

# *Nouveaux ligands de quadruplexes. Approches in silico et in vitro.*



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DNA and RNA G-rich sequences can adopt unusual arrangements that are known as G-quadruplexes (G4). The topologies and forms of these fascinating structures are very diverse. G4 are stabilized by the presence of monovalent cations and Hoogsteen Hydrogen bonds. Small molecules also contribute to the formation of stable forms mainly via  $\pi$ - $\pi$  stacking interactions. Although G4s are known for decades, interest in this field started with their potential effect on inhibition of telomerase enzyme, a Reverse Transcriptase involved in the malignant transformation of most cancer cells.

With regards to telomerase, cancer and G4, several groups have been involved in the discovery of new G4 stabilizers that would indirectly inhibit the enzyme. Most of the G4 ligands were identified following this paradigm. Hundreds of ligands have been identified during the past decade and this is still a very active field in science. Taking into account the advantages and easiness that offers the identification of new structures using computational techniques we built single and reproducible mathematical models with high screening capacity and low computational cost in order to use them on the identification of G4 ligands.

With the use of QSAR modeling we can predict the  $^{tel}IC_{50}$  of a congeneric set of compounds. We have also been able to relate the molecular descriptors that appear in our models with some structural features that scientific literature and SAR studies have reported in previous studies as appropriated for describing the above mentioned activity, also for congeneric set of ligands. Moreover, we built different models using non congeneric sets of compounds applying a consensus strategy and could identify six FDA approved ligands that stabilize G4 structures. Subsequently, by applying nonlinear techniques and a process for the cure of the database proposed for us in previous publications, we have performed a virtual screening of more than 500 000 ligands from a commercial database of compounds, followed of structure-based model in

order to reduce the number of candidates. We were able to identify new ligands with stronger potency than the previous ones, which can also stabilize other G4 structures involved in processes related to cancer. These observations open a wide-ranging spectrum of possibilities to be explored.

Despite the limitations of the QSAR modeling techniques explored along this work, we consider they can be combined and used carefully to address the search for new G4 stabilizers.