THE *IN SILICO* FISCHER LOCK-AND-KEY MODEL: THE COMBINED USE OF MOLECULAR DESCRIPTORS AND DOCKING POSES FOR THE REPURPOSING OF OLD DRUGS

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RUNNING HEAD:

Molecular descriptors and docking for the repurposing of drugs

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i. Summary/Abstract

Not always lead compound and/or derivatives are suitable for the specific biological target for which 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.

ii. 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, 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 (Figure 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.

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.

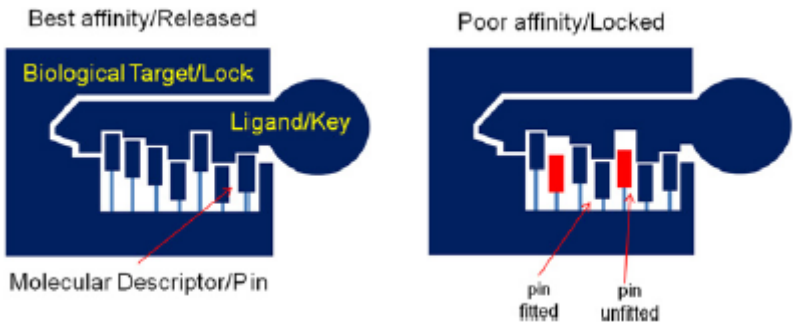

Figure 1. Lock release mechanism

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 above mentioned 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 and the VLKA approaches have 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

84 towards their own target, first. Secondly, the docked conformation were exploited for 3D molecular
85 descriptors calculation.
86 This more sophisticated approach, based on the calculation of 3D molecular descriptors on the
87 docked conformation of ligands helps to predict the possible biological target for new molecules
88 starting from the structural information contained in molecular descriptors calculated on a set of
89 known inhibitors.
90
91 **2. Materials**
92 2.1 A great amount of information has been collected by the Binding DB [22] by using a continuous
93 upload of biological data. The first step of the proposed protocol, Virtual Lock-and-Key Approach,
94 is the random choice of a suitable set of heterogeneous biological targets with known inhibitors
95 available in Binding DB. (Table 1)
96

97 Table 1. Selected biological targets for VLKA protocol

Biological Target Tn (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	10000
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 hormon receptor 1 (CRHR1)	62	46	100
Cyclin-dependent kinase (Cdk4)	631	52	100
Delta Opioid Receptor (DOR)	25	9	100
DiacylGlycerolAcylTransferase (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
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 Deacetilase 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	

98

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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).

2.2 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.

2.3 The structures of the drugs to be screened can be prepared through Ligprep software[24] for the 3D optimization. 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.

2.4 The matrix reporting the number of compounds (S_{iTn}) versus the calculated descriptors (Dj) is created. The compounds selection to define the “lock model” for each biological target (Tn), was

performed by means biological activity sampling. By applying the cut-off of the biological data (K_i, IC_{50}, EC_{50}) (Table 1). About one fourth of the compounds was 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 (Tn) were calculated.

2.5 In the case of Conf-VLKA:

2.5.1 Ligand structure similarity evaluation: to check the structural diversity of ligands set, preventing the enrichment of redundant molecular analogues, we set up a topological evaluation of the chosen database. For each target, ligand structures were submitted to calculation of radial fingerprint[25], molprint2D fingerprint [25] and MACCS keys [26] and then analysed in terms of Tanimoto distance [27] using similarity matrix on CANVAS[28].

2.5.2 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, the protonation of aminoacids 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.

2.5.3 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".

3.1: Calculate Mean (μ) and standard deviation (σ) of the molecular descriptors values (Xi,j) for each biological target (Tn): 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.

3.2: Convert each molecular descriptor value [Xi,j(Tn)] in α coefficient in relation to closeness to μ according to the equation 1:

$$\begin{aligned} &\text{if } Xi,j(Tn) > \mu \pm \sigma, \alpha = 0; \\ &\text{if } (\mu - \tfrac{1}{2}\sigma) < Xi,j(Tn) < (\mu + \tfrac{1}{2}\sigma), \alpha = 1; \\ &\text{if } -\sigma < Xi,j(Tn) < -\tfrac{1}{2}\sigma, \alpha = 0.5; \\ &\text{if } +\tfrac{1}{2}\sigma < Xi,j(Tn) < +\sigma, \alpha = 0.5. \end{aligned} \qquad \text{(eq. 1)}$$

Where:

X is the molecular descriptor value; **i** is related to the compound; **j** is related to the molecular descriptor; **Tn** is the biological target.

3.3: Molecular descriptors weighing by a coefficient for each biological target (Tn): 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 (Dj) for all compounds, belonging to the specific biological target $\sum \alpha$ i,j(Tn).

3.4: Normalization step by defining the ωDj coefficients;

The following step was to normalize these values by defining the ω Dj coefficients as reported in equation 2

$$\omega_{Dj} = \frac{\sum \alpha_{i,j(Tn)}}{\max[\sum \alpha_{i,j(Tn)}]} \quad \text{(eq. 2)}$$

Where i, j, and Tn are defined as above and max represents the higher α sum of all molecular descriptors belonging to the specific biological target.

3.5: Partial scores φ calculation;

The $\alpha_{i,j}(Tn)$ and ω_{Dj} coefficients were used to calculate the affinity of all the compounds under investigation for each biological target. Thus according to equation 3 the partial score φ was calculated:

$$\varphi_{i,j} = \alpha_{i,j(Tn)}\ \omega_{D_j} \quad \text{(eq. 3)}$$

3.6: Total score Φ calculation.

The total score Φ was defined as sum of the partial score φ (equation 4):

$$\Phi_{i_{(Tn)}} = \sum_{j=1}^{173} \varphi_{i,j(Tn)} \quad \text{(eq. 4)}$$

Where: $\varphi_{i,j}$ represents the partial score; Φi represents the total score; i, j, and Tn are defined in eq. 1.

All the calculated scores Φi, 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 equation 5:

$$E\% = \left(\frac{\sum W - \sum P}{\sum W - \sum B}\right) 100 \qquad \text{(eq. 5)}$$

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 others structural requirements of the specific biological target. This is the crucial point in the design of a suitable inhibitor.

4. Notes

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.

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].

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 constitute an approximation but it has the advantage not to constrain the molecular structure geometry to the single biological target.

The VLAK 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 against biological target panels[43].

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

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