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QSAR for the Characterization of Drug Resistance: Differential QSAR (DiffQSAR) Using Mathematical Chemodescriptors

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Abstract: Drug resistance is a serious issue that compromises the efficacy of many drugs and antibiotics. One mechanism underlying the development of resistance is the alternation in the target enzyme or receptor resulting in gradual silencing of the target to the effects of the ligands. Basak et al developed a method called differential QSAR (DiffQSAR) whereby test data of drugs on their effects on the sensitive and resistant targets are used to characterize the phenomenon of drug resistance using mathematical molecular descriptors. This paper will summarize our research in this area.

Keywords: Quantitative structure-activity relationship (QSAR); Differential QSAR (DiffQSAR); Drug resistance; Silencing of target; Mathematical descriptors; Ridge regression (RR); Dihydrofolate reductase (DHFR); Plasmodium falciparum (Pf); Topological Indices; Atom pairs

1. Introduction

Drug resistance is a phenomenon that is creating problems in the continuing clinical efficacy of drugs through the development of gradually declining potency of drugs. To give just a couple of examples, resistance to drugs have developed for diseases like cancer [1], H_5N_1 pandemic Bird Flu infection [2], and malaria [3]. In the case of malaria, dihydrofolate reductase (DHFR) of *Plasmodium falciparum (Pf)* is an important target for antimalarial drug discovery because it catalyzes a critical step in the biochemical pathway of the parasite, viz., the reduction of dihydrofolate to tetrahydrofolate,

which has a critical role in the DNA synthesis of the parasite [3-5]. As a result, various modelling methods have been used in understanding the structural basis of the antimalarial activity of DHFR inhibitors [6].

Recently, Sivaprakasam et al. [7] carried out quantitative structure-activity relationship (QSAR) and docking studies of cycloguanil PfDHFR-TS inhibitors.

The above indicates that fast screening of chemical databases for their activity against target macromolecules in *Pf* is essential for effective antimalarial drug discovery. This can be accomplished if the screening models are based on molecular descriptors which can be calculated fast and directly from the molecular structure without the input of any other experimental data. Therefore, we carried out a QSAR analysis of 58 cycloguanil *Pf*DHFR inhibitors using computed topological descriptors [8-16].

2 Results and Discussion

Data on cycloguanil derivatives and mathematical descriptors were used to develop QSARs that can be used for the screening of chemicals. . The results of statistical analysis showed that one compound, compound #22, in ref [7] was an influential outlier. The same conclusion was drawn from the QSAR studies of Sivaprakasam et al. [7]. Both topological indices (TIs) and TI plus atom pair (AP) combination give good QSARs for the binding affinity (K_i) of the cycloguanil derivatives. Some improvement in model quality was observed after the addition of APs to the set of topological indices. Of the three statistical methods used for modelling, viz., ridge regression (RR), partial least square (PLS) , and principal components regression (PCR), RR outperformed the other two This is in line with our numerous previous observations with QSAR modelling of various property/bioactivity data.
A total of 369 TIs were calculated using programs including POLLY, Triplet, and Molconn-Z. Atom pairs were calculated by APProbe [14]. A look at the top 20 descriptors extracted from the QSARs of the sensitive versus the resistant strains sorted by their t values show that only two descriptors, viz., AZV4 and ANV3, are common between the two models. For details see [16].

Thus it can be said that the descriptor space created by the set of calculated mathematical descriptors can provide a subsets of descriptors which can differentiate the chemical-biological interactions between the sensitive versus the resistant forms of the drug target, PfDHFR.

3. Materials and Methods

For materials and methods of data collection and statistical analyses, see [16].

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4. Conclusions

Using high dimensional structure space consisting of calculated topological indices and atom pairs, ridge regression was applied to develop QSARs for the sensitive and resistant forms of dihydrofolate reductase (DHFR) inhibitors of *Plasmodium falciparum* (Pf). The top 20 descriptors extracted from the QSAR models developed by ridge regression showed that the subsets of non-overlapping descriptors are capable of characterizing the silencing of the target arising out of mutation in the genetic apparatus of the organism, *Plasmodium falciparum* (Pf). It is expected that such research can be carried out with

other drug targets to characterize the molecular basis of resistance based on computed properties of the ligands involved in the interactions with biochemical targets.

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Author Contributions

Since the early 1970sn Subhash C. Basak has been involved in the development of novel topological indices and their applications in QSARs pertaining to the estimation of property/ bioactivity/ toxicity of chemicals.

Conflicts of Interest

This author declares no conflict of interest.

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