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Grid potential analysis, virtual screening studies and ADME/T profiling on N-arylsulfonylindoles as anti-HIV-1 agents

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A grid potential analysis employing a novel approach of 3D quantitative structure–activity relationships (QSAR) as AutoGPA module in MOE2009.10 was performed on a dataset of 42 compounds of N-arylsulfonylindoles as anti-HIV-1 agents. The uniqueness of AutoGPA module is that it automatically builds the 3D-QSAR model on the pharmacophore-based molecular alignment. The AutoGPA-based 3D-QSAR model obtained in the present study gave the cross-validated Q^2 value of 0.588, r^2_{pred} value of 0.701, r^2_m statistics of 0.732 and Fisher value of 94.264. The results of 3D-QSAR analysis indicated that hydrophobic groups at R_1 and R_2 positions and electron releasing groups at R_3 position are favourable for good activity. To find similar analogues, virtual screening on ZINC database was carried out using generated AutoGPA-based 3D-QSAR model and showed good prediction. In addition to those mentioned earlier, *in-silico* ADME absorption, distribution, metabolism and excretion profiling and toxicity risk assessment test was performed, and results showed that majority of compounds from current dataset and newly virtually screened hits generated were within their standard limit. Copyright © 2013 John Wiley & Sons, Ltd.

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Keywords: AutoGPA; 3D-QSAR; HIV-1; grid potential analysis; virtual screening

1. INTRODUCTION

Acquired immunodeficiency syndrome (AIDS), despite the efforts of researchers worldwide to unravel the mode of action of the virus and develop therapies, is currently a very serious global health threat and the leading cause of death [1]. Human immunodeficiency virus type-1 (HIV-1), the causative agent of AIDS, is a retrovirus from the *Lentiviridae* family. Currently, the drugs for treatment of HIV-1 infected patients belong to nucleoside/nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors and fusion inhibitors [2]. The development of combination antiretroviral therapy has provided a useful means of suppressing the viremia in infected people, resulting in dramatic reductions in HIV-1-associated morbidity and mortality. However, the current antiretroviral therapies are very far from being curative, as complexity of dosing regimens and its toxicity make it difficult to maintain patient compliance. Moreover, the incomplete suppression of HIV-1 replication is responsible for the emergence of drug-resistant HIV-1 strains. At present, although 32 drugs have US FDA approval and many are in clinical pilot phase, still, the cure of AIDS is a major problem. Consequently, many efforts have been endowed in recent years to design and develop novel, selective and safe drugs for treatment of HIV-1 [3].

The main objective of computer-aided drug design is predicting the activity of newer compounds. There are many important methods of drug design core technology, based on drug target interactions driven by molecular forces (docking); quantitative structure–activity relationships (QSAR), using molecular descriptors/potential field and pharmacophore modelling, are being utilized and applied successfully to predict different classes of inhibitors.

Several computational studies (3D-QSAR) have been successfully applied for modelling biological activities of series of anti-HIV agents. Reports on acylthiocarbamates [4], 1-(2-hydroxyethoxymethyl)-6-(phenylthio)thymine [5], efavirenz derivatives [6], pyridinones [7], 1,3,4,5-tetrasubstituted-pyrazoles [8], 2-amino-6-arylsulfonylbenzonitriles [9], indolyl aryl sulfones [10] and so forth are some recent examples.

Models of 3D-QSAR derived from grid potential analysis provide spatial distribution of important potential fields around active ligand [11]. Because the distribution usually vary widely depending on superimposed conformations of the active ligands, it is not easy to find the most appropriate model that represents the actual binding site. To develop the most reliable 3D-QSAR model [12], a novel approach of AutoGPA script in Molecular Operating Environment (MOE) 2009.10 [13] has been used. The AutoGPA script considers the conformations of the active ligands aligned over pharmacophoric points and uses partial least squares (PLS) regression method to calculate grid potential around aligned molecules.

In the present study, we have applied a novel approach of AutoGPA to develop a 3D-QSAR model on a series of N-arylsulfonylindole derivatives as anti-HIV-1 agents [14]. The AutoGPA-based 3D-QSAR model development, considers the

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