Sculpting and Evaluating the Bioactivity of Novel Flavonoid Analogues Derived through Modern Chemoenzymatic Approaches

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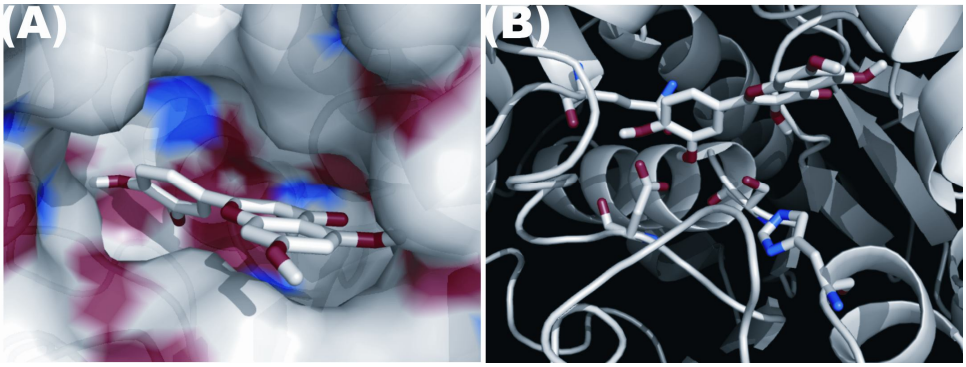
Natural products and especially plant derived flavonoids present numerous anti-angiogenic and anti-carcinogenic effects in cell culture and in animal models with more than 50% of the current effective drugs in the cancer chemotherapy area originating from natural products [1-3]. Although phenol-type OH groups constitute the most important and frequently encountered chemotypes conferring bioactivity, recent studies revealed that protection of these functional groups resulted in analogues with higher intestinal absorption, resistance to hepatic metabolism and better anticancer activity in respect to the original compounds. To achieve this in a regioselective way and to avoid the tedious protection/deprotection steps required in a classical chemical synthesis method, due to the numerous reactive hydroxyl groups of polyphenols, we established chemoenzymatic approaches [4] utilizing biocatalysts that were originally thought as inactive for the specific substrates. The relative importance of the hydroxyl group positions of the flavonone nucleus in anticancer activity against numerous cell lines was investigated. A structure activity relationship has been proposed and direct interaction of the resulted analogues with pro-apoptotic protein factors was determined.



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References

[1] C. G. Vasilopoulou, V. G. Kontogianni, Z. I. Linardaki, G. Iatrou, F. N. Lamari, A. A. Nerantzaki, I. P. Gerothanassis, A. G. Tzakos, M. Margarity, *Eur J Nutr* **2011,** *in press*.
[2] A. G. Tzakos, D. Fokas, C. Johannes, V. Moussis, E. Hatzimichael, E. Briasoulis, *Molecules* **2011**, *16*, 4408.
[3] D. H. Roukos, A. Tzakos, G. Zografos, *Expert Rev Anticancer Ther* **2009**, *9*, 1413.
[4] E. Kyriakou, A. Primikyri, P. Charisiadis, M. Katsoura, I. P. Gerothanassis, H. Stamatis, A. G. Tzakos, *Org Biomol Chem* **2012**, *10*, 1739.