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Synthesis and anticancer activity of bile acid dendrimers with triazole as bridging unit through click chemistry

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ABSTRACT

Triazole-based novel dendrimers with bile acid surface groups have been synthesized through click chemistry by divergent approach and characterized by spectral data. All the dendrimers exhibit excellent anticancer activity. Higher-generation dendrimers exhibit better anticancer activity than the lower-generation dendrimers.

1. Introduction

Dendrimers are well-defined, hyperbranched macromolecules with precisely defined structures and multiple controllable functionalities [1]. Dendrimers offer a variety of applications in the fields of material science and biological science such as drug delivery systems [2], sensors [3], solar cells [4] and efficient light harvesting antenna [5], molecular encapsulation [6] and medical applications [7]. The Cu (I)-catalyzed click reaction involving 1, 3-dipolar cycloaddition between an azide and a terminal alkyne has been used for the synthesis of multifunctional and star-like dendrimers. Click reaction is highly efficient, regioselectivity, results in high yields [8] under mild reaction conditions, without any protection and deprotection protocol, involving inexpensive, economical, environmentally as well as eco-friendly reagents.

Steroids are large class of natural compounds, many of which show very important roles in plants and animals and are also the main sex hormones in mammals which play important role in regulating metabolism [9]. Bile acid science has a history of more than a century with continuing importance in biology and medicine. In recent years, this class of compounds has gained considerable attention in supramolecular chemistry [10]. Bile acids are biological compounds with interesting properties due to their large, rigid, and curved steroidal skeletons, chemically different hydroxy groups, enantiomeric purities, and their unique amphiphilicity. Bile acids and their derivatives are attractive for synthetic chemists because these facially amphiphilic molecules are biological surfactants with multiple physiological functions. Modified bile acids have pharmaceutical importance as novel drug delivery systems and also have been used for regulating of cholesterol level [11], dissolution of gallstones [12], cancer treatment [13], and membrane transfection [14].

Bile acids can self-assemble because of their amphiphilic properties, which make them potential building blocks for the design of polymeric materials for biomedical applications [15] and have gained considerable attention in supramolecular chemistry in recent years. More recently, bile acids have became much more attractive in the construction of star-shaped derivatives called “molecular pockets” and they have been used as a drug delivery vehicles [16], nonpolymeric hydrogelators [17], chemo sensors for metal ions [18] and molecular containers [19]. Hence, based on such extensive applications of bile acid based dendrimers, it is worth to synthesize the following dendrimers with bile acid surface group using click chemistry (Fig. 1).

2. Result and discussion

Terminal alkynes were prepared by esterification of bile acids **13** and **14** using an excess of propargyl alcohol and a catalytic amount of *para*-toluenesulfonic acid to give propargyl esters **15** and **16** in 96% and 95% yields, respectively. In the ^{1}H NMR spectrum the compounds **15** and **16** displayed the ester acetylenic proton as a triplet at δ 2.48 ppm and –OCH_2 as doublet at δ 4.68 ppm in addition to the signal for the other aliphatic protons. The ^{13}C NMR spectrum of compound **15** and **16** showed signals at δ 173.4 for the carbonyl carbon in addition to the other carbon signals. The propargyl esters **15** and **16** were acetylated using Ac_2O and TMSOTf in DCM to give the acetylated terminal alkyne compounds **17** and **18** in 92% and 89% yields, respectively (Scheme 1).

In the ^{1}H NMR spectrum, the compound **17** displayed two singlets at δ 2.04 and 2.11 for the two CH_3COO-protons and the ester acetylenic proton appeared as a triplet at δ 2.48 ppm and -OCH_2 protons appeared as a doublet at δ 4.68 ppm in addition to the signals for the other

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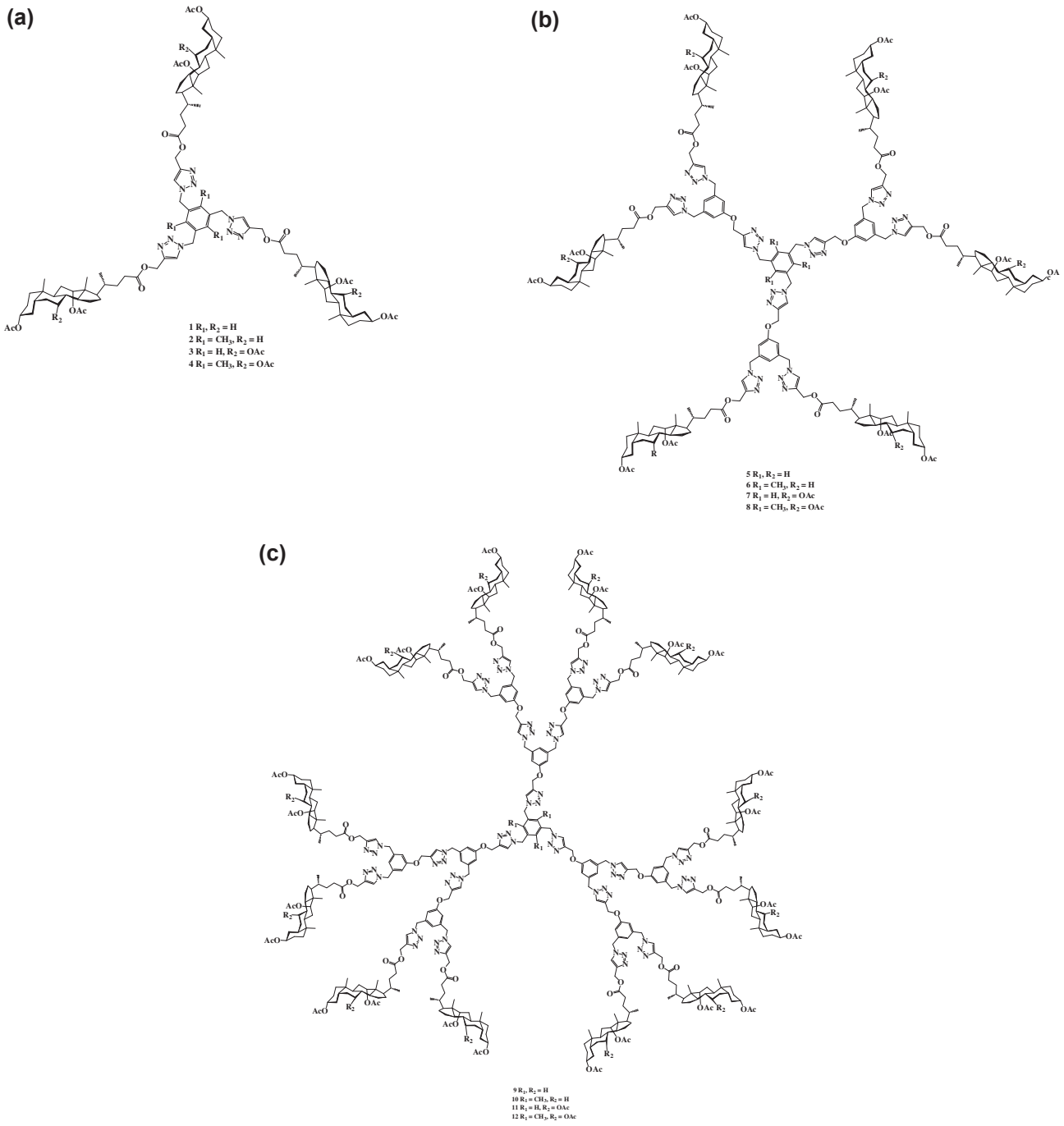
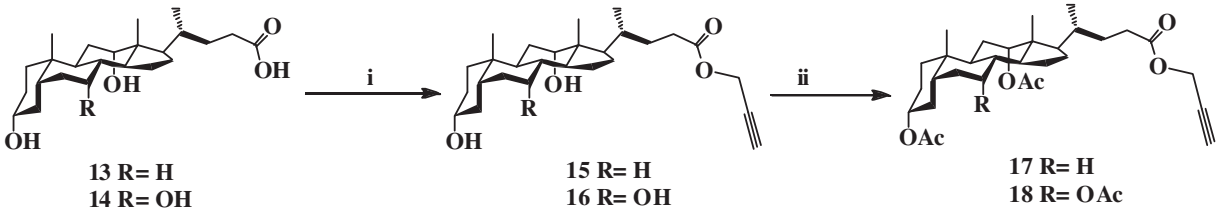


Fig. 1. The structure of bile acid dendrimers **1–12**.

aliphatic protons. The ^{13}C NMR spectrum of the compound **17** showed signals at δ 173.2 for the propargyloxy ester carbonyl carbon and the carbonyl carbons of the two CH_3COO-group appeared at δ 170.4 and δ 170.6 respectively in addition to the signals for the other aliphatic carbons. The ESI mass spectrum of the compound **17** showed the molecular ion peak at m/z 515 (M+1). Further the structure of the



Scheme 1. Reagents and conditions: (i) PTSA (10 mol %), propargyl alcohol (5–10 mL), 55–60 °C, 7 h, **15** (96%) and **16** (95%). (ii) $Ac_2O/TMSOTf/CH_2Cl_2$, 0 °C, 10 min, **17** (92%) and **18** (89%).