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Identification of a urea bioisostere of a triazole oxytocin antagonist

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ABSTRACT

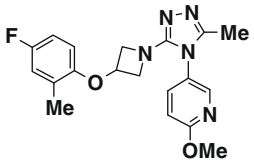
A series of azetidine ureas were investigated as potential bioisosteres of previously reported azetidinyltriazole oxytocin antagonists. Although potency was somewhat reduced in several close-in analogues, one compound, **9**, was both a potent oxytocin antagonist and demonstrated significant selectivity over the closely related vasopressin V_{1A} receptor.

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.

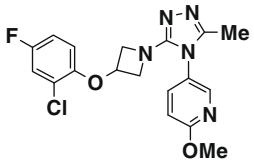
We have previously reported a series of azetidinyltriazoles, as represented by compounds **1** and **2** (Scheme 1), as potent, selective oxytocin antagonists with good oral bioavailability in the rat.[4] During the course of this work we established that, in systems of this type, it was reasonably straightforward to achieve high levels of selectivity over V_2 and V_{1B} receptors. However, achieving high levels of selectivity over V_{1A}, whilst achievable, was significantly more challenging. Our experience[4] suggested that this was best achieved by incorporation of small electron withdrawing *meta* or *para* substituents (typically F), along with a small (methyl or chloro) *ortho* substituent, in the phenyl ring of compounds such as **1** and **2**.

In our quest to understand the pharmacophore for this chemotype, we were interested in exploring alternative systems that probed the importance of some of the possible binding residues of our azetidinyltriazoles. Analysis of the proposed active conformation of **1** and **2** suggested an azetidine urea template (as in targets such as **3**) as a potential bioisostere of the azetidinyltriazole 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 overall shape of triazoles such as **1** and **2** (Scheme 2).

We therefore prepared a small set of azetidine ureas carrying *ortho* methyl/chloro substituents and *meta*/*para* fluoro substituents on the phenyl ring in an attempt to identify potent OT antagonists with high levels of V_{1A} selectivity. Functional potency and V_{1A} selectivity data for these compounds is shown in Table 1, along



1
OT Ki 17.5nM; V_{1A} Ki 608nM



2
OT Ki 28.4nM; V_{1A} Ki 2.4uM

Scheme 1. Azetidine triazoles previously reported by our group.

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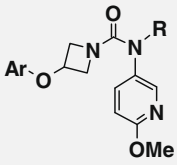
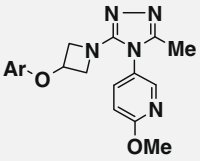
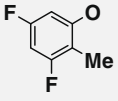
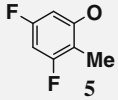
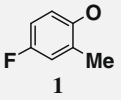
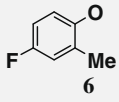
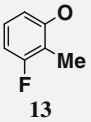
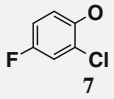
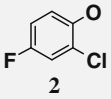
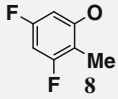
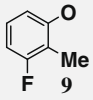
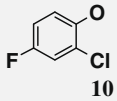
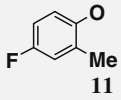
Table 1
potency and V_{1A} selectivity data for key analogues[6]





ArO	R	OT K_i	V_{1A} K_i	ArO	OT K_i	V_{1A} K_i
 **4**	Me–	159 nM	>4.2 μM	 **12**	41.4 nM	>4.2 μM
 **5**	Me–	237 nM	>4.2 μM	 **1**	17.5 nM	608 nM
 **6**	Me–	112 nM	1.3 μM	 **13**	19.7 nM	>4.2 μM
 **7**	Me–	67.2 nM	779 nM	 **2**	28.4 nM	2.4 μM
 **8**	Et–	36.7 nM	n.t.[a]			
 **9**	Et–	13.9 nM	>4.2 μM			
 **10**	Et–	48.4 nM	n.t.[a]			
 **11**	Et–	43 nM	n.t.[a]			

[a] Not tested.

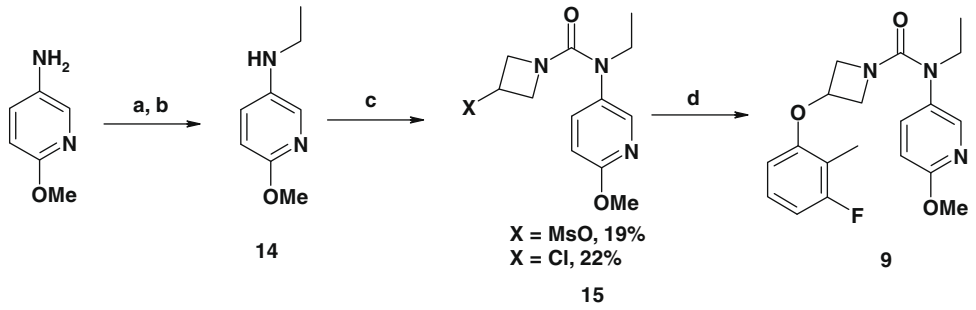


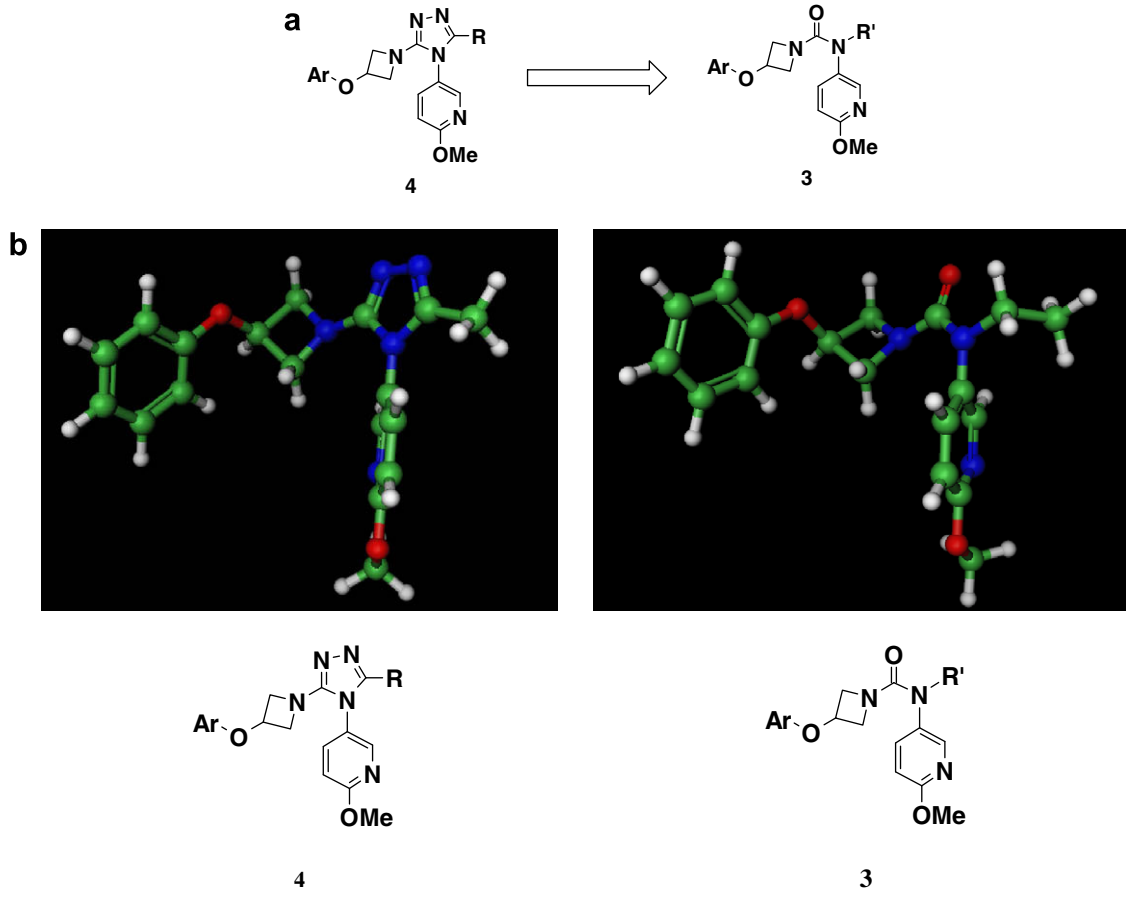
Figure 1. Synthesis of compound **9**. Reagents and conditions: (a) acetyl chloride, Et_3N, DCM, 0 °C, 56%; (b) 1 M $LiAlH_4$ in diethyl ether, THF, 0 °C, 96%; (c) azetidin-3-yl-methanesulphonate·HCl, bis (trichloromethyl) carbonate, *N*,*N*-diisopropyl ethylamine, DCM, 20 °C; (d) 3-fluoro-2-methylphenol, Cs_2CO_3, MeCN, 100 °C, 12%.

with data for representative examples of our previously reported azetidinyltriazole series.[6]

Two key SAR points emerged from this compound set:

(i) 3-Fluoro-2-methyl substitution on the phenyl ring leads to greater levels of V_{1A} selectivity than observed for the corresponding 2-methyl-4-fluoro or 2-chloro-4-fluoro analogues (compare **4** and **5** with **6** and **7**). This is entirely consistent with our findings in the azetidinyltriazole series (compare **12** and **13** with **1** and **2**).

(ii) Moving from a methylurea (R = Me) to the corresponding ethylurea (R = Et) typically gives a slight increase in OT potency (e.g., compare **6** with **11** and **4** with **9**).



Scheme 2. (a) Proposed azetidine urea targets **3** suggested by azetidinyltriazoles **4**. (b) Local minimum conformation of azetidine urea **3** alongside that of azetidinyltriazole **4**.[5] (Ar = Ph; R = Me and R′ = Et shown for clarity).

Compound **9** therefore emerged from this analysis as our most potent and V_{1A} selective azetidine urea of this type. This compound has a very similar potency and selectivity to the corresponding azetidinyltriazole, **13**, supporting the pharmacophoric overlap illustrated in Scheme 2.

The preparation of compound **9**[7] is described in Figure 1. Commercially available 5-amino-2-methoxypyridine was acylated with acetyl chloride and then reduced with lithium aluminum hydride to give *N*-ethylaminomethoxypyridine **14**. One pot urea formation using bis(trichloromethyl) carbonate and commercially available azetidin-3-yl-methanesulphonate then gave **15** as a mixture of chloro/mesylate azetidine. This key intermediate (mixture) was used without purification. Unoptimised reaction with 3-fluoro-2-methylphenol furnished compound **9**.

In summary, we have identified azetidine ureas as bioisosteres of our previously reported azetidinyltriazole oxytocin antagonist template. One analogue, **9**, is a potent OT antagonist with significant selectivity over the closely related V_{1A} receptor. Our further efforts in this area will be reported in due course.

Acknowledgements

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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. Investig. Drugs* **2005**, *14*, 1359.
3. See, for example, WO 2005028452 and the references cited therein.
4. Brown, A.; Brown, T. B.; Calabrese, A.; Ellis, D.; Puhalo, N.; Ralph, M.; Watson, L. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 516.
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 Ref. 4.
(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. (a) All activity data reported herein represents functional antagonism of an oxytocin stimulated agonist response, as measured against the corresponding cloned human receptor in a cell based β lactamase assay, using technology licensed from Rhoto Pharmaceuticals; (b) In additional studies compound **9** demonstrated no significant (<10% at 10 μM) antagonism of the V_{1B} and V_2 receptors.
7. ^{1}H NMR of compound **9** (400 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.40 (d, 1H), 7.00 (q, 1H), 6.80 (d, 1H), 6.65 (t, 1H), 6.10 (d, 1H), 4.65 (m, 1H), 4.00 (s, 2H), 3.90 (m, 2H), 3.70 (s, q, 5H), 2.10 (s, 3H), 1.10 (t, 3H). LRMS (ES)—*m*/*z* 360 (MH^+).