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Solid phase synthesis of a novel folate-conjugated 5-aminolevulinic acid methyl ester based photosensitizer for selective photodynamic therapy

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ABSTRACT

The development of a novel tumor-targeting photosensitizer delivery system, with potential ability to selectively transport the photosensitizer prodrug 5-aminolevulinic acid methyl ester (MAL) into the tumor site has been herein described. Conjugation of MAL to folic acid (FA) via an unnatural β-peptide linker has been carried out almost entirely by an efficient solid phase approach. This molecular system has been devised for possible applications in selective photodynamic diagnosis (PDD) and therapy (PDT).

Photodynamic therapy (PDT) represents a modern and non-invasive therapeutic approach devised for the treatment of various human disorders such as ophthalmic, dermatological, and cardiovascular diseases, and especially of malignant tumors. It consists in the selective uptake of a light-sensitive agent, a photosensitizer (PS) that upon exposure to a specific wavelength interacts with molecular oxygen to form a toxic species, the singlet oxygen ($^1O_2$), which is responsible of photo-induced cell death by either apoptosis and necrosis. PDT efficiency is essentially limited by the unselective PS transport to the tumor tissue and by alteration or loss in activity of the PS itself. The most promising strategy to improve PDT performance is the development of targeted PS systems, which exploit the presence of tag units, generally represented by receptor-targeting moieties. Most generally, over the past decades the evaluation of targeted drug delivery systems (DDSs) has attracted a great deal of attention from both chemistry and pharmacology worlds.[1–4] The search for such innovative drug delivery technologies has been mainly due to the need of obtaining more selective and efficient therapeutics able to reach, without alteration, only the diseased cells. Typically, DDSs comprise a prodrug and a targeting moiety[5] joined through a linker. Folic acid (FA), the natural vitamin B9,[6–8] has become one of the most popular molecular probes for these purposes thanks to its peculiar characteristics. In addition to its high stability, low cost and generally poor immunogenicity, FA is endowed with high affinity for folate receptors (FRs) which are overexpressed in a wide variety of malignant cells,[9] but it is more rarely expressed on healthy cells. Moreover, its conjugation to cytotoxic agents via its γ-carboxyl moiety usually provides molecules able to retain the affinity for FRs.[10] Since FA enters cells by receptor-mediated endocytosis,[11,12] a striking consequence is that those FRs expressed by cancer cells can be exploited to selectively convey specific anticancer drugs.[13]

Recently, FA has been successfully employed to build innovative molecular devices[14] with dual diagnostic and therapeutic purposes – the so called 'theranostic' approach– [15] which have opened new horizons in the field of contemporary design of imaging guided therapeutics. Despite the broad pharmacological applications, FA has been only seldom used in the field of targeted PDT.[16,17]

Based on these data and on our previous results,[18] we have herein designed and synthesized a new FA-based theranostic agent (**1**) for PDD (photodiagnosis) and PDT applications, bearing a precursor of the endogenous photosensitizer protoporphyrin IX (PpIX), that is, the 5-aminolevulinic acid methyl ester (methyl δ-aminolevulinate, MAL, mALA or Metvix®) as PS warhead and, as shown in Figure 1, containing a biostable β-peptide spacer which connects the targeting moiety and the photosensitizer prodrug.

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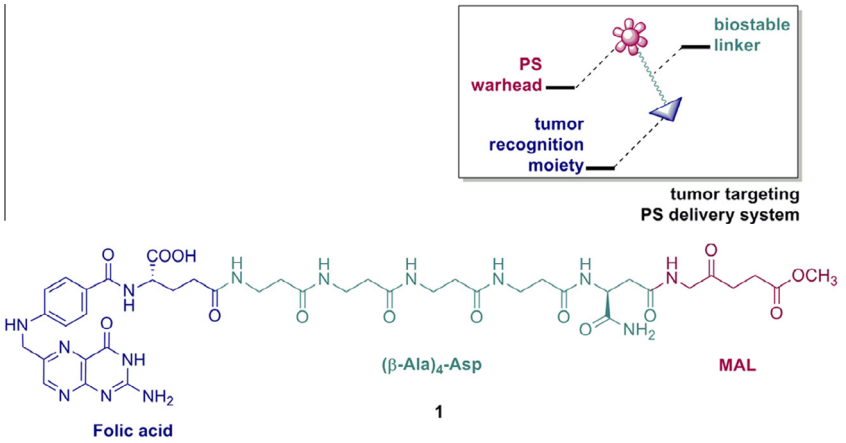
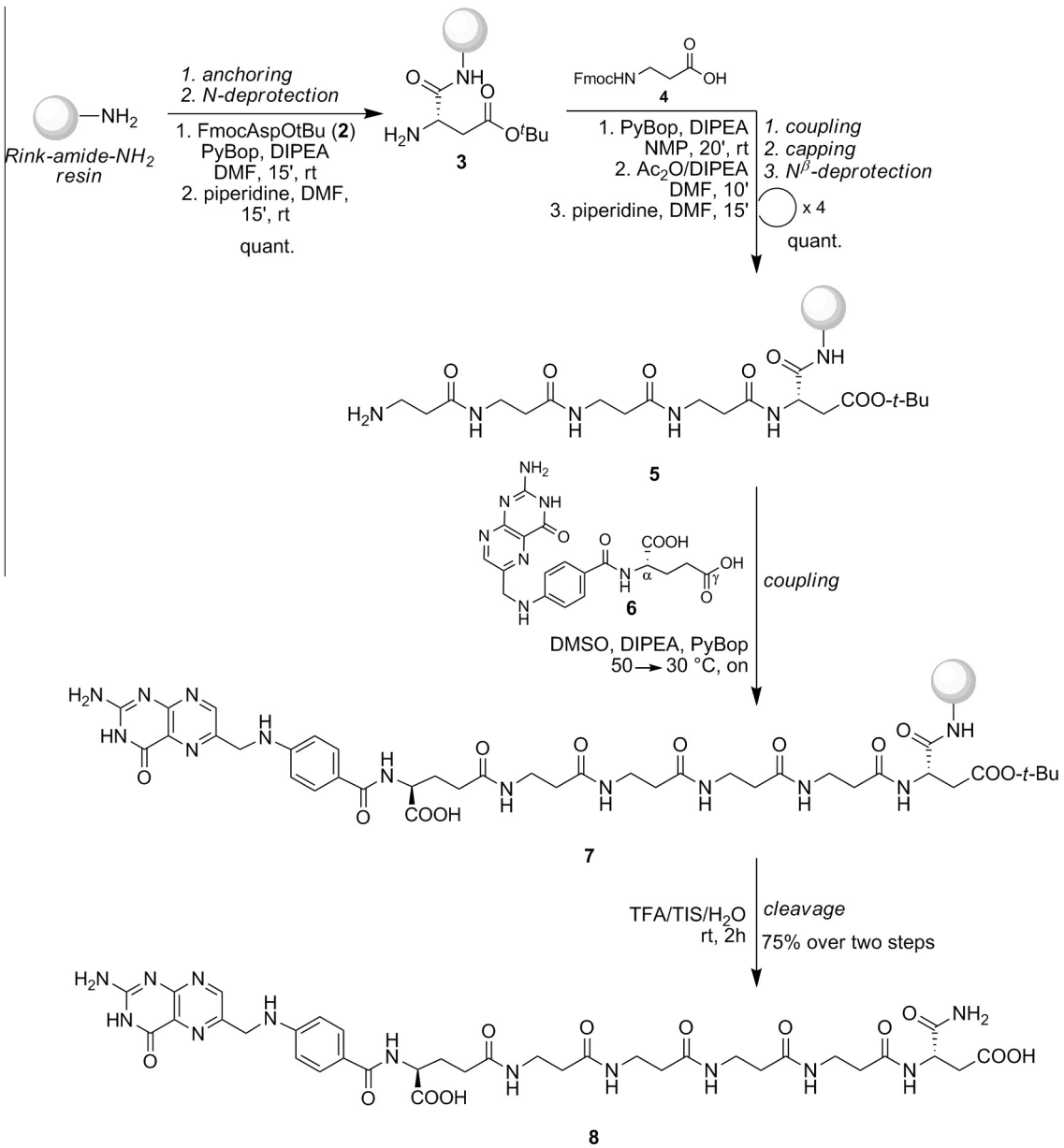


Figure 1. FA-conjugated MAL based photosensitizer **1**.



Scheme 1. Solid phase synthesis of FA-containing β-peptide **8**.