

USING BREED TO GENERATE NOVEL STRUCTURES FOR THE STUDY OF MDM2/MDMX. Courtney J. Du Boulay, Mary Falatek, Wayne C. Guida, Department of Chemistry, University of South Florida, 4202 E. Fowler Ave CHE205, Tampa, FL 33620.

A certain docking regiment using Schrödinger's GLIDE software applied to published inhibitors of MDM2 produces scores linearly correlating with published IC_{50} values (R^2 value = 0.6). Using the correlated equation, one finds that the minimum docking score -9 Kcal/mol should achieve $1\mu\text{M}$ IC_{50} value. With the BREED genetic algorithm, fragments of known inhibitors are “breed”, exchanging fragments of the inhibitors along overlapping bonds within docked positions bound to MDM2 and MDMX proteins producing a new generation of potential inhibitors. The “BREED”ing process allows for some flexibility in bond angles, 15 degrees, and position, 1\AA . From approximately 40 inhibitors, this methodology generates 14 thousand new molecules. The resulting inhibitors' docking scores produced 10 molecules that meet the desired scoring criteria.