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iScreen: world's first cloud-computing web server for virtual screening and de novo drug design based on TCM database@Taiwan

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Abstract The rapidly advancing researches on traditional Chinese medicine (TCM) have greatly intrigued pharmaceutical industries worldwide. To take initiative in the next generation of drug development, we constructed a cloud-computing system for TCM intelligent screening system (iScreen) based on TCM Database@Taiwan. iScreen is compacted web server for TCM docking and followed by customized de novo drug design. We further implemented a protein preparation tool that both extract protein of interest from a raw input file and estimate the size of ligand bind site. In addition, iScreen is designed in user-friendly graphic interface for users who have less experience with the command line systems. For customized docking, multiple docking services, including standard, in-water, pH environment, and flexible docking modes are implemented. Users can download first 200 TCM compounds of best docking results. For TCM de novo drug design, iScreen provides multiple molecular descriptors for a user's interest. iScreen is the world's first web server that employs world's largest TCM database for virtual screening and de novo drug design. We believe our web server can lead TCM research to a new era of drug development. The TCM docking and screening server is available at http://iScreen.cmu.edu.tw/.

Keywords Traditional Chinese medicine (TCM) · Cloud-computing · Docking · Screening · De novo

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Introduction

Traditional Chinese medicine (TCM) is a popular medical practice among Eastern Asia. For thousands of years, TCM has become a vast knowledge bank of medicine [1–7]. As more bioactive compounds isolated from TCM, a comprehensive drug design operating platform is required for systematically analyzing the therapeutic values of the TCM components. It came to our interest in developing a user-friendly online TCM-based computer-aided drug design (CADD) web server for both TCM docking and de novo drug design. Hence, we introduced a cloud-computing system for intelligent TCM screening (iScreen), which is world's first TCM docking and de novo drug design web server using TCM Database@Taiwan [8].

At present, there are several web servers available for virtual screening, such as PLANTS [9], GOLD [10, 11], DOCK Blaster [12], LEA3D [13], 3DLigandSite [14], and PharmMapper [15], as well as web servers for de novo drug design, such as GANDI [16], SPROUT [17], HISTE [18], LEGND [19], LEA3D [13], 3DLigandSite [14], PRO_LIGAND [20], GENSTAR [21], LUDI [22], BUILDER v.2 [23], CONCERTS [24], SYNOPSIS [25], and CoG [26]. However, iScreen is the first web server that introduces TCM into the web-based CADD service platform.

The schematic dataflow of iScreen is illustrated in Fig. 1. The web server utilized the uses of world's largest TCM database [8] to provide a novel CADD service for

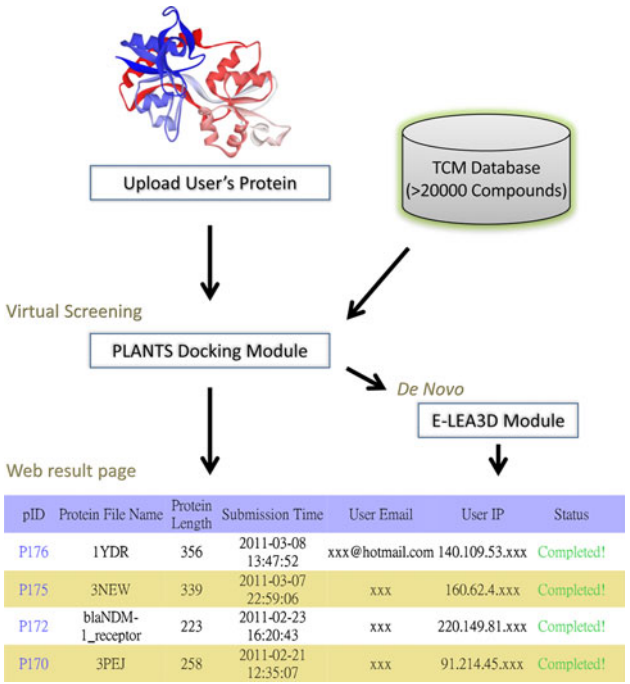

Fig. 1 Schematic dataflow diagram of iScreen. Users perform virtual screening for drug-like TCM compounds. The results compounds can be further derived using the de novo function

investigating therapeutic values of the TCM compounds. iScreen is free and open to all users and there is no login requirement.

Web server components

iScreen was optimized with the communication between web-based graphic interface and the core system, which comprises with the highly accurate PLANTS [9] and LEA3D [13] software packages. Our web server was further implemented with a tool for protein preparation and binding site estimation. In addition, iScreen provided customized parameter definition that better suit a user's needs.

TCM database

The database used in iScreen was synchronized with self-developed TCM Databse@Taiwan [8]. TCM and the corresponding information were collected from multiple TCM literature and text, including "Ben cao gang mu", "Shang han lun", "Shen nong ben cao jing", and others [27–31]. These texts characterized the medical properties and the uses of the TCM ingredients. Most of the TMC ingredients come from herbs, and some others come from animals and minerals. The bioactive components of each TCM were obtained from the research reports listed in Medline [32] or ISI Web of Knowledge [33]. The compound 2D and 3D structures were automated with ChemBioOffice2008 [34]. In addition, the 3D compound structures were optimized by MM2 force field [35]. The database was organized based on TCM classifications. All compounds have passed Lipinski's Rule of Five [36] for basic drug-like properties. In addition, for better customized docking analysis, each TCM compound was further optimized in all acidic, neutral, and alkaline forms.

Protein preparation tool

Based on the SPORE module in PLANTS docking package [9], the protein preparation tool can extract ligands from the input protein–ligand complex and to perform protonation on the purified protein. In addition, this tool was implemented with a function that calculates binding site radius based on user definition. The algorithm was implemented with an iterative evaluation on the space intersection between the binding site and the proposed radius until the customized maximum binding space allocation reached.

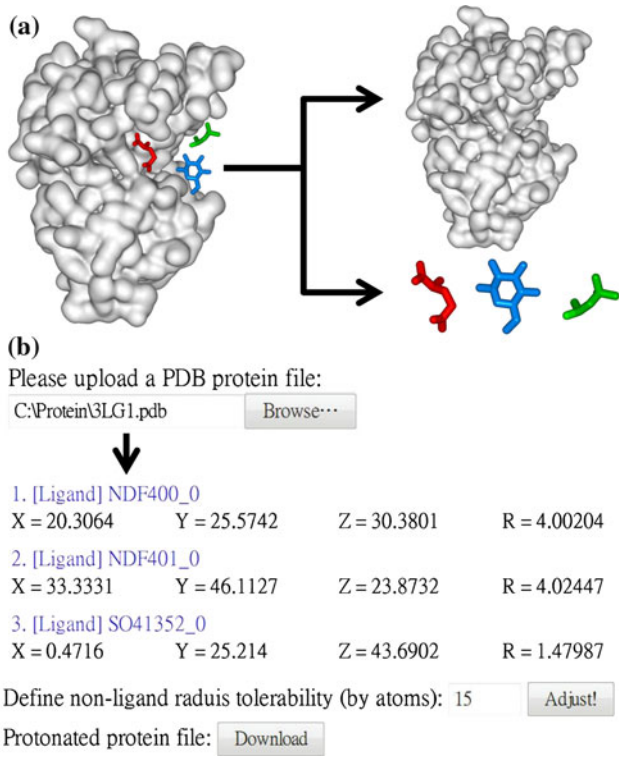

Fig. 2 Protein preparation tool for ligand extraction and protein protonation. **a** Graphical display of the functions of protein preparation tool. **b** Interface of the protein preparation tool. Based on the input protein, ligands are extracted and the binding site information is shown. The size of the binding site can be recalculated on user definition. The prepared proteins are downloadable

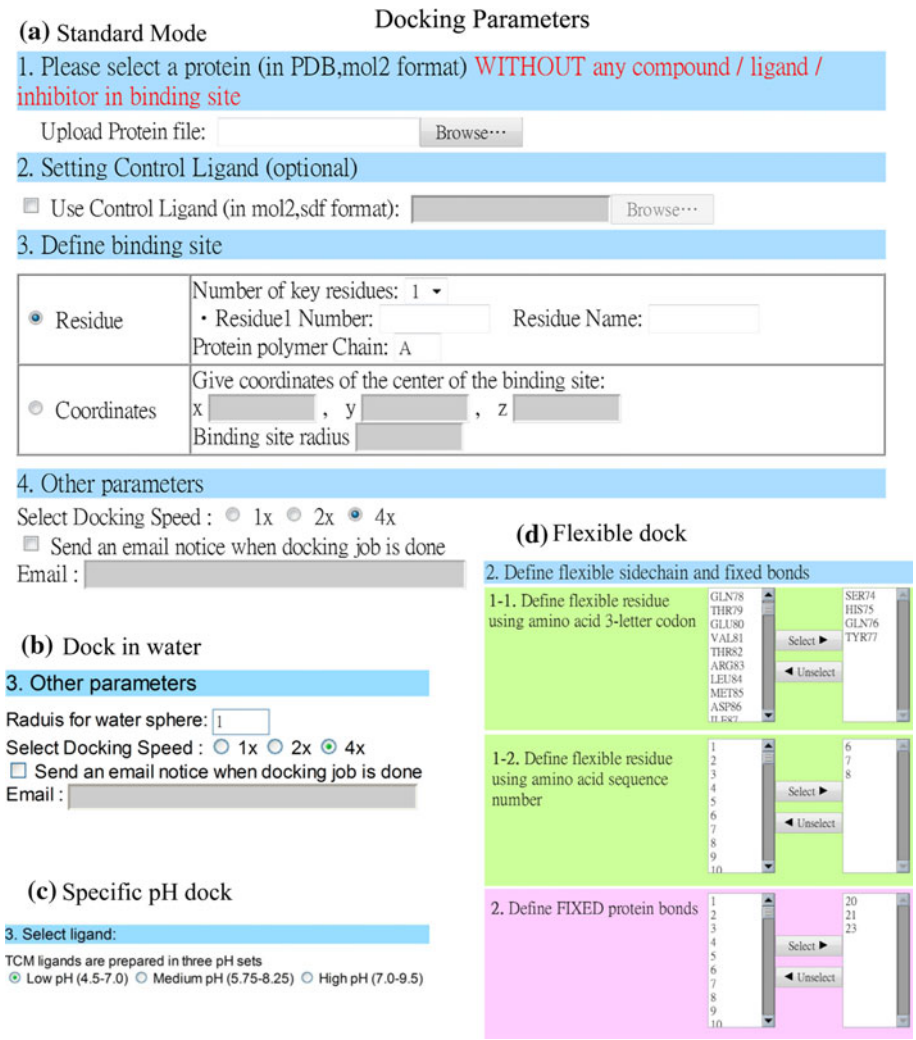

Fig. 3 iScreen provide customized docking modes for virtual screening function: **a** Standard mode that runs basic docking algorithm; **b** Dock in water mode, which considered the involvement of water as an additional parameter; **c** Specific pH dock mode, which performs docking algorithms based on the pH conditions; and **d** Flexible dock, which considered flexibilities of the residues for docking

Virtual screening

iScreen was optimized with the docking algorithm provided by PLANTS package. The docking algorithm used by PLANTS was based on ant colony optimization [9]. This optimization algorithm has been demonstrated having higher prediction accuracy than GOLD [9]. iScreen further permitted users to adjust docking speed as well as docking under various conditions, such as dock in water, dock in different pH, or flexible dock.

De novo drug design

After virtual screening, iScreen further provided an optional de novo drug design service based on genetic algorithm implemented in LEA3D software package [13]. iScreen reads each customized molecular descriptors, such as XLogP, atom number, and polar solvent accessible surface area, and then evaluates the maximum, minimum, and significances of each for the de novo algorithm.

Function and features

iScreen is an open web server for all users and there is no login requirement. The server focuses on TCM-based virtual screening and de novo drug design. Since all available TCM compounds were implemented within the system's database, users would only need to upload the proteins of interest and optional control ligands for virtual screening. The web system accepts .pdb or .mol2 as input formats and provides customized docking options. iScreen assigns a job ID to each screening or de novo service request. Users can check the job status in the server's queuing system.

Protein preparation tool in iScreen

The protein preparation tool can be accessed from the "Tool" panel iScreen main screen. The tool only accepts file in pdb format. On submission, the tool recognizes and pulls out all ligands, including water molecule, from the protein of interest. The protein would be prepared by

Queuing system

pID	Protein File Name	Protein Length	Submission Time	User Email	User IP	Status
P234	PDZ protein	98	2011-04-12 16:43:59	xxx@rediffmail.com	195.221.123.xxx	Queued
P233	2ka9WL	98	2011-04-11 18:58:33	xxx@gmail.com	195.221.123.xxx	Processing
P232	2ka9WL	98	2011-04-11 18:56:34	xxx@gmail.com	195.221.123.xxx	Processing
P231	anu m5	877	2011-04-08 18:42:37	xxx@gmail.com	210.212.95.xxx	Completed!
P230	anu m5	877	2011-04-08 18:37:12	xxx@ymail.com	210.212.95.xxx	Completed!
P229	anu m5	877	2011-04-08 18:21:36	xxx@ymail.com	210.212.95.xxx	Completed!
P228	1T2P	428	2011-04-07 20:03:27	xxx	203.190.147.xxx	Completed!
P227	1YDR	356	2011-04-07 17:41:32	xxx@gmail.com	203.190.147.xxx	Completed!
P226	3LFM	420	2011-04-06 21:29:03	xxx	140.128.63.xxx	Completed!

Virtual screening results

Protein sequence

Chain A:
PRGSHMTPKDDEFXQQWQLKXPKLILREASSVSEELHKEVQEAFLTLHKHGCLFRDLVRIQGKDLLTPVSRILIGNPGCTXKXLNTR
PVKAEIAAACETFLKLNDXLQIETIQALEELAADEVDIKSRAAXNVTLLNFMDPQKMPXLKEEPXFGMGKMAVSWHHDENLVDRS
XSCEGRDPDIWHVGFKISWDIETPGLAIPLHQGDCXFMLDDLNATHQHCVLAGSQPRFSSTHRVAECSTGTLDXILQRCQLALQNVC
DDVSLKSFEPAVLKQGEEIHNEVEFEWLRQFWFQGNRXRKCTDWWCQPMAQLEALWKKMEGVTNAVLHEVKREVEQRNEILTA
RQNLRREWHARCQSRIARTPADQKPECRPXWEKDDASMPLPFDLTDIVSELRGQ

Docking Ligand Ranking Download De Novo

Rank	Ligand Name	SCORE	SCORE RB_PEN	SCORE NORM_HEV ATOMS	SCORE NORM_CRT _HEVATOM S	SCORE NORM_WEI GHT	SCORE NORM_CRT _WEIGHT	SCORE RB_PEN_NO RM_CRT_HE VATOMS	SCORE NORM_CON TACT
Con.	Control	-72.4459	-64.4459	-4.02477	-27.6433	-0.282707	-11.4057	-24.5907	-3.81294
1	kukoamine_A	-112.826	-66.8264	-2.96912	-33.5596	-0.212617	-13.9361	-19.8771	-2.56424
2	salvianolic_acid_C	-107.723	-81.7233	-2.99231	-32.6244	-0.219212	-13.6509	-24.7502	-2.69308
3	kukoamine_B	-107.527	-61.527	-2.82966	-31.9833	-0.20263	-13.2815	-18.3009	-2.50063
4	kuwanon_S	-105.581	-87.5808	-3.51936	-33.979	-0.258476	-14.2297	-28.1861	-3.40583
5	indole_glycoside	-104.783	-76.7828	-3.17524	-32.6677	-0.222256	-13.4631	-23.9383	-2.75744

Fig. 4 Sample webpage for queuing system and virtual screening results. For queuing system, job information, masked user information, and job status are displayed. The virtual screening results shows protein sequence and ligands with multiple dock scores. Links for download ligands and de novo function are also displayed

protonation once the ligands were removed. The prepared protein and the ligands from the source file would be ready for download in separate links. Additionally, the binding site data, including the coordinates and the sizes of the cavities, would be measured and displayed. An option is provided to estimate the size of the binding site that best fit user definition. The schematic diagram for protein preparation tool is shown in Fig. 2. It is an independent iScreen feature aimed to reduce erroneous docking results due to wrong input data.

Virtual screening

The virtual screening function identifies potential TCM compounds by docking algorithm based on the protein structure and the binding site information. Both pdb and mol2 are acceptable input formats for proteins. The docking function gives users an option to upload a control ligand in either mol2 or sdf format. This ligand can be prepared independently, or obtained from the iScreen preparation tool (Fig. 2). For binding site definition, users can define key residues using standard 3-letter amino acid annotations and the residue number numbers with regard to the input protein (Fig. 3a). The binding site is defined by either key binding residues or coordination and cavity sizes, which can be calculated from the protein preparation tool. The docking function operates with 1×, 2×, or 4× speed options, where the 1× speed gives best docking results and the 4× speed runs faster with slightly reduced accuracy. Virtual screening function can be accessed from the "Protein Docking" panel. Five docking modes are available:

(a) Example Mode: Users can operate a sample protein to be familiarized with the iScreen docking system in the Example Mode. For the interactive demonstration, three prepared proteins are provided for sample docking. After selecting the protein of interest, a user can upload an optional control molecule, define binding site information, and choose running speed. Users are given three small ligand sets for the demonstration run.
(b) Standard Mode: The Standard Mode provides basic virtual screening options based on user-defined protein of interest. Most input settings in this mode are similar to the Example Mode, including optional control ligand, binding site information, and running speeds. Comparatively, Standard Mode employs the build-in TCM database for virtual screening (Fig. 3a).
(c) Docking in Water: This mode mimics molecular docking in solution condition. Users can customize the size of the virtual water globe on top of the Standard Mode (Fig. 3b).
(d) Specific pH dock: Since a protein may function differently depends on the pH condition, this mode

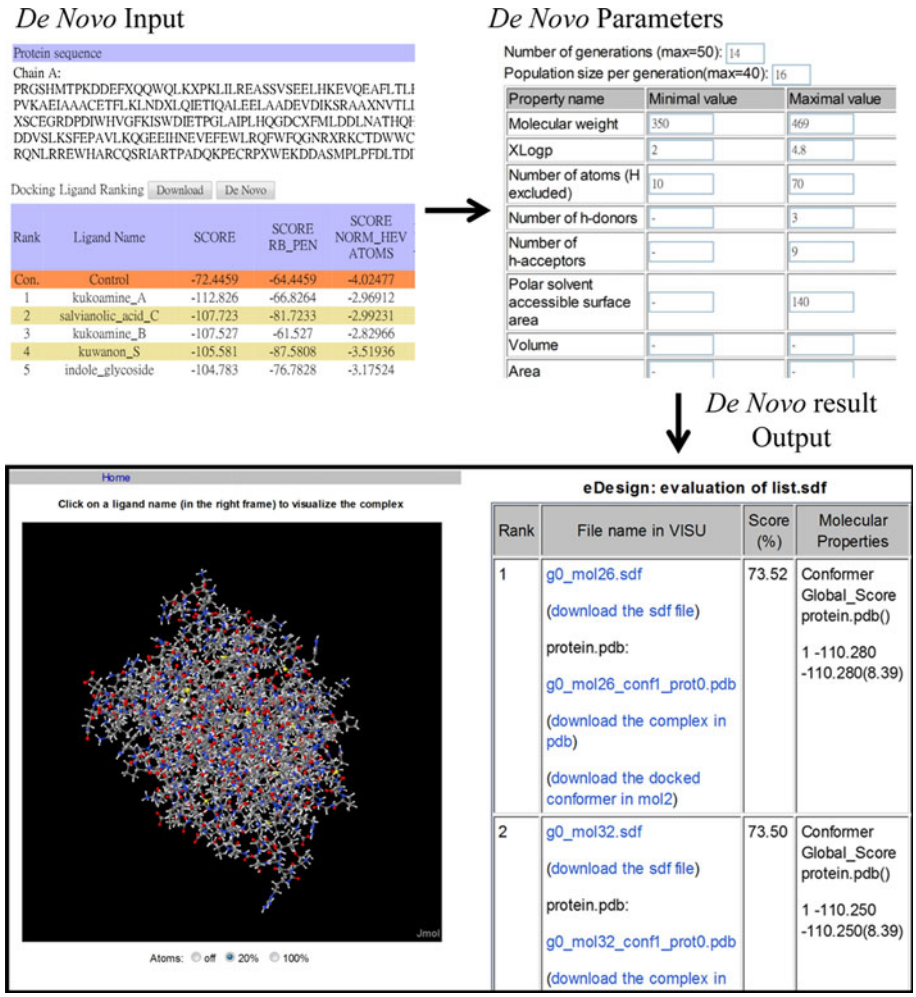

Fig. 5 The flowchart of de novo drug design: a follow-up option offers to one of the top 10 compounds after virtual screening. The de novo interface provides a list of molecular descriptors for customization. After de novo evolution process, users can visually inspect the new compounds with JMol visualization interface and download the results for further analysis

simulates the docking scenario in according to the pH condition. iScreen offers ligands under acidic, or neutral, or alkaline conditions (Fig. 3c). The web server provides a hyperlink to the H++ web server [37] for adjusting protein states for docking under the desired pH environment.

(e) Flexible dock: This mode is provided for experienced users who are familiar with the given protein structure. This mode allows users to define flexible residues by either or both residue annotation and sequence number. In addition, users can define fixed bonds to constrain the protein movement during flexible docking (Fig. 3d).

On submission, the job enters the queuing system for screening as shown in Fig. 4. A job ID and a hyperlink would be provided to view the status after job submission. Virtual screening usually takes several hours to several days to complete. Users can record the job IDs and check the job status under the "Browse Result" panel. In addition, iScreen will notify users through email when their jobs are completed. A result page provides the sequence of input protein, top 200 ligands with docking scores, ligands for download, and the de novo drug design option (Fig. 4).

De novo drug design

The de novo drug design option is a follow-up option that offers to one of the top 200 compounds after virtual screening. For customization, the de novo interface provides a list of molecular descriptors, including Molecular weight, XLogp, Number of atoms (H excluded), Number of H-donors, Number of H-acceptors, Polar solvent accessible surface area, Volume, Area, Molecular refractivity, Radius of gyration, Moment of inertia lxx & lyy, Number of rotatable bonds, Number of rings, and Number of aromatics rings. Users can define the minimum and maximum values of each descriptors as well as the corresponding significance by weight in the final score (Fig. 5). In addition, users are required to provide the number of generations (max = 50) and the population size per generation (max = 40) for the genetic algorithm used in the de novo drug design system. The de novo compounds will be re-evaluated by docking with the proteins of interest (Fig. 5).

The de novo jobs are listed in an independent queuing system that can be accessed through the "Browse Results" panel. By selecting the results from de novo job browser, a new window will pop up and list the result compounds with the corresponding evaluations. In addition, users can visually inspect the new compounds with JMol visualization interface. The de novo results are downloadable for further analysis (Fig. 5).

Performance and discussion

The core components of iScreen, including SPORE [9], PLANTS [9], and LEA3D [13], have been thoroughly tested according to the relevant publications. To validate the success rate of the docking algorithm, we redocked 20 known disease-related proteins and measured the root mean square deviation (RMSD) between ligands in crystal structure and the docking result. As shown in Table 1, we obtained the success rate of above 70% with the least accurate 4× speed. The outcome suggested the reliability of iScreen docking since these results matched with the validation data from the original publication. Considering iScreen provide TCM-based CADD services, the outcomes could provide insights of scientific approach for the relevant medical uses of TCM.

The uniqueness of the TCM database used in iScreen is that the compounds are derived from natural sources which have been recorded for medical uses. These compounds are likely to have implicit therapeutic effects. However, such property is usually not considered in other small molecule databases. It is also possible that the safety profiles of TCM derived compounds may be more favorable because of extended exposure by human beings spanning several 1000 years for human body to develop tolerance.

iScreen was built as a simple and comprehensive TCM-based CADD solution for users who are interested in TCM studies but lack operation experience for CADD software. Hence, the web server provides user-friendly interface and freedoms for the parameter settings. The 3D results of the de novo drug design function, however, are limited by Jmol viewer for website display, which the graphic option was less comparable to the commercial viewers. Nevertheless, all data are downloadable for users' own display software.

Table 1 Redock of protein–ligand crystalized structures

Protein name (PDB ID)	Tested ligand	PLANTS (RMSD)		
		Speed 1x	Speed 2x	Speed 4x
Glycosyltransferase A (1LZI)	BGH	1.4794	2.1000	1.4569
PDE5 (1UDT)	VIA	2.0974	2.1061	2.1108
HSP 90-alpha (1UY8)	PU5	5.9181	6.3677	6.2270
NAGAT (1ZI3)	NLC	4.1712	4.1426	4.1280
NR2A (2A5S)	GLU	0.3429	0.3449	0.8892
IDE (2G56)	DIO	1.0003	1.0136	1.0298
Src (2H8H)	H8H	2.3955	2.3868	1.2887
N1 (2HU0)	G39	1.7498	1.7389	1.6521
EGFR (2ITY)	IRE	2.0682	3.1272	6.832
GTB (2RIY)	BHE	5.2959	6.0614	6.1026
H1 (2WRG)	SIA	5.0830	5.0809	5.0806
p53 (2X0 W)	X0 W	4.6246	4.6288	4.1973
N1 (3CKZ)	SRT	1.6892	2.2944	2.2209
IDE-inhibitor (3E4A)	QIX	1.2224	1.4916	1.2855
CRFR1 (3EHT)	MAL	0.5642	0.6732	0.5714
IGF1R (3I81)	EBI	1.5962	1.5925	1.5965
PPARg (3K8S)	Z27	1.4043	1.4174	1.4131
HSP90 (3K97)	4CD	0.6169	0.6220	0.6177
COX2 (3LN0)	52B	0.6795	0.6507	0.6795
COX1 (3N8X)	NIM	0.6995	0.6976	0.7191
Success rate		75%	70%	70%

Twenty disease-linked proteins were randomly selected for the validation test. RMSD was calculated between ligands in the crystallization and after redock. Redock was run in 1×, 2×, and 4× speed. A test case is considered success with RMSD lower than 2.5 Å

Conclusion

iScreen is the world's first web server that employs world's largest TCM database for virtual screening and de novo drug design. This web server is designed with user-friendly graphic interface, multiple docking modes, independent protein preparation tools, and customized de novo drug design options. With cloud-computing architecture, users are able to operate TCM-based CADD through internet. iScreen is implemented with highly accurate PLANTS and LEA3D software package as the core system. On top of the core system, the attached tool provides both protein preparation and binding site estimation functions. iScreen is a sophisticated web server that not only offers a complete CADD service, but also a great contribution to scientific TCM researches.

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