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Aryloxypyrazines as highly selective antagonists of Oxytocin

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ABSTRACT

A series of aryloxypyrazines were designed based on structural overlap with previously reported arylpyrazine Oxytocin antagonists. Similarly high levels of Oxytocin antagonism were achievable in this new series. In addition, significant improvements in selectivity over the related vasopressin V_{1A} receptor were also possible.

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.

We have recently disclosed[4] arylpyrazinotriazole **1** as a potent OT antagonist which 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}

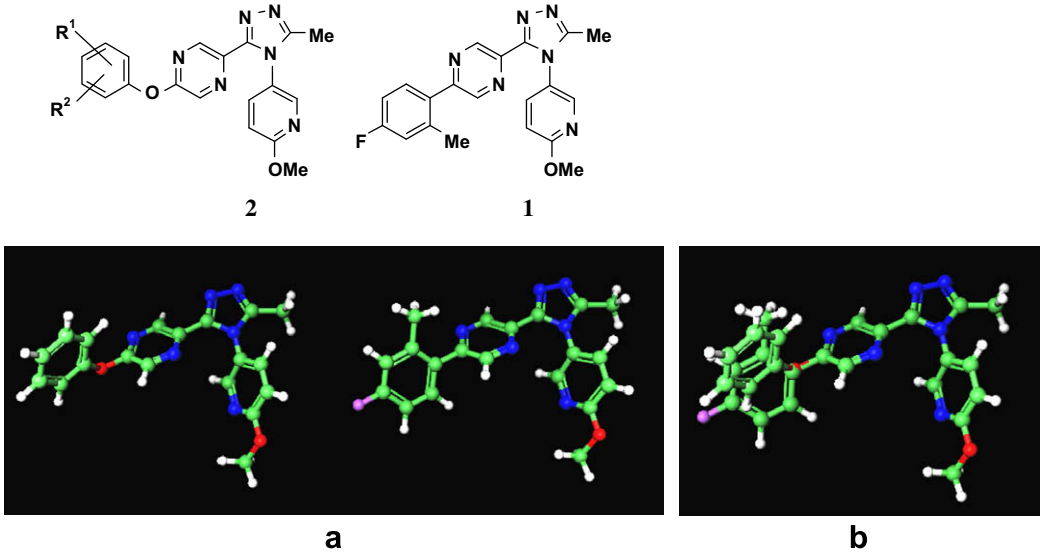

Figure 1. (a) Related local minimum conformations of **1** and **2** (b) superimposed representation of these local minimum conformations, illustrating the subtly different LHS aryl group orientations in these two systems.

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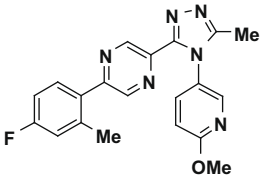
and V_2 receptors. Selectivity against the V_{1A} receptor (~65-fold) is reasonable but does fall a little short of the 100-fold window that we typically set ourselves for potential clinical candidates.



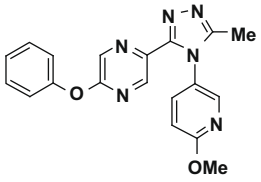
1

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

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

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 subtly different from that in compound **1** and (b) it would be straightforward to introduce a wide range of LHS aryl substituents to fully explore OT/V_{1A} potency/ selectivity SAR.

Considerations of synthetic ease and overlap of minimized conformation(s) with **1** suggested targets **2** (Fig. 1).[5] Parent compound **3** was thus prepared and profiled against OT and V_{1A}.[6] Although some OT activity was retained, this compound clearly had significantly reduced OT potency and V_{1A} selectivity (<7-fold) compared to **1**.



3

OT Ki 350nM; V_{1A} Ki 525nM; clogP 2.6

We were, however, cognisant of the fact that, in the LHS SAR around **1**, both OT potency and V_{1A} selectivity could be profoundly affected by aryl ring substituents.[4] As a result we were sufficiently encouraged to prepare a wider range of analogues, **2**. Data for a selection of these is disclosed in Table 1.

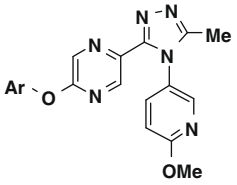
Several key LHS aryl SAR points emerged from this set of compounds:

(i) incorporation of a Me, Et or Cl 2-substituent gave a significant increase in OT activity with no increase in V_{1A} activity (compounds **4**, **5**, **6**). 2,6-dimethyl substitution gave a further increase in potency (compound **11**). However, 2-SMe or 2–OMe substitution gave no significant potency increase over **3** (compounds **8** and **7**).

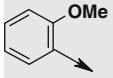
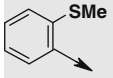
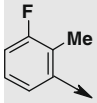
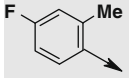
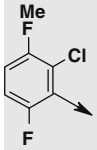
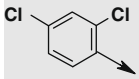
(ii) Incorporation of a 3-, 4-, or 6-F substituent was well tolerated (compounds **9**, **10** and **12**). A 4-Cl substituent was, however, slightly detrimental to activity (compound **13**).

All of the compounds profiled in this series had very low affinity for the V_{1A} receptor. Indeed, our most potent compound, **11**, had >330-fold selectivity for OT over V_{1A}. It is also worthy of note that compounds such as **5**, **9**, **10**, **11** and **12** had very similar heavy ligand efficiencies and clog*P*s to our lead compound, **1**.[7]

Table 1
OT Potency, V_{1A} selectivity data and clog*P* values for a range of analogues, **2**

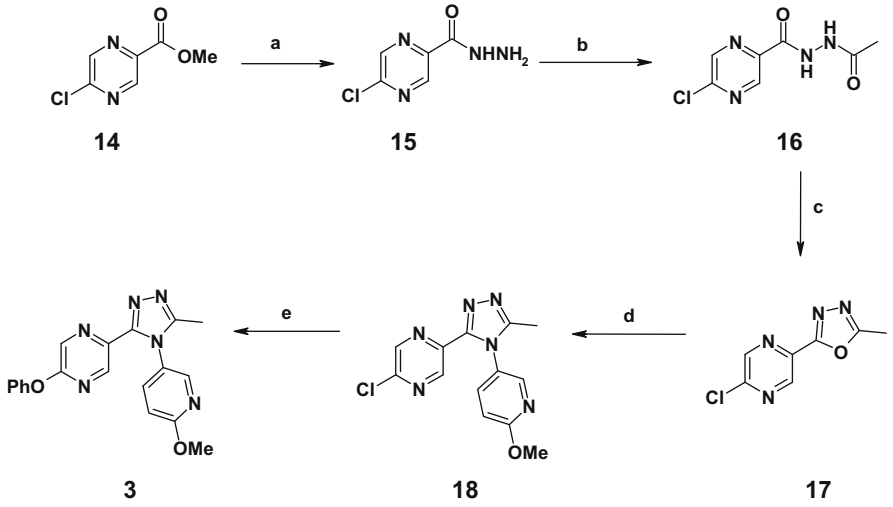


2

Ar–	Compound number	OT K_i (nM)	V_{1A} K_i[a] (nM)	clog*P*
	**3**	350	2320	2.6
	**4**	23.6	13% I @2 μM	3.1
	**5**	12.5	n.t.[b]	3.1
	**6**	52.3	14% I @2 μM	3.6
	**7**	253	10% I @2 μM	2.1
	**8**	198	17% I @2 μM	2.7
	**9**	14.6	25% I @ 10 μM	3.2
	**10**	9.4	n.t.	3.2
	**11**	5.9	20% I @ 2 μM	3.6
	**12**	8.8	n.t.	3.3
	**13**	37.5	15% I @ 2 μM	3.8

[a] For compounds with K_i > 1000 nM where K_i could not be detemined, % inhibition (I) at 2 μM is shown.
[b] Not tested.

The preparation of compound **3** is described in Scheme 1.[8] Commercial chloropyrazine **14** was converted to the corresponding hydrazide **15** by reaction with hydrazine in methanol. Acylation followed by dehydration yielded oxazole **17** which was reacted



Scheme 1. Synthesis of compound **3**.[8] Reagents and conditions: (a) $NH_2NH_2{\cdot}H_2O$, MeOH, 50%; (b) acetyl chloride, NMM, DCM, 64%; (c) $POCl_3$, 35%; (d) 6-methoxy-pyridin-3-ylamine, PTSA, xylene, 36%; (e) PhOH, Cs_2CO_3, NMP, 34%.

with 6-methoxy-pyridin-3-ylamine under acid catalysis to give key triazolochloropyrazine intermediate **18**. Reaction with phenol in the presence of cesium carbonate then gave **3** in moderate yield. In analogous fashion, intermediate **18** allowed ready access to a range of targets **2**, in a single step, by reaction with the appropriate phenol.

In summary, we have, using **1** as a starting point, designed and prepared a series of aryloxypyrazines to explore the key LHS aryl binding region of our initial lead. Several compounds of this new class, **2**, combined excellent OT activity with significantly improved V_{1A} selectivity (over arylpyrazines such as **1**). Our subsequent efforts in this area will be disclosed in due course.

Acknowledgements

We would like to acknowledge the contributions of the following co-workers: 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. (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 minimized conformation of compound **1** illustrated was, in fact, extremely close to that observed in the small molecule X-ray of this compound.
6. All biological 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.
7. See Ref. 4 and the references therein for a discussion on heavy atom ligand efficiency and lipophilicity versus drug-like properties for compounds such as **1**.
8. Abbreviations used in Scheme 1 as follows: NMM—*N*-methylmorpholine; PTSA—*p*-toluenesulphonic acid; NMP—*N*-methyl-2-pyrrolidinone.