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Reviews

Synthetic strategies in construction of organic low molecular-weight carrier-drug conjugates

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ABSTRACT

Inefficient transportation of polar metabolic inhibitors through cell membranes of eukaryotic and prokaryotic cells precludes their direct use as drug candidates in chemotherapy. One of the possible solutions to this problem is application of the 'Trojan horse' strategy, i.e. conjugation of an active substance with a molecular carrier of organic or inorganic nature, facilitating membrane penetration. In this work, the synthetic strategies used in rational design and preparation of conjugates of bioactive agents with three types of organic low molecular-weight carriers have been reviewed. These include iron-chelating agents, siderophores and cell-penetrating peptides. Moreover, a less known but very promising "molecular umbrella" conjugation strategy has been presented. Special attention has been paid on appropriate linking strategies, especially these allowing intracellular drug release after internalisation of a conjugate.

1. Introduction

Many organic compounds, known as effective inhibitors of enzymes of crucial importance for human pathogenic microorganisms or cancer cells, do not exhibit any chemotherapeutic activity. This is often due to the poor diffusion of an active substance through biological membranes. The 'Trojan horse' strategy is based on the idea of the conjugation of membrane-impermeable substance with any molecular carrier. As a result of this conjugation, unfavourable properties of drug molecules become masked in a way that makes them able to cross the cell membrane. In an ideal case, once internalized, the active component is released from the conjugate and reaches the intracellular target. Several types of drug carriers are known. One of them is inorganic nanoparticles, like quantum dots, silver and gold or iron oxide nanoparticles [1–5]. Another group comprises macromolecular organic carriers, carbon nanotubes [6–10] and dendrimers [11–14]. Both are supramolecular structures, able to penetrate biological membranes in a rather cell-unspecific manner (direct translocation or endocytosis), due to the overall shape and physico-chemical character of the macromolecular carrier.

In this review, attention is focused on another group of organic molecular carriers, low molecular-weight compounds, which due to the specific interactions of their particular functional groups with components of biological membranes (lipids or proteins), can effectively act as cell membrane penetrating agents. The most popular members of this group are cell-penetrating peptides (CPPs), composed of 5 – 30 amino acid residues of often cationic character [15–19]. Another members of this group, siderophores, are definitely cell-specific since they can effectively act as molecular carriers delivering cargo exclusively to cells containing membrane-located siderophore uptake systems [20,21]. Less extensively studied than aforementioned systems but conceptually interesting "molecular umbrellas" are rationally designed membrane translocators of potentially universal application [22,23]. Carrier-drug conjugates can be formed either through non-covalent interactions or

Abbreviations: Boc, *tert*-butoxycarbonyl group; Cbz, benzyloxycarbonyl group; DIC, *N,N'*-diisopropylcarbodiimide; DIPEA, diisopropylethylamine; DMAP, 4-(*N*-dimethylamino)pyridine; DPPA, diphenylphosphoryl azide; Fmoc, fluorenylmethyloxycarbonyl group; HATU, *N*-[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide; HBTU, 2-(1*H*-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; IBCF, isobutyl chloroformate; *m*-CPBA, 4-chloroperoxybenzoic acid; NaAsc, sodium ascorbate; NHS, *N*-hydroxysuccinimide; PEG, poly(ethylene glycol); PMB, *para*-methoxybenzyl group; SAR, structure-activity relationship; SPPS, solid-phase synthesis; TBTU, 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate; TBDMS, *tert*-butyldimethylsilyl group; TDBTU, *N,N,N',N'*-tetramethyl-*O*-(benzotriazol-1-yl)-uronium tetrafluoroborate; TBTA, tris[1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine; TFA, trifluoroacetic acid; THF, tetrahydrofuran.

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