Journal of Bioanalysis & Biomedicine

Bagchi, J Bioanal Biomed 2016, 8:4
DOI: 10.4172/1948-593X.1000e144

Editorial Open Access

Application of Chemoinformatics in Anti Tubercular Drug Design

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Editorial

It is only in recent years that chemotherapy of tuberculosis was in glare of publicity with the detection of some active anti-TB agents and programs to combat the disease were formulated. Short-course curative chemotherapy treatment healed a large number of patients with several newly introduced anti-tuberculosis drugs. Only one decade later, an outbreak of HIV-related multidrug-resistant tuberculosis made the disease suddenly the centre of attention. Tuberculosis was declared as a disaster more than one century after Koch's discovery. The situation compelled both the academia and drug industries to join hand in hand for developing efficient computational methods with a view to accurate predictions and less animal sacrifice. The computer assisted design programs will no doubt help in the planning of chemical synthesis and biological testing experimentally with more accuracy. A very significant approach in computer assisted design consists of QSAR that refers to the situation where structural properties are considered for prediction of biological activities. One can find the use of QSAR while screening a virtual library of potent anti tubercular compounds and for extraction of active fragment in databases. Three-dimensional (3-D) QSAR including 3-D pharmacophore mapping are now being applied for analysing ring substituted quinolines and diaryloxy-methano-phenanthrene derivatives as potent anti tubercular agents. Besides these, some spectacular applications of 3-D QSAR concerning dTMP derivatives, thymidine analogues and nitroaromatic compounds against tuberculosis deserves worth mentioning.

A comparative study of the relative effectiveness of several classes of molecular descriptors against biological activities was conducted on the second-line anti-tb agents viz., fluoroquinolone derivatives. Considering the efficiency spectrum, it appears that sparfloxacin is perhaps the most important agent against mycobacterial infections. Measurement of biological activities of N-1, C-7 and 8 substituted quinolone antibacterials against two mycobacteria viz., *Mycobacterium fortuitum* and *Mycobacterium smegmatis* brought to light that substituent of N-1 greatly influences contribution of the 8 position in respect of anti-mycobacterial activity [Figure 1]. From the regression summary associated with the QSARs of quinolone compounds, it is evident that the computed graphical invariants or the structural descriptors have a clear edge over the physico chemical data measured in the laboratory and lead to more significant predictions for N-1, C-7 and 8 substituted quinolone derivatives.

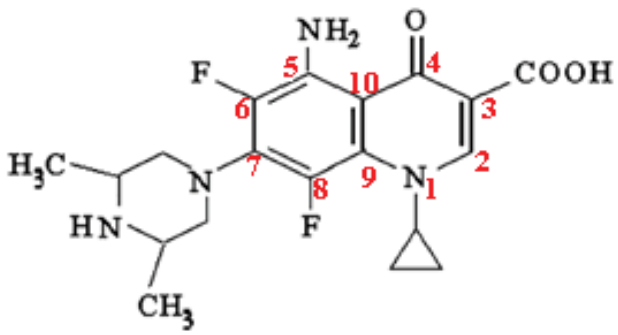

Figure 1: Structure of Sparfloxacin having activity values 0.06 & 0.13 against *Mycobacterium fortuitum* and *Mycobacterium smegmatis* respectively. Two quinolone rings are indicated. Variations are at N1, C7 and 8th positions.

While developing QSAR models in *Mycobacterium tuberculosis*, it may be pointed out that considering all the computed descriptors in the model, a very high correlation coefficient may be obtained but the model becomes so complex that interpretation of the outcome becomes next to impossible. Hence our attempt is directed towards screening the significant descriptors by eliminating multi collinearity and chance correlation factors. Feature selection monitors this task which acts as an important basis on a model building exercise. One can mention some popular optimization methods in model development relating to QSAR such as genetic algorithm and simulated annealing which can give an effective solution with limited number of variables. Feature selection methods in conjunction with regression analysis to develop more robust models seems to be very appropriate in our study with different anti-tubercular agents like fluoroquinolones, quinoxaline and nitrofuranyl amide derivatives. In all the cases, it has been shown that application of feature selection methods appreciably improves the model quality.

In some recent investigations on nitrofuranyl amide derivatives, different feature selection methods like stepwise method, genetic algorithms and simulated annealing were applied to develop 2D QSAR models separately with the compounds having ionizable functional groups and non-ionizable functional groups and a comparative study was performed among different feature selection criteria. A large number of nitrofuranyl amide compounds were used to formulate 3D QSAR model which, in turn, gave clear evidence that the positive and negative coefficients of steric descriptors are responsible for the enhancement and damaging inhibitory activities respectively.

The assignment of a ligand within a binding site and the prediction of the free energy of binding for such stances is the main purpose in docking. The key feature in molecular docking is to find the global energy minimization of the complex, and numerous programs have been developed to solve this non-trivial problem.The most important part of molecular docking is the calculation of binding energy so as to fit a ligand in a binding site. The binding affinities and scoring functions of ligands are computed by binding softwares. The descriptor based QSAR models are often very useful in predicting biological activities of molecules and thus enriches the concept of virtual screening. The fast expanding protein bank information coupled with molecular descriptor based virtual screening methods supplement the whole drug design process by identifying lead molecules.

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Received August 03, 2016; **Accepted** August 04, 2016; **Published** August 07, 2016

Citation: Bagchi MC (2016) Application of Chemoinformatics in Anti Tubercular Drug Design. J Bioanal Biomed 8: e144. doi: 10.4172/1948-593X.1000e144

Fluoroquinolones are considered to be second line anti-TB agents and are very efficient when the disease becomes drug resistant. Hence they play a major role in the treatment of tuberculosis. DNA gyrase protein is the main target of such fluoroquinolone derivatives and interaction pattern of fluoroquinolones and DNA gyrase is the key feature in molecular docking. Fluoroquinolone template is used for generating combinatorial library for obtaining a large number of virtual molecules which consists of permissible substituents at particular positions. Lipinski's rule of five criteria is again applied to screen the virtual library and the remaining molecules are then tested with QSAR models for activity prediction. Molecules with high predicted activities are subjected to docking studies to evaluate the dock score and scrutinize the interaction patterns. A selected number of molecules with high activity profiles, minimum dock scores and desired interaction patterns are recommended for further chemical synthesis and testing for lead identification against tuberculosis.

Thus QSAR models can be successfully used to predict the anti-mycobacterial activity of the virtual compounds using combinatorial chemistry approach. There is an explosion chemogenomics data generated by experimentalists. In the public domain databases, millions of chemical compounds with bioactivities are available, whereas high throughput screening platforms are becoming more and more common. In such context of enormous amount of chemical data, computational approaches seem to be the only way out for accessing, querying, mining, modeling, and screening the data. The in silico approaches are not only vital for cheminformaticians but also for medicinal chemists. QSAR concept is rather easy to understand for practicing synthetic chemists with knowledge of mechanistic organic chemistry. Genomic methods, computer aided screening techniques and receptor based drug design programs constitute the chemometric approaches which is very crucial for the invention of new and effective anti-TB compounds from existing drugs like sparfloxacin. QSAR modeling is of high interest not only for cheminformaticians and medicinal chemists but for both computational and experimentalist communities in general. It is believed that such chemoinformatic applications will definitely boost up the validation of targets in the near future.

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