Modeling of Radiometal Complexation Formation with Bifunctional Coupling Agents Using Ligand-Metal Interaction Profile

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ABSTRACT

This study aims to establish generalized models for predicting the complex formation \( K_{ML} \) of Ga(III), Cu(II) and In(III) radiometal ions with bifunctional coupling agents of diverse structures. The models were developed based on three different blocks of descriptors e.g. ligand descriptors, metal ions properties and cross-term variables for the analysis of ligand-metal interaction profile. Multiple linear regression (MLR) and support vector regression (SVR) have been utilized to construct the models. The final models showed the best statistical results with squared correlation coefficients of 0.84 and the standard error of estimation (SEE) and standard error of prediction (SEP) values of 2.8 and 3.2 \( \log K_{ML} \) units respectively. The final models were checked for chance correlation, reliability and robustness by permutation testing of y scrambling and cross-validation procedures. The results elucidate the contribution of hydrogen bonding and electrostatic interactions, shape and size of organic ligand and the coordination and electron configuration of metal ions to the complex formation.

KEYWORDS

Bifunctional Coupling Agents, Complexation Formation, Modelling, Radiometals

INTRODUCTION

Metal-based radiopharmaceuticals are of particular interest and widely used in both therapeutic or diagnostic medicinal purposes (Bhattacharyya & Dixit, 2011). Diagnostic metal radiopharmaceuticals are used for single photon emission computed tomography (SPECT) and positron emission tomography (PET) applications as imaging agents (Bhattacharyya & Dixit, 2011; Wadas, Wong, Weisman, & Anderson, 2010). Bifunctional coupling or chelating agents (BFCs), as a fundamental critical component of a radiometal-based radiopharmaceutical, are needed for the radiolabeling of biomolecules and target-specific delivery of metal radiopharmaceutical (Liu, 2008). The metal radiopharmaceuticals must be stable enough over the time and live longer to reach its destination for the diagnostic application or therapeutic procedure (Bartholomä, 2012). A BFC ligand binds the radiometal ion in a tight stable coordination complex so that it can be properly directed to a desirable molecular target in vivo (Price & Orvig, 2014). Thermodynamic formation constants \( (K_{ML} = [ML]/[M][L]) \) of a complex, as a useful index of the binding strength of the complex, provide important information on relative affinities of ligands for a specific metal. An ideal BFC should be able to form a stable radiometal chelate with high thermodynamic stability and kinetic inertness (Liu, 2008).
The computer models are useful for the inspection of trends in complexation phenomena. They provide alternative, robust and computationally cheap prediction of desired property in the absence of extensive experimental or computed data (González-Díaz & Prado-Prado, 2008). The main aim of the study was to develop the quantitative structure-property/activity relationships (QSPR/QSAR) models for the analysis of the interaction space of complexation formation of radiometals and different organic ligands. Most of the previous QSAR studies on the complex formation process are based on density functional theory (DFT) descriptors (Deng et al. 2012; Hancock and Bartolotti 2005; Varbanov et al. 2012). However, DFT calculations generally involve time-consuming tasks with high computational cost. Puzyn and coworkers have demonstrated (Puzyn et al. 2008) that the relatively costly DFT calculations could not always improve the quality of the models.

We applied same fundamental principles of proteochemometrics modeling, that has been widely used for the analysis of protein-ligand interactions (van Westen, Wegner, IJzerman, van Vlijmen, & Bender, 2011; Wikberg, Lapinsh, & Prusis, 2004) to develop QSAR models. The chemical descriptors of both small ligands and radiometals ion were used in a combined model (van Westen et al., 2011). In addition to the derived descriptors of ligands and targets, cross-term or interaction-term descriptors can be introduced to the joint models which can describe the effects of both ligands and targets and the specific interactions between them (Lapinsh, Prusis, Gutaucatis, Lundstedt, & Wikberg, 2001; Lapinsh, Prusis, Mutule, Mutulis, & Wikberg, 2003). Therefore, this approach can model the interaction complex or the ligand-target interaction space (Fernandez, Ahmad, & Sarai, 2010; van Westen et al., 2011). As QSAR approaches, different statistical methods, including multiple linear regression (MLR) and support vector regression (SVR) have been used to modeling of complex formation of \( {^{67}}\text{Ga(III)}, {^{64}}\text{Cu(II)}\) and \( {^{111}}\text{In(III)} \) radiometal ions with BCFs of diverse structures containing acyclic, heterocyclic and macrocyclic moieties.

MATERIALS AND METHODS

Data Set

Experimental data of stability constants of a set of diverse structure BFCs containing acyclic, heterocyclic and macrocyclic ligands were taken from the recent comprehensive published reviews (Price & Orvig, 2014; Wadas et al., 2010). The experimental values of the formation constant (\( \log K_{ML} \)) of different organic molecule were collected below 100 °C and in acidic media with \( {^{67}}\text{Ga(III)}, {^{64}}\text{Cu(II)}\) and \( {^{111}}\text{In(III)} \) radiometal ions. The chemical structures of BFCs along with their experimental values of formation constants (\( \log K_{ML} \)) in the complexation with these radiometals are displayed in Table 1.

Molecular Optimization and Descriptor Calculation

The three dimensional structure of the ligands were constructed using the standard tools available in SYBYL 7.3 molecular modeling package. Energy minimization was performed using the Tripos force field with a distance dependent dielectric and the Powell conjugate gradient algorithm with a convergence criterion of 0.001 kcal/molÅ. Partial atomic charges were calculated using the Gasteiger-Hückel method.

Ligand descriptors: VolSurf descriptors were calculated for BFCs as ligands. VolSurf is a computational procedure that generates useful quantitative 2D descriptors from the 3D maps of molecular interaction field (MIF) between different probes and all the atoms in a target molecule (Cruciani, Pastor, & Guba, 2000). In the present work, VolSurf+ 4.0.1 (Molecular Discovery Ltd., Oxford, UK) with four probes including water (OH\(_2\)), hydrophobic (DRY), H-bond donor (NH) and H-bond acceptor (=O) was used to produce VolSurf descriptors (grid spacing 0.5 Å).

Metal descriptors: Different isotopes of a given element have the same number of electrons and protons, thus they show similar electronic characteristics and have identical chemistry (Nayak, Garmestani, Baidoo, Milenic, & Brechbiel, 2011). Because the chemical behavior of an atom is...
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