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A one-pot synthesis of novel sugar derived 5,6-dihydro-quinazolino[4,3-*b*]quinazolin-8-ones: an entry towards highly functionalized sugar-heterocyclic hybrids☆

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Abstract—An efficient and practical one-pot method for the synthesis of novel diversified sugar derived dihydro-quinazolino-[4,3-*b*]quinazolin-8-ones has been reported. Various protected sugar hemiacetals were used to synthesize the hybrid tetracyclic ring system. The one-step reductive transformation of 2-(2-nitrophenyl)-3*H*-quinazolin-4-one with different sugar hemiacetals furnished the desired tetracyclic product in good yields and with high purity.

Over the past decade, the synthesis of privileged classes of heterocyclic molecules has become one of the prime areas of research in synthetic organic chemistry.[1] These privileged structures have gained much attention, owing to their potential role as ligands, which are capable of binding multiple biological targets.[2] Among the nitrogen-containing privileged class of molecules, substituted quinazolinones and quinazolines are considered as important therapeutic scaffolds.[3] Quinazolinone based compounds have shown considerable activity as anticancer, diuretic, anti-inflammatory, anticonvulsant, hypoglycemic and antihypertensive agents.[4]

Conventionally, the quinazolinone ring has been generated by the amidation of 2-aminobenzonitrile, 2-aminobenzoic acid or 2-aminobenzamide followed by acid- or base-catalyzed ring closure,[5] by the condensation of imidates with anthranilic acid,[6] and by aza-Wittig reactions of α-azido-substituted aromatic imides.[7] The synthesis of quinazolines has been achieved by chlorinating the oxygen atom of quinazolinone, either using phosphorus oxychloride[8] or thionyl chloride[9] followed by substitution with a primary amine, or by palladium-catalyzed intramolecular reductive N-heterocyclization.[10] However, these methods often involve multistep syntheses,[11] use expensive and toxic catalysts[12] and harsh reaction conditions,[13] and therefore are commercially undesirable. Although the use of new catalytic methodology and microwave assisted synthesis provides some technical advantages over existing methods, they lack versatility and do not employ any new chemistry in the construction of the ring system. Hence, there is a need to develop novel methods that are more efficient for the synthesis of these privileged molecules.

Various biologically active compounds are either glycosides, or compounds containing glycosidic residues along with different heterocyclic aglycon moieties.[14] Often the glycol-residue plays an important role that governs the activity as well as improves the pharmacokinetic profile of the compound. The natural abundance and the diverse chirality of the sugar have made compounds of this type attractive targets for novel synthetic methodologies. It was therefore envisioned that a scaffold consisting of a privileged class of molecule conjugated with a naturally occurring sugar entity might increase the bioavailability of an active molecule. In order to achieve this goal we sought to synthesize the pharmacologically important quinazolinones by conjugating the heterocyclic aglycon part with a glycosyl moiety.

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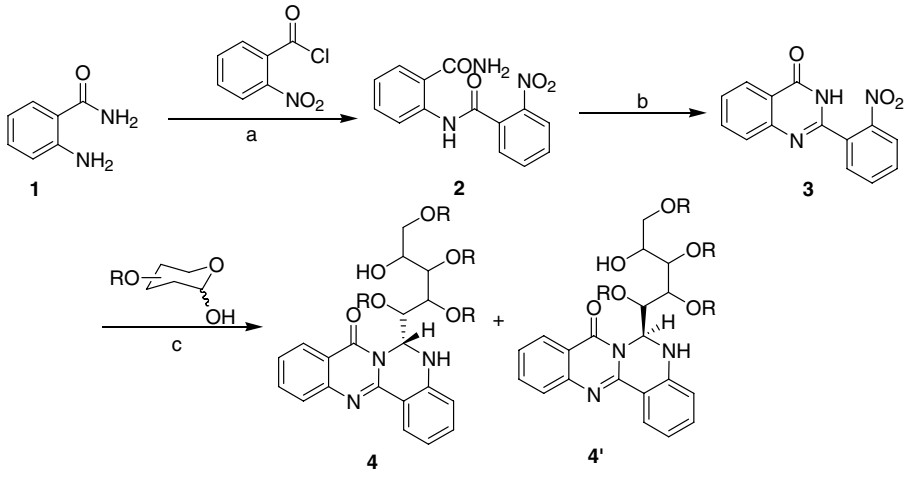
Our group has recently reported a novel method for the preparation of biheterocyclic 5,6-dihydro-quinazolino[4,3-*b*]quinazolin-8-ones.[15] In continuation of our efforts to develop newer methods to synthesize privileged heterocyclic molecules,[16] we herein report an efficient one-pot method for the synthesis of novel glycosyl 5,6-dihydro-quinazolino[4,3-*b*]quinazolin-8-ones wherein a set of cyclic sugar hemiacetals have been used along with 2-(2-nitrophenyl)-3*H*-quinazolin-4-one. In the present strategy, various sugar hemiacetals have been used, as an aldehyde source which are involved in cyclization with the resulting 2-(2-aminophenyl)-3*H*-quinazolin-4-one to furnish a highly functionalized glycoconjugated quinazolino[4,3-*b*]quinazolinone molecule. To the best of our knowledge this is the first report dealing with the formation of a glycosylated quinazolino[4,3-*b*]-quinazolin-8-one heterocyclic system utilizing a sugar molecule.

The strategy for the synthesis of 6-glycosyl substituted 5,6-dihydro-quinazolino[4,3-*b*]quinazolin-8-one is depicted in Scheme 1. The synthesis commenced with the amidation of anthranilamide **1** using 2-nitrobenzoyl chloride and triethylamine to give the amide intermediate **2**. Subsequently, 2-(2-nitrophenyl)-3*H*-quinazolin-4-one **3** was prepared by ring closure of **2** under basic conditions, using potassium hydroxide in ethanol, in excellent yield and purity. Further, to obtain the amine functionality for the synthesis of the 2-(2-aminophenyl)-3*H*-quinazolin-4-one, product **3** was treated with 5 equiv of stannous chloride in methanol at 80 °C which showed complete conversion (TLC) to the corresponding amine in about 1 h. Next, 1.2 equiv of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose was added in the same pot and the reaction mixture was allowed to stir at 80 °C for another 2 h to furnish the desired product as a diastereomeric mixture in 84% yield. The final products were purified by column chromatography and the structures were elucidated using various 1D and 2D NMR spectroscopic experiments.

The ^{1}H NMR spectrum of the product **4** showed all the glycosyl protons between 3.8 and 6.4 ppm apart from the anomeric H-6 proton which was shifted to 6.30 ppm because of its flanked position between two nitrogen atoms. Apart from the four-acetate proton signals and the H-5 amine proton at 4.83 ppm, eight aromatic protons were clearly observable. From the ^{13}C and HSQC spectrum, the position of the anomeric carbon was assigned at 61.8 ppm. In the HMBC spectrum the anomeric H-6 proton provided three long range correlations with the aglycon portion, namely, with the amide carbonyl at 160.3 ppm, the quaternary carbon (C2) at 146.5 ppm, and the NH-substituted aromatic quaternary carbon at 143.3 ppm, which confirmed the linkage between the sugar moiety and the intermediate diamine. Long-range heteronuclear proton carbon correlations established the structure as a novel 6-glycosyl substituted 5,6-dihydro-quinazolino[4,3-*b*]quinazolin-8-one.

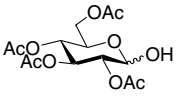
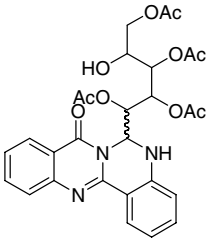
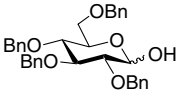
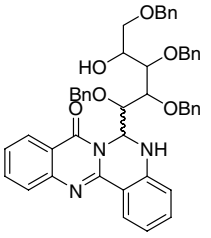
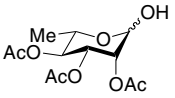
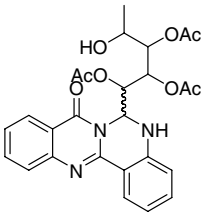
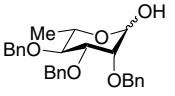
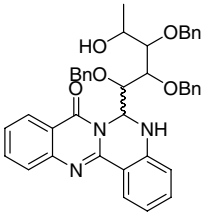
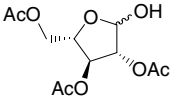
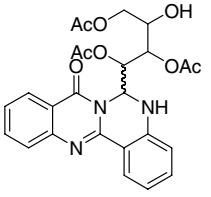
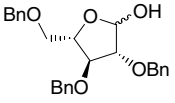
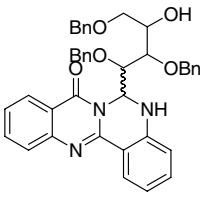
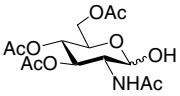
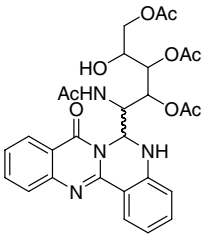
Prompted by a recent literature report[17] it was envisioned that the excess of stannous chloride present in the system might trigger the formation of the cyclic system utilizing the aldehydic property of the various sugar hemiacetals. It could be postulated that, in the present method, $SnCl_2{\cdot}2H_2O$ firstly reduces the nitro group to an amine functionality and also acts as an acid source that drives the formation of the Schiff base of the amine with the sugar hemiacetal which ultimately cyclizes in one-pot to furnish the 6-glycosyl-5,6-dihydro-quinazolino[4,3-*b*]quinazolinone.

Hemiacetals having benzyl protecting groups were also examined and provided the 6-glycosylated products in excellent yields and purity, but in longer reaction times than their acetylated counterparts. Based on the success towards the preparation of 6-gluco-derivatives, and in order to create more diversity and provide generality to the present protocol, the scope and limitations of the strategy was explored using three more acetylated



Scheme 1. Reagents and conditions: (a) 2 equiv of TEA, $CHCl_3$, rt, 2 h, 80–85% (b) 2 equiv of KOH, EtOH, reflux, 10 min, 90% and (c) 5 equiv of $SnCl_2{\cdot}2H_2O$, MeOH, 80 °C, 1.2 equiv of sugar, 1–2 h, 70–88% of **4** and **4′** (Table 1).

Table 1. Summary of the diversity and conditions used to synthesize the tetracyclic compounds **4a–g**

Compound no.	Sugar hemiacetal	Product	Time (h)	Yield (%)
4a			4	84
4b			5	75
4c			3	86
4d			3.5	88
4e			5	86
4f			6	70
4g			6	76

and benzylated sugar hemiacetals, viz. L-arabinose, L-rhamnose and *N*-acetyl-D-glucosamine. In each case, the target product was obtained in excellent yield and with a high degree of purity. In all cases, diastereomeric

products were obtained as was evident by two close spots on the TLC. However, the NMR spectra of the mixtures proved to be too complex for detailed characterization of the products. Thus, the mixtures were separated by rigorous column chromatography to obtain single diastereomers of adequate purity. For the glucose-derivative (**4a**), detailed NMR studies on both the faster and slower moving spots on TLC are reported separately (see Supplementry data). For other derivatives, only faster moving purified components are reported.

Further, the reactivity of the protected sugar hemiacetals followed the general pattern as the deoxy sugars reacted at a much faster rate than the pentopyranose and the hexopyranose sugars. Having thus prepared a series of 6-glycosylated 5,6-dihydro-quinazolino[4,3-*b*]quinazolin-8-ones, it was observed that the final products contained a free hydroxyl group in the glycon portion, which may be successfully utilized further as a potential acceptor for the glycosylation reaction, and could further create diversity in the molecule. A summary of the sugar hemiacetals utilized and the reaction conditions employed are presented in Table 1.

In summary, the present method provides a convenient one-step synthesis of novel sugar-heterocycle hybrid molecules leading to the formation of sugar-derived biheterocyclic 5,6-dihydro-quinazolino-[4,3-*b*]quinazolin-8-ones. The products not only represent a privileged class of structures but also have a glycosyl linker attached for improved bioavailability and bioactivity. Further work is in progress for the utilization of these compounds as glycosyl acceptors in glycosylation reactions for the synthesis of heterocycles containing biologically active oligosaccharides.

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Supplementary data

General experimental procedure and copies of NMR spectra of all the compounds are included. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.07.064.

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