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COMMUNICATION

Combinatorial synthesis of galactosyl-1,3,5-triazines as novel nucleoside analogues†‡

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Herein we report a parallel solid-phase synthesis of 1,3,5-triazine based nucleoside analogues by a three-step substitution, starting from 2,4,6-trichloro-1,3,5-triazine. A library of 80 galactosyl-1,3,5-triazine compounds was prepared in high purity without extensive reaction conditions or tedious purification, suggesting the generality of this method.

1,3,5-Triazine has proven to be a promising "druggable" scaffold in a number of studies, and compounds bearing this scaffold exhibit activities in diverse biological applications.[1] The high biological activity might be due to the structural similarity of the nitrogen and carbon fused aromatic ring to natural components in organisms, such as the bases in nucleosides and nucleotides (Fig. 1).

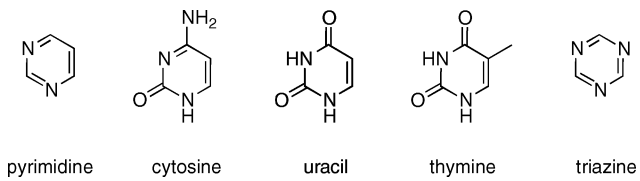


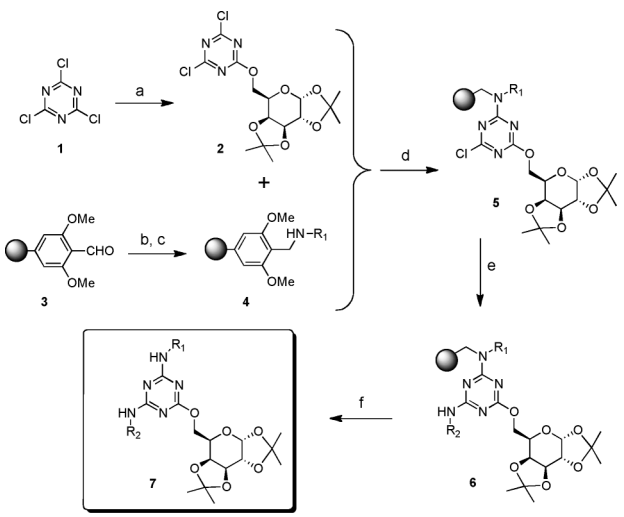
Fig. 1 Structures of pyrimidine, the nucleoside pyrimidines and triazine.

During the last decade, our group and others have reported a number of synthetic approaches for the rapid synthesis of 1,3,5-triazine derivatives from cyanuric chloride.[1a,b,2] It has been shown that the three addressable positions, although they appear the same in a three-fold rotational symmetry, have different reactivities toward substitution, which could be controlled by sequential elevation of the reaction temperatures. Thus these positions in the triple branching scaffold could be leveraged to generate a large structural diversity. The broad biological activity and ease of synthesis make triazine an ideal combinatorial library scaffold.

However, on the other side of the high bioactivity of this scaffold is its high cell toxicity. Some triazine compounds are commonly used as herbicides or pesticides.[3] The introduction of a carbohydrate moiety shows considerable promise in enhancing the properties of the derivatives. Carbohydrates increase water solubility and display a high density of functional groups for recognition, thus improving targeting and minimising toxicity.[4] To date, only a few examples of carbohydrate derivatized triazines have been reported.[5] In the monosaccharide family, galactose is present in a number of natural and synthetic compound structures and demonstrates unique biological properties.[6] The upregulation of galactosidase activity in breast and colon tumors suggests that galactose might be a good choice for a selective ligand in drug design.[7] A combination of galactose and triazine moiety might lead to nucleotide analogues with improved oral absorption and tissue targeting. In this article, we report an efficient solid-phase methodology for the preparation of 1,3,5-triazine galactose-based nucleoside analogue compounds.

First the 1,3,5-triazine scaffold was linked onto a diisopropylidene-protected galactopyranose in solution phase (Scheme 1). The reaction was carried out with an unusual combination of base and solvent, namely NaOH in benzene, affording a high yield of the mono-substituted triazine (95%).

Meanwhile, one dimension of diversity was introduced by parallel loading eight amines (Table 1, entry A–H) onto aldehyde functionalized PAL-polystyrene (PAL-PS) resin *via* reductive



Scheme 1 Solid-phase synthesis of a galactosyl-1,3,5-triazine library.

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† Electronic supplementary information (ESI) available: Experimental details and LC-MS data of the products. See DOI: 10.1039/c1ob05733b

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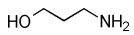
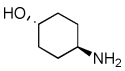
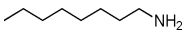
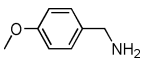
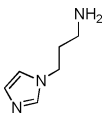
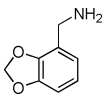
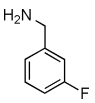
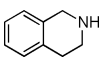
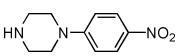
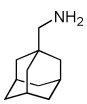
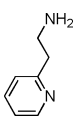
Table 1 Properties of amine building blocks

Entry	Structure	M. W.	H-bond Donors	H-bond Acceptors	Rings	log P[8]
A		75.11	2	1	0	–1.12
B		57.09	1	0	1	0.07
C		99.17	1	0	1	1.49
D		115.17	2	1	1	–0.06
E		101.15	1	0	1	–4.15
F		59.11	1	0	0	0.09
G		129.24	1	0	0	2.90
H		137.18	1	0	1	0.84
1		125.17	1	1	1	–0.64
2		151.16	1	0	2	0.59
3		125.14	1	0	1	1.24
4		87.12	1	0	1	–0.86
5		133.19	1	0	2	1.57
6		207.23	1	2	2	1.01
7		165.28	1	0	3	2.19
8		85.15	1	0	1	0.84
9		122.17	1	1	1	0.08
10		111.18	1	0	2	1.19

amination. The galactosyl triazine was attached onto the R_1-amine functionalized resin under mild heating. The other dimension of diversity was introduced by parallel substitution of the third chloride on the triazine scaffold. Each R_1-amine-triazine resin was divided into ten equal portions and reacted with ten amines (Table 1, entry 1–10) under elevated temperature. The final products were cleaved from the solid support by mild acidic conditions. In total, 80 compounds were prepared by this orthogonal solid-phase synthesis.

The amine building blocks were carefully chosen from common pharmacophore fragments based on Lipinski's rule-of-five.[9] Since the molecular weight of galactosyl triazine is around 260 Da, the combined molecular weight of the corresponding R_1 and R_2 amines was controlled around 240 Da. As there are already three hydrogen bonding receptors on triazine scaffold, the number of hydrogen bonding receptors on amine substituents was limited. The number of additional hydrogen bonding donors in the substituents was limited by the 2 donors already present on the scaffold. The building blocks represent a broad range of structural diversity, from acyclic to cyclic and polycyclic, and from aliphatic to aromatic. Furthermore, it was ensured that the building blocks had only one reactive amine group in each structure to confirm the identity of the products.

The cleavage of final product from the resin was carried out by 10% TFA in dichloromethane for only 5 min to ensure the isopropylidene protecting groups were left intact. Removal of these protecting groups will expose 4 free hydroxy groups, significantly decrease the log *P* and might lower the cellular uptake. On the other hand, the removal of acid-labile isopropylidene group might be accomplished in the cytosol, especially in lysozome. Thus, we decided to keep the current "prodrug-" like protected form.

While it is generally difficult to prepare nucleoside analogues with high purity before purification, compounds prepared using this method exhibited purities ranging from 75 to 99%, with an average of 92%. Thus, they could be used in the biological screenings directly without further purification. It is also worth noting that the high purity of the final products justifies that the triazinyl ether bond between galactose and triazine is stable under harsh basic conditions.

In conclusion, herein we report a methodology for the combinatorial solid phase synthesis of 1,3,5-triazine nucleoside analogues. This method is suitable for the rapid preparation of large collections of 1,3,5-triazine-based nucleoside analogues without extensive reaction conditions or steps or tedious purification, and is not only limited to galactose. The current set of compound will be tested in cell-based biological activity assays, as well as in a Caco-2 cell-based transportation study.[10] This method is being applied to other carbohydrate building blocks and a larger 1,3,5-triazine nucleoside library is in preparation.

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