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Computational modeling and design of renin inhibitors

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ABSTRACT

The recently introduced field-based QSAR was employed to develop robust quantitative 3D QSAR models to comprehend the activity of several structurally diverse classes of small molecule renin inhibitors reported in literature. A reasonable predictive model with an r^2 (pred) of ~0.67 and rmse of 0.79 was achieved for an external validation set of ~150 compounds centered on the model developed using ~450 training set compounds. Based on the developed 3D QSAR models and additional insights gained from reported X-ray structures, opportunity for activity improvements in the [aza]indole scaffold was explored using a carefully designed virtual library of ~2300 compounds. The potential for success of such combined structure-guided and ligand-based approach was justified when the resulting prediction was compared against a representative with supporting experimental results.

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Improving the affinity of small molecules by incorporating subtle modifications to the existing lead chemical scaffolds is a major undertaking of the lead-optimization efforts in preclinical drug discovery projects. While the X-ray structure of small molecules bound to the respective therapeutic protein target enhances our interpretation on where such modifications could be contemplated, the corresponding scoring functions that enable us to predict the effect of such modification seldom provide quantitative estimates on the effect of such changes.[1] Very often additional evaluations using techniques such as linear interaction energy,[2] MM-GBSA[3] and others are coupled to in silico docking to have a reasonable activity estimate with varied success rates in literature.[4–7]

On the other hand, purely ligand-based approaches that ignore the protein and solvent environments such as the 3D QSAR techniques like CoMFA®[8] and CoMSIA[9] that utilize a 'pseudo-receptor' hypothesis provide chemically insightful suggestions with quantitative affinity estimates. Unfortunately, the sensitivity of this approach to the correct guess of the 'bio-active' ligand conformation (in the absence of bound X-ray complexes) and bottleneck of achieving good molecular alignments to the reference template often restricts its wide spread application to large datasets or chemically diverse scaffolds.

In this letter, I used a computational workflow wherein the protein bound ligand conformation observed in X-ray structures of complexes is used as the source of the 'bio-active', small molecule conformation. Such an effort capitalizes on the positives in structure-guided approach that takes into account the binding site shape and features instead of relying on the 'global' energy minimum of flexible small molecules that may not be reflecting the true ligand bound state. However, the inherent deficiency in the scoring functions for rank ordering compounds in a congeneric or diverse chemical series is taken care by resorting to the time-tested ligand-based 3D QSAR techniques for quick activity estimates. Such hybridization of the two orthogonal techniques provides a reasonable framework for quantitative activity predictions of small molecules rapidly without the need to perform long time molecular dynamics simulations. The successful demonstration of this workflow is showcased using renin as the therapeutic target and the small molecule inhibitors reported for the same.

The renin-angiotensin-aldosterone system (RAAS) pathway plays a key role in regulating blood pressure.[10] Persistent stimulation of RAAS ultimately leads to kidney dysfunction and organ failure. Renin is considered to be a key enzyme involved in the control of hypertension as this aspartyl protease is the first and rate limiting step in the RAAS pathway. Therapeutic intervention by inhibiting renin with small molecules is expected to minimize the mechanism-based adverse events associated with the widely prescribed RAAS blockers. To date, Aliskiren[11] is the only direct renin inhibitor that is on the market. The relatively low bioavailability of Aliskiren prompted several pharmaceutical companies to pursue this druggable target in search of small molecules (representative **1**–**6** in Fig. 1) resulting in at least two additional small molecules, VTP-27999 (**1**)[12] and ACT-077825/MK-8141 (**6**),[13] reported to have entered clinical trials.

Efforts from pharmaceutical companies like Vitae (**1**),[14] Sanofi (**2**),[15] Pfizer (**3**, **4**),[16] Merck (**5**),[17] Roche/Actelion (**6**)[18] and others[10,19] have also provided diverse synthetic chemical scaffolds (Fig. 1) with over 40 small molecule inhibitor bound X-ray struc-

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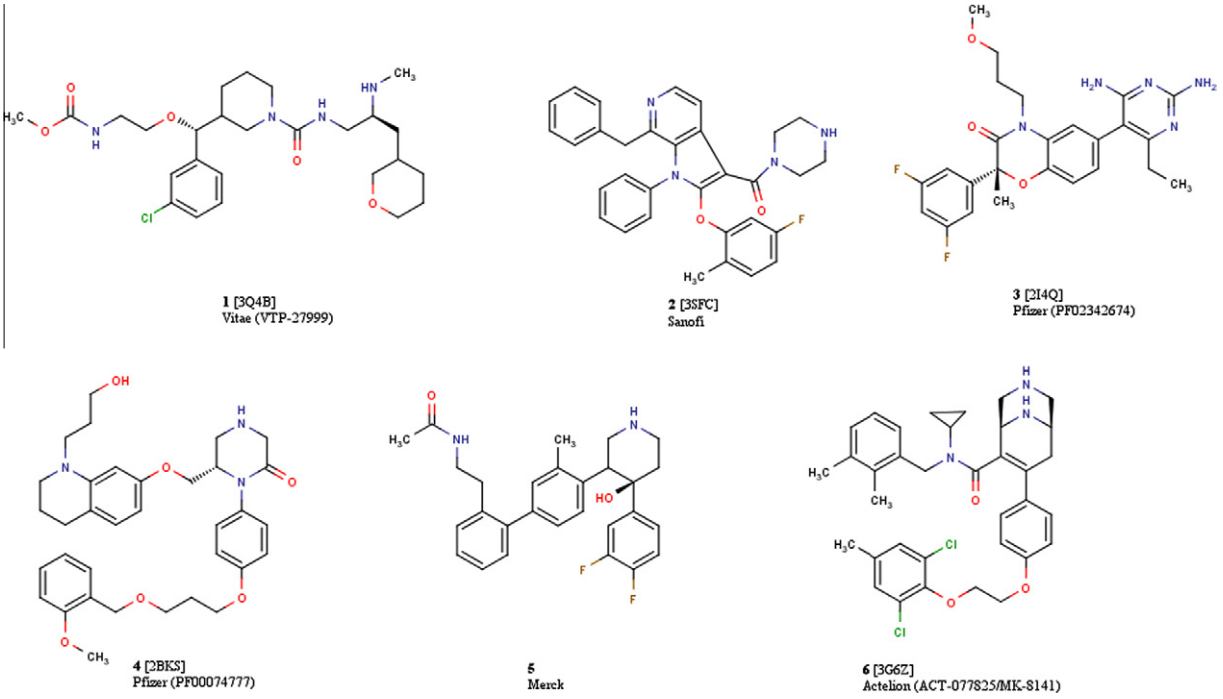

Figure 1. Representative small molecule renin inhibitors reported in literature rendered using Chemaxon's MarvinSketch (v5.9). The PDB codes and compound identifier, where available, are given in square brackets and parenthesis, respectively.

tures reported in the protein data bank (PDB).[20] The associated structure–activity relationship (SAR) data for more than 600 small molecules available in ChEMBL[21] and scientific literature offers a rich source of experimental data for pursuing in silico modeling activities. Such an effort enables an understanding of the molecular determinants and pharmacophoric features guiding effective target engagement and subsequently provide rational insights to improve upon the activity and other physicochemical properties of the inhibitors.

As a first step in the process, all the inhibitor bound renin X-ray structures were structurally aligned to the reference 2V0Z[11] PDB structure using the *structalign* python script distributed with the Maestro (v9.3) software suite from Schrödinger. Having obtained a unique reference framework, the bound small molecule inhibitor coordinates representing various chemical scaffolds were extracted and used to align the remaining SAR compounds (within the same/close series) reported in literature using a procedure described in our earlier work.[22] Through this unique small molecule alignment protocol, structures occupying different subsites of the renin-binding pocket to various extents were achieved and hence the relative contributions of the groups occupying these subsites to the overall activity can be assessed appropriately. It should be noted that unlike a traditional 3D QSAR modeling, the SAR compounds were not aligned to one common query small molecule, but were aligned to the closest small molecule X-ray in the bound ligand orientation (so called bio-active conformation). For instance, **3** and **4** occupy different binding sub-pockets in the renin and the aligned SAR compounds for the same would reflect such an arrangement. Such non-optimal molecular alignments of the different chemical scaffolds and representation of the proper 'bound ligand conformation' is hypothesized to capture the appropriate contributions of the various 'molecular fields' projected in the binding site of the target.

The final dataset of 596 inhibitors were split 75/25% into the training (447) and prediction (149) set, respectively. This was achieved by giving importance only to the biological activity (every 4th compound on activity sorted data was binned to the prediction set) so that inhibitors covering the full activity spectrum (pIC_{50} range between 4.6 and 10.7) are covered evenly irrespective of the chemical series they come from. An alternate data assembly of the same kind was pursued for the chemical series from the individual companies so that the respective chemical scaffolds and associated SAR was also covered evenly in the training (448) and prediction (148) set. Irrespective of the data set choice, both had a similar distribution of the scaffold representatives and activity for each chemical series.

An additional prediction set of 29 compounds[23] that had different substitution patterns not represented in the training set was used to validate the suitability of the models to new modifications in the structure that the model has not encountered before (chemical space extrapolation). Recognition of new "activity hotspots" for the [aza]indole series[15] was achieved by superposing the small molecule bound X-ray structure from Vitae (**1**). Appropriate extensions to the [aza]indole scaffold to reach this hotspot was identified by morphing the substitutions occupying this region in the series reported by Vitae[14] resulting in a virtual library design of 2345 compounds.

The recently introduced field-based QSAR (referred herein as F-QSAR) method implemented within Maestro was used to develop the 3D QSAR activity models. Both the forcefield (ff) and gaussian (gau) methods implemented within F-QSAR were employed. The results are also compared against the traditional CoMFA® and CoMSIA methods commonly used in literature (Table 1). In addition, partial-least square (PLS) regression models were also obtained using physicochemical (including the Molconn-Z) and topological descriptor based variables available within Canvas.[24] The stability and predictive power of the developed models were ascertained initially using the leave-1-out cross-validation (cv) procedure for the training set. Although not explicitly discussed, it should be noted that models have limited predictive power when the cv-r^2 is typically <0.5.

As seen in Table 1, the statistical models developed using standard descriptors had comparable performance to the 3D QSAR techniques. However, the descriptor contributions could not be

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