Exploring QSAR of Some Antitubercular Agents: Application of Multiple Validation Strategies

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ABSTRACT

The in vitro vero cell cytotoxicity of 93 antitubercular compounds belonging to the classes of chiral pentaamines, bis-cyclic guanidines, bis-cyclic thioureas, bis-cyclic piperazines, and quinolylhydrazones has been modeled in the present quantitative structure-activity relationship (QSAR) study. Genetic function approximation followed by multiple linear regression (GFA-MLR) based on the mean absolute error (MAE) based criteria was used as the chemometric tool for the model development using 2D descriptors available from open source PaDEL-Descriptor. The developed model was statistically robust (Q^2=0.868, R^2_{pred}=0.896). Additionally, the R^2_m metrics, concordance correlation coefficient (CCC) and MAE criteria for the test set validation were also tested. The models indicate importance of autocorrelation descriptors weighted by charge (ATSc3, ATSc5) and some electrotopological state atom type descriptor of fragments -NH-, -O-, >N- for cytotoxicity. The applicability domains of GFA-MLR models were also studied by applying both leverage and standardized residual approaches.

KEYWORDS

2D Descriptors, Antitubercular, Applicability Domain, Bis-cyclic Guanidine, Cytotoxicity, GFA-MLR, QSAR, Quinolylhydrazones

INTRODUCTION

Tuberculosis (TB) causes a high fatality as an infectious disease. After the human immunodeficiency virus (HIV), it is the second leading cause of death from an infectious disease around the world. The etiological agent of tuberculosis is Mycobacterium tuberculosis. The current major concern is its reemergence due to the coinfection with virus like HIV (Corbett et al., 2003; Harries and Mahler, 1996). Approximately 9.0 million people developed TB and 1.5 million died and out of which 360000 patients were HIV positive according to 2013 statistics in WHO nineteenth global report 2014 (WHO report, 2013). Multi drug resistant (MDR) TB is increasing annually (WHO report, 2011) due to difficulties in detection and cure of sufficient number in order to avoid transmission.

Cytotoxicity represents the toxicity / toxic properties of substances to the cells. The assay for cytotoxicity is generally performed for screening of new chemicals in pharmaceutical industry or research centers. Based on the therapeutic application, two main choice of cytotoxicity assays are practiced i.e., to select cytotoxic agents (for chemotherapy) and to select nontoxic agents for different therapeutic applications. Like other diseases, in vitro vero cell cytotoxicity assay is performed for screening of antitubercular agents by several groups. The focus is to find the SI (selectivity index)
which is the ratio of measured IC$_{50}$ in vero cell to minimum inhibitory concentration (MIC) (Bjorn et al., 2002; Antonio et al., 2009). An MIC value less than 1 µg/mL is a criterion for good lead compounds as antitubercular agents and an MIC $\leq$ 6.25 µg/mL and an SI $\geq$ 10 is a criterion for interesting antitubercular agents (Adams et al., 2001). Therefore, there is an urgent need of applications of in silico techniques in predicting cytotoxicity in drug discovery process.

Nowadays Quantitative Structure–Activity Relationship (QSAR) methods have broad spectrum of applications in drug discovery, risk assessment, toxicity prediction and regulatory decisions (Golbraikh and Tropsha, 2002). Accuracy of the input data, selection of appropriate descriptors and statistical tools, and most importantly, validation of the developed model are the key factors for the success of any QSAR. Reliability and acceptability of any QSAR model depend on validation which is one of the crucial parts for the QSAR study from the predictive point of view especially for regulatory applications (Golbraikh and Tropsha 2002; Gramatica, 2007; Roy, 2007).

Computational approaches like QSAR studies on various scaffolds were performed by different researcher groups to generate hit molecules with improved activity, selectivity and least toxicity along with experimental methods (Aparna et al., 2005; Coutinho et al., 2006; Baldi et al., 2006; Geetha Babu et al., 2007; Kumar et al., 2007; Kumar and Siddiqi, 2008; Cho et al., 2008; Dolezal et al., 2009; Brandt et al., 2010; Acharya et al., 2010; De-sousa et al., 2011; Chauhan et al., 2012). Recently, synthesis and QSAR studies were carried out on substituted quinolones which showed that steric and electrostatic properties were important for antimycobacterial activity (Patel et al 2015). Similarly, camphene based amino alcohols, halo bis-hydrazones were found to be leads as antitubercular agents (Abdel-Aziz et al. 2016; Petkova et al, 2014). In none of the studies, QSAR modeling was carried out on cytotoxicity of the compounds.

For the present study, we have taken the in vitro vero cell cytotoxicity data of some chiral pentaamines and bis-heterocyclic and quinolylhydrazones compounds showing good antitubercular activity (Arutyunyan et al., 2009; Savini et al., 2002). The study was done taking 2D descriptors available on PaDEL-Descriptor software (open source) (Yap, 2011) using Stepwise MLR technique. This study aims to provide a significant insight into the applicability of such statistical models in identifying the features relevant for cytotoxicity of antitubercular compounds.

**MATERIALS AND METHODS**

**Data Set and Descriptors**

In the present study, we have considered in vitro vero cell cytotoxicity (IC$_{50}$, µg/ml) of 93 anti-tubercular compounds (Table 1). The chemical classes of the compounds include chiral pentaamines, bis-cyclic guanidines, bis-cyclic thioureas, bis-cyclic piperazines and quinolylhydrazones (Arutyunyan et al., 2009; Savini et al., 2002). The structures of all the compounds were given in the supplementary material section (Tables S1-S3: https://doi.org/10.4018/IJQSPR.2018010102) The vero cell IC$_{50}$ values in µg/ml unit of selected data set compounds were firstly converted to the mole/ml unit and further converted to -logIC$_{50}$ (known as pIC$_{50}$) and used as the response variable for subsequent QSAR analysis. All the compounds were drawn in ChemDraw software package (ChemOffice, http://www.cambridgesoft.com/) and 2D descriptors (Acidic group count, ALOGP, APol, Aromatic atoms count, Aromatic bonds count, Atom count, Autocorrelation (charge), Autocorrelation (mass), Autocorrelation (polarizability), Basic group count, BCUT, Bond count, BPol, Carbon types, Chi chain, Chi cluster, Chi path cluster, Chi path, Crippen logP and MR, Eccentric connectivity index, Atom type electrotopological state, Extended topochemical atom, FMD Descriptor, Fragment complexity, Hbond acceptor count, Hbond donor count, Hybridization Ratio Descriptor, Kappa shape indices, Largest chain, Largest Pi system, Longest aliphatic chain, Mannhold LogP, McGowan volume, Molecular distance edge, Molecular linear free energy relation, Petitjean number, Ring count, Rotatable bonds count, Rule of five, Topological polar surface area, Van der Waals volume, Vertex adjacency information (magnitude),
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