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Identification of amide bioisosteres of triazole Oxytocin antagonists

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ABSTRACT

A series of amides were investigated as potential bioisosteres of previously reported triazole Oxytocin antagonists. A range of potent analogues were identified, although SAR for potency and selectivity over the related V_{1A} and V_2 receptors was found to be somewhat divergent from that observed for the corresponding triazole series. The high synthetic accessibility of this new amide series also facilitated the identification of a range of alternative left hand side (biaryl replacement) substituents which gave good levels of Oxytocin antagonism.

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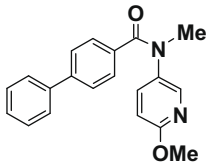
Oxytocin (OT) is a nonapeptide hormone that acts on the OT receptor, a seven-transmembrane (7TM) (Gq-coupled) receptor. The OT receptor has no subtypes but is related to the vasopressin receptors V_{1A}, V_{1B} and V_2. OT antagonists have therapeutic potential in a number of areas including pre-term labor;[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 reported the biaryltriazoles **1** and **2** (Scheme 1) as potent, selective Oxytocin antagonists with good oral bioavailability in the rat.[4] In following up these compounds we were keen to increase our understanding of the (antagonist) pharmacophore of these systems as well as developing an alternative template where it would be possible to explore left hand side (LHS) biaryl SAR using library chemistry.

Analysis of the proposed active conformation of **1** and **2** suggested a biarylamide template (as in targets such as **3**) as a potential bioisostere of the biaryltriazole present in these compounds. Molecular modeling and analysis of small molecule X-ray data on systems of this type[5] suggested that compounds such as **3** had the potential to mimic the aryl-triazole twist present in triazoles such as **1** and **2** (Scheme 2). In addition, this system opened up the possibility of using library chemistry to identify alternative LHS substituents.

Compound **3** was initially prepared to test the validity of this approach and was found to have a K_i of 90 nM against Oxytocin.



3, OT Ki 90nM

Encouraged by this result we prepared a range of phenylpyrazine amide analogues, based on the precedented advantages provided by this system in our previously reported triazole based work.[6] In addition we sought to explore the left hand side (LHS) aryl SAR in these analogues, placing particular emphasis on incorporation of an ortho substituent, as well as small electron withdrawing (cyano and fluoro) substituents—two key elements of obtaining potency and selectivity (respectively) in our earlier triazole work.

Key data for a range of such analogues is presented in Table 1.[7] Several key SAR points emerged from this compound set:

(i) As in the corresponding triazole series,[4] a LHS pyrazine linker is well tolerated (compare **3** with **4**, for example).
(ii) A range of simple right hand side (RHS) substituents (Me, Et, *i*-Pr, $MeOCH_2CH_2$) are all tolerated with no significant impact on OT potency (compounds **4**–**7**).
(iii) LHS (phenyl) OT SAR is somewhat different from that previously observed in our corresponding triazole series.[4] For example, incorporation of a 4-F or 4-CN substituent leads, if anything, to a slight drop off in OT potency (compare compounds, **8**, **9**, **10** and **11** with compound **6**). In the triazole series, these substituents were present in some of our most potent antagonists (such as **1** and **2**). In addition, a

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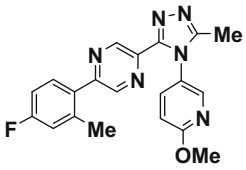
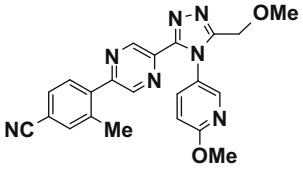


1

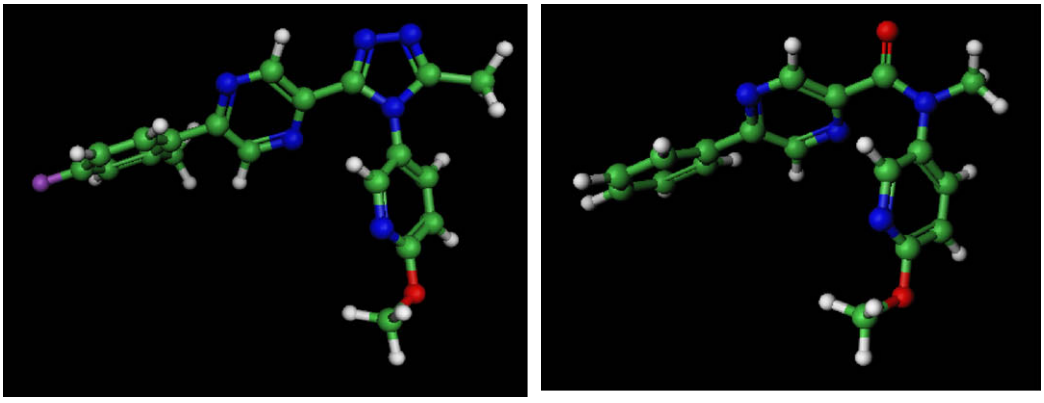
OT Ki 6nM; V_{1A} Ki 388nM;
V_{1B} >10uM; V_2 Ki > 10uM

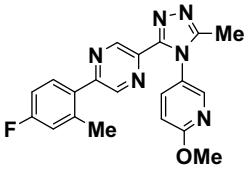


2

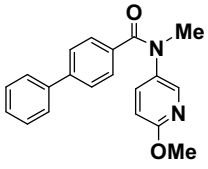
OT Ki 14nM; V_{1A} Ki 4.3uM;
V_{1B} >10uM; V_2 Ki > 10uM

Scheme 1. Biaryltriazoles previously reported by our group.





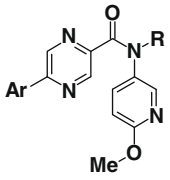
1



3

Scheme 2. Local minimum conformation of biaryl amides **3** alongside that of biaryltriazole **1**.[5]

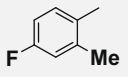
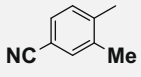
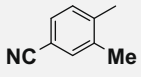
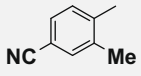
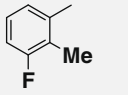
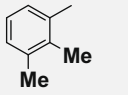
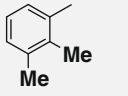
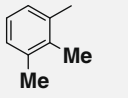
Table 1
Potency and selectivity data for key analogues[7]



Ar	R	OT K_i (nM)	V_{1A} K_i	V_2 K_i
 **4**	Me–	92	1.1 μM	>10 μM
 **5**	Et–	129	2.3 μM	>10 μM
 **6**	Pr^i–	150	>10 μM	>10 μM
 **7**	$MeOCH_2CH_2$–	115	3.3 μM	>10 μM

(*continued on next page*)

Table 1 (*continued*)

Ar	R	OT K_i (nM)	V_{1A} K_i	V_2 K_i
 **8**	Me–	218	2 μM	n.t.[a]
 **9**	Me–	620	>10 μM	>10 μM
 **10**	Et–	393	7.2 μM	>10 μM
 **11**	$MeOCH_2CH_2$–	433	12 μM	>10 μM
 **12**	Et–	29	5.9 μM	343 nM
 **13**	Et–	25	472 nM	2.83 μM
 **14**	Pr^i–	14	>10 μM	2.3 μM
 **15**	$MeOCH_2CH_2$–	11	539 nM	2.4 μM

[a] Not tested.

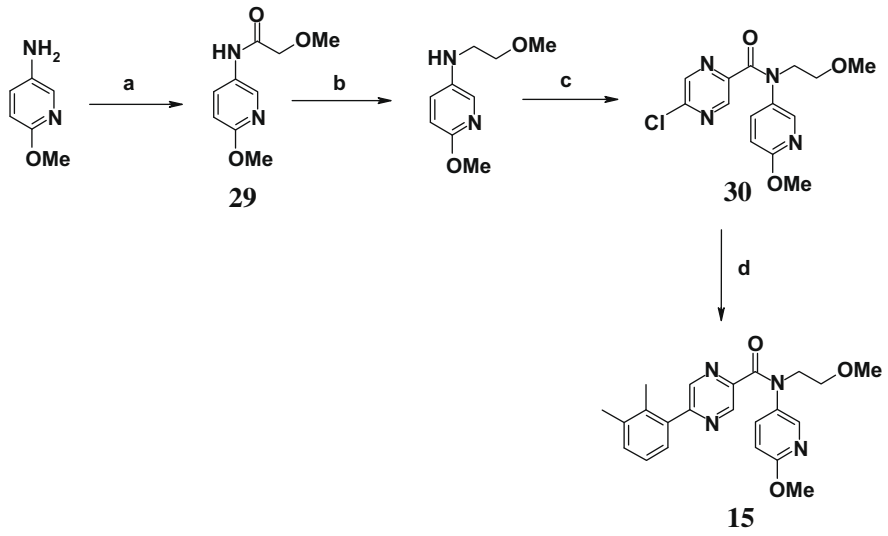
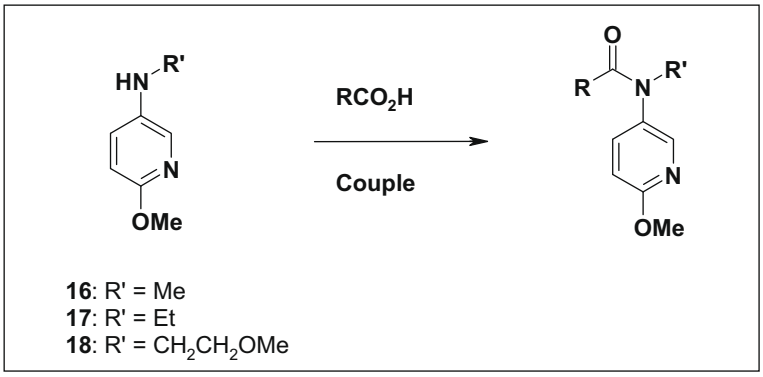
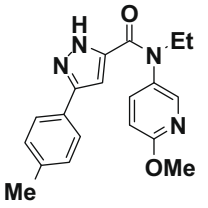


Figure 1. Synthesis of compound **15**. (a) $ClC(O)CH_2OMe$, pyridine, 50%; (b) $LiAlH_4$, THF, 89%; (c) 5-chloro-pyrazine-2-carboxylic acid, T3P, Et_3N, DCM, 26%; (d) 2,3-dimethylphenyl boronic acid, Cs_2CO_3, Pd catalyst, dioxane, 16%.

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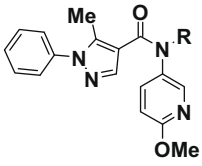
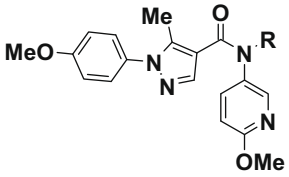
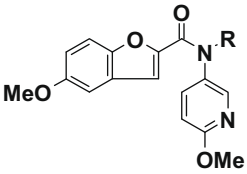
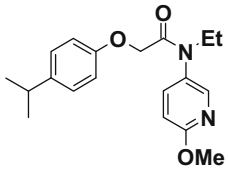

20: R = Et, OT Ki 85nM
21: R = MeOCH2CH2-, OT Ki 98nM


22: R = Et, OT Ki 91nM


23: R = Me, OT Ki 232nM
24: R = Et, OT Ki 85nM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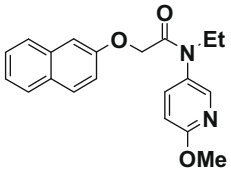
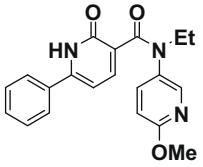
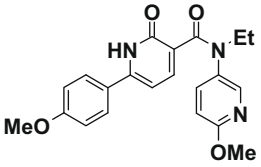

26: OT Ki 48nM


27: OT Ki 97nM


28: OT Ki 84nM

Scheme 3. Library strategy and OT potency data for alternative amide analogues identified by this approach.

2,3-dimethyl substituted LHS phenyl substituent was found to give a good balance of potency and selectivity (compounds **13**, **14** and **15**). This is again, somewhat at odds with the SAR observed in our triazole series where this substituent lead to relatively poor V_{1A} and V_2 selectivity.[4]

The preparation of compound **15**[8] is described in Figure 1. Commercially available 2-methoxy-5-aminopyridine was reacted with methoxyacetyl chloride in pyridine to give amide **29**. Reduction with $LiAlH_4$ followed by 1-propanephosphonic acid anhydride (T3P) mediated coupling[9] with commercially available 5-chloropyrazine-2-carboxylic acid then gave amide **30**, a key intermediate. Unoptimised Suzuki coupling then furnished compound **15**.

Given the high synthetic accessibility of amides of this type we were also able to utilize library synthesis to search for alternative LHS substituents (beyond the simple biaryl substituents present in compounds such as **15**). Several focused libraries were therefore prepared (Scheme 3), coupling amines **16**, **17** and **18** to a range of acids designed to explore close-in chemical space around the LHS substituent of leads such as **15**. Several promising new leads emerged from this library, including aryl pyrazoles (**19**–**22**), benzofurans (**23**, **24**), aryloxyacetic acids (**25**, **26**) and pyridones (**27**, **28**) (Scheme 3). These systems clearly offer a range of alternative starting points in the identification of further OT ligands with desirable physicochemical properties.

In summary, we have identified *N*-pyridylbiarylamides as biosisosteres of our previously reported biaryltriazole Oxytocin antagonist template. In addition, library chemistry has been utilized to identify several attractive biaryl replacements in these leads. Our further efforts in this area will be reported in due course.

Acknowledgments

We would like to acknowledge the contributions of the following co-workers: Gwen Easter; 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. (a) Brown, A.; Brown, L.; Ellis, D.; Puhalo, N.; Smith, C. R. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4278; (b) Closer inspection of our pharmacophoric overlap (as illustrated in Scheme 2) suggests that the LHS aryl substituents in our amide systems gives a subtly different trajectory to this ring as compared to that in corresponding triazole analogues. In addition, our previous triazole work (Ref. 4a) revealed a poor toleration of substituents with more than one or two heavy atoms on this LHS aryl substituent. The subtle differences in amide and triazole SAR observed here are consistent with these two facts.
5. (a) Our conformational analysis was based on comparison of local minima conformations (as assessed by in-house modeling software) as well as analysis of in-house and publicly available small molecule X-rays of compounds containing structural motifs similar to that in proposed target **3** and triazoles such as **1**. Both suggested that the conformation of **3** shown in Scheme 2 represents a low energy local minimum for this compound. For a discussion on the conformation of compound **1** see: Brown, A.; Ellis, D.; Pearce, D.; Ralph, M.; Sciametta, N. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2634.; (b) Since this work was carried out, workers at GlaxoSmithKline have reported the utilization of a somewhat similar pharmacophoric overlap approach to identify two structurally related classes of OT antagonists. See: (i) Barton, N. P.; Bellenie; B. R.; Doran, A. T.; Emmons, A.J.; Heer, J. P.; Salvagno, C. M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 528; (ii) Barton, N. P.; Bellenie; B. R.; Emmons, A. J.; Heer, J. P.; Salvagno, C. M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 990.
6. Moving from a phenyl to a pyrazine linker had, in our previously reported triazole series, lead to a significant improvement in metabolic stability as well as an increase in V_2 selectivity. See Ref. 4 for details.
7. (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) As with our previous triazole based OT antagonists (see Ref. 4), no significant V_{1b} activity (<20% antagonism) was observed at 10 μM for a range of compounds, including **13** and **15**, profiled in this series.
8. ^{1}H NMR of compound **15** ($CDCl_3$; 400 MHz): δ 8.76 (s, 1H), 8.31 (s, 1H), 7.82 (s, 1H), 7.48 (d, J = 10.2 Hz), 1H), 7.2–7.09 (m, 3H), 6.60 (d, J = 8.6 Hz, 1H), 4.03 (t, J = 5.5 Hz, 2H), 3.80 (s, 3H), 3.64 (t, 2.5 Hz, 2H), 3.30 (s, 3H), 2.26 (s, 3H), 2.07 (s, 3H).
9. For example, see: Kopach, M. E.; Singh, U. K.; Kobierski, M. E.; Trankle, W. G.; Murray, M. M.; Pietz, M. A.; Frost, M. B.; Stephenson, G. A. *Org. Process Res. Dev.* **2009**, *13*, 209. and the references therein.