Med Chem Res
DOI 10.1007/s00044-014-1105-y

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Topomer-CoMFA-based predictive modelling on 2,3-diaryl-substituted-1,3-thiazolidin-4-ones as non-nucleoside reverse transcriptase inhibitors

Surendra Kumar · Meena Tiwari

Received: 27 January 2014 / Accepted: 12 June 2014

Abstract The reverse transcriptase enzyme has been identified as an attractive target to inhibit the HIV-1 proliferations. Studies about the structure activity relationship on a dataset of thiazolidin-4-ones were performed using the topomer-CoMFA. The obtained topomer-CoMFA model with steric and electrostatic field parameters based on two (labelled R1 and R2) fragments gave a statistically robust model ($R^2 = 0.938$; $Q^2 = 0.719$). The predictability of the developed model was assessed on a test set data with $r^2_{pred} = 0.798$. The results of topomer-CoMFA suggested that at R1 position, the large bulky groups at C-2 position with less electronegativity and small bulky groups with large electronegativity at C-6 position are favourable for bioactivity. The topomer-CoMFA results for electrostatic contour maps at R2 position, electron releasing groups at C-4, C-5 and C-6 position along with electronegative atoms at N_1 and N_3 of pyrimidine, N_1 of pyridine or O_1 of furan moiety, whereas steric contour maps favour the substitution of small bulky groups at the same position. Finally, the applicability domain of the model was defined on external dataset of thiazolidin-4-ones and the results further supported the reliability and robustness of topomer-CoMFA model, which could be further used for prediction of potential new thiazolidin-4-one analogues.

Electronic supplementary material The online version of this article (doi:10.1007/s00044-014-1105-y) contains supplementary material, which is available to authorized users.

S. Kumar · M. Tiwari (✉)
Computer-Aided Drug Design Lab, Department of Pharmacy, Shri Govindram Seksaria Institute of Technology and Science, 23, Park Road, Indore 452003, M.P., India
e-mail: mtiwari@sgsits.ac.in

S. Kumar
e-mail: skumar@sgsits.ac.in

Keywords Topomer-CoMFA · Thiazolidin-4-one · HIV-1 · 3D-QSAR · Reverse transcriptase enzyme inhibitors

Introduction

Human immunodeficiency virus type 1 (HIV-1) was identified as the causative agent in the transmission and the development of acquired immune deficiency syndrome (AIDS) (Turner and Summers, 1999). The unique nature of the replicative cycle of HIV-1 provides many potential targets for therapeutic intervention. One of these, reverse transcriptase (RT) is a key enzyme, within the HIV virion capsid, which represents an attractive target to inhibit the HIV-1 proliferation (Jonckheere *et al.*, 2000) for several reasons: (i) it is a crucial enzyme in the viral replication cycle; (ii) its properties are quite different from those of the other cellular DNA polymerases; (iii) it is active in the cytoplasmic compartment of the infected cell (Tarrago-Litvak *et al.*, 1994). RT enzyme is necessary for the catalytic transformation of single-stranded viral RNA into the double-stranded linear DNA which is integrated into host cell chromosomes (Barreca *et al.*, 2002). Nucleoside and Non-nucleoside RT inhibitors are two broadly classified groups that target the RT enzyme. Nucleoside reverse transcriptase inhibitors (NRTIs), which act as chain terminators to block the elongation of the HIV-1 viral DNA strand, whereas non-nucleoside reverse transcriptase inhibitors (NNRTIs), a group of structurally diverse compounds directly inhibit RT enzyme by binding to the allosteric site near the polymerase active site (Balzarini, 2004; Ren *et al.*, 1995). Considering the toxicity of both classes of inhibitors, NRTIs possess limited therapeutic index and more severe side effects in humans, due to their

Published online: 10 July 2014