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Preparation of triazolobenzodiazepine derivatives as Vasopressin V1a antagonists

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ABSTRACT

This Letter describes the synthesis of a number of fused tricyclic and bicyclic triazolobenzodiazepines for the Vasopressin V1a antagonist programme.

The arginine Vasopressin V1a receptor is expressed mainly in the liver, vascular smooth muscle cells and the brain. In vascular smooth muscle cells the V1a receptor regulates vasoconstriction and contractility. V1a receptor antagonists have been progressed to the clinic for a range of indications[1] including Raynauds syndrome and dysmenorrhoea. In this Letter we describe the synthesis of a number of fused tricyclic compounds as potential Vasopressin V1a antagonists (Fig. 1). In addition, two alternative routes are described for lead compounds which allowed rapid exploration of SAR within this chemical series.

Our initial route to these targets allowed us to synthesize a number from the common oxadiazole intermediate **4** shown in Scheme 1.

The formation of the acyl hydrazide **2** proceeded in 73% yield, from known ester **1**[2] simply by heating with hydrazine hydrate in methanol. Subsequent reaction with chloroacetyl chloride in the presence of *N*-methyl morpholine furnished the bis-acyl hydrazide **3** in 84% yield. A number of methods were investigated for the final dehydration step to give oxadiazole **4**. The mildest method using trifluoroacetic anhydride and pyridine[3] was attractive for potential scalability. However, due to isoliphophilic by products being produced this method was deemed unsuitable. Use of Burgess' reagent[4] gave a good reaction profile but was not pursued further due to the cost of reagents. The method of choice, due to purity profiling and cost was the neat phosphorus oxychloride method which gave oxadiazole **4** in 80% yield[5] and allowed the excess phosphorus oxychloride to be recovered by simple distillation. The synthesis of this intermediate proved to be robust and was scaled to multigram quantities and avoided the use of column chromatography over the three steps.

With this oxadiazole intermediate in hand we were able to prepare a number of triazolobenzodiazepines in an expedient manner as described in Scheme 2.

Benzyl alcohol **5** and benzylamine **6** were obtained by lithium aluminium hydride reduction of the respective commercial benzoic acid[6] and benzonitrile.[7] Alkylation of chloromethyl oxadiazole **4**, with nucleophiles **5** and **6** gave the ether **7** and amine **8** intermediates. Cyclisation was achieved using acid catalysis in a high boiling solvent to give triazolo ether **9**[8] and triazolo amine **10** in 65% and 76% yields, respectively. Subsequent derivatisation of secondary amine **10** by either amide coupling or reductive amination

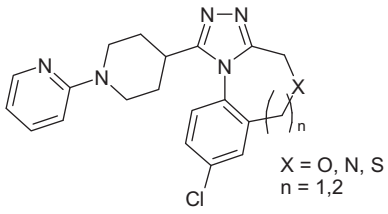

Figure 1.

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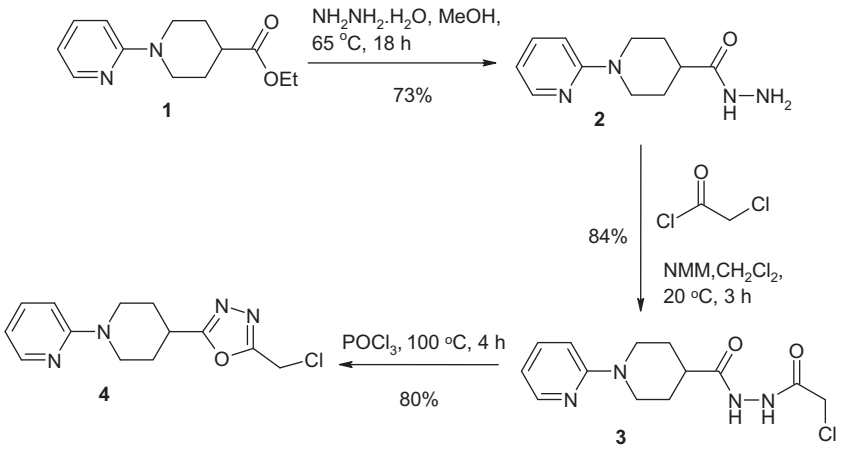
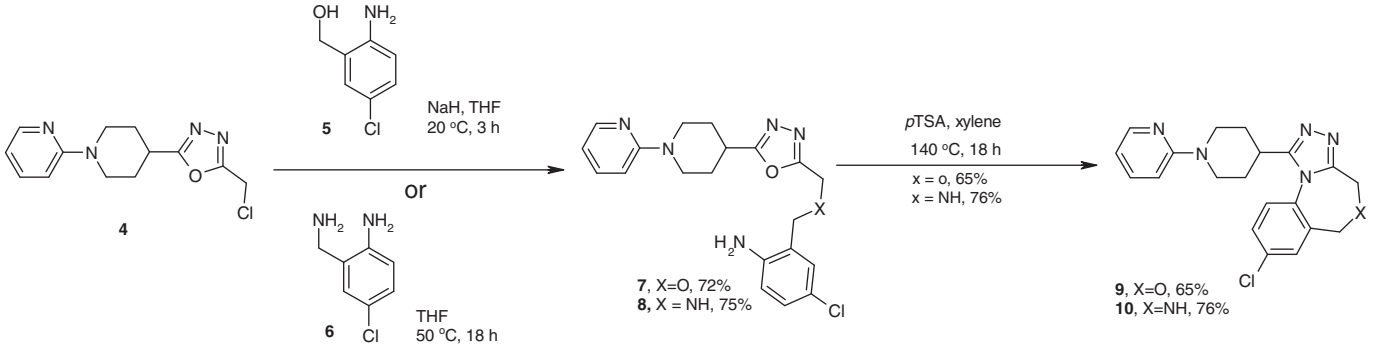
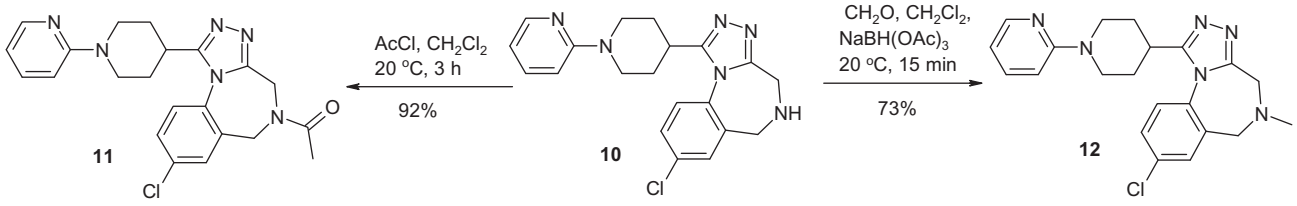


Scheme 1.



Scheme 2.



Scheme 3.

allowed rapid analogue generation, furnishing useful SAR data, as exemplified in Scheme 3.

Due to concerns about atropisomerism with these triazolobenzodiazepine templates we carried out further NMR studies on compound **12**.[9] The free energy of activation for rotation about the aryl-triazole bond was estimated from variable temperature ^{1}H NMR experiments conducted in tetrachloroethane-d_2 from 248 to 343 K. The hydrogens of the two methylene groups in the seven-membered ring each form a pair of AB systems at low temperature that coalesce to two A_2 systems at higher temperature (Fig. 2). From the geminal coupling constants and frequency separation measured at low temperature (248 K) and the observed temperature of coalescence (T_{coal}) an approximate value of k_{coal} was calculated[10] as 801 s^{-1}. Using this value for k_{coal} in the Eyring equation gives an estimate of the free energy of activation of 55 kJ mol^{-1}, which is lower than that required to satisfy the condition for the existence of atropisomerism.[11] In the case of ether **9** the two methylene groups in the seven-membered ring appeared as two A_2 systems in the ^{1}H NMR spectrum at room temperature. Although broadening was observed at lower temperatures (253 K) the free energy of activation for rotation about the aryl-triazole bond is clearly lower than that in **12**.

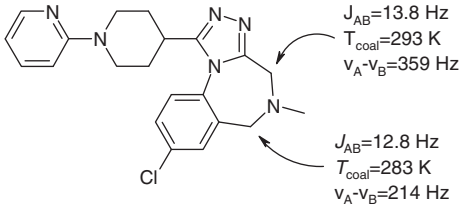
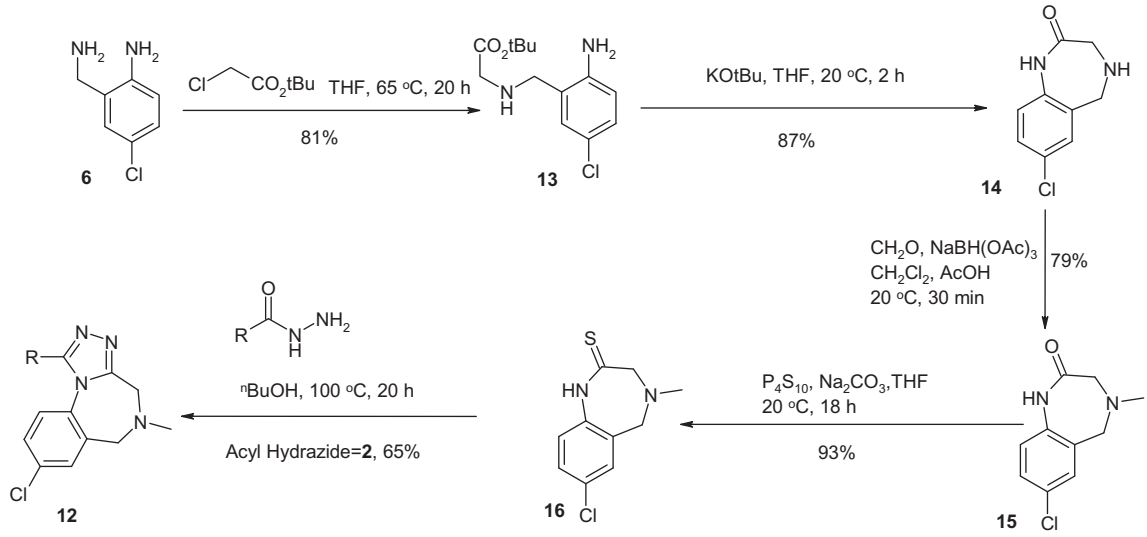
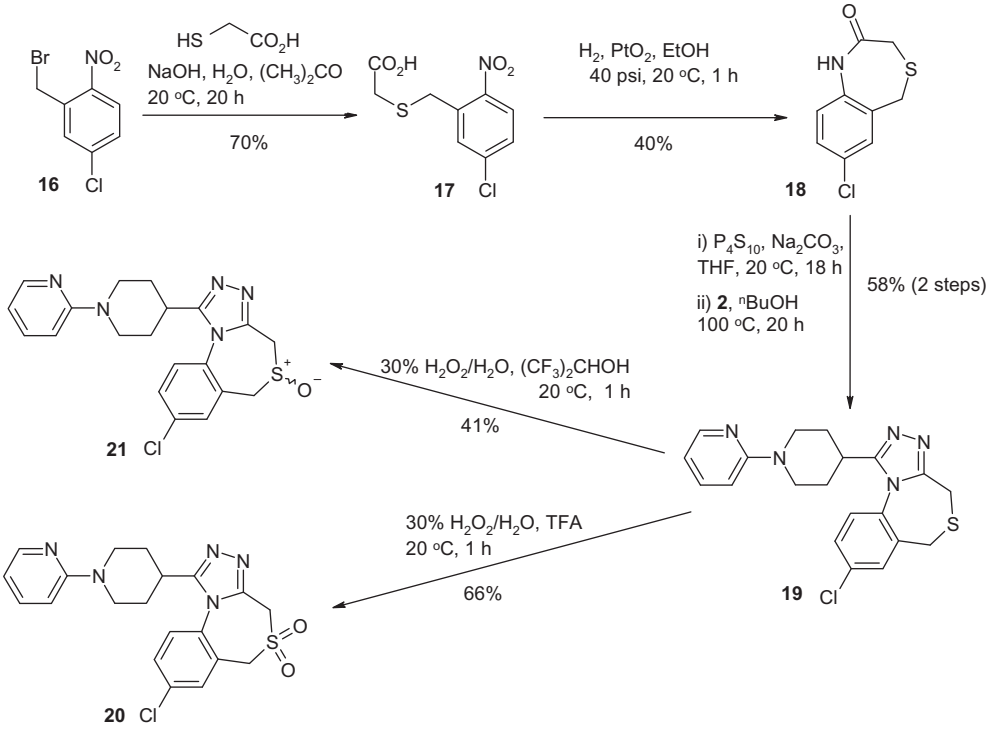


Figure 2.

An alternative route was required which allowed rapid manipulation of the piperidine functionality. Formation of thiolactam **16** gave the ability to introduce hydrazide **2**, and analogues, at a late stage allowing additional SAR studies shown in Scheme 4.



Scheme 4.



Scheme 5.

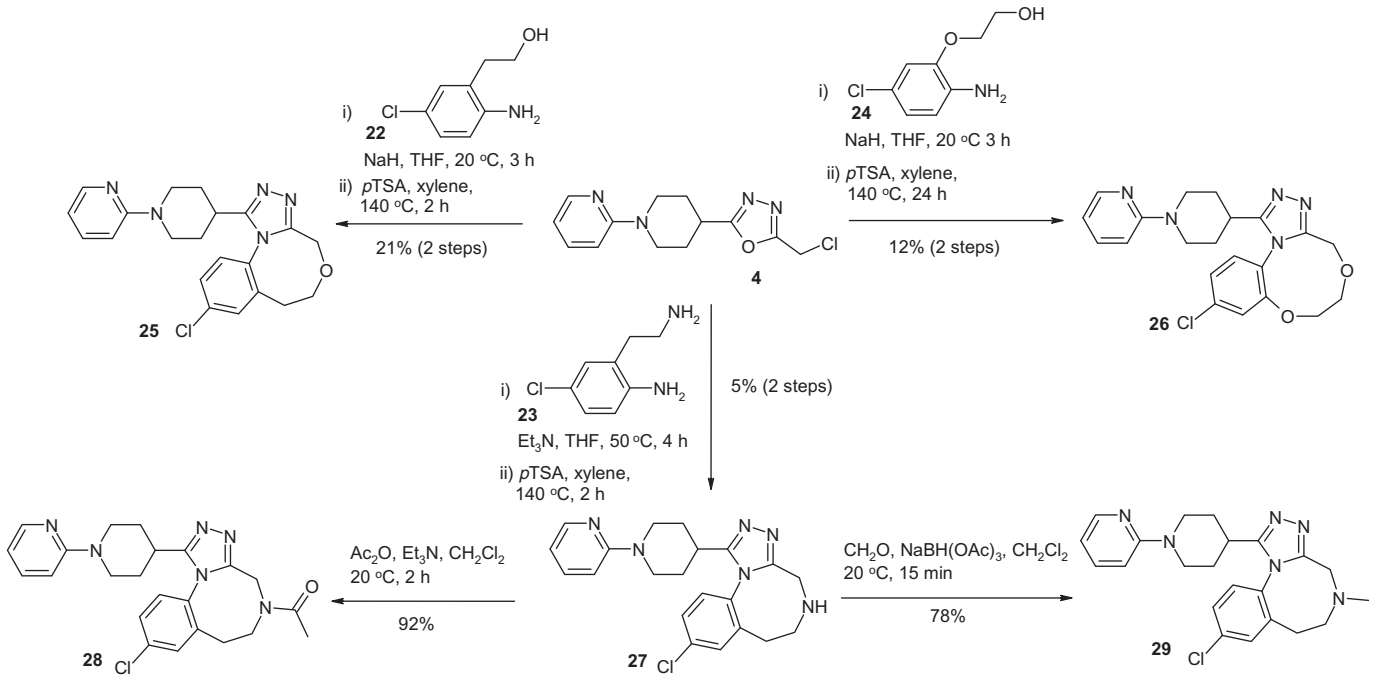
Alkylation of benzylamine **6** with the sterically hindered chloroacetic *tert*-butyl ester gave secondary amine **13** in 81% yield. Cyclisation under basic conditions and subsequent reductive amination with formaldehyde gave lactam **15** in 79% yield. Formation of more reactive thiolactam using phosphorus pentasulfide furnished the desired intermediate **16** in 93% yield.[12] Triazole formation then occurred by simply heating thiolactam **16** with hydrazides such as compound **2**, giving compound **12**.[13]

This second route also allowed us to access alternative tethered analogues such as the sulfur linked compounds **19**, **20** and **21** as outlined in Scheme 5.

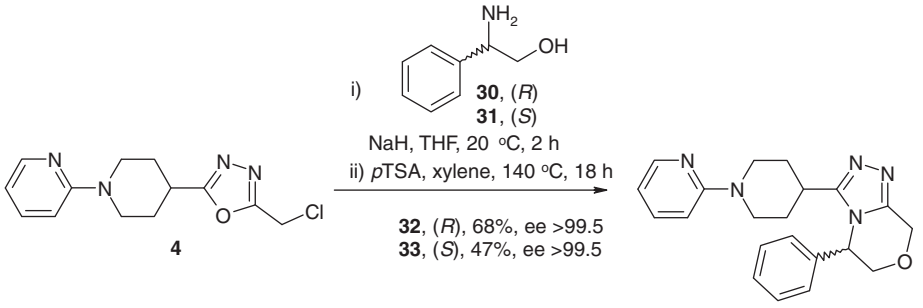
Reduction of the nitro intermediate **17** directly gave lactam **18**.[14] Treatment with phosphorus pentasulfide gave the thiolactam which reacted smoothly with hydrazide **2** to furnish triazolo thioether **19** in an overall yield of 58%. Standard oxidation conditions[15] gave sulfone **20**.[16] However by using 1,1,1,3,3,3-hexafloro-2-propanol as a solvent we were able to obtain sulfoxide **21**.[17] This partial reaction is believed to be due to H-bonding stabilization between the solvent and the sulfoxide.[18]

Variable temperature ^{1}H NMR spectroscopy showed that the sulfur analogues **19**, **20** and **21** existed as atropisomers. Thus the hydrogens of the methylene groups on the seven-membered ring appear as AB systems even at 355 K. Sulfoxide **21** was observed as a mixture of diastereoisomers by ^{1}H NMR spectroscopy in a 2:1 ratio.

Pleasingly, the methodology from the first route (Scheme 2) allowed us to explore larger, eight- and nine-membered, ring systems (Scheme 6).



Scheme 6.



Scheme 7.

Alkylation of either alcohol **22**[19] or alcohol **24**[20] with oxadiazole **4** and subsequent cyclisation gave the tethered eight-membered ether **25** and the tethered nine-membered ether **26**. A similar reaction sequence was carried out using the amine **23**[21] to give the tethered eight-membered amine **27** which was further elaborated by amide formation or reductive amination to furnish compounds **28** and **29**, respectively.

We are also pleased to report that this methodology allows further potential in the formation of bicylic six-membered ring systems, as outlined in Scheme 7. Using chiral amino alcohols **30** and **31** we were able to show the retention of stereochemistry allowing access to appealing analogues such as **32** and **33**.

In summary, we have described the synthesis of attractive tricylic and bicyclic systems as potential Vasopressin V1a antagonists. Two reaction sequences have been discussed which allow expedient exploration of the triazolobenzodiazepine chemical series. Further exploration has been possible by reduction and expansion of these ring systems using the same methodology.

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9. *8-Chloro-5-methyl-1-(3,4,5,6-tetrahydro-2H-[1,2′]bipyridinyl-4-yl)-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulene* (***12***): ^1H NMR (400 MHz, CD_3OD):

δ = 2.00 (m, 2H), 2.27 (m, 1H), 2.58 (m, 1H), 3.11 (s, 3H), 3.36 (m, 1H), 3.62 (m, 2H), 4.21 (m, 4H), 4.40 (m, 1H), 4.55 (m, 1H), 7.00 (m, 1H), 7.44 (m, 1H), 7.88 (m, 2H), 7.92 (m, 2H), 8.06 (m, 1H). APCI MS *m*/*z* 395 $[MH]^+$. Anal. Calcd for $C_{21}H_{23}ClN_6 \cdot 0.33CH_2Cl_2$: C, 44.37; H, 5.53; N, 14.53. Found: C, 44.30; H, 5.52; N, 14.65.

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17. *8-Chloro-1-(3,4,5,6-tetrahydro-2H-[1,2′]bipyridinyl-4-yl)-4H,6H-5-thia-2,3,10b-triaza-benzo[e]azulene-5-oxide (**21**)*: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.55 (m, 1H), 1.75 (m, 1H), 2.20 (m, 1H), 2.30 (m, 1H), 2.82 (m, 1H), 3.03 (m, 2H), 3.18 (m, 1H), 3.28 (m, 1H), 3.90 (m, 1H), 4.22 (m, 1H), 4.42 (m, 1H), 5.02 (m, 1H), 6.60 (m, 1H), 6.65 (m, 1H), 7.40 (m, 1H), 7.45 (m, 1H), 7.60 (m, 2H), 8.18 (m, 1H). APCI MS *m*/*z* 436 $[MNa]^+$.
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