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Triazole oxytocin antagonists: Identification of aryl ether replacements for a biaryl substituent

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This paper is dedicated to the memory of Olga Wallace.

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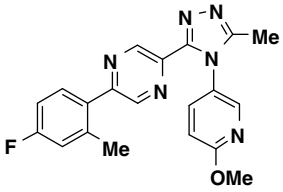
ABSTRACT

Several potent aryl ether/triazole oxytocin antagonists are described. The lead compound in this series had significantly improved aqueous solubility over related systems containing a biaryl substituent.

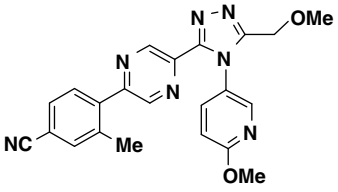
Oxytocin (OT) is a nonapeptide hormone that acts on the OT receptor, a seven-transmembrane (7TM) (Gq-coupled) receptor. The OT receptor has no subtypes. It is, however, related to the vasopressin receptors V_{1A}, V_{1B} and V_2. OT antagonists have therapeutic potential in areas such as pre-term labour,[1] benign prostatic hyperplasia[2] and sexual dysfunction.[3] There is, as a result, significant interest in the identification of potent, selective, orally bioavailable OT antagonists.



1

OT Ki 6 nM; MWt 376; clogP2.9; L.E. 0.41
V_{1A} Ki 388 nM; V_{1B} >10 μM; V_2 Ki > 10 μM
Aqueous solubility: 6 μg/ml at pH7.4[5]

We have recently disclosed **1** and **2**, as potent, selective OT antagonist with oral bioavailability in the rat.[4]



2

OT Ki 14 nM; MWt 413; clogP 1.7; L.E. 0.35
V_{1A} Ki 4.3 μM; V_{1B} >10 μM; V_2 Ki > 10 μM
Aqueous solubility: 24 μg/ml at pH7.2[5]

In following up these compounds, one key issue we were keen to address was the relatively low aqueous solubility[6] typically seen with biaryl triazoles in this series. Based on the assumption that this low solubility was driven in part by the presence of a biaryl substituent,[7] we investigated a number of potential biaryl replacements. Amongst these were a series of ether targets, **3**, designed by putative overlap of **1** and **2** with the previously disclosed[8] OT antagonist **4** (Fig. 1). Encouragingly, our first wave of targets of this type contained a range of potent, highly ligand efficient[9] OT

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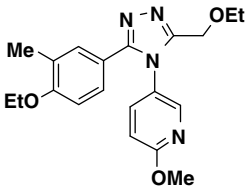
antagonists, as illustrated by compounds **5**–**8** (Fig. 2). These compounds typically had good to excellent selectivity over the related vasopressin receptors.[10] One of these compounds, **6**, was crystalised[5] and shown to have an aqueous solubility of 170 μg/ml at pH 7.4, a 28-fold improvement over biaryl **1**, to which it has a similar lipophilicity.

Subsequent modification of the right-hand side substituent in lead **5** then yielded several sub 100 nM OT antagonists such as compounds **9**–**11** (Fig. 3). Interestingly V_{1A} selectivity was somewhat reduced in these systems, with the 2-triazole substituent , as exemplified by **9**, routinely yielding compounds with (approximately) balanced activity versus OT and V_{1A}. However, small ether substituents, as exemplified by **10** and **11**, resulted in an increase in OT potency whilst allowing good V_{1A} and V_2 selectivity to be maintained. One of these, compound **11,** was also crystalised[5] and fully profiled.

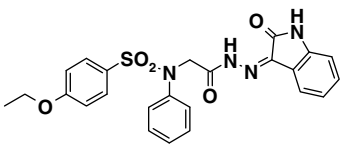
Despite its increased *c*log*P*, **11** also had significantly improved aqueous solubility over that measured for related biaryl analogues, as represented by compounds **1** and **2**. Compound **11** also had reasonable in vitro metabolic stability,[11] and wide ligand profiling showed no significant activity (<30% binding at <1 μM) across a range (>70) of receptors and enzymes. Furthermore, with a ligand efficiency of 0.4, compound **11** represents one of the most ligand efficient OT antagonists reported to date.



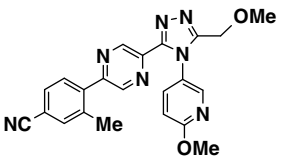
11

OT Ki 28 nM; MWt 367; clogP3.2; L.E. 0.40
V_{1A} Ki 549 nM; V_{1B} > 10 μM; V_2 Ki > 10μM
Aqueous solubility: 344 μg/ml at pH7.4[5]

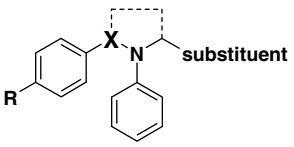
The preparation of compound **11** is described in Scheme 1. Commercially available 4-hydroxy-3-methylbenzoic acid was converted to benzoic hydrazide **12**. Acylation with chloroacetylchloride followed by $POCl_3$ catalysed cyclisation furnished



4: OT Ki 6 nM



2: OT Ki 14 nM



R = Ar, EtO-
X = -SO_2- or C of triazole ring

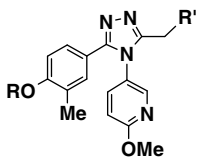


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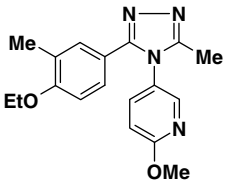
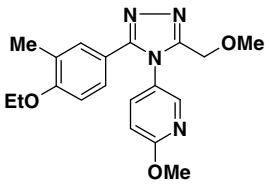
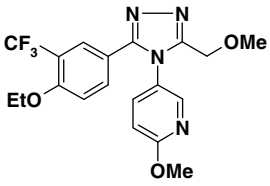
Figure 1. Putative overlap of OT antagonists **2** and **4**, illustrating possible use of ethoxyphenyl substituent as a biaryl replacement in targets **3**.



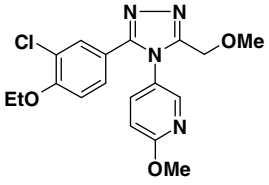
5: OT Ki 143 nM
V_{1A} Ki > 10 μM
V_2 Ki > 10 μM



6: OT Ki 102 nM
V_{1A} Ki 3.8 μM
V_2 Ki > 10 μM
clogP 2.7

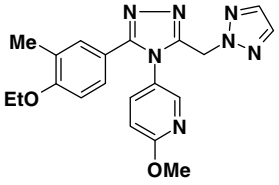


7: OT Ki 190 nM
V_{1A} > 10 μM
V_2 Ki > 10 μM

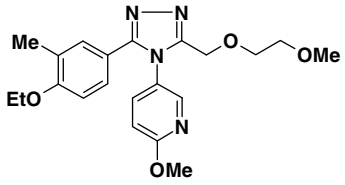


8: OT Ki 114 nM
V_{1A} Ki 2.9 μM
V_2 Ki > 10 μM

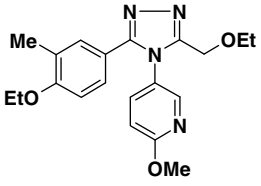
Figure 2. Initial aryl ethers and their OT activity.



9: OT Ki 45 nM
V_{1A} Ki 214 nM
V_2 Ki 1 μM



10: OT Ki 19 nM
V_{1A} Ki 1.7 μM
V_2 Ki 6.4 μM

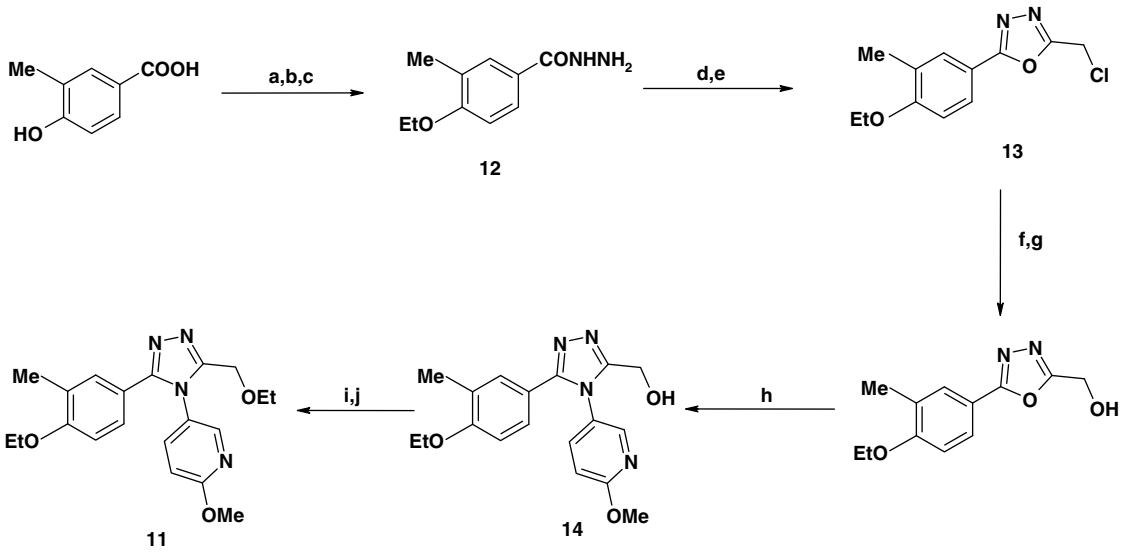


11: OT Ki 28 nM
V_{1A} 594 nM
V_2 Ki > 10μM

Figure 3. OT antagonists with modified right-hand side substituents.

chloromethyloxazole **13** which was in turn converted to the corresponding hydroxylmethyloxazole via its acetate ester. Acid catalysed reaction with 5-amino-2-methoxypyridine then gave triazole **14**, a key project intermediate. Compound **14** was converted to ether **11** following activation with methane sulphonyl chloride and subsequent reaction with sodium ethoxide.[12]

In summary, we have utilized overlap of known OT antagonists to identify aryl ether left-hand side substituents as replacements for biaryl substituents. One such compound, **11**, had significantly improved aqueous solubility and is a selective and potent OT antagonist. Further work in this area will be reported in due course.



Scheme 1. Reagents and conditions: (a) MeOH/cH_2SO_4, 88%; (b) EtI/K_2CO_3/DMF/rt, 82%; (c) NH_2NH_2:H_2O/MeOH/reflux, 70%; (d) $ClCH_2COCl$/*N*-methylmorpholine/DCM, 90%; (e) $POCl_3$ reflux, 68%; (f) KOAc/DMF/rt, 96%; (g) Na_2CO_3/MeOH/H_2O/60 °C/97%; (h) 5-amino-2-methoxypyridine/toluene/*p*-TsOH/reflux, 69%; (i) CH_3SO_2Cl/Me_3N:HCl/DCM/TEA, 42%; (j) Na metal/EtOH/50 °C/54%.

Acknowledgment

We acknowledge the contributions of the following co-workers: Mark Lewis, Simon Pegg and Nicola Robinson.

References and notes

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2. Tiwari, A.; Nanda, K.; Chugh, A. *Expert Opin. Investig. Drugs* **2005**, *14*, 1359.
3. See, for example, WO 2005028452, and the references therein.
4. Brown, A.; Brown, L.; Ellis, D.; Puhalo, N.; Smith, C.; Wallace, O.; Watson, L. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4278.
5. (a) All solubilities described in this paper were measured on fully crystalline material.; (b) All in vitro biological data reported herein represents functional antagonism, as measured against the corresponding cloned human receptor in a cell based β lactamase reporter assay using technology licensed from Rhoto Pharmaceuticals.
6. For a discussion on the solubility requirements of biotherapeutics, see Lipinski, C. A. *J. Pharmacol. Toxicol. Methods* **2000**, *44*, 235.
7. For an example of solubility increasing with replacement of a biaryl substituent, see: (a) Neff, D. K.; Lee-Dutra, A.; Blevitt, J. M.; Axe, F. U.; Hack, M. D.; Buma, J. C.; Rynberg, R.; Brunmark, A.; Karlsson, L.; Breitenbucher, J. G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6467; b Examination of the crystal packing in small molecule X-ray structures of a range of biaryls in this series (including **1** and **2**) revealed a range of quite different stacking interactions involving the biaryl substituent(s). We are therefore unable to offer a unifying explanation for the poor solubility of biaryl compounds of this type. However, our general experience in this programme has been that replacement of a biaryl substituent with a range of alternative substituents generally resulted in a significant jump in aqueous solubility for a given lipophilicity. Data for additional bioisosteres will be disclosed in forthcoming publications.
8. Quattropani, A.; Dorbais, J., et al *J. Med. Chem.* **2005**, *48*, 7882.
9. Hopkins, A. L.; Groom, C. R.; Alex, A. *Drug Discov. Today* **2004**, *9*, 430.
10. All of the compounds herein described had no significant binding (<20%) to the V_{1B} receptor at 10 μM.
11. Profiling of **11** in an in vitro Human Liver Microsome assay gave a Clint of 12 μl/min/mg. In house experience suggested that this value was consistent with good to moderate stability towards Cytochrome P450 oxidation.
12. Spectroscopic data for compound **11** as follows: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.20 (t, 3H), 1.40 (t, 3H), 2.20 (s, 3H), 3.50 (q, 2H), 4.00 (m, 5H), 4.50 (s, 2H), 6.70 (d, 1H), 6.80 (d, 1H), 7.10 (d, 1H), 7.40 (s, 1H), 7.50 (d, 1H), 8.20 (s, 1H). Mass Spectroscopy (APCI+): *m*/*z* 369 [MH^+].