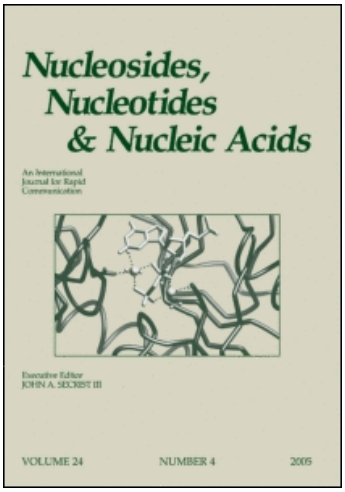

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New Solid Supports Linking Nucleoside Scaffolds

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ABSTRACT

An easy and efficient strategy to obtain new nucleoside based solid supports in which the nucleoside moieties have been anchored to the solid support through the nucleobase is here proposed. A simple and efficient solid-phase synthesis of 5′ and 3′-derivatized uridine analogues has so been developed, following methodologies well established in organic chemistry.

Key Words: Combinational chemistry; Modified nucleosides; Solid phase synthesis; Nucleoside-based solid supports.

The combinatorial approach to the simultaneous, solid-supported synthesis of a large number of chemical compounds is an important tool for the development of biological and medicinal chemistry. The design and synthesis of such libraries of

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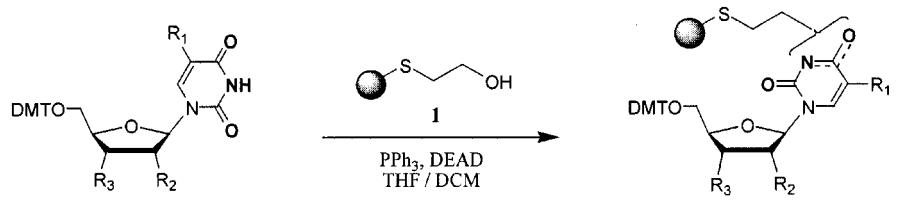
"*small organic molecules*" is often based on a unique molecular skeleton which is typically a polyfunctional molecule.[1,2]

In this frame also nucleosides can be regarded as very useful scaffolds to be incorporated into polymeric supports for combinatorial libraries since they contain functional groups which can be differently manipulated and a number of stereogenic centres useful for a defined spatial presentation of the various substituents. In addition, the biomedical potential of nucleoside derivatives is well known. Therefore nucleosides are particularly attractive as platforms for the design of primary screening libraries.

As a part of our ongoing studies, we are interested in the construction of new nucleoside based solid supports of use in combinatorial libraries, with the aim of synthesizing novel biologically active agents. Particularly, we have turned our attention to the preparation of *ad hoc* modified polymeric supports linking suitably derivatized nucleosides (*core scaffold*) in which the ribosidic functions are susceptible of further manipulation and/or modification.

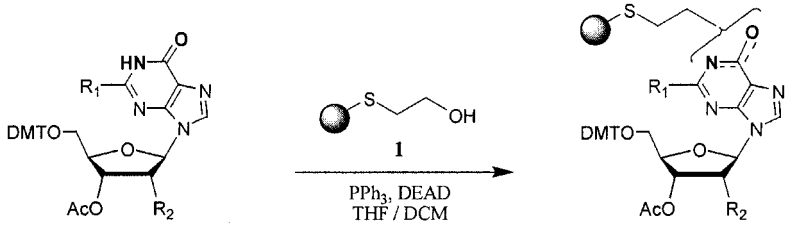
To this purpose we have devised a new synthetic approach involving the Mitsunobu reaction[3] of hydroxyalkyl TentaGel® resin (**1**, Scheme 1) with the amido or imino function of suitably modified nucleosides.

We recently[4] reported a general synthetic strategy to obtain a variety of thymidine analogues by exploiting supports **6** and **7** which can undergo reactions to form phosphoester linkages using the OH functions, and amide bonds exploiting the N_3 group, previously reduced to amine.



2 $R_1 = CH_3$; $R_2 = H$; $R_3 = OTBDMS$
3 $R_1 = CH_3$; $R_2 = H$; $R_3 = N_3$
4 $R_1 = H$; $R_2 = N_3$; $R_3 = OTBDMS$
5 $R_1 = H$; $R_2 = OTBDMS$; $R_3 = N_3$

6 $R_1 = CH_3$; $R_2 = H$; $R_3 = OTBDMS$
7 $R_1 = CH_3$; $R_2 = H$; $R_3 = N_3$
8 $R_1 = H$; $R_2 = N_3$; $R_3 = OTBDMS$
9 $R_1 = H$; $R_2 = OTBDMS$; $R_3 = N_3$



10 $R_1 = H$; $R_2 = OAc$
11 $R_1 = NHiBut$; $R_2 = H$

12 $R_1 = H$; $R_2 = OAc$
13 $R_1 = NHiBut$; $R_2 = H$

Scheme 1.

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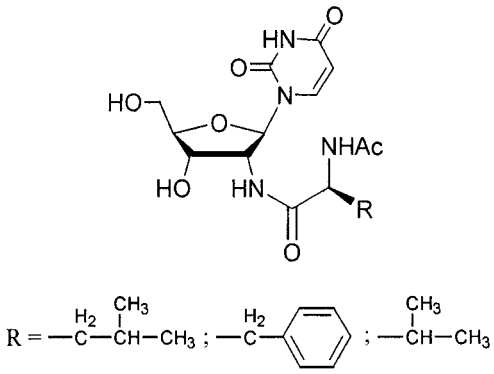

14 (95%), **15** (75%), **16** (70%)

In an effort to render more general this approach, attaching to modified polymeric supports also other nucleosides through the base, including ribo- and less usual nucleosides, we have investigated the possibility to immobilize in the solid phase uridine, inosine and deoxyguanosine derivatives and to manipulate their ribosidic functions.

Nucleoside derivatives **4**, **5** and **10**, **11** were loaded onto resin **1** (Scheme) in the presence of PPh_3-DEAD complex in THF/DCM to produce supports **8**, **9** and **12**, **13**. Incorporation yields of derivatives **4**, **5** and **10**, **11** were determined by DMT test performed on dried and weighed samples of supports **8** (90%), **9** (93%) and **12** (95%), **13** (12%).

Starting from support **12** we have devised a versatile synthetic strategy to obtain a variety of uridine hybrids (**14**, **15**, **16**) following well established solid phase organic reactions. Total detachment from the supports of the modified nucleosides was achieved by treatment with con. aq. ammonia solution after oxidation of the thioether function to sulfone.

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