Bioorganic & Medicinal Chemistry Letters 19 (2009) 6018–6022

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Tetrahydroquinoline sulfonamides as vasopressin 1b receptor anatgonists

Jack D. Scott [a,*], Michael W. Miller [a], Sarah W. Li [a], Sue-Ing Lin [a], Henry A. Vaccaro [a], Liwu Hong [a], Deborra E. Mullins [b], Mario Guzzi [b], Jay Weinstein [a], Robert A. Hodgson [c], Geoffrey B. Varty [c], Andrew W. Stamford [a], Tin-Yau Chan [a], Brian A. McKittrick [a], William J. Greenlee [a], Tony Priestley [b], Eric M. Parker [b]

[a] Department of Chemical Research, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA
[b] Department of Central Nervous System, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA
[c] Department of Neurobiology, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA

ARTICLE INFO

Article history:
Received 26 August 2009
Revised 11 September 2009
Accepted 14 September 2009
Available online 17 September 2009

Keywords:
Vasopressin
V1b antagonist
V1b receptor
Anxiety
Depression

ABSTRACT

Vasopressin 1b (V1b) antagonists have been postulated as possible treatments for depression and anxiety. A novel series of potent and selective V1b antagonists has been identified starting from an in-house screen hit. The incorporation of a sulfonamide linker between a tetrahydroisoquinoline core and amino piperidine lead to the identification of a V1b antagonist with similar affinity for human and rat receptors. Further optimization of the right hand portion afforded potent V1b antagonists that possessed moderate to high selectivity over other receptors.

Vasopressin (AVP) is a nonapeptidic hormone that plays a role in several physiological processes. Three vasopressin receptors, V1a, V1b and V2, have been identified and cloned to date. Vasopressin V1a receptors are primarily responsible for vasoconstriction while the V2 receptor regulates water homeostasis. Vasopressin V1b receptors (also known as V3) are expressed at high levels in the anterior pituitary and at lesser levels elsewhere in the brain. Vasopressin has been shown to regulate the hypothalamic–pituitary–adrenal (HPA) axis by stimulating the release of ACTH[1] and acts synergistically with corticotropin releasing factor (CRF).[2] Overactivity of the HPA axis has been linked to stress-related disorders, including depression and anxiety. A role for the V1b receptor in depression was identified through the use of V1b receptor knockout mice.[3] ACTH levels were significantly lower in the knock-out mice than in the control wild type mice following a forced swim stress. It is believed that V1b receptor antagonists would be effective therapeutic agents for the treatment of anxiety and/or depression. Furthermore, structurally unique V1b antagonists are of great interest as tools for pharmacological characterization.

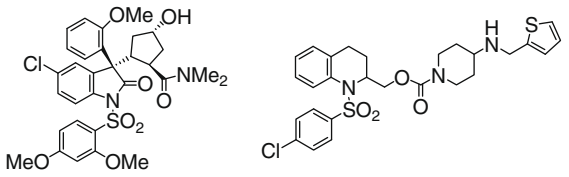
The potent V1b antagonist SSR149415 (**1**) has been shown to have both anxiolytic and anti-depressive properties in several rodent models.[4] This antagonist has also been shown to directly regulate the release of ACTH. The selectivity of SSR149415 over other receptor subtypes that bind to vasopressin (V1a, V2 and oxytocin[5]) is high in the rat; however, it has been reported that this compound is also a potent antagonist of the human oxytocin receptor.[6] Recently, a selective and potent V1b antagonist, Org, has been described.[7] This compound has also been shown to regulate the release of ACTH in rats in response to various acute stressors.

In-house screening identified the tetrahydroquinoline sulfonamide (**2**)[8] as a moderately active V1b receptor antagonist with a human K_i value of 114 nM. However, there was little activity against the rat receptor (K_i = 4456 nM). A goal of this project was to identify selective V1b antagonists that possessed similar affinities for both the human and rat receptors.[9] This would allow for the use of in vivo rodent models to evaluate compounds of interest. Initially, an effort was made to prepare analogs of **2** by replacing the carbamate moiety and varying the linker length between the tetrahydroquinoline and the aminopiperidine (see Fig. 1).

Amide linked analogs (Scheme 1) were prepared from a common tetrahydroquinoline methyl ester **9** which was readily prepared from quinolinone **6**. Quinolinone **6** was protected as the carbamate followed by reduction of the lactam to afford the amino alcohol **7**. Oxidation of the alcohol to form aminol **8** was accomplished using sulfur trioxide pyridine complex. Ester **9** was prepared via treatment of **8** under Wittig conditions. Amide **11** was prepared directly from **9** first by hydrolysis of the ester

* Corresponding author. Tel.: +1 908 740 3462; fax: +1 908 740 7441.
E-mail address: jack.scott@spcorp.com (J.D. Scott).

0960-894X/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2009.09.050



1 SSR149415

hV1b K_i = 0.6 nM
rV1b K_i = 1 nM
hV1a K_i = 22 nM
hV2 K_i = 325 nM
hoxt K_i = 19 nM

2

hV1b K_i = 114 nM
rV1b K_i = 4456 nM

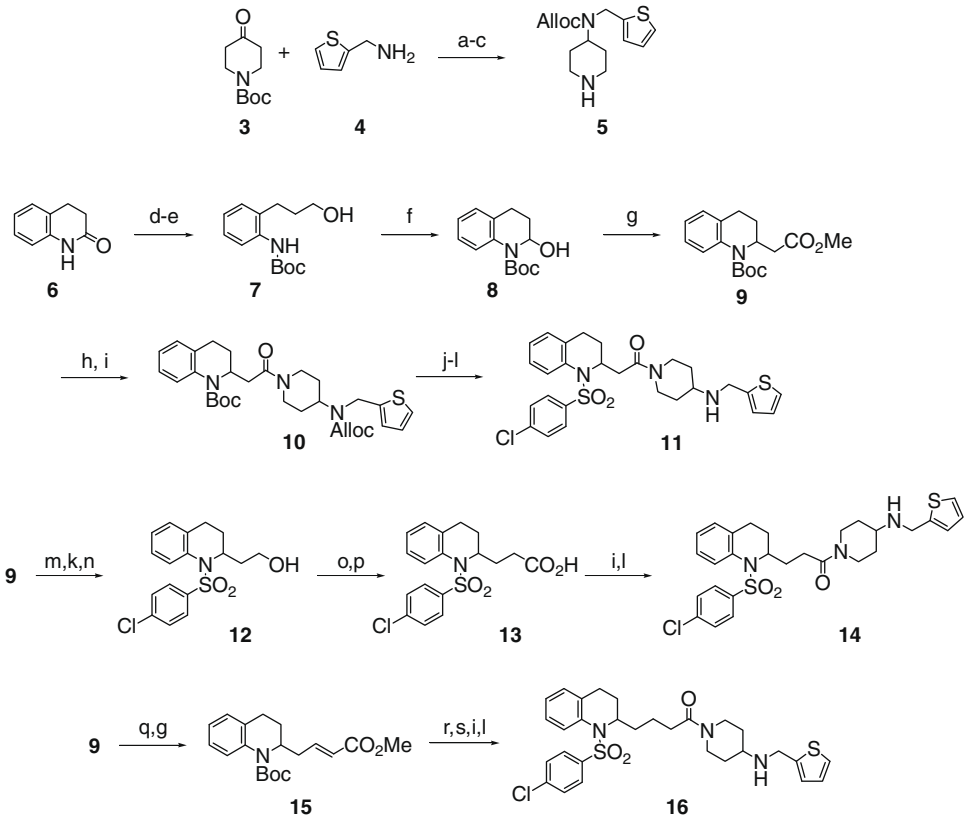
Figure 1.

followed by amide coupling with piperidine **5** to afford **10**. Cleavage of the *t*-butyl carbamate of **10** followed by sulfonamide formation and allyl carbamate deprotection afforded amide **11**. Amides **14** and **16** were prepared from homologated analogs of **9** using similar chemistry.

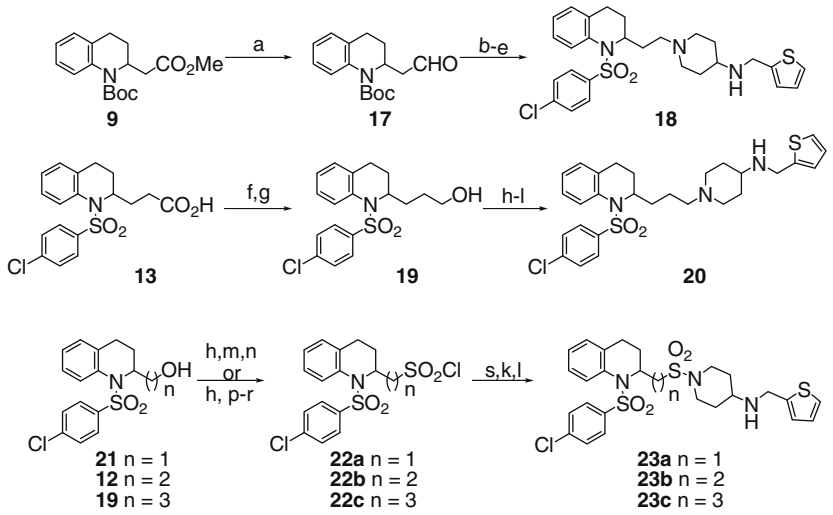
Amine, sulfonamide and urea linked analogs were also prepared (Schemes 2 and 3). Amine **18** was prepared through a reductive amination of aldehyde **17** with the amino piperidine **5**, while the homologated amine **20** was prepared through a mesylate displacement. The three sulfonamide analogs were prepared by the activation of the hydroxyl moiety of alcohols **12**, **19** and **21**[8] as a mesylate or iodide. Displacement of the leaving group by either a sulfate or a thiolate was followed by oxidation and/or chlorination to afford the sulfonyl chlorides in moderate, but not reproducible yields. The sulfonamides **23a–23c** were completed via coupling with the commercially available piperidine ketal followed by ketone formation and finally reductive amination. The urea analogs were prepared starting with alcohol **21**[8] (Scheme 3). Formation of the amines **24** and **25** was followed by condensation with the activated urea of piperidine **5** to provide the ureas **26a** and **26b.**

The binding data for these analogs are summarized in Table 1.[10] The optimum linker length of these compounds was found to be 3 atoms between the piperidine nitrogen and the tetrahydroquinoline. This trend was observed in both the amide and sulfonamide linker series, compounds **14** and **23b** respectively. Overall, compared to the carbamate **2**, the human V1b affinities decreased for all of the analogs that were prepared. The urea **26b** did have a comparable affinity for the human receptor, but the affinity for the rat receptor was not improved. The only compound that achieved similar affinities between the human and rat receptors, albeit with five times lower affinity compared to carbamate **2**, was the sulfonamide linked **23b**. All further structure–activity investigations were based on this general structure.

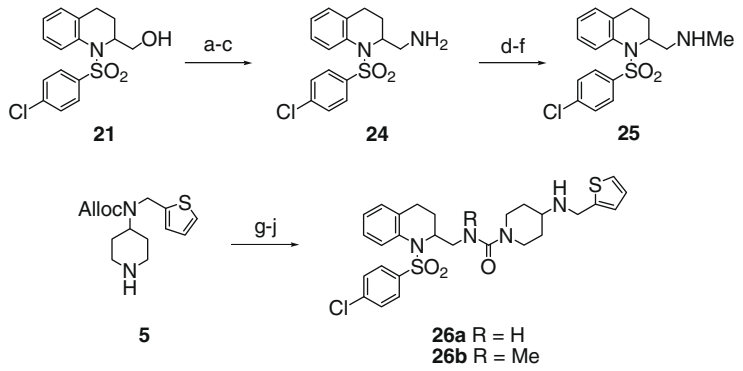
Conversion to the 2,4-dimethoxybenzene sulfonamide, as is present on SSR149415 (**1**), provided analogs with a substantial improvement in both human and rat V1b binding affinities. As shown in Table 2, a 10-fold improvement in binding was observed between **30a** (hV1b K_i = 66 nM) compared to the 4-chlorobenzene sulfonamide **23b** (hV1b K_i = 600 nM). With the 2,4-dimethoxybenzene sulfonamide moiety fixed, substitution of the basic amine was explored (Scheme 4). To facilitate this, the chemistry route was modified to include a more robust and reproducible formation of the sulfonyl chloride. Ester **9** was reduced and the *t*-butyl carbamate was exchanged for a methyl carbamate that was compatible



Scheme 1. Reagents and conditions: (a) $NaBH(OAc)_3$, AcOH, DCE, rt, 16 h (48%); (b) AllocCl, K_2CO_3, EtOAc/H_2O, rt, 16 h (99%); (c) TFA, CH_2Cl_2, 1,3-dimethoxybenzene, rt, 3 h (69%); (d) Boc_2O, DMAP, Et_3N, CH_2Cl_2, 0 °C–rt, 16 h; (e) $NaBH_4$, EtOH, 0 °C–rt, 3 h (57%, two steps); (f) SO_3–pyridine, DMSO, rt, 16 h (99%); (g) sodium trimethylphosphonoacetate, THF, reflux 2.5 h (56–77%); (h) 2 M LiOH (aq), EtOH, rt, 3 h; (i) **5**, EDCI, HOBt, *i*Pr_2NEt, MeCN, rt, 16 h (53–83%); (j) TFA, CH_2Cl_2, 3 h, rt; (k) 4-Cl–$PhSO_2Cl$, DMAP, pyr (39–46%); (l) $Pd(OAc)_2$; Et_2NH, P(*m*-SO_3Na–$Ph)_3$, H_2O, MeCN (69%); (m) 4 N HCl (dioxane), MeOH; (n); DiBAL, toluene, 0 °C (o) acetonecyanohydrin; DIAD, PPh_3, THF −20 °C to rt (93%); (p) 20% KOH (aq); EtOH, reflux (85%); (q) DiBAL, tol, −78 °C; (r) H_2, Pd/C, MeOH; (s) 1 M NaOH (aq), MeOH, 65 °C (96% two steps).

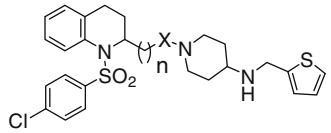


Scheme 2. Reagents and conditions: (a) DiBAL, tol, −78 °C 3 h; (b) **5**, $NaBH(OAc)_3$, CH_2Cl_2, 16 h (56%); (c) TFA, CH_2Cl_2, 3 h (94%); (d) 4-Cl–$PhSO_2Cl$, DMAP, pyr; (e) $Pd(OAc)_2$; Et_2NH, P(*m*-SO_3Na–Ph)$_3$, H_2O, MeCN, 16 h; (f) MeOH, H_2SO_4, reflux, 16 h (63%); (g) DiBAL, toluene 0 °C–rt (99%); (h) MsCl, Et_3N, CH_2Cl_2 16 h; (i) NaI, acetone, reflux, 24 h; (j) 1,4-dioxa-8-azaspiro[4.5]decane, Cs_2CO_3, MeCN, reflux 5 h (74%); (k) 4 N HCl (aq), dioxane, reflux, 16 h (77%); (l) 2-thiophenemethylamine, $NaBH(OAc)_3$, CH_2Cl_2, 16 h (63%); (m) Na_2SO_3, EtOH, H_2O, reflux 16 h, (n) oxalyl chloride, DMF, PhH, reflux; (o) MsCl, Et_3N, CH_2Cl_2; (p) KSAc, DMF 55 °C; (q) NaOMe, MeOH 55 °C, 2 h; (r) KNO_3, SO_2Cl_2, MeCN 0 °C (74%, three steps); (s) 1,4-dioxa-8-azaspiro[4.5]decane, *i*Pr_2NEt, CH_2Cl_2, rt, 16 h (28–71%).



Scheme 3. Reagents and conditions: (a) MsCl, Et_3N; (b) NaN_3, 18-C-6, DMF; (c) PS–PPh_3, THF, H_2O; (90% two steps); (d) Boc_2O, CH_2Cl_2 (89%); (e) NaH, MeI, DMF (92%); (f) HCl, dioxane (100%); (g) CDI, THF; (h) MeI, MeCN; (i) **24** or **25**; (j) $Pd(OAc)_2$; Et_2NH, P(*m*-SO_3Na–Ph)$_3$, H_2O, MeCN, 16 h (47–70% three steps).

Table 1
Structure–activity relationship of various linkers



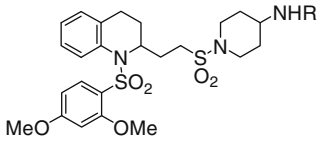
Compound	*n*	X	hV1b[a] K_i (nM)	rV1b[a] K_i (nM)	hV1a[a] K_i (nM)
2	1	–OC(O)–	114 ± 40	4456 ± 356	6164 ± 1234
11	1	–C(O)–	1523 ± 77	>10,000	3654 ± 85
14	2	–C(O)–	715 ± 37	>10,000	6888 ± 472
16	3	–C(O)–	1137 ± 28	3244 ± 408	>8000
18	2	—	7196 ± 376	9587 ± 998	>10,000
20	3	—	1184 ± 25	2776 ± 500	4617 ± 324
23a	1	–S(O)$_2$–	748 ± 58	2690 ± 90	8734 ± 703
23b	2	–S(O)$_2$–	600 ± 116	813 ± 76	4963 ± 882
23c	3	–S(O)$_2$–	1036 ± 21	3941 ± 74	5564 ± 657
26a	1	–N(H)C(O)–	416 ± 103	>10,000	>10,000
26b	1	–N(Me)C(O)–	295 ± 43	>10,000	8866 ± 2309

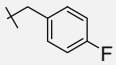
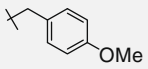
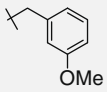
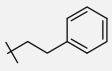
[a] Inhibition of 2 nM [^{3}H]Arg^8-vasopressin (AVP) binding to human or rat vasopressin receptors. All values reported are an average of three independent results.

with the acidic conditions used to prepare the sulfonyl chloride. Conversion of the alcohol to the thioacetate followed conditions described previously. A one-step cleavage of the thioacetate and oxidation to the sulfonic acid was accomplished in high yield using H_2O_2 in acetic acid.[11] Treatment with Pd/C eliminated the excess hydrogen peroxide. Chlorination was accomplished using phosgene to afford the sulfonyl chloride **28** in excellent yields. Coupling with the previously mentioned piperidine ketal was followed by methyl carbamate cleavage and sulfonylation. Subsequent ketal cleavage afforded the ketone **29** which was treated with primary amines under reductive amination conditions to afford the final targets. These reductive aminations were either accomplished in solution (Method A) or via high throughput library synthesis (Method B).

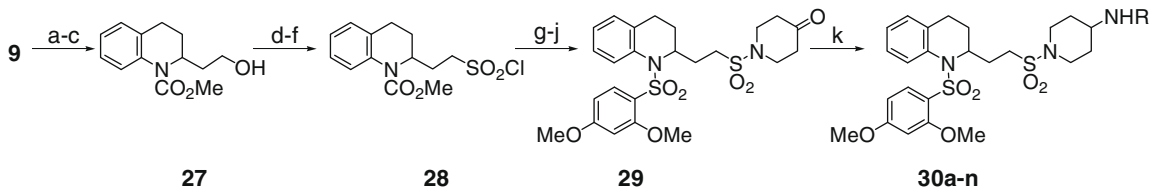
As shown in Table 2, the two methylenethiophene analogs, **30a** and **30b**, and the unsubstituted benzyl **30c** analogs exhibited similar affinities for both species. Substitution of the benzyl group decreased the affinity especially in the 4-methoxy example **30e** (hV1b K_i = 939 nM). Furthermore, substitution α to the amine group also decreased the affinity significantly (examples **30g** and **30l**). Aliphatic side chains were equipotent to the benzyl analogs

Table 2
Structure–activity relationship of right-hand amines



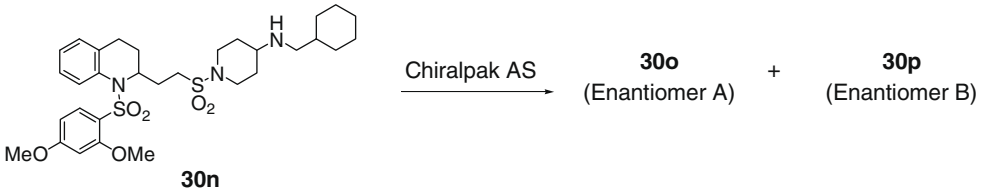
Compound	R	Method[a]	hV1b[b] K_i (nM)	rV1b[b] K_i (nM)	hV1a[b] K_i (nM)
30a		A	66 ± 4	23 ± 3	720 ± 60
30b		B	96 ± 7	145 ± 29	33 ± 97
30c		B	104 ± 7	83 ± 8	192 ± 26
30d		B	218 ± 12	158 ± 8	395 ± 23
30e		B	939 ± 58	637 ± 29	4926 ± 1092
30f		B	279 ± 24	270 ± 9	2600 ± 477
30g		B	717 ± 52	999 ± 108	4803 ± 920
30h		B	122 ± 7	91 ± 11	486 ± 46
30i		B	152 ± 3	227 ± 7	1268 ± 112
30j		B	35 ± 2	27 ± 3	947 ± 85
30k		B	78 ± 2	62 ± 4	1257 ± 125
30l		B	413 ± 39	557 ± 27	709 ± 86
30m		A	138 ± 13	56 ± 6	553 ± 49
30n		A	70 ± 4	16 ± 5	188 ± 16

[a] Method of preparation as listed in Scheme 4 step k.
[b] Inhibition of 2 nM [^{3}H]Arg^8-vasopressin (AVP) binding to human or rat vasopressin receptors. All values reported are an average of three independent results.



Scheme 4. Reagents and conditions: (a) $LiBH_4$, EtOH, THF; (b) 4 N HCl (dioxane), MeOH; (c) $ClCO_2Me$, K_2CO_3, EtOAc, H_2O (80% three steps); (d) MsCl, Et_3N, CH_2Cl_2; (e) KSAc, DMF (85% two steps); (f) H_2O_2, AcOH; Pd/C, then phosgene, DMF, CH_2Cl_2 (100%); (g) 1,4-dioxa-8-azaspiro[4.5]decane, iPr_2NEt, CH_2Cl_2 (79%); (h) LiSBu, HMPA (63%); (i) 2,4-dimethoxybenzenesulfonyl chloride, DMAP, pyr (79%); (j) 4 N HCl (aq), dioxane (81%); (k) Method A: RNH_2, $NaBH(OAc)_3$, AcOH, CH_2Cl_2; Method B: RNH_2, PS-$BH(OAc)_3$, DCE, MeCN, AcOH; PS-β-keto ester; MP-TsOH; NH_3 (MeOH).

Table 3
Structure–activity relationship of separated enantiomers of **30n**



Compound	hV1b[a] K_i (nM)	rV1b[a] K_i (nM)	hV1a[a] K_i (nM)	rV1a[a] K_i (nM)	hV2[a] K_i (nM)	hOxt[b] K_i (nM)
30o	208 ± 16	874 ± 62	1129 ± 123	3718 ± 169	>10,000	>10,000
30p	44 ± 1	21 ± 1	314 ± 25	1912 ± 502	>10,000	5525 ± 372

[a] Inhibition of 2 nM [^{3}H]Arg^8-vasopressin (AVP) binding to human or rat vasopressin receptors. All values reported are an average of three independent results.
[b] Inhibition of 2 nM [^{3}H]Oxytocin binding to human oxytocin receptor. All values reported are an average of three independent results.

when there was branching in the β- or γ- position relative to the amine group (**30k** and **30j**, respectively).

To determine the importance of the stereogenic chiral center on affinity, the enantiomers of **30n** were separated via preparative chiral HPLC.[12] The slower eluting enantiomer, **30p**, was found to have greater affinity at both the human and rat V1b receptors compared to the faster eluting enantiomer, **30o** (Table 3). Furthermore, for use as a possible tool in a rat in vivo model to evaluate V1b potency, **30p** was found to be 90-fold more selective for the rat V1b receptor over the rat V1a receptor. The human V2 and oxytocin affinities[10] were also determined for these enantiomers to determine the selectivities compared to the human V1b receptor. Compound **30p** possessed greater than 100-fold V1b selectivity compared to those two receptors.

In conclusion, a tetrahydroquinoline core that contained a sulfonamide linker was identified that possessed equipotent activities in both human and rat V1b receptor binding assays. From this core potent analogs were prepared, several with double digit nanomolar K_i's. Compound **30p** was also identified as a possible tool for use in an in vivo rat model. Subsequent reports will describe the evolution of this series to provide V1b receptor antagonists with in vivo activity along with further improvements in affinity and selectivity.

References and notes

1. Aguilera, G.; Rabadan-Diehl, C. *Regul. Pept.* **2000**, *96*, 23.
2. Gillies, G. E.; Linton, E. A.; Lowry, P. J. *Nature* **1982**, *299*, 355.
3. Tanoue, A.; Ito, S.; Honda, K.; Oshikawa, S.; Kitagawa, Y.; Koshimizu, T.; Mori, T.; Tsujimoto, G. *J. Clin. Invest.* **2004**, *113*, 302.
4. For a review of SSR149415 see: Serradeil-Le Gal, C.; Wagnon, J.; Tonnerre, B.; Roux, R.; Garcia, G.; Griebel, G.; Aulombard, A. *CNS Drug Rev.* **2005**, *11*, 53.
5. Oxytocin is a nonapeptidic hormone with similar structure to vasopressin.
6. (a) Hodgson, R. A.; Higgins, G. A.; Guthrie, D. H.; Lu, S. X.; Pond, A. J.; Mullins, D. E.; Guzzi, M. F.; Parker, E. M.; Varty, G. B. *Pharmacol. Biochem. Behav.* **2007**, *86*, 431; (b) Griffante, C.; Green, A.; Curcuruto, O.; Haslam, C. P.; Dickinson, B. A.; Arban, R. *Br. J. Pharmacol.* **2005**, *146*, 744.
7. (a) Craighead, M.; Milne, R.; Campbell-Wan, L.; Watson, L.; Presland, J.; Thomson, F. J.; Marston, H. M.; MacSweeney, C. P. *Prog. Brain Res.* **2008**, *170*, 527; (b) Spiga, F.; Harrison, L. R.; Wood, S.; Knight, D. M.; MacSweeney, C. P.; Thomson, F.; Craighead, M.; Lightman, S. L. *J. Endocrinol.* **2009**, *200*, 273; (c) Spiga, F.; Harrison, L. R.; MacSweeney, C. P.; Thomson, F. J.; Craighead, M.; Lightman, S. L. *J. Endocrinol.* **2009**, *200*, 285.
8. Asberom, T.; Bara, T. A.; Clader, J. W.; Greenlee, W. J.; Guzik, H. S.; Josien, H. B.; Li, W.; Parker, E. M.; Pissarnitski, D. A.; Song, L.; Zhang, L.; Zhao, Z. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 205.
9. The human and rat V1b receptors have 83% homology: Lolait, S. J.; O'Carroll, A.-M.; Mahan, L. C.; Felder, C. C.; Button, D. C.; Young, W. S., III; Mezey, E.; Brownstein, M. J. *Proc. Natl. Acad. Sci.* **1995**, *92*, 6783.
10. Competition binding assays were performed using membranes from CHO-K1 cells expressing the various vasopressin or oxytocin receptors, 2 nM [^{3}H]Arg^8-vasopressin (AVP) or 2 nM [^{3}H]Oxytocin (for the human oxytocin receptor) and various concentrations of antagonist in 50 mM BisTrisPropane, pH 7.4, 5 mM $MgCl_2$ and 0.1% BSA (200 μl total volume). Non-specific binding was determined using 1 μM AVP or 1 μM oxytocin (for the human oxytocin receptor). The reaction mixtures were incubated for 60 min at room temperature, and then filtered through Millipore MAFC glass fiber filter plates presoaked in 0.5% (v/v) polyethyleneimine. The filters were washed three times with 150 μl of ice cold 50 mM BisTrisPropane, pH 7.4, and filter-associated radioactivity was measured in a Packard TopCount scintillation counter. The data were analyzed using GraphPad PRISM, and the K_i was determined using the Cheng–Prusoff equation.
11. Brouwer, A. J.; Monnee, M. C. F.; Liskamp, R. M. J. *Synthesis* **2000**, *11*, 1579.
12. Analytical chiral HPLC conditions: Chiralpak AS column, 70:30 hexanes/EtOH, flow 1 mL/min, UV detector: 254 nm. Retention time enantiomer (A) 10 min, enantiomer (B) 13.6 min. Each enantiomer from preparative scale separation was determined to be ⩾98% ee via analytical HPLC.