Bioorganic & Medicinal Chemistry Letters 18 (2008) 4278–4281

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Design and optimization of potent, selective antagonists of Oxytocin

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ARTICLE INFO

Article history:
Received 9 June 2008
Revised 25 June 2008
Accepted 28 June 2008
Available online 3 July 2008

This paper is dedicated to the memory of Olga Wallace.

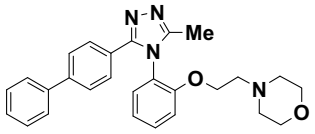
Keywords:
Oxytocin
Antagonist
Triazole

ABSTRACT

A novel series of Oxytocin antagonists are described. This series was identified through pharmacophoric overlap of in-house and literature antagonists. Subsequent optimization led to a series of potent, selective antagonists. Several analogues displayed oral bioavailability in vivo in the rat.

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 but is related to the vasopressin receptors V_{1A}, V_{1B} and V_2. OT antagonists have therapeutic potential in a number of areas including pre-term labour:[1] Benign Prostatic Hyperplasia[2] and sexual dysfunction.[3] As a result there is significant interest in the identification of potent, selective, orally bioavailable OT antagonists.

Several templates have been investigated in the search for potential OT antagonists, as represented by such compounds as sulphonamide **1**,[4] piperidine amide **2**,[5] diketopiperazine **3**[6] and oxime **4**[7] (Scheme 1). The latter compound is particularly noteworthy as it represents one of the most (heavy atom) ligand efficient OT antagonists reported to date.[8] In addition, high throughput screening (HTS) of the Pfizer file identified triazole **5** as a possible starting point in our quest for a potent, selective OT antagonist.[9] In fact, **5** has been previously disclosed as a selective antagonist for the V_{1A} receptor.[10] We were unaware of its OT activity until it was fully profiled in HTS follow-up.



5
OT Ki 304nM; V1A Ki 28nM; MWt 440, cLogP 5.1; L.E. 0.28

The fact that **5** is inversely selective for OT over V_{1A} makes it considerably less attractive as a starting point for the design of OT selective antagonists. This and several other key issues had to be addressed if this hit were to yield an attractive lead series. Specifically, to increase our chances of achieving an acceptable oral pharmacokinetic profile, potency and ligand efficiency (L.E.) had to be improved and it was likely that inherent lipophilicity had to be reduced.[11] Comparison of antagonists **4** and **5**, as well as other HTS actives suggested a simple OT pharmacophore, as depicted in Scheme 2. Direct comparison of oxime **4** and triazole **5** using this analysis suggested simplification of hit **5** to compounds such as **6**. This compound was prepared and shown to have slightly improved OT antagonist potency but with significantly reduced molecular weight, and hence greatly superior ligand efficiency.

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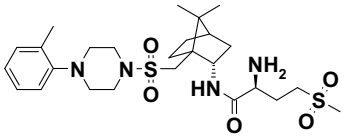
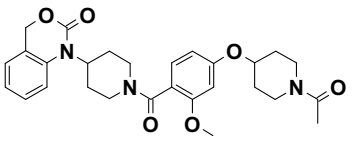
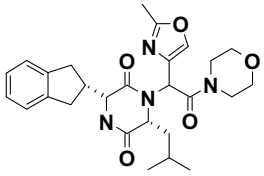
doi:10.1016/j.bmcl.2008.06.098



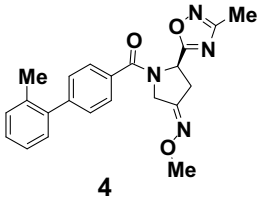
1
OT Ki 8nM
MWt 555
L.E. 0.31



2
OT Ki 20nM
MWt 507
L.E. 0.29

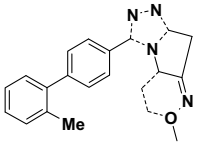


3
OT Ki 3nM
MWt 495
L.E.0.33

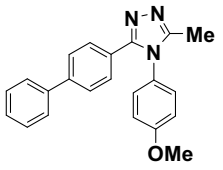


4
OT Ki 50nM
MWt 376
L.E. 0.36

Scheme 1. Representation of published OT antagonists with calculated heavy atom ligand efficiencies (L.E.).



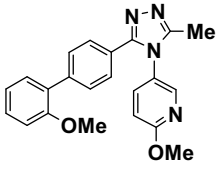
Scheme 2. OT pharmacophore overlay based on compounds **4** and **5**.



6

OT Ki 143nM; MWt 341, clogP 5; LE 0.36

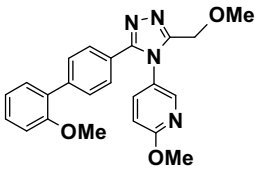
Closer inspection of our pharmacophoric overlap model suggested incorporation of a pyridyl N in **6** (overlapping with the oxime N of **4**), as well as incorporation of an ortho substituent in the biaryl substituent. These changes gave compound **7**, where OT antagonism had increased further, whilst lipophilicity had been reduced by 1.8 log units. Selectivity profiling of this compound revealed a somewhat improved profile with respect to V_{1A} antagonism. However, significant (antagonist) activity against V_2 receptors was also observed. No activity was observed against V_{1B}.[12] Nonetheless, the potency, (low) lipophilicity and excellent ligand efficiency of compound **7** encouraged us to focus on this lead series. We thus set about optimising potency, selectivity and pharmacokinetic properties.



7

OT Ki 56nM; MWt 372; clogP 3.2; L.E. 0.36
V_{1A} Ki 525nM; V_{1B} >10uM; V_2 Ki 500nM

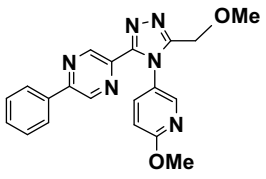
Exploration of SAR around the C5 (methyl) triazole substituent of **7** identified methoxymethyl as a substituent which typically gave ca. 3× improvement in OT potency. However, incorporation of this substituent also (typically) resulted in a slight reduction in selectivity over V_2, as demonstrated by compounds such as **8**.



8

OT Ki 16nM; MWt 402; clogP3.4; L.E. 0.36
V_{1A} Ki 270nM; V_{1B} >10uM; V_2 Ki 160nM

Replacement of the central aryl of the C3 biaryl triazole substituent with a pyrazine, as in compound **9**, gave a significant reduction in V_2 antagonism. In addition, this modification routinely gave a >1 log unit reduction in clog*P*, which we believe would be potentially beneficial in terms of optimising metabolic stability and aqueous solubility.[13]

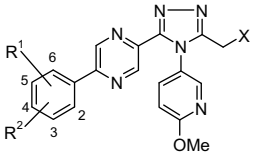


9

OT Ki 43nM; MWt 374; clogP2.1; L.E. 0.37
V_{1A} Ki 44nM; V_{1B} >10uM; V_2 Ki > 10uM

We next switched our attention to the optimisation of the left-hand side aryl substituent in **9**. The compounds described in Table 1 illustrate three key SAR points for this region of our OT antagonists:

Table 1
LHS aryl SAR

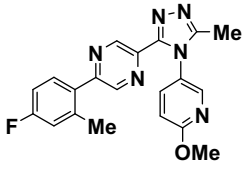


Compound	R^1	R^2	X	K_i (nM)		
				OT	V_{1A}	V_2
9	H	H	$-OCH_3$	43	44	>10,000
10	2-CH_3	3-CH_3	$-OCH_3$	4	132	103
11	3-CH_3	4-F	$-OCH_3$	17	1220	>10,000
12	3-CN	H	$-OCH_3$	84	3230	>10,000
13	2-CH_3	4-F	H	6	388	>10,000
14	2-Cl	H	H	2	202	n.t.[a]
15	2-CH_3	4-CH_3CH_2S–	H	232	n.t.[a]	>10,000
16	3-CH_3	4-CH_3O–	$-OCH_3$	537	2410	>10,000
17	2-CH_3	4-CN	$-OCH_3$	14	4300	>10,000
18	3-CH_3	4-CH_3	$-OCH_3$	201	432	>10,000
19	2-Cl	3-F	H	1	732	n.t.[a]

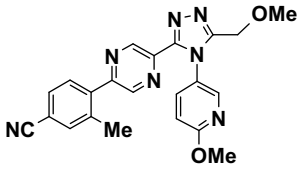
[a] n.t., not tested.

(1) Highly potent compounds typically carry two substituents such as methyl and chloro (e.g., compounds **10**, **13, 14** and **19**).
(2) Electron-withdrawing substituents in the 3 or 4 position typically result in a drop in V_{1A} activity (e.g., compounds **9** vs **12** and compounds **14** vs **19**).
(3) Larger four substituents (beyond Fluoro and Cyano) result in a drop in OT potency (e.g., compounds **13** vs **15** and compounds **16** and **18**).

Compounds **13** and **17** emerged from this analysis as our most promising OT antagonist from this series.



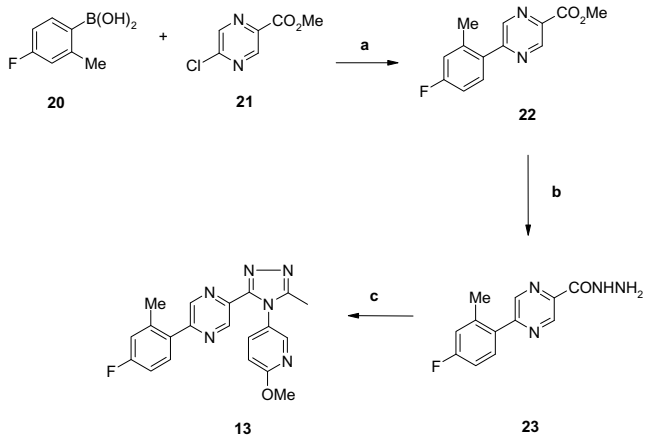
13
OT Ki 6nM; MWt 376; clogP2.9; L.E. 0.41
V_{1A} Ki 388nM; V_{1B} >10uM; V_2 Ki > 10uM



17
OT Ki 14nM; MWt 413; clogP1.7; L.E. 0.35
V_{1A} Ki 4.3uM; V_{1B} >10uM; V_2 Ki > 10uM

Compounds **13** and **17** were then subjected to wider profiling. Although they displayed relatively low solubilities[14] both displayed promising pharmacokinetic profiles in the rat.[15] In addition, wide ligand profiling of **13** and **17** showed no significant activity (<50% binding at <3 μM) across a range (>70) of receptors and enzymes.[16]

The preparation of compound **13** is described in Scheme 3. Commercially available boronic acid **20** underwent smooth Suzuki coupling[17] with commercial chloropyrazine **21**. Hydrazinolysis was then followed by a two-step/one-pot conversion to **13**.[18]



Scheme 3. Reagents and conditions: (a) Pd(0) catalyst,[17] Cs_2CO_3, Dioxan, reflux, 2 h, quant; (b) NH_2NH_2, ethanol, reflux, 15 h, 80%; (c) i—dimethoxyacetamidedimethylacetal, AcOH, 60 °C, 3 h; ii—5-amino-2-methoxypyridine, AcOH, 100 °C, 6 h; iii—recrystallisation, 30% overall for step c.

In summary, we have utilised pharmacophoric overlap of a high throughput screening hit and published OT antagonists followed by subsequent optimisation to yield several potent, selective Oxytocin antagonists. Two of these compounds displayed promising pharmacokinetic profiles in the rat and represent potential tools for further preclinical investigation of the therapeutic potential of OT antagonism. Further development of this series will be reported in due course.

Acknowledgments

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

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9. All 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.
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11. See for example Leeson, P. D.; Springthorpe, B.*Nat. Rev. Drug Disc.* **2007**, *6*, 881–890. and the references therein.
12. In fact, no significant V_{1B} activity was detected (at 10 μM) for any of the compounds screened in the series disclosed in this letter.
13. Subsequent analysis across this series suggested that there was indeed a greater probability of achieving improved in vitro metabolic stability at lower clog *P*.
14. Aqueous solubilities measured for compounds **13** and **17** were 6 μg/ml at pH 7.4 and 24 μg/ml at pH 7.2, respectively; solubilities measured on fully crystalline material.
15. Rat PK parameters were as follows. (a) Compound **13**: oral pharmacokinetics (dose: 0.5 mg/kg of a crystalline suspension)—Cl 50 ml/min/kg; *T*1/2 1 h; F

24%. Iv pharmacokinetics (1 mg/kg bolus dose)—Cl 48 ml/min/kg. (b) Compound **17**: oral pharmacokinetics (dose 2 mg/kg of a crystalline suspension) Cl 28 ml/min/kg; *T*1/2 0.7 h; F 30%. Iv pharmacokinetics (2 mg/kg, bolus dose)—Cl 28 ml/min/kg.

16. Representative examples of (off target) pharmacology targets against which **13** and **17** were profiled: Angiotensin Converting Enzyme; human Cyclooxygenase 2 enzyme; human 5-HT1A receptor; human Endothelin A and B receptors; human Cannabinoid 1 and 2 receptors; hERG Potassium channel.
17. See Bedford, R. B.; Cazin, C. S. J. *Chem. Commun.* **2001**, 1540–1541. Suzuki catalyst 3 from this paper was utilised in this coupling. More generally, this catalyst was successfully utilised in a wide range of related Suzuki couplings in this series.
18. Spectroscopic data for compound **13** are as follows: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.39 (s, 3H), 2.41 (s, 3H), 4.01 (s, 3H), 6.89 (d, 1H), 6.95–7.03 (m, 2H), 7.33 (dd, 1H), 7.54 (dd, 1H), 8.09 (d, 1H), 8.38 (d, 1H), 9.49 (d, 1H). Mass Spectroscopy (APCI+): *m*/*z* 377 [MH^+].