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Synthesis of bridged aza-rebeccamycin analogues

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Abstract—The syntheses of rebeccamycin analogues possessing a 7-azaindole moiety instead of an indole unit, and with both indole and azaindole moieties linked to the carbohydrate are described. In these bridged aza compounds, the oxygen of the pyranose heterocycle is oriented towards either the indole, or the azaindole unit. In these series, compounds bearing a free imide nitrogen were synthesized by coupling the corresponding aglycones with a sugar pre-tosylated in 2-position via a Mitsunobu reaction. To obtain a precursor for bridged aza-rebeccamycin analogues substituted in 6-position on the sugar moiety, a 2,6-ditosylated sugar was used.

1. Introduction

Rebeccamycin, isolated from cultures of *Saccharothrix aerocolonigenes*, contains an indolocarbazole framework, an imide upper heterocycle and a sugar part linked to one of the indole nitrogens like other natural products such as some tjipanazoles E, F1 and F2 and AT2433-A1 and B1 but unlike staurosporine and UCN-01 in which the carbohydrate moiety is linked to both indole nitrogens (Fig. 1).[1–4] Rebeccamycin is a topoisomerase I inhibitor without inhibitory properties toward kinases such as CDK1/cyclinB, CDK5/p25 and PKC whereas staurosporine and UCN-01 are not topoisomerase I poisons but exhibit inhibitory properties against a variety of kinases.[5–7] In the course of structure–activity relationship studies on rebeccamycin analogues, we have synthesized 7-aza-rebeccamycin analogues in which one or both indole moieties have been replaced by a 7-azaindole unit.[8,9] When only one azaindole was introduced, the sugar part was linked either to the indole or to the azaindole (Fig. 2). Important differences in DNA binding properties and in topoisomerase I poisoning were observed between the two series. Compounds with the sugar moiety attached to the indole moiety exhibited strong DNA binding and topoisomerase I inhibitory properties whereas with compounds in which the sugar was attached to the azaindole, DNA binding and topoisomerase I poisoning were highly weakened or completely abolished. However, compounds in both series could exhibit strong in vitro cytotoxicities toward some tumor cell lines with IC_{50} values in the nanomolar range, suggesting other biological targets

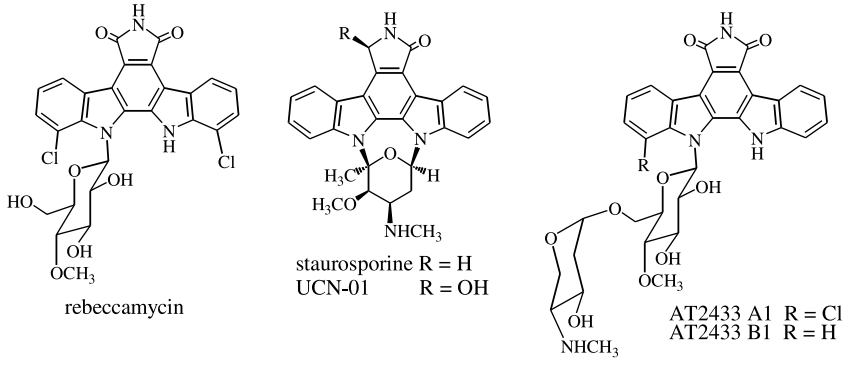

Figure 1. Chemical structures of the bacterial metabolites rebeccamycin, staurosporine, UCN-01, AT2433 A1 and B1.

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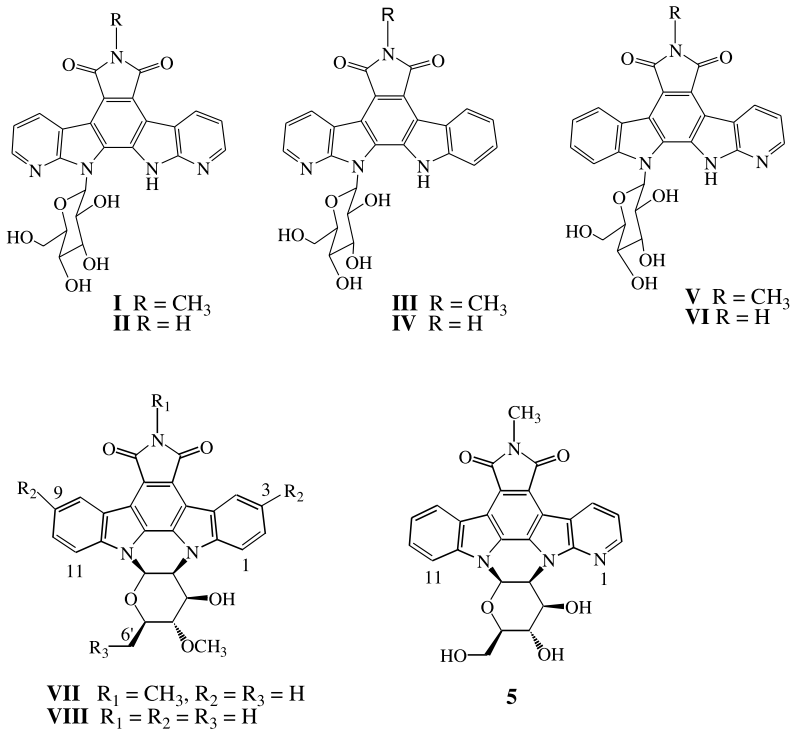
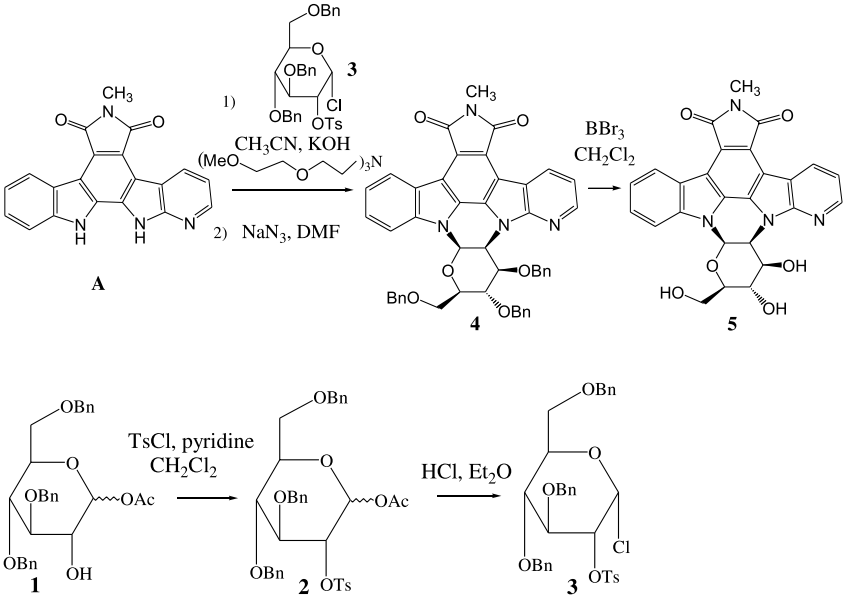


Figure 2. Aza-rebeccamycin analogues previously described.

than DNA and topoisomerase I for compounds in which the sugar is linked to the azaindole. To get an insight into the structural parameters inducing enzyme selectivity, we have synthesized staurosporine analogues from rebeccamycin by coupling the sugar moiety to the second indole nitrogen in non aza series at first and recently, one *N*-methylated compound has been prepared in 7-azaindole series.[10–12] In a previous brief communication, we described the synthesis of the 7-aza staurosporine analogue **5** with the sugar attached to both indole and azaindole nitrogens, with a methyl group on the imide nitrogen and with the oxygen heteroatom of the sugar ring oriented toward the indole unit (Fig. 2).[12] This compound was synthesized by coupling an α-1-chloro-glucose on the *N*-methylated indolocarbazole aglycone in the presence of a phase transfer catalyst. As deduced from the crystal structures of staurosporine in complex with various kinases, a free nitrogen in the upper heterocycle seems to be necessary to establish a hydrogen bond with the carbonyle of glutamate 81 in the ATP binding pocket of the kinases.[13,14] In this paper, the syntheses of new 7-aza bridged compounds, without the methyl group on the imide nitrogen and with the oxygen of the sugar ring oriented either toward the indole or toward the azaindole moiety, are reported. The replacement of an indole moiety



Scheme 1. Synthetic scheme for compound **5**.