Title: **Synthesis of tigecycline derivatives with potential antibacterial activity**

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Date: January 2020

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Antibiotic resistance is an important health challenge associated with high mortality that society is nowadays facing. This situation is aggravated by several facts: prevention measures are insufficient, the number of effective therapies is decreasing and only few antibiotics are being actively developed.

Tigecycline is a third-generation tetracycline developed in 1980s. It shows a broad spectrum of activity against aerobic and anaerobic gram-positive and gram-negative bacteria, and it is also effective against some tetracycline-resistant strains. On the other hand, antisense therapy is a breakthrough therapy that uses antisense oligonucleotides (short strands of nucleic acids or chemical analogs) to treat genetic disorders, cancer or infections. It is called antisense because its base sequence is complementary to the target gene mRNA. An example of chemically modified oligonucleotides are phosphorodiamidate morpholino oligomers (PMOs), which are stable to nuclease enzymes.

In this work we are focused on the synthesis of two tigecycline analogs, which maintain the active pharmacophore of the antibiotic, conjugated to an 11-nucleobase PMO that targets the *acpP* gene, an essential gene in bacteria.

Two analogs were designed with different linkers, based on their intracellular stability. One was a non-cleavable linker which provided a stable structure, while the other one has a disulfide bridge that can be cleaved in the reducing environment of the cytoplasm, thus releasing the active molecules. Both conjugates were successfully obtained by stepwise chemical synthesis in solution, purified by reverse-phase HPLC and characterized by UPLC, mass spectrometry and NMR spectroscopy.

Finally, their bactericidal activity against a panel of multi-resistant strains of *A.Baumannii, K.Pneumoniae* and *P.Aureoginosa* is currently being tested by the group of Dr. Jordi Vila at Hospital Clínic de Barcelona.

Keywords: Antibiotic resistance, tigecycline, PMO, bactericidal activity