PEARLS: Program for Energetic Analysis of Receptor−Ligand System

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Analysis of the energetics of small molecule ligand−protein, ligand−nucleic acid, and protein−nucleic acid interactions facilitates the quantitative understanding of molecular interactions that regulate the function and conformation of proteins. It has also been extensively used for ranking potential new ligands in virtual drug screening. We developed a Web-based software, PEARLS (Program for Energetic Analysis of Ligand−Receptor Systems), for computing interaction energies of ligand−protein, ligand−nucleic acid, protein−nucleic acid, and ligand−protein−nucleic acid complexes from their 3D structures. AMBER molecular force field, Morse potential, and empirical energy functions are used to compute the van der Waals, electrostatic, hydrogen bond, metal−ligand bonding, and water-mediated hydrogen bond energies between the binding molecules. The change in the solvation free energy of molecular binding is estimated by using an empirical solvation free energy model. Contribution from ligand conformational entropy change is also estimated by a simple model. The computed free energy for a number of PDB ligand−receptor complexes were studied and compared to experimental binding affinity. A substantial degree of correlation between the computed free energy and experimental binding affinity was found, which suggests that PEARLS may be useful in facilitating energetic analysis of ligand−protein, ligand−nucleic acid, and protein−nucleic acid interactions. PEARLS can be accessed at http://ang.cz3.nus.edu.sg/cgi-bin/prog/rune.pl.

INTRODUCTION

Cellular processes and underlying molecular events involve interactions between individual molecules.[1,2] Quantitative as well as mechanistic understanding of these interactions is important for exploration and engineering of molecular interactions to regulate cell behavior and to combat diseases. Energetic analysis of molecular interactions has been extensively used in the study of molecular recognition[3,4] and regulation,[5] ligand-binding and its effect on activities of proteins,[6−11] and structure-based drug design.[12] Computational methods and force parameters for computing the energetic of intermolecular interactions from 3D structures have been developed,[13−21] refined,[22−24] and applied to a wide variety of studies of biomolecular interactions[25−29] and structure-based drug design.[30−33] To the best of our knowledge, no freely accessible Web-based software is available for computing biomolecular interaction energies. It is thus desirable to introduce such software for facilitating the study of biomolecular interactions and new drug development.

We have developed a computer program for estimating the interaction energies of small molecule ligand−receptor complexes.[34,35] The ligand−receptor interaction energy and its components are computed by an atomic level molecular mechanics-based force field involving intermolecular van der Waals, electrostatic and hydrogen bond interactions between the binding molecule and its receptor, where the effect of crystal waters has also been taken into consideration. This program has been used in the energetic analysis of ligand−DNA[34] and ligand−protein[35,36] systems and in the development of a computed ligand-binding energy database CLiBE.[37] A Web version of this software, PEARLS (Program for Energetic Analysis of Receptor−Ligand System), was set up for facilitating the energetic study of small molecule ligand−protein, ligand−nucleic acid, protein−nucleic acid, and ligand−protein−nucleic acid interactions. This software was tested on a number of ligand−receptor complexes to determine whether there is a significant correlation between the computed energies and experimental binding affinities.

SOFTWARE ACCESS

PEARLS Web page is at http://ang.cz3.nus.edu.sg/cgi-bin/prog/rune.pl which is shown in Figure 1. The 3D structural file of a small molecule ligand−protein, ligand−nucleic acid, protein−nucleic acid, or ligand−protein−nucleic acid system, in PDB format, can be input in the upload data window provided. Advanced options are provided for users to view, revise, or use their own derived force field parameters for computing the binding energy (as shown in Figure 1b). The computed result is displayed in a separate window as shown in Figure 2. This software provides the computed binding free energy and its energy components including van der Waals, electrostatic, individual ligand−receptor/protein−nucleic acid/water-mediated hydrogen bond (H-bond), metal−ligand bonding, solvation free energy change arising from the binding of the constituent molecules, and conformational entropy change. The energy of each individual intraprotein or intranucleic acid H-bond is also given.

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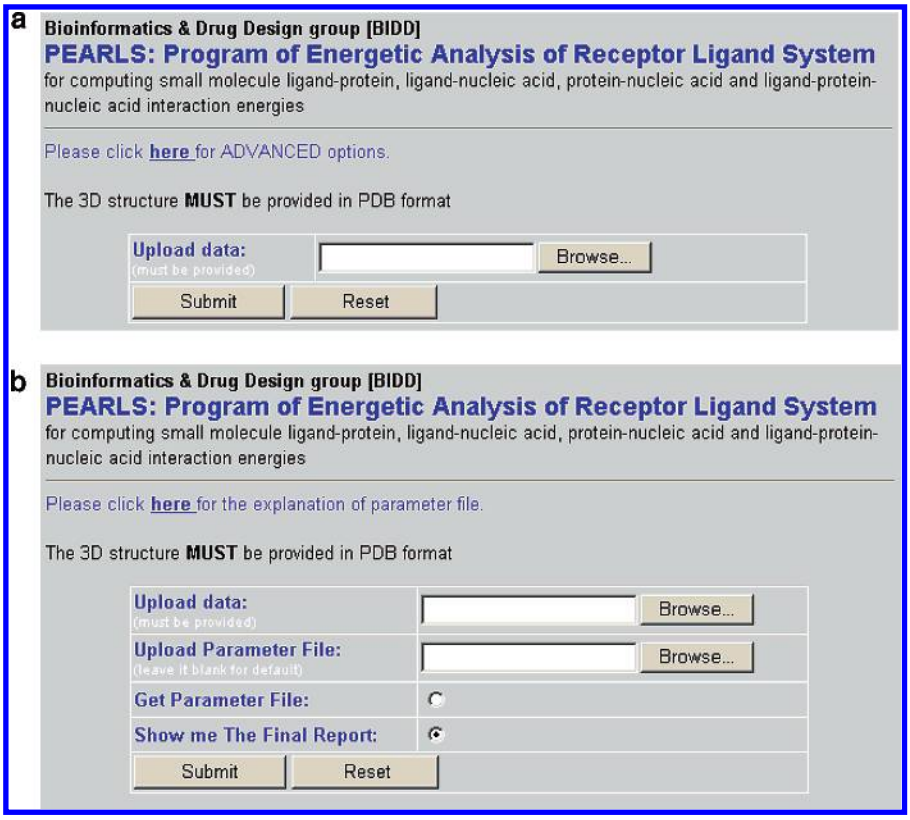

Figure 1. (a,b) The Web interface of PEARLS. A 3D structure file of a ligand−receptor, protein−nucleic acid, or ligand−protein−nucleic acid system in PDB format can be input in the upload data window provided.

COMPUTATIONAL METHOD

In computing the energy of small molecule ligand−receptor or protein−nucleic acid interactions, a molecular mechanics force field AMBER[13] is used for the nonbonded van der Waals and electrostatic interactions. For the ligand atoms, the van der Waals parameters are derived from the AMBER force field according to their atom types and the partial charges are the Sanderson charge.[38] Morse potential,[39] which is a function of H-bond donor−acceptor distance, is used to represent hydrogen bond interactions.[34,40,41] This potential has been shown to give a reasonable description of hydrogen bond energy and the dynamics of hydrogen bond disruption in biomolecules.[34,40,41] The energy functions for van der Waals, electrostatic, and H-bond interactions are given by

$$V_{\mathrm{VdW}} = \sum_{\mathrm{VdW}}[A_{ij}/r_{ij}^{12} - B_{ij}/r_{ij}^{6}]$$

$$V_{\mathrm{elect}} = \sum_{\mathrm{elect}}[q_i q_j/\epsilon_{\mathrm{r}} r_{ij}]$$

$$V_{\mathrm{H-bonds}} = \sum_{\mathrm{H-bonds}}[V_0(1 - e^{-a(r-r0)})^2 - V_0] \quad (1)$$

where A_{ij} and B_{ij} are the van der Waals parameters given in the AMBER force field;[13] ϵ_{r} is a dielectric constant, q_i and q_j are partial charges of the ith and jth atoms given in the AMBER force field[13] and r_{ij} is the distance between the two atoms; r is the H-bond donor−acceptor distance, and V_0, a, and r_0 are the hydrogen bond potential parameters given in our previous publications.[40,41]

Some proteins are known to have metal cations, such as Mg^{2+}, Ca^{2+}, Mn^{2+}, and Zn^{2+}, in their active sites. Coordination bonding between a metal cation in the receptor binding site and an O or a N atom of the ligand is known to contribute to the stability of the ligand−receptor complex. Based on an earlier study,[16] the metal−ligand bonding energy $V_{\mathrm{M-bonds}}$ can be given by

$$V_{\mathrm{M-bonds}} = \sum_{\text{metal bond}} V_{\mathrm{Metal}}(d)$$

$$V_{\mathrm{metal}}(d) = V_{\mathrm{M}} \quad d < 2.0\ \text{Å}$$

$$= V_{\mathrm{M}}(3.0 - d) \quad 2.0\ \text{Å} < d < 3.0\ \text{Å} \quad (2)$$

$$= 0 \quad d > 3.0\ \text{Å}$$

where V_{M} is the metal−ligand stabilization energy and d is the distance between the metal cation attached to the receptor and an O/N atom of the ligand. A computed value of −18.0 kcal/mol[42] is used for V_{M}.

There are explicit water molecules in the structural files of a number of biomolecular complexes. In addition to shielding electrostatic interactions, some of these water molecules may stabilize biomolecular structures through water-mediated hydrogen bonding.[40] The electrostatic shielding effect is represented by the use of dielectric constants. The contribution of ligand−water-receptor hydrogen bonding can be estimated by computing the energy of each of the ligand−water and water-receptor hydrogen bond using the same Morse potential and parameters in eq 1.

The solvation free energy change resulting from the molecular binding can be estimated by Eisenberg's method of atomic solvation parameters.[14,43] This energy takes the form of

$$\Delta G_{\mathrm{solv}} = \sum_{\text{atoms } i} \Delta\sigma_i A_i \quad (3)$$

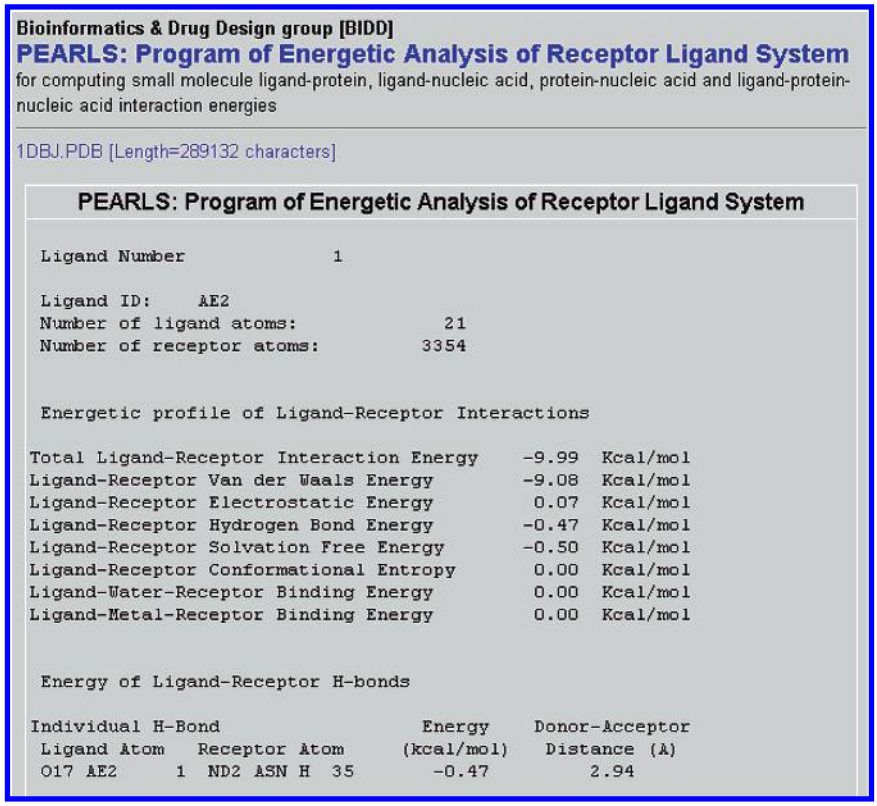

Figure 2. The interface of a computed result of PEARLS. The computed total binding free energy, van der Waals energy, electrostatic energy, hydrogen bond energy, water-mediated hydrogen bond energy, metal bond energy, conformational entropy change, and solvation free energy change of a ligand−receptor system is given. The computed intraprotein hydrogen energies are also given.

where $\Delta\sigma_i$ is the atomic solvation parameter and A_i is the Lee and Richards solvation accessible surface area[44] for atom i. The $\Delta\sigma_i$s used in work are from the literature.[14,43]

The contribution from changes in conformational entropy during the ligand-binding process can be estimated by using an empirical formula[45]

$$\Delta G_{\text{entropy}} = 0.59N \tag{4}$$

where N is the number of rotatable bonds. A rotatable bond is defined as a single bond not residing in a ring and is covalently linked to two non-hydrogen atoms. The count of rotatable bonds is restricted to a ligand based on the conclusion from a study which found that inclusion of the rotatable bonds of proteins does not help to improve the results.[16] Rotations of terminal atoms are ignored as these do not produce meaningful new conformers.[16]

The total free energy for the molecular interactions is given by

$$\Delta G = \alpha V_{\text{VdW}} + \beta V_{\text{elect}} + \gamma V_{\text{H-bonds}} + \delta V_{\text{M-bonds}} + \epsilon \Delta G_{\text{solv}} + \phi \Delta G_{\text{entropy}} + \eta \tag{5}$$

where α, β, χ, δ, ϵ, ϕ, and η are scaling parameters introduced to fit the computed free energy with experimental binding affinity by using a multiple linear regression method.[16,45,46] Introduction of these parameters has been found to significantly improve the agreement between the computed ligand−receptor binding free energies and experimental binding data.[16,45,46] To obtain representative and more accurate regression parameters, we used 124 ligand−receptor complexes[16,46−48] (listed in the Supporting Information) as the regression training set. These complexes were selected based on the criteria that the structure has no close contact and covalent bond between a ligand atom and protein atom. From the multiple linear regression on the training set, these parameters were derived as $\alpha = 0.21$, $\beta = 0.17$, $\gamma = 0.21$, $\delta = 0.18$, $\epsilon = 0.24$, $\phi = 0.24$, $\eta = 0.15$. The computed correlation coefficient R between the experimental and computed free energies is 0.70. The standard error for the computed free energies is 0.21 kcal/mol. By using this regression model, the computed R value for all of the qualified ligand-structures in the PDBbind database[49] is 0.40. These parameters and computed R values are comparable to those derived in earlier studies of ligand−protein and ligand−RNA interactions.[45,46] The computed R value is altered to 0.36, 0.65, 0.65, 0.65, 0.67, and 0.69, respectively, if van der Waals, electrostatic, hydrogen bond, metal-receptor binding, solvation free energy, and conformational entropy terms are omitted. The omission of the ligand−water-receptor binding term has a negligible effect on R. These suggest that our regression model is most sensitively dependent on van der Waals interactions and to a lesser extent on electrostatic interactions, hydrogen bonds, metal-receptor binding, and salvation.

RESULTS AND DISCUSSION

To evaluate whether the computed intermolecular interaction energy is useful in facilitating the analysis of molecular interactions, we selected an independent testing set of 23 ligand−receptor complexes to compare the computed free energies with experimental binding affinity to examine if there is a significant correlation between them. These ligand−receptor complexes are not in the training set and thus can be used to objectively evaluate our computed results.

Table 1. List of Ligand−Receptor Complexes Studied in This Work[a]

PDB ID	ligand name	receptor name	no. of non-hydrogen ligand atoms	exptl binding affinity (kcal/mol)	computed binding energy (kcal/mol)
1G46	N-(2,3-diflourobenzyl)-4-sulfamoylbenzamide	carbonate dehydratase	20	−12.13	−11.46
1J14	benzamidine	trypsin	9	−6.13	−7.42
1SRE	2-((4′-hydroxyphenyl)-azo)benzoate	streptavidin	18	−5.26	−7.06
1TNI	4-phenylbutylamine	trypsin	11	−5.46	−7.51
1G52	N-(2,3-diflourobenzyl)-4-sulfamoylbenzamide	carbonate dehydratase	22	−13.02	−11.31
1DRJ	ribose(pyranose form)	D-ribose-binding protein (G134R)	10	−10.10	−7.74
1ABF	beta-D-fucose	L-arabinose-binding protein	11	−7.40	−8.42
1CE5	benzamidine	trypsin	9	−6.46	−7.97
1MNC	hydroxamate	neutrophil collagenase	25	−12.28	−8.49
1FH8	xylopyranose	cellulose 1,4-beta-cellobiosidase	17	−9.40	−9.90
1A99	1,4-diaminobutane	putrescine-binding protein	6	−7.78	−6.78
1BCJ	N-acetyl-D-galactosamine	mannose-binding protein-A	15	−5.05	−2.84
1C5T	thieno[2,3-b]pyridine−2-carboxamidine	trypsin	8	−5.59	−8.54
1APB	D-fucose	L-arabinose binding protein P254G	11	−7.94	−9.12
2DRC	methotrexate	dihydrofolate reductase	33	−13.49	−14.97
3PTB	benzamidine	trypsin	9	−6.13	−8.03
5SGA	acetyl group	proteinase A (SGPA)	3	−3.90	−2.92
1FKH	1-cyclohexyl-3-phenyl-1-propyl-1-(3,3-dimethyl-1,2-dioxypentyl)-2-piperidine carboxylate	FK506 binding protein (FKBP)	33	−11.13	−11.95
1C2D	bis(5-amidino-2-benzimidazolyl)methane ketone	trypsin	26	−11.31	−12.10
5STD	(6,7-difluoroquinazolin-4-yl)-(1-methyl-2,2-diphenylethyl)amine	scytalone dehydratase	28	−14.32	−13.78
1KOD	citrulline	RNA aptamer	12	−6.80	−6.95
1TOB	RNA(5′-R(GGCACGAGGUUUAGCUACACUCGUGCC)-3′)	RNA aptamer	32	−12.40	−13.86
1STP	biotin	streptavidin	16	−18.18	−11.58

[a] The experimental binding affinity is from refs 46, 48, 50, and 54.

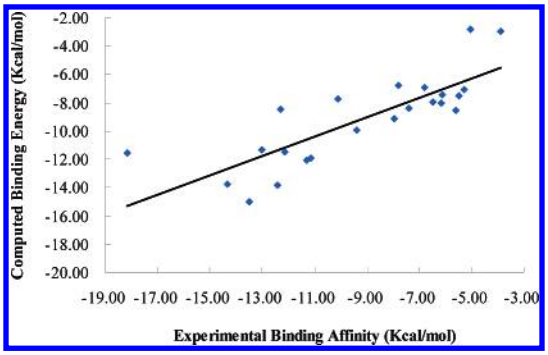

Figure 3. Scatter plot of computed ligand−receptor binding free energy against experimental binding affinity for the PDB ligand−receptor complexes listed in Table 1. The experimental binding affinity is from refs 46, 48, 50, and 54. The line in the figure is the linear curve fitted to the data. The correlation coefficient *R* between the experimental and computed free energies is 0.79. The standard error for the computed free energies is 0.45 kcal/mol.

Table 1 gives a list of these complexes together with the computed ligand−receptor interaction energy and experimental binding affinity.[45,50] The ligand−receptor complexes studied include dihydrofolate reductase, proteinase, carbonate dehydratase, trypsin, sugar-binding proteins, RNA-binding proteins, and others bound by a diverse set of small molecule ligands.

Figure 3 shows the scatter plot of computed ligand−receptor interaction energy against the corresponding experimental binding affinity for the 23 ligand−receptor complexes listed in Table 1. The correlation coefficient *R* between the experimental and computed free energies is 0.80. The standard error for the computed free energies is 0.45 kcal/mol. Thus the computed free energies show a substantial degree of linear correlation with the observed binding affinity of the corresponding ligand−receptor complexes. Such a correlation may be partially due to the substantial role the enthalpic effect plays in ligand−receptor binding in some systems.[51−53] Inclusion of estimates of the contribution from entropic effect, metal binding, explicit water is also expected to contribute to the correlation between computed and observed free energies. This seems to suggest that the computed free energy may be useful in qualitatively indicating the binding affinity. However, the discrepancy between the computed and observed free energies indicates that the modeling of entropic and solvent effects as well as enthalpic effect need to be further improved.

It is noted that our study is based on a limited set of ligand−receptor complexes whose experimental binding affinity is available. A more comprehensive study involving a statistically significant number of groups of complexes of the same receptor with a wide variety of binding ligand may be needed to provide a more comprehensive assessment of the usefulness of the computed ligand−receptor interaction energy.

CONCLUSION

A Web-based software for computing ligand−receptor and protein−nucleic acid interaction energy is presented. The intermolecular interaction energy is computed based on molecular-mechanics-based energy functions. An examination of the computed energy for a number of ligand−receptor complexes from the PDB database shows a substantial degree of correlation between the computed energy and the corresponding experimental binding affinity. Our study suggests that this molecular-mechanics-based energy may be useful in facilitating qualitative analysis of biomolecular binding.

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Supporting Information Available: List of ligand−receptor complexes studies in this work. This material is available free of charge via the Internet at http://pubs.acs.org.

REFERENCES AND NOTES

(1) Downward, J. The ins and outs of signaling. *Nature* **2001**, *411*(6839), 759−62.

(2) Lengeler, J. W. Metabolic networks: a signal-oriented approach to cellular models. *Biol. Chem.* **2000**, *381*(9−10), 911−20.

(3) Davis, S. J.; Schockmel, G. A.; Somoza, C.; Buck, D. W.; Healey, D. G.; Rieber, E. P.; Reiter, C.; Williams, A. F. Antibody and HIV-1 gp120 recognition of CD4 undermines the concept of mimicry between antibodies and receptors. *Nature* **1992**, *358*(6381), 76−9.

(4) Bravo, J.; Heath, J. K. Receptor recognition by gp130 cytokines. *EMBO J.* **2000**, *19*(11), 2399−411.

(5) Shimaoka, M.; Takagi, J.; Springer, T. A. Conformational regulation of integrin structure and function. *Annu. Rev. Biophys. Biomol. Struct.* **2002**, *31*, 485−516.

(6) Galon, J.; Bouchard, C.; Fridman, W. H.; Sautes, C. Ligands and biological activities of soluble Fc gamma receptors. *Immunol. Lett.* **1995**, *44*(2−3), 175−81.

(7) Strange, P. G. The energetics of ligand binding at catecholamine receptors. *Trends Pharmacol. Sci.* **1996**, *17*(7), 238−44.

(8) Guzman-Casado, M.; Sanchez-Ruiz, J. M.; El Harrous, M.; Gimenez-Gallego, G.; Parody-Morreale, A. Energetics of myo-inositol hexasulfate binding to human acidic fibroblast growth factor effect of ionic strength and temperature. *Eur. J. Biochem.* **2000**, *267*(12), 3477−86.

(9) Manderson, G. A.; Michalsky, S. J.; Johansson, J. S. Effect of four-alpha-helix bundle cavity size on volatile anesthetic binding energetics. *Biochemistry* **2003**, *42*(38), 11203−13.

(10) Jones, M. V.; Jonas, P.; Sahara, Y.; Westbrook, G. L. Microscopic kinetics and energetics distinguish GABA(A) receptor agonists from antagonists. *Biophys. J.* **2001**, *81*(5), 2660−70.

(11) Hensley, P.; Doyle, M. L.; Myszka, D. G.; Woody, R. W.; Brigham-Burke, M. R.; Erickson-Miller, C. L.; Griffin, C. A.; Jones, C. S.; McNulty, D. E.; O'Brien, S. P.; Amegadzie, B. Y.; MacKenzie, L.; Ryan, M. D.; Young, P. R., Evaluating energetics of erythropoietin ligand binding to homodimerized receptor extracellular domains. *Methods Enzymol.* **2000**, *323*, 177−207.

(12) Whittle, P. J.; Blundell, T. L. Protein structure−based drug design. *Annu. Rev. Biophys. Biomol. Struct.* **1994**, *23*, 349−75.

(13) Cornell, W. D.; Cieplak, P.; Bayly, C. I.; Gould, I. R.; Merz KM, J.; Ferguson, D. M.; Spellmeyer, D. C.; Fox, T.; Caldwell, J. W.; Kollman, P. A. A second generation force field for the simulation of proteins and nucleic acids. *J. Am. Chem. Soc.* **1995**, *117*, 5179−5197.

(14) Eisenberg, D.; McLachlan, A. D. Solvation energy in protein folding and binding. *Nature* **1986**, *319*(6050), 199−203.

(15) Brooks, B. R.; Bruccoleri, R. E.; Olafson, B. D.; States, D. J.; Swaminathan, S.; Karplus, M., CHARMM: A Program for Macromolecular Energy, Minimization, and Dynamics Calculations. *J. Comput. Chem.* **1983**, *4*(2), 187−217.

(16) Wang, R.; Liu, L.; Lai, L.; Tang, Y. SCORE: a new empirical method for estimating the bind affinity of a protein−ligand complex. *J. Mol. Model.* **1998**, *4*, 379−394.

(17) Kortemme, T.; Baker, D. A simple physical model for binding energy hot spots in protein−protein complexes. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*(22), 14116−21.

(18) Wang, J.; Morin, P.; Wang, W.; Kollman, P. A. Use of MM-PBSA in reproducing the binding free energies to HIV-1 RT of TIBO derivatives and predicting the binding mode to HIV-1 RT of efavirenz by docking and MM-PBSA. *J. Am. Chem. Soc.* **2001**, *123*(22), 5221−30.

(19) Muegge, I.; Martin, Y. C. A general and fast scoring function for protein−ligand interactions: a simplified potential approach. *J. Med. Chem.* **1999**, *42*(5), 791−804.

(20) Jones, G.; Willett, P.; Glen, R. C.; Leach, A. R.; Taylor, R. Development and validation of a genetic algorithm for flexible docking. *J. Mol. Biol.* **1997**, *267*(3), 727−48.

(21) Bohm, H. J. LUDI: rule-based automatic design of new substituents for enzyme inhibitor leads. *J. Comput.-Aided Mol. Des.* **1992**, *6*(6), 593−606.

(22) Aqvist, J.; Luzhkov, V. B.; Brandsdal, B. O. Ligand binding affinities from MD simulations. *Acc. Chem. Res.* **2002**, *35*(6), 358−65.

(23) Perakyla, M.; Pakkanen, T. A. Ab initio models for receptor−ligand interactions in proteins. 4. Model assembly study of the catalytic mechanism of triosephosphate isomerase. *Proteins* **1996**, *25*(2), 225−36.

(24) Aqvist, J.; Marelius, J. The linear interaction energy method for predicting ligand binding free energies. *Comb. Chem. High Throughput Screening* **2001**, *4*(8), 613−26.

(25) Verkhivker, G. M.; Bouzida, D.; Gehlhaar, D. K.; Rejto, P. A.; Freer, S. T.; Rose, P. W. Computational detection of the binding-site hot spot at the remodeled human growth hormone-receptor interface. *Proteins* **2003**, *53*(2), 201−19.

(26) Settanni, G.; Cattaneo, A.; Carloni, P. Molecular dynamics simulations of the NGF-TrkA domain 5 complex and comparison with biological data. *Biophys. J.* **2003**, *84*(4), 2282−92.

(27) Botelho, A. V.; Gibson, N. J.; Thurmond, R. L.; Wang, Y.; Brown, M. F. Conformational energetics of rhodopsin modulated by nonlamellar-forming lipids. *Biochemistry* **2002**, *41*(20), 6354−68.

(28) Kovrigin, E. L.; Cole, R.; Loria, J. P. Temperature dependence of the backbone dynamics of ribonuclease A in the ground state and bound to the inhibitor 5′-phosphothymidine (3′-5′)pyrophosphate adenosine 3′-phosphate. *Biochemistry* **2003**, *42*(18), 5279−91.

(29) Paci, E.; Caflisch, A.; Pluckthun, A.; Karplus, M. Forces and energetics of hapten-antibody dissociation: a biased molecular dynamics simulation study. *J. Mol. Biol.* **2001**, *314*(3), 589−605.

(30) Wang, R.; Lai, L.; Wang, S. Further development and validation of empirical scoring functions for structure-based binding affinity prediction. *J. Comput.-Aided Mol. Des.* **2002**, *16*(1), 11−26.

(31) Rarey, M.; Kramer, B.; Lengauer, T. Docking of hydrophobic ligands with interaction-based matching algorithms. *Bioinformatics* **1999**, *15*(3), 243−50.

(32) Perez, C.; Pastor, M.; Ortiz, A. R.; Gago, F. Comparative binding energy analysis of HIV-1 protease inhibitors: incorporation of solvent effects and validation as a powerful tool in receptor-based drug design. *J. Med. Chem.* **1998**, *41*(6), 836−52.

(33) Clark, R. D.; Strizhev, A.; Leonard, J. M.; Blake, J. F.; Matthew, J. B. Consensus scoring for ligand/protein interactions. *J. Mol. Graphics Modell.* **2002**, *20*(4), 281−95.

(34) Chen, Y. Z.; Prohofsky, E. W. Premelting base pair opening probability and drug binding constant of a daunomycin-poly d(GCAT).poly d(ATGC) complex. *Biophys. J.* **1994**, *66*(3 Pt 1), 820−6.

(35) Chen, Y. Z.; Zhi, D. G. Ligand-protein inverse docking and its potential use in the computer search of protein targets of a small molecule. *Proteins* **2001**, *43*(2), 217−26.

(36) Chen, Y. Z.; Ung, C. Y. Prediction of potential toxicity and side effect protein targets of a small molecule by a ligand-protein inverse docking approach. *J. Mol. Graphics Modell.* **2001**, *20*(3), 199−218.

(37) Chen, X.; Ji, Z. L.; Zhi, D. G.; Chen, Y. Z. CLiBE: a database of computed ligand binding energy for ligand−receptor complexes. *Comput. Chem.* **2002**, *26*(6), 661−6.

(38) Sanderson, R. T. Principles of electronegativity. *J. Chem. Educ.* **1988**, *65*(2), 112−131.

(39) Baird, N. C. Simulation of hydrogen bonding in biological systems: Ab initio calculations for NH3−NH3 and NH3−NH4+. *Int. J. Quantum Chem. Symp.* **1974**, *1*, 49−53.

(40) Chen, Y. Z.; Prohofsky, E. W. The role of a minor groove spine of hydration in stabilizing poly(dA).poly(dT) against fluctuational interbase H-bond disruption in the premelting temperature regime. *Nucleic Acids Res.* **1992**, *20*(3), 415−9.

(41) Cao, Z. W.; Chen, Y. Z. Hydrogen-bond disruption probability in proteins by a modified self-consistent harmonic approach. *Biopolymers* **2001**, *58*(3), 319−28.

(42) Trachtman, M.; Markham, G. D.; Glusker, J. P.; George, P.; Bock, C. W. Interactions of metal ions with water: ab initio molecular orbital studies of structure, vibrational frequencies, charge distributions, bonding enthalpies, and deprotonation enthalpies. 2. Monohydroxides. *Inorg. Chem.* **2001**, *40*(17), 4230−41.

(43) Wesson, L.; Eisenberg, D. Atomic solvation parameters applied to molecular dynamics of proteins in solution. *Protein Sci.* **1992**, *1*(2), 227−35.

(44) Lee, B.; Richards, F. M. The interpretation of protein structures: estimation of static accessibility. *J. Mol. Biol.* **1971**, *55*(3), 379−400.

(45) Filikov, A. V.; Mohan, V.; Vickers, T. A.; Griffey, R. H.; Cook, P. D.; Abagyan, R. A.; James, T. L. Identification of ligands for RNA targets via structure-based virtual screening: HIV-1 TAR. *J. Comput.-Aided Mol. Des.* **2000**, *14*(6), 593−610.

(46) Wang, R.; Lu, Y.; Fang, X.; Wang, S. An extensive test of 14 scoring functions using the PDBbind refined set of 800 protein−ligand complexes. *J. Chem. Inf. Comput. Sci.* **2004**, *44*(6), 2114−25.

(47) Sassanfar, M.; Szostak, J. W. An RNA motif that binds ATP. *Nature* **1993**, *364*(6437), 550−3.

(48) Yang, Y.; Kochoyan, M.; Burgstaller, P.; Westhof, E.; Famulok, M. Structural basis of ligand discrimination by two related RNA aptamers resolved by NMR spectroscopy. *Science* **1996**, *272*(5266), 1343−7.

(49) Wang, R.; Fang, X.; Lu, Y.; Yang, C. Y.; Wang, S. The PDBbind database: methodologies and updates. *J. Med. Chem.* **2005**, *48*(12), 4111−9.

(50) Baxter, C. A.; Murray, C. W.; Clark, D. E.; Westhead, D. R.; Eldridge, M. D. Flexible docking using Tabu search and an empirical estimate of binding affinity. *Proteins* **1998**, *33*(3), 367−82.
(51) Erickson, J. W.; Burt, S. K. Structural mechanisms of HIV drug resistance. *Annu. Rev. Pharmacol. Toxicol.* **1996**, *36*, 545−71.
(52) Ala, P. J.; Huston, E. E.; Klabe, R. M.; McCabe, D. D.; Duke, J. L.; Rizzo, C. J.; Korant, B. D.; DeLoskey, R. J.; Lam, P. Y.; Hodge, C. N.; Chang, C. H. Molecular basis of HIV-1 protease drug resistance: structural analysis of mutant proteases complexed with cyclic urea inhibitors. *Biochemistry* **1997**, *36*(7), 1573−80.
(53) Rozwarski, D. A.; Grant, G. A.; Barton, D. H.; Jacobs, W. R., Jr.; Sacchettini, J. C. Modification of the NADH of the isoniazid target (InhA) from Mycobacterium tuberculosis. *Science* **1998**, *279*(5347), 98−102.
(54) Wang, Y.; Killian, J.; Hamasaki, K.; Rando, R. R. RNA molecules that specifically and stoichiometrically bind aminoglycoside antibiotics with high affinities. *Biochemistry* **1996**, *35*(38), 12338−46.

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