Synthesis of 1,2,3- Triazole Nucleoside Analogues

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ABSTRACT: Both 1,2,3-triazoles and nucleosides have proved to be useful pharmacophores for antiviral and anticancer agents. A series of novel 1,2,3-triazole nucleoside analogues were designed and synthesized in order to find new antiviral or antitumor compounds.
KEYWORD: Triazole; Nucleoside; Virus; Cancer

1 INTRODUCTION

Cancer is one of the leading causes of death in the world, the war on cancer should never be stopped. Many nucleoside analogues have been rationally designed as anticancer drugs used in clinical therapy for both solid tumors and hematological malignancies[1], such as capecitabine[2], cladribine[3], fludarabine[4], clofarabine[5]. The structural diversity of nucleoside analogues with anticancer and antiviral activity suggests that any new nucleoside analogue is worth explored[6]. Triazole ring widely exists in the compounds with biological activity in drugs, and has been received much attention in chemistry and biochemistry.[7] Ribavirin[8], 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, is a broad-spectrum antiviral[9] drug that has been clinically used for treating broad DNA and RNA virus, e.g. respiratory syncytial virus, and hepatitis C virus [10]. Introduction of a triazole ring into nucleoside maybe improve their bioactivity for antitumor and/or antivirus [6]. A number of nucleosides with 1,2,3-triazole ring show good or excellent anticancer activity. [6] In addition, 1,2,3-triazole core is stable against acidic and basic hydrolysis as well as against oxidative and reductive conditions[11], and 1,2,3 triazoles prove to be good pharmacophores in antimicrobial, antivirus [12]. According to the molecular docking experimental data, we designed and synthesized a series of triazole nucleosides described as below.

2 RESULTS AND DISCUSSION

The coupling of 4-methoxybenzyl azide **1** with but-2-yne-1,4-diol via Huisgen [3+2] cycloaddtion reaction formed the desired triazole compound **2** in 90% yield (Scheme 1). Using trityl protecting group，the one expected of hydroxyls in compound **2** was selectively masked to give **3** in 85% yield, which was subsequently mesylated with methanesulfonyl chloride to form **4**. Treatment of **4** with purines afforded the desired nucleoside analogues **5** or **6** in good yields. The trityl group was selectively removed in the presence of TFA to give **7** or **8**. Substitution of the chloro atom in **7** or **8** was smoothly carried out with amine or alkoxide to form the desired purine derivatives **9a**—**9e** or **10a** –**10e**. Finally, the PMB was removed in net TFA under reflux and the expected triazol nucleoside derivatives were obtained in good yields. The bioactivity is still undergoing screening at present.

3 CONCLUSIONS

A series of novel 1,2,3-triazole nucleoside analogues were designed and synthesized successfully via seven steps with total *ca* 10% yields.

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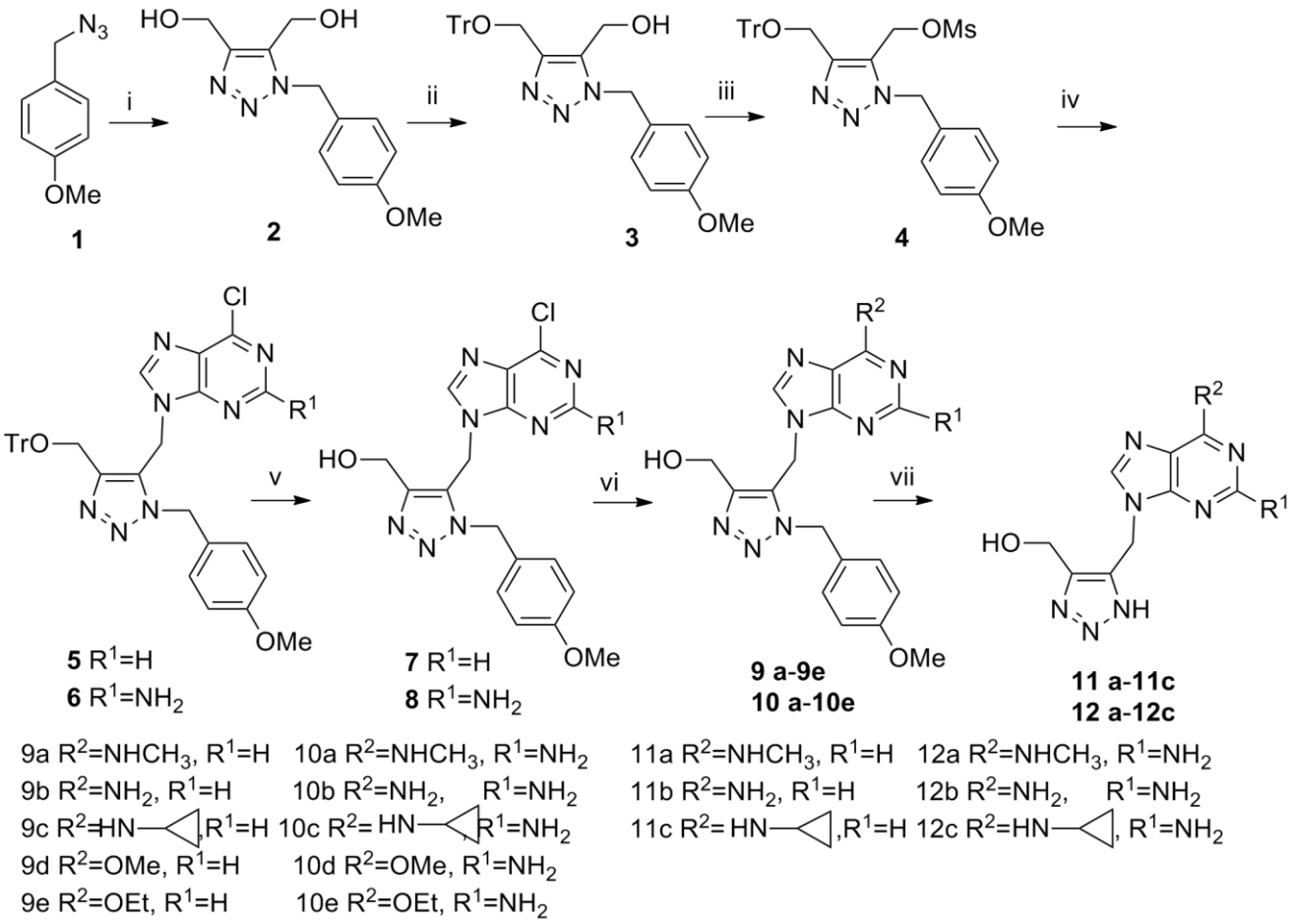

Scheme 1 Reagents and conditions: i) 2-Butyne-1,4-diol, tolune, 110°C, 90%; ii) TrCl, Et_3N, CH_2Cl_2, 0°C, 85%; iii) MsCl, Et_3N, CH_2Cl_2, 0°C, 90%; iv) 6-chloro-purine, K_2CO_3, DMF, rt, 60%; v) 6-Chloroguanine, K_2CO_3, DMF, rt, 65%; vi) CF_3COOH, CH_2Cl_2, rt, 75%; vii) a) CH_3NH_2/EtOH, 60°C, 65%; b) NH_3 H_2O/EtOH, 60°C, 74%; c) cyclopropylamine, EtOH, 60°C, 70%; d) MeONa, MeOH, 60°C, 75%; e) EtONa, EtOH, 60°C, 80%; ix) CF_3COOH, reflux, 70%.

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