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Acetophenone substituted phthalocyanines and their graphene quantum dots conjugates as photosensitizers for photodynamic antimicrobial chemotherapy against *Staphylococcus aureus*

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ABSTRACT

This work reports on the synthesis and characterization of novel acetophenone substituted phthalocyanines along with the self-assembled nanoconjugates formed via π-π stacking interaction between the synthesized unmetalated (**2**), zinc (**3**) and indium (**4**) phthalocyanines and graphene quantum dots (GQDs) to form **2**@GQDs, **3**@GQDs and **4**@GQDs. The complexes and conjugates exhibited high singlet oxygen ranging from 0.20 to 0.79 in DMSO for Pcs and nanoconjugates where in all cases, the indium complexes showed the highest singlet oxygen quantum yields. The photodynamic antimicrobial chemotherapy activity of both phthalocyanines and nanoconjugates were tested against *Staphylococcus aureus*. **4**@GQDs was found to be highly effective causing a 9.68 log reduction of the bacteria at 10 μM (based on Pc) when compared to 3.77 log reduction of **3**@GQDs.

1. Introduction

Multidrug resistance by microorganisms (such as Methicillin-resistant *Staphylococcus aureus*) [1] has limited the use of some of the commercially available drugs for the treatment of infections caused by pathogens. Photodynamic antimicrobial chemotherapy (PACT), also termed Antimicrobial Photodynamic Therapy (a-PDT), is a potential alternative treatment to address drug resistance by pathogens [2–10].

In PACT a photosensitizer molecule absorbs energy from light of a specific wavelength. The photoexcited photosensitizer in its triplet state interacts with triplet (ground) state molecular oxygen to produce reactive oxygen species (ROS) such as singlet oxygen, that destroy cells or force them into death pathways [2–13]. Phthalocyanine (Pc) dyes are known photosensitizers for PACT [5,7,12].

Pc dyes have recently caught the attention of scientists for applications in PACT due to their physical and chemical stability [14,15], and good production of reactive oxygen species such as singlet oxygen [16–21]. Metallophthalocyanines (MPcs) that have diamagnetic central metals (such as Zn^{2+}, Si^{4+}, In^{3+}, Ga^{3+}, etc.) give high singlet oxygen quantum yields [22,23], and are favored for PACT. Therefore, this study reports the synthesis and use for PACT of Zn (II) and In (III) Pcs as well as the metal free derivative.

Previous reports have proved that non-covalently linking MPcs to carbon nanomaterials such graphene quantum dots (GQDs) may result in the enhancement of their photophysicochemical properties which are very important for PACT. GQDs, which are carbon based nanomaterials with planar π-electron rich structure, are gaining attraction due to their various properties such as stable photoluminescence, low toxicity, chemical stability, high singlet oxygen production and their good ability to form π-π interaction with other π-electron rich molecules such as phthalocyanines [24–31].

In this work, we report on the synthesis of novel acetophenone substituted MPcs: [2,9(10), 16(17), 23(24)-tetrakis-(4-acetophenoxy) phthalocyaninato (TAPPc, **2**); 2,9(10), 16(17), 23(24)-tetrakis-(4-acetophenoxy) phthalocyaninato zinc(II) (ZnTAPPc, **3**) and 2,9(10), 16(17), 23(24)-tetrakis-(4-acetophenoxy) phthalocyaninato indium (III) chloride (InClTAPPc, **4**)], Scheme 1 with high singlet oxygen quantum yields and the formation their nanoassemblies by π-π stacking interaction to GQDs. The linkage of MPcs to GQDs has been done before, but with applications mostly toward photodynamic therapy (PDT) [32], non-linear optics [33], electrocatalysis [34], optical sensing [30], just to cite a few. In this work, we report for the first time, on the use of these type of nanocomposites (MPcs-GQDs) for applications in photodynamic antimicrobial chemotherapy against *Stapylococcus aureus*, a gram positive bacteria. Also note that GQDs and the acetophenoxy substituents are chosen in this study due to their earlier reported antibacterial properties with reactive carbonyl group [35,36].

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