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Oral Oxytocin Antagonists

Alan D. Borthwick*

DrugMolDesign, 15 Temple Grove, London NW11 7UA, U.K.

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Introduction

Oxytocin is a mammalian nonapeptide hormone produced in the hypothalamus and secreted by the posterior pituitary gland into the circulation. It is also synthesized in the peripheral tissues of the uterus, testis, and heart. Oxytocin exhibits a range of physiological roles[1] including mammary and uterine smooth muscle contraction, neurotransmission in the central nervous system, and autocrine and/or paracrine functions in the ovaries and testes. In the uterus, oxytocin is involved in the onset and progression of labor and has been long regarded as a pregnancy hormone as it stimulates labor and milk ejection. It is also recognized as having a wide spectrum of functions outside pregnancy especially in the central nervous system, where it is involved in the control of human behavior[2] including social behavior, reproductive behavior, and emotions.[3]

Oxytocin is a clinically proven inducer of labor in pregnant women. It works as a potent stimulant of uterine contractions via the interaction with oxytocin receptors that are expressed in myometrial cells in the mammalian uterus. These receptors in the uterus vastly increase in number during pregnancy. The agonist oxytocin binds to the extracellular region and transmembrane domain of the receptor, which enables the intracellular part to couple to G-proteins and initiate a cascade of events liberating Ca^{2+}, which causes smooth muscle contractions.[4] The oxytocin receptor (OTR),[1] a member of the superfamily of seven-transmembrane (7TM) G-protein coupled receptors (GPCRs[a]) has no subtypes but is structurally related to the vasopressin receptors (V1aR, V1bR, V2R).[4] The V1aR and V2Rs are mainly expressed peripherally and involved in the modulation of blood pressure and kidney function, respectively, while the V1bR is expressed in the brain and pituitary gland and controls ACTH and β-endorphin release.

The key role played by oxytocin and its receptor in the initiation and maintenance of uterine contractions of labor during childbirth has prompted many research groups to seek an effective antagonist of these effects in the search for tocolytic agents that inhibit preterm labor and delay premature birth. The starting point for these endeavors was the cyclic part of the peptide structure **1**, found in the endogenous agonist oxytocin (Figure 1). Interest in OTR antagonists began after the initial finding by du Vigneaud that modification to the 1 position of **1** by gemdimethyl (1966)[5] and by cyclic spiro substituent (1975)[6] gave OTR antagonism. Similar simple modifications of the cyclic peptide oxytocin such as introduction of an ornithine at position 8 and capping of the 2-tyrosine hydroxyl group as a methyl or ethyl ether, introduction of non-natural and D-amino acids as well as preparing conformationally constrained bicyclic analogues, were exploited subsequently by several research groups which gave a number of potent cyclic peptidic OTR antagonists.[7−10] This effort led to the most prominent OTR antagonist available to date, atosiban[11] (Tractocile) **2** (Figure 1), which has been shown to inhibit uterine contractions and delay preterm delivery. Intravenously administered atosiban has been established as an acute treatment of preterm labor.[12] However atosiban is a peptide and a mixed oxytocin/vasopressin V1a antagonist that has to be given by iv infusion and is not suitable for long-term maintenance treatment as it is not orally bioavailable.[11−14] Hence there has been considerable interest during the last two decades in overcoming the shortcomings of the first generation peptide antagonists by identifying orally active nonpeptide oxytocin antagonists with a higher degree of selectivity toward V1aR, V1bR, and V2R with good levels of oral bioavailability. With the discovery that oxytocin has a wide spectrum of functions outside pregnancy,[2] interest has also developed in oxytocin antagonists as a potential treatment of sexual dysfunction including premature ejaculation[15] and the treatment or prevention of benign prostate hyperplasia.[16]

Oxytocin antagonists have been reviewed in 1997,[7,17] and recently covering the literature to the end of 2006,[8,18] while a general review of the condition of preterm labor and treatment options was published in 2003.[19] More recently, peptide oxytocin antagonists[9] and the patent literature of oxytocin receptor ligands[10] have also been reviewed. Here the focus is on advances made in the design and development of orally bioavailable oxytocin antagonists from the first orally active nonpeptide antagonist to the most recent highly selective orally bioavailable clinical candidates.

The Structure of Oxytocin and the Oxytocin Receptor

The structure **1** of oxytocin is very similar to vasopressin, which differs from oxytocin by two amino acids, Arg-8 and Phe-3. Because of the close structural similarity of these cyclic peptide natural ligands and their receptors, a major challenge has been to find selective peptide oxytocin antagonists and this selectivity has also been one of the chief goals in developing

*To whom correspondence should be addressed. Phone: +44 (0)7772112742. E-mail: alan.d.borthwick@drugmoldesign.com.

[a] Abbreviations: 7TM, seven-transmembrane; GPCRs, G-protein coupled receptors; hOTR, human oxytocin receptor; rOTR, rat oxytocin receptor; ACTH, adrenocorticotropic hormone; Rec CHO, transfected chinese hamster ovary cells; hV1aR, human vasopressin V1a receptor; hV1bR, human vasopressin V1b receptor; hV2R, human vasopressin V2 receptor; LE, ligand efficiency; LipE, lipophilic efficiency; MDCK, Madin−Darby canine kidney; DKPs, 2,5-diketopiperazines; EHOA, estimated human oral absorption; CHI log *D*, HPLC measured lipophilicity.

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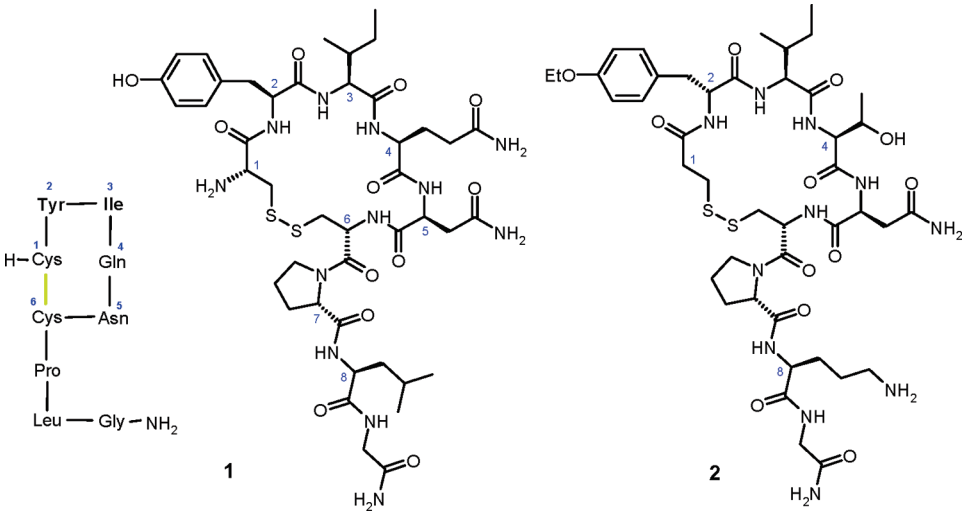


Figure 1. Structure of agonist oxytocin **1** and antagonist atosiban **2**.

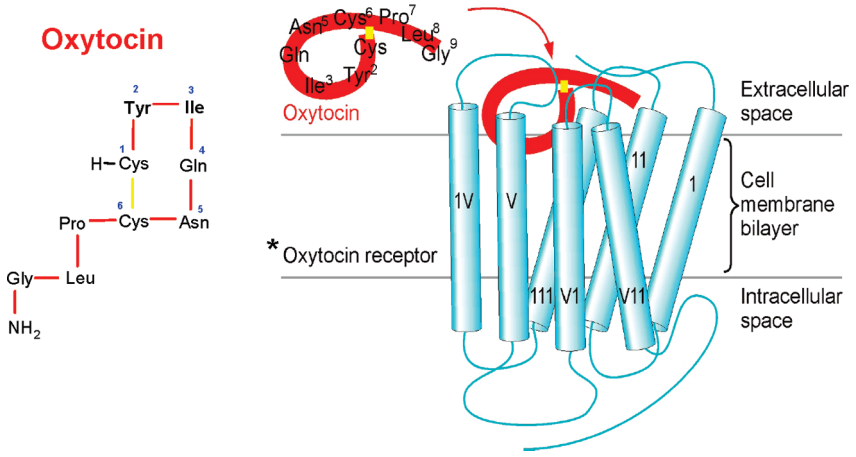


Figure 2. Oxytocin and the 7TM G-protein-coupled oxytocin receptor. Reprinted with permission from ref 4. Copyright 2003 Elsevier.[63]

novel orally bioavailable nonpeptide oxytocin antagonists. The structure and the binding mode of oxytocin and the OTR have been extensively investigated to aid the design of selective oxytocin antagonists

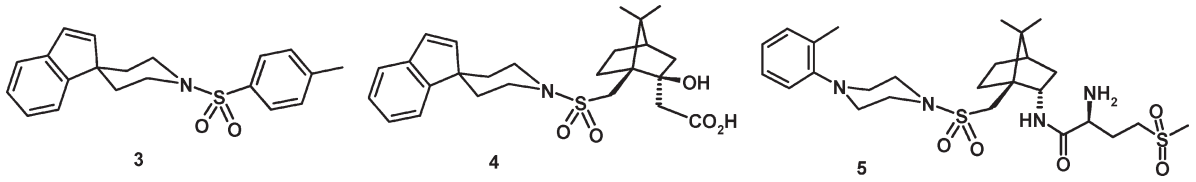
The endogenous ligand oxytocin is a cyclic nonapeptide in which a hexapeptide ring is formed as a result of disulfide bonds between Cys-1 and Cys-6 residues; it has high affinity (~1 nM) for the receptor. The OTR[4] is a 389-amino acid polypeptide whose gene is located on the human chromosome 3p25 and is a member of the superfamily of seven-transmembrane (7TM) G-protein coupled receptors (GPCRs) that has no subtypes but is structurally related to the vasopressin receptors.[4] The combined evidence from studies involving site-directed mutagenesis, photoaffinity labeling, and molecular modeling indicate that in interacting with its receptor the cyclic part of oxytocin is lodged in the upper one-third of the receptor binding pocket (Figure 2) and interacts with transmembrane domains III, IV, and VI, whereas the linear C-terminal part of oxytocin remains closer to the surface and interacts with transmembrane domains II and III in addition to the first extracellular loop.[4]

The key functionalities for agonist activity in oxytocin are the 2-Tyr and 3-Ile amino acids which occur in the cyclic part of oxytocin that binds in the upper one-third of the receptor binding pocket (Figure 2). The hydrophobic 3-Ile residue is the residue that differs between oxytocin and vasopressin in the cyclic part of the molecule. Modification of the tyrosine residue at the 2-position of oxytocin produces antagonist activity. The deamino OEt-Tyr^2 oxytocin analogue is a potent antagonist of oxytocin-induced contractions in the rat uterus in vitro and in vivo.[20] Modification of the 4 and 8 positions of this deamino OEt-Tyr^2 oxytocin analogue gave the antagonist atosiban.[21] In addition, structure−activity studies of oxytocin analogues have revealed that the antagonist property depends on a specific conformation, and the appropriate modification of Tyr^2 plays a crucial role in this function. The incorporation of bulky apolar side chain amino acids in position 2 increased potency and made more effective oxytocin antagonists. The use of D-indanylglycine (D-IgL) as a rigid homophenylalanine analogue resulted in OTR affinity higher than that of D-Phe^2 with greater selectivity for oxytocin over the vasopressin receptors.[22] Hence recognizing and mimicking the 2-Tyr and 3-Ile amino acids interaction of oxytocin with the OTR is one of the key targets in the design of oxytocin antagonists.

Templates for Orally Bioavailable Nonpeptide Oxytocin Antagonists

Since the early days of oxytocin peptide antagonists, there has been significant interest in developing orally active agents. Researchers at Merck[8,17] in the early 1990s made the first major impact in the area of nonpeptide oxytocin antagonists

Table 1. Human and Rat Oxytocin/Vasopressin Receptor Binding, Oxytocin Antagonism in the Rat, and Oral Bioavailability in Rat and Humans of the Camphor Sulphonamides [24–27]



	oxytocin receptors	vasopressin receptors		oxytocin antagonism in rat		bioavailability	
compd	hOTR/*rOTR* K_i (nM)[a]	hV1aR / *rV1aR* K_i (nM)[a]	hV2R/*rV2R* K_i (nM)[a]	iv AD_{50} (mg/kg)[b]	id AD_{50} (mg/kg)[b]	rat *F*%	human *F*%
3	1000/*1600*	−/*9800*	−/*>40000*				
4	530/*370*	1600/*26000*	5600/*29000*	10	30		
5	13/*3.6*	180/*110*	590/*200*	0.35	7.0	35	20

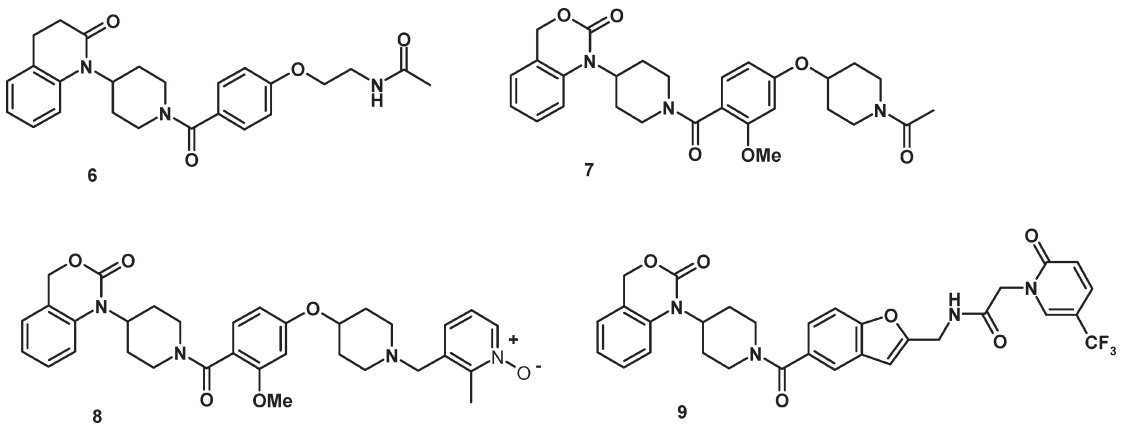
[a] K_i values refer to displacement of of [3H]-oxytocin or [3H]-vasopressin from specific binding sites in the indicated tissue. hOTR in human uterus tissue, rOTR in rat uterus tissue, hV1aR in human liver or platelet tissue, rV1aR in rat liver tissue, hV2R in human kidney tissue, rV2R in rat kidney tissue. [b] AD_{50} values refer to the intravenous (iv) or intraduodenal (id) dose to inhibit oxytocin-induced uterine contractions by 50% in the rat.

by investigating natural products, compound collections, and vasopressin antagonist templates. They produced the first report of an orally active nonpeptide oxytocin antagonist and the first oral oxytocin antagonist in phase one clinical trials shown to block the uterine response to exogenous oxytocin in women in the immediate postpartum period. With the cloning of OTR in 1992 (Kimura et al.),[23] screening strategies to identify nonpeptide leads became viable, and in the past decade Merck's pioneering work on oral oxytocin antagonists was carried forward by Serono/Applied Systems, GSK, Sanofi-Synthelabo, and Pfizer. Numerous examples of nonpeptide OTR antagonists appeared in the literature, demonstrating that a wide range of chemical structures can satisfy the requirements for high affinity binding to the receptor. However, several factors need to be considered to obtain a viable drug from an orally bioavailable OTR antagonist. In addition to the appropriate physicochemical properties required for good aqueous solubility and permeability, there is a need to achieve high selectivity and safety in the compounds that are designed. Because V1aR is involved in modulating blood pressure, V2R in kidney function, and V1bR in ACTH and β-endorphin release, and there is close structural similarity between oxytocin and vasopressin, the high selectivity of an oral OTR antagonist over these three receptors of vasopressin is a key consideration. Also as the OTR occurs in the brain as well as peripherally, blocking blood−brain barrier penetration to achieve selective activity peripherally or targeting brain penetration for a CNS driven activity are important considerations. Good aqueous solubility and permeability to attain high orally bioavailability and good animal pharmacokinetics should be a requirement to enable sufficient exposure in humans.

Camphor Sulphonamides (Spiroindenepiperidines and *o*-Tolylpiperazines)

Screening the chemical collection at Merck identified the relatively rigid spirotetralinpiperidine derivative **3**, L-342,643, as an active oxytocin antagonist.[25] The spirotetralinpiperidine **3** has a low binding affinity for the human oxytocin receptor (hOTR) of 1 μM with comparable activity at the rat oxytocin receptor (rOTR) and with some selectivity with respect to the receptors of vasopressin (Table 1). SAR studies showed that the spiroindenepiperidine ring system was more active than the related six-membered spirotetralinpiperidine analogue. Replacing the piperidine ring with an ethylamine chain led to reduced activity, and bulky lipophilic group replacements of the aromatic ring in the *p*-tolyl sulfonamide increased potency, whereas replacement with amides and ureas reduced potency. This led to the camphor sulphonamide **4**, L-366,509, containing an *endo* carboxylic acid for water solubility, which has modest activity and selectivity for the OTR (Table 1). However, **4** given iv or id to rats caused a significant and long lasting inhibition of oxytocin induced uterine contractions. Significantly, OTR antagonist activity resulted after iv and oral dosing in a late gestation pregnant rhesus monkey, which established **4** as the first orally active nonpeptide oxytocin antagonist.[24,25] Extensive SAR investigations to exploit this significant lead showed that both the aromatic ring of the spiroindenepiperidine and the camphor ring were important hydrophobic regions for binding to the receptor and the *o*-tolylpiperazine ring could be interchanged with the spiroindenepiperidine ring and maintain activity. Modification at the C-2 *endo* position on the camphor ring with one or more polar functionalities capable of forming hydrogen bonds led to derivatives with single figure nanomolar potency at the rOTR, of which **5**, L-368,899, was chosen for further investigation (Table 1.).[26] This revealed that **5** possessed good potency as an antagonist of oxytocin induced uterine contractions in rats (AD_{50} = 0.35 mg/kg iv) and late gestation pregnant rhesus monkeys (AD_{50} = 0.027 mg/kg iv). Although it had good affinity for the hOTR, it only exhibited 14-fold and 45-fold selectivity versus the hV1aR and the hV2R, respectively, in vitro (Table 1), however it had a 75-fold separation of oxytocin and vasopressin antagonist activities in vivo in rats. It also had oral bioavailability in several species (F = 35% rat, 25% dog, 21% chimpanzee), sufficient aqueous solubility (~2.5 mg/kg at pH 5.2) for iv formulation, and an excellent overall preclinical toxicology profile.[27] The amine **5** had an oral bioavailability of 20% in humans and in phase one clinical trials was shown to block the uterine response to exogenous oxytocin in women in the immediate postpartum period. However, further development of **5** was discontinued because of the high oral dose, 600 mg at 6 h intervals, required to maintain the trough plasma levels associated with complete block of the uterine response to oxytocin in the study in postpartum women.[28] Further investigation showed that first pass metabolism involving hydroxylation at the C-5 *exo* position and the C-9 methyl group in the camphor moiety

Table 2. Human and Rat Oxytocin/Vasopressin Receptor Binding, Oxytocin Antagonism in the Rat, and Oral Bioavailability in the Rat, Dog, and Rhesus Monkey of the Benzoxazinylpiperidines[31−33,35,36]



	oxytocin receptors	vasopressin receptors		oxytocin antagonism in rat		bioavailability		
compd	hOTR/*rOTR*[a] K_i (nM)	hV1aR/ *rV1aR*[a] K_i (nM)	hV2R/*rV2R*[a] K_i (nM)	iv AD_{50} (mg/kg)[c]	id AD_{50} (mg/kg)[c]	rat *F*%	dog *F*%	monkey[d] *F*%
6	170/*230*	52000/*32*	> 81000/ > *30000*					
7	4.6/*19*	3200/*3.7*	37000/ > *30000*	*0.55*	*2.5*	39		13
8	4.9/*14*	3200/*0.76*	28000/*9700*	*0.78*	*5.2*	80	90	36
9	2/−[b]	1260/−[b]	> 3000/−[a]			16	51	

[a] K_i values refer to displacement of of [^{3}H]-oxytocin or [^{3}H]-vasopressin from specific binding sites in the indicated tissue. hOTR in human uterus tissue, *rOTR* in rat uterus tissue, hV1aR in human liver or platelet tissue, *rV1aR* in rat liver tissue, hV2R in human kidney tissue, *rV2R* in rat kidney tissue. [b] Binding affinity inhibition constant K_i (nM) versus [^{3}H]oxytocin or [^{3}H]vasopressin at human receptors in CHO cells. [c] AD_{50} values refer to the intravenous (iv) or intraduodenal (id) dose to inhibit oxytocin-induced uterine contractions by 50% in the rat. [d] Rhesus monkey.

of **5** was found to be a limiting factor for obtaining good plasma levels after oral dosing in rhesus monkeys and incubations with human liver microsomes produced hydroxylated camphor derivatives as the major metabolites.[29] Attempts to improve the overall metabolic stability by modification of the camphor portion of the structure by substitution or isomeric replacements were unsuccessful.

Recently, it has been shown[30] that **5**, accumulates in limbic brain areas in monkeys when peripherally administered and alters female maternal and sexual behavior. It is therefore a useful pharmacological tool for the study of social motivation in nonhuman primates

Benzoxazinylpiperidines

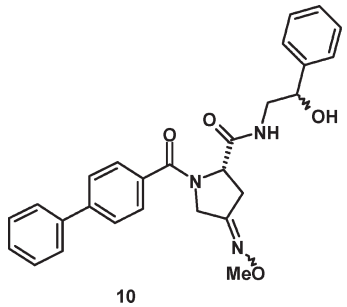
Merck scientists showed[31] that the orally bioavailable V1aR antagonist **6**, OPC-21268, originally developed by researchers at Otsuka, had significant affinity for the rOTR and the hOTR (Table 2) and used it as a starting point for lead optimization to obtain more potent and selective oxytocin antagonists. Three types of modification were discovered that increased binding affinity. Replacement of the quinolinone by a benzoxazinone ring gave a 2-fold enhancement in affinity. Constraining the acetamidopropyloxy chain in the form of an *N*-acetyl-4-piperidinyloxy ring gave a further 6-fold improvement, and addition of an *ortho* methoxy substituent on the benzoyl ring gave 5-fold greater affinity. A compound with these modifications **7**, L-371,257, had single figure nanomolar affinity for the hOTR and exhibited 690-fold and > 8000-fold selectivity versus the hV1aR and the hV2R, respectively (Table 2).[31]

Compound **7** was shown to dose dependently inhibit oxytocin induced uterine contractions in anaesthetized rats by iv and intraduodenal routes, with AD_{50} values of 0.55 mg/kg and 2.5 mg/kg, respectively, and was orally bioavailable in the rat (F = 39%) and rhesus monkeys (F = 13%). The compound optimization program was continued with the aim of further improving pharmacokinetic half-life, solubility, potency, and bioavailability. SAR studies indicated that changes to the benzoyl, benzoxazinone, and central piperidine portions of the molecule were generally deleterious to OTR affinity, whereas the piperidinyl ether terminus was more tolerant to change. Several new compounds resulted from these efforts, the most prominent being the pyridine *N*-oxide **8**, L-372,662, which retained excellent single figure nanomolar hOTR affinity and exhibited 650-fold and > 5700-fold selectivity versus the hV1aR and the hV2R, respectively (Table 2).[32]

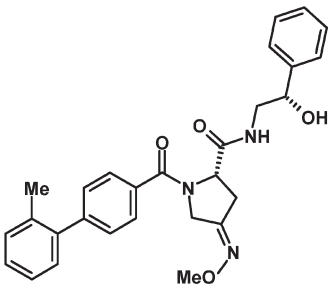
It was a potent oxytocin antagonist in late-gestation pregnant rhesus monkeys (AD_{50} = 0.036 mg/kg iv) had excellent oral bioavailability in several species (F = 90% dog, 80% rat, 36% rhesus monkey) with a half-life of 2 h and possessed good aqueous solubility (10 mg/mL at pH 5) to allow for iv formulation.[33] Molecular modeling has shown that the methoxy group present in **7** and **8** provides a direct hydrophobic contact with Ala-318 in helix 7 of the hOTR required for high affinity binding of benzoxazinone-based antagonists.[34]

Researchers at GlaxoSmithKline used **7** as a starting point for a combinatorial chemistry program based on libraries from fragments derived from cleavage of the central amide bond. Separate exploration of the SAR within the amine and the carboxylic acid fragments keeping the other half constant showed that no alternatives were found for replacement of the benzoxazinylpiperidine moiety, but several heterocyclic acids were identified as replacements for the methoxy benzoic acid core.[35,36] This led to the potent hOTR antagonist benzofuran **9** (K_i = 2 nM), which exhibited ≥630-fold selectivity versus the hV1aR and hV2R (Table 2). The trifluoromethyl pyridine moiety of **9** conferred favorable pharmacokinetic parameters

Table 3. Human and Rat Oxytocin/Vasopressin Receptor Binding, Oxytocin Antagonism in the Rat, and Oral Bioavailability in Rat and Humans of the Pyrrolidine Oximes[37−40]



10



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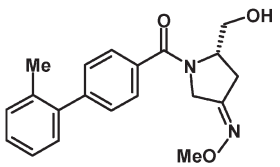


12

	oxytocin receptors	vasopressin receptors		oxytocin antagonism in rat		bioavailability
compd	hOTR/*rOTR* K_i (nM)[b]	hV1aR/ *rV1aR* K_i (nM)[b]	hV2R/*rV2R* K_i (nM)[b]	iv ED_{50} (mg/kg)	po ED_{50} (mg/kg)	rat *F*%
10	[a] 260/−					
11	28/*135*	170/−	> 10000/−	*3.5*	*89*	*49*
12	95/*210*	330/−			*~30*	*55*

[a] IC_{50}. [b] Binding affinity inhibition constant K_i (nM) versus [^{3}H]-oxytocin or [^{3}H]-vasopressin at human and rat receptors in CHO cells.

(F = 51% dogs and F = 16% rats). However, potency in the oxytocin-induced rat uterine contraction model was much lower (IC_{50} = 3 μM) than predicted from its in vitro potency at the rOTR (IC_{50} = 20 nM). This significant lower potency was attributed to high protein binding (96%). Also a 46-fold shift in in vitro oxytocin-binding affinity at the hOTR was observed when the compound was tested in the presence of physiologically relevant concentrations of human serum albumin, and the compound was not pursued further.

Pyrrolidine Oximes

High-throughput screening of the GPCR-directed compound collection in the Serono organization led to the identification of the pyrrolidine oxime ether **10**, showing good affinity to the hOTR, (IC_{50} = 260 nM) and promising selectivity against the hV1aR (68% inhibition at 10 μM) (Table 3). Subsequent SAR in this series showed that the (*Z*)-double bond isomers were 3−4-fold more potent than the corresponding (*E*)-isomers and (*S*)-configuration at the α-carbon of the proline core was critical for activity in contrast to the configuration of the carbinol center, which was not critical for activity.[37] Also substitution on the distal ring of the biphenyl at the *ortho* position with methyl or chlorine gave a 2−4-fold increase in potency. Although cyclization of the amide carbinol chain to an oxadiazole ring (e.g., **24** Scheme 2) gave derivatives with single to double figure nanomolar binding affinity,[38] the compound preferred for further progression was the (*Z*)-isomer of the chirally pure amide carbinol **11** containing an *ortho* methyl biphenyl (Table 3). Although it had good affinity for the hOTR (K_i = 28 nM) with 350-fold selectivity versus the hV2R, it only exhibited 6-fold selectivity versus the hV1aR. It was also somewhat less active against the rOTR (K_i = 135 nM). However, it was active at inhibiting contractions in isolated rat uterine strips (pA_2 = 7.8) and it inhibited oxytocin-induced contractions in the nonpregnant rat with an ED_{50} of 3.5 mg/kg after intravenous dosing and 89 mg/kg after oral administration. Furthermore, it showed some inhibition of spontaneous uterine contractions in the pregnant rat and favorable pharmacokinetics were observed (F = 49%, $t_{1/2}$ = 2.8 h) in this species.[39]

Subsequent optimization iterations to identify compounds with better pharmacokinetic properties led to the hydroxymethyl derivative **12** (Table 3). SAR round this series showed that potent activity was observed with a number of hydroxymethyl, hydroxyethyl, and methoxymethyl derivatives, but aminomethyl substitution was poorly tolerated.[8,40] The compound **12** had a K_i of 95 nM against hOTR, with modest rat activity (K_i = 210 nM) against the rOTR and weak (< 4-fold) selectivity versus the hV1aR (Table 3). It had good pharmacokinetic properties in rat, being 55% orally bioavailable, and exhibited low levels of human serum protein binding (71%). Consistent with these drug-like properties, the compound was active in a number of in vivo models. At 30 mg/kg po, it inhibited oxytocin-induced contractions in nonpregnant rats by 51% and spontaneous contractions in pregnant rats were inhibited in a dose-dependent manner (around 40% inhibition observed with a 60 mg/kg oral dose). A possible issue with this series is the potential isomerization of the oxime group and its low level of selectivity verses the hV1aR.

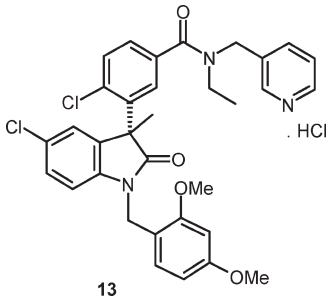
Indolin-2-ones

Sanofi have described a series of indolin-2-one derivatives that are potent and selective oxytocin antagonists.[41] The lead compound SSR126768A (**13**) has high affinity for both the hOTR and the rOTR in uterus tissue (K_i = 0.5 nM and K_i = 1.6 nM, respectively) and 280-fold lower affinity for the hV1aR and even much lower (> 2000) for the hV2R in rec. CHO cells (Table 4).[42] In rat-isolated myometrium, oxytocin-induced uterine contractions were competitively antagonized by **13** (pA_2 = 8.47). In addition, the indolin-2-one **13** has oral activity. Oral administration of a 3 mg/kg dose of **13** to rats was found to be effective for up to 24 h in the competitive inhibition of uterine contractions. At higher doses, **13** (30 mg/kg po) was comparable in the delay of labor in pregnant rats to the β-adrenergic agonist tocolytic, ritodrine (10 mg/kg po).

Biaryl Sulfonamides

Screening a library of compounds biased toward G protein coupled receptors, researchers at Serono identified a series of isatin hydrazone sulfanilides that potently inhibited radioligand binding to the OTR.[43] The most potent compound was

Table 4. Human and Rat Oxytocin/Vasopressin Receptor Binding, and Oxytocin Antagonism in the Rat, of the Indolin-2-one **13**[42]

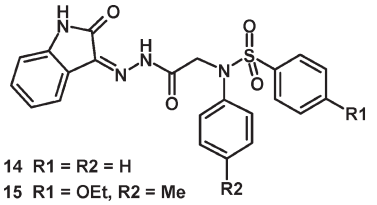


13

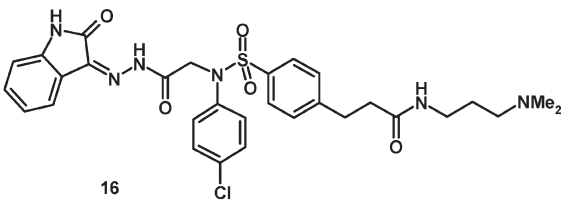
	oxytocin receptors	vasopressin receptors			oxytocin antagonism in vivo
compd	hOTR/*rOTR* K_i (nM)	hV1aR/*rV1aR* K_i (nM)	hV1bR/*rV1bR* K_i (nM)	hV2R/*rV2R* K_i (nM)	rat po (3 mg/kg) ED_{50} (nM) 1 h/5 h/24 h
13	0.5/*1.6*[a]	143[b]/*99*[c]	−/*46*[d]	> 1000[e]/ > 1000[f]	14/24/4.7

[a] hOTR in human uterus tissue, *rOTR* in rat uterus tissue. [b] hV1aR in Rec.CHO cells. [c] *rV1aR* in rat liver tissue. [d] *rV1bR* in Rec.CHO cells. [e] hV2R in Rec.CHO cells. [f] *rV2R* in rat kidney tissue.

Table 5. Human and Rat Oxytocin/Vasopressin Receptor Binding, Oxytocin Antagonism in the Rat of the Isatin Hydrazone Sulfanilides **14**−**16**[43]



14 R1 = R2 = H
15 R1 = OEt, R2 = Me



16

	oxytocin receptors	vasopressin receptors			oxytocin antagonism in vivo rat	
compd	hOTR/*rOTR* K_i (nM)[a]	hV1aR K_i (nM)[a]	hV1bR K_i (nM)[a]	hV2R K_i (nM)[a]	iv ED_{50} (mg/kg)	po ED_{50} (mg/kg)
14	90/−	< 50% @ 10 μM				
15	14/*25*	1410	> 10000	2500	10	
16	0.65/*0.67*	42	3539	377	1.4	*35%* (30 mg/kg)

[a] Binding affinity inhibition constant K_i (nM) at hOTR and rOTR in HEK293-EBNA cells, and at hV1aR, hV1bR, and hV2R in CHO cells.

14 (hOTR: K_i = 90 nM) (Table 5). SAR studies showed that the isatin hydrazone ring was preferred for good activity over secondary and tertiary amide replacements. Changing the phenyl ring in the anilide part of sulfonamide **14** for a phenethyl or alkyl group abolishes activity, and substitution in this phenyl ring is more restrictive compared to the sulfonyl aryl ring. Only small *para* substituents increase activity, whereas large *para* or *meta* substituents decrease activity. Replacement of the sulfonyl aryl ring with a nonaromatic sulphonyl group was detrimental to affinity. However, a range of *para* substituents in this aryl ring conferred good potency. This led to the more potent oxytocin antagonist sulfanilide **15** (hOTR: K_i = 14 nM), which was 100-fold selective over the vasopressin receptor hV1a (Table 5). It was also shown to be active in vivo by inhibiting the oxytocin-induced uterine contractions in nonpregnant anaesthetized rats (ED_{50} = 10 mg/kg iv). However, a major deficiency was its poor aqueous solubility (< 1 μg/mL), resulting in a very low oral bioavailability in rats (F = 6%). Oral bioavailability was achieved by incorporating water solubilizing groups into the sulfonyl aryl ring of the sulfonamide by modifying the preferred 4-alkyl or 4-alkoxy groups. This furnished the lead compound **16**, (hOTR: K_i = 0.65 nM) which was 65-fold, 23000-fold, and 245-fold selective for the hV1aR, the hV1bR, and the hV2R, respectively (Table 5). It was shown to dose dependently inhibit oxytocin-induced uterine contractions in anaesthetized nonpregnant rats by the iv route (ED_{50} = 1.4 mg/kg), while by the oral route it was also found to inhibit oxytocin-induced uterine contractions in anaesthetized nonpregnant rats by 35% at 30 mg/kg and to reduce spontaneous uterine contractions in late-term pregnant rats by 30% at 30 mg/kg.[43]

High-throughput screening of the GSK compound collection for oxytocin antagonists also identified a similar tertiary sulfonamide **17**, which contained a tricyclic quinolinone ring.[44] It was shown to be moderately potent as an OTR antagonist with good selectivity (> 50 fold) against the related hV1aR (Table 6). However, it had poor aqueous solubility (< 1 μg/mL) and oral bioavailability (F = 4%) in rats.

SAR studies to improve potency, solubility, and oral bioavailability while not significantly increasing molecular weight (< 500) involved biaryl replacements of the tricyclic quinolinone ring. The initial biaryl compounds **18** were moderately potent (OTR pK_i = 7.2−7.4). In an attempt to improve the potency of **18**, these compounds were mapped to the consensus pharmacophore based on known active OTR antagonists **20** and **37** (Scheme 1). This suggested a hydrogen bond acceptor (pyridine) in the proximal ring and a nonplanar distal ring which was achieved by a 2′ substituent. This gave a range of potent compounds **19**, for example, the *ortho* chloro derivative **21**, where the increase in functional potency was encouraging (Table 6). However, its selectivity against the hV1aR was poor.

Scheme 1. Design of Biaryl Tertiary Sulfonamides Based on Consensus Pharmacophore Derived from Compounds **20** (grey) and **37** (gold) (Reprinted with permission from ref 44. Copyright 2003 Elsevier.[64])

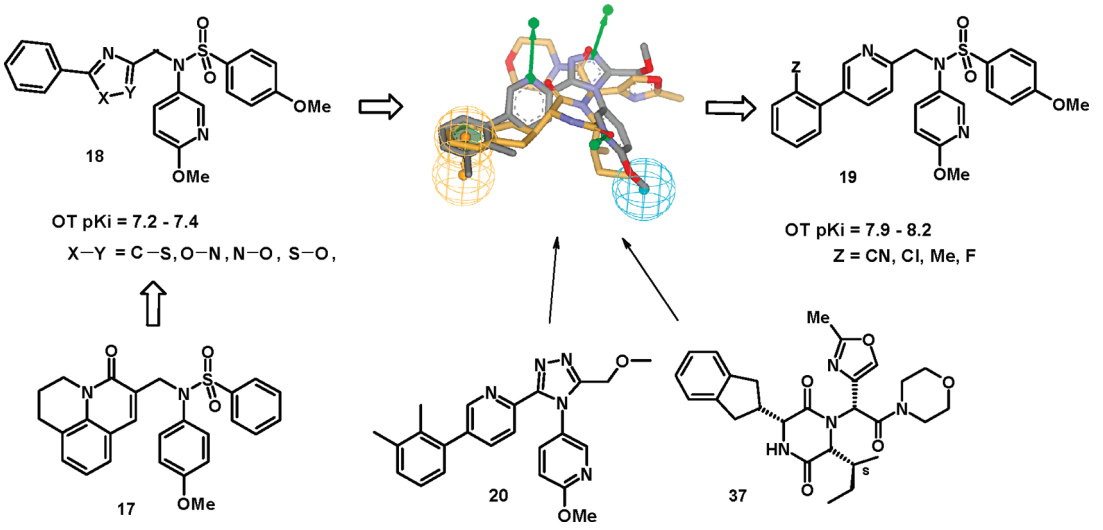
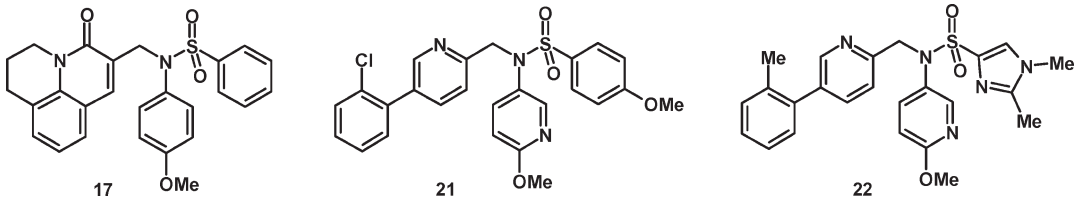


Table 6. Human and Rat Oxytocin/Vasopressin Receptor Binding, and Rat Oral Bioavailability of the Biaryl Tertiary Sulfonamides[44]



	oxytocin receptor		vasopressin receptors						PK	sol	Cyp450 (μM)					
	hOTR		hV1aR		hV1bR		hV2R		rat	aq						
compd	fpK_i[a]	pK_i[b]	fpK_i[a]	pK_i[b]	fpK_i[a]	pK_i[b]	fpK_i[a]	pK_i[b]	F %	μM	1A2	2C9	2C19	2D6	3A4 DEF	3A4 7BQ
17	6.7		< 5						4	< 1						
21	8.5		7.6		inact		5.9		12	9	> 33	0.52	0.45	> 33	0.75	2.2
22	8.3	9.1	6.1	7.2	inact	7.5	6.5	4.9	40	259	18	6.7	13	31	1.3	4.8

[a] Functional receptor antagonism (fpK_i) was determined in FLIPR assays using recombinant hOTRs or hV1aRs/hV1bRs stably transfected in CHO cells, and recombinant hV2Rs stably transfected in yeast cells. [b] Filtration binding was determined by displacement of [^{3}H]-oxytocin from recombinant hOTRs stably transfected in CHO cells.

Also it had relatively poor Cyp450 (cytochrome P450 enzyme) profiles and poor solubility, resulting in low oral exposure. The serious PK shortcomings were tackled by in silico profiling of derivatives suggested by pharmacophore analysis, which showed that although the sulfonamide oxygen atoms are required as hydrogen bond acceptors, the aryl sulfonyl ring can be replaced to optimize the PK properties and retain potency.

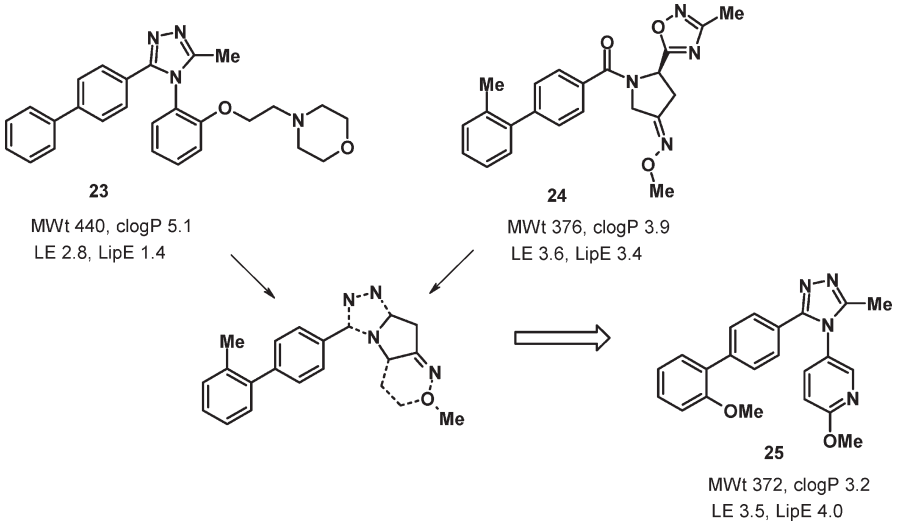
A number of highly potent oxytocin receptor antagonists were prepared with both electron rich and electron deficient aryl sulfonamides, which led to the imidazole sulfonamide **22** which was predicted to have good solubility and a improved Cyp450 profile. This proved to be the case, and the oral bioavailability of **22** in the rat (F = 40%) was found to be superior to that of **21**. Selectivity profiles for **22** were determined in functional assays and in lower throughput filtration binding assays. A significant improvement in selectivity was achieved with **22** (Table 6) which had good binding affinity at the hOTR (K_i = 0.8 nM) and was 80-fold, 40-fold, and 15856-fold selective for the hV1aR, the hV1bR, and the hV2R, respectively.[44]

Triazoles

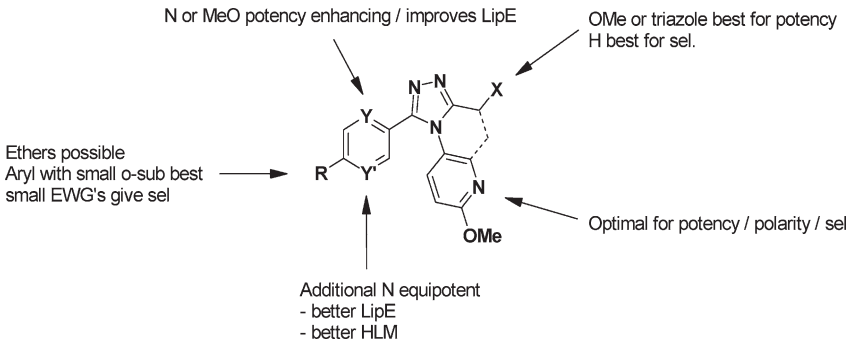
The known hV1aR antagonist **23**[45] was also identified as an OTR antagonist by researchers at Pfizer by high throughput screening (HTS) of their compound collection.[46] Although 10-fold more selective for the hV1aR (Table 7), the triazole **23** was used as a starting point for the development of selective orally bioavailable oxytocin antagonists. Pharmacophoric overlap of **23** with the oxime template **24** (similar to that present in the oxytocin antagonists **11** and **12**) suggested (Scheme 2) replacement of the alkoxy aryl ring in **21** with the methoxy pyridyl ring and incorporation of an *ortho* substituent in the biaryl substituent to give the pyridyl triazole **25**. This improved the oxytocin potency and selectivity with respect to hV1aR antagonism, reduced lipophilicity (clogP = 3.2), and improved the heavy atom ligand efficiency (LE)[47] and the lipophilic efficiency (LipE)[48] (Scheme 2). They used the latter two parameters to track the success of this new lead series during an optimization program to improve the metabolic stability, selectivity, and aqueous solubility properties.

Heavy atom ligand efficiency is the normalization of MW and potency and is used to rank lead series. It shows the

Scheme 2. Pharmacophore Design of Biaryl Triazole Template



Scheme 3. Triazole SAR[51]



efficiency of each heavy atom.

$$\text{LE} = -1.4\log K_i/n \quad (n = \text{no. of non-H atoms})$$

For example, a desirable value would be LE 0.36; K_i = 10 nM, MW 405.

$$\text{LipE} = -\log(\text{IC}_{50}) - \text{cLogP}$$

Introduction of the concept LipE was used to avoid medicinal chemists being seduced by potency driven by lipophilicity and enabled the focus to be on the efficiency of each lipophilic fragment. Their goal was to identify a series where compounds routinely have LE > 0.35 and LipE > 5.

Replacement of the central aryl of the C-3 biaryl triazole substituent with a pyrazine gave a significant reduction in hV2R antagonism. Further SAR optimization involving substitution in the distal aryl ring of the biaryl substituent suggested that disubstitution with small groups at the 2,4-positions gave the best oxytocin activity and selectivity vs the vasopressin receptors. Also exploration of SAR around the C-5 (methyl) triazole substituent identified methoxymethyl as a substituent which typically gave ca. 3-fold improvement in oxytocin potency (Scheme 3).

This led to the potent triazole OTR antagonist **26** (K_i = 6 nM), which had good levels of selectivity over the hV1bR and the hV2R (> 1600-fold) and moderate selectivity over the hV1aR (65-fold) (Table 7). Encouragingly, **26** had a reasonable rat PK profile with moderate oral bioavailability (F = 24%) and a clearance of 50 mL/min/kg but had low aqueous solubility (6 μg/mL).

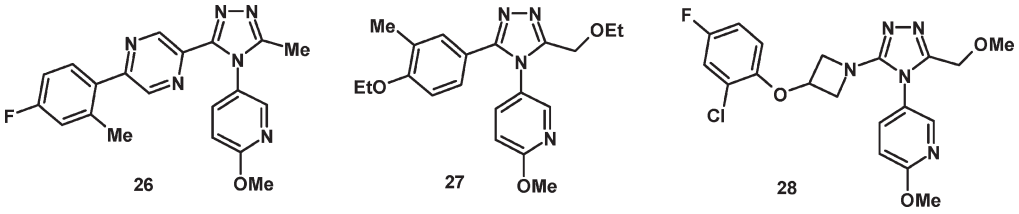
Further developments to address the low aqueous solubility of **26** led to replacement of the biaryl substituent with an ethoxy aryl ring in **27** (Table 7), which had increased aqueous solubility (344 μg/mL) but lower OTR antagonist potency (K_i = 28 nM) and lost selectivity over the hV1aR (20-fold).[49] However, replacement of the biaryl substituent with N-linked ethers[50] led to the potent triazole OTR antagonist **28** (PF-3274167) with good levels of activity (K_i = 9.5 nM), selectivity over the hV1aR (118-fold), and the hV2R (> 1000-fold) and aqueous solubility (59 μg/mL)[50] (Table 7).

Modeling the minimized X-ray structure of **26** and **28** showed good overlay of the terminal aryl rings required for good levels of potency. The azetidine aryl ether **28** had good oral bioavailability in the rat (62%) and dog (81%)[50,51] showed no significant Cyp450 inhibition, good CNS penetration (in vitro MDCK 34/37), and was clean in both the Ames and micronucleus test and was selected for progression as a potential clinical candidate.[51] In first time in human exposure it was well tolerated across the dose range 0.3−2400 mg (single dose) and the estimated human PK data from this was ($F \sim 80\%$, $t_{1/2} \sim 12$ h, 1.5 > Cl > 8 mL/min/kg).[51] However, no in vivo oxytocin antagonist activity was reported and the preferred therapeutic target: preterm labor, benign prostatic hyperplasia, or sexual dysfunction was not indicated

2,5-Diketopiperazines

Screening the GSK compound collection and various libraries produced several templates with moderate levels

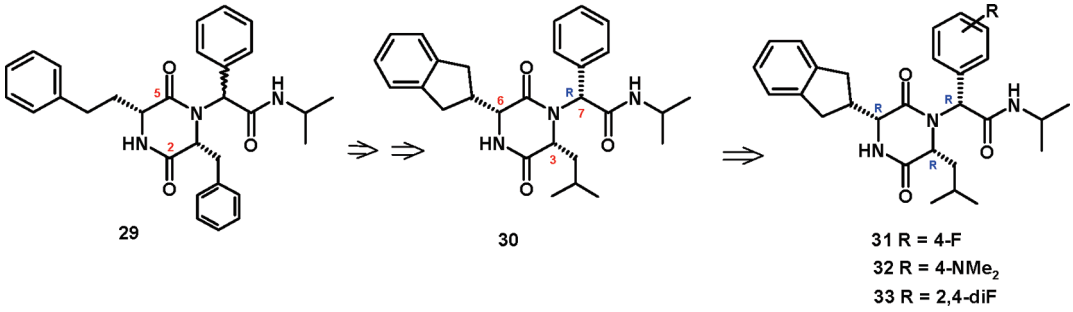
Table 7. Human Oxytocin/Vasopressin Receptor Binding, and Animal Pharmacokinetics of Triazoles **26**–**28**[47–51]



	oxytocin receptor	vasopressin receptors			PK rat/*dog*			physical properties		
compd	hOTR K_i (nM)[a]	hV1aR K_i (nM)[a]	hV1bR K_i (nM)[a]	hV2R K_i (nM)[a]	*F*%	Cl	$t_{1/2}$	sol[b] @ pH 7.4	LE	LipE
23	304	28							0.28	1.4
24	50	60							0.36	3.4
25	56	525	> 10000	500					0.36	4.0
26	6	388	> 10000	> 10000	24/–	50/–	1 h/–	6	0.41	5.6
27	28	549	> 10000	> 10000				344	0.40	4.5
28	9.5	1120	> 10000	> 10000	62/*81*	36/*8*	0.9 h/*1.9* h	59	0.40	4.8

[a] Binding affinity inhibition constant K_i (nM) at hOTR and rOTR in HEK293-EBNA cells and at hV1aR, hV1bR, and hV2R in CHO cells. [b] Solubility in μg/mL on crystalline material.

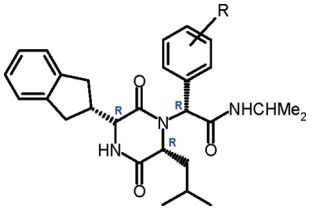
Scheme 4. Indanyl 2,5-Diketopiperazine Template



of antagonist activity at the OTR. A key consideration was to choose a template with good levels of selectivity over the three vasopressin receptors rather than to try and build this in during the lead optimization stage. It was hoped this would avoid the problem in the past of having to repeatedly increase the size of the template in an attempt to increase receptor selectivity. Furthermore, as blocking OTRs in the uterus was the objective in developing an oral treatment for preterm labor, all templates were also assessed by in silico profiling and suitable templates were evaluated in vitro for predicted CNS penetration. This was to decrease the risk that templates would be chosen that would cross the blood–brain barrier and thus block the central effects of oxytocin both in the fetus and in the mother. The screening program identified 2,5-diketopiperazines (DKPs) exemplified by **29** as novel templates for antagonists of the hOTR. The lead, **29**, showed potency of pK_i = 6.5 (K_i = 300 nM) as a mixture of isomers in the amide side-chain. Initial SAR studies led to the semirigid and chirally pure DKP **30**, pK_i = 8.4, (K_i = 4 nM), with *cis* disposed substituents at C-3 and C-6 and the *R* side-chain configuration (Scheme 4).

Optimal activity was shown to lie in the *RRR* series, e.g., **31**–**33**: the *RRS* isomers, where the stereochemistry in the amide side-chain at C-7 is inverted, were 10-fold less potent. At C-6, an indanyl group was preferred; its replacement by phenethyl and benzyl groups led to a progressive weakening of activity. At C-3, a 4-carbon branched alkyl was shown to be optimal; smaller alkyl groups result in reduced antagonist activity (Scheme 5).[52] The *RRR* series showed very good levels of selectivity relative to the vasopressin receptors, e.g., **31** (hOTR K_i = 4 nM), > 1500-fold selective over the hVIaR and the hVIbR, and > 300-fold selective over the hV2R, and **32** (hOTR K_i = 3nM) > 13000-fold selective over the hVIaR, the

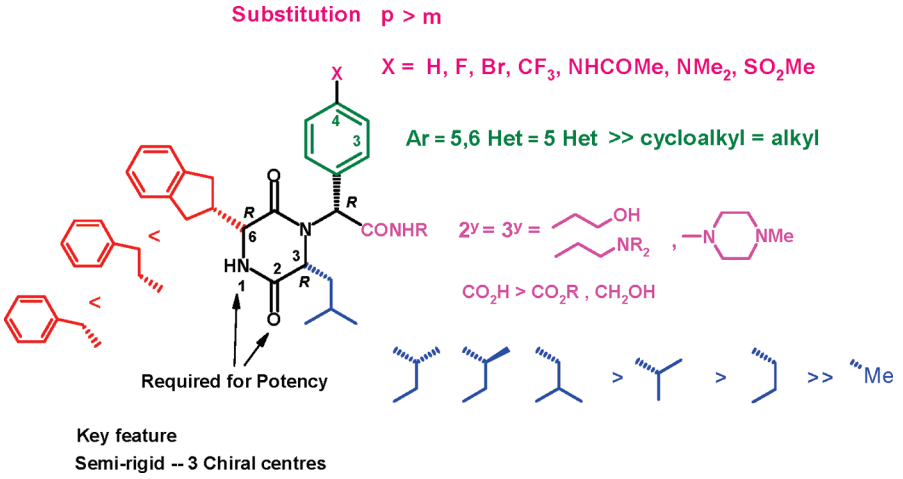
Table 8. Substituted Aryl (3*R*,6*R*,7*R*)-2,5-Diketopiperazines Oxytocin Antagonists: Inhibition of Oxytocin Binding at the hOTR and Vasopressin Binding at the hV1aR, hV1bR, and hV2R, and Oral Bioavailability in the Rat and Dog[55]



		oxytocin receptor	vasopressin receptors			bioavailability	
compd	R	hOTR pK_i[a]	hVIaR pK_i[a]	hVIbR pK_i[a]	hV2R pK_i[a]	rat *F* %	dog *F* %
31	4-F	8.4	< 5.2	< 5.2	5.9	13	13
32	4-NMe_2	8.5	< 4.4	< 4.3	< 4.1	2	50
35	2,4-diF	8.9	5.2	< 5.2	6.2	46	13

[a] Displacement of [^{3}H]-oxytocin from hOTR or [^{3}H]-vasopressin from hV1aR, hV1bR and hV2R by the test compound.

Scheme 5. 2,5-Diketopiperazine SAR[52,55−59]



hVIbR, and the hV2R, Table 8, and low predicted CNS penetration from in silico[53] and in vitro studies.[54]

Further SAR studies on this chiral system revealed that alkylation of the ring *N*-atom or removal of the C-2 carbonyl group decreased potency. Potency was retained when the aryl group on the *N*4-glycinamide was replaced by 5-membered heteroaryl or 5,6-fused heteroaryl systems; cycloalkyl or alkyl groups were not well tolerated. *Para* substitution was preferred on the arylglycinamide moiety and a broad range of groups at this position (Scheme 5) conferred good antagonist activity; *meta* substitution was less well tolerated.[52,55] Potency was maintained by a wide range of *N*-substituted and *N*,*N*-disubstituted glycinamides.[55]

In these 2,5-diketopiperazine oxytocin antagonists, the *RRR* stereochemistry of the three chiral centers at the 3, 6, and 7 positions, together with 6-indanyl and 3-isobutyl substituents linked via the key functionality of the carbonyl at the 2-position and the NH at the 1-position, are essential for high antagonist potency and hence must be crucial elements in binding to the OTR. This can be explained by the similar pharamacophores (those in bold Figure 3) exhibited by the X-ray crystal structure of the 2,5-diketopiperazine **33** and deamino oxytocin **34**.[55] This shows that there is a similar stereochemical relationship of the required aryl ring, peptide backbone, and isoleucine in **34** (2-Tyr 3-Ile) and the required aryl ring, diketopiperazine fragment, and leucine in the 2,5-diketopiperazines.

Although all the *RRR* isomers of the monosubstituted aryl DKPs with wide range of different functionality (Scheme 5) had similar high levels of potency, they all had low bioavailability in the rat (eg see Table 8). Optimization of the pharmacokinetic profile of this template was achieved by a combination of analogy and property-based design. The 2,4-difluoro derivative **35** (R = 2,4-diF) was prepared by analogy with the benzoxazine series **9** (GW 575695X), where aromatic fluoro substitution next to a ring junction produced a >3-fold improvement in rat bioavailability. A similar improvement (*F*: 13−46%) was seen in the bioavailability of **35** (R = 2,4-diF) in this species (Table 8). To achieve good bioavailability in both rat and dog, optimization was taken further by using property-based design to estimate the human oral absorption (EHOA) derived from HPLC measured lipophilicity (CHI log *D*) and calculated size (cMR) see eq 1[56] for a whole range of disubstituted 7-aryl and 7-heteroaryl 2,5-diketopiperazines.

$$\text{EHOA}\% = 182.9 + 7.22\ \text{CHI log}\ D_{7.4} + 4.21\ \text{PosCh} - 10.93\ \text{cMR} \quad (1)$$

The highest EHOA was obtained with small DKPs, where large aryl/heteroaryl rings at the 7- exocyclic position and large amides were avoided. This led to the tertiary amide 2′,4′-difluorophenyl-dimethylamide **36** with high levels of potency (pK_i = 9.2) and good oral bioavailability in the rat (53%) and dog (51%) with low clearance (Table 9). It was >60-fold more potent than atosiban in vitro at the hOTR and had comparable potency to atosiban in the rat (IC_{50} = 227 nM). In addition, **36** showed a high degree of selectivity toward the vasopressin receptors (>10000 for hV1aR/hV1bR and ~500 for hV2R) and had a satisfactory safety profile in the 4-day oral toxicity test in rats.[56]

However, **36** had a suboptimal solubility and Cyp450 profile. Increased solubility was achieved by increasing the polarity of substituents on the 7-aryl ring or the amide function, but this resulted in a worse PK profile. Focusing away from this peripheral functionality by increasing the polarity of the aromatic ring itself by replacing it with an heterocyclic ring increased solubility without losing the excellent PK profile achieved with this template. This led to a range of 2′-substituted 7-(1′,3′-oxazol-4′-yl)-(3*R*,6*R*,7*R*)-2,5-diketopiperazine amides with increased solubility and an improved Cyp450 profile. Branching at the α-carbon of the 3-butyl group led to a superior rat pharmacokinetic profile that resulted in the discovery of the 2′-methyl-1′,3′-oxazol-4′-yl morpholine amide derivative **37** GSK221149A (Retosiban), which had the best oral exposure and bioavailability in the rat.[57] Retosiban has nanomolar affinity (K_i = 0.65 nM) for the hOTR with >15000- and >1400-fold selectivity over the closely related hV1aR/hV1bR and the hV2R, respectively (Table 9). It has good solubility, low protein binding, and has a good Cyp450 profile with no significant inhibition IC_{50} > 100 μM and low predicted CNS penetration.[59] Retosiban is >15-fold more potent at the hOTR than atosiban (a marketed iv peptide oxytocin antagonist), and it has been shown to be an effective tocolytic by iv and by oral administration in rats[58] and was selected for progression as a potential clinical candidate for preterm labor.[59] Follow up compounds in this series can be seen in the most recent patent applications where heterocyclic variants of the arylglycinamide moiety, including

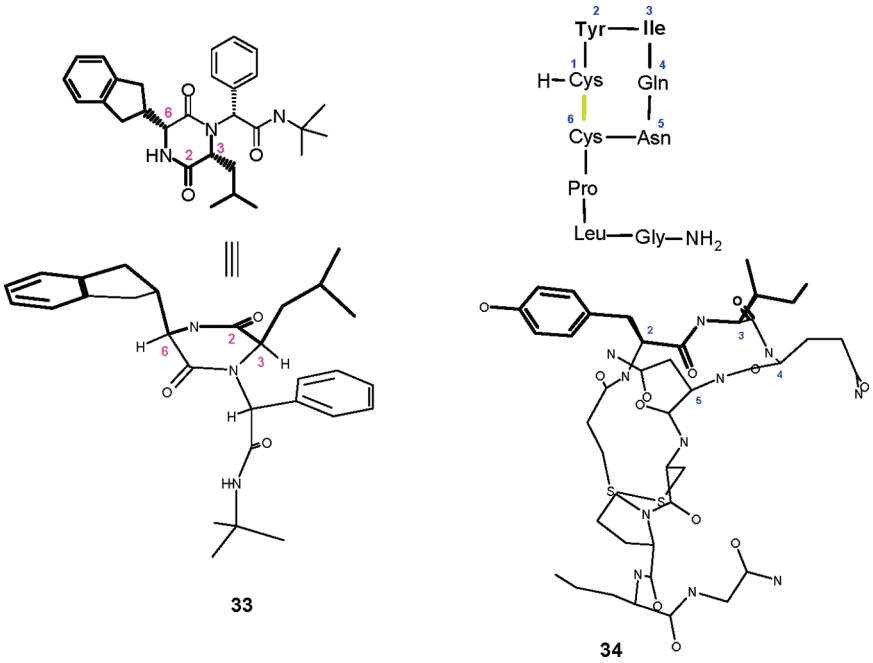
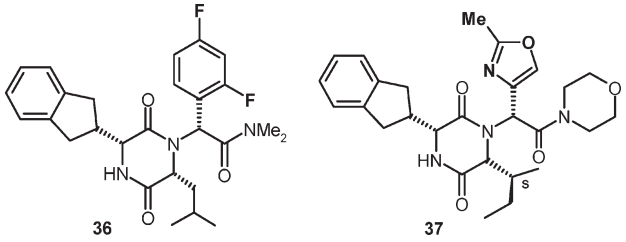


Figure 3. X-ray Crystal Structures of 2,5-Diketopiperazine **33** and Deamino-oxytocin **34**[55]

Table 9. Comparison of the Oxytocin Antagonist Potency, Selectivity vs the Human Vasopressin Receptors, Pharmacokinetic Profile in Rat and Activity in Vivo of **36** and **37**[56,57]



	oxytocin receptors			vasopressin receptors										
	hOTR		rOTR	hV1aR	hV1bR	hV2R	oxytocin antagonism	rat PK[f]			sol aq[g]		hum serum Al[i]	Cyp 450[j]
compd	fpK_i[a]	pK_i[b]	pK_i[c]	pK_i[b]	pK_i[b]	pK_i[b]	in vivo rat IC_{50}[d]	Auc po	Cl	*F*%	mg/mL	CHI Log *D*[h]	%	3A4 IC_{50} μM
36	8.8	9.2	8.0	< 5.2	< 5.2	6.5	227	2971	15	53	0.083	3.4	94	5
37	8.2	9.2	8.4	< 4.9	< 5.0	6.0	180	5465	19	~100	> 0.22	2.2	< 80	> 100
atosiban	-	7.9	7.2	9.8	7.4	6.5	~186							

[a] Functional receptor antagonism (fpK_i) was determined in FLIPR assays using recombinant human oxytocin receptors stably transfected in CHO cells [b] Displacement of [^{3}H] oxytocin from hOTR or vasopressin from hV1aR, hV1bR, and hV2R by the test compound, [c] Displacement of [^{3}H] oxytocin from rOTR by the test compound. [d] Plasma IC_{50} nM in the rat. [f] Rat PK (n = 4): AUC (h ng mL^{-1}) at 5 mg/kg, 5%DMSO/95%PEG400 formulation, Cl in mL min^{-1} kg^{-1}. [g] Solubility (mg/mL) a precipitation/HPLC based measurement. [h] An HPLC method based measurement of lipophilicity [i] % Human serum albumin binding. [j] Cypex Cyp450.

Table 10. Comparison of Potency Selectivity and Bioavailability of Oral Oxytocin Antagonists

		hOTR		selectivity		rat				
compd	date[e]	K_i (nM)	pK_i	hOTR/hV1aR	hOTR/hV2R	*F*%	LE[f]	M_w[c]	Log P[d]	rule 5[c]
4	1992	**530**[a]	6.3	**3**	**11**					
5	1994	**13**[a]	7.9	**14**	**45**	**35**	0.30	554.8	2.1	1
7	1995	**4.6**[a]	8.3	**690**	**8043**	**39**	0.31	507.6	3.0	1
8	1998	**4.9**[a]	8.3	**650**	**5714**	**80**	0.27	586.7	3.3	2
9	2002	**2**[b]	8.7	**630**	**> 1500**	**16**	0.28	608.6	3.1	2
11	2003	**28**[b]	7.5	**6**	**> 357**	**49**	0.31	455.6	3.7	0
13	2004	**0.5**[b]	9.3	**280**	**> 2000**		0.31	604.5	6.0	2
16	2005	**0.65**[b]	9.2	**60**	**580**		0.30	625.2	4.1	2
22	2009	**0.8**[b]	9.1	**80**	**15738**	**40**	0.39	463.6	3.1	0
28	2009	**9.5**[b]	8.0	**118**	**1053**	**62**	0.39	419.8	2.7	0
37	2008	**0.63**[b]	9.2	**> 18,000**	**1587**	**100**	0.36	494.6	2.6	0

[a] K_i values refer to displacement of [^{3}H]-oxytocin from hOTR binding sites in human uterus tissue. [b] Binding affinity inhibition constant K_i (nM) versus [^{3}H]-oxytocin at hOTRs in CHO or HEK293-EBNA cells. [c] ChemSpider. [d] PubChem XLogP3-AA. [e] Date publication in literature. [f] Ref 47.

the 1-methyl-1*H*-indazol-5-yl[60,61] and the 2,6- dimethyl-3-pyridinyl[62] ring systems, are described.

Conclusions

The suboptimal pharmacokinetics and oral bioavailability of the initial oxytocin antagonist **5** which caused its clinical trials to be suspended has been superseded with the more recent oxytocin antagonists **28** (Pfizer) and **37** (GSK) Table 10. It can be seen from Table 10 that the templates investigated in the previous decade contravene the Lipinski "rule of five", which accounts for their poor oral bioavailability, but this is not the case with the more recent compounds **28** and **37** that have lower MWt and logP. While the earlier compounds investigated, e.g., **7** and **8** did have single figure nanomolar potency at hOTR with 10^2 and 10^3 selectivity over hV1aR and hV2R, respectively, they all had inferior ligand efficiency of ≤ 0.31, in contrast to the superior ligand efficiency of ≥ 0.36 exhibited by the later compounds **22**, **28**, and **37**. An advantage of the DKP template is that in contrast to the typical planarity/mobility of the benzamides (benzoxazinylpiperidine, **6**−**9**, **13**, and pyrrolidino oximes **10**−**12**), tertiary arylsulphonamides (**14**−**17**, **21**) or triazole **28** templates, it has 3 chiral centers and a semirigid ring that presents a similar pharmacophore for the key functionality required for activity to that found in the natural ligand oxytocin. Retosiban has superior subnanomolar potency at the hOTR and 10^4 and 10^3 selectivity over hV1aR and hV2R ,respectively, compared to the oral nonpeptide oxytocin antagonists reported by Merck, Serono, Sanofi, and Pfizer and has a better rat bioavailability. Furthermore, unlike **5**, which accumulates in the brain, and **28**, which has good brain penetration, Retosiban, which was developed as an oral treatment for preterm labor, has low predicted CNS penetration and this reduces the risk that this drug might cross the blood−brain barrier and thus block the central effects of oxytocin both in the fetus and in the mother.

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Biography

Alan D. Borthwick is a Drug Design/Medicinal Chemistry Consultant with over 35 years of experience in the pharmaceutical industry. He received his Ph.D. in Organic Chemistry from the University of London, UK (1971). After joining Glaxo, he designed the once a day antihypertensive Lacidipine and was coinventor of the α2-antagonist Fluparoxan. He then moved to GlaxoWellcome, Stevenage, UK, and as Project Leader for the HSV and HCMV Protease Projects 1995−1999, designed a novel class of α-methyl-translactams as antiviral HCMV protease inhibitors. At GlaxoSmithKline 2000−2006, he was a senior scientific manager for two research groups involved in factor Xa inhibitors for thrombosis related diseases and oxytocin antagonists for preterm labor which lead to Retosiban. His interests are structure- and property-based drug design.

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