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QSPR studies of 9-aniliioacridine[Ed1] derivatives for their DNA drug binding properties based on density functional theory using statistical methods: Model, validation and influencing factors

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***Abstract*:** *As a continuation of our research on the development and optimization of the biological activities/proprieties of acridine derivatives, a series of 31 molecules based on 9-aniliioacridines (25 training set and 6 test set) were subjected to 3D quantitative structure propriety relationship QSPR analyses for their drug-DNA binding proprieties using multiple linear regression (MLR) and multiple non-linear regression (MNLR). Quantum chemical calculations using density functional theory (B3LYP/6-31G (d) DFT) methods was performed on the studied compounds and used to calculate the electronic and quantum chemical parameters.*

The models were used to predict the association constant of the DNA drug binding of the test set compounds, and the agreement between the experimental and predicted values was verified. The descriptors determined by QSPR studies were used for the study and design of new compounds. The statistical results indicate that the predicted values were in good agreement with the experimental results (r= 0.935 and r= 0.936 for MLR and MNLR, respectively). To validate the predictive power of the resulting models, the external validation multiple correlation coefficients were 0.932 and 0.939 for the MLR and the MNLR, respectively. These results show that both models possess a favourable estimation stability and good prediction power.

Keywords: QSPR, DFT, MLR, MNLR, Acridine, Antitumour.

1. INTRODUCTION

The ease of synthesis, attractive colouration and crystallinity of acridine derivatives has long attracted the attention of medicinal chemists. The acridine family includes a wide range of planar tri-cyclic aromatic molecules with various biological properties and consists of a nitrogen atom (N-atom) in its heterocyclic nucleus. The natural and synthetic compounds of the acridine family are well known therapeutic agents due to their wide range of pharmacological and biological activities, including anti-leishmanial [1,2], anti-microbial [3], anti-oxidant [4], anti-malarial [5], anti-inflammatory [6], analgesic [7], anti-parasitic [8], anti-tumoural [9], anti-bacterial or anti-cancer chemotherapy [10-13] activities, among others.

The diversity of the biological and pharmacological activities has given acridines a respectable reputation in chemotherapy in the 20th century [14].

One of the important phenomena of DNA is their ability to reversibly bind planar molecules that can be inserted between the base pairs of the double helix [15]. Acridines are fused linear tri-cyclic aromatic molecules with planar geometry that bind tightly, but reversibly, to DNA by intercalating between adjacent base pairs [16-17]. The driving force for this binding comes primarily from stacking interactions between the acridine nucleus and the DNA bases and is sufficiently large to physically unwind the DNA double helix to accommodate the inserted ligand. The majority of the biological effects of acridine derivatives are considered to result from this mode of non-covalent interactions with DNA [18].