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# ROLE OF COMPUTER AIDED DRUG DESIGN IN DRUG DEVELOPMENT AND DRUG DISCOVERY

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**ABSTRACT:** The process of drug development and drug discovery is very challenging, expensive and time consuming. It has been accelerated due to development of computational tools and methods. Over the last few years, computer aided drug design (CADD) also known as *in silico* screening has become a powerful technique because of its utility in various phases of drug discovery and development through various advanced features. *In silico* screening also paves path for the synthesis and screening of selected compounds for better therapeutics. This review focuses on computational chemistry and computer aided drug discovery which are aimed to cover a wide range of computational approaches including new methodologies as well as practical aspects in this area. This review provides an insight about the developmental chain, approaches and applications of CADD; various data sources; computational methods for the discovery of new molecular entities; clinically approved drugs developed through CADD; and also summarizes the crucial steps of *in silico* drug designing like homology modelling, docking, multi-target searching and design, pharmacophore development, conformation generation and quantitative structure activity relationship (QSAR).

**INTRODUCTION:** The drug discovery process is a very complex and includes an interdisciplinary effort for designing effective and commercially feasible drug. In pharmaceutical, medicinal as well as in other scientific research; a computer plays a very important role, even in development of new compound in quest for better therapeutic agents [1, 2, 3]. Combination of rational drug design and structure biology leads to discovery of novel therapeutic agents.

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For this purpose Computer aided drug design (CADD) centre works with collaboration between structure biologists, biophysicists and computational scientists for discovery of new chemical entities. CADD and bioinformatics tools provide benefits like cost saving, time to market, in-sight knowledge of drug receptor interactions, speed up drug discovery and development [4, 5, 6]. The development and discovery of any drug takes many years like it begins with scientific studies like determination of disease, determination of specific target receptor and determination of active compound from the mass of compounds, etc. The drug discovery pipeline has been shown in **Fig.1**.

## Factors Affecting Drug Discovery:

- Medicinal requirements

- Screening facilities
- Drug development facilities
- Expenses of drug development process

There are various parameters which have to be considered in designing of drugs; drug should be:

- Safe and effective
- Bioavailable
- Metabolically stable
- Minimal side effects
- Selective target tissue distribution [7, 8].

Computational power by taking together with advanced analytical techniques like X-ray crystallography, NMR, *etc*. have improved application of CADD in the field of pharmaceutical industries like numerous of approved drugs that credited their discovery in large part to the tools of CADD were reported, such as: angiotensin-converting enzyme (ACE) inhibitor captopril for the treatment of hypertension [9, 10], Carbonic anhydrase inhibitor dorzolamide for the treatment of cystoid macular edema [11, 12], renin inhibitor aliskiren, which is used for essential hypertension [13, 14, 15], Human immunodeficiency virus (HIV) protease inhibitors saquinavir, ritonavir and indinavir for the treatment of HIV [16, 17, 18].

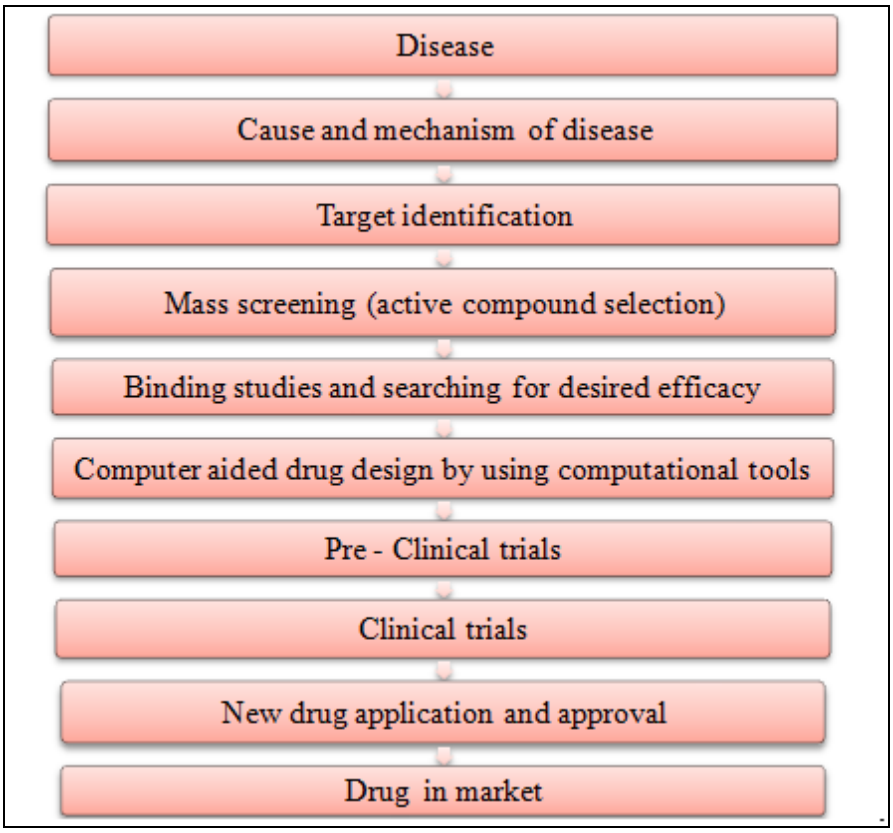


**FIG. 1: FLOW DIAGRAM OF DRUG DISCOVERY PIPELINE**

Computational methods are based on the fact that any compound which is pharmacologically active acts through interaction with targets like proteins and nucleic acids. Major factors are molecular surface, electrostatic force, hydrophobic interaction and hydrogen bond formation which govern such type of molecular interactions between drug and receptor. These are only factors which are considered at the time of analysis and prediction of interaction between two molecules. CADD designs any product in a documented way and facilitates the process of manufacturing. The compounds which have to be tested can be from various natural sources like plants, animals, microorganisms and also synthetic. After testing; test compound can be accepted or rejected according to result like absence/presence of toxicity or carcinogenicity, synthesis is complex, insufficient efficiency, *etc*.

**Applications of CADD:**

**CADD Methods are Used for:** Target structure analysis (possible binding site detection), candidate molecule generation, docking of generated molecules with target, give them rank according to

bio affinities and optimization of molecules for further improvement [19, 20]. CADD applied in the field of Research and development, target identification validation and preclinical study (Pharmacokinetic; ADMET prediction). By using technologies like the automation in which high throughput screening offers leads to drug discovery more fast in it millions of compound could be synthesized as soon as possible [21, 22]. It takes approximately 7 - 12 years and $ 1.2 billion for new drug to the market and also approx. Five out of 40,000 reach to a stage of preclinical testing, finally 1 out of 5 reach to clinical trials [23]. Success rates of molecules have been shown in **Fig. 2**.

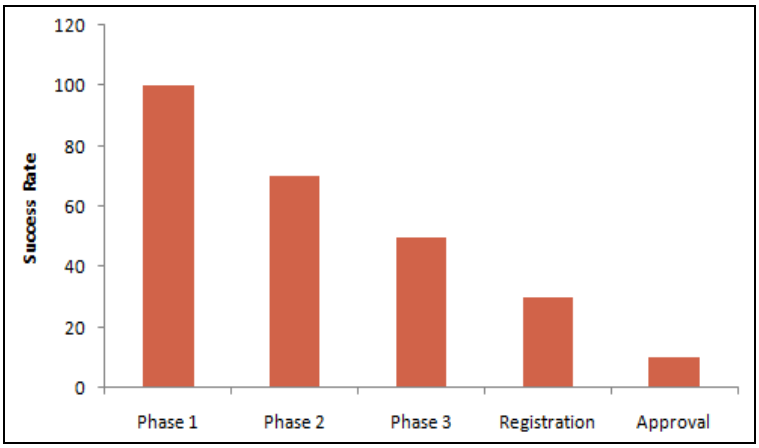


**FIG. 2: SUCCESS RATES OF CANDIDATE MOLECULES IN CLINICAL TRIALS [24]**
(One out of five candidate molecules reach into the market)

Lipinski's Rules provide an approach for selecting compounds that can qualify for properties of drugs [25, 26]. CADD hastens as well as increases the number of drug discovery process and development by aiding in and providing experimental data derived from various experiments through different databases. A better balance between computational chemistry and experimental area will promote better flow of information between the two spheres [27, 28].

***In silico* Drug Discovery Process Consists of 3 Stages:**

**Stage 1:** Identification of therapeutic target and generation of small compounds library for the testing and screening against the target molecule.

**Stage 2:** Interaction testing of selected hits by docking at the binding sites.

**Stage 3:** Subjection of selected compounds to pharmacokinetic studies and the compound that passes the pharmacokinetic parameters is used as a lead compound [29].

**Approaches Used in Rational Drug Design:**

**A)** Known 3-D structure of protein

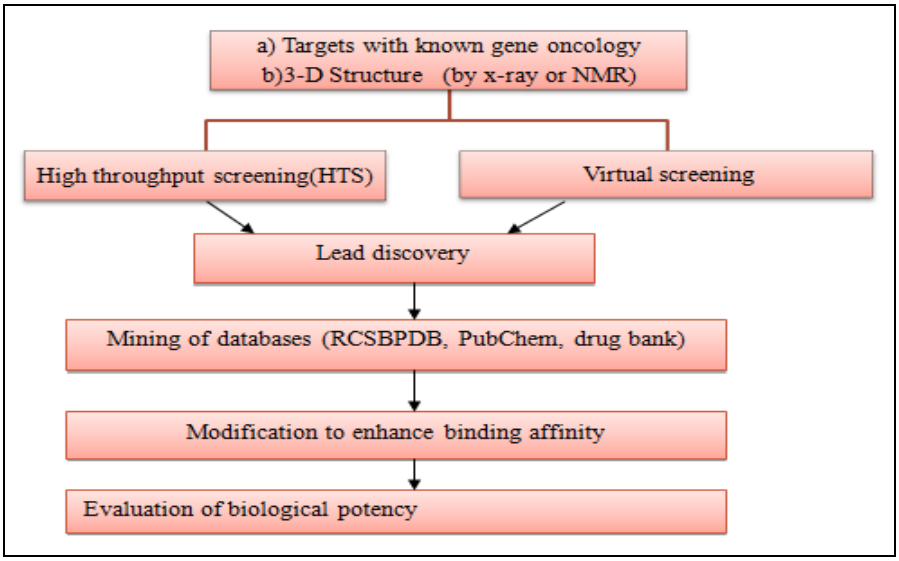


**FIG. 3: APPROACH OF DRUG DESIGN WITH KNOWN TARGET**

**B)** Structure of 3-D protein is not known (For new molecules)

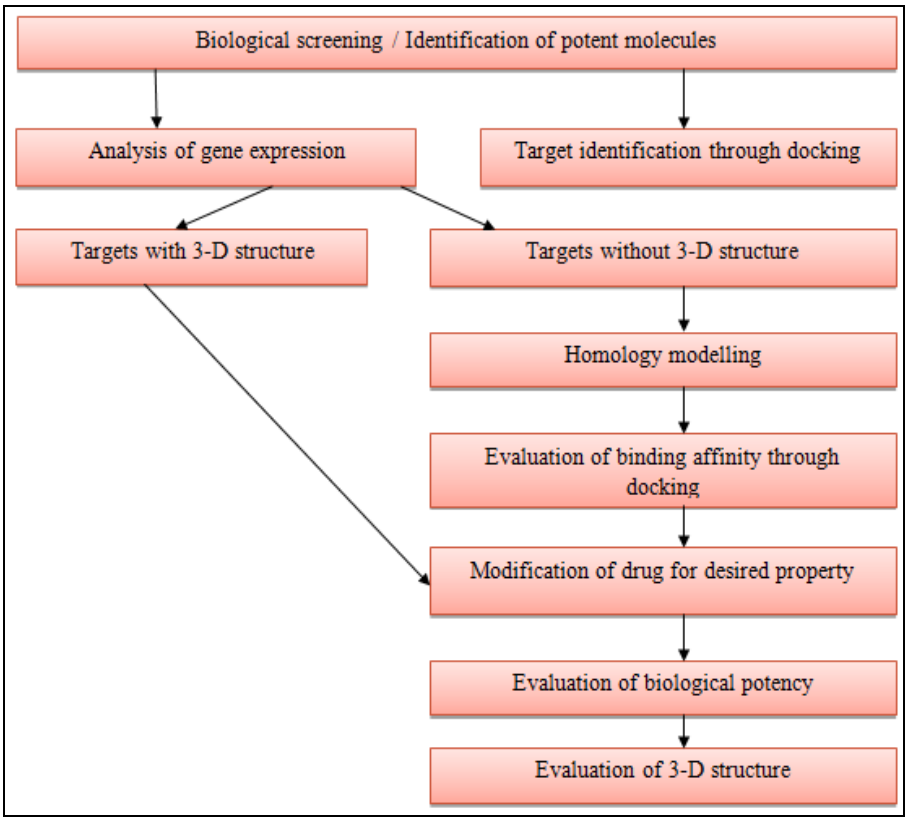


**FIG. 4: APPROACH OF DRUG DESIGN WITH UNKNOWN TARGET**

After the above two approaches those have been shown in **(Fig. 3)** and **(Fig. 4),** following properties are required to be checked for the examination of drug like properties in compound**:**

- Examination of QSAR, potency, docking and scoring, multi - regression analysis.
- Reactivity evaluation like nucleophilic, electro-philic and radial attack.
- Evaluation of *in-vivo* experiments, bioinforma-tics analysis, *etc*.
- Preclinical evaluation [30, 31, 32].

**Significance of CADD in Drug Discovery and Development:** CADD searches target based new compounds through hits screening and combinatorial chemistry than traditional methods, thus it increases the filtration of many compounds in a short time. CADD gives predictions about possible derivatives for improving the activity, as well as therapeutic activity on molecular basis. It is useful for following purposes:

- Filtration of large compound libraries into smaller compounds sets of predicted activity those could be further tested experimentally.
- Gives information about optimization of lead compounds, whether to increase bio affinity and pharmacokinetic properties like absorption, distribution, metabolism, excretion (ADME) as well as toxicity knowledge.
- Designing of novel compounds containing one functional group in a chemical compound or new chemo types by joining different fragments [33].

**Prediction and Analysis of Protein Structure Through CADD:** *In silico* studies also helps in protein modelling (3-D - protein models) for active sites residues identification. Prediction of protein structure is done *via* various methods like 'Homology modelling' and 'ab-initio' methods. Homology modelling works through similarities in sequences of unknown structure of to that of known structure (present in databases) of target. Steps involves in homology modelling.

- Selection of template and fold assignment.
- Alignment between the sequence of target and structure of template.
- Building of 3-D model.
- Modelling of loop regions.

- Modelling of side chain.
- Model evaluation.

The 'ab-initio' method is used if there is lower identification of sequences (<25%) with the structure of template [34].

Applications are:

- Study of effect related to mutation [35, 36]
- Identification of active binding sites [37, 38]
- Searching of ligands for detected binding sites (Mining of database) [39, 40, 41]
- Modelling of substrate [42, 43]
- Predicting the antigenic epitopes[44, 45]
- Protein-protein docking simulations[46, 47]
- Replacing of molecules in X-ray structures [48, 49]
- Rationalizing of known experimental observations [50, 51]
- Planning of new computational experiments with new provided models [52, 53, 54].

**Drug - Receptor Interaction Analysis Through CADD:** Experimental work, analysis and computer simulation used for information of drug- receptor interaction and finding a new active compound. They all work together, as analysis needed information of 3-D structure of molecules involved. After acquiring knowledge of bio molecular structure bio molecular docking is performed; which involves confirmation and orientation 'pose' of small molecule (ligand) in the cavity (active site) of target protein. Schematic diagram of molecular docking has been shown in **Fig. 5**.

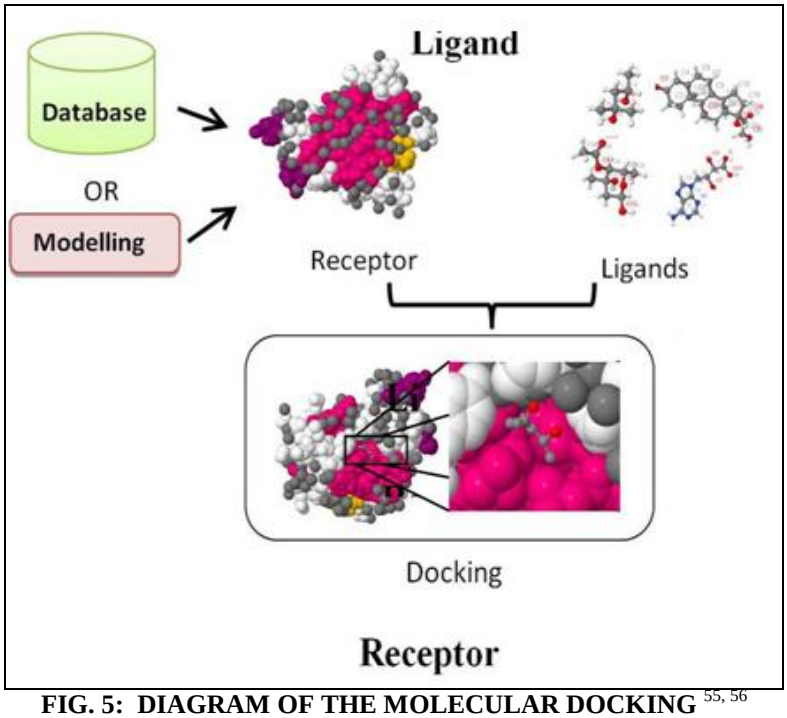


**FIG. 5: DIAGRAM OF THE MOLECULAR DOCKING** [55, 56]

These are the following types could be:

- Protein docking: Most of the computer studies needed protein which is involve in docking because majority of structures are known.
- Protein - protein docking: In this, two proteins bodies are assumed as two rigid solid bodies also with the help of geometric surface models and data structures binding mode is selected.
- Protein - ligand docking: It gives accurately analysis about molecular interaction. Here complementary contact surfaces are smaller than protein-protein docking. Small ligand adapt surface of receptor and fit into complementary site (ligand should be flexible molecule).
- Other important phenomenon than structure flexibility: Presence of single water molecules between ligand molecule and protein molecule leads to complex formation and plays an important role [57, 58, 59].

**Multi-target Drug Searching and Designing Through CADD:** The CADD technique is very useful in; searching drugs against multiple targets could be performed in which various hits are generated against multiple targets. In which the true- hits rates should be high than comparison to false- hits rates against of targets because it is needed in searching of multi-target searching for enrichment [60, 61, 62].

**Pharmacophore Development Through CADD:** Pharmacophore is defined as the three-dimensional arrangement of chemical functional groups which is responsible of biological activity. Now a days pharmacophore model (has been shown in **Fig. 6**) development has become an important part of drug discovery, design, optimization and development [63, 64]. Through the CADD, screening of Pharmacophore is performed which contains different scaffold containing compound but contains similar 3-D functional group arrangement [65, 66]. Pharmacophore methods find different types of compounds having common arrangement. Before using generated pharmacophore it should be validated with external data. If any suitable pharmacophore formed, virtual screening fastens [67, 68].

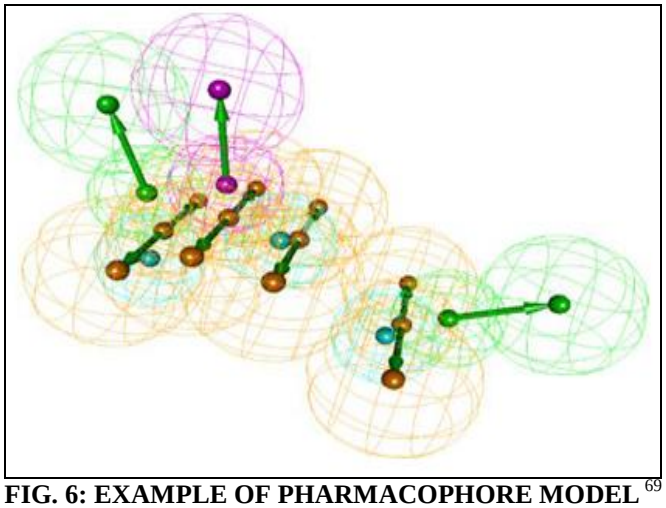

**FIG. 6: EXAMPLE OF PHARMACOPHORE MODEL** [69]

A pharmacophore gives good knowledge about molecular interactions of various compounds to their target structure and these features are complimentary to each other in 3-D space. Pharmacophore could be more better though combination with shape and volumes for proper fitting into the site of the receptor because wrong shape prevents fitting of compound into the receptor [23].

**Quantitative Structure Activity Relationship (QSAR) Studies Through CADD:** For many cases in which structural based approaches are not applicable because of absence of target macromolecule structure information, in those cases QSAR approach is used [70, 71].

QSAR gives information about relationship between chemical structure and biological activity in the form of a mathematical expression. The main advantages of QSAR method is to identification of properties of novel chemical compounds in which there is no need of synthesis and testing of them. Studies also relate all of them like structural descriptor of compounds, physiological properties and biological activities [72].

**Conformation Generation Through CADD:** One of the important aspects of drug design and development is that generation of conformation of small compound because it governs the physical and biological properties. It is necessary that conformer should have reasonable energy and good binding property in relation to a particular target. Cyndi is a highly efficient method of conformation generation.

It is based upon MOEA *i.e.* multi-objective evolution algorithm. Through using MOEA, Cyndi searches the conformational space in constant time, also controls geometric diversity as well as energy accessibility. Another one is Macro Model integrated in MaestroV7.5 (Schrodinger Inc.) which is different from Cyndi in terms of sampling depth of conformational space and the conformational cost [73, 74]. Some examples of conformational search algorithms have been shown in **Table 1**.

**TABLE 1: EXAMPLES OF CONFORMATIONAL SEARCH ALGORITHMS** [75 - 110]

| Systematic Search | Random Search |
|---|---|
| FRED | Auto Dock |
| DOCK | GOLD |
| GLIDE | CDocker |
| EUDOC | Mol Dock |
| FLOG | Ligand Fit |
| SLIDE | PLANTS |
| ADAM | Molegro Virtual Docker |
| FlexX | ICM |
| eHiTS | EADock |

**Clinically Approved Drug Discovered Through CADD Approaches:** Some examples of clinically approved drugs with year of approval and therapeutic actions developed through CADD approaches have been shown in **Table 2**.

**TABLE 2: LIST OF SOME CLINICALLY APPROVED DRUG DISCOVEREDTHOUGH CADD APPROACHES** [11, 16, 111 - 121]

| Drug | Year of approval | Therapeutic action |
|---|---|---|
| Captopril | 1981 | Antihypertensive |
| Saquinavir | 1995 | Human immunodeficiency Virus (HIV) inhibitor |
| Dorzolamide | 1995 | Carbonic anhydrase inhibitor |
| Indinavir | 1996 | Human immunodeficiency Virus (HIV) inhibitor |
| Ritonavir | 1996 | Human immunodeficiency Virus (HIV) inhibitor |
| Triofiban | 1998 | Fibrinogen antagonist |
| Zanamivir | 1999 | Neuraminidase inhibitor |
| Oseltamivir | 1999 | Active against influenza A and B viruses. |
| Raltegravir | 2007 | Human immunodeficiency Virus (HIV) inhibitor |
| Aliskiren | 2007 | Human renin inhibitor |
| TMI-005 | Phase II clinical trials | In Rheumatoid arthritis |
| LY-517717 | Phase II clinical trials | Serine protease Inhibitor |
| Boceprevir | Phase III clinical trials | Hepatitis C virus (HCV) inhibitor |
| Nolatrexed | Phase III clinical trials | In Liver cancer |
| NVP-AUY922 | Phase I clinical trials | Inhibitor for HSP90 |

Drug development and drug discovery needs different databases and tools which are the necessary parts in drug design. Different tools and databases which are employed in drug development and drug design have been shown in **Table 3**.

**TABLE 3: DIFFERENT TOOLS AND DATABASES EMPLOYED IN DRUG DESIGN PROCESS** [122 – 128]

| Tool | Brief description with uses |
|---|---|
| BLAST | Basic local alignment search tool; used for sequencing of DNA and protein |
| RasMol | Raster molecule tool; used for molecular visualization of RNA/DNA and protein |
| Discovery studio | Software; used for modelling and simulation |
| Pub Med | Free search engine; used for searching matter related to medical and life sciences |
| PDB | Protein data bank; used to collect information related to macromolecule |
| Chem Draw | Part of the Chem office programs; used to draw chemical molecule |
| Marvin Sketch | Advanced chemical editor; used to draw chemical structures and reactions |
| PubChem | Database; used to collect information about structure and physiochemical properties of chemical compound. |
| Auto Dock | Software; used for molecular docking |

**CONCLUSION:** The success stories of CADD in drug discovery in past few years demonstrated the utility in the process of drug development. CADD gives valuable information about target molecules, lead compounds, screening and optimization. The latest advancements like QSAR, combinatorial chemistry, different databases and available new software tools provide a basis for designing of ligands and inhibitors that require specificity. Different approaches, stages of designing, docking, pharmacophore modelling, homology modelling are the backbone of the CADD process. The utility of computational chemistry is also for understanding the three-dimensional aspects of drug - receptor interaction on the molecular basis and access the medicinal chemistry in designing of new therapeutic agents. CADD provides information about the chemistry of the chemical entities which is basically inaccessible through laboratory experiments, reducing cost and labour. Certainly, CADD will improve quality of research in near future and facilitate the development of numerous drugs.

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**CONFLICT OF INTEREST:** Nil

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