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2,5-Diketopiperazines as potent and selective oxytocin antagonists 1: identification, stereochemistry and initial SAR

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Abstract—This paper covers efforts to discover orally active potent and selective oxytocin antagonists. Screening pooled libraries identified a novel series of 2,5-diketopiperazine derivatives with antagonist activity at the human oxytocin receptor. We report the initial structure–activity relationship investigations and the determination of the stereochemistry of the most potent compounds.
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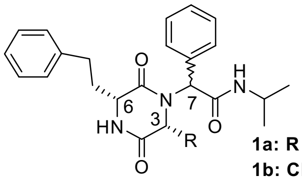
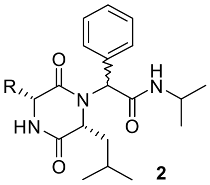
To address the need for oral agents to delay preterm birth[1] (the major cause of infant mortality and morbidity), nonpeptide oxytocin (OT) antagonists have been investigated.[2–4] In previous papers, a number of potent oxytocin antagonists were described.[4–6] However, these compounds did not have suitable pharmacokinetic parameters or sufficient in vivo potency to be progressed. To identify alternative templates, unencoded



1a: R = CH_2Ph
1b: $CH(CH_3)_2$



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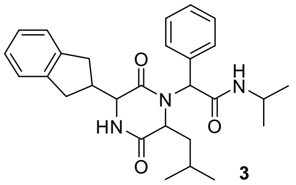

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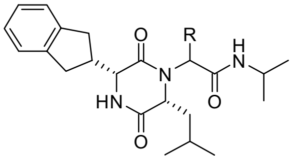

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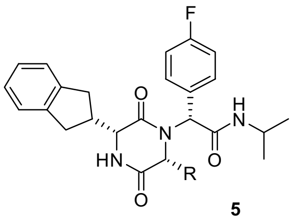

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Keywords: Oxytocin; Oxytocin receptor; Preterm birth; Antagonists; Unencoded libraries; 2,5-Diketopiperidines; Ugi reaction; Screening; Pooled libraries; Solid phase; Structure–activity relationships.

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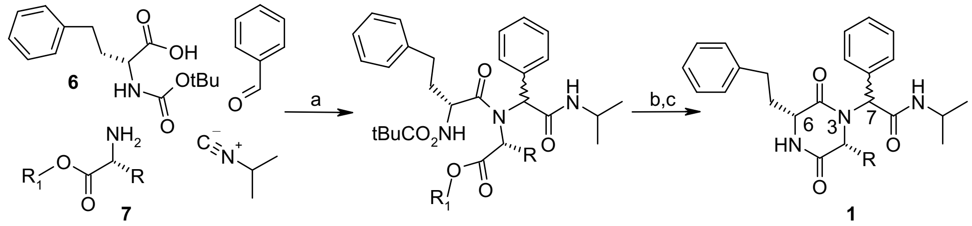


Scheme 1. Solid phase see Ref. 7: Solution phase conditions: (a) amine, aldehyde, triethylamine, methanol, rt, 3–18 h; then isonitrile and acid added, rt, 18–48 h; (b) TFA or 4 N HCl in dioxane, rt, 3–18 h; (c) Et_3N in dioxane, rt, 3–18 h.

pooled libraries were screened in an OT receptor binding assay.[6] This process discovered 2,5-diketopiperazine derivatives **1a**,**b** with moderate levels of potency. This paper describes initial structure–activity relationship investigations from the series.

Screening unencoded pooled libraries for binding at a number of G protein coupled receptors identified a number of pools that bound at the OT receptor. In particular, a pool of 48 2,5-diketopiperazines of general structure **1** showed activity when screened at a nominal concentration of 0.5 μM per compound. The pool was generated using 24 amino esters **7** in a four component Ugi reaction on solid phase[7] (Scheme 1). The reaction produced a mixture of stereoisomers at the exocyclic 7-position and therefore the pool contained 48 compounds.

Deconvolution of the library gave compounds with a range of potencies and revealed that small lipophilic amino esters **7** with *R*-stereochemistry gave 2,5-diketopiperazines with the best levels of activity, for example, **1a**,**b** (pK_i 6.5 and 6.7, respectively, as mixed isomers at the 7-position). Further investigation of the 3-substituent of **1** is described later.

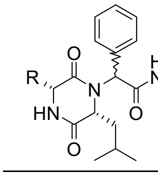
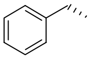
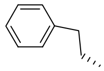
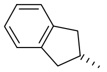
Analysis of the results from the other library pools suggested that *R*-amino acids containing aromatic groups (e.g., **6**), which gave 2,5-diketopiperazines with aryl groups in the 6-position and an aromatic group directly attached to the 7-position had the greatest potency. To further investigate the former finding an array of such amino acids was investigated. In summary, shortening or lengthening the linker to the aromatic functionality (e.g., benzyl **2a**) resulted in a loss of potency (Table 1). Further substitution of the phenyl group of the benzyl or phenethyl moiety failed to increase the potency of the compounds (data not shown). However, conformationally constraining the phenethyl group of **2b** as an indanyl group **2c** resulted in a significant increase in potency. This group has been shown to give compounds at least 10–15 fold more potent than those with alternative functionality in the 6-position (Table 1).

To this point the isomers at the exocyclic position had not been separated. The stereochemistry at the other two chiral centres was assumed to be *R* as both the amino esters and the amino acids in the Ugi reaction had this chirality. In order to confirm this and determine the preferred chirality at the exocyclic centre all the stereoisomers of compound **3** (**3a**–**h**) were made using solution phase Ugi chemistry[8] (Scheme 1) and their oxytocin antagonist potency determined (Table 2). The compounds with *R*,*R*-stereochemistry in the DKP ring (**3a**,**b**) had the greatest potency with one isomer at the 7-stereocentre 10-fold more potent than the other. The stereochemistry of the most potent isomer (**3a**) was determined to be *R*,*R*,*R* by an alternative stereospecific synthesis[9] and confirmed by X-ray crystallography.[10] As **3a** the *R*,*R*,*R* isomer was the most potent antagonist, all the subsequently described compounds have this stereochemistry.

To confirm the requirement for an aromatic group in the 7-position, a limited number of compounds (**4a**–**f**) were synthesised (Table 3). Compounds with alkyl or cycloalkyl substituents such as **4a**,**b** were at least a 100-fold less potent than **3a**. To further optimise this functionality, an array of *para*-substituted phenyl derivatives was synthesised (Table 3).

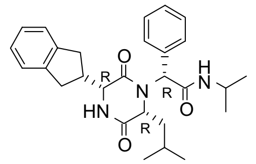
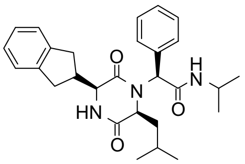
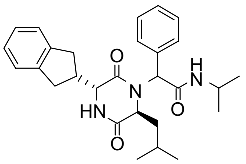
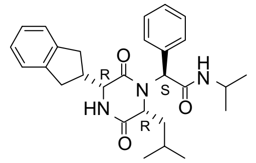
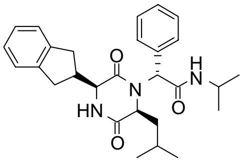
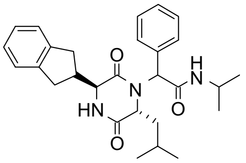
A range of functionality was tolerated (**4c**–**e**). The phenyl could also be replaced with pyridyl **4f**, however, this compound rapidly epimerised at the 7-position and therefore could not be tested as separate isomers. As previously mentioned, the results from the pooled libraries demonstrated that a small lipophilic alkyl group was required in the 3-position, so a number of deriva-

Table 1. Inhibition of the binding of OT with human OT receptor (hOTr)[a] by compounds **2**

		R	pK_i hOT		R	pK_i hOT		R	pK_i hOT
 **2**	**2a**		6.1	**2b**		6.7	**2c**		8.0

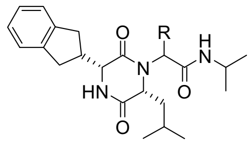
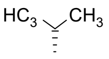
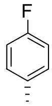
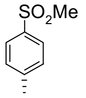
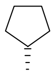
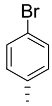
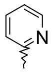
[a] Displacement of ^{3}[H] oxytocin from hOTr by the test compound.[6]

Table 2. Inhibition of the binding of OT with human OT receptor (hOTr)[a] by isomers of compound **3**

		pK_i hOT			pK_i hOT			pK_i hOT
3a *R,R,R*		8.4	**3c** *S,S,S*		<5.7	**3e** *R,S,S* **3f** *R,S,R*		Isomer 1 7.1 Isomer 2 <5.7
3b *R,R,S*		7.3	**3d** *S,S,R*		<5.7	**3g** *S,R,R* **3h** *S,R,S*		Isomer 1 <5.7 Isomer 2 <5.7

[a] Displacement of ^{3}[H] oxytocin from hOTr by the test compound.[6]

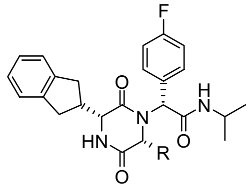
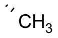
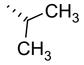
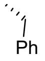
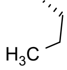
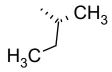
Table 3. Inhibition of the binding of OT with human OT receptor (hOTr)[a] by compounds **4**

		R	pK_i hOT		R	pK_i hOT		R	pK_i hOT
	**4a**[b]		5.5 6.0	**4c**		8.4	**4e**		8.0
	4b[b]		5.5 5.9	**4d**		8.2	**4f**		8.1

[a] Displacement of ^{3}[H] oxytocin from hOTr by the test compound.[6]

[b] Single isomers at 7-position *RRR* and *RRS*.

Table 4. Inhibition of the binding of OT with human OT receptor (hOTr)[a] by compounds **5**

		R	pK_i hOT		R	pK_i hOT		R	pK_i hOT
	**5a**		6.3	**5c**		8.3	**5e**		7.1
	5b		7.7	**5d**		8.6			

[a] Displacement of ^{3}[H] oxytocin from hOTr by the test compound.[6]

tives with small alkyl substituents (**5a–e**) in this position were synthesised (Table 4). The results, together with the isopropyl derivative **4c**, clearly demonstrate that a small branched chain alkyl group was optimal, with the methyl–propyl isomer **5d** affording the greatest level of activity. Increasing the size of the group to benzyl **5e**, identified in the original library deconvolution, resulted in a reduction in potency.

In conclusion, screening of libraries against the oxytocin receptor identified a series of 2,5-diketopiperazine derivatives with moderate levels of potency. Optimisation of the 6-position to an indanyl group and identification of the most potent stereoisomer as *R,R,R* gave compounds with potent activity. Investigation of the 3-position identified the need for a small, branched alkyl substituent for potency. Although the 7-position prefers a directly attached phenyl group for potency, a range of further substitution is allowed in the *para*-position. Studies are underway to optimise the potency, physicochemical properties and pharmacokinetic parameters of this novel class of oxytocin antagonists.

References and notes

1. Mitchell, B. F.; Schmid, B. *J. Soc. Gynecol. Invest.* **2001**, *8*(3), 122.
2. Schwarz, M. K.; Page, P. *Curr. Med. Chem.* **2003**, *10*(15), 1441.
3. Vatish, M.; Thornton, S. *Exp. Opin. Therapeut. Patents* **2002**, *12*(9), 1403.
4. Wyatt, P. G.; Allen, M. J.; Chilcott, J.; Foster, A.; Livermore, D. G.; Mordaunt, J. E.; Scicinski, J.; Woollard, P. M. *Bioorg. Med. Chem. Lett.* **2002**, *12*(10), 1399, and references cited therein.

5. Wyatt, P. G.; Allen, M. J.; Chilcott, J.; Gardner, C. J.; Livermore, D. G.; Mordaunt, J. E.; Nerozzi, F.; Patel, M.; Perren, M. J.; Weingarten, G. G.; Shabbir, S.; Woollard, P. M.; Zhou, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*(10), 1405.
6. Human OT binding assay method see: Wyatt, P. G.; Allen, M. J.; Chilcott, J.; Hickin, G.; Miller, N. D.; Woollard, P. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*(10), 1301.
7. Szardenings, A. K.; Burkoth, T. S.; Lu, H. H.; Tien, D. W.; Campbell, D. A. *Tetrahedron* **1997**, *53*(19), 6573.
8. Hulme, C.; Morrissette, M. M.; Volz, F. A.; Burns, C. J. *Tetrahedron Lett.* **1998**, *39*(10), 1113.
9. Sollis, S. L. A Novel Stereospecific Synthesis of 2,5-Diketopipazines. *J. Org. Chem.* **2005**, *70*, in press.
10. The X-ray crystal structure will be published elsewhere.