Multivalent phosphorus-containing dendrimers: anchor for multi-target anti-cancer and anti-infectious (pro)drugs

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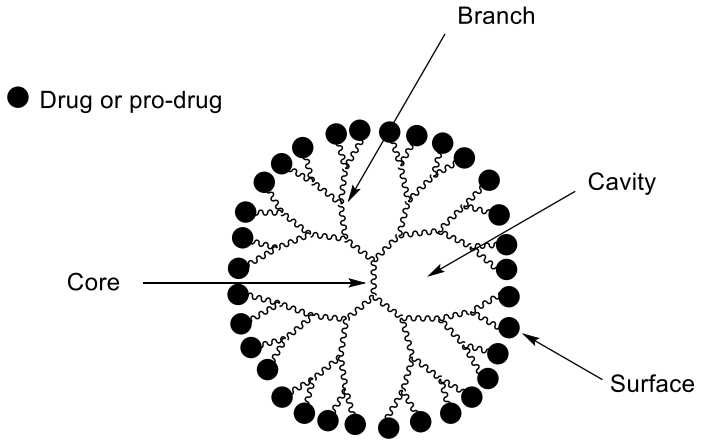
Dendrimers, unlike polymers, are *hyperbranched* three-dimensional and *well-defined spherical* macromolecules, which have a high compatibility with the biological systems. In general, they are prepared by divergent synthetic approaches that consist, starting from a multivalent core, in reacting branched monomers in a repetitive manner, so that the branches grow. For several decades, dendrimers have found applications in different fields such as materials, catalysis or biology.[1] In the field of biology, dendrimers have mainly been used as nano-carriers to improve solubility and facilitate the gradual release of active substances encapsulated in the cavities of the dendritic structure. Although dendrimers covalently linked to drugs or pro-drugs at different levels of the dendritic structure (at the core, in the branches or at the surface) have been described in the literature,[2] there are very few examples and nothing has yet been proposed with phosphorus dendrimers.

Phosphorus dendrimers studied for many years in Anne-Marie Caminade's team have a phosphorus atom at each divergence point of their structure, thus allowing the efficient and precise monitoring of each step of their synthesis by ^{31}P NMR and consequently a high chemical purity essential in the pharmaceutical field.[3]



1. A.-M. Caminade, C. O Turrin, R. Laurent, A. Ouali, B. Delavaux-Nicot, *Dendrimers: towards catalytic, material and biomedical uses*, Wiley: Chichester, UK, **2011**, 1-538.
2. J. Wang, L. Boxuan, L. Qiu, X. Qiao, H. Yang, *J. Bio. Eng*. **2022**, *16*, 18.
3. J.-P. Majoral, A.-M. Caminade, *Eur. J. Inorg. Chem*. **2019**, 1457-1475.

This project proposes the use of multivalent phosphorus dendrimers as an anchor for drugs and prodrugs with the aims of (i) improving the effectiveness of existing drugs by multivalence effect, (i) improving the solubility or the membrane permeability by acting on the physicochemical properties of dendrimers and (iii) controlling the progressive release of active molecules by a tunable cleavage of ester, amide or other bonds in biological medium. The use of dendrimers in this field of application is attractive because a wide variety of functional groups can be introduced on the structure of the dendrimers, which makes it possible to envisage the grafting of drugs at their periphery via a large variety of links. The grafting of two active molecules having different mechanisms of action on the surface of the same dendrimer could also be planned with the aim of having a complementary effect via a multi-target type mechanism of action. This approach could contribute to limiting the risks of development of resistance to certain drugs. In addition, a double alternating grafting of a drug and a polar group at the periphery of the same dendrimer will also be considered in order to make the overall solubility of the dendrimer compatible with physiological media. As part of this thesis, dendrimers carrying anti-cancer and anti-infectious (pro)drugs will be particularly studied.

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Required profile: The candidate should have a good theoretical knowledge in organic chemistry, and basic knowledge in phosphorus chemistry will be appreciated. He/she should have experimental skills in synthesis (work under inert atmosphere with vacuum line), in purification methods (distillation, column chromatography on silica gel, crystallization, extraction...), in analysis and characterization of organic and organophosphorus molecules (NMR, IR, MS...). Working experience at the interface between chemistry and biology will also be appreciated.