Bioorganic & Medicinal Chemistry Letters 21 (2011) 4724–4727

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Improved performance by replacing iminodiacetic residues with glyceryl residues in symmetrically branched oligoglycerols

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ARTICLE INFO

Article history:
Received 15 April 2011
Revised 9 June 2011
Accepted 16 June 2011
Available online 25 June 2011

Keywords:
Symmetrically branched oligoglycerols
Dendron
Water-solubility
Liposome
Duration period

ABSTRACT

Synthesis of a symmetrically branched diglycerol (BGL002, involving one iminodiacetic residue) as a G2 dendron, and the tetradecaglycerol (BGL014, involving one iminodiacetic residue) as a G4 dendron, is described. Several members of the BGL family of G2–G4 dendrons were assembled, with G2 bearing four hydroxyl groups at the terminus region, G3 bearing eight, and G4 bearing sixteen. It is noteworthy that triglycerol (BGL003, including no iminodiacetic residue), has a water-solubility ten times higher than BGL002, and the liposome surrounded by BGL014 has a duration period in blood vessel roughly two times longer than the liposome surrounded by dodecaglycerol (BGL012, including three iminodiacetic residues).

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Derivates of medicinal compounds with polyethylene glycol (PEG) group attached via covalent bonding (PEGylation) have been reported in the recent decades.[1] Such PEGylation often provides the derivatives with greater in vivo biologically or thermally stability than the original molecules and/or a greater duration period in blood vessels.

To enhance such biologically favorable properties, glyceryl oligomers or polymers, mainly involving dendric skeletons, have also been studied as rival candidates to PEG.[2] As shown in Figure 1, three basic types of oligomers **1**, **2**, and **3**, can be listed. Although a vague mixture probably containing **1** and **2** was reported in an earlier papers,[3] practical methods to produce oligomers with known chemical structure came later with the synthesis of **1** by Koma in 1986,[4] and of **2** by Vanlerberghe in 1969,[5] and also by Yoshii et al.[6] and Yasukochi et al.[7] in 1997. In contrast, no reports were made on symmetrically branched oligoglycerols **3** (BGL) before our publication in 1992.[8]

The synthesis we developed for **3** yielded a single product (no statistical mixture) with a peculiar symmetrical cascade-shape, and *no asymmetric center*. Therefore **3** may be more potentially applicable for medicinal use than **1** and **2**. We have previously reported the preparation of a trimer (BGL003) as a second generation (G2) of dendron,[8] a hexamer (BGL006)[9,10] and a heptamer (BGL007)[11] as third generation (G3) of dendrons, and dodecamer (BGL012)[12] as a fourth generation (G4) of dendron,

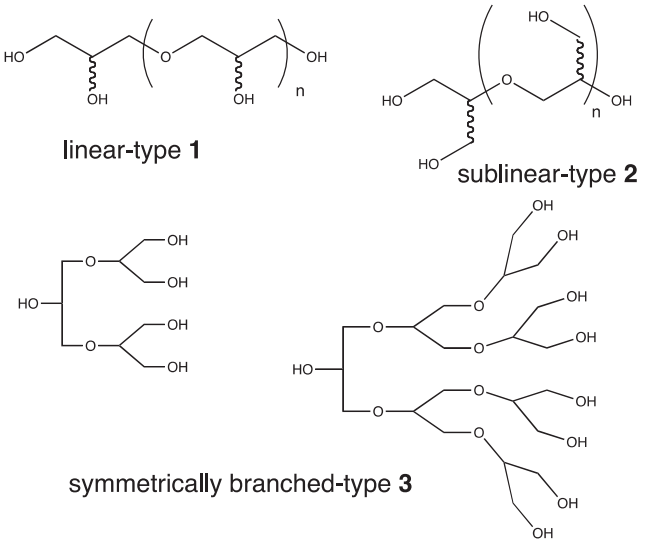

Figure 1. Various oligoglycerols including our developed symmetrical ones.

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doi:10.1016/j.bmcl.2011.06.064

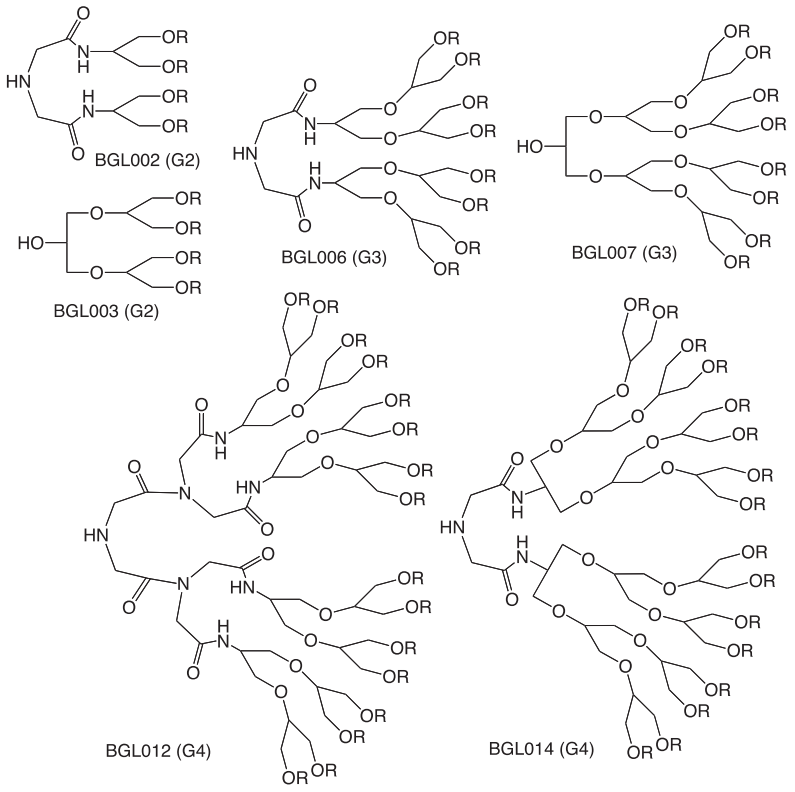
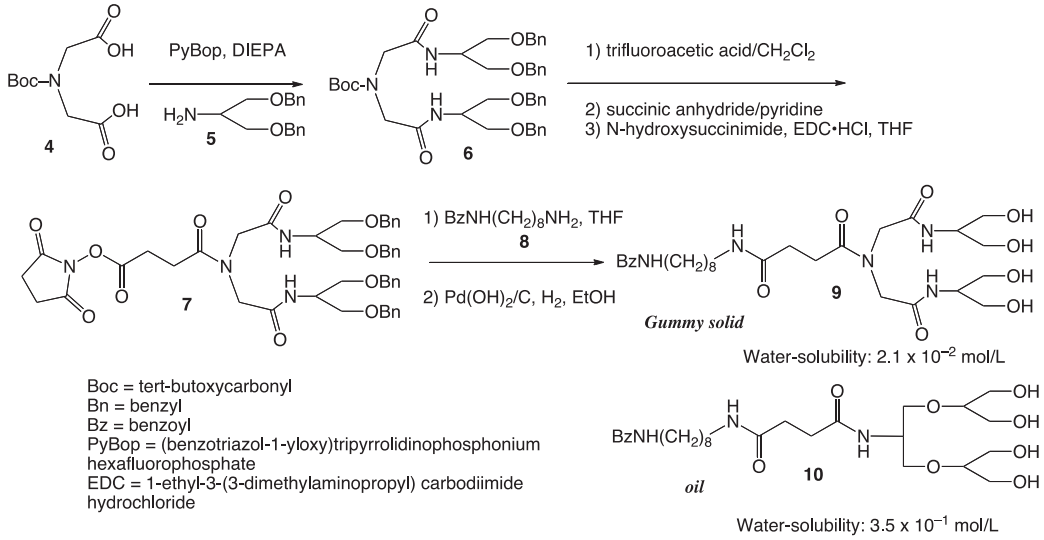


Figure 2. Previously prepared BGL family and newly disclosed two BGL (BGL002 and BGL014).



Scheme 1.

including the molecules with protecting groups (R) at the terminus region and those with free hydrogens (R = H) (Fig. 2).

In this Letter, we describe the preparation of an alternative G2 dendron, BGL002 derivative **9** (Scheme 1) and a G4 dendron, BGL014 derivative **17** (Scheme 2), to complement the existing G2–G4 series of BGL family. Moreover, we report on the improved performance obtained by replacing iminodiacetic residues with glyceryl residues in the dendric BGL.

Because we have previously measured the water-solubility of BGL003 derivative **10**,[9] an equivalent BGL002 derivative **9** was prepared for comparison. Condensation of **4**[13] and **5**[14] using (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) in DMF in the presence of diisopropylethylamine (DIPEA) at room temperature for 9.5 h afforded **6** in 80% yield. The Boc group of **6** was removed by trifluoroacetic acid (TFA)/dichloromethane at room temperature for 30 h, then treatment of succinic anhydride in pyridine at 100 °C for 15 h, and condensation of the resulting acid and *N*-hydroxysuccinimide (HOSu) with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC·HCl) in the presence of triethylamine (TEA) in THF at reflux for 18 h gave **7** in 68% yield from **6**. Finally, condensation between **7** and **8**[15] in THF at room temperature for 40 h, followed

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