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In silico proteome-wide affinity fingerprinting of known drugs

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There are many drugs that have long been used for therapeutic purposes with their molecular mechanisms of actions not fully understood. The same more or less applies to recent drugs developed to target specific proteins. It is generally not well known how they may act on many other 'non-target' proteins from the whole proteome. Recent advances in structural proteomics are making it possible to evaluate affinities of those known drugs against proteins ('affinity fingerprinting') on a proteome-wide scale *in silico*. In the present study, a non-redundant set of 561 human proteins (683 ligand binding regions) of known structure was used for *in silico* affinity fingerprinting of 2,140 drugs taken from the MDDR database. For each pair of the drugs and the protein binding regions, the complex structure and the affinity (*p*Ki value) were predicted using the molecular docking program LigandFit on 400 PCs connected by the grid-computing system 'cell computing'. Of the total of 1,461,620 pairs, 5,827 showed predicted *p*Ki values of ≥ 6.4, suggesting possible high affinities. Through the examination of the physico-chemical validity of binding modes and the consistency with known pharmacological actions, some possible new drug-protein interactions were detected, including the inhibition of matrix metalloproteinase-9 by a gpIIb/IIIa antagonist. The results as a whole show the feasibility and significance of the *in silico* proteome-wide affinity fingerprinting approach and its efficacy in understanding molecular mechanisms of actions of known drugs as well as in designing new drugs with high specificity.