Synthesis of modified dendrimers and conjugation with selected apoptosis inhibitors

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Apoptosis is a biological process relevant to different human diseases stated that is regulated through protein-protein interactions and complex formation.[1] One point of regulation is the formation of a multiprotein complex known as apoptosome.[2] In our group, it has been previously reported a peptidomimetic compound bearing a 3-substituted-piperazine-2,5-dione moiety and a seven-membered ring moiety as potent apoptotic inhibitors.[3] We reduced the conformational freedom of the exocyclic tertiary amide bond of the diketopiperazine by an isosteric substitution of a triazole. For one of the proposed structures a β-lactam compound was isolated, that resulted to be the most potent inhibitor.[4]

At this point, we wanted to conjugate our potential drugs with a polymer that could offer a more specific intracellular transport and release to reach the molecular target.

Dendritic polymers are widely used as multifunctional materials with specific properties for potential biomedical and pharmaceutical applications. These multifunctional macromolecules have been used as carrier systems of drugs in the study of bio-interaction against different bio-active molecules and systems.[5] The most important drawback of these types of dendrimers is their toxicity due to the positive charge on their surface. Thus, a high generation of poly(propylene imine) dendrimers with densely organized oligosaccharide shells in which each peripheral amino group is modified by two chemically coupled oligosaccharide units has been reported.[6] This attachment resulted in much lower cytotoxicity towards different cell lines.[7]

In this work, 5th generation PPI dendrimers modified with maltose units were synthesized and coupled with previously mentioned modified small molecules which have shown activity as potential apoptosis inhibitors.

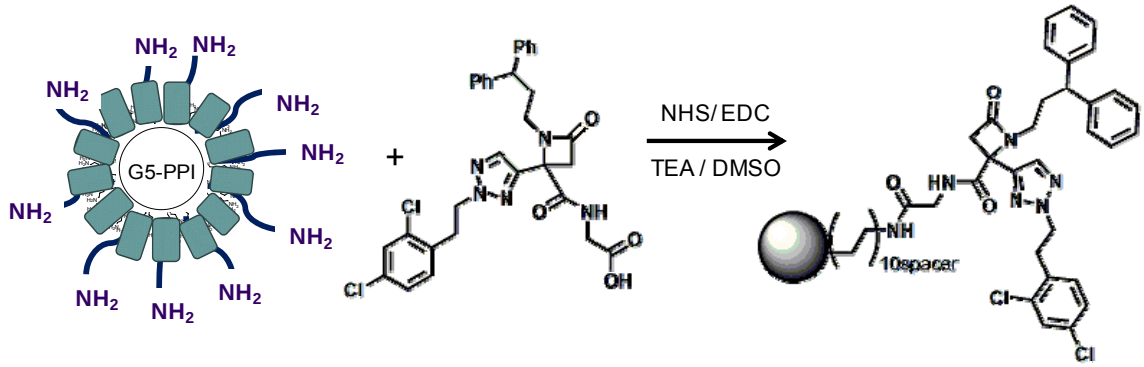

Figure 1: Coupling of a small molecule with a dense-shell glycodendrimer bearing an amino-terminal group.

References

[1] Mondragón, L.; Orzáez, M.; Sanclimens, G.; Moure A.; Armiñán, A.; Sepúlveda, P.; Messeguer, A.; Vicent, M. J.; Pérez-Payá. J. Med. Chem. **51** (2008) 521-529.
[2] Martin, A. G.; Nguyen, J.; Wells, J. A.; Fearnhead, H. O. Biochem. Biophys. Res. Comm. **319** (2004) 944-950.
[3] Moure, A.; Sanclimens, G.; Bujons, J.; Masip, I.; Alvarez-Larena, A.; Pérez-Payá, E.; Alfonso, I.; Messeguer, A. Chem. Eur. J. **17** (2011) 7927-7939.
[4] Corredor, M.; Bujons, J.; Orzáez, M.; Sancho, M.; Pérez-Payá, E.; Alfonso, I.; Messeguer, A. Eur. J. Med. Chem. **63** (2013) 892-896.
[5] Boas, U.; Heegaard, P.M; Chem. Soc. Rev. **33** (2004) 43-63.
[6] Klajnert, B.; Appelhans, D.; Komber, H.; Morgner, N.; Schwarz, S.; Richter, S.; Brutschy, B.; Ionov, M.; Tonkikh, A. D.; Bryszewska, M.; Voit, B. Chem. Eur. J. **14** (2008) 7030-7041.
[7] Arima, H.; Chihara, Y.; Arizono, M.; Yamashita, S.; Wada, K.; Hirayama, F.; Uekama, K. J. Control Release **116** (2006) 64-74.