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Computational chemistry approaches to drug discovery in signal transduction

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Table 1. A non-exhaustive list of receptor-based virtual screening applications.[a]

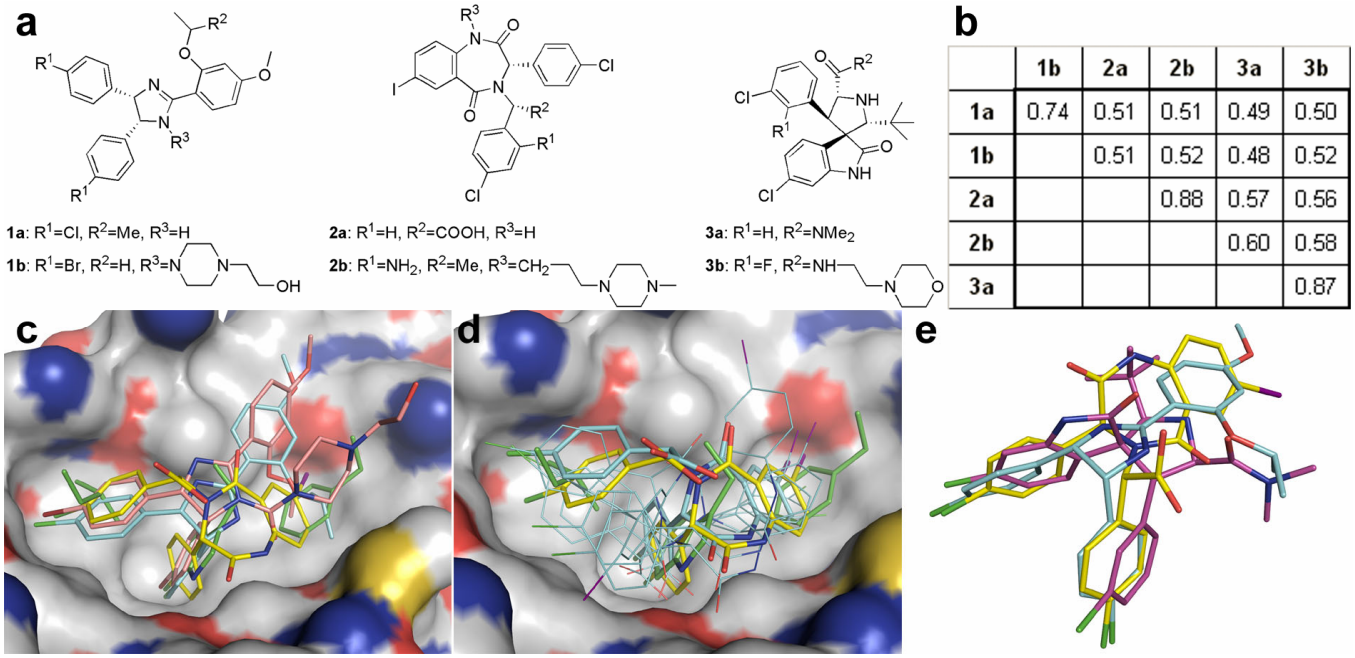
Application	Scoring function	Search algorithm	Flexibility		Ref.	URL
			Ligand	*Receptor*		
ArgusLab	Several	Several	Yes	Rigid	[1]	http://www.planaria-software.com/
AutoDock 3 (4)	Force field	Stochastic (GA)	Yes	Grid average	[2,3]	http://autodock.scripps.edu/
C2.LigandFit	Several (consensus)	Stochastic (MC)	Yes	Rigid	[4,5]	http://www.accelrys.com/products/cerius2/cerius2products/c2ligandfit.html
DOCK 4 & 5 (6)	Force field	Incremental	Yes	Grid average	[6,7]	http://dock.compbio.ucsf.edu/
DockIt	Several (consensus)	Incremental	Yes	Rigid		http://www.metaphorics.com/products/dockit.html
eHITs	Empirical	Incremental	Yes	Rigid	[8,9]	http://www.simbiosys.ca/ehits/index.html
FlexX & FlexE	Empirical	Incremental	Yes	Ensembles	[10-12]	http://www.biosolveit.de/FlexX/
FRED	Various available	Systematic	Multi-conformer search	Rigid	[13,14]	http://www.eyesopen.com/products/applications/fred.html
Glide	Empirical	Stochastic (MC)	Yes	Rigid	[13,15,16]	http://www.schrodinger.com/ProductDescription.php?mID=6&sID=6&cID=0
Glide-Prime (IFD)	Empirical	Stocjasitc (MC)	Yes	Binding site	[17,18]	https://www.schrodinger.com/SolutionDescription.php?mID=15&sID=18&cID=0
GOLD	Semi-empirical (various)	Stochastic (GA)	Yes	Side chains	[19,20]	http://www.ccdc.cam.ac.uk/products/life_sciences/gold/
ICM-Dock	Force field	Stochastic (MC)	Yes	Binding site	[21,22]	http://www.molsoft.com/docking.html
Insight II Affinity	Force field	Stochastic (MC)	Yes	Binding site		http://www.accelrys.com/products/insight/all_modules.html
MOE-Dock	Empirical		Yes		[23,24]	http://www.chemcomp.com/software-sbd.htm
MVD MolDock	Empirical	Stochastic (GA)	Yes	Side chains	[25]	http://www.molegro.com/products.php
rDock	Semi-empirical	Stochastic (MC)	Yes	Rigid	[26]	http://www.ysbl.york.ac.uk/rDock/
SLIDE	Empirical	Incremental	Yes	Side chains	[27,28]	http://www.bch.msu.edu/~kuhn/projects/slide/home.html
Surflex-Dock	Empirical	Incremental	Yes	Rigid	[29,30]	http://www.biopharmics.com/products.html http://www.tripos.com/index.php?family=modules,SimplePage,,,&page=surflex_dock&0

[a] Many of the applications listed are commercial products. For an overview of open-source software for computational chemistry and drug discovery see [31,32].

Table 2. Some software applications used in ligand-based drug discovery.[a]

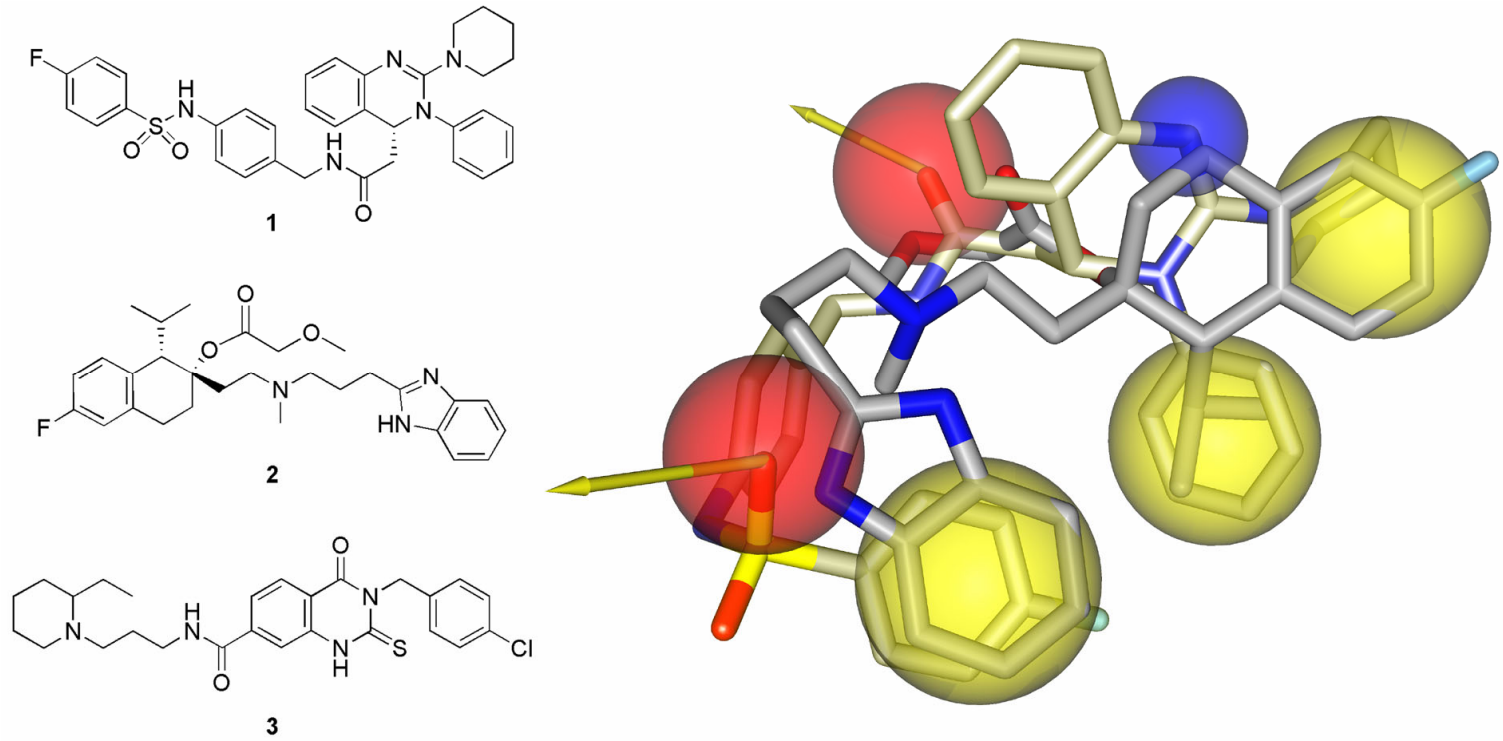
Application	Type	Ref.	URL
C^2.LudiI	*De novo* design	[33,34]	http://www.accelrys.com/products/cerius2/cerius2products/listing.html#dock
FlexNovo		[35]	http://www.biosolveit.de/FlexNovo/
GrowMol		[36]	
LeapFrog		[37]	http://www.tripos.com/index.php?family=modules,SimplePage,,,&page=sybyl_leapfrog&s=0083e3389a3ddba7917ab4b124d37bdd
LigBuilder		[38]	http://mdl.ipc.pku.edu.cn/download/htdocs/modules/PDdownloads/viewcat.php?cid=1
Sprout		[39]	http://www.simbiosys.ca/sprout/
C^2.QSAR+	QSAR		http://www.accelrys.com/products/cerius2/cerius2products/qsar_page.html
CoMFA		[40-42]	http://www.tripos.com/index.php?family=modules,SimplePage,sybyl_advanced_comfa
GOLPE		[43]	http://www.miasrl.com/golpe.htm
GRID		[44,45]	http://www.moldiscovery.com/soft_grid.php
HQSAR		[46,47]	http://www.tripos.com/index.php?family=modules,SimplePage,sybyl_hqsar
Quasar		[48]	http://www.biograf.ch/index.php?id=software
SOMFA		[49]	http://bellatrix.pcl.ox.ac.uk/Downloads/
Catalyst	Pharmacophore	[50-52]	http://www.accelrys.com/products/catalyst/
DISCOtech		[53,54]	http://www.tripos.com/index.php?family=modules,SimplePage,sybyl_discotech
GASP		[55]	http://www.tripos.com/index.php?family=modules,SimplePage,sybyl_gasp
MOE			http://www.chemcomp.com/software-ph4.htm
MOLPRINT 2D		[56,57]	http://www.molprint.com/
PHASE		[58,59]	http://www.schrodinger.com/ProductDescription.php?mID=6&sID=16&cID=0
ROCS		[60]	http://www.eyesopen.com/products/applications/rocs.html
Surflex-Sim		[61]	http://www.biopharmics.com/products.html http://www.tripos.com/index.php?family=modules,SimplePage,,,&page=surflex_sim&s=0
UNITY			http://www.tripos.com/index.php?family=modules,SimplePage,sybyl_unity
CAVEAT	Bioisostere	[62]	http://www.cchem.berkeley.edu/~pabgrp/Data/caveat.html
BROOD			http://www.eyesopen.com/products/applications/brood.html
JChem, Marvin	Chemoinformatics		http://www.chemaxon.com/
Molinspiration			http://www.molinspiration.com/cgi-bin/properties
Moloc			http://www.moloc.ch/index.html
VCC Lab		[63]	http://www.vcclab.org/

[a] Many of the applications listed are commercial products. For an overview of open-source software for computational chemistry and drug discovery see [31,32].



	1b	2a	2b	3a	3b
1a	0.74	0.51	0.51	0.49	0.50
1b		0.51	0.52	0.48	0.52
2a			0.88	0.57	0.56
2b				0.60	0.58
3a					0.87

Supplementary Figure 1. Mdm2 inhibitors: similarity. Mdm2 is a regulator of the tumour suppressor protein p53 and the p53–Mdm2 interaction is an important new oncology drug target [64]. (**a**) A number of lead series of compounds that mimic the three p53 residues (Phe, Trp, and Leu side chains shown as green sticks in **c** & **d**; PDB # 1T4F; [65]) that are responsible for the majority of the p53 interaction with Mdm2 (grey CPK surfaces in **c** & **d** [239]) have been identified. These include the 4,5-dihydro-1*H*-imidazoles **1** (nutlins [66,67]), the 3,4-dihydro-1*H*-benzo[*e*][1,4]di-azepine-2,5-diones **2** [65], and the 1*H*-spiro[indole-3,3'-pyrrolidin]-2-ones **3** [68], all potent p53–Mdm2 inhibitors. (**b**) 2D-fingerprint Tanimoto similarity values were calculated using the programme Instant JChem 1.0 from Chemaxon, (http://www.chemaxon.com/). It can be seen that whereas derivatives within each of the 3 series are obviously similar (≥ 0.74), there is little overall similarity (≤ 0.60) between the series, despite the fact that the pharmacophoric relationship between the series is rather obvious. (**c**) This pharmacophoric similarity is borne out by comparison of the experimental Mdm2-binding poses [**1a,** cyan (PDB # 1TTV); **1b**, pink (PDB # 1RV1); and **2a**, yellow CPK sticks (PDB # 1T4E)]. (**d**) Various docking/scoring routines (using some of the applications listed in Supplementary Table 1) were used in an attempt to reproduce these poses but none were very successful [shown are 5 high-scoring predicted poses of **2a** as cyan CPK sticks, including one (thick sticks) that approximates the binding mode found by XRC (yellow CPK sticks)]. (**e**) 3D pharmacophore-based comparisons without assumption of bioactive conformation, on the other hand, readily showed how series **1**–**3** are related [shown are the results of shape-based docking using the programme ROCS (Supplementary Table 2) of compounds **2a** (yellow) and **3a** (magenta) onto **1a** (cyan)].



Supplementary Figure 2. QSAR. The first pharmacophore hypothesis for T-type calcium channel blockers, based on 3D-QSAR analysis of structurally diverse compounds was recently reported [69]. The model, mapped onto one of the training set compounds (**1**; gold CPK sticks) is shown, together with mibefradil (**2**; grey CPK sticks), a calcium channel blocker drug withdrawn from clinical use due to toxicity arising from drug–drug interactions [70]. The yellow, red, and blue spheres represent hydrophobic, cationic, and HBA (with arrows showing directionality) pharmacophore features (diagram created using the MarvinSpace programme; http://www.chemaxon.com/product/mspace.html). This and related models were subsequently used to identify potent and selective T-type calcium channel blockers such as compound **3**, which are structurally unrelated to **2** [71].

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