Bioorganic & Medicinal Chemistry Letters 19 (2009) 528–532

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Discovery and optimisation of a potent and selective tertiary sulfonamide oxytocin antagonist

Nicholas P. Barton [a], Benjamin R. Bellenie [a], Andrew T. Doran [a], Amanda J. Emmons [a], Jag P. Heer [a,*], Cristian M. Salvagno [b]

[a] GlaxoSmithKline Pharmaceuticals, New Frontiers Science Park (North), Coldharbour Road, Harlow, Essex CM19 5AD, England, UK
[b] GlaxoSmithKline S.p.A., Medicines Research Centre, Via Fleming 2, Verona, Italy

ARTICLE INFO

Article history:
Received 13 October 2008
Revised 5 November 2008
Accepted 7 November 2008
Available online 12 November 2008

Keywords:
Oxytocin
Pharmacophore
HTS

ABSTRACT

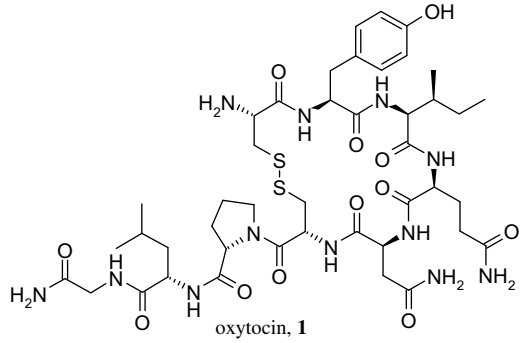
The optimisation of a tertiary sulfonamide high-throughput screening hit is described. A combination of high-throughput chemistry, pharmacophore analysis and in silico PK profiling resulted in the discovery of potent sulfonamide oxytocin receptor antagonists with oral exposure and good selectivity over vasopressin receptors.

Oxytocin, **1** is a peptide hormone acting on the G protein-coupled oxytocin receptor which modulates numerous physiological roles including the control of uterine contractions.[1–3] Antagonism of the oxytocin receptor is a potential treatment for threatened pre-term birth and has been clinically validated by the peptidic antagonist atosiban, **2,** administered by iv infusion.[4] A small molecule, orally administered oxytocin receptor antagonist is an attractive next generation therapeutic agent (Fig. 1).

High-throughput screening of the GSK compound collection identified the tricyclic quinolinone, **3** as a moderately potent oxytocin receptor antagonist with good selectivity against the related V1a vasopressin receptor but poor solubility and bioavailability.[5] A related, high molecular weight, oxytocin receptor antagonist **4** with in vivo activity has been reported by Serono Pharmaceutical Research Institute.[6] Our aim was to optimise the potency, solubility and oral bioavailability of **3** without significantly increasing molecular weight (<500) (Fig. 2).

Chemistry (Scheme 1) was carried out to find novel isosteres for the tricyclic quinolinone group of **3**.

The moderately potent compounds **5–8** (Table 1) were identified in a fluorescence polarisation binding assay.[5] All the tricyclic quinolinone replacements (R1, Table 1) contained a distal phenyl ring and were derived from commercially available heterocyclic biaryl aldehydes (Scheme 1). Further rounds of high-throughput chemistry with templates derived from these aldehydes failed to improve potency.



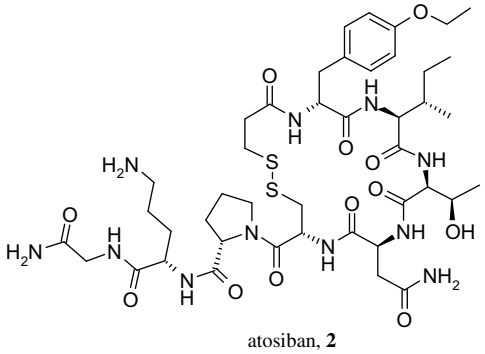
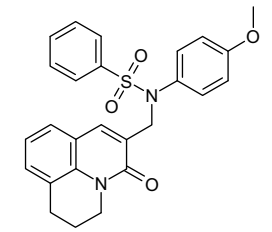


Figure 1. Structures of oxytocin and atosiban.

* Corresponding author.
E-mail address: Jag_P_Heer@gsk.com (J.P. Heer).

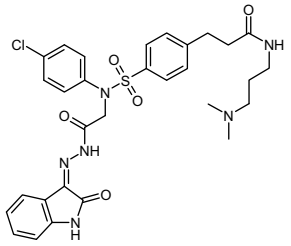
0960-894X/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2008.11.018



3

OT fpKi = 6.7
V1a fpKi < 5
Molecular weight = 460

Solubility < 1 ug/mL
Fpo = 4%

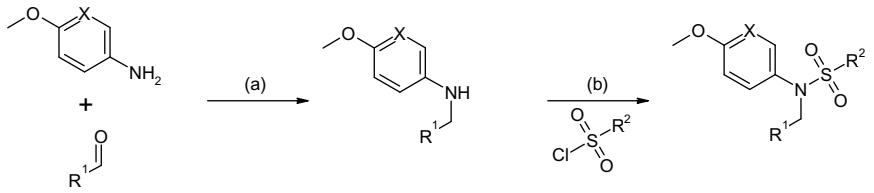


4

OT Ki = 0.65 nM
V1a Ki = 42 nM
Molecular weight = 624

Inhibition of rat uterine contractions:
72% @10 mg/kg(iv) (non-pregnant)
35% @30 mg/kg(po)(non-pregnant)
30% @30 mg/kg(po) (late-term pregnant)

Figure 2. Tertiary sulfonamide oxytocin receptor antagonists.

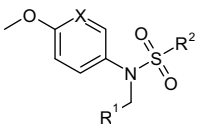


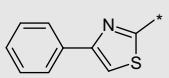
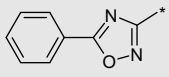
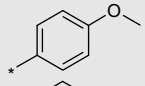
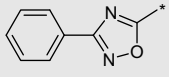
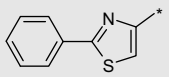
Scheme 1. Reagents and conditions: (a) i—Na_2SO_4, DCM, 100 °C, 10 min (sealed microwave vial); ii—$NaBH_4$, DCM/MeOH, rt, 1 h (yield 60–95%); (b) pyridine, rt, 1 day then 150 °C, 10 min (yield 40–90%).

A pharmacophore based on known active oxytocin receptor antagonists **9** and **10** (Figs. 3 and 4) was generated in an attempt to overcome the potency plateau without increasing molecular weight.[7,8]

Mapping compounds **5–8** to the pharmacophore in Figure 4 (Fig. 5) suggested poor alignment of the biaryl unit to the plane of the indane aromatic element.

Table 1
SAR from optimisation of **3**.



Compound	R^1	R^2	X	OT pK_i
5			N	7.4
6			N	7.4
7			N	7.2
8			CH	7.2

Sulfonamide **11** (Fig. 6), containing a biaryl motif similar to that found in **9**, showed better pharmacophore alignment but binding affinity did not improve (Table 2). Presumably this was due to lack of conformational rigidity compared to **9**.

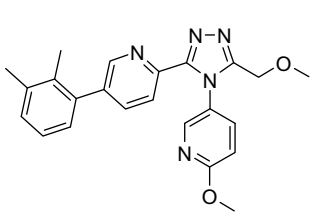
The pharmacophore maps the biaryl fragment as a plane aromatic (distal phenyl) and hydrogen bond acceptor (pyridine) (Fig. 7). The model requires the vectors of the pyridine and distal phenyl ring to adopt a non-co-planar arrangement (45 deg from co-planar). Compounds **12–15** were prepared (Scheme 2) to increase conformational rigidity, preventing the rings adopting a co-planar arrangement.

This strategy resulted in the discovery of potent compounds (Table 2). Compounds were profiled in binding and functional assays to confirm functional antagonism and selectivity.[5]

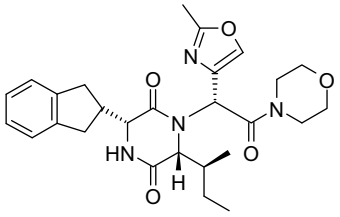
Selectivity against V1a was poor but the functional potencies of **13** and **14** were encouraging and PK (pharmacokinetic) profiling was carried out (Table 3). Both compounds had relatively poor CYP (cytochrome P450 enzyme) profiles and poor solubility, resulting in low oral exposure.

The serious PK shortcomings were tackled by in silico profiling. Our efforts targeted the aryl sulfonamide because pharmacophore analysis (Fig. 7) suggested only the sulfonamide oxygen atoms are required as hydrogen bond acceptors. The phenyl ring can be replaced to optimise 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 (Table 4).

Only the compounds with low *c*log$D_{7.4}$ (calculate log distribution coefficient at pH 7.4), the imidazole sulfonamides **21** and **22**, were predicted to have good solubility and improved CYP profiles. Measured solubility and CYP inhibition of **21** and **22** were



9



10

Figure 3. Antagonists used in pharmacophore generation.

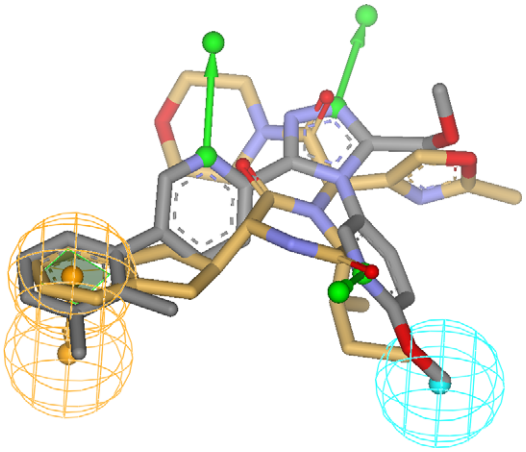


Figure 4. Consensus pharmacophore derived for compounds **9** (grey) and **10** (gold). Key elements of note include two hydrogen bonding acceptors (green arrows) mapped on pyridines of **9** and diketopiperazine amide carbonyl groups of **10**, a plane aromatic (bronze spheres) mapped on the phenyl group of **9** and indane group of **10**, a small hydrophobe (cyan spheres) based on pyridine methoxy group of **9** and the sec-butyl group of **10** and a hydrogen bonding acceptor (green arrow) mapped to the triazole of **9** and the morpholine amide carbonyl group of **10.**

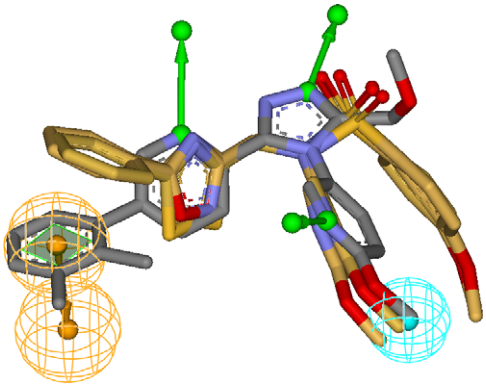


Figure 5. Pharmacophoric alignment of **5**–**8** (in gold) and **9**.

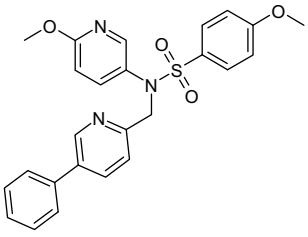
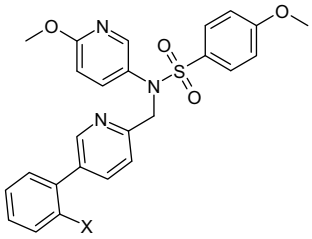


Figure 6. Structure of sulfonamide **11**.

Table 2
Selectivity SAR for tertiary sulfonamides.



Compound	X	OT pK_i	OT fpK_i (FLIPR)	V1a fpK_i (FLIPR)	V1b fpK_i (FLIPR)	V2 fpK_i (Yeast)
11	H	6.9	–	–	–	–
12	CN	8.0	8.2	7.3	Inactive	6.3
13	Cl	7.9	8.5	7.6	Inactive	5.9
14	Me	8.1	8.7	7.8	Inactive	6.6
15	F	8.2	8.1	7.3	Inactive	7.2

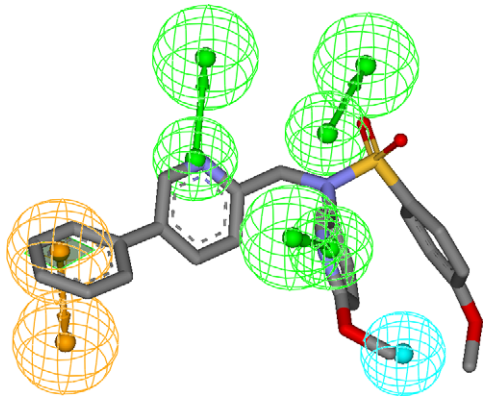
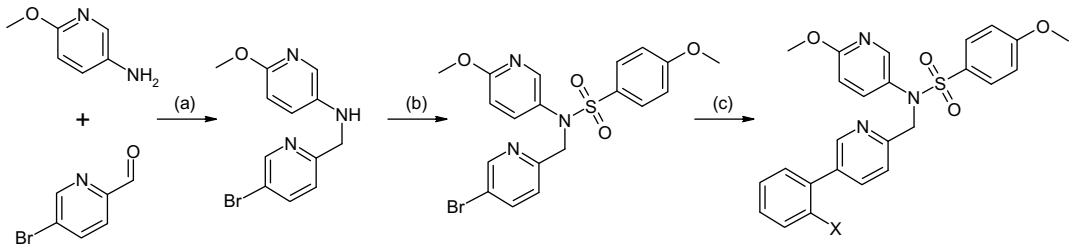


Figure 7. Pharmacophoric alignment of **11**.

better than **13** and **14** in agreement with in silico profiling (Table 5). The oral bioavailability was determined for **21** and found to be superior to **13** and **14**.

Selectivity profiles for **21** were determined in functional assays and in lower throughput filtration binding assays.[9] A significant improvement in selectivity was achieved (Fig. 8).

In summary, the moderately potent tricyclic quinolinone **3** has been optimised to give a highly potent tertiary sulfonamide antagonist **21** with encouraging PK properties using a combination of high-throughput chemistry, pharmacophore analysis and in silico profiling. Data generated for **21** met requirements for hit to lead transition.



Scheme 2. Reagents and conditions: (a) i—Na_2SO_4, DCM, 100 °C, 10 min; ii—$NaBH_4$, DCM/MeOH, rt, 1 h (yield 84%); (b) 4-MeO-Benzenesulfonyl chloride, pyridine, rt, 1 day then 150 °C, 10 min (yield 92%); (c) 2-X-Phenylboronic acid, Na_2CO_3, DME:H_2O:EtOH (7:3:2), $Pd(PPh_3)_4$, 140 °C, 5 min (yield 62–93%).

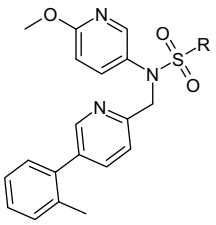
Table 3
PK profiles of potent tertiary sulfonamides.

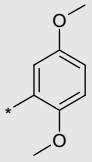
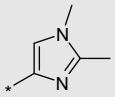
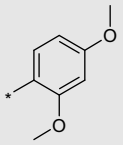
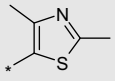
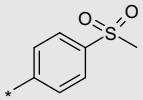
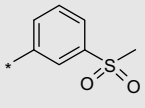
Compound	**13**	**14**
Solubility (μM)	9	6
CYP (μM)		
1A2	>33	>33
2C9	0.52	0.81
2C19	0.45	0.69
2D6	>33	>33
3A4 (DEF)	0.75	0.71
3A4 (7BQ)	2.2	2.1
Fpo (%)	12	9

Table 5
Optimised PK profiles of potent tertiary sulfonamides.

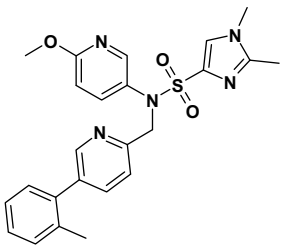
Compound	**21**	**22**
Solubility (μM)	259	214
CYP (μM)		
1A2	18	19
2C9	6.7	0.78
2C19	13	25
2D6	31	29
3A4 (DEF)	1.3	2.8
3A4 (7BQ)	4.8	>33
Fpo (%)	40	—

Table 4
Sulfonamide SAR.



Compound	R	OT pK_i	logD^a	Compound	R	OT pK_i	logD^a
16		8.8	3.7	**21**		7.9	1.0
17		8.6	3.6	**22**		7.9	0.9
18		8.4	2.3	**23**		7.9	2.7
19		8.2	2.5	**24**		7.9	2.9
20		8.0	3.3	**25**		7.9	2.6

[a] *c*log$D_{7.4}$ determined by ACD V8.0.



21

Functional Assays:	
OT (FLIPR) fpKi	8.3
V1a (FLIPR) fpKi	6.1
V1b (FLIPR) fpKi	inactive
V2 (Yeast) fpKi	6.5
Filtration Binding Assays:	
OT pKi	9.1
V1a pKi	7.2
V1b pKi	7.5
V2 pKi	4.9

Figure 8. Selectivity profile of orally bioavailable sulfonamide.

Acknowledgment

The authors acknowledge the contribution of Blaise Bridier to the preparation of example compounds.

References and notes

1. Gimpl, G.; Fahrenholz, F. *Physiol. Rev.* **2001**, *81*, 629.
2. Borthwick, A. D. *Annu. Rep. Med. Chem.* **2006**, *41*, 409.
3. Stubbs, T. M. *Clin. Obstet. Gynaecol.* **2000**, *43*, 489.
4. Tsatsaris, V.; Carbonne, B.; Cabrol, D. *Drugs* **2004**, *64*, 375.
5. Functional vasopressin (V1a/V1b) and oxytocin receptor antagonism (fpK_i) was determined in functional FLIPR assays using recombinant human oxytocin or vasopressin (V1a/V1b) receptors stably transfected in CHO cells. Functional vasopressin V2 receptor antagonism (fpK_i) was determined in functional FLIPR assays using recombinant human vasopressin V2 receptors stably transfected in yeast cells. Oxytocin receptor binding (pK_i) was determined by fluorescence polarisation (FP) using recombinant human oxytocin receptors stably transfected in CHO cells and Bodipy TMR-oxytocin obtained from Perkin Elmer.
6. Quattropani, A.; Dorbais, J.; Covini, D.; Pittet, P.; Colovray, V.; Thomas, R. J.; Coxhead, R.; Halazy, S.; Scheer, A.; Missotten, M.; Ayala, G.; Bradshaw, C.; De Raemy-Schenk, A.; Nichols, A.; Cirillo, R.; Tos, E. G.; Giachetti, C.; Golzio, L.; Marinelli, P.; Church, D. J.; Barberis, C.; Chollet, A.; Schwarz, M. K. *J. Med. Chem.* **2005**, *48*, 7882.
7. Compound **9**: Brown, A. D.; Ellis, D.; Smith, C. R. U.S. Patent 7,291,640.
8. Compound **10**: Liddle, J.; Allen, M. J.; Borthwick, A. D.; Brooks, D. P.; Davies, D. E.; Edwards, R. M.; Exall, A. M.; Hamlett, C.; Irving, W. R.; Mason, A. M.; McCafferty, G. P.; Nerozzi, F.; Peace, S.; Philp, J.; Pollard, D.; Pullen, M. A.; Shabbir, S. S.; Sollis, S. L.; Westfall, T. D.; Woollard, P. M.; Wu, C.; Hickey, D. M. B. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 90.
9. Filtration binding was determined by displacement of 3H-oxytocin from recombinant human oxytocin receptors stably transfected in CHO cells.