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A mixed ligand – Autogrid based pharmacophore model for the rational design of multi-kinase inhibitors

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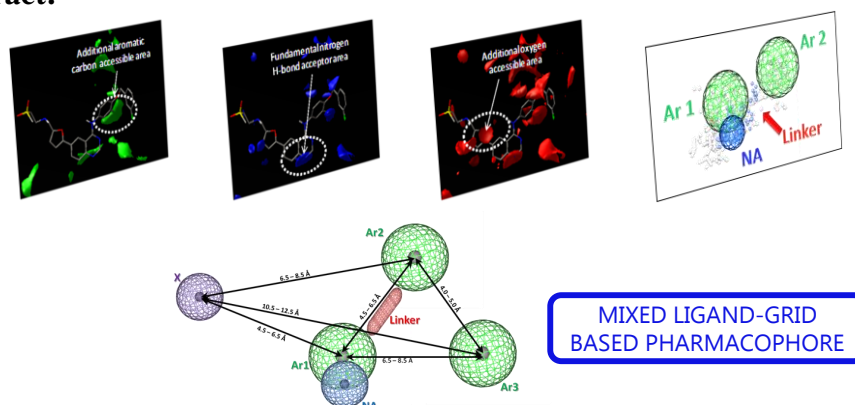
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Abstract:

A number of *in silico* methods have been recently applied for searching and designing multi-target compounds. The simplest approach consists in docking the compounds into all the targets independently. Then, only those molecules that show a high score against all the targets at the same times are collected as hit compounds. This approach, however, is quite computationally expensive, particularly when more than two proteins are considered as targets. Moreover, it does not furnish any information on the structural features required for the multi-target potency, thus it is not suitable for the hit optimization process. Several authors circumvented some of these problems by combining pharmacophore models with docking studies. Do to our interest in multi-kinase inhibitor discovery, we decided to derive a multi-kinase pharmacophore model, facing a two stage approach. Firstly, starting from the structures of the ligands we extracted the features of an appropriate multi-TKI scaffold (*scaffold pharmacophore*). Then, we decorated this scaffold through information derived from the target structures (*multi-TKI pharmacophore*). The presented methodology for identifying pharmacophore model could be applied also to other interesting pharmacological models for which a multi-target activity would be valuable.

Keywords: *kinase inhibitors; pharmacophore; autogrid; multi-targeting compounds*

Graphical Abstract:

Introduction. Alteration in the cell cycle regulatory system may cause cancer onset, progression and metastasis[1]. Among the proteins involved in signal recognition, transduction and amplification, tyrosine kinases (TKs) play a key role[2]. Despite the increasing interest in multi-TKIs discovery, the rational drug discovery methodologies are often applied only to the design of dual inhibitors. For example, several EGFR/src inhibitors or src/abl inhibitors have been discovered through docking studies[3,4]. However, since there is a complex relationship among the several TKs involved in the signal transduction pathway, it would be useful to find TKs inhibitors effective on more-than-two kinases.

Results and Discussion

Among all the TKs involved in cancer, we considered EGFR, FGFR-1, VEGFR-2, abl and src. In almost all the cases, more than one tridimensional structure was available in the Protein Data Bank (PDB). For the purpose of the present work, the resolved structures relative to mutant proteins and those containing an irreversible inhibitor were not considered. Thus, a total number of 57 tridimensional structures were initially considered. The superimposition of all these structures revealed a high degree of structure similarity (mean RMSD obtained: 1.11 Å). In order to define the features of the appropriate scaffold for multi-TKIs development, all the atoms with a formal negative partial charge and all the carbon atoms common to the majority of the ligands have been selected. As depicted in Figure 1, two aromatic carbon atom allowed area connected by a linker chain and one

nitrogen H-bond acceptor allowed area could be easily identified.

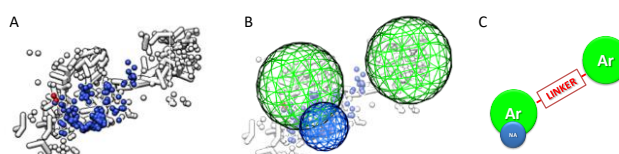


Figure 1. Scaffold pharmacophore derivation. (A) Atoms with negative partial charge (blue) and carbons (white) common to at least the 80% of the ligands. (B) Ligand based pharmacophore. (C) Schematization of the derived pharmacophore. NA = Nitrogen H-bond acceptor allowed area; Ar = aromatic carbon allowed area.

The second stage of the pharmacophore model generation has been faced employing the AutoDock (AD) 4.2 software. To compute the ligand-protein interaction energy and the geometry of interaction, AD makes use of several atomic affinity grid maps, calculated prior to the ligand docking. This method, also known as the “grid approximation” protocol, dramatically reduces the computational cost with respect to the continuous scoring function methodologies. Furthermore, as AD calculates one map for each desired ligand atom type, the affinity grids can be used to identify those regions in which a specific ligand atom favor the binding with the receptor.

The atom affinity maps for aromatic carbon, aliphatic carbon, H-bond acceptor nitrogen, non-H-bond acceptor nitrogen, oxygen, H-bond acceptor sulfur, non-H-bond acceptor sulfur, fluorine, bromine and chlorine atoms have been calculated in the ATP binding site of EGFR, FGFR-1, VEGFR2, src and abl. For each atom

type, the grids computed in the six kinases have been contemporaneously loaded in AD, setting the isovalue to about -0.60 Kcal/mol, thus permitting the determination of those ligand atoms allowed areas common to all the TKs. The grid derived information have been then overlapped to the *scaffold pharmacophore*, furnishing the final multi-TKIs pharmacophore model (Figure 2).

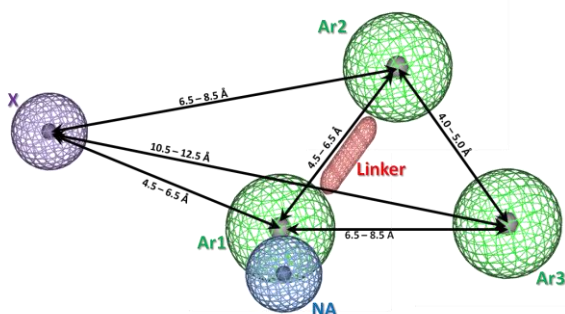


Figure 2. Multi-TKIs pharmacophore model.

Conflicts of Interest: *The authors declare no conflict of interest*

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Conclusions

Through the combination of a ligand-based and an AutoGrid-based approach we have identified a novel pharmacophore model potentially useful for the design of multi-kinase inhibitors. Interestingly, our recently reported multi-kinase inhibitors bearing biarylaminquinazoline scaffold [5] perfectly fit the pharmacophore model, thus demonstrating its usefulness. The presented methodology for identifying pharmacophore model could be applied also to other interesting pharmacological models for which a multi-target activity would be valuable.

Notes:

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