Pergamon

Tetrahedron Letters 41 (2000) 1837–1840

TETRAHEDRON LETTERS

A stepwise synthesis of triazine-based macrocyclic scaffolds

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Received 3 December 1999; accepted 23 December 1999

Abstract

The synthesis of a non-peptidic triazine-based macrocyclic scaffold is presented. The strategy employed allows for the facile functionalisation of the macrocyclic molecules and combinatorial construction of putative receptor molecules.

Keywords: triazines; macrocycles; combinatorial chemistry; scaffold.

There is growing interest in macrocyclic molecules that may be used as scaffolds in the combinatorial synthesis of receptor molecules. Many macrocyclic molecules have been synthesised to date,[1] although, in most cases, their synthesis is difficult and/or relatively inflexible towards functionalisation.[2] A stepwise approach which allows for a combinatorial synthesis seems to be an attractive proposition. In this communication, we report a synthetic route to functionalisable macrocycles based on building blocks comprising a triazine ring and a piperidine linker, as shown in Fig. 1. Triazine was chosen as a constituent of the ring molecules in view of our interest in the moiety and previous success in using it as part of an affinity ligand.[3]

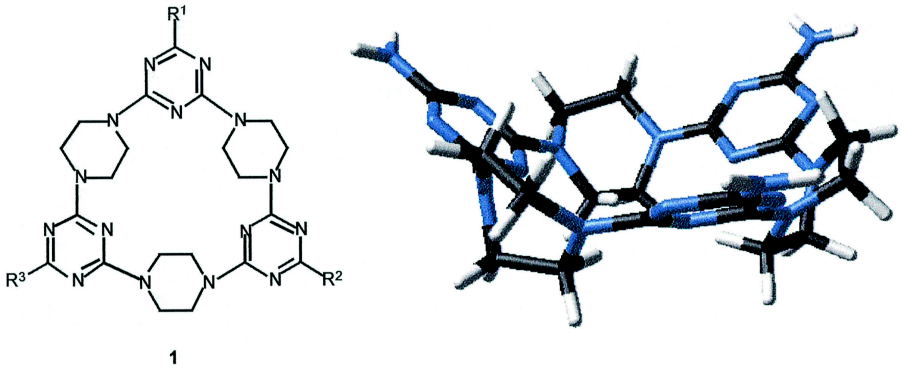

Fig. 1. General structure of a tristriazine scaffold and a low energy conformer[4] with $R^{1-3}=NH_2$

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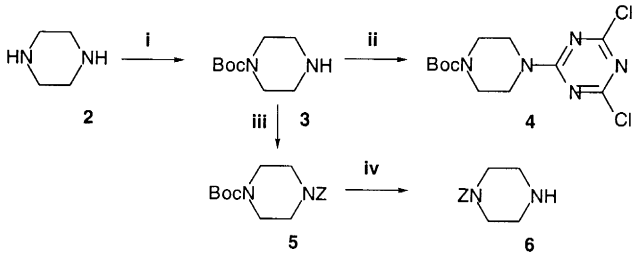
0040-4039/00/$ - see front matter
PII: S0040-4039(00)00027-7

At each stage of the synthesis, the chain can be either elongated or cyclised to the macrocycle of interest. The use of two orthogonal protective groups on either side of the oligomers allows control of the length of the triazine–piperazine chain. Furthermore, it is possible to functionalise each triazine unit in the chain with different amines as the chain is elongated. In the synthesis described below, only cyclic trimers were considered and piperazine was used as a linker, in order to create relatively rigid macrocycles. However, in due course, larger rings may be prepared and other diamines might be used as linkers, thereby increasing the diversity even further.[5]

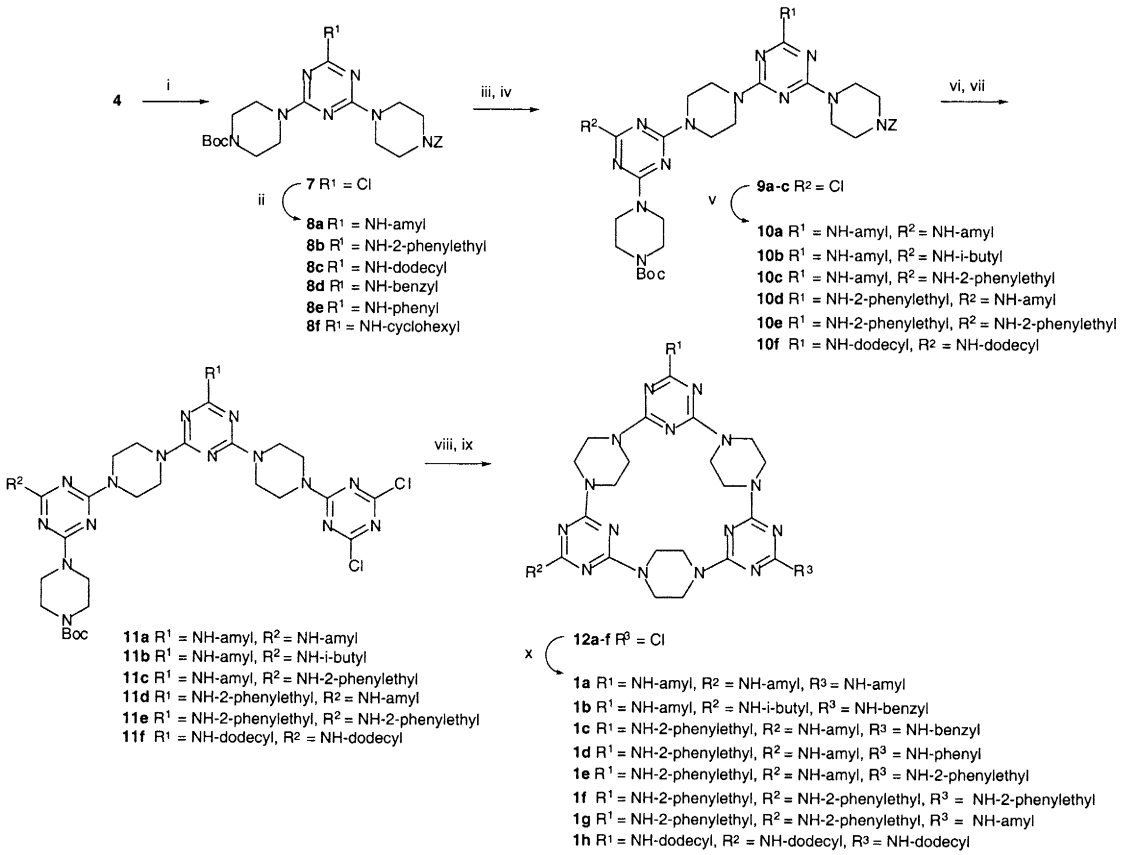
The synthesis of the required building blocks commenced with mono-Boc protection of piperazine **2** using a modification of a literature procedure[6] (Scheme 1). Reaction of monoprotected piperazine **3** with cyanuric chloride gave monosubstituted product **4** in 93% yield, using a procedure described by Koopman et al.[7] Compound **4** could be used throughout the synthesis as a convenient building block for the elongation of triazine–piperazine oligomers. Mono-Z-protected piperazine was chosen as the second substituent on triazine **4**, since it provides a second orthogonally protected piperazine moiety. The mono-Z-protected piperazine **6** was obtained in a quantitative yield by a subsequent reaction of **3** with Z-chloride and TFA. This route was preferred to literature procedures[8] because of its convenience and high yield. In addition, the reaction of piperazine with Z-chloride, gave only the bisubstituted product.



Scheme 1. Synthesis of building blocks. Reaction conditions and yields: (i) Boc_2O, CH_2Cl_2, 83%; (ii) cyanuric chloride, $NaHCO_3$, H_2O/acetone, 93%; (iii) Z-Cl, Et_3N, CH_2Cl_2; (iv) TFA, DCM, quantitative from **3**

As is shown in Scheme 2, a reaction of Z-protected piperazine **6** with **4** afforded bisubstituted triazine **7** in 85% yield.[7] Subsequently, the third substituent was introduced by refluxing **7** with an excess of amine to give trisubstituted triazines **8a**–**f** in 75–99% yield.[9] These reactions show that a plethora of amines may be used in this reaction to provide the desired diversity. The triazines **8** are the starting point for the preparation of a series of functionalised triazine–piperazine oligomers that can be eventually cyclised. At this point, compounds **8a**–**c** were selected to continue the synthesis: either the Boc or the Z-group could be removed to functionalise these compounds further. Preliminary results had revealed that higher yields of macrocycles could be obtained if the last protective group to be removed before cyclisation was a Boc- rather than a Z-group. Thus, in order to obtain oligomers containing two triazines, compounds **8a**–**c** were treated with TFA, followed by a reaction with dichloride **4**, using triethylamine as a base to give bistriazines **9a**–**c**[10] in 78–100% yield. The remaining chloride was then substituted using an excess of a second amine to afford compounds **10a**–**f** in 92–96% yield, providing further diversity. Removal of the Z-group and reaction with cyanuric chloride gave dichlorides **11a**–**f** in 54–85% yield, as a precursor for synthesis of tristriazine–piperazine macrocycles.

The respective macrocycles **12a**–**f** were prepared from the triazine–piperazine oligomers **11a**–**f** by subsequent treatment with acid and base. All compounds were converted to their corresponding macrocycles in fair yields (40–85%). Insignificant dimer formation was observed under the reaction conditions employed. It is worth noting that compounds **11c** and **11d** afford macrocycles **12c** and **12d**, respectively, which are identical, as was confirmed by both their spectral[11] and chromatographic properties. Finally, the remaining chlorine in **12a**–**f** was substituted using an excess of a third amine to give the fully



Scheme 2. Synthesis of macrocyclic triazine–piperazine trimers. Reaction conditions and yields: (i) **6**, H_2O/acetone, Na_2CO_3, 95%; (ii) R^1-NH_2, THF, 75–99%; (iii) TFA, CH_2Cl_2; (iv) **4**, Et_3N, DCM, 78–100%; (v) R^2-NH_2, THF, 92–96%; (vi) H_2/Pd/C, THF, EtOH; (vii) cyanuric chloride, $NaHCO_3$, H_2O/acetone, 54–85%; (viii) HCl, dioxane; (ix) Et_3N, DMF, 40–85%; (x) R^3-NH_2, THF, 60–90%

functionalised macrocycles **1a**–**h** in 60–90% yield. Compounds **1e** and **1g** were found to be identical and confirmed the symmetry of the macrocyclic structures.

The synthetic route described is an efficient and novel[12] way to obtain macrocycles that may act as receptor molecules towards a variety of complementary ligands. The evaluation of their binding properties is currently under investigation as is their solid phase synthesis.

Acknowledgements

These investigations were supported by a LINK grant from the BBSRC (UK) and Prometic BioSciences Inc. (Canada).

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