Eigen Value ANalySis (EVANS) – A Tool to Address Pharmacodynamic, Pharmacokinetic and Toxicity Issues: Proof of Concept Study on Pharmacodynamic Datasets

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ABSTRACT

Drug discovery is a continuously evolving area, essential for mankind albeit a very expensive process with a high attrition rate. The main challenge faced by pharmaceutical researchers today is to identify the major hurdles and validate the “developability” of a compound in the initial stages of drug development in order to select superior drug candidates with the best chances of success. This motivated us to introduce a “universal” approach for analyzing the pharmacodynamics, pharmacokinetics and toxicity profile of compounds based on the philosophy of QSAR. The present work deals with the development, validation and application of a novel QSAR formalism entitled EigenValue ANalySis (EVANS). This methodology encodes 3D structural information in terms of the atom pair distances along with molecular physicochemical properties to generate a set of unique hybrid descriptors, termed as “Eigenvalues.” The present article deals with the intricacies of the methodology and explores its applicability on a series of datasets for building pharmacodynamic QSAR models.

KEYWORDS

2D, Applicability Domain, Computational Method, Covariance Matrices, Drug Discovery, GA-MLR, In Silico, PD Matrices, Predictive Models, Validation Metrics
INTRODUCTION

A recent report published by the Tufts Centre for the Study of Drug Development (CSDD) estimates the cost of developing a drug molecule that is approved for clinical use at $2.6 billion. The major reason for this is a failure rate of more than 90% in the latter stages of development. With each new drug candidate requiring an astronomical investment, reducing the high attrition rate in drug discovery and development is a key challenge for the pharmaceutical industry. However, the overall attrition rate remains high for small-molecule drug candidates due to poor pharmacokinetic profiles, efficacy and safety issues (Bunagge; Hay, Thomas, Craighead, Economides, & Rosenthal; Kola & Landis, 2004).

The development of high-throughput biological screens (van de Waterbeemd, 2002), genomics, and combinatorial chemistry (Gennari, Seneci, & Miertus, 2000) have dramatically increased the number of pharmacologically active molecules although many possess unfavourable biopharmaceutical properties. The main challenge for pharmaceutical researchers is to identify the major hurdles and validate the “developability” of a compound in the early stages of drug development. This will improve the selection of superior drug candidates with enhanced chances to reach the clinic.

Towards this end, attempts are being made to reduce the number of safety and efficacy related failures by analysing possible links of biological failure to the physicochemical properties of drug candidates. Research has focused on reducing the likelihood of failure by controlling physicochemical properties of small molecules, such as lipophilicity, size and polarity (Gleeson, 2008; Gleeson, Hersey, Montanari, & Overington; Hughes et al., 2008; Leeson & Springthorpe, 2007; Lipinski, 2000; Luker et al.; Peters, Schnider, Mattei, & Kansy, 2009). Clearly, establishing a link between biologically important endpoints such as efficacy, kinetic parameters and in vivo toxicity is necessary. One method to achieve this is the optimization of absorption, distribution, metabolism, excretion and toxicity (ADMET) properties by theoretical methods like Quantitative Structure-Property Relationship (QSPR). QSPR is an in silico tool that aims to quantify chemical information and the subsequent development of a logical mathematical relationship with its response property or biological activity (Hansch, Leo, Mekapati, & Kurup, 2004; Roy, Kar, & Das, 2015; Verma, Khedkar, & Coutinho, 2010). Establishing a correlation between experimentally determined biological data and structures of compounds by QSPR analysis will not only provide clues for further molecular modification but will also help to delineate intermolecular forces that govern the biological response.

A survey of literature indicates that various tools are available to individually assess different attributes of drug development, namely biological activity (e.g. CoMFA (Clark, Cramer Iii, Jones, Patterson, & Simeroth, 1990; Cramer, Patterson, & Bunce, 1988), CoMSIA (Klebe, 1998), CoRIA (Datar, Khedkar, Malde, & Coutinho, 2006; Dhaked, Verma, Saran, & Coutinho, 2009; Khedkar, Joseph, Pissurlenkar, Saran, & Coutinho, 2015), LISA (Verma, Malde, Khedkar, Iyer & Coutinho, 2009), CoOAn (Verma, Malde, Khedkar, & Coutinho, 2012)) or pharmacokinetic properties (e.g. Symcyp (Jamei et al., 2009)) or toxicity (e.g. TOPKAT(Venkatapathy, Moudgal, & Bruce, 2004)). However, the disparate nature of these tools and the need for non-uniform method for data input make their routine use discomforting. Moreover, in most cases a host of additional and sometimes complex information, e.g., bioactive/receptor-bound conformation; is required to apply the existing tools. Some tools also demand application of molecular dynamics derived or quantum chemical-based descriptors that are computationally expensive and tedious that hamper their ease of use and applicability (Kubinyi, 1997; Schneider & Fechner, 2005; Winkler, 2002). Thus, tools that can assess various parameters simultaneously, namely efficacy, potency, selectivity, pharmacokinetics and toxicity will dramatically reduce the number of steps and computational time, and therefore, prove to be a boon to the drug discovery process.

Here, we propose the development and validation of a novel QSPR formalism entitled EigenValue ANalySis (EVANS). This is a redevelopment of our previously reported QSPR formalism for peptides (Pissurlenkar, Khedkar, Iyer, & Coutinho, 2011) extending its application to small organic molecules. The central dogma of this methodology is the use of molecular and atomic physicochemical
QSAR Modeling Using Quantum Chemical Descriptors of Benzimidazole Analogues With Antiparasitic Properties
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Predicting Degradation Half-life of Organophosphorus Pesticides in Soil Using Three-Dimensional Molecular Interaction Fields
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