European Journal of Medicinal Chemistry 44 (2009) 4070–4082

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

3D-QSAR with the aid of pharmacophore search and docking-based alignments for farnesyltransferase inhibitors

Madhura Vaidya, Mathias Weigt, Michael Wiese*

Pharmaceutical Institute, University of Bonn, An der Immenburg 4, 53121 Bonn, Germany

ARTICLE INFO

Article history:
Received 2 December 2008
Received in revised form
26 January 2009
Accepted 29 April 2009
Available online 8 May 2009

Keywords:
Farnesyltransferase inhibitors
3D-QSAR
CoMFA
CoMSIA

ABSTRACT

Farnesyltransferase is a potential drug target for treating various types of cancers. Three-dimensional quantitative structure–activity relationships (3D-QSAR) for a series of farnesyltransferase inhibitors were investigated using comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) techniques. Pharmacophore search and molecular docking methods were used for construction of the molecular alignments. While the 3D-QSAR models were created for a training set of 33 compounds, their external predictivity was proven using a test set of 12 compounds. The results provided a comprehensive insight into the relationship between the structural features and the activities of farnesyltransferase inhibitors. This investigation will facilitate optimization of the design of new potential farnesyltransferase inhibitors.

© 2009 Elsevier Masson SAS. All rights reserved.

1. Introduction

Farnesyltransferase (Ftase) inhibitors (FTIs) are potential therapeutic agents for the treatment of a variety of cancers. Ftase catalyzes the transfer of farnesyl moiety from farnesyl pyrophosphate to a cysteine (C) residue found in the polypeptide CAAX motif (A, aliphatic amino acid, X, Met or Ser) in the carboxy terminal of a group of membrane-bound small G proteins such as Ras, RhoB, RhoE, lamins A and B, and transducin. Ras farnesylation is a post-translational modification step required for association with the plasma membrane where the Ras proteins function. The latter play a pivotal role in the cell surface growth receptor signal transduction pathways that regulate cell differentiation, proliferation, migration, and survival [1]. Although the farnesylation assists in the subcellular localization and transformation of the oncogenic Ras variants, the efficacy of FTIs in preclinical testing does not correlate with the presence or absence of activating mutations of Ras [2]. The antineoplastic effects of FTIs are due to malignant transformation blockage by the inhibition of farnesylation of proteins other than Ras (e.g. centromere-binding proteins CENP-E and CENP-F) [3]. Thus FTIs may stop cancer growth by interfering with bipolar spindle formation during transition from prophase to metaphase in mitosis. While FTIs are active against the tumors driven by oncogenic H-Ras, they are inefficient against those by N-Ras and K-Ras. The latter are possible substrates for alternative prenylation by geranylgeranyl-transferase when Ftase is blocked by FTIs [4].

A wide range of structural classes have been identified as FTIs. Novel inhibitors can be classified either as molecules designed on the CAAX motif (peptidomimetics) that interact with the Ftase residues involved in Ras protein binding or the Farnesyl moiety (FPP mimetics) that interact with the FPP binding site or bisubstrate inhibitors that incorporate structural motifs of both FPP and the CAAX tetrapeptide [5–7]. In the past few years non-thiol, non-peptidic and imidazole-containing chemical entities have emerged as FTIs [8]. Tipifarnib (R 115777), a selective non-thiol FTI, has been extensively used as a template in designing novel classes of FTIs. Abbott Laboratory has reported different series of compounds containing a cyanobenzyl group on the imidazole ring [9–13]. These inhibitors have shown promising results in the preclinical testing in cell culture and animal models of cancer. However, only a few QSAR studies have been reported by now for this class of compounds [14,15].

An important challenge for the compounds treated in the present study is to deal with their flexibility since the applications of CoMFA and CoMSIA require the optimized 3D conformations of all molecules. As crystal structures of Ftase with some FTIs are available in the published literature [16–22], new FTIs could be designed by virtual screening and docking. However, unlike QSAR methods, these methods do not readily yield information regarding the importance of molecular substructures for activity. In order to facilitate the design of selective Ftase inhibitors, a three-dimensional quantitative structure–activity relationship (3D-QSAR) study was conducted using comparative molecular field

* Corresponding author.
E-mail address: mwiese@uni-bonn.de (M. Wiese).

0223-5234/$ – see front matter © 2009 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2009.04.045

analysis (CoMFA) [23] and comparative molecular similarity indices analysis (CoMSIA) [24] based on pharmacophore elucidation and docking. Alignments of ligands that are known to bind to the Ftase protein were generated by superimposition on pharmacophore points and docking into the protein binding site. Subsequently, these alignments were used to derive 3D-QSAR models. The 3D-QSAR models may be useful in the design of novel FTIs.

2. Results and discussion

A dataset of 46 FTIs containing an imidazole and cyanophenyl group as structural key elements was used to perform 3D-QSAR studies. In such investigations, the molecular alignment and conformation determination are very important for the reliability and validity of the resulting model. Due to the flexibility of the compounds, it is difficult to choose a suitable conformation that achieves a meaningful superimposition. In an ideal alignment the biologically active conformations should be aligned taking into account the orientations that the ligands adopt at the binding site of the protein. Receptor-guided alignment has been shown to produce models with better statistics than those from the ligand-based approach, presumably because the alignment using receptor information is more realistic [25,32]. The availability of X-ray data from crystallized protein ligand complexes enabled the inclusion of additional information from the receptor site. Therefore, we applied a strategy of combining conformations obtained from docking and pharmacophoric alignment. For the 3D-QSAR methods, CoMFA and CoMSIA, this provides a reasonable solution.

2.1. Pharmacophore elucidation and statistics of CoMFA and CoMSIA

The crystal structures of Ftase were aligned using MOE and ligands from these aligned structures were taken as the pharmacophore template. The essential pharmacophore features of the FTIs for interaction with Ftase are the two aromatic rings and the imidazole nitrogen (hydrogen-bond acceptor). The cyano group representing another hydrogen-bond acceptor and the other aromatic/hydrophobic ring served as optional features. The cyanophenyl and imidazole ring atoms remained as the main pharmacophore features (Fig. 1). The constructed pharmacophore model was comparable to that reported by Equbal et al. [26]. The pharmacophore served as a helpful tool in constructing an alignment of a set of 46 compounds. The alignment of the compounds under study is illustrated in Fig. 2.

The PLS results of the CoMFA which are summarized in Table 2 show that all statistical indices are reasonably high. As depicted in Table 2, the used CoMFA model leads to a q^2 value of 0.761 and an estimated standard error of prediction of 0.348 ($r^2_{conv} = 0.997$, $F = 2016$, $n = 5$). These values indicate that the CoMFA model has a good conventional statistical correlation and it allows good predictions of the biological activity data of the FTIs also for the test

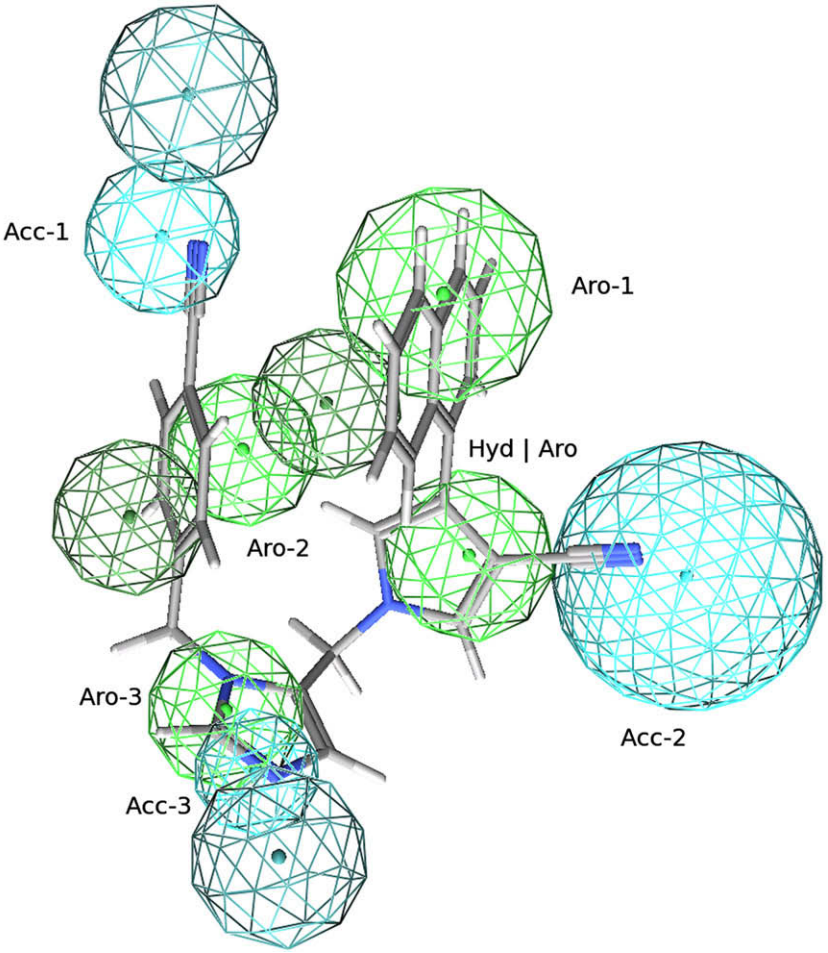

Fig. 1. Pharmacophore mapping of compound **43**. Pharmacophore features are color coded with cyan and green contours representing the hydrogen-bond acceptor feature (HA), hydrophobic feature (HY) and/or ring aromatic features (RA), respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Download English Version:

https://daneshyari.com/en/article/1396616

Download Persian Version:

https://daneshyari.com/article/1396616

Daneshyari.com