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Synthesis and Biological Evaluation of Novel Indoloazepine Derivatives as Non-peptide Vasopressin V2 Receptor Antagonists

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Abstract—A series of novel 3,4,5,6-tetrahydro-1*H*-azepino[4,3,2-*cd*]indoles was synthesized and tested for vasopressin receptor antagonist activity. We identified compounds with high affinity for the human V2 receptor and good selectivity over the human V1a receptor. Compound **6c** bound to V2 receptors with an IC_{50} value of 20 nM, had >100-fold selectivity over V1a receptors, and inhibited cAMP formation in a cellular V2 functional assay with an IC_{50} value of 70 nM.

Arginine vasopressin (AVP) is a peptide hormone that is principally secreted from the posterior pituitary gland. Its interaction with G-protein-coupled receptors results in inter alia vasoconstriction and water reabsorption, via V1a and V2 subtypes, respectively.[1] The V2 receptors located in the kidneys are responsible for controlling water reabsorption. Thus, there is potential to develop a vasopressin V2 receptor antagonist for the treatment of disorders such as congestive heart failure, hypertension, renal disease, edema and hyponatremia.[2] A V2 receptor antagonist would have a benefit of exerting specific, electrolyte-sparing diuresis.

Many efforts to discover non-peptidic, orally active V2 selective antagonists for treating excessive renal reabsorption of water have been reported, exemplified by compounds such as OPC-31260[3–6] and VPA-985[7–10] (Fig. 1). Herein, we report on the synthesis and biological activity of novel indoloazepine derivatives as selective V2 receptor antagonists.

Results and Discussion

Scheme 1 shows the primary route used to prepare the indoloazepine scaffold. The 3,4,5,6-tetrahydro-*1H*-azepino[4,3,2-*cd*]indole 3 was prepared in seven steps from 4-nitroindole **2**,[11–13] which was prepared from 2-methyl-3-nitroaniline **1** in two steps.[14,15] Acylation of **3** with a 4-nitroaroyl chloride ($RNO_2PhCOCl$) provided **4**, which was subsequently reduced with zinc and ammonium chloride to provide aniline **5**. Acylation of **5** with acyl acid chlorides ($R_1PhCOCl$) provided compounds of generic structure **6**.

N-Substituted indoles of generic structure **9** (R_2 varied) were prepared according to Scheme 2. Alkylation of the indole nitrogen with a variety of electrophiles provided intermediates **7**, which were converted to products **9** by using the reduction/acylation steps mentioned above.

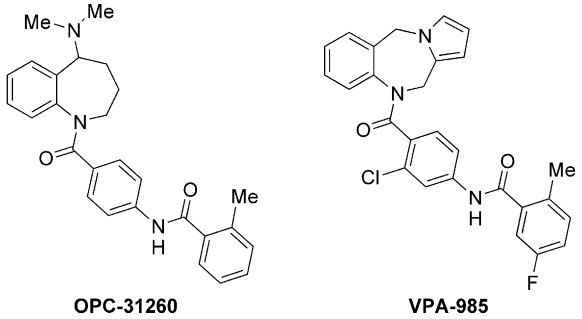

Figure 1. Structures of OPC-31260 and VPA-985.

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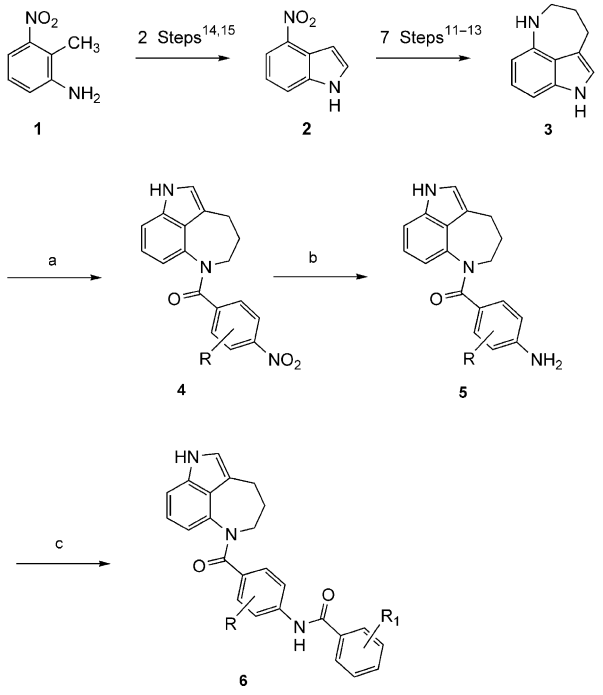
For derivatization at R_3 (Scheme 3), **6c** was treated with *N*-chlorosuccinimide at 23 °C to provide a mixture of indolinone **10**[16] and 2-chloroindole **11**. Reaction of derivatives **6c** with chlorosulfonic acid provided sulfonic acid product **12**.

Compounds were assessed for their ability to displace [^{3}H]-AVP from human V1 or V2 receptors transfected into HEK-293 cells; IC_{50} values are shown in Table 1.

Assays were run in duplicate with an assay variability of 20%. Vasopressin antagonist activity was determined by measuring the accumulation of cAMP in HEK-293 transfected with the human V2 receptor; the respective data is shown in Table 1.[17]



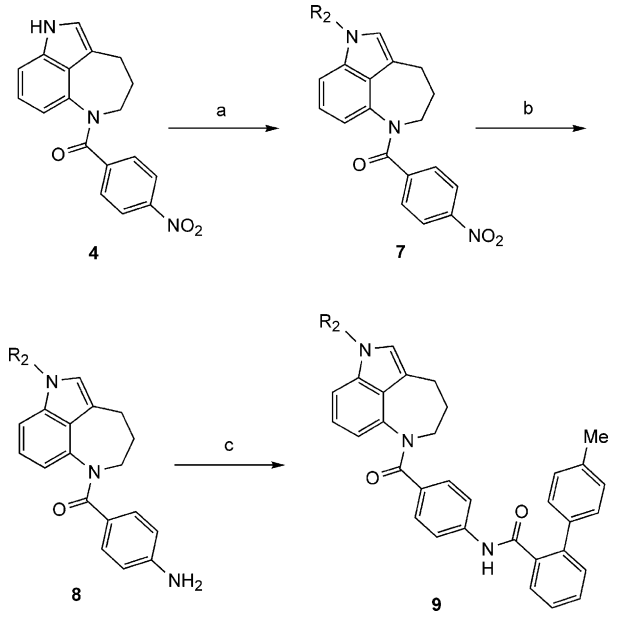
Scheme 1. (a) CH_2Cl_2, Et_3N, 4-NO_2ArCOCl, 0 °C; (b) Zn dust, NH_4Cl, MeOH, reflux; (c) CH_2Cl_2, Et_3N, ArCOCl, 0 °C.

Ogawa[4] reported that introduction of lipophilic groups, such as an *o*-tolyl moiety, leads to compounds with similar V1a and V2 receptor affinities. As shown in Table 1, incorporation of a 2-methyl group in the indoloazepine scaffold (**6a**) has virtually no binding affinity. On the other hand, replacing the *o*-tolyl group with 2-methyl-5-fluorophenyl, as shown by Albright et al.,[7] led to **6b**, which has modest binding affinity to the V2 receptor. Tanaka et al.[18] described replacing the *o*-tolyl group with an *o*-phenyl group, which led to compounds with enhanced V2 potency. Indeed, replacing the *o*-tolyl moiety (**6a**) with an *o*-phenyl moiety (**6c**) led to an indoloazepine analogue with superior binding affinity. Replacing the *o*-phenyl with a 2-(4-methyl)phenyl resulted in a 2-fold increase in potency (**6d**). Compounds **6c** and **6d** also demonstrate functional activity with the human V2 receptor; their IC_{50} values are each a respectable 70 nM (cf. result for VPA-985). Introduction of a chloro in the 3-position of the PABA ring (**6e**) provided an analogue that is equipotent to unsubstituted **6c**, while substitution of the C-2 position of the PABA ring (**6f**) with a chloro led to a decrease in V2 affinity.

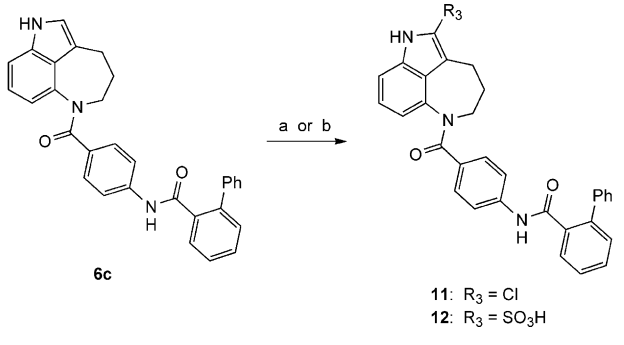
Substitution on the indole nitrogen (R_2) suggested that hydrogen substitution was optimal, as demonstrated in the significant loss of activity when a methyl group (**9a**) was substituted for the hydrogen, resulting in a 14-fold decrease in activity compared to the unsubstituted analogue **6d**.

Compound **11** demonstrates that the introduction of a lipophilic moiety (chloro) to the indole ring of **6c** leads to a slight decrease in V2 binding affinity ($IC_{50} = 44$ nM), while the addition of a polar sulfonate moiety to the indole ring, **12** and **13**, leads to analogues that are equipotent to unsubstituted **6c**.

Binding to the V1a receptor was also performed on all compounds in Table 1 by using [^{3}H]-AVP and recombinant human vasopressin V1a receptor. The compounds demonstrated >100-fold selectivity for the V2 receptor over the V1a receptor. Three of the compounds

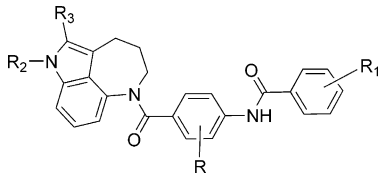


Scheme 2. (a) NaH (60%), DMF, R_2X; (b) Zn dust, NH_4Cl, MeOH, reflux; (c) CH_2Cl_2, Et_3N, 2-(4-MePh)COCl, 0 °C.



Scheme 3. (a) CH_2Cl_2, NCS, rt; (b) CH_2Cl_2, $ClSO_3H$, rt.

Table 1. Vasopressin V2 and V1a binding data for indoloazepines



Compd[a]	R	R_1	R_2	R_3	V2 IC_{50}, μM[b]	cAMP IC_{50}, μM[c]
6a	H	2-Me	H	H	IA	
6b	H	2-Me, 5-F	H	H	0.19	
6c	H	2-Ph	H	H	0.020	0.070
6d	H	2-(4-MePh)	H	H	0.011	0.070
6e	3-Cl	2-Ph	H	H	0.015	
6f	2-Cl	2-Ph	H	H	0.05	0.33
6g	H	2-Me, 3-F	H	H	0.18	
9a	H	2-(4-MePh)	Me	H	0.21	
9b	H	2-(4-MePh)	COMe	H	0.17	
9c	H	2-(4-MePh)	CH_2Ph	H	IA	
9d	H	2-(4-MePh)	Pr	H	IA	
9e	H	2-(4-MePh)	CH_2CO_2Et	H	0.55	
11	H	2-Ph	H	Cl	0.044	
12	H	2-Ph	H	SO_3H	0.013	
13	3-Cl	2-Ph	H	SO_3H	0.012	
VPA-985[d]					0.005	0.091

[a]Target compounds were all purified by reverse-phase semi-prep HPLC. Purities were >95% as judged by reverse-phase HPLC/MS at 215 and 254 nm; all compounds were analyzed by 300-MHz ^1H NMR.
[b]Inhibition of [^3H]-AVP binding to recombinant human vasopressin V2 receptor. IA = inactive, that is <30% inhibition of radioligand binding at a concentration of 0.1 μM. All analogues demonstrated >100-fold selectivity for the V2 over V1a receptor.[17]
[c]Functional activity of the human V2 receptor, assessed by the accumulation of cAMP in transfected HEK-293 cells.[17]
[d]Reference standard. V1a binding IC_{50} = 0.15 μM.

exhibited V1a binding in excess of 30% at 1 μM: **6b**—58%; **6d**—33%; **9a**—49%.

Compound **6c** was viewed with particular interest, given its functional V2 antagonist activity of 70 nM. The IC_{50} value for V1a binding for **6c** was found to be 3.1 μM, giving it a V1a/V2 selectivity of 155. Compound **6c** also demonstrated potent rat V2 receptor binding, with an IC_{50} of 1 nM. Compound **6c** was subjected to an in vivo evaluation in Sprague–Dawley rats by measuring urine output and osmolality following oral administration. Unfortunately, although **6c** is a potent V2 antagonist in vitro, it lacked in vivo activity when dosed orally at 10 mg/kg. Given the potency of compound **6c** in rodents, the lack of in vivo activity may relate to low oral absorption of the compound.

In summary, we have identified a novel series of vasopressin V2 receptor antagonists that contain an indoloazepine tricyclic nucleus. Some of the analogues, such as indoloazepine **6c**, show excellent binding affinities and high selectivity for the recombinant human vasopressin V2 receptor.

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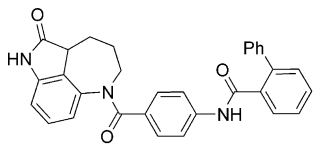
16. Compound **10** gave a V2 IC_{50} value of 8 nM with >100-fold selectivity over the V1a receptor.



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