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# Aryloxypyrazines as highly selective antagonists of Oxytocin

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## ARTICLE INFO

## ABSTRACT

also possible.

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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<sup>1</sup>; benign prostatic hyperplasia<sup>2</sup> and sexual dysfunction.<sup>3</sup> As a result there is

2

significant interest in the identification of potent, selective, orally bioavailable OT antagonists.

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A series of aryloxypyrazines were designed based on structural overlap with previously reported arylpyr-

azine Oxytocin antagonists. Similarly high levels of Oxytocin antagonism were achievable in this new ser-

ies. In addition, significant improvements in selectivity over the related vasopressin V1A receptor were

We have recently disclosed<sup>4</sup> 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<sup>4</sup> and specifically against the  $V_{1B}$ 



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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.



OT Ki 6nM; MWt 376; clogP2.9; L.E. 0.41 V<sub>1A</sub> Ki 388nM; V<sub>1B</sub>>10uM; V<sub>2</sub> 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).<sup>5</sup> Parent compound **3** was thus prepared and profiled against OT and V<sub>1A</sub>.<sup>6</sup> Although some OT activity was retained, this compound clearly had significantly reduced OT potency and V<sub>1A</sub> selectivity (<7-fold) compared to **1**.



OT Ki 350nM; V<sub>1A</sub> 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.<sup>4</sup> 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<sub>1A</sub> receptor. Indeed, our most potent compound, **11**, had >330-fold selectivity for OT over V<sub>1A</sub>. It is also worthy of note that compounds such as **5**, **9**, **10**, **11** and **12** had very similar heavy ligand efficiencies and  $c\log Ps$  to our lead compound, **1**.<sup>7</sup>

#### Table 1

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



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Ar-	Compound number	OT $K_i$ (nM)	$V_{1A} K_i^a (nM)$	clog P
	3	350	2320	2.6
CI	4	23.6	13% Ι @2 μM	3.1
Me	5	12.5	n.t. <sup>b</sup>	3.1
Et	6	52.3	14% Ι @2 μM	3.6
OMe	7	253	10% Ι @2 μM	2.1
SMe	8	198	17% Ι @2 μM	2.7
F Me	9	14.6	25% Ι @ 10 μΜ	3.2
F	10	9.4	n.t.	3.2
Me	11	5.9	20% I @ 2 µM	3.6
F F	12	8.8	n.t.	3.3
CI	13	37.5	15% I @ 2 μM	3.8

<sup>a</sup> For compounds with  $K_i > 1000$  nM where  $K_i$  could not be detemined, % inhibition (I) at 2  $\mu$ M is shown.

<sup>b</sup> Not tested.

The preparation of compound **3** is described in Scheme 1.<sup>8</sup> 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.<sup>8</sup> Reagents and conditions: (a) NH<sub>2</sub>NH<sub>2</sub>·H<sub>2</sub>O, MeOH, 50%; (b) acetyl chloride, NMM, DCM, 64%; (c) POCl<sub>3</sub>, 35%; (d) 6-methoxy-pyridin-3-ylamine, PTSA, xylene, 36%; (e) PhOH, Cs<sub>2</sub>CO<sub>3</sub>, 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.

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### **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.
- Abbreviations used in Scheme 1 as follows: NMM–Nmethylmorpholine; PTSA–p-toluenesulphonic acid; NMP–N-methyl-2pyrrolidinone.