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COMPUTER AIDED DRUG DESIGN: A PARADIGM SHIFT TO RATIONAL DRUG DESIGN (A CASE STUDY OF ALZHEIMER'S DRUG INTERPIRDINE FAILURE)

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Abstract:

Drug discovery and design is a tedious and lengthy process which takes enormous time, and when this process reaches it's final stage that is the final stage of clinical trials 90% of the promising drug candidates fail levying a huge financial burden of around $2-3bn on the developer company. The drug failure not only incurs a financial loss to the company, but also smashes the hopes of the patients and families waiting for the successful approval of the drug. The scenario is even complicated when it comes to the drug approval for diseases like Alzheimer's. Computer aided drug design may help in the drug discovery process by slashing the time required for searching the potential drug target through computer aided software and programs. However the key to the success of the drug still lies in the understanding of the mechanism of the cause of disease and prognosis. Computer aided drug design help in the selection and modification of leads out of number of hits available. The present study deals with a case study of Intepridine an ambitious Axovant drug molecule which failed in the final phase of clinical trials and was withdrawn from the market by Axovant the developer pharma company.

Keywords: *Drug Discovery; Clinical Trials; Computer Aided Drug Design; Leads; Intepridine.*

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1. Introduction

Drug discovery and designing is a rigorous and time consuming process where thousands of chemical compounds may qualify as potential drug candidates however after early testing only a small number of these potential drug candidates look promising and call for further study. Coming on to the final stages of clinical trials around nine out of every ten drug candidates fail to win approval. This failure takes a toll on the drug company in the form of huge implications for

the overall cost of drug development, making the journey of molecule from laboratory to the market a much expensive and difficult affair. According to Tufts Center for the study of Drug Developments the average cost for a potential drug molecule to reach market with approvals is just under $2.6 bn. Tuft's reported $1.4bn in out-of-pocket costs whereas more than $1.1bn amounts to time costs which is the investment lost during the development process. Successful drugs reaching their endpoints with rock-solid safety profiles are far less expensive than $2.6bn as cited by Tuft's for failed drugs. Many actions are taken to rein in rising development costs at discovery and validation level, biomarker uses and new adoption approaches for recruitment and retention of patients are employed by drug developers but looking at the complexity of problems they seem to be helpless at some point.

For new drugs, where the target is poorly understood complex problem, drug failure is not a risk it is closer to certainty, sometimes the failure rate in such cases is more than 90%. Failure rate for new drugs targeting Alzheimer's related dementia was 99.6% between 2002 and 2012, and the big breakthrough has yet to arrive. Merck has to close its phase 3 EPOCH trial for Alzheimer's in February 2017 after its BACE inhibitor (1) verubecestat virtually failed in finding a positive clinical effect. In late 2016 i.e. in November 2016 Eli Lilly had to announce another failed phase 3 trial for Alzheimer's. The drug in question this time was solanezumab (2), an antibody targeting the amyloid plaques in the brain that are strong biomarkers for the Alzheimer's related dementia. This was also a blow to the theory of amyloids as prime target for Alzheimer's and slashed Eli Lilly shares by 14%.

Theoretically when the clinical studies reach phase 3, failure rates should be relatively low, but as per data gathered by life sciences consulting firm parexel, around 50% of phase 3 trials witness failure. As per AstraZeneca researchers five reasons behind the most expensive failures are: right target, right tissue, right safety, right patient and the right commercial potential.

2. Computer Aided Drug Design (CADD) : Rational Drug Design Approach

Computer aided drug design directly refers to the use of computers in the drug discovery and development process, chemical and biological information about ligands and targets is utilized extensively to identify and optimize new drugs. In silico filters are deviced to eliminate molecules with undesirable ADMET properties and most promising molecules are selected to act like potential drug candidates. The technique is rapidly showing growth in popularity, implementation and appreciation. Advancement in computational power of software and hardware and availability of huge chemical libraries and protein data banks has further increased the potential of computer aided drug design. CADD helps in identification of biologically active drug candidates (hits), selection of most likely candidates for further evaluation (leads), and optimization of leads into suitable drugs by improving physicochemical, pharmaceutical and pharmacokinetic properties of these leads. New drug candidates are discovered from different chemical scaffolds through virtual screening (3, 13), which reduces the size of vast chemical space, allowing researchers to concentrate on best promising candidates for lead discovery and optimization. In silico modeling thus significantly minimize time and resource required for chemical synthesis and biological testing, as reported by Green of GlaxoSmithKline (4).

Use of CADD in the lead optimization phase of drug development has substantial cost benefits. As per different reports out of the total cost incurred for a drug molecule to reach market which amounts in the range of $400 million to $2.6bn , the large contribution is dedicated to synthesis and testing of lead analogs(5).Computationally different hit compound can be optimized and compared through structure based analysis of their docking poses ,energy profiles , PK_a values and ADMET Properties.The cost incurred in computational methods is drastically low as compared to the chemical synthesis and biological characterization of compounds.The second advantage of CADD lies in the huge saving of time.

3. Intepirdine An Alzheimer's Drug By Axovant : Key Study Failure | A Case Study

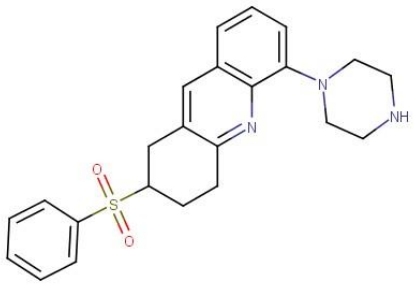

Figure1: Chemical structure of 3-(Phenylsulfonyl)-8-(Piperazin-1-yl)Quinoline (Intepirdine)

3-(Phenylsulfonyl)-8-(Piperazin-1-yl)Quinoline Intepirdine is a sulphur compound with molecular formula $\boldsymbol{C_{19}\,H_{19}\,N_3\,O_2\,S}$ and average weight equal to 353.44, considered as potent antagonist of the serotonin receptor 6(5HT6)(10). Originally developed under the name SB-742457, RVT-101.Development and progress of Alzheimer's related dementia leads with the impairment of serotonergic neurotransmitter system. Controlling this impairment is seen as a major therapeutic breakthrough(6).The drug has been reported to reverse learning deficits in rats (7,8).Drug enhances cognition in Alzheimer's and other forms of dementia (9). 5HT6 receptor is expressed exclusively in central nervous system and antagonist action of Interpirdine promotes the release of acetylcholine in the brain by blocking 5HT6 receptor.

Intepirdine therapy did not demonstrate statistically significant improvements in the cognitive ability of patients with mild to moderate Alzheimer's and showed no difference in the daily living activities of patients compared with a placebo.

Intepirdine was an ambitious drug of Axovant Sciences Ltd. and it has to pull plug on this ambitious Alzheimer's drug after the failure of key study. The company's share tumbled as soon as the news about withdrawal came in the market. The failure also put serious question marks on the mechanism of drug, which targets 5HT6 receptors. February 2017 also witnessed the failure of another 5 HT-6 antagonist based drug in its late stage trials by Denmark based Lundbeck. Baird analyst Brian Skorney stated the Intepirdine failure as a "death blow" to the hypothesis and wrote that "Following a slew of failures with other 5HT6 receptor antagonists, Axovant's Intepridine put the nail in the coffin for the mechanism in Alzheimer's disease. The failure is also end of hopes for patients and their families; in the light when the other path to treat Alzheimer's by targeting beta-amyloid protein has already suffered setbacks. Eli Lilly has also reported a key drug failure in last stage in 2017 targeting beta amyloid proteins. However a slew

of drug makers which includes Biogen Inc. ProMIS Neurosciences and Roche's Genentech are still developing Alzheimer's drugs targeting beta-amyloid proteins.

4. Intepridine Antagonist of Seretonin -6(5HT-6) Receptors

Intepridine acts as antagonist of 5HT-6 receptors. Intepridine docking with 5HT-6 Receptor gives results in favour antagonist activity. For the present study structure of 5HT-6 receptor is created by homology modeling through online Swiss model workspace. 5 HT-6 Receptor is expressed through HTR-6 gene, the gene sequence was taken from UniprotKB in Blast format and submitted to Swiss model workspace for homology modeling (11, 12).

Figure 2: Structure of 5HT-6 through Homology modelling

5. Docking Results

Molegro Virtual Docker (MVD) version 4.0.2 was used to perform docking; MVD is a coherent environment for predicting ligand protein interactions. Ligand binding modes are identified by iterative evaluation of a number of ligand conformations and estimation of the energy of interactions with the receptor protein. The highest scoring solutions are then taken up for further analysis. In the present study 5 binding modes are identified out of these modes, the mode with highest scoring values is given in Figure 3. The binding energy for the pose with highest scoring function is -59.9091 and RMSD value is 0.191148. Docking shows two hydrogen bond interactins between Intepridine and 5HT-6 receptor. Chemical properties by Osiris give favourable cLogP and cLogS values for Intepridine as 2.0627 and -4.78 respectively. Polar surface area for Intepridine is 71.01 and drug likeness is -6.517. lower cLog P values emphasizes good absorption properties of the drug and more than -4 cLogS values point towards good solubility of drug. Surface sum over all polar atoms including attached hydrogens give the polar surface area, and is used for optimization of cell permeability. Ideally molecules with less than 60 square angstrom are considered as having good penetration through blood-brain barrier. Intepridine has 71.01 square angstrom PSA, making it slightly hard to penetrate the blood-brain barrier. There are many approaches for a compound to study its druglikeness, however positive values are always favoured ones. The drug under study shows negative druglikeness values.

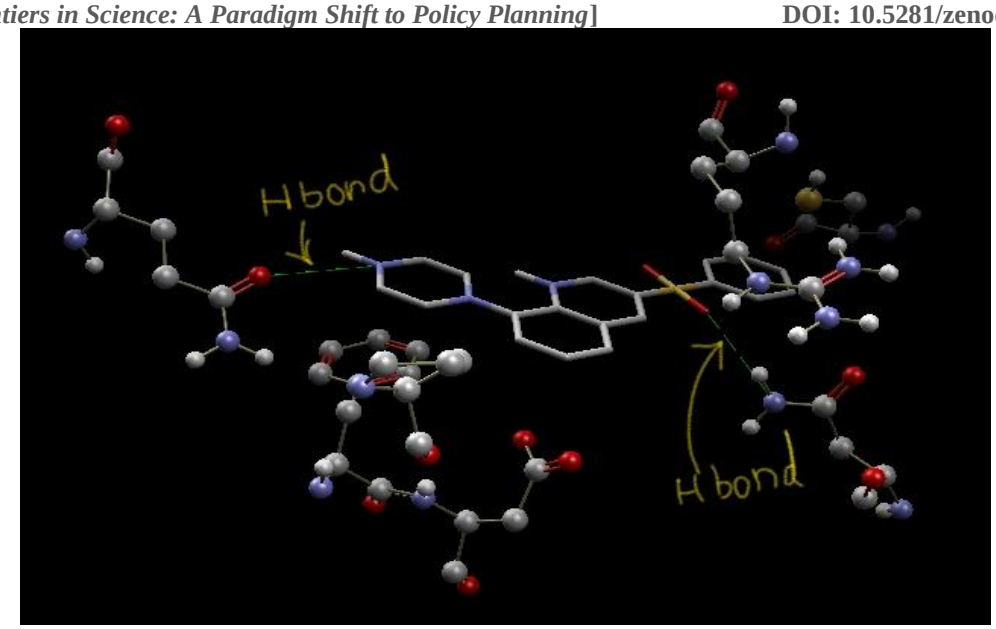

Figure 3: Docking of Intepridine with 5HT6 Receptor

6. Discussion

Central nervous system is the most challenging area when it comes to development and approval of new and effective drugs. Process is time consuming as well as carries huge amount of financial display. In case of Alzheimer's clinical trials have had failures as inevitable. In the present insilico study, as per the docking results the values are in favour of antagonist action except polar surface area and fragment based drug likeness values. Phase 3 clinical trial failure clearly points towards either the lack of therapeutic efficacy or the failure of mechanism for Alzheimer's i.e. targeting 5HT-6 receptors. More focus should be paid on the understanding of the mechanism. However good antagonist behavior of drug for 5HT-6 receptors makes it to qualify as potential candidate for treating other forms of dementia and improvement of cognition in patients. The focus finding an effective drug for AD should now be concentrated upon agents acting upon the beta-amyloid, such as vaccines, antibodies and inhibitors modulators of γ- and β- secretase agents directed against tau kinases which causes tau proteins to misfold and clump, forming neurofibrillary tangles.

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