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Quantum computations of electronic structures of oligonucleotides used in antisense research

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Quantum mechanical calculations as well as clinical experiments are carried out on different important oligonucleotides with modifications used in anti-sense research. The anti-sense research in this context is about silencing certain genes and proteins in various diseases. The oligonucleotides are modified as phosphorothioates with LNA (Locked Nucleic Acid) being changes which are crucial for cellular uptake and for binding to targeted strands. The theoretical and experimental techniques employed are molecular computation using quantum mechanics (QM), for producing electronic structures for the target molecules and chromatography experiments to distinguish and characterize the various molecules under investigation. The huge computer calculations on these large molecules, containing more than 600 atoms, are performed with ab initio Hartree-Fock quantum methods that are giving detailed electronic information on energy and bonding, and can differentiate between diastereoisomers i.e. chiral states. Furthermore differential geometry techniques are used to develop and analyze electrostatic isopotential surfaces that in principles can tell how drug molecules interact with others. Physical and chemical descriptors of the oligonucleotides are derived from the atomic calculations and used for characterizing the theoretical and experimental data for the chiral state of the oligonucleotides. Selecting the right chiral state of a drug is crucial for its effect and for avoiding side-effects. Experiments have shown that a particular one out of two chiral states could be an effective drug based on its surface form. However, it can be demonstrated that even a small change, e.g. interchanging the positions of two atoms, can have a huge effect on the overall structure of the molecule but on the other hand also used to design new drug molecules. Anti-sense compounds are expected to play an important role in e.g. cancer therapy.

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