Establishment of Structure Based Drug Design (SBDD) Lab.

“Need of the Hour”

Department of Pharmaceutical Chemistry  
College of Pharmacy  
Prince Salman bin Abdulaziz University
Establishment of Structure Based Drug Design (SBDD) Lab: A proposal submitted by Abdul Samad
ACKNOWLEDGEMENT

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Vision, Mission and Objectives of the SBDD Lab.

Vision

• To be an internationally recognized drug discovery group and partner of choice for both academic and industrial sectors. The SBDD lab’s vision is to be the preeminent leader in achieving freedom from diseases like cancer, diabetes, hypertension, Alzheimer etc, by extending and enhancing the lives of individuals regionally, nationally, and throughout the world.

Mission

• To increase the efficiency and success in translating life sciences research into therapeutic applications to address unmet medical needs. Further to serve humanity by means of contributing some leads to cure the fatal maladies and again take the world to the Golden age.

Objective

The College's pharmaceutical Chemistry department is exceptionally strong. To maintain high standards and keep pace with the needs of a fast-changing discipline, we seek to establish a Center for Drug Design and Discovery. Ongoing research in the Department of Pharmaceutical Chemistry is directed at discovering novel agents to treat maladies like Cancer, diabetes, Alzheimer's disease and infections etc. Studies are also in progress examining the pharmacological mechanisms associated with these disorders. To keep pace with rapid advancements in the field of pharmaceutical sciences, faculty and students need access to the latest technologies, scientific instruments and equipment. Opportunities to assist in establishing the structure-based drug design Lab including additional laboratory space and purchasing highly sophisticated scientific equipments.
1. Introduction

During the early 1980s, the ability to rationally design drugs using protein structures was an unrealized goal for many structural biologists. The first projects were underway in the mid-80s, and by the early 1990s the first success stories were published [1–3]. Today, even though there is still quite a bit of fine-tuning necessary to perfect the process, structure-based drug design (SBDD) is an integral part of most industrial drug discovery programs [4] and is the major subject of research for many academic laboratories.

The completion of the human genome project, the start of both the proteomics and structural genomics revolutions, and developments in information technology are fueling an even greater opportunity for structure-based drug design to be part of the success story in the discovery of new drug leads. Excellent drug targets are identified at an increased pace using developments in bioinformatics. The genes for these targets can be cloned quickly, and the protein expressed and purified to homogeneity. Advances in high-throughput crystallography, such as automation at all stages, more intense synchrotron radiation, and new developments in phase determination, have shortened the timeline for determining structures. Structure determination using nuclear magnetic resonance (NMR) has also seen a number of advances in the past years, including magnet and probe improvements, automated assignment [5–7], and new experimental methods to determine larger structures [8]. Faster computers and the availability of relatively inexpensive clusters of computers have increased the speed at which drug leads can be identified and evaluated in silico.

Structure-based drug design is most powerful when it is a part of an entire drug lead discovery process. A review by J. Antel [9] states that the combination of combinatorial chemistry and structure-based design can lead to the parallel synthesis of focused compound libraries. It is also important to consider that structure-based drug design directs the discovery of a drug lead, which is not a drug product but, specifically, a compound with at least micro-molar affinity for a target [10]. The time devoted to the structure-based drug design process, may represent only a fraction of the total time toward developing a marketable drug product. Many years of research may be necessary to convert a drug lead into a drug that will be both effective and tolerated by the human body. Additional years of research and
development will bring the drug through clinical trials to finally reach the market.

Drug discovery to drug development pipeline

- **Identification**
  - HTS
  - De novo design
  - Virtual screening
  - SAR studies
  - In vivo efficacy
  - ADMET studies

- **Development**
  - Bioavailability studies
  - ADME
  - Long-term toxicity
  - In vivo efficacy
  - Synthesis scale-up

- **Efficacy**
  - Bioavailability
  - Dose
  - Safety assessments
  - Drug interactions

**Time-consuming**
- 2.5 yrs discovery; ~13.2 yrs development

**Cost-intensive**
- Total R&D costs for Discovery²
  - 25% (UK), 33% (US)

¹ Gilbert, J. et al. (2005) In Vivo, the Business & Medicine Report 21 (10)
During the past few decades, there has been a steep rise in the volumes of software packages that can assist in carrying out the different phases of SBDD effectively. Although these computational resources have much to offer SBDD, it has eventually become a challenge to choose successful combinations of strategies and tools for efficient lead discovery [11]. Thus, in the following sections, we have presented the different protocols and relevant computational programs that are used in in-silico hit discovery as shown in Table-1.

### Table 1

<table>
<thead>
<tr>
<th>Drug discovery software packages</th>
<th>Software</th>
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</table>

Abbreviations: TS, target 3D structure prediction; BS, binding site prediction; MB, molecule builder; DB, database search; MM, molecular mechanics; Pc, pharmacophore; MD, molecular dynamics simulation; QSAR, quantitative structure activity relationship; Sc, screening; ADME, absorption distribution metabolism excretion; TP, toxicity prediction; [-], selective channels.
<table>
<thead>
<tr>
<th>Database</th>
<th>Number of records</th>
<th>Sub-structure search</th>
<th>Structure formats</th>
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<td>&gt;37 Million(C) &gt; 70 Million(S)</td>
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</table>

*Yes*: information from other linked database. Abbreviation: BD, binding data.
2. Process of Structure-Based Drug Design

Structure-based drug design (SBDD) plays a major role in the development of novel drugs against many diseases. Recent advances in large scale determination of protein structures are improving the drug discovery process by starting with the protein structure and using it to design and identify new ligands. The objective of the background is to cover the significant steps involved in structure-based drug design.

Steps Involved in Structure-Based Drug Design

1. Identification of drug target
2. Binding site recognition
3. Computational drug design methods
   - Virtual Screening
   - De novo Design
   - Docking and Scoring Function
   - 2D & 3D QSAR
   - Pharmacophore Mapping
4. Evaluation of potential lead candidate
   - Lipinski’s rule of five.

Target Identification

Complete genome sequences have provided a glut of potential biological targets [12]. Practices such as systems biology, clustering, probabilistic networks and drug affinity response have matured to help with the identification of biological targets [13]. A typical SBDD begins with the identification and validation of the target structure [14]. The structural information for all targets is generally obtained by X-ray crystallography or NMR. However, in the case of targets with no experimentally determined structures, several computational approaches such as ab initio modeling, threading and comparative modeling can be used to predict 3D structures. Homology modeling or comparative modeling is the most reliable method for target structure prediction that builds 3D structures for unknown proteins based on the known homologous protein structures (i.e. >40% similarity) [15]. There are numerous automated programs that can make such high quality protein structure predictions. Because 3D structures are the fundamental requirements to begin SBDD, most of the drug design packages listed in Table 1 include structure prediction utilities. For
example, Discovery Studio from Accelrys, Prime Module from Schrodinger and Advanced Protein Modeling from Sybyl are a few widely used modeling programs. When the target structure is predicted a few steps of validation are essential to confirm the stereochemical quality of the predicted structures before proceeding further in SBDD. One common method for such quality checks includes a Ramachandran plot analysis that displays the backbone conformational angles for all of the amino acids in the protein structures [16]. Structural analysis and verification server (SAVES; http://nihserver.mbi.ucla.edu/SAVES/) is a structure validation server that offers a combination of structure evaluation tools attributing to different structural parameters. It is one example of the programs that are used for structure quality evaluation. A detailed description of the evaluation procedures can be found in several reviews [15,17,18].

**Binding site recognition**

The binding site is a small region, a pocket or bumps, where ligand molecules can best fit or bind to activate the receptor and/or target and produce the desirable effect. Thus, recognizing the binding site or the active site residues in the target structure is of high importance in SBDD. Because the proteins are capable of undergoing conformational changes, recognizing the accurate binding site residues is difficult [19]; but still there are just a few computational programs, such as Ligsitecsc [19], Qsite finder [20] and CASTp [21], that can capably spot out the binding site residues. Qsite finder [20] locates and clusters the favorable binding sites using the interaction energy and Van der Waal’s probes, whereas CASTp [21] employs functionally annotated residues for mapping the surface pockets. Thus, more-reliable active site predictions can be carried out with the available software resources for SBDD. With the targets and their binding site having been defined, the next crucial step in SBDD is hit discovery, which probably results in a library of compounds that can interact with the target. It is an accepted fact that proper selection of chemical compounds, with minimal potency and specificity, during the early phases of drug discovery plays a vital part in the success of the final lead optimization stages [22]. Thus, hunting for novel chemical entities with therapeutic values remains the central goal of pharmaceutical chemistry. To date, HTS has been considered to be the main process used for hit identification. Although this technique is very efficient and powerful in screening compounds of interest, it consumes a lot of time and materials.
to perform experimental studies for huge combinatorial space (i.e. cost is high). Further, with the increased size of a screening library the efficiency of HTS tends to decrease [23]. Hence, employing alternative hit identification approaches that can handle varieties of biological targets effectively and identify pharmacologically sound hits becomes inevitable [24]. This demands the use of SBDD in hit discovery. SBDD incorporates two diverse strategies for the identification of potential hits such as virtual high-throughput screening (vHTS) and de novo design.

**Computational Drug Design Methods**

The goal of all computational studies used in drug design is to evaluate the inhibitor binding complex. After identifying the possible binding regions on a target structure, potential ligands that bind and inhibit the target are evaluated. Computational and experimental methods are followed for finding a good lead. Computational methods for structure-based drug design are not mature enough to replace existing practices, but new approaches and computer programs continue to appear. Most work falls into the categories of De novo design, Docking, and Scoring.
Proposal For Structure-Based Drug Design Lab
**Virtual screening**

Although looking for a ‘fresh recipe’ for novel medicines is a process of invariable selection, researchers try to identify the most effective assortment from millions of potential compounds by the most efficient method. Virtual screening (VS), also called vHTS, has been globally attributed as being an alternative approach to HTS. vHTS computationally screens large chemical libraries to search for compounds that possess complementarities toward the targets [25,26]. The screening of compounds in vHTS is carried out using docking calculations where the compounds are filtered based on their binding energies against the target [26, 27]. Because these types of screening techniques are mainly data driven, data accessibility remains highly significant. The past decade has seen a number of useful chemical databases that serve as knowledge bases for efficient VS [28]. Table 2 lists a few commonly available small molecule databases that hold millions of chemical information that is freely accessible. Also, several chemical suppliers provide free access to their compound catalogues which can be used for screening purposes [29]. These days, faster and relatively inexpensive clusters of computers have increased the speed at which drug leads can be identified and evaluated [30]. VS is generally categorized into two methods: viz. Structure based VS and ligand-based VS [31], structure-based VS is very useful when the target structure is available and is more popular among the research community. Equally, ligand-based VS that uses predictive compound activity models based on previously available experimental data is also gaining popularity [32, 33]. Any type of VS results in a library of short-listed compounds with increased potency and selectivity. The initial VS library basically has three different classifications: ‘general’, ‘focused’ and ‘targeted’. The ‘general libraries’ are the ones that correspond to the broad category of targets; the ‘focused library’ mainly deals with a family of related targets only; and the ‘targeted libraries’ are particular to a specific target, for instance kinase inhibitor libraries for ‘cyclin dependant kinase b’ [34]. The outcome of the screening process is highly dependent on the type of virtual library created. The size of each library generated through the VS procedure is very high and libraries often consist of a greater number of compounds than expected. Every compound in the library is individually docked into the receptor-binding site and is ranked based on the interactions with the target and the relative scoring functions. Docking and scoring functions are discussed later as part of this review.

The potential of computer-based screening has already been well demonstrated by the Proposal For Structure-Based Drug Design Lab
identification of several inhibitors and antagonists [35]. A successful effort on VS led to the development of the patented drug candidate SC12267 for the treatment of rheumatoid arthritis. SC12267 is currently in Phase II clinical trials. Screening of commercially available compounds with the crystal structure of dihydroorotate dehydrogenase (DHODH) resulted in the identification of novel cyclic aliphatic carboxylic acids that led to the discovery of SC12267 [36]. VS demonstrated tenfold higher ‘hit rates’ (i.e. number of compounds that bind at a specific concentration and/or total number of experimentally tested compounds) than the empirical screening techniques. This factor makes VS as important as HTS in ‘hit discovery’ [29, 37, 38].

De novo design

De novo design is a process of creating or building new lead compounds from scratch. This process complements vHTS and HTS in hit discovery. The main principle of de novo design is to construct the small-molecule chemical structures that best fit the target space [39]. This can be achieved through two different strategies: namely receptor/target-based design and ligand-based design, the former method being more prevalent than the latter. In receptor based de novo design high quality protein structures and their respective binding sites are essential because the hits are designed based on the target structures by placing small fragments in the key interaction sites of the proteins. The positioning of fragments can be either pre-docked with the structure or placed by the program [40].

Receptor-based design can be carried out by two means: linking and growing techniques. In the linking process different small fragments such as amines, single rings and hydrocarbons from the libraries are added simultaneously to different active site residues of the target [41]. Thus, the small fragments positioned at the binding site link to each other and form a final single compound (Fig. 2). This approach is widely preferred by the researchers because the fragment design strategy is insightful in that most biological targets encompass discrete binding sites for each piece of a ligand. It would be more significant if the ligand key regions were focused through sectional planning. Whereas, in the growing technique a single small fragment is placed in the active site of the target and this fragment grows well complementarily against the receptor-binding site – thereby resulting in a library of chemical compounds that are more specific to the target (Fig. 2). Fragment placing can be carried out via two different approaches: namely, the ‘outside-in’ approach and the ‘inside-out’ approach.
During the ‘outside-in’ approach the fragment is initially placed at the edges of the binding site and the fragment is built inward. Software programs such as Caveat [42] and SPROUT [43] are used for this approach. During the ‘inside-out’ approach the fragments are randomly attached to the binding site and built outward. For this approach, a software program such as LUDI [44] can be useful.

There are a number of reliable software programs for generating novel scaffolds through a de novo design strategy (Fig. 2). Such automated de novo design has demonstrated its potential in hit and lead discovery. Recently, Ni et al. have successfully designed a highly potent lead for Cyp A PPIase using the de novo design strategy and the SAR study revealed that two of the inhibitors showed 31.6 ± 2.0 nm inhibition [45]. Thus, the mixture of a well characterized target and fragment-based methods favors the discovery of novel lead molecules with improved affinity, selectivity and physiochemical properties [46].

**Docking and scoring functions**

The key advantage with SBDD is the ability of the method to depict the experimental binding mode of a small molecule bound to the target structure. Docking, a process of predicting the ligand conformation and its orientation inside the target structure plays a vital part in SBDD. The interaction or fit between the ligand and the protein structure is best represented as the ‘hand and glove’ model [47]. Docking is often carried out in two parts. The first part includes the effective search of conformational space through a ‘posing’ mechanism where the ligand is placed inside the receptor in different orientations to facilitate the identification of the actual binding mode of the ligand molecules. Several algorithms such as genetic algorithms, the Monte Carlo algorithm, Evolutionary algorithms, simulated annealing algorithms, empirical approaches, knowledge-based algorithms, the SIS algorithm, the Hammerhead algorithm, and the Fast Fourier Transform approach are used for the effective search of parameter space. An energy based score, ‘scoring functions’, is provided for each pose in terms of their interactions with the receptor. These scoring functions are features that aid in investigating the interactions between the small molecule and the biological target, thereby providing context about biological activity. The methods such as force field, empirically derived methods or knowledge-based methods are generally used to position the ligand into the binding site (Box 1) [48]. Other possibilities such as rule-based methods, grid-based methods and multiple copy
simultaneous search (MCSS) are used to obtain the primary target constraints (i.e. the binding affinity energy). The second part of the docking process is the ordering of poses based on their computed scores [49].

Although the concept of docking seems to be simple, it appends higher complexity at each level and this is usually initiated by the algorithm beneath the docking process. For instance, the insertion of a flexibility factor to some active regions of the protein can help in identifying new hits with better interaction very quickly, when compared with traditional rigid docking. But, this requires more complex calculations because the protein of high conformational energy score would result in idealistic positioning of the ligand. Comprehensive reviews featuring comparisons of the different algorithms and scoring functions are frequently available in the literature [50, 51]. A list of common software resources available for protein–ligand and protein–protein docking and their scoring functions are presented in Table 3.
Quantitative structure–activity relationship (QSAR)

Quantitative structure–activity relationship is a widely used technique in drug designing process. It employs statistics and analytical tools to investigate the relationship between the structures of ligands and their corresponding effects. Hence, mathematical models are built based on structural parameters to describe this structure–activity relationship. Before, 2D-QSAR was widely used to link structural property descriptors (such as hydrophobicity, steric, electrostatic and geometric effects) to molecular biological activity; the results were often analyzed with multiple regression analysis. One of the most commonly used 2D- QSAR methods was
proposed by Hansch [52,53]. However, because 2D-QSAR cannot accurately describe the correlation between the 3D spatial arrangement of the physiochemical properties, and the biological activities, recently 3D-QSAR approaches have been adapted. The two very frequently and most popular 3D-QSAR methodologies are comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA). Comparative molecular field analysis (CoMFA) is established on the concept that the biological activity of a molecule is dependent of the surrounding molecular fields, such as steric and electrostatic fields. The steric and electrostatic fields were calculated by CoMFA using Lennard–Jones potential, and coulombic potential, respectively. Although this method has been widely adopted, it has several problems. Both potential functions changes dramatically near the van der Waals surface of the molecule and thus, cut-off values are often required. In addition, alignment of ligands must be conducted before energy calculation, but the orientation of the superimposed molecules is correlative to the calculation grid. It could cause large changes in CoMFA results. Moreover, in order to examine both fields in the same PLS analysis, a scaling factor needs to be added to the steric field [54]. CoMSIA is insensitive to the orientation of the aligned molecules and correlates to the grid by using Gaussian function. Furthermore, the improved function algorithm is least influenced by the relative distance to the van der Waals surface. Overall, this model can offer a more accurate structural activity relationship than CoMFA [55]

THREE-DIMENSIONAL PHARMACOPHORE MAPPING

The 3D pharmacophore search is an important, robust and a facile approach to rapidly identify lead compounds against a desired target. Traditionally, a pharmacophore is defined as the specific 3D arrangement of functional groups within a molecular framework that are necessary to bind to a macromolecule and/or an enzyme active site. The designation of a pharmacophore is the first essential step towards understanding the interaction between a receptor and a ligand. Once a pharmacophore is established, the medicinal chemist has a host of 3D database search tools to retrieve novel compounds that fit the pharmacophore model. The search
Proposed algorithms have evolved over the years to effectively identify and optimize leads, focus combinatorial libraries and assist in virtual high throughput screening. Thus, this technology has been clearly established as one of the successful computational tools in modern drug design [56,57].

**Drug Lead Evaluation**

Once a small molecule has been identified as potentially binding to the target molecule, it must be evaluated before proceeding to further stages. It is important to consider that the ranking assigned by the scoring function is not always indicative of a true binding constant, since the model of the target:ligand interaction is inherently an approximation. Both the solvent effect and the effects of target and ligand flexibility are usually imprecisely described. Usually, several molecules which scored well during the docking run are evaluated in further tests since even the top scoring molecule could fail in vitro assays. Leads are first evaluated visually with computer graphics and can often be optimized at this step for increased affinity. Leads are also evaluated for their likelihood to be orally bioavailable using the “Rule of 5” [58], which states that good leads generally have less than five hydrogen bond donors and less than ten hydrogen bond acceptors, a molecular weight less than 500, and a calculated log of the partition coefficient (clogP) less than 5. Rigidifying the lead can also impart a lower binding constant by decreasing the conformational entropy in the unbound state to approach the presumably very low conformational entropy in the bound state. Veber and colleagues [59] state that the number of rotatable bonds should be less than ten in order to increase the potential for oral bioavailability. Other factors, such as chemical and metabolic stability and the ease of synthesis, can also factor into the decision to proceed with a particular candidate lead. Finally, leads are brought into the wet lab for biochemical evaluation.

Promising leads reenter the structural determination process to find the exact binding mode and to evaluate any further optimization that becomes evident. A few examples of designed leads have shown significant differences between predicted and actual binding modes [60], but in many cases the docked and experimental conformations are within 2 Å rmsd [61].
3. Literature Review: Success stories

The literature is flooded with SBDD driven break through, so to make the long story of literature review short, we have discussed here the only candidates which crossed all the drug discovery processes and reached market successfully.

Some successful drugs of market using structure-based drug design

<table>
<thead>
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<th>Drugs</th>
<th>against / inhibits</th>
</tr>
</thead>
<tbody>
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<td>HIV protease</td>
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<td>HIV protease</td>
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<tr>
<td>Zanamivir (Relenza)</td>
<td>Neuraminidase</td>
</tr>
<tr>
<td>Tomudex</td>
<td>Thymidylate synthase</td>
</tr>
<tr>
<td>Imitinabmesylate (Gilvec)</td>
<td>Abi tyrosine kinase</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>Microbes</td>
</tr>
<tr>
<td>Captopril</td>
<td>ACE</td>
</tr>
<tr>
<td>Dorzolamide</td>
<td>Glaucoma</td>
</tr>
<tr>
<td>Raltitrexed</td>
<td>thymidylate synthase</td>
</tr>
</tbody>
</table>

The design of the angiotensin-converting enzyme (ACE) inhibitor **captopril** [62, 63] may be considered as the first real success of structure-based drug design. Long-lasting attempts to derive bioavailable small molecule inhibitors from snake venom peptides were without much success. A breakthrough resulted from the 3D structure of carboxypeptidase A, another zinc protease, in complex with its inhibitor 1,2-benzylsuccinic acid. A model of the ACE binding site guided the way to the weakly active ACE inhibitor lead structure N-succinoyl-l-proline (IC50 = 330µM). The antihypertensive drug **captopril** (IC50 = 23nM; Fig. 16.1) resulted after minor modifications, namely, the introduction of a methyl group (mimicking an alanine side chain) and an exchange of the carboxylate group with a sulfhydryl group [62, 63].

The topically active antiglaucoma agent **dorzolamide** (Ki = 0.37nM; Fig. 16.1), a carbonic anhydrase inhibitor, may be considered as the first drug in the market that originated from the experimentally determined X-ray structure of its target protein.
the very last steps of its design, a favorable conformation of the six-membered ring was stabilized by the shift of a methyl group of an N-alkyl substituent to this ring, in this manner enhancing the affinity of the molecule by a factor of two [64].

Agouron Pharmaceuticals and Vertex Pharmaceuticals, were both successful in designing the HIV protease inhibitors nelfinavir ($K_i = 2.0$ nM; Fig. 16.1) and amprenavir ($K_i = 0.6$ nM; Fig. 16.1), respectively [65,66]. Nelfinavir and amprenavir were designed by Modelling and simulation while raltitrexed (against thymidylate synthase) by group modification [67,68] and norfloxacain (fluoroquinolone antibiotic) by QSAR modeling [69,70].

An example of a straightforward 3D structure-based design was published by von Itzstein and his group [71]. Inspection of the surface of neuraminidase with the computer program GRID indicated a pocket that could accommodate a relatively large positively charged group. Exchange of the $\sim$OH group of the weak transition state inhibitor Neu-5Ac-2en ($K_i = 1$ μM) with an ammonium group produced an inhibitor with $K_i = 50$ nM. If the larger guanidinium group was introduced instead, the strong inhibitor zanamivir resulted ($K_i = 0.1$–0.2 nM; ) [71].
Researchers at the University of Sydney identified novel PPAR-γ agonists from a natural product library via Virtual screening and Induced fit Docking methods.
Molecular modeling plays an important role in all steps of lead discovery and lead optimization. Several computer-aided techniques for automated database searches and docking into protein 3D structures have developed over time. If only ligand structures are available but no 3D structures of the biological target, as until recently was the case for all membrane-embedded proteins, pharmacophore generation and 2D or 3D searches in structural databases are the method of choice [e.g., 72–74]. Starting with the programs DOCK [75] and LUDI [76], the docking of ligands into the binding sites of various proteins, for which 3D structures are available, is now a well established technique [e.g., 77–86]. A certain problem is the poor reliability of the scoring functions that rank the docking results [e.g., 87–90]. Extensive comparisons of different docking programs and scoring functions [e.g., 91–94], to rediscover known ligands within 3D databases provide evidence that there is no unique solution to the problem. Certain docking and scoring combinations are appropriate for one target, whereas they fail with another target.

Consensus scoring, that is, the simultaneous use of several different scoring functions, has been proposed to solve this problem [95]. However, for the most common programs the quality of the obtained results seems to depend more on the experience and skill of the modeler than on the options used.

4. Significance

The College's pharmaceutical Chemistry department is exceptionally strong. To maintain high standards and keep pace with the needs of a fast-changing discipline, we seek to establish a Unit for Structure Based Drug Design Lab. Ongoing research in the Department of Pharmaceutical Chemistry is directed at discovering novel agents to treat maladies like Cancer diabetes, Alzheimer’s disease and infections etc. Studies are also in progress examining the pharmacological mechanisms associated with these disorders. To keep pace with rapid advancements in the pharmacy field, faculty and students need access to the latest technologies, scientific instruments and equipment. Opportunities to assist in establishing the Center for Drug Design and Discovery include adding additional laboratory space and purchasing highly sophisticated scientific equipment. The importance and need of the SBDD lab can be illustrated by highlighting the following points:
Economic Factor:

The ‘birth’ of a new drug in the pharmaceutical market usually costs millions of dollars, very recently estimated at US$800 million. Hence, pharmaceutical companies and researchers are ready to make use of every chance that can help in reducing the monetary burden of drug design. SBDD is one such computational methodology that has been quickly recognized and globally accepted by drug researchers and medicinal scientists. Also, this method has demonstrated a considerable amount of success over the past decades. The foremost success of SBDD includes the identification of inhibitors targeting HIV-1 that have been approved by the FDA and have therefore reached the market effectively [96]. The CADD paves a way to stop Blind Synthesis of thousands of failed molecules by medicinal chemists which is the major part by economic point of view by involving expensive chemicals and solvents.

Time Factor

The development of any prospective drug begins with years of strenuous research to figure out the complexity of the medical problem. Often, it takes 5 years, minimum, to discover the drug, 2-5 years of preclinical testing, and 3-10 years of clinical testing. A patent is granted for 20 years at the end of the preclinical phase. The whole process takes 5-10 years after which the drug is forwarded to the FDA (Food and Drug Administration) for final approval [3G1]. This means that the company is left with less than 10 years to earn back the research and development cost before the patent expires. So the SBDD reduces the effort and time significantly so that the patent holding party can enjoy more time of patented era. Further SBDD will create a driving force to companies for developing more new chemical entities by reducing the time and cost involved in the drug discovery process.

Environment affable:

The huge amount of chemicals and solvents being used in chemical syntheses are resulting in thousands of failed compounds, which are hazard and threat to the Ecological and environmental system. After Tailor made approach of SBDD the number of synthesized molecules will plunge down significantly, thereby reducing the
amount of chemicals and solvents requisite in the wet lab procedures and ultimately SBDD has been credited as Environment friendly discipline.

**Curriculum obligation:**

Recently the research in medicinal chemistry has witnessed a significant development in the field of drug design with the advancement of NMR and information technology. Most of the renowned universities have established a CADD lab to furnish the need of the demanding research. To keep pace with the world in terms of technology-driven teaching with up-to-date knowledge database in pharmaceutical arena. Although Drug design is the important part of the student curriculum but seldom taught through real practices. Thus, it is must to endow our faculty members and student with the practical knowledge of this flourishing segment.

**International Competency:**

In the technology driven arena it is must to be competent with world to contribute in the field of drug design and discovery process. For instance, Monash University and University of Sydney hold good position in the world with respect to their research and contribution in Structure based drug discovery process. Further to support the Idea few links of the Universities having SBDD labs have been given below:

http://cancer.ufl.edu/research/shared-resources/structure-based-drug-design-lab-2/

**University of Florida**


http://www.ibb.gatech.edu/research/drug-design-development-and-delivery  **Georgia Parker H. Petit Institute for Bioengineering and Bioscience. Georgia State University.**

http://www.med.monash.edu.au/biochem/staff/rossjohn-rational.html  **University of Monash.**


http://bidd.nus.edu.sg/group/bidd.htm  **Bioinformatics & Drug Design group [BIDD]**

National University of Singapore.

http://www.uab.edu/gbs/bsb/faculty/computational-biologydrug-design ,

Proposal For Structure-Based Drug Design Lab
Graduate biomedical sciences, UAB, Birmingham.

These are just few examples to support the idea of international competency via the establishment of SBDD lab.

**Summary and Future prospects**

Structure-based drug design is a powerful method, especially when used as a tool within an armamentarium, for discovering new drug leads against important targets. After the target and a structure of that target are chosen; new leads can be designed from chemical principles or chosen from a subset of small molecules that scored well when docked *in-silico* against the target. Following a preliminary assessment of bioavailability, the candidate leads continue in an iterative process of reentering structural determination and reevaluation for optimization. Focused libraries of synthesized compounds based on the structure-based lead can create a very promising lead which can continue to phase-I clinical trials.

As structural genomics, bioinformatics, and computational power continue to explode with new advances, further successes in structure-based drug design are likely to follow. Each year, new targets are being identified, structures of those targets are being determined at an amazing rate, and our capability to capture a quantitative picture of the interactions between macromolecules and ligands is accelerating.

Although SBDD holds a few drawbacks, it serves the medicinal researchers in making a drug discovery effort with minimum time and an added level of confidence. With the vast numbers of available resources it is necessary to choose an appropriate resource that could envisage the genuine state of the biological system to fabricate better therapeutic achievements. Synchronization and enrichment of the experimental data availability and addressing the challenges and limitations countenanced can elevate SBDD to hold the primary role for identifying a compound as a ‘lead’ in future drug discovery research.

There are few computational/informatics tools available to guide this process currently, and successful design crucially relies on effective inter-working and understanding between the different disciplines, e.g. with pharmacology department to lead the direction of study towards molecular pharmacology.

The justification, discussion and success stories of SBDD clearly indicates the urgent need of the establishment of a “SBDD Lab” to take the college and university as well to the fore front of knowledge arena at the international education Map.
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