European Journal of Medicinal Chemistry 115 (2016) 438–452

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Review article

Biological applications of hydrophilic C_{60} derivatives ($hC_{60}s$)– a structural perspective

Xiaolei Zhu [a], Matthieu Sollogoub [a], Yongmin Zhang [a, b, *]

[a] Sorbonne Universités, UPMC Univ Paris 06, CNRS, Institut Parisien de Chimie Moléculaire (UMR 8232), 4 Place Jussieu, 75005 Paris, France
[b] Institute for Interdisciplinary Research, Jianghan University, Wuhan Economic and Technological Development Zone, Wuhan 430056, China

ARTICLE INFO

Article history:
Received 8 January 2016
Received in revised form
9 March 2016
Accepted 10 March 2016
Available online 11 March 2016

Keywords:
Hydrophilic C_{60} derivatives
ROS generation
Radical scavenger
Biological applications

ABSTRACT

Reactive oxygen species (ROS) generation and radical scavenging are dual properties of hydrophilic C_{60} derivatives ($hC_{60}s$). $hC_{60}s$ eliminate radicals in dark, while they produce reactive oxygen species (ROS) in the presence of irradiation and oxygen. Compared to the pristine C_{60} suspension, the aqueous solution of $hC_{60}s$ is easier to handle *in vivo*. $hC_{60}s$ are diverse and could be placed into two general categories: covalently modified C_{60} derivatives and pristine C_{60} solubilized non-covalently by macromolecules. In order to present in detail, the above categories are broken down into 8 parts: $C_{60}(OH)_n$, C_{60} with carboxylic acid, C_{60} with quaternary ammonium salts, C_{60} with peptide, C_{60} containing sugar, C_{60} modified covalently or non-covalently solubilized by cyclodextrins (CDs), pristine C_{60} delivered by liposomes, functionalized C_{60}-polymer and pristine C_{60} solubilized by polymer. Each hC_{60} shows the propensity to be ROS producer or radical scavenger. This preference is dependent on $hC_{60}s$ structures. For example, major application of $C_{60}(OH)_n$ is radical scavenger, while pristine C_{60}/γ-CD complex usually serves as ROS producer. In addition, the electron acceptability and innate hydrophobic surface confer $hC_{60}s$ with O_2 uptake inhibition, HIV inhibition and membrane permeability. In this review, we summarize the preparation methods and biological applications of $hC_{60}s$ according to the structures.

Contents

1. Introduction 439
   1.1. Physicochemical property of C_{60} 439
   1.2. ROS producer and radical scavenger 439
   1.3. Pristine C_{60} suspensions and $hC_{60}s$ in water 440
2. $C_{60}(OH)_n$ 440
   2.1. Radical scavenger: prevent oxidative damage from DOX and CCl_4 440
   2.2. Radical scavenger: protect cells from the radiation 441
   2.3. Other protection 441
   2.4. Radical scavenger and ROS producer 441
3. C_{60} with carboxylic acid 441
   3.1. Radical scavenger 441
   3.2. ROS producer 442
4. C_{60} with quaternary ammonium salts 442
   4.1. O_2 uptake inhibition 442
   4.2. ROS producer 443
   4.3. Drug and DNA vectors 443

* Corresponding author. Sorbonne Universités, UPMC Univ Paris 06, CNRS, Institut Parisien de Chimie Moléculaire (UMR 8232), 4 Place Jussieu, 75005 Paris, France.
E-mail address: yongmin.zhang@upmc.fr (Y. Zhang).

http://dx.doi.org/10.1016/j.ejmech.2016.03.024
0223-5234/

5. C_{60} with peptide 443
5.1. Radical scavenger 443
5.2. ROS producer 443
5.3. ROS producer and radical scavenger 443
5.4. Delivery 443
5.5. HIV inhibitor 444
6. C_{60} containing sugar 444
6.1. Radical scavenger 444
6.2. ROS producer 445
6.3. Drug vector 445
7. C_{60} and cyclodextrins (CDs) 445
8. C_{60} delivered by liposomes 446
8.1. ROS producer 446
8.2. Radical scavenger 447
9. C_{60} and polymers 447
9.1. Radical scavenger 447
9.2. ROS producer 447
9.2.1. C_{60} and PNVP 447
9.2.2. C_{60} and PEG 448
9.3. Drug delivery 449
10. Conclusion 449
Acknowledgments 449
References 449

1. Introduction

Hydrophilic C_{60} derivatives ($hC_{60}s$) serve as either photosensitizer or radical scavenger. The intriguing co-existence of two opposite capacities leads to in-depth study of $hC_{60}s$. The photodynamic ability has applications on DNA cleavage, antitumor, antibacterial activities *etc*., while the ability of absorbing radical causes $hC_{60}s$ to be antioxidant agents. In most of state-of-the-art research, the native C_{60} is produced by two most common ways, Krätschmer-Huffman method and combustion of laminar flames of benzene and oxygen [1–3]. Both of the two methods generate C_{70} by-product, which is removed through chromatography [4]. The pristine C_{60} with poor hydrophilicity limits its further development. Three strategies are adopted to get biocompatible $hC_{60}s$: (1) the introduction of head-top groups on C_{60} cage, such as hydroxyl, carboxyl, quaternary ammonium salts, (2) the conjugation of small hydrophilic molecules (saccharides, peptides) *via* different linkers, (3) the encapsulation of macromolecules (CDs, liposomes and polymers). In this review, we present $hC_{60}s$, their biological applications and try to explain them based on structures.

1.1. Physicochemical property of C_{60}

Fullerene (C_n, n is an even number) is a spheroid made of at least 20 carbon atoms. The formation of the peculiar spheroid structure has been explained by a 'shrink-wrapping' mechanism [5]. Multiwall nanotubes wrap into the giant fullerenes, which will sublime several C_2 and twine further to form the more stable C_{70} and C_{60}. If the reaction continues, the carbon atoms are removed to form the smaller fullerenes (like C_{20}), which are instable and prone to open and disappear irreversibly [6]. All of the fullerene members contain different number of hexagons and 12 pentagons which are essential to constitute the spheroid. Small fullerenes ($C_{20} \leq C_n \leq C_{58}$) have been predicted to possess narrow HOMO-LUMO gaps and high reactivity owing to the adjacent pentagons, which violate isolated pentagon rule (IPR) [7]. C_{60} is the first fullerene to conform to IPR and without any other IPR isomers, so is the second abundant fullerene C_{70}. Larger fullerenes ($C_n \geq 76$) have at least 2 IPR isomers. The number of IPR isomers increases with the enlargement of the size of fullerene, except C_{84} (24 IPR isomers) and C_{86} (19 IPR isomers) [8].

C_{60}, constituted by 60 $sp^{2.28}$-hybridized carbon atoms, is an icosahedron of 12 pentagons which are separated by 20 hexagons [9]. Each carbon atom connects with each other by three nonplanar σ bonds, which leads to the angle strain and a p orbit forming a large π electron cloud. The angle between the π orbital and σ bond is 11.6°, while the angels of normal alkene and alkyl are 0° and 19.47°, respectively [10]. The way to alleviate the angle strain is that $sp^{2.28}$-hybrid transforms to sp^3-hybride. These carbon atoms compose [6,6] bond (located between two fused 6-membered rings) and [5,6] bond fused by 5- and 6-membered rings. The pristine C_{60} is prone to produce [6,6] cycloadduct on account of [6,6] bond much closer to olefinic bond than [5,6] bond [9,11]. Various C_{60} adducts can be obtained through Bingel reaction [12–14], Diel–Alder reaction [15], [3 + 2] cycloaddition reaction, [2 + 2] cycloaddition reaction [16], SET-promoted photoaddition reaction [17] and other different addition patterns [18–20].

1.2. ROS producer and radical scavenger

C_{60} behaves like an electron-deficient olefin attributed to poor electron delocalization. It could accept at most 6 electrons, which has been confirmed by 6 measured potentials [21,137]. The high electron affinity endows C_{60} with radical scavenging ability [138].

C_{60} generates ROS under UV irradiation, even under white light (Fig. 1). The dominant one is single oxygen ($^1O_2$), quantitatively produced by oxygen accepting energy from $^3C_{60}$ (Type II Energy Transfer). $^3C_{60}$ with lower energy (37.5 kcal/mol) is obtained *via* intersystem crossing from $^1C_{60}$ with relatively high energy (46.1 kcal/mol) (Fig. 1) [22]. If there are electron donor (such as, triethylamine and NADH) in the solution, $^3C_{60}$ accepts an electron to form $C_{60}^{\bullet-}$ (Type I Electron Transfer). O_2 obtains the electron from $C_{60}^{\bullet-}$ to get $O_2^{\bullet-}$, which is followed by disproportionation catalyzed by superoxide dismutase (SOD) and Fenton reaction. •OH is generated [23–25]. ROS is applied for tumor inhibition, antibacterial, DNA cleavage, delay of arthritic progress, *etc*..