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ARTICLE *in* EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY · JANUARY 2014

Impact Factor: 3.45 · DOI: 10.1016/j.ejmech.2014.01.025

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European Journal of Medicinal Chemistry 75 (2014) 106–110

Contents lists available at ScienceDirect

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Short communication

Multivariate analysis in the identification of biological targets for designed molecular structures: The BIOTA protocol

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ARTICLE INFO

Article history:
Received 28 June 2013
Received in revised form
16 January 2014
Accepted 19 January 2014
Available online 28 January 2014

Keywords:
BIOTA protocol
Biological target
Inhibitors
PCA
Drugs repurposing

ABSTRACT

In this work the new protocol BIOlogical Target Assignation (BIOTA) for the prediction of the biological target from molecular structures is proposed. BIOTA is based on the Principal Components Analysis (PCA) application on a matrix of ligands *versus* molecular descriptors. The application of BIOTA could allow to hypothesize the mechanism of action of a candidate drug prior to its biological evaluation or to repurpose old drugs. The protocol can be fine-tuned by choosing opportune targets (biological or not) and molecular descriptors, and it can be useful in every fields in with it is possible to collect set of compounds with known properties.

The robustness of the protocol depends from different factors: the correctness of biological data, the optimization of the molecular structures and their molecular descriptors calculation, the selection of the biological targets. The application of BIOTA to a new class of Hsp90 inhibitors was able to predict quite correctly their affinity for Hsp90.

1. Introduction

Since many years the computational approaches in the discovery of new drugs have seen the massive use of increasingly powerful hardware and software performance. This fact has allowed handling the structures of biological macromolecules of increasing larger sizes in an attempt to simulate their function into the cell. During the last decade for example, molecular docking protocol became “flexible” to simulate more reliably the ligand-binding site interactions [1–3].

Nevertheless, the first developed ligand based approaches, like the classical QSAR or pharmacophore modeling, are nowadays considered outdated. Unfortunately not all research groups have the access to high performance computing resources. Thus, there is still the need to implement appropriate protocols to be successfully used for research purposes even on desktop computers. In this context, to improve the ligand based approach by using the molecular descriptors, recent works have dealt the application of Virtual Lock And Key (VLAK) protocol [4] in the search of heterocyclic compounds with antitumor activity [5–9]. The common feature of these works is the use of molecular descriptors, the calculation of which can be performed through latest generation desktop computers.

Recent results [10,11] revealed that the application of statistics to biological data could provide clues to the classification of drugs whose target is unknown or controversial. This kind of studies is approached by representing all the property data as rectangular matrix. In the latter, 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 work we propose the protocol BIOTA (BIOlogical Target Assignment) with the aim to assign a correct biological target of designed molecular structures by using the multivariate analysis applied on a molecular descriptors matrix.

BIOTA protocol can be useful in order to hypothesize the biological target of a candidate drug prior to its biological evaluation or to repurpose old drugs [12]. In the development of the protocol there are few crucial aspects that must be considered. Firstly, the quality of the prediction is strictly linked to quality of biological data. Thus the method could be useful also to identify not correlated biological data. Second, the choice of the biological targets could influence the results, thus it is wise to insert in the BIOTA protocol biological targets with sharp structural features (e.g. binding sites with specific hallmarks). Finally, to be underlined that the protocol is not able to assign exclusively a biological target, it can give a trend. Indeed, it is known, as a structure can be suitable to different biological targets, as it is known in the design of multitarget drugs.

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http://dx.doi.org/10.1016/j.ejmech.2014.01.025

2. Material and methods

The BIOTA protocol steps are depicted in the flowchart reported in Fig. 1.

In the first step, the selection of the biological targets was randomly performed from the deposited data of the binding database [13]. Ligands with $IC_{50} > 1$ μM or Ki > 1 μM and molecular targets with less than 20 known ligands were excluded. Thus, the selected dataset consisted of eighty biological targets with a total of 9497 ligands (Table 1; Supplementary data S1 and S2).

In the following step, on the 9497 molecular structures 422 molecular descriptors belonging to different classes (charge related 225; constitutional l37; geometrical 17; semiempirical 67; thermodynamical 38; topological 38) were calculated [14]. The resulting matrix (Supplementary data S2) was submitted to Principal Component Analysis (PCA) (Fig. 1). This multivariate technique is able to detect similarities among a set of variables (descriptors) or objects (compounds) providing a statistically reliable criterion to classify the compounds upon their different structural pattern against different classes of descriptor. These similarities are related to the biological target of such compounds [15,16].

Thus, significant components were extracted, and principal component factor scores were used to project the compounds in the two-dimensional space. As evidenced in Table 2, the first two PCs explain 50% of total variance, with a maximum of 30% in the first component.

To evaluate the capability of the PCA to cluster compounds belonging to a specific biological target, the Spread Distribution Area (SDA) was defined as the area of the ellipse with major axis two-fold σ_1 (the standard deviation calculated for the first principal component score for a specific biological target) and minor axis two-fold σ_2 (the standard deviation calculated for the second principal component score) (Fig. 2; Eq. (1)).

$$\mathrm{SDA} = \pi\sigma_1\sigma_2 \tag{1}$$

The SDA calculated for the selected biological targets are reported in Table 1.

The following step of the protocol (Fig. 1) is the barycentric coordinates calculation for each biological target. Starting from the scores values for set compounds belonging to the same biological target, the barycentric coordinates for each biological target were calculated (Supplementary data, S3). In Fig. 2 the biological targets barycenters considering the first two principal components for three out eighty biological targets, as example, are reported. Whereas in Fig. 3 the projection of the barycenters, in the two-dimensional space, for the full biological targets dataset is reported.

With the aim to assign the biological target affinity to a new compound or to a known drug (entry X in Fig. 2), the next step of the protocol (Fig. 1) consists in molecular descriptors calculation for the tested compound and the merging of these values to full matrix. Then, PCA was applied to calculate the principal component scores (PCS) for the tested compound. To assign a biological target to the test entry, the distance from each biological target barycenter $D(i,b)$ is calculated, according to Eq. (2). The shortest distance could give an account of the suitable biological target for the test compound.

$$D(i,b) = \sqrt{\sum_{j=1}^{n} (S(i)j + S(b)j)^2} \tag{2}$$

where: $D(i,b)$ is the distance of the test compound i from the barycenter on the biological target b; n: number of principal component used; $S(i)j$ is the j factor score of the test compound i, $S(b)j$ is the j factor score of the barycenter coordinates of the biological target b.

Take into account only the barycentric distances could be more restrictive for different reasons. First, the ligands number for each biological target is different, giving the results a different statistical robustness. Second, it is important to give a spreading score to each target. A sharp distribution of the ligand belonging to a biological target, along each principal component analysis score is more reliable that a broad one.

For these reasons the Weighted Spreading Score (WSS) that takes into account the described factors, was defined (Eq. (3)).

$$WSS(\mathrm{Ti}, n) = \frac{\sum_{j=1}^{n} \sigma j(T_i)\gamma j}{N_{(\mathrm{Ti})}} \tag{3}$$

Where: $\sigma j(\mathrm{Ti})$ is the standard deviation for the factor score j; γ is the eigenvalue of the factor score j; N is the number of the ligands for the biological target Ti.

This score gives a weight to the reliability of the biological target assignment and allows improving the method by changing the training set for the interesting biological target. In Table 1 the WWS, extended to first two-principal components, for each biological target is reported.

3. Results and discussion

The analysis of the defined parameters allows to evaluate the robustness of each biological target data selected for the protocol. The data used in this work reveals as the best clustered biological

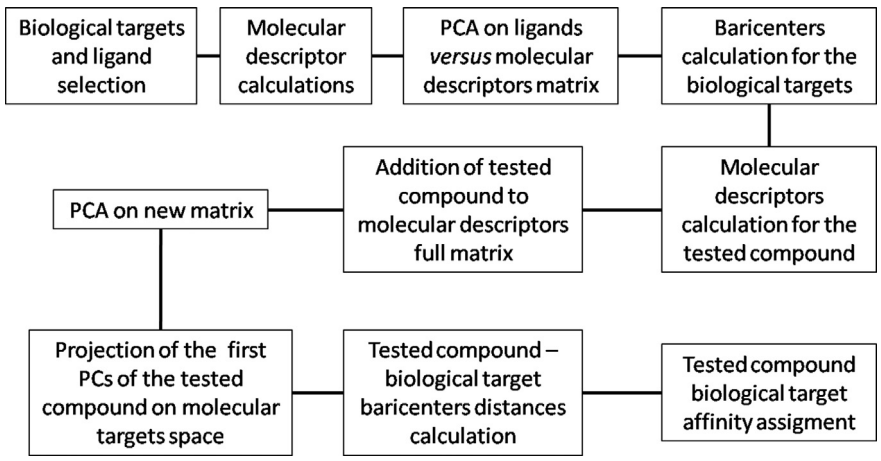


Fig. 1. Flowchart of the BIOTA protocol.

Table 1
Selected biological targets.

Biomolecular target	Number ID	Letter ID	[a]	SDA[b]	WSS[c]
Aldose Reductase (ALR2)	2	**b**	52	44	20
Asparaginyl Endopeptidase (AE)	4	**d**	21	20	35
3-Phosphoinositide-dependent Protein Kinase 1 (PDK1)	5	**e**	78	123	20
Acetylcholinesterase (AChE)	6	f	383	75	3
Adenosine Receptor A1	7	g	24	13	25
Aldosterone synthase (CYP11B2)	8	h	77	37	13
Androgen Receptor (AR)	9	k	200	103	8
Angiotensin-converting enzyme	10	l	27	5	15
Angiotensin-converting Enzyme 2	11	m	22	54	51
Anthrax Lethal Factor (LF)	12	n	42	242	53
Apoptosis Regulator Bcl-2	13	o	51	12	11
Aromatase (CYP19)	14	p	123	79	13
Aurora Kinase A (Aurora-A)	15	q	46	65	28
Cannabinoid Receptor 1	17	s	45	46	26
Carbonic Anhydrase (hpCA)	18	t	42	141	44
Carbonic Anhydrase I	19	u	96	219	23
Carbonic Anhydrase II	20	v	60	92	23
Caspase-3	22	a	147	167	13
Cathepsin B	23	b	31	84	45
Cathepsin D	24	c	68	73	21
Cathepsin K	25	d	116	60	11
Checkpoint Kinase (Chk1)	26	e	128	63	10
Collagenase (ChC)	27	f	49	69	26
Corticotropin-releasing Factor Receptor 1	28	g	56	50	19
Cyclin-Dependent Kinase 1 (CDK1)	29	h	320	121	5
Cyclin-Dependent Kinase 2 (CDK2)	30	k	569	77	2
Cyclin-Dependent Kinase 4 (CDK4)	31	l	64	65	20
Delta Opioid Receptor	32	**m**	25	100	65
Dihydrofolate Reductase (DHFR)	33	**n**	47	73	29
Dipeptidyl Peptidase IV (DPP-IV)	34	**o**	206	74	7
Dopamine Transporter (DAT)	35	**p**	35	13	21
EGF-R Tyrosine Kinase	36	**q**	475	100	3
ERK-2	37	**r**	23	22	41
Estrogen Receptor (ER-alpha)	38	**s**	97	93	16
FGFR-1 Tyrosine Kinase	39	**t**	141	55	8
FLT3	40	**u**	33	62	36
Factor IXa (fIXa)	41	**v**	51	96	30
Factor VIIa (fVIIa)	42	**z**	145	84	11
Factor XIa (fXIa)	43	a	25	30	33
Factor Xa (fXa)	44	b	627	75	2
Ghrelin Receptor (Growth Hormone Secretagogue Receptor T1)	46	d	75	35	13
Glucocorticoid Receptor (GR)	47	e	83	40	15
Glycogen Synthase Kinase-3	48	**f**	145	87	9
HCV NS3-NS4A Serine Proteinase	49	**g**	122	35	8
HIV-1 Protease	50	**w**	356	79	4
HIV-1 Reverse Transcriptase	51	**h**	741	92	2
HMG-CoA Reductase	52	**k**	91	15	8
Heat Shock Protein 90 (Hsp90)	53	**l**	58	64	20
Histone Deacetylase 1 (HDAC1)	54	**m**	28	55	45
Inosine Monophosphate Dehydrogenase Type 2 (IMPDH2)	55	**n**	34	637	110
Integrin alpha4beta1 (VLA-4)	56	**o**	213	94	6
Lck	57	**p**	92	101	16
Liver X Receptor alpha (LXR-alpha)	58	**q**	22	72	56
MAP Kinase p38 alpha	59	**r**	247	57	4
Matrix Metalloproteinase-3 (MMP-3)	60	**s**	43	34	21
Methionine Aminopeptidase Type 2 (MetAP2)	61	**t**	160	82	9
Mitogen-Activated Protein Kinase 8 (JNK1)	62	**u**	58	51	19
Monoamine Oxidase Type A (MAO-A)	63	**v**	43	73	32
Monocarboxylate Transporter 1	64	**z**	27	38	36
Neuraminidase A	65	**a**	142	40	8
Phosphodiesterase Type 3 (PDE3A)	66	**b**	39	27	22
Phosphodiesterase Type 10 (PDE10A)	67	**c**	30	20	27
Prostaglandin D2 Receptor CRTH2	68	**d**	47	30	17
Protein Farnesyltransferase (PFT)	69	**e**	55	39	18
Protein Kinase C	70	**f**	61	42	15
Protein Kinase C, alpha	71	**g**	27	24	27
Protein kinase B (Akt 1)	72	**h**	186	46	6
Protein-Tyrosine Phosphatase 1B (PTP1B)	73	**k**	110	127	15
Renin	74	**l**	151	50	9
Rho-kinase (ROCK I)	75	**m**	28	89	53
Src	76	**n**	284	68	4
Thrombin	77	**o**	56	58	21
Thyroid Hormone Receptor (TR-alpha)	78	**p**	66	67	18
Tie-2	79	**q**	104	71	13
Tumor Progression Loci-2 Kinase	80	**r**	25	50	41
VEGFR-1 (Flt-1)	81	**s**	47	60	26
VEGFR-2 (KDR)	82	**t**	291	93	5
Vanilloid Receptor 1 (TRPV1, VR1)	83	**u**	81	89	18
beta-Secretase (BACE-1)	84	**v**	121	83	11
tRNA synthetase (PheRS)	85	**z**	41	74	32

[a] Number of compounds.
[b] Spread distribution area (SDA).
[c] Weighted spreading score (WSS).

target is Angiotensin-Converting Enzyme which revealed a spread distribution area of related compounds (4.622 a.u.^{2}) about three times smaller than Apoptosis Regulator Bcl-2 (12.067 a.u.^{2}), which is the second best clustered target followed by Adenosine Receptor A1, Dopamine Transporter (DAT), HMG-CoA Reductase, Phosphodiesterase Type 10 (PDE10A), and Asparaginyl Endopeptidase (AE) (13–20 a.u.^{2}), which targets have similar SDA. The mean SDA of the eighty sample targets is 73.531 a.u.^{2} but this value is particularly biased by Inosine Monophosphate Dehydrogenase Type 2 (IMPDH2) which although was represented by a small number of compounds (**34**) has a large SDA (637.041 a.u.^{2}). The majority of biological targets showed SDA comprised within 20–66 a.u.^{2} values, and only few targets, such as Delta Opioid Receptor, Lck, Androgen Receptor (AR), Cyclin-Dependent Kinase 1 (CDK1), 3-Phosphoinositide-Dependent Protein Kinase 1 (PDK1), Protein-Tyrosine Phosphatase 1B (PTP1B), Carbonic Anhydrase (hpCA), Caspase-3, Carbonic Anhydrase I, have SDA $>$ 100 a.u.^{2}. The best clustered targets are well distributed on the principal component factors plane, but some overlap regions can be observed, in particular in the central region where EGF-R Tyrosine Kinase, Protein Farnesyltransferase (PFT), Src, Phosphodiesterase Type 3 (PDE3A), Matrix Metalloproteinase-3 (MMP-3), Lck, MAP Kinase p38 alpha are located. The majority of biological targets clustered in the central region, while the most distant ones are Delta Opioid Receptor, Factor XIa (fXIa), Aldosterone Synthase (CYP11B2), Corticotropin-releasing Factor Receptor 1, Protein Kinase C alpha, Carbonic Anhydrase I.

Further, the WSS scores can be useful in the choice of the number of principal components to be used in the protocol. The increase percentage between principal component and the next one was calculated for each biological target and for the first five principal components (Supplementary data, S4). The number of the PCs is fixed when the increase percentage is 5% or lower, according

Table 2
Principal components eigenvalues.

	Eigenvalue	% Total	Cumulative eigenvalue	Cumulative %
1	126.8875	30.06813	126.8875	30.0681
2	84.0760	19.92323	210.9635	49.9914
3	35.0796	8.31269	246.0431	58.3041
4	25.8984	6.13706	271.9415	64.4411
5	17.5715	4.16385	289.5130	68.6050
6	15.6753	3.71453	305.1882	72.3195
7	11.3388	2.68693	316.5271	75.0064
8	7.8347	1.85658	324.3618	76.8630
9	6.4885	1.53756	330.8503	78.4006
10	5.8531	1.38699	336.7034	79.7875

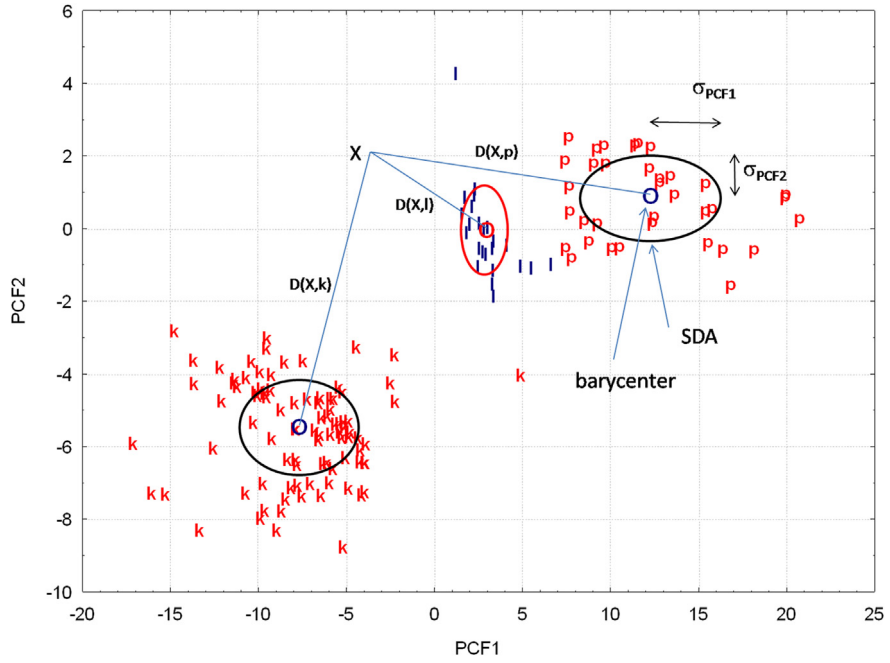


Fig. 2. Barycentric calculation for the three example targets: HMG-CoA Reductase (k), Angiotensin-Converting Enzyme (l), Dopamine Transporter DAT (p).

to the following condition: IF WSS($J+1$)((Ti) − WSSj)/WSSj*100<5 THEN PCs = J.

It is evident that the lower the score for a biological target, the higher is the reliability of the protocol. It is known as in statistic science the results are more realistic how much bigger is the sample. Also for WSS, target with a large number of compounds often showed a lower WSS value [HIV-1 Reverse Transcriptase, Factor Xa (fXa), Cyclin-Dependent Kinase 2 (CDK2), EGF-R Tyrosine Kinase, Acetylcholinesterase (AChE), HIV-1 Protease]. Biological targets with smaller number of compound showed higher WSS values such as Inosine Monophosphate Dehydrogenase Type 2 (IMPDH2), Delta Opioid Receptor, Liver X Receptor alpha (LXR-alpha), Anthrax Lethal Factor (LF), Rho-kinase (ROCK I). But although a relative small compounds set, WSS showed a low value for some targets such as HMG-CoA Reductase, Apoptosis Regulator Bcl-2, Aldosterone Synthase (CYP11B2), Protein Kinase C, Angiotensin-Converting Enzyme. Thus, the evaluation of both SDA and WSS could give an account on the accuracy in the identification of the biological target for a test compound.

Taking in account these parameters, the BIOTA protocol was applied on inhibitors of Heat Shock Protein 90 (Hsp90). Heat shock proteins (HSPs) are biological entities involved in the folding and

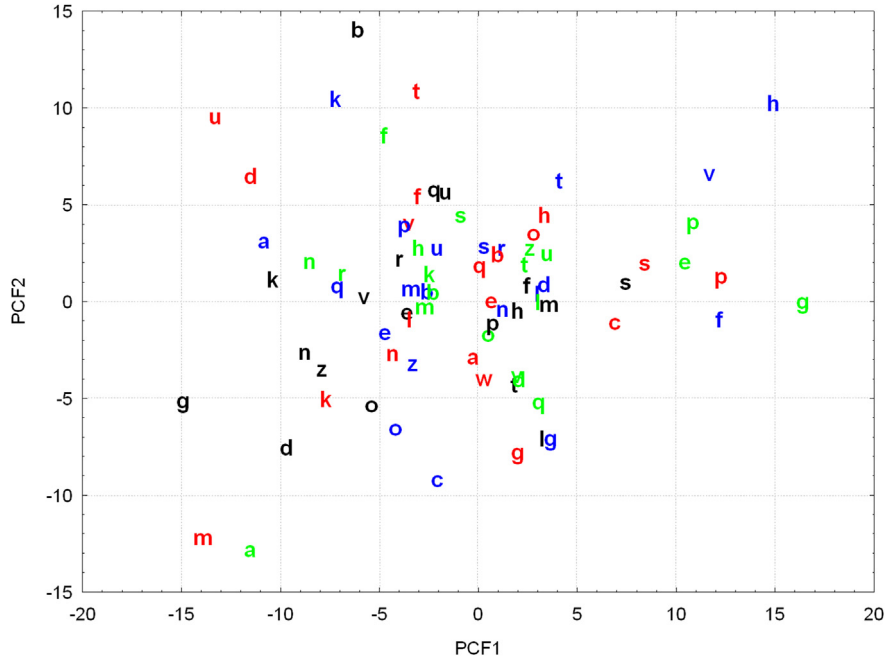
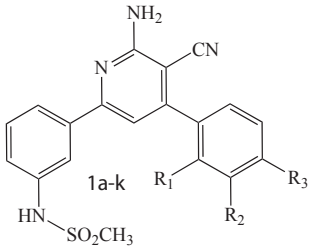


Fig. 3. Scatterplot of barycenter coordinates of the eighty selected targets. The legend for the biological targets is reported in Table 1.

Table 3
BIOTA application on aminocyano pyridine derivatives **1a**–**k**, as Hsp90 inhibitors.



Cmd	R_1	R_2	R_3	EC_{50} (nM)	*D* (Cmd, Hsp90)
1a	Cl	H	H	950 ± 35	10.57
1b	H	H	NMe_2	371 ± 28	7.90
1c	H	F	H	$>10^4$	9.96
1d	OMe	H	H	634 ± 22	8.64
1e	H	OMe	OMe	867 ± 27	7.54
1f	H	H	OMe	541 ± 29	8.17
1g	H	H	OH	$>10^4$	7.89
1h	OH	OMe	H	252 ± 23	7.02
1i	H	OMe	H	$>10^4$	8.86
1j	H	H	NEt_2	783 ± 19	8.38
1k	Br	H	H	$>10^4$	9.02

unfolding of other proteins. Their expression is increased when cells are exposed to stress as elevated temperatures, tumor progression, etc. Hsp90 is the most widely studied together with Hsp60 [17] and Hsp70 [18]. A set of Hsp90 inhibitors (Table 3), incorporating the aminocyano pyridine skeleton, recently designed and synthesized by us [19], was submitted to BIOTA protocol. By analyzing the SDA and WSS for Hsp90 (Table 1), it emerges as this target is well ranked from the protocol, thus the application of the BIOTA could be reliable. Moreover, the WWS scores selection routine suggest as four the number of principal components to use in the application of the protocol (Supplementary data, S4).

For each compound **1a**–**k** the score, as defined in Eq. (2) was computed (Supplementary data, S5). By analyzing the output results, it emerges as the method assigns a quite good score to the pyridine derivatives. Moreover, the more active derivative (**1h**) showed the best score (D(Cmd, Hsp90) = 7.02). The analysis of the Table S5 (supplementary data) can be useful to deepen interesting issues on the biological targets involved in the Hsp90 pathway. Moreover could be used as multi-target drugs discover.

4. Conclusions

Few aspects are to be clarifying to address the application of BIOTA. The success of the protocol depends from different factors: the correctness of biological data, the optimization of the molecular structures and their molecular descriptors calculation, the selection of the biological targets. The protocol is an attempt to rationalize and correlate the *in silico* with the *in cell*, and, of course, it lends itself to further improvements to make it more robust.

The application of BIOTA could allow to hypothesize the mechanism of action of a candidate drug prior to its biological evaluation or to repurpose old drugs, without request of expensive hardware. The proposed protocol can be fine-tuned by choosing opportune targets (biological or not) and molecular descriptors, and it can be useful in every fields in which it is possible to collect set of compounds with the same target.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.01.025.

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