Med Chem Res (2011) 20:1530–1541
DOI 10.1007/s00044-010-9406-2

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

QSAR modeling of the inhibition of reverse transcriptase enzyme with benzimidazolone analogs

Surendra Kumar · Vineet Singh · Meena Tiwari

Received: 27 February 2010 / Accepted: 4 August 2010 / Published online: 19 August 2010
© Springer Science+Business Media, LLC 2010

Abstract The reverse transcriptase inhibitory activity of a set of 27 compounds of benzimidazolone analogs is predicted, applying the quantitative structure activity relationship (QSAR) theory. The physicochemical properties representing the 2D and 3D features of molecules were calculated from MOE 2008.10 software. For building the regression models three different variable selection approaches namely, enhanced replacement method (ERM), forward stepwise regression (FSWR), genetic function approximation (GFA) were used and compared to predict the inhibition activity. The ERM outperform at four variables against both FSWR and GFA as evidenced by statistical parameters ($n = 21$, $r^2_{\text{training}} = 0.8864$, $Q^2 = 0.8243$, $r^2_{\text{pred}} = 0.6423$, $r^2_{\text{m}} = 0.5614$). The derived QSAR models have shown that hydrophobicity and size of molecules holds promise for rationalizing the reverse transcriptase inhibitory activity of benzimidazolone analogs. The result of present study may help in designing analogs with better activity.

Keywords Anti-HIV agents · Enhanced replacement method · Forward stepwise regression analysis · Genetic function approximation · QSAR

Electronic supplementary material The online version of this article (doi:10.1007/s00044-010-9406-2) contains supplementary material, which is available to authorized users.

S. Kumar · V. Singh · M. Tiwari (✉)
Department of Pharmacy, Shri G. S. Institute of Technology and Science, 23 Park Road, Indore 452003, MP, India
e-mail: mtiwari@sgsits.ac.in

Introduction

The rapid global spread of human immunodeficiency virus (HIV-1) and the emergence of drug resistance make the development of new therapy/new drug for the treatment of acquired immunodeficiency syndrome (AIDS) an important problem. The replication of HIV-1 in infected patients can be reduced considerably by highly active anti-retroviral therapy (HAART), a high active combination of drugs with multiple targets (Monforte *et al.*, 2008). However, in spite of success of HAART, there are continuing problems of toxicity and drug resistance, including the emergence of multiple drug-resistant strains of HIV-1 (Carr and Cooper 2000). It is thus important to develop more potent drugs active against resistant strains. The unique nature of the replication cycle of retrovirus (HIV-1) offers a variety of potential areas of chemotherapeutic intervention (Mitsuya *et al.*, 1990). Officially approved drugs for HIV treatment belong to the class of nucleoside/nucleotide and non-nucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs), protease inhibitors (PIs), integrase inhibitors (IN) and more recently viral entry inhibitors (De Clercq, 2005a, b; Opar, 2007). One particularly important target is the virally encoded reverse transcriptase (RT), which mediates conversion of the single-stranded viral RNA genome into double stranded DNA. Indeed, nucleoside analogs, such as 3′-azido-2′,3′-dideoxythymidine (AZT), 2′,3′-dideoxyinosine (ddI) and 2′,3′-dideoxycytidine (ddC), which inhibit the process of reverse transcription are used clinically for the treatment of HIV-1 infection (Butler *et al.*, 1991; Fischl *et al.*, 1987; Lambert *et al.*, 1990; Moore *et al.*, 1991). However, the utility of these nucleoside analogs are limited by significant toxicities which may be attributed to inhibition of cellular DNA polymerases (Dournon *et al.*, 1988;