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Triazole oxytocin antagonists: Identification of an aryloxyazetidine replacement for a biaryl substituent

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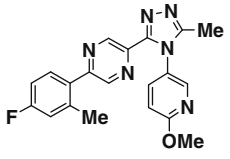
ABSTRACT

A series of aryloxyazetidines, aryloxypyrrolidines and aryloxypiperidines were designed based on structural overlap with previously reported arylpyrazine Oxytocin antagonists. Similarly high levels of Oxytocin antagonism were achievable in these new series. Several aryloxyazetidines also showed high levels of selectivity, with one compound, **25**, displaying promising in vivo pharmacokinetics and significantly improved aqueous solubility over related compounds containing a biaryl substituent.

Oxytocin (OT) is a cyclic 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.

We have previously disclosed[4] arylpyrazinyltriazole **1**, a potent OT antagonist that has an attractive in vivo pharmacokinetic profile in the rat. Compound **1** shows excellent selectivity both against a wide range of unrelated targets[4] and specifically against the V_{1B} and V_2 receptors. Selectivity against the V_{1A} receptor (~65-fold) is also reasonable but falls short of the 100-fold window that we typically set ourselves for potential clinical candidates. In addition, compound **1** also suffers from relatively low aqueous solubility.[5]



1

OT Ki 6nM; MWt 376; clogP2.9; L.E. 0.41
V_{1A} Ki 388nM; V_{1B} >10uM; V_2 Ki > 10uM
Aqueous solubility 6μg/ml at pH 7.4

As part of our efforts to follow-up **1**, we targeted close-in analogues in which we hoped to maintain the attractive features of this compound whilst further improving both selectivity over the V_{1A} receptor and aqueous solubility.

Experiences in the arylpyrazine series that yielded compound **1** suggested that key OT/V_{1A} potency/selectivity interactions were made by the left hand side (LHS) 4-fluoro-2-methylphenyl substituent of this compound. We therefore set out to design analogues where:

(a) The trajectory of our LHS aryl substituent would be very similar to that in compound **1**.
(b) The physicochemistry of our targets (specifically number of heavy atoms/molecular weight and *c* log *P*) would be similar to **1**.[6]
(c) In an attempt to improve aqueous solubility, the LHS arylpyrazine of **1** would be replaced by a non-biaryl substituent.[7]

Overlap of minimised conformation(s) with **1** suggested targets **2**–**4** (Fig. 1).[8] A range of analogues of this type were therefore prepared and profiled (Table 1).[9]

Several key SAR points emerged from this set of compounds:

Good levels of OT potency and V_2 selectivity could be obtained in all three series (e.g, compounds **9**, **16** and **25**).

SAR across the three series was broadly similar. Specifically

(i) Incorporation of an 2-chloro or 2-methyl on the LHS aryl substituent gave a significant increase in OT activity but was also typically accompanied by an increase in V_{1A} activity (e.g., compare compounds **5** and **6**; **11** and **12**; **18** and **19**).

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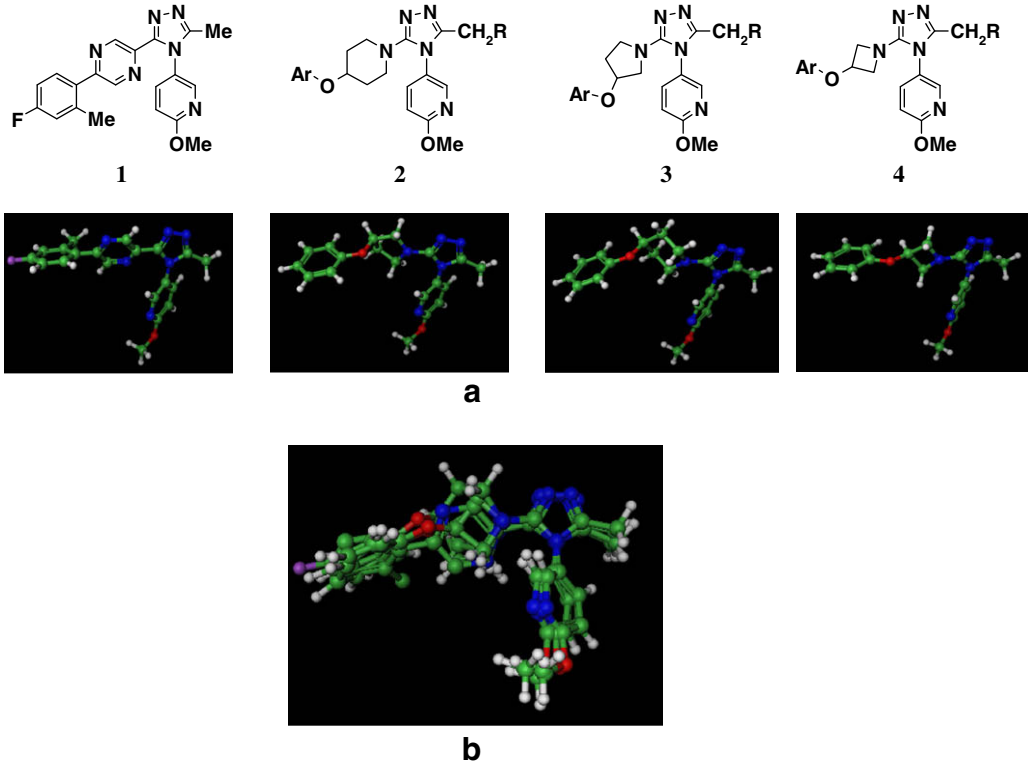
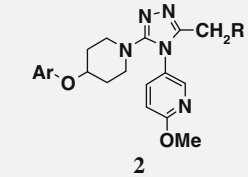
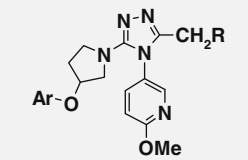


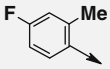
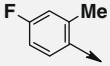
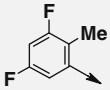
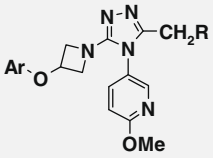
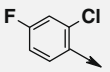
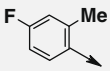
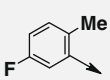
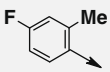
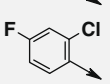
Figure 1. (a) Related local minimum conformations of **1**, **2**, **3** and **4**. [Ar = Ph and R = H shown for illustrative purposes], (b) superimposed representation of these local minimum conformations, illustrating the closely related left hand side aryl group orientations in these systems.

Table 1
Key data for a range of analogues **2**–4

Ar	R	Compound	OT K_i (nM)	V_{1A} K_i (nM)	V_2 K_i (nM)	*c* log *P*	HLM CI[a]
							
	H	**5**	114	127	>10,000	2.9	n.t.[b]
	H	**6**	5.4	21.6	>10,000	3.5	n.t.[b]
	H	**7**	4.2	111	>10,000	3.7	23
	H	**8**	2.6	n.t.[b]	>10,000	3.7	24
	H	**9**	0.4	175	>10,000	3.9	n.t.[b]
	–OMe	**10**	2.2	24.4	>10,000	2.7	n.t.[b]
							

(*continued on next page*)

Table 1 (*continued*)

Ar	R	Compound	OT K_i (nM)	V_{1A} K_i (nM)	V_2 K_i (nM)	*c* log *P*	HLM Cl[a]
	H	**11**[c]	170	1840	>10,000	3.2	n.t.[b]
	H	**12**[c]	35.9	734	>10,000	3.4	32
	H	**13**[c]	31.8	941	>10,000	3.7	95
	–OMe	**14**[c]	28.5	255	>10,000	2.9	n.t.[b]
	–OMe	**15**[c]	17.9	586	>10,000	3.2	>440
	–OMe	**16**[c]	5.8	1000	>10,000	3.4	107
	–OMe	**17**[d]	207	522	>10,000	2.9	n.t.[b]
			 **4**				
	H	**18**	304	>10,000	>10,000	2.8	<7.0
	H	**19**	55.1	1940	>10,000	3.5	n.t.[b]
	–OMe	**20**	32.5	1340	>10,000	3.0	21
	H	**21**	28.4	2430	>10,000	3.7	22
	H	**22**	17.5	608	>10,000	3.6	n.t.[b]
	H	**23**	40	1680	2770	3.6	n.t.[b]
	–OMe	**24**	18.4	719	1190	3.1	n.t.[b]
	–OMe	**25**	9.5	1120	>10,000	3.2	10

[a] Human liver microsome intrinsic clearance value in μL/min/mg.
[b] Not tested.
[c] (*R*)-enantiomer.
[d] (*S*)-enantiomer.

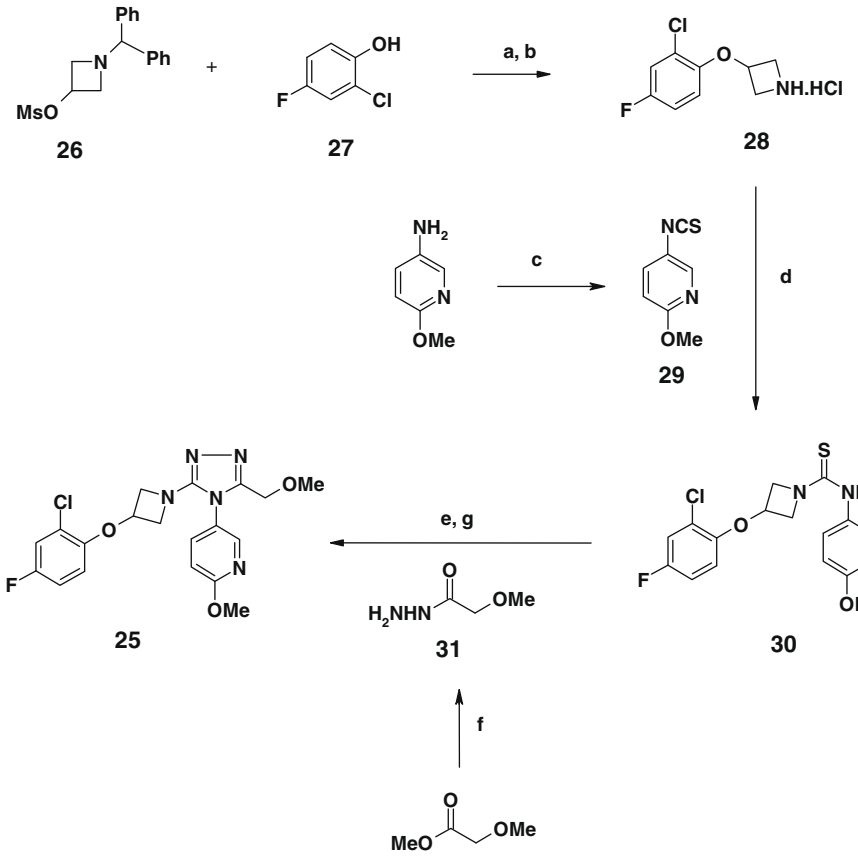
(ii) Additional incorporation of a 3, 4 or 5-fluoro on the LHS aryl substituent gave a further increase in OT potency. This was typically accompanied by a slight drop off in V_{1A} activity, leading to compounds with significantly improved selectivity (e.g., compare compounds **6** and **9**; **17** and **16**; **19** and **21**).

(iii) Incorporation of a methoxy right hand side substituent (R = H to R = MeO) typical led to a slight increase in OT potency (e.g, compare compounds **6** and **10**; **13** and **15**; **19** and **20**).

Table 2
Oral pharmacokinetic data for compounds **25** and **1**

Compound	Species	Cl (mL/min/kg)	$T_{1/2}$ (h)	*Vd* (L/Kg)	*F*[a] (%)
25	Rat[b,c]	36	0.9	2.5	62
25	Dog[b,c]	8	1.9	1.3	81
1	Rat[d,c]	50	1.0	4.4	24

[a] Oral bioavailability, measured by comparison with iv pharmacokinetic data (not shown).
[b] Doses were 2 mg/Kg and 0.2 mg/Kg for rat and dog, respectively.
[c] Both studies were carried out using a suspension of fully crystalline material.
[d] Dose 0.5 mg/Kg.

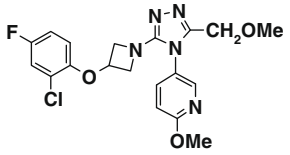


Scheme 1. Synthesis of compound **25**. Reagents and conditions: (a) K_2CO_3, CH_3CN, reflux, quant; (b) (i) $CH_3(Cl)CHOCOCl$, Et_2NPr^i, CH_2Cl_2, reflux, (ii) MeOH, reflux, 62%; (c) thiocarbonyldiimidazole, THF, quant; (d) *N*-methylmorpholine, CH_2Cl_2, 0–25 °C, quant; (e) $KOBu^t$, methyl *p*-toluenesulfonate THF; (f) NH_2NH_2, methanol, reflux, quant; (g) THF, CF_3CO_2H, reflux, 56% (for steps e and g).

In the pyrrolidine series, **3**, the (*R*)-enantiomers prepared were typically more potent than the corresponding (*S*)-enantiomers (compare compounds **14** and **17**).[10]

Of the three series, azetidines **4** carried the highest levels of inherent V_{1A} selectivity. Compare, for example, parent compounds **5** versus **11** versus **18**.

Of the analogues prepared, compound **25** was, on the basis of potency, selectivity and human liver microsomal stability, selected for further progression. Profiling against a wide range of receptors, enzymes and ion channels identified no significant off target activity.[11] Fully crystalline material was produced and this material was found to have an aqueous solubility of 59 μg/mL at pH 7.5—significantly greater than that observed for lead compound **1** (6 μg/mL at pH 7.4), supporting our strategy of moving away from a biaryl LHS substituent to promote increased solubility. In addition, profiling of **25** in the rat and dog showed that this compound demonstrated promising oral pharmacokinetics. Across these species clearance was moderate (rat) to low (dog) and high levels of oral bioavailability were observed. Moreover, comparison with **1** indicated a significantly improved profile with respect to rat oral pharmacokinetics (Table 2).



25

OT Ki 9.5nM; V_{1A} Ki 1,120nM; clogP 3.2

The preparation of compound **25** is described in Scheme 1. 2-Chloro-4-fluorophenol **27** was alkylated with commercially available azetidine mesylate **26**. Following deprotection the resulting NH azetidine, **28**, reacted smoothly with **29**, the isothiocyanate from 5-amino-2-methoxy pyridine, to give thiourea **30** in excellent yield. Conversion to the corresponding *S*-methylisothiourea, followed by acid catalysed condensation with hydrazide **31**, then gave **25** in an overall yield of 35%.[12]

In summary, we have, using **1** as a starting point, designed and prepared a series of potent, aryl ether triazole Oxytocin antagonists. One of these compounds, **25**, has significantly improved V_{1A} selectivity and aqueous solubility over **1**, as well as a promising pharmacokinetic profile in both rat and dog. As a result of this data and subsequent profiling, a decision was taken to progress **25** as a candidate for subsequent clinical studies.

Acknowledgements

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

References and notes

1. Gullam, J. E.; Chatterjee, J.; Thornton, S. *Drug Discovery Today* **2005**, *2*, 47.
2. Tiwari, A.; Nanda, K.; Chugh, A. *Expert Opin. Invest. 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. R. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4278.
5. All solubilities disclosed in this paper were measured on fully crystalline material, as assessed by powdered X-ray diffraction analysis.

6. See reference 4 and the references therein for a discussion on heavy atom ligand efficiency and lipophilicity versus drug-like properties for compounds such as **1**.
7. For a discussion on the strategy of removing the biaryl substituent from systems of this type to improve aqueous solubility see: Brown, A.; Brown, L.; Brown, T. B.; Calabrese, A.; Ellis, D.; Puhalo, N.; Smith, C. R.; Wallace, O.; Watson, L. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5242. and the references and notes therein.
8. (a) Conformational analysis was carried out using in-house software. Local minimum conformations of potential targets such as **2** were overlapped with compound **1**.; (b) The minimised conformation of compound **1** illustrated was, in fact, extremely close to that observed in the small molecule X-ray of this compound.
9. (a) All activity data reported herein represents functional antagonism, as measured against the corresponding cloned human receptor in a cell based β lactamase assay, using technology licensed from Rhoto Pharmaceuticals.; (b) No significant V_{1b} activity was observed for any of the compounds profiled.
10. This trend was repeated across a range of additional (*R*)/(*S*) enantiomers (data not shown).
11. The only activities identified below 10 μM were affinity for NK_1, κ-opiod and Ghrelin receptors, where binding K_i's were 6.5 μM, 3 μM and 4.4 μM, respectively.
12. *Spectroscopic data for compound **25** as follows*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.32 (s, 3H), 4.00 (s, 3H), 4.02 (dd, 2H), 4.15 (dd, 2H), 4.32 (s, 2H), 4.90 (m, 1H), 6.53 (dd, 1H), 6.83-6.86 (m, 2H), 7.12 (d, 1H), 7.60 (d, 1H), 8.20 (s, 1H); mass spectroscopy (APCI+): *m*/*z* 420 [MH+].