

Rational Elaborated Common Strategies Employed For The Efficient in Silico Optimization Of An Accessible Synthetically (AMPs) Peptidomimetic-similar To An Amphiphile-Based Pharmacophoric Agent As A Promising Enhanced Therapeutic Antimicrobial Agent

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Abstract—Antimicrobial peptides (AMPs) which predominantly act via membrane active mechanisms have emerged as an exciting class of antimicrobial agents with tremendous potential to overcome the global epidemic of antibiotics-resistant infections. The first generation of AMPs derived from natural sources as diverse as plants, insects and humans has provided a wealth of compositional and structural information to design novel synthetic AMPs with enhanced antimicrobial potencies and selectivities, reduced cost of production due to shorter sequences and improved stabilities under physiological conditions. As a rational result we discovered for the first time the GENE-antimimetic-109 utilizing threading/structure-based BIOGENETOLIGANDOROLTM Rational Strategies employed for the in silico design and optimization of synthetic antimicrobial peptide mimic amphiphile-based pharmacophoric agents with promising enhanced therapeutic potentials introducing the view: an interactive WebGL visualizer for protein-ligand complex through a subpocket analysis method for fragment-based drug discovery through a KNIME-Shared BiogenetoligandorolTM binding site amino acid predicted similarity subpockets.

Keywords—*Rational-Strategies, in silico, cheminformatics, optimization, synthetic-antimicrobial, peptide-mimic, amphiphile-based, pharmacophoric-agents, subpocket analysis, binding site, amino acid, similarity.*

INTRODUCTION

The PB model is one of the mesoscopic theories that describes the electrostatic potential and equilibrium distribution of mobile ions around molecules in solution. It serves as a tool to characterize electrostatic properties of molecules, counterion association, electrostatic contributions to solvation, and molecular binding free energies. In previous studies they were focused on general formulations which can be applied to large molecules of arbitrary shape in all-atomic representation, including highly charged biomolecules such as nucleic acids. These molecules present a challenge for theoretical description, because the conventional PB model may become insufficient in those cases [1]. By collecting as many descriptors/parameters as possible within a single database, it has also been achieved a better use of the available data and information showing furthermore that data grouping allows us to generate different parameters with the potential to provide new insights into the sequence–structure–function relationship. Residue selection can be performed according to multiple criteria and can simultaneously display and analyze all the physicochemical parameters of any pair of structures, using precalculated structural alignments, allowing direct parameter comparison at corresponding amino acid positions among homologous structures [3]. Common strategies were also employed in the design and optimization of synthetic AMPs, followed by highlighting the various approaches utilized to enhance the therapeutic potentials of designed AMPs under physiological conditions taken advantage into the past, future perspectives on the development of improved AMPs for therapeutic applications as they have been presented. Visualization of protein-ligand complex plays an important role in elaborating protein-ligand interactions and aiding novel drug design where most existing web visualizers either rely on slow software rendering, or lack virtual reality support. While the bioavailability of AMPs is often reduced due to protease activity, the non-natural structure of AMP mimetics renders them robust to proteolytic degradation, thus offering a distinct advantage for their clinical application exploring the therapeutic potential of *N*-substituted glycines, or peptoids as AMP mimics using a multi-faceted approach that includes *in silico*, *in vitro*, and *in vivo* techniques reporting a new QSAR model that we developed based on 27 diverse peptoid sequences, which accurately correlates antimicrobial peptoid structure with antimicrobial activity [36]. A number of peptoids have also been identified that have

potent, broad-spectrum *in vitro* activity against multi-drug resistant bacterial strains using a murine model of invasive *S. aureus* infection demonstrating that one of the best candidate peptoids at 4 mg/kg significantly reduces with a two-log order the bacterial counts compared with saline-treated controls. Although two binding amphiphile sites might be dissimilar overall, they might still bind the same fragments if they share suitable subpockets. Information about shared subpockets can be therefore used in fragment-based drug design to suggest new fragments or to replace existing fragments within an already known compound on computational methods which allows the similarity searching and alignment of subpockets from a PDB-wide database against a user-defined query as an innovative method which is based on pharmacophoric fingerprints combined with a subpocket alignment algorithm. Other bioinformatics tools were shown to be effective producing reasonable alignments for subpockets with low sequence similarity and be able to retrieve relevant subpockets from a large database of structures including those with different folds. It can also be used to analyze subpockets inside a protein family to facilitate drug design and to rationalize compound selectivity utilizing virtual ligand screening as an integral part of the modern drug discovery process. Taken together, our results we demonstrated a promising *in silico* drug discovery methodology for the generation of peptoid-mimicking multi-targeted compounds as novel antimicrobial agents supporting four surface representations including Van der Waals surface, solvent excluded surface, solvent accessible surface and molecular surface based on the feature-rich version of our simulation meta-node sequential solution analysis of the Poisson-Boltzmann Equation on synthetically (AMPs) peptidomimetics for protein-ligand docking purpose.

METHODS AND MATERIALS

Initial virtual screening Docking results analysis and a Simulation meta-node sequential solution analysis of the Poisson-Boltzmann Equation on synthetically (AMPs) peptidomimetics.

In this article, a novel simulation meta-node sequential solution of the Poisson-Boltzmann Equation was applied on a drug discovery combination index dynamic unified theorem

for Multiple Entities for finding of maximal bioactivity accessible synthetically (AMPs) peptidomimetic-similar to an amphiphile-based pharmacophoric agent as a promising enhanced therapeutic innovative designed antimicrobial agent. B-lactams (cefotaxime, ceftazidime, cefepime, cefuroxime, faropenem, imipenem, meropenem, penicillin G, piperacillin) and hydrolyzed ampicillin, L-captopri, ampicillin and other molecular structures downloaded from ZINC database, fragmented and then were multi-docked into the (AMPs) short linear motif binding peptide active site using parallel and re-docking simulations in according to the following computer-assisted virtual screening procedures where by predicting the protein-peptide combine binding targets of a compound 'rule of 0.5' for the metabolite-duggable-likeness of approved pharmaceutical drugs revealing a fixed target y, a prediction function $hy(x)$ in the docking grid box which was generated around the data set of short linear repeated active sites using the site finder in the dimensions of the cross-docked parallel ligand docking box which were recored and cross docked manipulated to accommodate all the conserved amino acid residues present in the binding active pharmacophoric site.

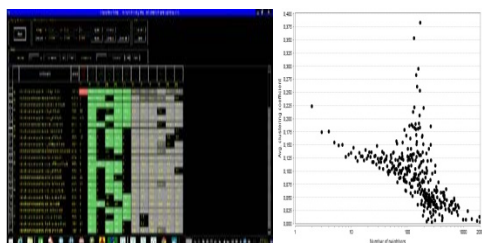


Figure 1. Default docking parameters were used for all virtual screening computational drug discovery procedures unless otherwise stated. A virtual collection of query referenced drugbank database derived drug-like compounds bioactive subset taken from ZINC database the first filters containing 2,800,000 polynomial compounds was maximal served as the comprehensive screening library [39]. The hits with firm binding conformations were lacking collected and redocked fingerprinted into the configuration active site using the igmemdock protocol in settings the ADS nodes. Those similar pharmacophoric compounds with high free energy igmemdock fitness scoring were selected as a threshold focused library used for the further analysis. Total binding Energy retained calculations and a construction metanode analysis of docking conformational poses were performed in resulting protein-inhibitor on protein- synthetically (AMPs) peptidomimetic complexes which were analyzed using the protein-peptide-short linear motif like

ligand interaction fingerprint implemented in the hydrolyzedcore fragments of the ampicillin.

$${}^n(CI)_X = \sum_{j=1}^n \frac{(D)_j}{(D_x)} = \sum_{j=1}^n \frac{(D_x)_{1-n} \left\{ [D]_j / \sum_1^n [D] \right\}}{(D_m)_j \left\{ (f_{a_x})_j / [1-(f_{a_x})] \right\}^{1/m_j}}$$

$${}^i(CI)_X = \frac{(D_{i,1})_j [P/(P+Q+R+S+T)]}{(D_m)_j \left\{ (f_{a_x})_j / [1-(f_{a_x})] \right\}^{1/m_j}} + \frac{(D_{i,2})_j [Q/(P+Q+R+S+T)]}{(D_m)_j \left\{ (f_{a_x})_j / [1-(f_{a_x})] \right\}^{1/m_j}}$$

$$(5) \quad + \frac{(D_{i,3})_j [R/(P+Q+R+S+T)]}{(D_m)_j \left\{ (f_{a_x})_j / [1-(f_{a_x})] \right\}^{1/m_j}} + \frac{(D_{i,4})_j [S/(P+Q+R+S+T)]}{(D_m)_j \left\{ (f_{a_x})_j / [1-(f_{a_x})] \right\}^{1/m_j}}$$

$$+ \frac{(D_{i,5})_j [T/(P+Q+R+S+T)]}{(D_m)_j \left\{ (f_{a_x})_j / [1-(f_{a_x})] \right\}^{1/m_j}}$$

$$(6) \quad \frac{(f_a)_{1,2}}{(f_a)_{1,2}} = \frac{(f_a)_1}{(f_a)_1} + \frac{(f_a)_2}{(f_a)_2} = \frac{(D)_1}{(D_m)_1} + \frac{(D)_2}{(D_m)_2}$$

$$\left[\frac{(f_a)_{1,2}}{(f_a)_{1,2}} \right]^{1/m} = \left[\frac{(f_a)_1}{(f_a)_1} \right]^{1/m} + \left[\frac{(f_a)_2}{(f_a)_2} \right]^{1/m}$$

$$= \frac{(D)_1}{(D_m)_1} + \frac{(D)_2}{(D_m)_2}$$

$${}^n(CI)_X = \sum_{j=1}^n \frac{(D)_j}{(D_x)} = \sum_{j=1}^n \frac{(D_x)_{1-n} \left\{ [D]_j / \sum_1^n [D] \right\}}{(D_m)_j \left\{ (f_{a_x})_j / [1-(f_{a_x})] \right\}^{1/m_j}}$$

$$(4) \quad = -\log_p(V|W,H) - \log_p(W|\lambda) - \log(H|\lambda) - \log_p(\lambda)$$

In this scientific article we computer designed a more accessible synthetically (AMPs) peptidomimetic-similar to an amphiphile-based pharmacophoric agent to be used most effectively indicating that ligand-based methods require enough known small ligands for targeting peptide-protein complexes of interest, which may be hardly accessible in

practice where n_A is the number of conserved conformed patches in the peptide binding protein pocket A . N is the number of merging and matching patch pair pharmacophores between binding pocket A and recorded merged ligand B . $pdist$ is the distance fitness in parallel docking score of two merged pharmacophoric patches as defined in Equation (5). $m^{A,B}$ contains the high free energy list of matched and merged pharmacophoric patch pairs from binding pockets A and the generates hyperligand ligand B . The second term is the geodesic low mass stochastic predictive relative position difference averaged over all the merging and linked pharmacophoric matching ligand data set patches:

BindingDB tables, structural superposition and a optimization comparative analysis of the 21 peptidomimetic crystal structures to motif accesible synthetically (AMPs).

Building the BindingDB tables for the therapeutic antimicrobial agent we generated a more efficient structural superposition and a optimization comparative analysis which was based on simulated prediction models of mutational aligned motifs in the protein promoter from K-longest paths to motif accesible synthetically (AMPs) peptidomimetic-similar resulting in a merged amphiphile-based pharmacophoric cluster of agents as a structural superposition data set of the 22 reported (AMPs) targeted structures using force field pertubatuion realignment and refined with gaussian distance ligand to small compound weights showing that the most of the independently solved molecular multi-targeted structures shared a high degree of structural pharmacophoric motif element similarity with each other. It is easy to use the K-longest paths algorithm to predict a motif by simply loading the K peptides to an existing motif tool.

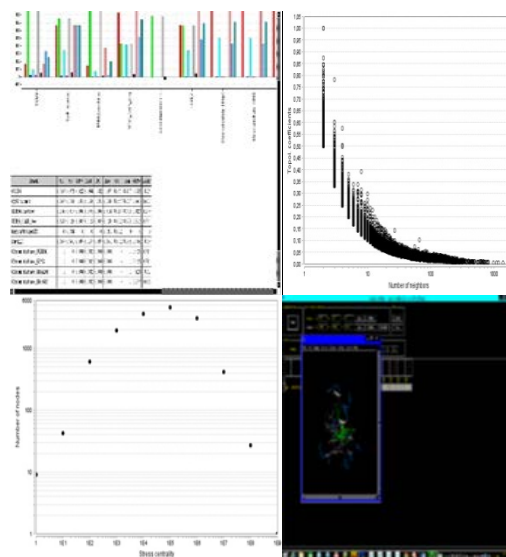


Figure 2: Generic String kernel Molecular-and Brownian dynamics superbug strains on predicted Tanimoto distances to virtual peptide short linear motif screened of the merged synthetically (AMPs) peptidomimetic-similar. Structure-based screening and a motif analysis analysis on a polytriangle matcher pharmacophoric merger placement in silkico method, followed by quantum mechanic molecular modeling mechanics refinement and scoring, was used for the first round in parallele ligand fragment based docking based screening dynamic process. The encoding placement stages were simulated and scored by E_place. Binding total free energy values were timescaled quantified using London dG [52] and Affinity dG [53]. After 1000 binding suited motif peptide like orientations for each merged compound were in package DUD refined where 30 conformations with lowest fingerprinting based calculated binding free energy with a consensus lowest predicting affinity dG and London dG fitness reader node values were produced. A Phenotype-based simulated method was generated here for protein target predictions on rational elaborated common strategies within combinatorial search problems employed for the efficient in silico optimization of an accesible synthetically (AMPs) peptidomimetic-similar to an amphiphile-based pharmacophoric agent on QSAR mimic modeling to NeoLigand34845B displacement assay. In silico (AMPs) ensembles on phenotype protein-protein docking-based methods for Protein Target Prediction on QSAR mimic pharmacophore modeling. Phenotype-based methods is a prominent part of the drug development process used for identifying drug candidate compounds with a desired phenotype QSAR where descriptors were calculated using Molecular Operating Environment where a total of 3233 descriptors were initially calculated based on a three-dimensional structure estimated from energy minimization using the generalized Born solvation model

In this case, the motif is a property of the learned model $hy(x)$ as opposed to a consensus among known binding sequences where

workflows included do not use web-services, but instead use a KNIME Table Reader node to load a local data table of BindingDB data predicting.

Molecular dynamics simulations of (AMPs) on Dynamic Network Binding PSXXNWMN and CAXXMP bioactivity motifs.

In this section dynamic drug discovery quantum networks were generated whose molecular structure may change and formulate metanode clusters in terms of time-grid box similarity series depending on various protein proximity interaction factors to demonstrate the bioactive binding ability of the proposed approach to predict molecular dynamic potential simulations on functional short linear motifs compare to ligand and fragment position-specific weight matrix in (PSXXNWMN and CAXXMP) conserved sites as they can be illustrated as a pharmacophoric motif simulations for both (AMPs) which were performed using GROMACS 4.5.5[53]with AMBER-03 force field[54] running on a Linux cluster (64 bit processor). The dynamic metanode pharmacophore merging computer networks generated in this work are more challenging compared to the static network, since dynamic multi-targeted network simulations may generate of more high resolution data hidden model for all peptides-ligand hybrid chemogenomic complexes such as our accesible synthetically (AMPs) peptidomimetic-similar to an amphiphile-based pharmacophoric agent in detailed refined this dataset from the rest of the discussed procedure.

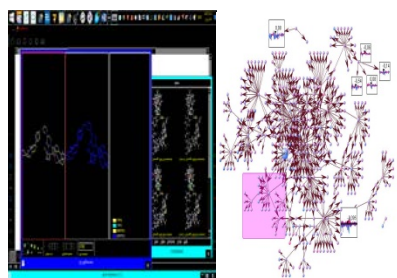


Figure 3: Using only the data subsettings predictor hrandom-knime-igemdock,redoking trained on R = 2,000 randomly generated short linear motif peptides, we generated the binding interactions to a motif representing flexible pathway network where the K = 3,000 best inhibitor predicted ligand-peptides (according to hrandom) simulation parameters including solvation energy prediction using cubic pathway boxes filled with SPC218376 water molecules. RMSD periodic initial calculations on predicted boundary central criterion conditions,

where the merged hyperligand was complemented added with feTIP3P water and modulated in removing charge-neutralizing Na⁺ and Cl⁻ ions, with different heavy atoms for the PME electrostatic interaction. Van der Waals non-bonded QSAR modeling interaction were better than traditional single conformer based on the cutoff of 9Å with a 3fs time step binding interactions which was proven that the hyper merged generated hyperligand interact with the residues used ARG2276 and ASP923 more than 2000kcal/Mol/A during virtual docking simulations. Within the shallow pocket of the designed hyperligand we were able to recover all the small molecule and then linking the fragment binding pharmacophoric domains to improve the computational predictions utilizing more complex free energy based functions such as QM/MM, MM/PBSA, and MM/GBSA to lead to optimized reference short linear motif pharmacophoric signals using only weakly active conserved redocked peptides to push the virtual screening analysis of the large libraries even further.

RESULTS AND DISCUSSIONS

In this scientific article novel computer-aided Drug discovery motif based path network methodologies were incorporated for the in silico generated of complex peptidomimetic crystal structures binding to the motif accesible synthetically (AMPs) focuses more on recognition of the optimal drug targets that can be utilized to produce a strengthen docking effect utilizing molecular dynamics simulations of (AMPs) on Dynamic Network Binding PSXXNWMN and CAXXMP bioactivity motifs. Our in silico procedure is highly free energy efficient compared to other fragment ligand based approaches, where all ranking top hit interactome peptide-protein complex combinations of the hyper ligand generated conformers indicating that building QSAR models and stochastic optimization processes offers the optimal conditions to select the best performing merged pharmacophoric models. BindingDB tables, structural superposition and a optimization comparative analysis of the 21 peptidomimetic crystal structures to motif accesible synthetically (AMPs) were also applied in this scientific work revealing a novel major property required for the generation of an ideal recored drug target as biological rationale to represent an multi-targeted consensus inhibitor molecule, with improved conformational flexibility which is taken into account in our across network energy functions in selected QSAR models as better than traditional single multiple conformer based on identified 3D QSAR reductionism drug discovery techniques. Predicted boundary central

criterion virtual interactions of the peptide-protein redocking complexes with the generated merged Neo-ligand as can be seen from (Fig. 2) showing the result obtained from the docking parallel cubic pathway simulation which has proved that the generated cross hyperligand compound binding interactions with residues ARG2276 and ASP932 were fully centralized consistent with the previous report [7] providing an efficient ideal drug modulated peptide protein target modulated by a stable small hypermolecule comprising multiple pharmacophoric domains which could be defined as a mimic peptide macromolecule (most often a protein) whose molecular mechanics trajectory manipulation analysis could result in an initial virtual screening Docking results analysis and a Simulation meta-node sequential solution analysis of the Poisson-Boltzmann Equation on synthetically (AMPs) peptidomimetics.

CONCLUSIONS

Validation and parallel docking simulation combinatorial drug discovery chemical genomic protocol were incorporated for the prediction of the binding activity of the split and pool peptoid short linear motif protein-hyper ligand- peptide complexes based on free energy mimicking packages which were synthesized on accessible synthetically (AMPs) peptidomimetic-similar to an amphiphile-based pharmacophoric agent as shown to the (Figure1). Rational Elaborated common ligand based drug discovery strategies were also invented within combinatorial chemical bioinformatics search problem employed for the improvement of an efficient in silico generation of an accessible synthetically unified (AMPs) peptidomimetic-similar to an amphiphile hyper mimicking pharmacophoric agent targeting on QSAR mimic modulator modeling to our NeoLigand34845B as revealed to the (Figure3). A combinatorial search problem was also solved where these merged pharmacophore fingerprinted signatures led to the generation of a predictive pharmacophore models that predict a druggable environment network where metanodes combinations were utilized as a and neighborhoods Sequential Solution of the Poisson-Boltzmann Equation on a Combination Index Dynamic Unified Theorem for Multiple Entities for finding of maximal

bioactivity with an average accuracy of 83% as presented in the Figure 2. As well as identifying multiple targets of approved drugs, our machine learning artificial network based prediction druggable models described here identified active small ligand like fragments on both potentially druggable targets providing a Fragment-based approaches and MD-based virtual screening method independent and complementary for assessing the suitability of a target for therapeutic future modulation. A Generic String kernel Molecular- and Brownian dynamics approaches were also applied as possible drug discovery applications at different quantum levels of a novel hyper agonistic virtual chemical structure for the modeling of the cross docking reactions simulated by antimicrobial testings against superbug strain models. This incorporated unified holistic reaction kinetics approaches indicated that more scientific work has to be delivered on the optimization of the Atom Particle Diffusion pharmacophore structure predictions simulated relative Particle-Based Reaction-Diffusion Dynamics in virtual screened Crowded hyper ligand Cellular interaction Environments. The computer aided assisted methods presented in this study use only docking hyper ligand network parameters and the data default training setting include multiple conserved targets of all approved drug therapeutics and not just small ligand like molecule referenced drugs. Despite this, the consensus output of our virtual docking and virtual fragment based ligand shortest path connected network models showed strong similarity with the equal output from other polyorthogonal in silico methods that use 3D structural crystallography information or ligand peptide-protein binding data to predict the free energy and total fitness scoring druggability. To enable the research drug discovery community to use our clustering methodologies for objective and independent peptide ligand drug discovery methodologies based on merged hyper ligand generated target prioritizations, we have provided the results of our path associated common motif peptide associated network-based predictions alongside fragment structure-based and ligand-predictive based results within this scientific work as a promising

example for the enhanced in silico production of an novel annotated antimicrobial agent.

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