Development of New Integrin Beta 1 Inhibitors by Molecular Docking and *de novo* Receptor-Based Design

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Introduction. Integrins are cell adhesion receptors that transmit bidirectional signals across the plasma membrane and link the extracelular environment to the actin cytoskeleton. They are noncovalently linked heterodimeric molecules consisting of one α and one β subunit. Integrins play an important role in inflammation and cancer, due to their properties in cell proliferation processes. Three integrin inhibitors have been docked with three receptors α4β1, α5β1 and αVβ1. **Objectives.** The aim of this study is to develop new integrin antagonists as drug candidates. **Material and Methods**. The crystal structures of α4, α5, αV and β1 were obtained on PDB database (ID: 3V4P, 3VI4, 4O02 and 3VI4, respectively). The complexes α4β1, α5β1 and αVβ1 were created by aligning the monomers to their respective partner. The chosen ligands (BIO1211, BIO5192 and TCS2314) are three commercial α4β1 inhibitors. Their structures were built using Avogadro software, according to their protonation state. After the complexes and ligands setup, they were submitted to a minimization. For Molecular Docking simulations, Vina was chosen, using Pyrx software. Rachel, a Sybyl module, was used for the design of the new compounds, by an automated combinatorial optimization. Therefore, the ligand that showed the lowest binding energy to the receptor was chosen. Lead optimization was performed keeping the ligand carboxylate moiety rigid. **Results and Discussion.** The lowest calculated energy was -9.2 kcal/mol for α4β1 and BIO5192. Thus, the docking poses revealed a close interaction between the BIO5192 carboxylate oxygen and one Mg ion in the integrin. Rachel generated more than 200 new BIO5192 derivatives. The scores, calculated as –logKi, ranged the first tenth ligands from 9.08 to 8.45. **Conclusions.** These results show that BIO5192 is promising to be chosen as a lead compound for the development of new integrin inhibitors. However, further studies must be developed for designing of new drug candidates.

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