced activity of V3 receptors may be the more important modulator during chronic stress. This in turn may be more clinically relevant to the development of affective disorders.[2,4]

Therefore, a selective antagonist of the V3 receptor represents a therapeutically relevant approach for treatment of the dysfunctional HPA axis in depressive illness. In fact, a previously reported V3 selective antagonist, SSR149415, has been demonstrated to be active in animal models predictive of antidepressant and anxiolytic activity,[5,6] and this compound advanced into phase IIb clinical trials.[7]

In a program aimed at the identification of a novel and structurally distinct class of V3 antagonists, high-throughput screening (HTS) of a diverse three million-member compound collection, prepared using ECLiPS™ technology,[8] was undertaken. The compounds were screened utilizing a 384-well whole cell binding displacement assay using tritium labeled arginine vasopressin ([^{3}H]-AVP).[9] Multiple active structures, or hits, were identified in this HTS campaign. Among these hits was compound **1** (Fig. 1), possessing an IC_{50} value of 0.20 μM. Compound **1** was chosen as a starting point for a hit-to-lead (HtL) program, with the task of evaluating this hit class in terms of both target independent (e.g., physicochemical properties) and target dependent (e.g., potency, selectivity, etc.) criteria.[10]

The main objective of this HtL program was to generate a lead compound with appropriate potency and drug-like physicochemical properties[11] to serve as the basis for further lead optimization efforts. One immediate concern about compound **1**, was that from a perspective of 'drug likeness' it possessed less than optimal physicochemical properties such as high molecular weight (M_W), high 'fast polar surface area' (FPSA), a high degree of lipophilicity, and a high degree of conformational flexibility (M_W = 613, FPSA = 148.48 Å^2, *A* log *P* = 4.73, # of rotatable bonds = 17).[11,12]

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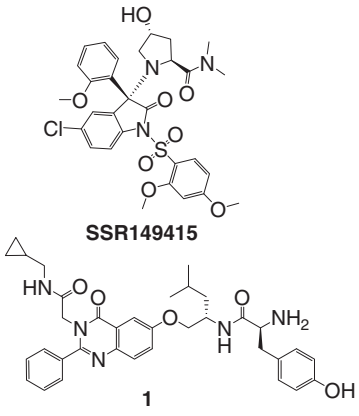


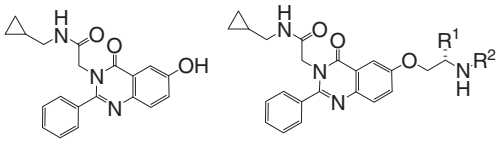
Figure 1. V3 antagonists.

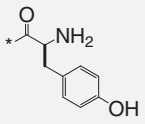
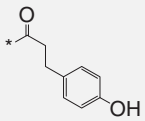
A calculation of the binding energy of compound **1** by Andrew's analysis[13] gave a significantly higher binding energy (ΔG_{calc} = 18.3 kcal/mol) compared to the experimental value (ΔG_{obs} = 9.2 kcal/mol). This large difference suggested that not all parts of the molecule were optimally involved in binding to the receptor. This indicated the possibility for deletions and alterations to the structure without a major decrease in binding affinity. We reasoned that the molecule could be greatly simplified, by strategic deletion of unnecessary structural elements, to deliver a potent and tractable lead compound with improved physicochemical properties. In this report, we describe the synthesis and SAR of novel V3 antagonists resulting in the identification of potent lead compounds with improved physicochemical properties versus compound **1**.

The compounds detailed in Tables 1–3 were synthesized via the outlined general syntheses (Schemes 1–3). The synthesis of the penultimate phenol intermediate **2** has been described elsewhere.[14]

As depicted in Scheme 1, a Mitsunobu reaction[15] between phenol **2** and either Boc-L-leucinol or Boc-2-aminoethanol followed by Boc deprotection gave amines **3** and **4**, respectively. Amine **3** was then coupled with Boc-protected tyrosine which, followed by Boc deprotection, yielded compound **1**. In a similar fashion both amines **3** and **4** were coupled with Boc-protected glycine and deprotected to yield compounds **5** and **6**. Amine **4** was also coupled with 3-(4-hydroxyphenyl)propanoic acid giving compound **7**. As

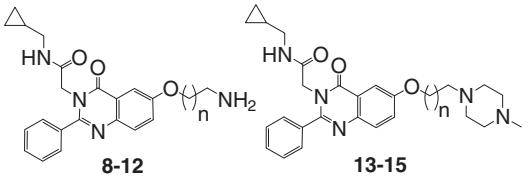
Table 1
Simplification/truncation of right-hand side



Compds	R^1	R^2	hV3 IC_{50}[a] (μM)
1			0.2 (±0.07)
5			5.1 (±3.3)
6	H		30.5 (±0.7)
7	H		>100
2			>100
3		H	2.1 (±0.1)

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

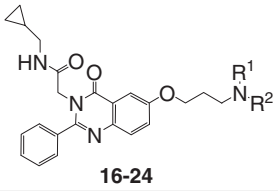
Table 2
Exploration of chain length between amino functionality and scaffold

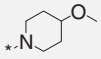
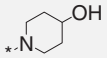


Compds	*n*	hV3 IC_{50}[a] (μM)
8	1	4.0 (±1.6)
9	2	3.6 (±0.2)
10	3	>30
11	4	>30
12	5	>100
13	1	22[b]
14	2	1.7 (±0.6)
15	3	4.8 (±1.0)

[a] Values are means of at least two experiments unless otherwise indicated, standard deviation is given in parentheses.
[b] Value was obtained from a single experiment.

Table 3
N-Methylpiperazine replacements



Compds	NR^1R^2	hV3 IC_{50}[a] (μM)
16		25.8 (±2.1)
17	NHMe	7.6 (±0.6)
18	$N(Et)_2$	3.8 (±1.9)
19		0.31 (±0.15)
20		1.8 (±1.0)
21		0.34 (±0.11)
22		0.71 (±0.13)
23		1.1 (±0.02)
24		0.12 (±0.046)

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