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Optimization of antiproliferative activity of substituted phenyl 4-(2-oxoimidazolidin-1-yl) benzenesulfonates: QSAR and CoMFA analyses

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ABSTRACT

Multiple separate quantitative structure–activity relationships (QSARs) models were built for the antiproliferative activity of substituted Phenyl 4-(2-Oxoimidazolidin-1-yl)-benzenesulfonates (PIB-SOs). A variety of descriptors were considered for PIB-SOs through QSAR model building. Genetic algorithm (GA), available in QSARINS, was employed to select optimum number and set of descriptors to build the multi-linear regression equations for a dataset of PIB-SOs. The best three parametric models were subjected to thorough internal and external validation along with *Y*-randomization using QSARINS, according to the OECD principles for QSAR model validation. The models were found to be statistically robust with high external predictivity. The best three parametric model, based on steric, 3D- and finger print descriptors, was found to have $R^2 = 0.91$, $R^2_{ex} = 0.89$, and $CCC_{ex} = 0.94$. The CoMFA model, which is based on a combination of steric and electrostatic effects and graphically inferred using contour plots, gave $F = 229.34$, $R^2_{CV} = 0.71$ and $R^2 = 0.94$. Steric repulsion, frequency of occurrence of carbon and nitrogen at topological distance of seven, and internal electronic environment of the molecule were found to have correlation with the anti-tumor activity of PIB-SOs.

1. Introduction

Recent reports from WHO and other organizations clearly highlights cancer as a leading cause of mortality, and economic problems for millions of peoples (WHO, 2012, 2013). Chemotherapy is a preferred method of treatment, although, various therapies like radiation, different types of surgeries etc. are available Chemotherapy for cancer treatment usually involves three or four anti-cancer drugs in combination (Aziz et al., 2013; Natarajan and Senapati, 2012; Temirak et al., 2012). Few examples of anticancer drugs are presented in Fig. 1. Despite high treatment success in many cases, severe side effects and emergence of resistance for marketed anti-cancer drugs are serious concerns for modern chemotherapy (Fortin et al., 2011; Krishnegowda et al., 2011; Temirak et al., 2012). Therefore, extensive search for a drug with high activity against cancer and good ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) profile is a challenge for modern medicinal chemistry.

Modern medicinal chemists employ different strategies to optimize the pharmacological activity, the ADMET profile and a viable synthesis route for an available lead candidate (i.e. lead optimization). In modern drug designing process, computer-aided drug design (CADD) is helpful in identifying new potent compounds and saves drug development time, and money. It provides a useful alternative to animal testing, as well. CADD is a method of choice in drug designing process due to its faster, economical, and result oriented high success rate (Mahajan et al., 2012, 2013; Masand et al., 2012a,b, 2013a,b). QSAR, molecular docking, pharmacophore modeling, etc. are some of the successful brushwood of CADD that have led to the introduction of many drugs in the market (Jawarkar

Abbreviations: CoMFA, comparative molecular field analysis; PIB-SOs, Phenyl 4-(2-Oxoimidazolidin-1-yl)-benzenesulfonates; GA, genetic algorithm; MLR, multiple linear regression; QSAR, quantitative structure–activity relationship; ADMET, Absorption, Distribution, Metabolism, Excretion and Toxicity; CADD, computer aided drug designing; OLS, ordinary least square; QSARINS, QSAR insubria.

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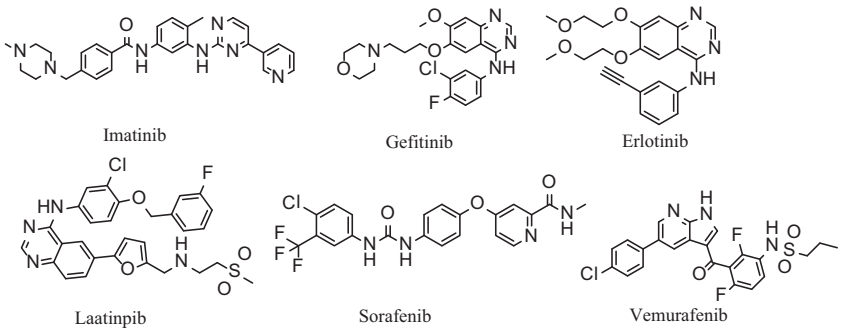

Fig. 1. Few examples of approved anti-cancer drugs.

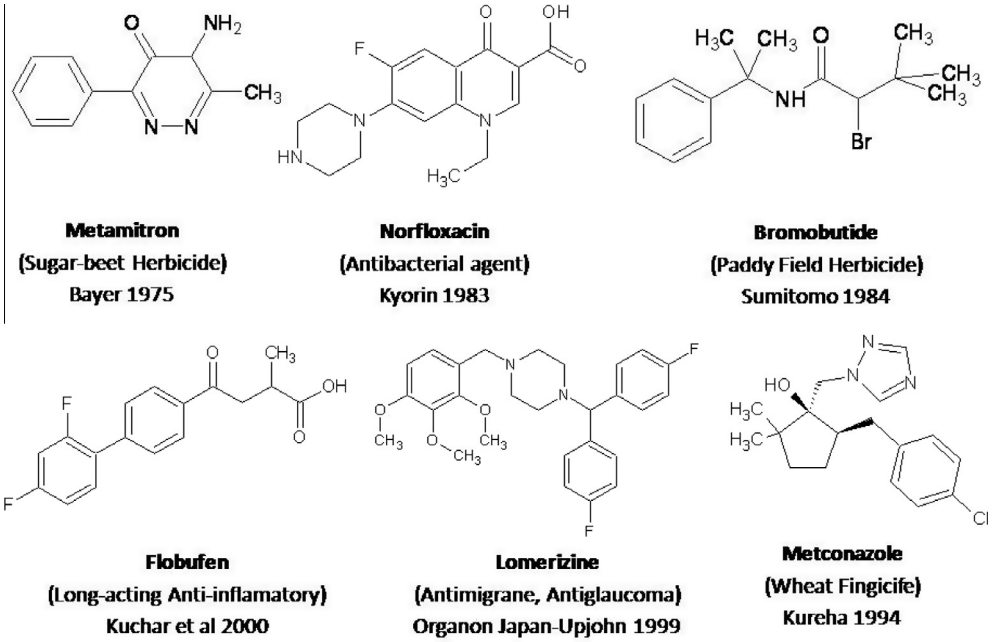

Fig. 2. Some of the commercial drugs developed using QSAR.

et al., 2010; Mahajan et al., 2010, 2012, 2013; Masand et al., 2011, 2012a,b, 2010a,b, 201s3a,b) (see Fig. 2).

Molecular docking can be effectively used for optimization of drug when the 3D structure of the protein/enzyme with which the drug interacts is known (Mahajan et al., 2012). According to one school of thought, in absence of information about the target protein/receptor, QSAR and pharmacophore modeling are preferable techniques for lead optimization (Mahajan et al., 2012). Since the exact mechanism of action and the receptors with which PIB-SOs interact are unknown (Fortin et al., 2011; Turcotte et al., 2012), we have performed extensive QSAR, and CoMFA (ligand based drug design) analyses on PIB-SOs to determine the structural features that control their anti-proliferative activity. This will provide understanding of drug mechanism for PIB-SOs class and will help in developing potentially active and better drug candidates against cancer.

The selected dataset (Fortin et al., 2011; Turcotte et al., 2012) consists of ninety seven PIB-SOs having diverse substituents like $-NH_2$, $-OH$, $-OCH_3$ and $-Cl$. The compounds were assayed against skin melanoma M-21 cell lines according to the NCI/NIH Developmental Therapeutics Program (Fortin et al., 2011; Turcotte et al., 2012). The activity expressed as the concentration of drug inhibiting cell growth by 50% (IC_{50}) was converted to pIC_{50} ($-\log_{10}$ IC_{50}) for QSAR analysis (Jawarkar et al., 2010; Mahajan et al., 2010, 2012; Masand et al., 2013a). The substituents, experimental IC_{50} and pIC_{50} have been listed in Table 1.

The standard procedure as specified in SYBYL was followed to build a database of ninety-seven PIB-SOs. For thriving CoMFA analysis, proper alignment of 3D structures of the molecules is very important (Mahajan et al., 2012; Masand et al., 2012a, 2010a). To enhance the fruitfulness of CoMFA analysis, Gasteiger–Marsili partial charges were assigned to all the molecules before carrying out descriptor calculation and alignment. The lowest energy conformer of most active compound **92** was used as a template structure for aligning the compete set of molecules. The molecules in their respective lowest conformations were superimposed on the template using the atom based alignment option in SYBYL. It was followed by partial least square (PLS) analysis and 3D contour generation with optimum number of components set to 5. Default settings and procedure as implemented in SYBYL were used throughout the work.

The central idea of the present work is to use conventional QSAR to obtain extensive information about the structural features that govern the activity. Therefore, a new strategy was employed, in which, multiple models were built using 50% training set and validating them on remaining set (50% prediction set) using random splitting. In next step, the training and the prediction sets were interchanged for model building and validation. Thus, new