Chapter 2

The In Silico Fischer Lock-and-Key Model: The Combined Use of Molecular Descriptors and Docking Poses for the Repurposing of Old Drugs

Marco Tutone and Anna Maria Almerico

Abstract

Not always lead compound and/or derivatives are suitable for the specific biological target for which they are designed but, in some cases, discarded compounds proved to be good binders for other biological targets; therefore, drug repurposing constitute a valid alternative to avoid waste of human and financial resources. Our virtual lock-and-key methods, VLKA and Conf-VLKA, furnish a strong support to predict the efficacy of a designed drug a priori its biological evaluation, or the correct biological target for a set of the selected compounds, allowing thus the repurposing of known and unknown, active and inactive compounds.

Key words Lock-and-key model, Molecular docking, Descriptors, Drug repurposing, Statistics

1 Introduction

Modern medicinal chemistry takes advantage of computational methodologies to save time and, above all, money during the lead identification and/or optimization [1, 2]. However not always the designed lead, once screened, results suitable for the chosen biological target, and the alternative choice is either to change lead or to change biological target.

Moreover, also the discarded compounds could be good inhibitors for other biological targets. These considerations are also supported by several lines of evidence suggesting that drugs may have many physiological targets [3, 4].

For these reasons, in the last years, computational chemistry has been intensively used for a new drug design approach switching this process from the concept "one drug one target" to "one drug multiple target" known as polypharmacology [5–12].

Several computational methodologies are available to medicinal chemist researchers: i.e., molecular docking, induced fit docking,

Nikolaos E. Labrou (ed.), *Targeting Enzymes for Pharmaceutical Development: Methods and Protocols*, Methods in Molecular Biology, vol. 2089, https://doi.org/10.1007/978-1-0716-0163-1_2,

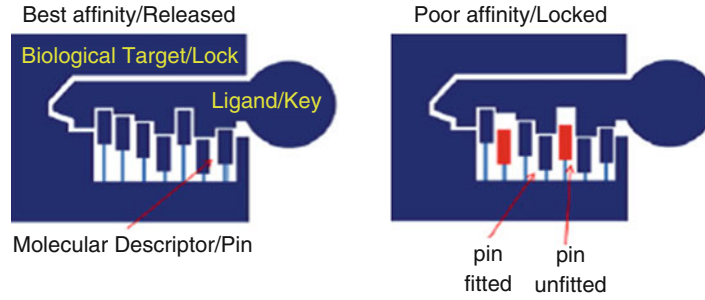

Fig. 1 Lock release mechanism

molecular dynamics, pharmacophore modeling, QSAR, and others, and all of them can be applied on biological fields. Some of them could be considered as derived from the old Emil Fischer lock-and-key model [13–15].

Taking into account all these considerations, we have proposed and developed an in silico methodology that can be for good reasons considered the heritage of original Fischer theory and that we have called "virtual lock-and-key approach" (VLKA) [16, 17].

The protocol allows to set up a "lock model" for a biological target, starting from the respectively known inhibitors. In order to release a real lock it is necessary that the pins of the lock fit the key (Fig. 1). We can use the molecular descriptors as pins, and a tested compound can be considered an inhibitor of a biological target if the values of its molecular descriptors fall in the calculated range values for the set of known inhibitors (*see* **Notes 1** and **2**).

Thus, the proposed protocol can transform a biological target into a "lock model" starting from its known inhibitors as Fisher suggested in his famous Lock-and-Key model.

In our works, we proved the real versatility of the VLKA protocol which is free user-defined. Compounds, biological targets, and molecular descriptors can be chosen by every scientist, which is interested in discovering new biological targets for old inhibitors or new inhibitors for old biological targets.

The application of statistics to biological data, testified also by recent results [18], revealed useful to provide clues to the classification of drugs whose target is unknown or controversial. In this kind of studies, all the property data are represented in the form of a matrix where each compound in each line is represented as an array characterized by a sequence of molecular descriptors values, in each of the matrix columns. In this fashion we developed the so-called BIOTA (BIOlogical Target Assignment) protocol with the aim to assign a correct biological target of designed molecular structures by using the multivariate analysis applied on the abovementioned type of molecular descriptors matrix [19]. The protocol resulted

useful to hypothesize the biological target of a candidate drug prior to its biological evaluation or to repurpose old drugs.

Either the BIOTA or the VLKA approach has been used by us to successfully assess the biological activities of classes of inhibitors studied by us, such as molecules targeting heat shock protein 90 (Hsp90) [18] or topoisomerase II [20, 21].

The latest version of the protocol named "Conf-VLKA" introduced the use of other techniques such as docking to measure the capability of docking scoring function in correctly ranking compounds toward their own target, first. Secondly, the docked conformation was exploited for 3D molecular descriptors calculation.

This more sophisticated approach, based on the calculation of 3D molecular descriptors on the docked conformation of ligands, helps to predict the possible biological target for new molecules starting from the structural information contained in molecular descriptors calculated on a set of known inhibitors (*see* **Note 3**).

2 Materials

1. A great amount of information has been collected by the Binding DB [22] by using a continuous upload of biological data. The first step of the proposed protocol, virtual lock-and-key approach, is the random choice of a suitable set of heterogeneous biological targets with known inhibitors available in Binding DB (Table 1).

   Other databases of public access or developed in-house, of course, could be used. For example, drug screening data are available in the National Cancer Institute (NCI) Anti-Cancer Agent Mechanism (ACAM). In this case, for each designed ligands (our keys) the lock models can be prepared by using the available data included in the DB as measurement of their growth inhibition ability over a panel of about 60 human tumor cell lines. In particular, the database is constituted by 114 antitumor drugs ranked according to their MA (Mechanism of Action) belonging to each class of drugs (alkylating agents, antimitotic agents, topoisomerase I inhibitors, topoisomerase II inhibitors, RNA/DNA antimetabolites, and DNA antimetabolites).
2. A set of molecular descriptors for the inhibitors structure was calculated by CODESSA PRO software [23]. This package is able to calculate more than 900 molecular descriptors, but for the protocol aims only molecular descriptors without blanks, common for all the compounds and with a high variance, should be selected.
3. The structures of the drugs to be screened can be prepared through Ligprep software [24] for the 3D optimization.

Table 1
Selected biological targets for VLKA protocol

Biological target T_n (BindingDB acronym)	#Total[a]	# Lock[b]	Cut-off activity[c]
11-beta-hydroxysteroid dehydrogenase (11betaHSD1)	40	35	100
ABL kinase (ABL)	70	14	500
Adenosine A1 receptor (ARA1)	110	16	100
Aldose reductase (ALR2)	126	46	100
Aldosterone synthase (CYP11B2)	129	76	100
Androgen receptor (AR)	244	82	10
Angiotensin converting enzyme (ACE)	51	19	100
Angiotensin converting enzyme 2 (ACE2)	73	22	1000
Anthrax lethal factor (ALF)	130	36	1000
Aromatase (AROM)	440	66	100
Asparaginyl endopeptidase (AE)	27	15	100
Aurora kinase A (AurKA)	179	47	100
BCL-2 (BCL-2)	31	17	1000
BCL-xl (BCL-xl)	50	7	200
Ca-Moduline kinase 2 (CaMK2)	20	5	200
Cannabinoid receptor 2 (CB2)	104	58	100
Carbonic anhydrase 1 (CA-1)	305	12	100
Carbonic anhydrase 2 (CA-2)	402	183	100
Carbonic anhydrase 4 (CA-4)	203	64	100
Caspase-1 (CASP1)	83	12	10,000
Caspase-3 (CASP3)	226	42	100
Checkpoint kinase (CHEK1)	57	35	100
α-Chymotrypsin (CT)	33	10	500
Collagenase (CLG)	309	83	100
Corticotropin-releasing hormone receptor 1 (CRHR1)	62	46	100
Cyclin-dependent kinase (Cdk4)	631	52	100
Delta opioid receptor (DOR)	25	9	100
Diacylglycerol acyltransferase (DGAT-1)	14	13	100
Dihydrofolate reductase (DHFR)	144	25	100
Dopamine transporter (DAT)	58	11	100
EGFR tyrosine kinase (EGFR TK)	979	209	10

(continued)

Table 1
(continued)

Biological target T_n (BindingDB acronym)	#Total[a]	# Lock[b]	Cut-off activity[c]
ERK-2 kinase (ERK-2)	66	35	500
Estrogen receptor (ER-alpha)	199	45	100
Factor Xa (Fxa)	109	66	10
Ghrelin receptor(GHSR)	90	44	100
Glucocorticoid receptor (GR)	109	54	100
Glutaminyl cyclase (GC)	183	36	1000
Glycogen synthase kinase 3α (GSK3α)	229	48	100
Histone deacetylase 1 (HD1)	143	64	100
Matrix metalloproteinase 13 (MMP-13)	142	32	100
Matrix metalloproteinase 3 (MMP-3)	80	25	100
Neutrophil endopeptidase (NEP)	26	15	10
Phosphoinositide-dependent kinase (PDK1)	97	48	100
Phosphodiesterase 10A (PDE10A)	41	16	100
Plasmepsin 1 (PSP1)	51	17	10
Protein-tyrosine phosphatase (PTP1B)	336	48	100
Tyrosine kinase C-kit (TKC-kit)	96	40	100
Total inhibitors	7352	2000	

[a] Total number of inhibitors used for each biological target.
[b] Number of inhibitors used for each lock set selected by cut-off activity values espressed in c.
[c] cut-off activity are expressed in nM.

Different force field protocols, such as OPLS_2005, could be used and all possible states at the selected pH range were generated using Ionizer. The structures were desalted, all possible tautomers were generated, and specified chiralities were retained. Molecular descriptors selected are 1D and 2D, which are not affected by conformation variability. But for the calculation of 3D molecular descriptors, in spite of its approximation, global minimum conformations were selected. This approximation allows not to constrain the molecular structure geometry to the single biological target.

4. The matrix reporting the number of compounds (S_{iTn}) versus the calculated descriptors (D_j) is created. The compounds selection to define the "lock model" for each biological target (T_n) was performed by means biological activity sampling by applying the cut-off of biological data (K_i, IC_{50}, EC_{50})

(Table 1). About one-fourth of the compounds were selected for building the different lock models (training sets). Mean (μ) and standard deviation (σ) of the molecular descriptors values ($X_{i,j}$) for each biological target (T_n) were calculated.

5. In the case of Conf-VLKA:
   (a) Ligand structure similarity evaluation: To check the structural diversity of ligands set, preventing the enrichment of redundant molecular analogs, we set up a topological evaluation of the chosen database. For each target, ligand structures were submitted for calculation of radial fingerprint [25], molprint2D fingerprint [25], and MACCS keys [26] and then analyzed in terms of Tanimoto distance [27] using similarity matrix on CANVAS [28].
   (b) The 3D structures of the biological targets included in the VLKA have been downloaded from the RCSB Protein Databank (PDB) [29], complexed with co-crystalized ligands. The selected structures were submitted to the optimization and refinement process using Protein Preparation Wizard utility of Maestro Schrödinger suite [30]. During this process, bond orders were assigned, the missing hydrogens were added, the disulfide bonds were assigned, the water molecules were deleted, and the protonation of amino acids were determined. At the end, the hydrogen bonds of the proteins were optimized, and restrained minimization was carried out on heavy atoms converging to RMSD equal to 0.30 Å, and on the hydrogen atoms.
   (c) Glide software [31] was used to perform the molecular docking and experiments were carried out using the default parameters and the two different protocols: standard precision (SP) level of accuracy for the generation and scoring of 10 poses for each ligand, top-scored conformation are further re-docked by using the extra-precision (XP) algorithm. Further the compounds were submitted to the docking and scoring procedure versus the own target, and then versus the entire biological targets dataset. The best pose for each compound is selected according to Glide score and on the best pose retrieved 3D molecular descriptors were recalculated.

3 Methods

The individual steps necessary to carry out the technique are reported in the virtual lock-and-key approach flow chart [17].

The first step of the VLKA protocol consists in the conversion of the biological target in a "lock model" in which the keys (the structures) could be "fitted."

1. Calculate mean (μ) and standard deviation (σ) of the molecular descriptors values ($X_{i,j}$) for each biological target (T_n): the hypothesis is that the value of each molecular descriptor of a suitable inhibitor should be close to the molecular descriptors mean (μ) calculated for all the inhibitors of the same biological target.
2. Convert each molecular descriptor value [$X_{i,j}(T_n)$] in α coefficient in relation to closeness to μ according to Eq. 1:

$$\begin{aligned} &\text{if } X_{i,j}(T_n) > m \pm \sigma, \alpha = 0; \\ &\text{if } (\mu - 1/2\sigma) < X_{i,j}(T_n) < (\mu + 1/2\sigma), \alpha = 1; \\ &\text{if } -\sigma < X_{i,j}(T_n) < -1/2\sigma, \alpha = 0.5; \\ &\text{if } +1/2\sigma < X_{i,j}(T_n) < +\sigma, \alpha = 0.5. \end{aligned} \tag{1}$$

   where X is the molecular descriptor value; i is related to the compound; j is related to the molecular descriptor; T_n is the biological target.
3. Molecular descriptors weighing by a coefficient for each biological target (T_n): this was carried out on the basis of the α coefficients determined for the lock set, by considering the sum of the α value for each descriptor (D_j) for all compounds, belonging to the specific biological target $\Sigma\alpha_{i,j}(T_n)$.
4. Normalization step by defining the ωD_j coefficients: The following step was to normalize these values by defining the ωD_j coefficients as reported in Eq. 2:

$$\omega_{Dj} = \frac{\sum \alpha_{i,j(Tn)}}{\max\left[\sum \alpha_{i,j(Tn)}\right]} \tag{2}$$

   where i, j, and T_n are defined as above and max represents the higher α sum of all molecular descriptors belonging to the specific biological target.
5. Partial scores φ calculation: The $\alpha_{i,j}(T_n)$ and ωD_j coefficients were used to calculate the affinity of all the compounds under investigation for each biological target. Thus, according to Eq. 3 the partial score φ was calculated:

$$\varphi_{i,j} = \alpha_{i,j(Tn)}\ \omega_{D_j} \tag{3}$$

6. Total score Φ calculation. The total score Φ was defined as sum of the partial score φ (Eq. 4):

$$\Phi_{i_{(Tn)}} = \sum_{j=1}^{173} \varphi_{i,j(Tn)} \tag{4}$$

where $\varphi_{i,j}$ represents the partial score; Φ_i represents the total score; i, j, and T_n are defined in Eq. 1.

All the calculated scores Φ_i for all the structures for each biological target were converted into ranking positions. At the end, the Φ scores rank all the database compounds with respect to the biological targets. The final hypothesis is that inhibitors related to each biological target should occupy the higher rankings. To verify this hypothesis, the enrichment score (E%), considered as the percentage of correct classification, was calculated according to Eq. 5:

$$E\% = \left(\frac{\sum W - \sum P}{\sum W - \sum B}\right) 100 \tag{5}$$

where ΣW represents the sum of hypothetical lowest rankings; ΣB represents the sum of hypothetical highest rankings; ΣP represents the sum of obtained rankings.

Because each biological target needs specific chemico-physical requests, it is wise to assume that some molecular descriptors could express better than the other structural requirements of the specific biological target. This is the crucial point in the design of a suitable inhibitor (*see* **Note 4**). Drug polypharmacology is tightly linked to the concept of the re-purposing of old drugs or inactive derivatives for new biological targets and drug re-purposing is one of the goals of VLKA computational approach. The more sophisticated procedure Conf-VLKA evaluated also the influence of 3D conformation of ligands on the accuracy of the prediction. The same algorithm of scoring and ranking was employed but, this time, combining it with a structure-based approach as docking. The docking protocol was used to retrieve docking scores, then, from the docked poses of each molecule, 3D descriptors were calculated (Conf-VLKA). While the use of the simple docking scores proved to be inadequate to improve compounds classification, the Conf-VLKA showed some interesting variations compared to the original VLKA. This was particularly true especially for targets whose ligands present a high number of rotamers. This study can be further completed using other techniques such as induced fit docking or molecular dynamics structure clustering to take into account the protein side chains adaptation to ligands structures.

4 Notes

1. The developed in-house virtual lock-and-key approach (VLKA) allowed evaluating target assignment starting from molecular descriptors calculated on known inhibitors used as an information source.

2. The use of molecular descriptors as the starting point to build lock models for biological targets was necessary because a simple analysis of structural similarity does not always imply similarity in the biological activity [32] and does not involve descriptors similarity [33].
3. For the correct development of the models, whereas by using 1D and 2D molecular descriptors it is not important to consider the conformation variability, in the calculation of 3D molecular descriptors, global minimum conformations were selected. Of course, this constitutes an approximation but it has the advantage not to constrain the molecular structure geometry to the single biological target.
4. The VLKA protocol predicts the correct biological target for the whole dataset with a good degree of reliability (80%), and proved experimentally, which was useful for the target fishing of unknown compounds.

   To be noted that drugs may have many physiological targets [3, 4, 34, 35], aspect called "polypharmacology," which is recognized to be therapeutically essential in the treatment of several types of diseases such as schizophrenia [36].

The importance of drug polypharmacology has pushed the efforts to predict and characterize drug-biological target associations [37–40]. The use of chemical similarities among molecules has allowed to identify drugs with multiple biological targets [41, 42], and early drug candidates are screened against biological target panels [43].

Acknowledgements

The work reported in this chapter is based on the reference [17] (Tutone M, Perricone U, Almerico AM (2017) Conf-VLKA: A structure-based revisitation of the virtual lock-and-key approach. J Mol Graph Model 71:50–57. doi: 10.1016/j.jmgm.2016.11.006) and was adapted with permission.

References

1. Dimasi JA, Feldman L, Seckler A, Wilson A (2010) Trends in risks associated with new drug development: success rates for investigational drugs. Clin Pharmacol Ther 87:272–277. https://doi.org/10.1038/clpt.2009.295
2. Dickson M, Gagnon JP (2004) Key factors in the rising cost of new drug discovery and development. Nat Rev Drug Discov 3:417–429. https://doi.org/10.1038/nrd1382
3. Peterson RT (2008) Chemical biology and the limits of reductionism. Nat Chem Biol 4:635–638. https://doi.org/10.1038/nchembio1108-635
4. Nobeli I, Favia AD, Thornton JM (2009) Protein promiscuity and its implications for biotechnology. Nat Biotechnol 27:157–167. https://doi.org/10.1038/nbt1519
5. Reddy AS, Zhang S (2013) Polypharmacology: drug discovery for the future. Expert Rev Clin

Pharmacol 6:41–77. https://doi.org/10.1586/ecp.12.74
6. Hopkins AL (2008) Network pharmacology: the next paradigm in drug discovery. Nat Chem Biol 4:682–690. https://doi.org/10.1038/nchembio.118
7. Peters JU (2013) Polypharmacology—foe or friend? J Med Chem 56:8955–8971. https://doi.org/10.1021/jm400856t
8. Overington JP, Al-Lazikani B, Hopkins AL (2006) How many drug targets are there? Nat Rev Drug Discov 5:993–996. https://doi.org/10.1038/nrd2199
9. Hopkins AL, Mason JS, Overington JP (2006) Can we rationally design promiscuous drugs? Curr Opin Struct Biol 15:104–111. https://doi.org/10.1016/j.sbi.2006.01.013
10. Aislyn DW, Boran RI (2010) Systems approaches to polypharmacology and drug discovery. Curr Opin Drug Discov Devel 13:297–309. https://doi.org/10.1126/scisignal.2001965.Introduction
11. Anighoro A, Bajorath J, Rastelli G (2014) Polypharmacology: challenges and opportunities in drug discovery. J Med Chem 57:7874–7887. https://doi.org/10.1021/jm5006463
12. Gujral TS, Peshkin L, Kirschner MW (2014) Exploiting polypharmacology for drug target deconvolution. Proc Natl Acad Sci 111:5048–5053. https://doi.org/10.1073/pnas.1403080111
13. Fischer E (1895) Ueber den Einfluss der Konfiguration auf die Wirkung der Enzyme III. Berichte der Dtsch Chem Gesellschaft 28:1429–1438. https://doi.org/10.1002/cber.18950280243
14. Forster MO (1920) Emil Fischer memorial lecture. J Chem Soc Trans 117:1157–1201. https://doi.org/10.1039/CT9201701157
15. Fischer E (1899) Bedeutung der Stereochemie für die Physiologie. Hoppe Seylers Z Physiol Chem. https://doi.org/10.1515/bchm2.1899.26.1-2.60
16. Lauria A, Tutone M, Almerico AM (2011) Virtual lock-and-key approach: the in silico revival of Fischer model by means of molecular descriptors. Eur J Med Chem 46:4274–4280. https://doi.org/10.1016/j.ejmech.2011.06.033
17. Tutone M, Perricone U, Almerico AM (2017) Conf-VLKA: a structure-based revisitation of the Virtual Lock-and-Key Approach. J Mol Graph Model 71:50–57. https://doi.org/10.1016/j.jmgm.2016.11.006
18. Lauria A, Ippolito M, Almerico AM (2009) Principal component analysis on molecular descriptors as an alternative point of view in the search of new Hsp90 inhibitors. Comput Biol Chem 33:386–390. https://doi.org/10.1016/j.compbiolchem.2009.07.010
19. Lauria A, Tutone M, Barone G, Almerico AM (2014) Multivariate analysis in the identification of biological targets for designed molecular structures: the BIOTA protocol. Eur J Med Chem 75:106–110. https://doi.org/10.1016/j.ejmech.2014.01.025
20. Lauria A, Patella C, Abbate I et al (2012) Lead optimization through VLAK protocol: new annelated pyrrolo-pyrimidine derivatives as antitumor agents. Eur J Med Chem 55:375–383. https://doi.org/10.1016/j.ejmech.2012.07.046
21. Lauria A, Abbate I, Patella C et al (2013) New annelated thieno[2,3-e][1,2,3]triazolo[1,5-a] pyrimidines, with potent anticancer activity, designed through VLAK protocol. Eur J Med Chem 62:416–424. https://doi.org/10.1016/j.ejmech.2013.01.019
22. Liu T, Lin Y, Wen X et al (2007) BindingDB: a web-accessible database of experimentally determined protein-ligand binding affinities. Nucleic Acids Res 35:D198–D201. https://doi.org/10.1093/nar/gkl999
23. Karelson M, Lobanov VS, Katritzky AR (1996) Quantum-chemical descriptors in QSAR/QSPR studies. Chem Rev 96:1027–1044. https://doi.org/10.1021/cr950202r
24. LigPrep, version 2.5. In: Suite. Schrödinger, LLC, New York NY; 2012
25. Rogers D, Brown RD, Hahn M (2005) Using extended-connectivity fingerprints with Laplacian-modified Bayesian analysis in high-throughput screening follow-up. J Biomol Screen 10:682–686. https://doi.org/10.1177/1087057105281365
26. Duan J, Dixon SL, Lowrie JF, Sherman W (2010) Analysis and comparison of 2D fingerprints: insights into database screening performance using eight fingerprint methods. J Mol Graph Model 29:157–170. https://doi.org/10.1016/j.jmgm.2010.05.008
27. Gilbert G (1972) Distance between sets. Nature 239:174. https://doi.org/10.1038/239174c0
28. Sastry M, Lowrie JF, Dixon SL, Sherman W (2010) Large-scale systematic analysis of 2D fingerprint methods and parameters to improve virtual screening enrichments. J Chem Inf Model 50:771–784. https://doi.org/10.1021/ci100062n
29. Dutta S, Berman MH, Bluhm FW (2005) RCSB Protein Data Bank. Curr Prot

Bioinformatics chapter 1: Unit 1.9. doi: https://doi.org/10.1002/0471250953.bi0109s20

30. Maestro, version 9.4, Schrödinger, LLC, New York, NY; 2013
31. Halgren TA, Murphy RB, Friesner RA et al (2004) Glide: a new approach for rapid, accurate docking and scoring. 2. Enrichment factors in database screening. J Med Chem 47:1750–1759. https://doi.org/10.1021/jm030644s
32. Martin YC, Kofron JL, Traphagen LM (2002) Do structurally similar molecules have similar biological activity? J Med Chem 45:4350–4358. https://doi.org/10.1021/jm020155c
33. Kubinyi H (2002) Chemical similarity and biological activities. J Braz Chem Soc 13:717–726. https://doi.org/10.1590/S0103-50532002000600002
34. Marona-Lewicka D, Nichols DE (2007) Further evidence that the delayed temporal dopaminergic effects of LSD are mediated by a mechanism different than the first temporal phase of action. Pharmacol Biochem Behav 87:453–461. https://doi.org/10.1016/j.pbb.2007.06.001
35. Marona-Lewicka D, Nichols DE (2009) WAY 100635 produces discriminative stimulus effects in rats mediated by dopamine D4 receptor activation. Behav Pharmacol 20:114–118. https://doi.org/10.1097/FBP.0b013e3283242f1a
36. Roth BL, Sheffer DJ, Kroeze WK (2004) Magic shotguns versus magic bullets: selectively non-selective drugs for mood disorders and schizophrenia. Nat Rev Drug Discov 3:353–359. https://doi.org/10.1038/nrd1346
37. Bajorath J (2008) Computational analysis of ligand relationships within target families. Curr Opin Chem Biol 12:352–358. https://doi.org/10.1016/j.cbpa.2008.01.044
38. Oprea TI, Tropsha A, Faulon JL, Rintoul MD (2007) Systems chemical biology. Nat Chem Biol 3:447–450. https://doi.org/10.1038/nchembio0807-447
39. Newman DJ (2008) Natural products as leads to potential drugs: an old process or the new hope for drug discovery? J Med Chem 51:2589–2599. https://doi.org/10.1021/jm0704090
40. Siegel MG, Vieth M (2007) Drugs in other drugs: a new look at drugs as fragments. Drug Discov Today 12:71–79. https://doi.org/10.1016/j.drudis.2006.11.011
41. Young DW, Bender A, Hoyt J et al (2008) Integrating high-content screening and ligand-target prediction to identify mechanism of action. Nat Chem Biol 4:59–68. https://doi.org/10.1038/nchembio.2007.53
42. Wagner BK, Kitami T, Gilbert TJ et al (2008) Large-scale chemical dissection of mitochondrial function. Nat Biotechnol 26:343–351. https://doi.org/10.1038/nbt1387
43. Krejsa CM, Horvath D, Rogalski SL et al (2003) Predicting ADME properties and side effects: the BioPrint approach. Curr Opin Drug Discov Devel 6:470–480