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New mannose derivatives: The tetrazole analogue of mannose-6-phosphate as angiogenesis inhibitor

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ABSTRACT

Two novel compounds with mannose-derived structure, bearing a tetrazole (compound **3**) and a sulfone group (compound **4**) in terminal position, have been prepared from methyl α-D-mannopyranoside in reduced number of steps. The angiogenic activity of **3** and **4** has been screened using the chick chorioallantoic membrane (CAM) method. Tetrazole **3** has been identified to possess a promising bioactivity, being identified as angiogenesis inhibitor, with 68% of neovascular vessels when compared to control (PBS).

Angiogenesis is the process of generating new capillary blood vessels from pre-existing ones.[1] In healthy adults, angiogenesis is normally absent, excepting two specific phenomena: the cutaneous wound healing[2] and the intervention in female reproductive functions.[3,4] An abnormal vascularisation (either insufficient, either excessive) can cause or contribute to the development of various diseases.[5] Therefore, angiogenesis activators have wide applications in medicine, in the treatment of diseases caused by insufficient angiogenesis, linked to the ischemia of a part of the vascular system. At the same time, a considerable amount of attention has been dedicated to angiogenesis inhibitors, due to their intensive employment, among other therapeutic applications, in cancer treatment. It has been demonstrated that tumors cannot develop to a volume bigger than 1–2 mm^3 without the participation of blood vessels.[6] Therefore, angiogenesis inhibitor therapy[7] became an important actor in cancer therapy. It is supposed hat angiogenesis inhibitors act by inhibiting the development of blood vessels inside tumors and by normalizing the blood vessel network, facilitating the access of medication at tumor site.

Angiogenesis is a complex process, involving numerous biological mediators.[8] Recent studies indicate that the cation-independent mannose-6-phosphate receptor (CI-M6PR) is also involved in angiogenesis.[9,10] CI-M6PR, also known as the mannose-6-phosphate/insulin like growth factor II receptor (M6P/IGFIIR), is a 275 kDa, P-type glycoprotein,[11] whose main function is represented by the transport of newly synthesized enzymes from the cell membrane or from Golgi apparatus to lysosomes.[12] The binding specificity of the receptor has been intensively studied.[13] In our ongoing research on mannose-6-phosphate (M6P) and its derivatives, different M6P analogues have been synthesized and their affinity for the M6P/IGFIIR has been tested.[14–17] In a recent study, we have reported the synthesis of different M6P analogues, bearing various functional groups (azido, aminomethyl, carboxyl, malonate, sulfonate, carboxymethyl, phosphonate) in the C6 position of the carbohydrate and a methyl group in anomeric position, using a method involving a key cyclic sulfate intermediate. The angiogenic activity of these compounds has been evaluated and the tested analogues proved to be angiogenesis regulators.[18] The most potent angiogenesis inhibitor in this series was the methyl mannopyranoside of M6P itself (MeM6P) (compound **1**, Fig. 1), but its therapeutic applications are limited by its instability in biological environment, caused by the presence of hydrolytic enzymes. Besides MeM6P, another compound with promising antiangiogenic properties was the carboxylic acid **2**. Because tetrazoles are known as nonclassical bioisosteres of carboxylic acids,[19,20] the evaluation of the angiogenic properties of compound **3** became an interesting target, presented in this Letter. At the same time, we prepared a second mannose-6-functionalized derivative: the sulfone **4**. Sulfones have previously been investigated as phosphate mimics in carbohydrate series, both in the anomeric[21] and terminal position of carbohydrates, when a

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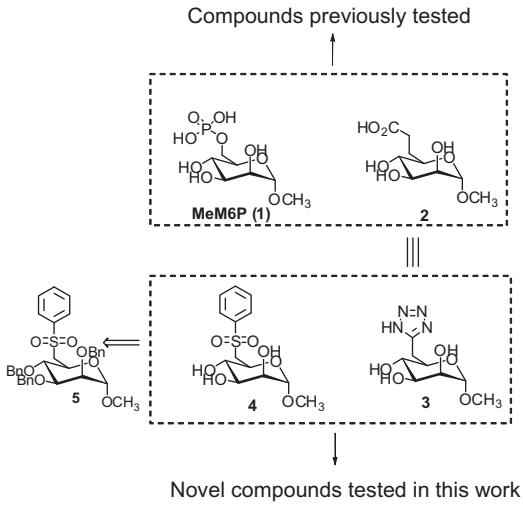
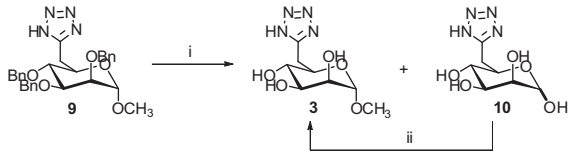


Figure 1. Mannose derivatives functionalized in terminal position.

dimethylene sulfone linker has been used as a replacer of the phosphodiester group in oligonucleotides.[22] Compound **4** is not a bioisostere of M6P. It has heteroatoms in the C6 position, but, unlike other M6P analogues tested by now, it does not possess negatively charged groups in the C6 position at physiologic pH. Moreover, besides the biological applications of **4**, intermediate **5**, which is used for the preparation of the final compound **4**, can open important perspectives in the synthetic carbohydrate chemistry. Carbanions of methylene groups in α position of sulfones can react with a variety of electrophiles, like, for example, carbonyl compounds, followed by subsequent elimination of the sulfone using samarium diiodide or sodium/mercury amalgam[23] (Julia olefination method).[24]

In order to prepare compounds **3** and **4**, we have chosen an efficient pathway that involves the iodinated compound **7** as common intermediate in the synthesis of the desired carbohydrates (Scheme 1). This intermediate was obtained from methyl α-D-mannopyranoside, using an Appel reaction[25] and among various protocols available[26–28] we have chosen the procedure of Skaanderup et al.,[26] followed by introduction of benzyl protective groups on carbohydrate hydroxyls. Because benzylation under standard basic conditions (benzyl bromide and sodium hydride or potassium hydroxide) is not compatible with our iodinated compound, we have realized this step in acid catalysis,[26] with benzyl trichloroacetimidate prepared from benzyl alcohol and 1,1,1-trichloroacetonitrile.[29] The benzylation reaction is usually realized with triflic acid as catalyst, but our tests with boron



Scheme 2. Two-steps synthesis of **3**, by deprotection of hydroxyl groups of **9** followed by methylation of the obtained reaction mixture. Reactions, conditions and yields: (i) BCl_3, Cl_2H_2; 3 min at −78 °C; (ii) $SOCl_2$/MeOH, 3 h at rt; 36% over the two steps (i) and (ii).

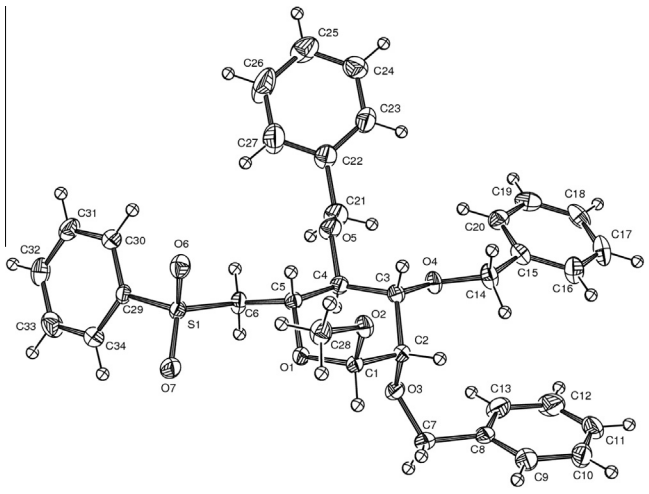
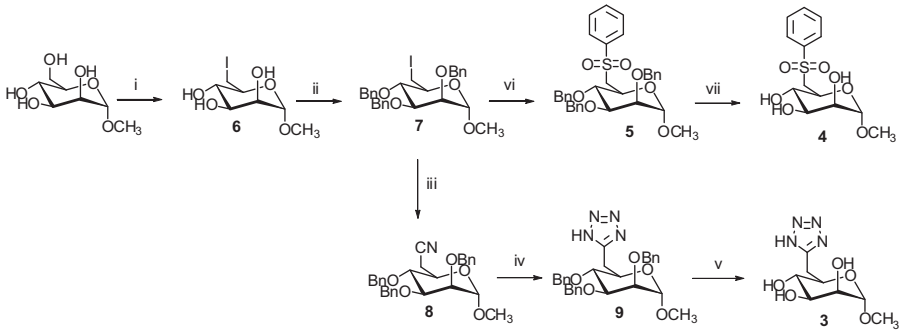


Figure 2. ORTEP drawing of **5**.

trifluoride diethyletherate (0.3 equiv/hydroxyl group) have given the same result.

The tetrazole derivative **3** was prepared using the nitrile intermediate **8**, obtained by reacting **7** with sodium cyanide in DMF. The conversion of nitriles to tetrazoles supposes, in a classical manner, the usage of hydrazoic acid, prepared from sodium azide and acids[30] or of tributyltin azide, prepared from sodium azide and tri-*n*-butyltin chloride.[31] Other methods include the usage of $Al(N_3)_3$, prepared in situ from trimethylaluminium and trimethylsilyl azide[32] or salts of hydrazoic acid.[33] We decided to use the last method, already applied with success in glucose series, using sodium azide and ammonium chloride, that allowed us to obtain the tetrazole **9** in 70% yield. The last step was represented by carbohydrate hydroxyl groups' deprotection. Based on our knowledge, no literature data has reported by now the synthesis of an unprotected glycoside bearing a tetrazole moiety in terminal



Scheme 1. Synthesis of **3** and **4**. Reactions, conditions and yields: (i) I_2, PPh_3, Imidazole, THF, 2 h at refluxing temperature, 81%; (ii) benzyl trichloroacetimidate, triflic acid, dioxane, 10 min at 0 °C, 67%; (iii) NaCN, DMF, 2 h at 70 °C, 87%; (iv) NaN_3, NH_4Cl, DMF, 144 h at 95 °C, 70%; (v.a) BCl_3, CH_2Cl_2, 3 min at −78 °C; (v.b) $SOCl_2$, methanol, 3 h at rt; 36% over the two steps v.a and v.b; (vi) sodium phenylsulfinate, DMF, 12 h at 60 °C, 67%; (vii) H_2, Pd/C, ethyl acetate/methanol, HCl, 2 h at rt, 80%.