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1 **Comparing Sixteen Scoring Functions for Predicting Biological Activities of** 2 **Ligands for Protein Targets** 3 Weijun Xu, Andrew J. Lucke, David P. Fairlie^{*} 4 5 6 Division of Chemistry and Structural Biology, Institute for Molecular Bioscience, The 7 University of Queensland, Brisbane, QLD 4072, Australia 8 9 To whom correspondence should be addressed: Professor David Fairlie, Institute for Molecular Bioscience, University of Queensland, Brisbane, Qld 4072, Australia, Tel: 10 +61-733462989; Fax: +61-73346 2990; E-mail: d.fairlie@imb.ug.edu.au 11 12 13 Abstract

14 Accurately predicting relative binding affinities and biological potencies for 15 ligands that interact with proteins remains a significant challenge for computational chemists. Most evaluations of docking and scoring algorithms have focused on 16 17 enhancing ligand affinity for a protein by optimizing docking poses and enrichment 18 factors during virtual screening. However, there is still relatively limited information 19 on the accuracy of commercially available docking and scoring software programs for 20 correctly predicting binding affinities and biological activities of structurally related 21 inhibitors of different enzyme classes. Presented here is a comparative evaluation of eight molecular docking programs (Autodock Vina, Fitted, FlexX, Fred, Glide, 22 23 GOLD, LibDock, MolDock) using sixteen docking and scoring functions to predict 24 the rank-order activity of different ligand series for six pharmacologically important 25 protein and enzyme targets (Factor Xa, Cdk2 kinase, Aurora A kinase, COX-2, 26 pla2g2a, β Estrogen receptor). Use of Fitted gave an excellent correlation (Pearson 27 0.86, Spearman 0.91) between predicted and experimental binding only for Cdk2 28 kinase inhibitors. FlexX and GOLDScore produced good correlations (Pearson > 0.6) 29 for hydrophilic targets such as Factor Xa, Cdk2 kinase and Aurora A kinase. By 30 contrast, pla2g2a and COX-2 emerged as difficult targets for scoring functions to 31 predict ligand activities. Albeit possessing a high hydrophobicity in its binding site, β 32 Estrogen receptor produced reasonable correlations using LibDock (Pearson 0.75, 33 Spearman 0.68). These findings can assist medicinal chemists to better match scoring

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