TRIFUNCTIONAL SELF-IMMOLATIVE SPACERS LINKED TO AMIDES: A NEW OPPORTUNITY FOR BIOCONJUGATION

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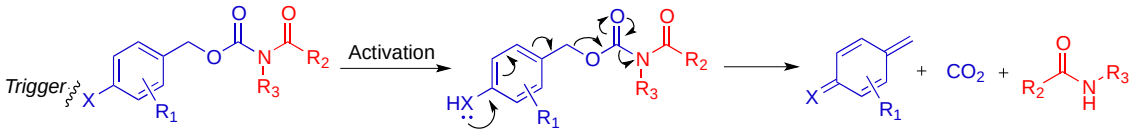
Antibody-Drug Conjugates (ADCs) belong to a class of bioconjugates that are attracting an ever-increasing interest as powerful systems for targeted oriented therapy in particular in treatment of cancer [1] as well as of bacterial infections resistant to conventional antibiotics [2]. A key role in the efficiency displayed by an ADC is played by the linker moiety that connects the antibody to the drug. The linker needs to be stable enough in the biological systems to reach undamaged the target so that the drug can be released in a high efficient way. One of the most popular release systems is represented by the so called "self-immolative spacer" that, after a proper activation, is able to kick off a cascade process able to release the bioactive compound through a 1,6-elimination mechanism [3]. Actually, the drug selected is connected to the linker by one of its hydroxyl or amino functionalities. However, many drugs possess other functional groups that would be worth exploring as possible sites of connections to linkers. In this context we focused our attention on amides since a notable number of commercially available drugs embed in their structure this functionality. This work reports the synthesis of different linkers made up by trifunctional aromatic compounds with different trigger moieties. These linkers have been subsequently conjugated to the amido group of bioactive molecules through the carbamate framework exploiting different synthetic routes. Preliminary tests on the stability and releasing ability of these conjugates will be also reported showing their efficiency as ADCs devices.



[1] Chari, R. V., Miller, M. L., Widdison, W. C., *Angew. Chem. Int. Ed.* **2014**, 53, 3796 – 3827.

[2] Mariathasan, S., Tan, M. W., *Trends Mol. Med.* **2017**, 23, 135-149.

[3] Alouane, A.; Labruere, R.; Le Saux, T.; Schmidt, F., Jullien, L., *Angew. Chem. Int. Ed.* **2015**, 54, 7492-7509.