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Identification of Potent and Selective Oxytocin Antagonists. Part 1: Indole and Benzofuran Derivatives

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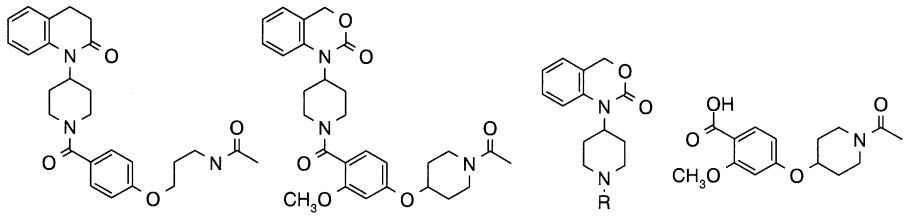
Abstract—Studies to discover novel, potent and selective oxytocin antagonists are reported. Combinatorial libraries designed to find novel replacements of fragments of oxytocin antagonist L-371,257, identified pyrimidine, thiazole, indole and benzofuran as potential alternatives to the benzoic acid moiety of L-371,257. Additional investigations identified indole and benzofuran derivatives with potent oxytocin antagonist activity.

Introduction

Although preterm birth accounts for 66% of all infant mortality and morbidity, no safe and effective therapy for maintenance of gestation is available.[1] Limited efficacy and/or maternal or fetal safety restrict the use of current therapies.[2] Oxytocin (OT), a neurophyseal hormone, is a potent contractor of the uterus and is used (as Syntocinin®) for the induction or augmentation of labour.[3] Also the density of myometrial oxytocin receptors increases by 100-fold in women at term when compared with non pregnant women and is elevated in prematurely labouring women when compared with non-labouring women of a similar stage of pregnancy.[4] OT antagonists have been investigated in the search for effective therapies with alternative modes of action. Although the peptide OT/vasopressin **1a** antagonist atosiban® (Tractocile) has recently been approved for use in Europe, it is not suitable for long-term maintenance treatment, as it is not orally bioavailable.[5] In the search for orally active agents suitable for maintenance treatment, potent and selective non-peptide OT antagonists have been identified, but none has been extensively investigated in the clinic.[6]



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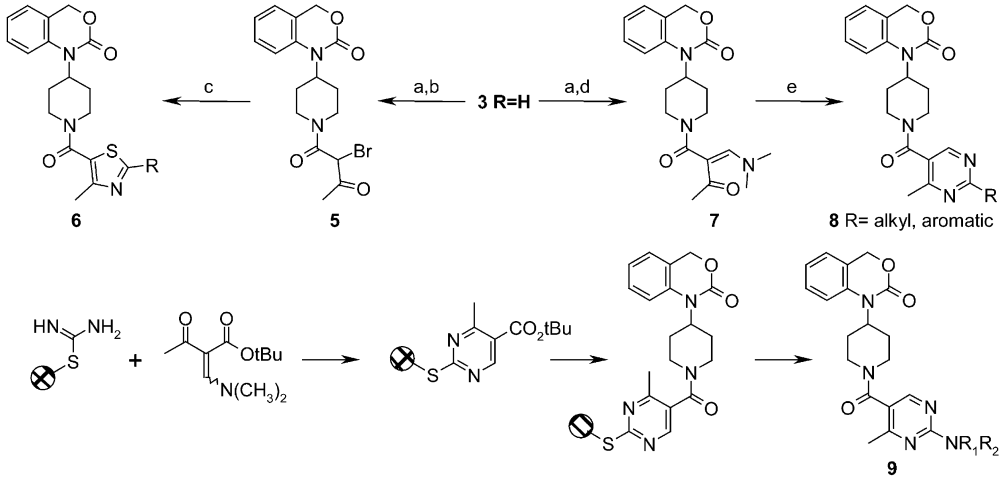
Merck Research Laboratories have developed potent and selective OT antagonists, for example L-371,257 **2** from Otsuka's OPC 21268 **1**,[7] but no compounds are reported to be in clinical development.[8] We have recently reported a potent benzodiazepine OT antagonist.[9] As an alternative strategy, **2** was used as a starting point for a chemistry programme. The amine **3 R = H** and acid **4**, precursors to **2**, were used as cores in combinatorial libraries to identify replacements for the other halves of the molecule. This paper reports on initial investigations to discover novel potent and selective OT antagonists.

Replacements of Amine 3

Replacements of the amine moiety **3 R = H** of **2** were sought by coupling acid **4** with sets of amines, some of which were selected to contain the pharmacophoric characteristics of **3**, that is, an aromatic ring and a hydrogen-bond acceptor. The resulting discrete libraries were tested without purification, but no significant OT binding antagonism was observed (data not shown).

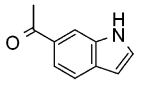
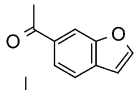
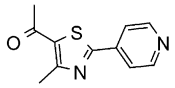
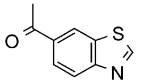
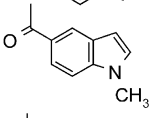
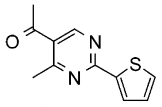
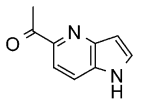
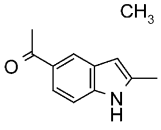
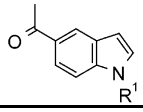
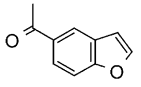
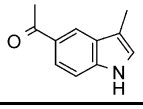
Replacements of Acid 4

To identify alternatives to the benzoic acid moiety **4**, structurally diverse acids were coupled to amine **3 R = H**. Of particular interest were heteroaromatic rings such as pyrimidine, thiazole, indole and benzofuran, examples of which were included in the acid sets. In the first iteration 500 compounds were made and tested as individual unpurified samples. Examples of the above ring systems gave moderate levels of OT binding inhibition. Additional libraries were synthesised to further investigate the thiazole and pyrimidine leads. Thiazole libraries of general structure **6** were synthesised using α-bromo-ketone **5** and a diverse set of thioamides (Scheme 1).[10] Although a number of compounds had moderate activity e.g., **3a** (Table 1), none was sufficiently active to progress. The pyrimidine derivatives



Scheme 1. (a) $CH_3C(O)CH_2CO_2CH_3$, DMAP, *i*PrOH, Na_2CO_3, reflux, 55%; (b) 4-(dimethylamino)pyridinium bromide perbromide, AcOH, 74%; (c) $RC(S)NH_2$, DMF, 70 °C; (d) $(CH_3O)_2CHNH(CH_3)_2$, $PhCH_3$, reflux, 81%; (e) $RC(=NH)NH_2$, NaOEt, EtOH, reflux.

Table 1. Inhibition of the binding of OT with human OT receptor (hOT)[a]

	R	pK_i hOT		R	pK_i hOT		R	pK_i hOT
2		8.0	**3d**		6.7	**3h**		6.4
3a		6.9	**3e**		6.1	**3i**		6.9
3b		6.8	**3f**		6.1	**3j**		6.9
3c		R^1 = H 6.7	**3g**		6.6	**3k**		6.1

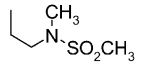
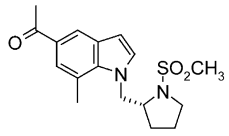
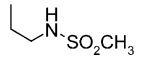
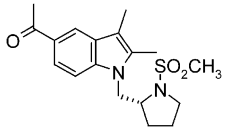
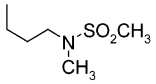
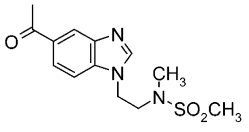
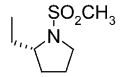
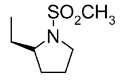
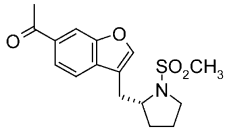
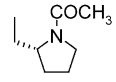
[a]Displacement of ^{3}[H] oxytocin from hOT by the test compound.[9]

were investigated using solution chemistry to synthesise compounds of structure **8** and solid-phase chemistry to obtain 2-amino-pyrimidines **9**. A library of pyrimidines **8** was obtained from the clean reaction of enamine **7** with a diverse set of amidines,[11] but none of the compounds had significant activity, for example **3b** (Table 1). A library of 2-amino-pyrimidines **9** was synthesised on solid phase (Scheme 1),[12] but the most potent compounds were at best only moderately active.

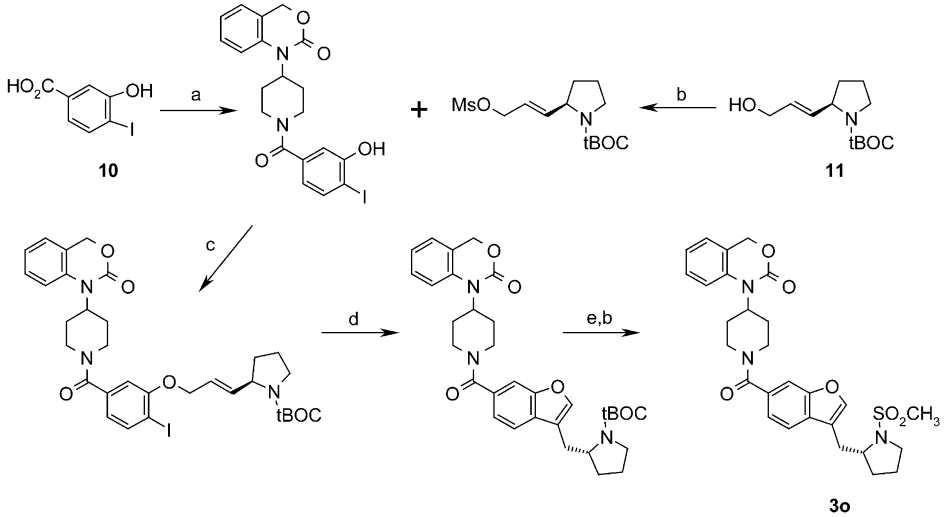
6,5-Fused Ring Systems

As the initial library identified interesting activity for some indole and benzofuran derivatives a number of 6,5 fused aromatic systems were investigated (Table 1). The indole isomers **3c** ($\mathbf{R^1 = H}$) and **3d** were equally potent, but increasing the number of heteroatoms e.g., **3e**,**f** gave a significant loss of activity. The benzofuran isomers **3g**,**h** had similar activity to the indoles **3c** ($\mathbf{R^1 = H}$) and **3d**.

Table 2. Inhibition of the binding of OT with human OT receptor (hOT)[a]

	3c R_1 =	pK_i hOT		**3** R =	pK_i hOT
3ca		7.4	**3l**		8.0
3cb		7.2			
3cc		6.5	**3m**		6.4
3cd		6.4			
3ce		6.8	**3n**		6.4
3cf		7.7			
3cg		6.9	**3o**		6.7
3ch		6.8			

[a]Displacement of ^{3}[H] oxytocin from hOT by the test compound.[9]



Scheme 2. (a) **3**. HCl salt, 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide HCl, *N*-hydroxybenzotriazole, *i*Pr_2EtN, DMF; (b) CH_3SO_2Cl, Et_3N, CH_2Cl_2; (c) NaH, DMF; (d) $Pd(OAc)_2$, Bu_4NCl, NaO_2CH, Na_2CO_3, DMF; (e) TFA, CH_2Cl_2.

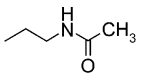
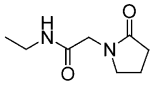
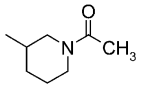
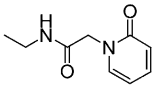
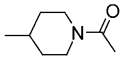
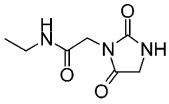
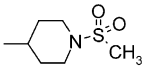
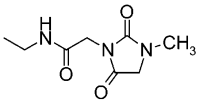
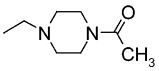
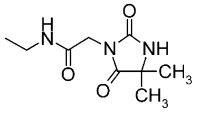
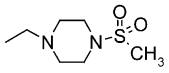
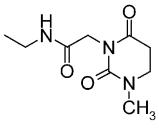
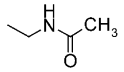
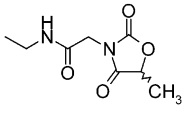
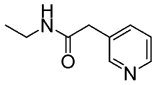
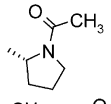
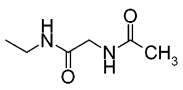
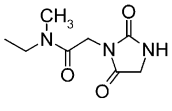
Indoles

To investigate indole **3c** for potential positions for substitution, the methyl-substituted indoles **3i–k** were synthesised. The results indicated that substitution is tolerated in the 1- and 2- positions, **3i** and **3j**, respectively, but not the 3-position **3k** of the indole ring. The latter finding was confirmed by the results from a limited number of additional 3-substituted indoles (data not shown). The significant activity of **3i** led to the synthesis of an array of 1-substituted indole derivatives by the sodium hydride mediated alkylation of **3c** ($\mathbf{R^1 = H}$) (Table 2).

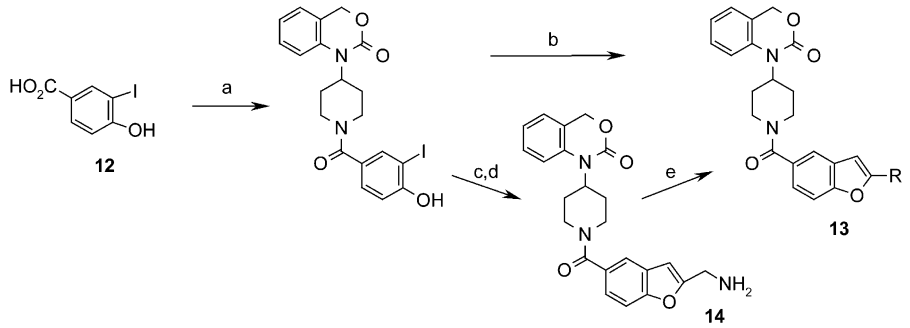
Most of the resulting compounds did not have improved activity over **3i** although, the sulphonamide **3ca** was significantly more potent, possibly indicating that the sulphonamide moiety was forming a hydrogen bond with the receptor. Further compounds related to **3ca** were synthesised to exploit this finding. The acetamide **3cb** had activity comparable to **3ca**, so a series of amide and sulphonamide libraries were made. Although a number of compounds had activity equal to **3ca** and **3cb** none was significantly more potent. Removal of the *N*-methyl group of the sulphonamide **3cc** or amide **3cd** or lengthening the chain **3ce** caused a 4- to 8-fold loss of activity. The activity difference between **3ca**,**cb** and **3cc**,**cd** suggested that the side chains bound in a *cis*-orientation, so a number of cyclic compounds were made to mimic the conformation of **3ca** and **3cb**. Of the rings synthesised, the *R*-pyrrolidine sulphonamide derivative **3cf** gave a 2-fold increase in activity, whereas the corresponding *S*-isomer **3cg** had a 4-fold loss of activity. Incorporation of a 7-methyl group **3l** to further conformationally constrain the sulphonamide moiety resulted in a further 2-fold increase in activity.

Although compounds in this series were beginning to show potent in vitro activity, all the compounds had high clearances in rats after iv administration, equivalent to

Table 3. Inhibition of the binding of OT with human OT receptor (hOT)[a] and dog IV clearance (mL/min/kg) and bioavailability (%F)

	R_1	pK_i hOT	Cl	F%		R_2	pK_i hOT	Cl	F%
13a		7.4	9	27	**13j**		7.6	34	
13b		6.7			**13k**		8.2	34	
13c		7.2	6	49	**13l**		8.2	17	8
13d		7.1	9	69	**13m**		8.5	20	
13e		7.1	11	44	**13n**		7.8	20	
13f		7.2	7	100	**13o**		8.4	27	
13g		7.2	8		**13p**		7.6		
13h		7.6	49		**13q**		7.6	31	
13i		7.8	18	16	**13r**		7.6	15	12

[a]Displacement of ^{3}[H] oxytocin from hOT by the test compound.[9]



Scheme 3. (a) **3**. HCl salt, 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide HCl, *N*-hydroxybenzotriazole, *i*Pr_2EtN, DMF, 71%; (b) RC≡CH, $PdCl_2(PPh_3)_2$, Et_3N, CuI, DMF or for alkynes containing basic groups, $Pd(OAc)_2$, *n*$BuNH_2$, PPh_3, CuI, THF; (c) *t*BuOCONHCH_2C≡CH, $PdCl_2(PPh_3)_2$, Et_3N, CuI, DMF; (d) TFA, H_2O, CH_2Cl_2, 100%; (e) R_1COCl or R_1SO_2Cl, Et_3N, CH2Cl_2; or R_1CO_2H, 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide HCl, *N*-hydroxybenzotriazole, *i*Pr_2EtN, DMF.

approximately two-thirds liver blood flow. Investigation of the metabolism of this series indicated that the major metabolites were associated with oxidation of the indole 2,3-double bond. As data from other derivatives (not shown) indicated that it could be blocked by substitution of the 2- and 3-position, the 2-methyl and 2,3-dimethyl derivatives of **3ce** were synthesised. Inclusion of the 2-methyl group (data not shown) did not affect the activity or clearance on the compounds, whereas the further substitution to give **3m**, as predicted from previous results, gave a significant loss of activity. This data confirmed that within this series, potent activity and good pharmacokinetics could not be achieved simultaneously. To circumvent the metabolic instability alternatives to the indole ring were investigated. However, the systems investigated, for example **3n** and **3o** (the latter synthesised from **10**[13] and **11**[14] Scheme 2), resulted in less potent compounds compared with the corresponding indole derivatives.

Benzofurans

The benzofuran core **3g** (pK_i 6.6) was elaborated by substitution of the 2- or 3-positions. Derivatives with 3-substituents gave no compounds of interest (data not shown). However, the 2-acetamidoethyl derivative **13a** (Table 3; synthesised from acid **12**,[15] Scheme 3) proved to have promising activity and pharmacokinetic parameters, so a number of amide, sulphonamide or urea derivatives of **13** (R = $(CH_2)_2NH_2$) were synthesised.

Some amides and ureas showed activity comparable with **13a**, but none was more potent, whereas the sulphonamides were less potent (data not shown). Further compounds with the amide functionality constrained in a ring **13b–f** failed to give an improvement in activity over **13a**. This data suggests that, even though **13a** is significantly more active than the unsubstituted benzofuran core **3g**, the additional amide of **13a** does not form a hydrogen bond with the receptor. Despite compounds such as **13c–f** having moderate levels of activity, their good pharmacokinetic parameters in dogs gave an impetus for an extensive investigation of 2-substituted benzofurans. Whereas the shortened amide **13g** gave similar levels of activity to **13a**, amide libraries derived from **14** (Scheme 3) suggested improved activity could be achieved in this series. On testing purified samples from the library, a moderate increase in activity was seen for the pyridyl derivative **13h**. Compounds containing other nitrogen heterocycles, for example imidazoles and tetrazoles were synthesised to expand on this finding, but no significant increase in activity was observed (data not shown). It was then postulated that the pyridyl moiety was acting as a weak hydrogen bond acceptor, so a range of compounds containing a hydrogen bond acceptor, for example **13i–k** was synthesised.

The increased activity of compounds such as **13i–k** suggested that the theory was correct. Elaboration of **13j** to the hydantoin **13l** gave potent activity, although the pharmacokinetic parameters were disappointing when compared to **13c–f**. Further substitution of the hydantoin, for example **13m**,**n** and ring expansion **13o** was explored in an attempt to decrease plasma clearance. These modifications gave compounds with potent activity but not improved clearances. Alternative saturated heterocycles such as the carbamate **13p** either gave less potent compounds or no improvement in plasma clearances. Attempts to improve activity or reduce plasma clearance by modifying the linking amide chain to the hydrogen bond acceptor, for example **13q** and **13r**, again failed to identify compounds with improved activity or pharmacokinetic parameters.

Investigation of heteroaromatic templates derived from **13k** gave compounds with potent activity and promising pharmacokinetic parameters; the results will be described in a subsequent paper.

Conclusion

Combinatorial chemistry has been used extensively to identify novel oxytocin antagonists. Libraries to find replacements of amine **3** failed to give compounds of interest. However, libraries to discover replacements of the benzoic acid moiety **4** identified pyrimidine, thiazole, indole and benzofuran as possible alternatives. Further focused libraries failed to identify compounds with potent activity in the cases of pyrimidine and thiazole. Elaboration of the indole template identified

potent compounds, but further studies demonstrated that the poor pharmacokinetic properties of the series could not be improved on whilst retaining potent activity. The benzofuran template identified compounds with potent activity and a range of pharmacokinetic properties; these compounds have been used as leads for further chemical programmes.

References and Notes

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