Construction of 4D-QSAR models for use in the design of novel p38-MAPK inhibitors

Nelilma Correia Romeiro\textsuperscript{a,b,*}, Magaly Girão Albuquerque\textsuperscript{a}
Ricardo Bicca de Alencastro\textsuperscript{a}, Malini Ravi\textsuperscript{b} & Anton J. Hopfinger\textsuperscript{b}
\textsuperscript{a}Departamento de Química Orgânica, Laboratório de Modelagem Molecular (LabMMol), Instituto de Química, Universidade Federal do Rio de Janeiro, Centro de Tecnologia, Bloco A, Ilha do Fundão, 21949-900 Rio de Janeiro, RJ, Brasil; \textsuperscript{b}Department of Medicinal Chemistry and Pharmacognosy, Laboratory of Molecular Modeling and Design (LMMD), M/C 781, College of Pharmacy, The University of Illinois at Chicago, 833 South Wood Street, Illinois, Chicago, 60612-7231, USA

Received 16 February 2005; accepted 22 May 2005
© Springer 2005

Key words: 4D-QSAR, anti-inflammatory drugs, inflammation, p38-MAPK, pyridinyl-imidazole, SB–203580

Summary
The p38-mitogen-activated protein kinase (p38-MAPK) plays a key role in lipopolysaccharide-induced tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)) and interleukin–1 (IL–1) release during the inflammatory process, emerging as an attractive target for new anti-inflammatory agents. Four-dimensional quantitative structure-activity relationship (4D-QSAR) analysis [Hopfinger et al., J. Am. Chem. Soc., 119 (1997) 10509] was applied to a series of 33 (a training set of 28 and a test set of 5) pyridinyl-imidazole and pyrimidinylimidazole inhibitors of p38-MAPK, with IC\textsubscript{50} ranging from 0.11 to 2100 nM [Liverton et al., J. Med. Chem., 42 (1999) 2180]. Five thousand conformations of each analogue were sampled from a molecular dynamics simulation (MDS) during 50 ps at a constant temperature of 303 K. Each conformation was placed in a 2 Å grid cell lattice for each of three trial alignments. 4D-QSAR models were constructed by genetic algorithm (GA) optimization and partial least squares (PLS) fitting, and evaluated by leave-one-out cross-validation technique. In the best models, with three to six terms, the adjusted cross-validated squared correlation coefficients, \(Q^2_{\text{adj}}\), ranged from 0.67 to 0.85. Model D (\(Q^2_{\text{adj}} = 0.84\)) was identified as the most robust model from alignment 1, and it is representative of the other best models. This model encompasses new molecular regions as containing pharmacophore sites, such as the amino-benzyl moiety of pyrimidine analogs and the N1-substituent in the imidazole ring. These regions of the ligands should be further explored to identify better anti-inflammatory inhibitors of p38-MAPK.

Introduction
Lipopolysaccharide (LPS), a component of the cell wall of gram-negative bacteria, induces macrophages to produce the pro-inflammatory cytokine tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)) and interleukin-1 (IL-1), key factors in immune responses against infection [1]. However, the uncontrolled production of these pro-inflammatory cytokines may generate chronic inflammatory diseases such as rheumatoid arthritis [2]. Amongst the most attractive targets in drug discovery for the suppression of LPS-induced synthesis of TNF-\(\alpha\) and release of IL–1, p38-mitogen-activated protein kinase (p38-MAPK) [3–7] has been the focal point of many studies involving the search for new anti-inflammatory agents [8–16].

*To whom correspondence should be addressed. Fax: +21-2560-2518, E-mail: nelilma@far.fiocruz.br
The co-crystal structure of p38-MAPK with SB-203580 (4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-1H-imidazole) (1a, Figure 1), the prototype inhibitor of the pyridinyl-imidazole class and other analogous compounds, showed that these inhibitors partially occupy the ATP binding site, preventing further phosphorylation of p38-MAPK [17, 18].

The most important interactions observed between p38-MAPK and SB-203580 in the co-crystal structure are (Figure 1): (i) a hydrogen bond between the N3 of the imidazole core and a hydrogen atom of the –NH2 group of Lys53 (N–N distance = 2.92 Å); (ii) a hydrogen bond between the N4 of the pyridine ring and the hydrogen atom of the N–H group of the peptide backbone of Met109 (N–N distance = 2.75 Å), something, which is also observed for the ATP adenosine ring; and (iii) a π-stacking interaction between the phenyl ring of the methylsulfinylphenyl moiety and the phenyl ring of Tyr35. Additionally, the 4-fluorophenyl ring of SB-203580 binds in a cavity close to Thr106, which is mostly composed of hydrophobic residues, and located behind and orthogonally to the ATP binding site [17, 18].

Liverton and co-workers have recently reported the synthesis and the anti-inflammatory activity evaluation of a series of potent and selective substituted imidazole inhibitors of p38-MAPK [16], which are improved analogues of compound 1a (IC50 = 39 nM) (SB-203580, Figures 2 and 3), the prototype p38-MAPK inhibitor. One of the most potent inhibitors in this series, compound 4g (IC50 = 0.19 nM) (Figure 3), shows good oral bioavailability in rat and rhesus monkeys, and reduces disease significantly in a rat adjuvant-induced arthritis model [16].

Three-dimensional (3D) quantitative structure–activity relationship (QSAR) studies can be useful in the search for sites on molecules that can be modified to make the molecules better specific ligands [19–22]. Among the 3D-QSAR methods, the receptor-independent (RI) 4D-QSAR method, proposed by Hopfinger and co-workers [23–29], is advantageous because it can incorporate molecular flexibility and multiple alignments, allowing the identification of the conformation that maximizes the predicted activity using the best 4D-QSAR model [26]. This conformation is defined as the active (or bioactive) conformation [26].