ABSTRACT

The reliance of mankind on synthetic pesticides, particularly dichlorodiphenyl-trichloro ethane (DDT) reached its zenith during 1950s-60s, since its first application during World War II. But very soon it faced a serious scientific opposition due to its bio-magnifying nature and was banned during 1970s in most part of world with certain exceptional usage in health control programs in developing and undeveloped countries. But the pesticidal activity range and economic viability of DDT has never been questioned and still there are several voices to bring back DDT. To answer this controversy is the search for new DDT like pesticide with similar pesticidal efficacy and lower ecological accumulative effects. Recent advances in computer aided molecular design has provided us very robust, economic and time &labour saving tool to design and develop new chemical entities with pesticidal activity similar to DDT and has good commercial prospects as well. Therefore, the present work was carried out to look for QSAR insights into design of OC molecule with good pesticidal activity, lower toxicity and biodegradability potential compared to the most successful OC pesticide i.e., DDT. The QSAR model generated was integrated with QSTR and QSBR models of EPI Suite of USEPA. A set of new DDT-based compounds were designed and generated through virtual combinatorial library. They were evaluated and screened for their bioactivity, toxicity and degradability using QSAR models. A few screened OC compounds of virtual combinatorial library were also evaluated for in-vitro analysis, after chemical synthesis, for their pesticidal activity, toxicity and biodegradability alongwith natural degradation profile.

A set of statistically and computationally good 2D- and 3D-QSAR (with CoMFA) models were generated to predict the larvicidal (insecticidal) activity of DDT type organochlorine molecules. The models were integrated with QSTR (ECOSAR) and QSBR (BIOWIN) models of EPI Suite. The integrated QSAR models were used to predict the mosquito larvicidal activity, toxicity and biodegradability of a set of compounds generated by combinatorial library. These predicted activities were then used to validate the QSAR models using in-silico and in-vitro approach. In-silico method used the technique of molecular docking, which was 1st of its own kind of application of docking technique, reported till date. The docking study data and corresponding predictions of QSAR models were 77.8% (2D-QSAR) & 60.5% (3D-
QSAR) correlated. The docking study data and corresponding predictions of ECOSAR (QSTR) models were 70.361% (Fish toxicity) & 73.964% (Algal toxicity) correlated. The docking study data and corresponding predictions of BIOWIN (QSBR) models were 78.404% (Linear biodegradability probability) & 69.368% (Primary biodegradation timeframe) correlated. The 5-better predicted compounds (potential pesticides) were synthesized. A good correlation coefficient (r) value of 0.774504 and 0.600062 were obtained when experimental pIC$_{50}$ values were correlated with pIC$_{50}$ of 2D-QSAR and 3D-QSAR with CoMFA models, respectively (Anopheles larvicidal activity), thus supporting the validation of QSAR models of our study. Negligible teratogenic effects were seen for test compounds at 10X effective insecticidal concentrations, in Zebrafish embryos. The correlation analysis of experimental EC$_{50}$ and ECOSAR predicted EC$_{50}$ for algal systems, revealed them to be well correlated with the correlation coefficient of 0.5006, thus supporting the validation of QSTR models of our study. The experimental values of biodegradation of DDT and its selected analogues by P. chrysosporium when analyzed for correlation with the biodegradation potential values as predicted by BIOWIN IV module of EPI Suite, it was observed that the predictions of QSBR models of BIOWIN IV were highly correlated to the experimental values of biodegradation. The coefficient of correlation was observed to be 0.70381, thus supporting the validation of QSTR models of our study. Thus the present investigation has provided a good platform of computer-aided pesticide design using the QSAR method to evaluate the larvicidal activity of any novel DDT-type molecule. Also, the study is probably the first report of validating the QSAR models DDT using molecular docking studies.