Journal of Molecular Graphics and Modelling 32 (2012) 39–48

Contents lists available at SciVerse ScienceDirect

Journal of Molecular Graphics and Modelling

journal homepage: www.elsevier.com/locate/JMGM

Study of differences in the VEGFR2 inhibitory activities between semaxanib and SU5205 using 3D-QSAR, docking, and molecular dynamics simulations

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ARTICLE INFO

Article history:
Received 5 August 2011
Received in revised form
30 September 2011
Accepted 15 October 2011
Available online 20 October 2011

Keywords:
VEGFR2
Semaxanib
CoMFA
Docking
Molecular dynamics
MM-GBSA

ABSTRACT

Semaxanib (SU5416) and 3-[4′-fluorobenzylidene]indolin-2-one (SU5205) are structurally similar drugs that are able to inhibit vascular endothelial growth factor receptor-2 (VEGFR2), but the former is 87 times more effective than the latter. Previously, SU5205 was used as a radiolabelled inhibitor (as surrogate for SU5416) and a radiotracer for positron emission tomography (PET) imaging, but the compound exhibited poor stability and only a moderate IC_{50} toward VEGFR2. In the current work, the relationship between the structure and activity of these drugs as VEGFR2 inhibitors was studied using 3D-QSAR, docking and molecular dynamics (MD) simulations. First, comparative molecular field analysis (CoMFA) was performed using 48 2-indolinone derivatives and their VEGFR2 inhibitory activities. The best CoMFA model was carried out over a training set including 40 compounds, and it included steric and electrostatic fields. In addition, this model gave satisfactory cross-validation results and adequately predicted 8 compounds contained in the test set. The plots of the CoMFA fields could explain the structural differences between semaxanib and SU5205. Docking and molecular dynamics simulations showed that both molecules have the same orientation and dynamics inside the VEGFR2 active site. However, the hydrophobic pocket of VEGFR2 was more exposed to the solvent media when it was complexed with SU5205. An energetic analysis, including Embrace and MM-GBSA calculations, revealed that the potency of ligand binding is governed by van der Waals contacts.

1. Introduction

Semaxanib (or SU5416) is a potent and selective inhibitor of the vascular endothelial growth factor receptor-2 (VEGFR2) tyrosine kinase [1]. Inhibition of VEGFR2 blocks signal transduction of the VEGF pathway, thereby affecting many of the processes involved in tumor growth, progression, metastasis, and angiogenesis [2]. Therefore, semaxanib has been studied for use in antiangiogenic therapies.

Positron emission tomography (PET) is a nuclear medicine imaging technique that allows for visualization of specific targets on the molecular level [3]. Monitoring the antiangiogenic effects of a compound is an important step toward clinical trials for a potential cancer treatment. Direct, noninvasive molecular imaging of angiogenesis allows for an adequate selection of patients for antiangiogenesis therapy and a better assessment of the efficacy of treatments that target angiogenesis. The development of small molecule tyrosine kinase inhibitors labeled with the short-lived positron emitters represents an attractive basis for monitoring the overexpression of VEGFR2 tyrosine kinases. Fluorine-18 is the most frequently used radionuclide in PET imaging due to its excellent physical characteristics for imaging. The half-life of ^{18}F is 109.8 min, which allows for complex radiosynthesis reactions and extended pharmacological *in vivo* studies.

Recently, one of the authors of the present study (Kniess) and his co-workers used semaxanib as a lead structure for the development of an ^{18}F-labeled radiotracer [4]. The introduction of the radionuclide into the oxindole core as well into the pyrrole core of semaxanib was unsuccessful; therefore, the authors developed 3-[4′-fluorobenzylidene]indolin-2-one (SU5205) as a surrogate for semaxanib by substitution of the dimethylpyrrol moiety with a 4-fluoro-phenyl ring (Fig. 1). SU5205 was found not to be a suitable radiotracer for imaging receptor tyrosine kinases due to its poor stability and its only moderate IC_{50} affinity for VEGFR2 [4].

The design of a derivative compound based on the structure of oxindole with sub-nanomolar affinity for VEGFR2 similar to that of the original structure of semaxanib is desirable. For this purpose, knowledge of the relevant structural features that positively

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doi:10.1016/j.jmgm.2011.10.005

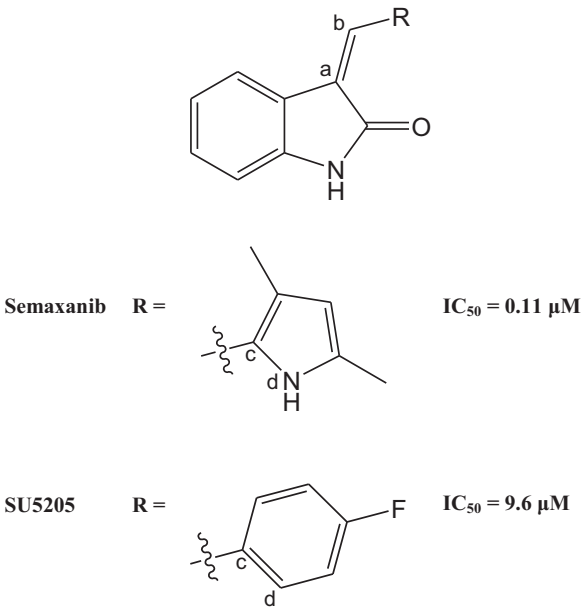

Fig. 1. The structures of semaxanib and SU5205. The atoms involved in the torsional angle φ are labeled.

influence the activity of VEGFR2 and that affect the molecular interactions between VEGFR2 and its inhibitors would be useful. The atomistic analysis of enzyme–inhibitor complexes can be carried out with structural bioinformatics methods. Models that are able to explain the interactions and predict the biological activity of compounds based on their structural properties are considered powerful tools to design highly active kinase inhibitors. Computational methods, such as docking [5–7], quantitative structure–activity relationship (QSAR) [7–13], pharmacophore modeling [14,15], de novo design [16,17], quantum mechanics/molecular mechanics (QM/MM) [5,13,18–20], and molecular dynamics (MD) [21], have been used to study kinase inhibitors. In the recent literature, there are several reports that carried out computational studies on VEGFR2 inhibitors. Most of these studies combined molecular docking and three dimensional (3D) QSAR to understand the structure–activity correlation of VEGFR2 inhibitors [22–24]. In a recent paper, Li et al. [25] developed a predictive nonlinear QSAR model for the inhibition activities for a set of inhibitors of VEGFR2 based on least squares support vector machines. In other report, Planesas et al. [26] proposed a three-step virtual screening protocol, which includes the conventional docking step, a pharmacophore postfilter step, and a similarity search postprocess and applied this protocol to the prediction of VEGFR2 inhibitors.

In the current work, we used the 3D-QSAR method comparative molecular field analysis (CoMFA) to explain the differences in activity between semaxanib and SU5205, and we studied the complexes that formed between these drugs and VEGFR2 using docking and MD simulations. We analyzed the dynamics and energetics of the interactions between the inhibitors and residues at the VEGFR2 active site.

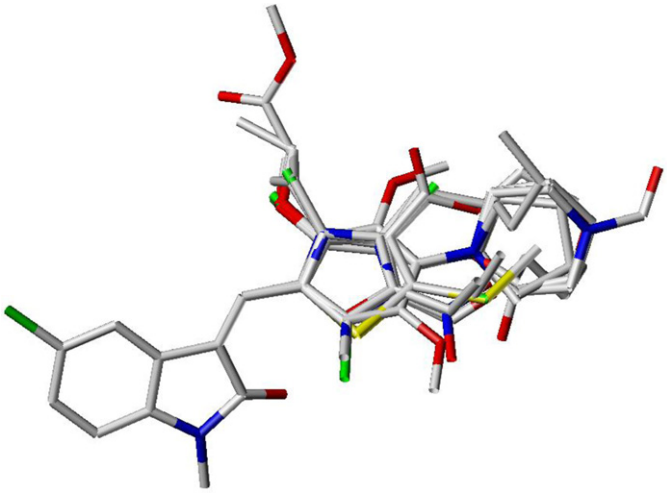

Fig. 2. Superposition used for CoMFA.

2. Methods and computational details

2.1. CoMFA

CoMFA [27] is a methodology of 3D-QSAR employing both interactive graphics and statistical techniques for correlating physico-chemical properties of molecules with their observed biological activities. For the molecules the steric and electrostatic interaction energies with a test probe atom are calculated at regularly spaced grid points surrounding the mutually aligned molecules. The contributions due to dispersion forces between molecules are described by Lennard–Jones-type potentials, and electrostatic properties are characterized by Coulomb-type potentials. Subsequent analysis of the calculated data by a partial least squares (PLS) cross-validation technique yields a set of coefficients which reflect the relative contribution of the physico-chemical elements of the molecules to differences in biological activities. 3D maps represented in an interactive graphics environment of the spatial volumes highly associated with biological activity yields an understanding of intermolecular associations. CoMFA can also predict the biological activity of new molecular species.

The primary structures and activities of 48 2-indolinone derivatives were taken from the patent of Tang et al. [28]. For the 3D-QSAR calculations, the compound set was randomly divided into a training set (40 compounds) and a test set (8 compounds). This subdivision was performed in such a way that both sets represent equally well the chemical and biological properties of the whole data set. Compounds SU4312, SU4793, SU4794, SU4798, SU4799, SU4932, SU4952, SU4967, SU4979, SU4981, SU4982, SU4983, SU4984, SU5204, SU5208, SU5214, SU5404, SU5405, SU5406, SU5407, SU5408, SU5418, SU5419, SU5421, SU5424,

Table 1
CoMFA analysis results.[a]

Model	NC	R^2	s	F	Q^2	s_{CV}	Fraction	
							Steric	Electrostatic
CoMFA-S	4	0.747	0.404	25.83	0.315	0.665	1	
CoMFA-E	1	0.070	0.744	2.88	−0.013	0.776		1
CoMFA-SE	5	0.848	0.318	37.92	0.517	0.578	0.544	0.456

[a] NC is the number of principal components from the PLS analysis; R^2 is the square of the correlation coefficient; s is the standard deviation of the regression; F is the Fisher ratio; and Q^2 and s_{CV} are the correlation coefficient and standard deviation, respectively, of the LOO cross-validation.