Chapter 21
Retrained Classification of Tyrosinase Inhibitors and “In Silico” Potency Estimation by Using Atom–Type Linear Indices: A Powerful Tool for Speed up the Discovery of Leads

Gerardo M. Casañola-Martín
Universitat de València, Spain, & Central University of Las Villas, Cuba

Mahmud Tareq Hassan Khan
GenØk – Center for Biosafety, Norway

Huong Le-Thi-Thu
Central University of Las Villas, Cuba

Yovani Marrero-Ponce
Central University of Las Villas, Cuba, & Universitat de València, Spain

Ramón García-Domenech
Universitat de València, Spain

Francisco Torrens
Universitat de València, Spain

Antonio Rescigno
Università di Cagliari, Italy

Concepción Abad
Universitat de València, Spain

ABSTRACT

In this paper, the authors present an effort to increase the applicability domain (AD) by means of retraining models using a database of 701 great dissimilar molecules presenting anti-tyrosinase activity and 728 drugs with other uses. Atom-based linear indices and best subset linear discriminant analysis (LDA) were used to develop individual classification models. Eighteen individual classification-based QSAR models for the tyrosinase inhibitory activity were obtained with global accuracy varying from 88.15-91.60% in the training set and values of Matthews correlation coefficients (C) varying from

DOI: 10.4018/978-1-4666-4010-8.ch021
Retrained Classification of Tyrosinase Inhibitors and “In Silico” Potency Estimation

0.76-0.82. The external validation set shows globally classifications above 85.99% and 0.72 for C. All individual models were validated and fulfilled by OECD principles. A brief analysis of AD for the training set of 478 compounds and the new active compounds included in the re-training was carried out. Various assembled multiclassifier systems contained eighteen models using different selection criterions were obtained, which provide possibility of select the best strategy for particular problem. The various assembled multiclassifier systems also estimated the potency of active identified compounds. Eighteen validated potency models by OECD principles were used.

1. INTRODUCTION

Melanin is the principal dark surface pigments of uncertain structure that is widespread in nature and play a major role in protect the skin from ultraviolet (UV) damage by absorbing UV sunlight and removing reactive oxygen species (ROS) (Kim & Uyama, 2005; Prota, 1992). Melanin is found in bacteria, fungi, plants, animals and subserves a multitude of diverse functions with evolutionary significance (Prota, 1988). In humans (and in vertebrates in general), the biosynthesis of melanin involves a metabolic pathway beginning with the oxidation of tyrosine to an orthoquinone, dopaquinone, followed by a series of divergent steps that give rise to a predominantly indolic pigment (eumelanin) and a closely related pigment containing benzothiazine subunits (phaeomelanin) (Prota, 1992). Normal skin coloration is a result of both efficient melanization of the melanosome in the melanocyte and proper transfer to and receipt of the melanosome in the keratinocyte (Boissy, 2003; Seiberg, 2001). It is determined by a number of factors, the most important of which is the degree and distribution of melanin pigmentation (Spritz & Hearing, 1994). When a person is healthy, his or her skin will appear normal in color. In the case of illness or injury, the person’s skin might change color, becoming darker (hyperpigmentation), or lighter (hypopigmentation).

Hyperpigmentation such as melasma (also known as chloasma), freckles and moles is caused by an increase in melanin production and deposition. As a result of their prevalent localization in photoexposed areas, acquired hyperpigmentation have psychosocial and cosmetic relevance, and many efforts have been devoted to screening recognized and putative depigmenting agents (Briganti, Camera, & Picardo, 2003). Melanogenesis has been defined as the entire process leading to the formation melanin (Rescigno, Sollai, Pisu, Rinaldi, & Sanjust, 2002). In this process, tyrosinase (monophenol, polyphenol oxidase; EC 1.14.18.1) is the rate-limiting enzyme, catalyzing the first two initial steps of this pathway in the presence of molecular oxygen (Lerch, 1981; Robb, 1981; Solomon, Sundaram, & Machonkin, 1996). Therefore, tyrosinase inhibitors (TI) have attracted considerable interest in medicinal and cosmetic products, primarily in relation to the treatment of hyperpigmentation (Chen & Kubo, 2002). The most popular depigmenting agent is hydroquinone (dihydroxybenzene; HQ) as a TI introduced for clinical use since 1996. Several trials have demonstrated its therapeutic efficacy alone or in association with other compounds (Fisher, 1998; Guevara & Pandya, 2001; Kang, Chun, & Lee, 1998; Kauh & Zachian, 1999; Perez-Bernal, Munoz-Perez, & Camacho, 2000; Sanchez & Vazquez, 1982). Other whitening agents specifically acting on tyrosinase by different mechanisms have been also discovered. Moreover, all of them have presented problems related with the efficacy and safety that limit their uses in clinic. Wherefore, the discovery of new TI compounds needs special attention. But actually this type of study is mostly based in traditional method “trial and error” that implicates expensive and time consuming (Watson, 2003).

At the same time, the paradigm of the Quantitative Structure-Activity Relationships (QSAR) has been of interest for the discovery and development
Related Content

An Efficient Algorithm for Automating Classification of Chemical Reactions into Classes in Ugi’s Reaction Scheme
www.igi-global.com/chapter/efficient-algorithm-automating-classification-chemical/77082?camid=4v1a

Logistic vs. W-Lambert Information in Quantum Modeling of Enzyme Kinetics
www.igi-global.com/chapter/logistic-lambert-information-quantum-modeling/77068?camid=4v1a

Graph Mining in Chemoinformatics
www.igi-global.com/chapter/graph-mining-chemoinformatics/45467?camid=4v1a

Interactions Between Weighting Scheme and Similarity Coefficient in Similarity-Based Virtual Screening
John D. Holliday, Peter Willett and Hua Xiang (2013). Methodologies and Applications for Chemoinformatics and Chemical Engineering (pp. 310-321).
www.igi-global.com/chapter/interactions-between-weighting-scheme-similarity/77084?camid=4v1a