Development of a 3D pharmacophore model for inhibitors of NF-κB activation by combining structure-derived information and bias from a set of potent inhibitors

S.M. Noha[1], A.G. Atanasov[2], E.H. Heiss[2], N. Fakhrudin[2], A. Grzywacz[2], V.M. Dirsch[2], G. Wolber[3], and D. Schuster[1]

[1] Institute of Pharmacy / Pharmaceutical Chemistry, Computer-Aided Molecular Design (CAMD) Group and Center for Molecular Biosciences Innsbruck (CMBI), Innrain 52c, A-6020 Innsbruck, Austria

[2] Molecular Targets Group, Department of Pharmacognosy, University of Vienna, Althanstrasse 14, A-1090 Vienna, Austria

[3] Institute of Pharmacy / Pharmaceutical Chemistry, Königin-Luise-Str. 2+4, D-14195 Berlin, Germany

The interfacial binding of the NF-κB transcriptional factor to the DNA is assumed to be crucial step of the activation of NF-κB signaling, which is relevant in several diseases such as inflammation, HIV-1 infection, and cancer [1]. Herein, we report the development of a 3D pharmacophore model by combining structure-based and ligand-based methods using the espresso module in LigandScout 3.02 [2]. The pharmacophore-bias option in espresso was employed to modify a structure-derived pharmacophore model with information from a set of two highly active inhibitors of the NF-κB activation, which were selected from a series of 6-amino-quinazoline derivatives [3, 4]. The retrieved 3D models were quantitatively evaluated by screening a validation dataset, using two enrichment metrics. The 3D pharmacophore model with the highest enrichment rate in this theoretical validation was used to virtually screen the Specs database (www.specs.net). Out of 199 hits, 20 structurally diverse compounds were selected for biological evaluation.

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