Identification of potential Lead molecule for Schizophrenia through Docking based approach

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INTRODUCTION

Schizophrenia, neuro-degenerative disorder, a serious mental illness which influences the ability to think, write, learn and deteriorating the frolics of Life. Common problems are getting **Hallucinations** & **Delusions**. About ~4.3 to 8.7 million people in India are suffering with Schizophrenia. Anti –psychotic drugs provide chemical interactions with neurotransmitters, closely relates to clinical efficacy by treating acute psychosis and reducing the risk for future psychotic episodes. Lead discovery is an intensive search which ensures to find a drug-like small molecule termed as development candidate, that progresses into preclinical, and if successful, in to clinical development to ultimately be a marketed medicine. As the existing drugs have extra-pyramidal and cardiac related side –effects, development of dopamine D3 receptor antagonism is of therapeutic value to treat the symptoms of schizophrenia. Therefore, docking is used to predict binding mode of FDA drug molecules against D3 receptor which is known as therapeutic target against the disease.

DISEASE PROCESS

A Drug Development Approach to a devastating psychiatric disorder that warps a person's understanding of reality and sense of self. Schizophrenia is an active brain process which may have more than one disease process (Fig. 1)

Schizophrenia is a neurodevelopmental disorder characterized by deficits in cognitive processes mediated by circuiting of the DLPFC within synaptic circuitary of NMDA Pathway (Fig. 2).
Following are its causes:

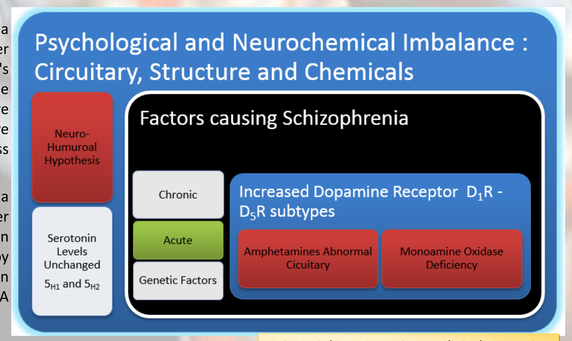
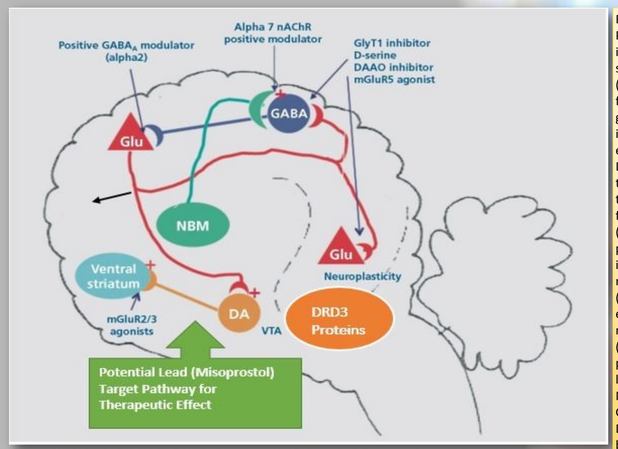


Fig 1. Linking Dopamine to Clinical Expression

- Increase in neuronal density in DLPFC.
- Decrease in synaptophysin protein.
- Synthesis & reuptake of GABA are lower in a subset of DLPFC neurons.
- The increased agonist-induced Dopamine activity in the brain leads to Fronto – Temporal Dysfucntion.
- The increased D_3 Receptor and Aberrant Salience [Psychosis], the casual symptoms of Schizophrenia begin to reveal.
- With the penetration of Anti-Psychotic Drugs in the brain, Dopamine Activity suppresses.

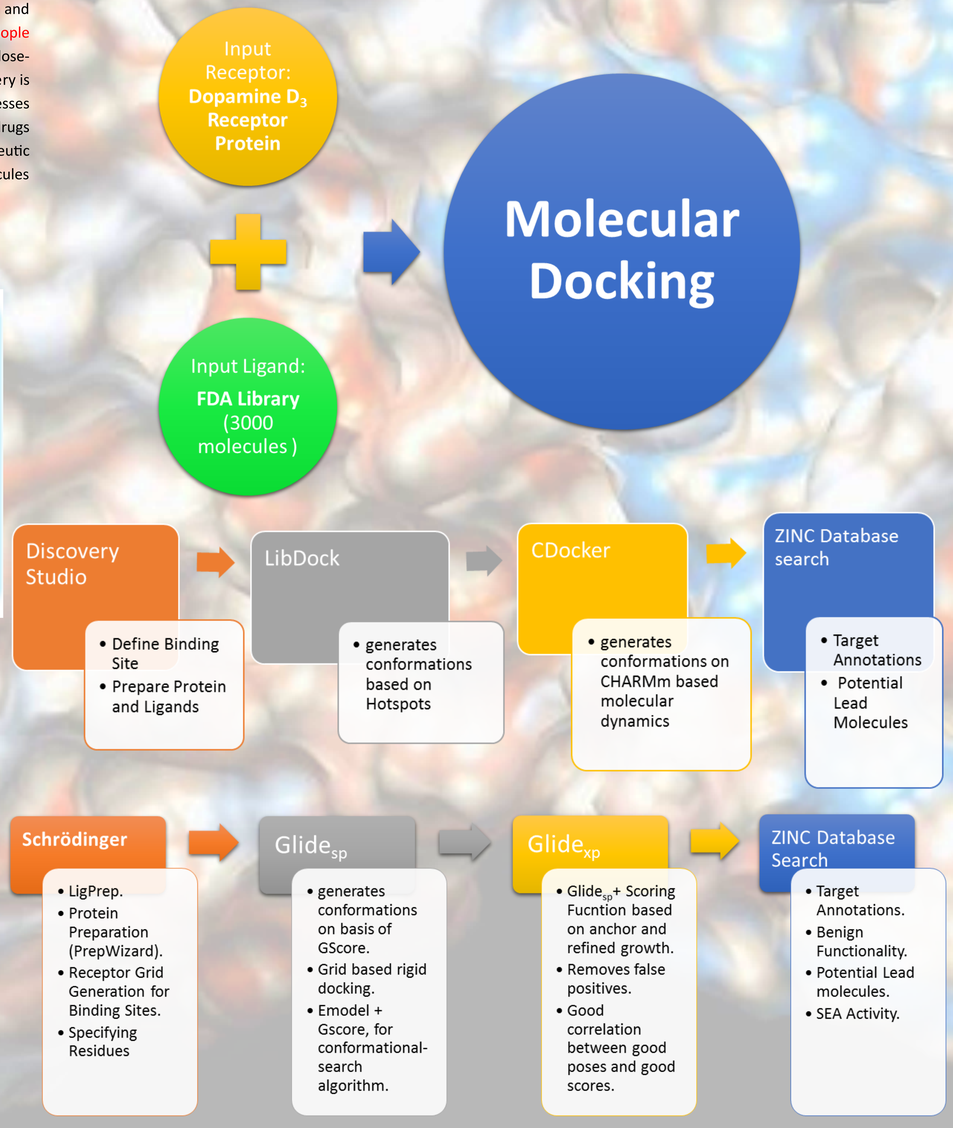
In our search for Lead Molecules for Schizophrenia , We selected "**D_3 Human Receptor Protein**" as our Drug Target due to its highly localized regions in limbic brain and FDA Library as our Ligand in a hope for selective antagonist acting as therapeutic agent for Schizophrenia.



Source: © 2010 LLS . Coyle, J. T., Balu, D., Benneyworth, M., Basu, A., & Roseman, A. (2010). Beyond the dopamine receptor: novel therapeutic targets for treating schizophrenia. *Dialogues in Clinical Neuroscience*, *12*(3), 359–382.

Fig. 2
Potential pharmacologic interventions to treat schizophrenia:
(i) Enhance NMDA receptor function by increasing synaptic glycine concentrations with an inhibitor of GlyT1 , administering exogenous D-serine, inhibiting D-amino acid oxidase or by treating with an mGluR5 agonist that augments NMDA receptor function.
(ii) Increase the excitability of the parvalbumin-positive GABAergic interneurons with a c_7nicotine receptorpositive modulator.
(iii) Reduce pyramidal neuron excitability with $GABA_A$ receptor-positive modulator.
(iv) Decrease disinhibited pyramidal neuron glutamate release with an mGluR2/3 agonist.
NMDA, N-methyl-D-aspartate; GABA, γ-aminobutyric acid
DA= dopamine; NBM= nucleus basalis of Meynert; mAchR= metabotrophic acetylcholine receptor; Glu= glutamate.

METHODOLOGY



RESULTS & DISCUSSION

Popular Name	ZINC ID	Docking Score (XP Gscore)	XP Glide Energy	Docking Score (SP Gscore)	SP Glide Energy
Carvedilol	ZINC01530580	-8.214	-38.856	-5.532	-36.646
Terfenadine	ZINC03831511	-6.112	-40.876	-6.235	-38.212
Misoprostol	ZINC15848260	-6.38	-33.33	-4.09	-29.172

Popular Name	ZINC ID	CDOCKER ENERGY	CDOCKER INTERACTION ENERGY	LIBDOCK SCORE
Misoprostol	ZINC15848260	159.055	-1.49436	116.595
Methotrexate	ZINC01529323	-42.4168	-63.4914	147.1
Cisapride	ZINC03775140	-3.80182	-32.4241	106.747

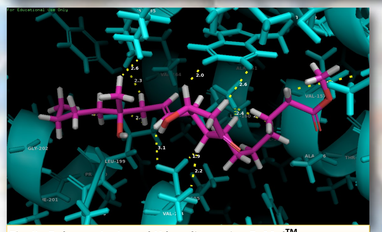


Fig. 3 : Polar contacts and H bonding using PyMol™

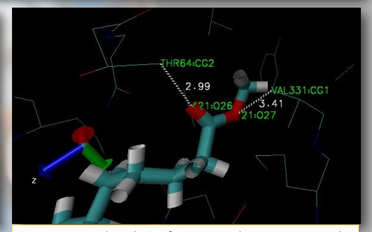


Fig. 4 : Structural Analysis of Interaction between 3PBL and Misoprostol using VMD™

Fig. 5 : Pairwise Alignment of DRD2 and DRD3 receptor proteins for using EMBOSS/NEEDLE

Current objective is to develop drug with lesser side-effects that can be achieved by designing molecules that are more selective for a particular type of dopamine receptor. Each dopamine receptor subtype (D1, D2 & D3) has its own set of pharmacological properties with different affinities of specific drugs. None of the antipsychotic compounds including haloperidol clinically effective against Schizophrenia by targeting dopamine D1 receptors. The atypical neuroleptics have high dissociation constants (between 30 and 100 nM) and bind loosely to D2 receptors thereby showing a less potent antagonism (Seeman, Corbett, et al.). Hence, dopamine D3 receptor is a good therapeutic target as it is consistently found in all post-mortem schizophrenic brain tissues and has comparative binding energies with the antipsychotics (Semba et al.). Developing potential lead molecules may provide a new direction to treatment against the disease.

The two software's that were used **Discovery Studio**[R] and **Maestro**[R]. The former use receptor flexibility while ligand flexibility was incorporated in later.

SIGNIFICANCE OF OUTCOMES:

- The potential lead molecule found from both the software's is **Misoprostol** (Fig. 4 and Fig. 5).
- **Cisapride**, known as a serotonin 5-HT_4 agonist for treatment of Schizophrenia, is another potential lead molecule found from DS. The current analysis suggests that this lead may be further designed and developed as Dopamine D3 antagonist.
- **Methotrexate** is an immunosuppressant and anti-inflammatory drug and it targets Dopamine D2 receptor for treatment of Schizophrenia. As D2 & D3 receptors are almost identical and binding site is conserved, this drug may also bind to D3 receptor (Fig. 5). Recent studies reveal that the early treatment for brain inflammation could prevent Schizophrenia (Irwin, Shoichet et al.).
- **Carvedilol** and **Terfenadine**, known as inhibitors for hERG K^+channels, are potential lead molecules found from Glide XP docking. Studies have shown that they also block dopamine receptors as their major therapeutic mechanism (Heide, Mann et al.) and from this study it may be inferred that they may bind to D3 receptors.

ABBREVIATIONS

GABA = gamma Aminobutyric Acid
NMDA = N- methyl D- Aspartate
hERG = Human Ether a-go-go related gene
DLPFC = Dorsolateral Prefrontal Cortex
DA = Dopamine

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REFERENCES

1. Seeman, P., et al. (1997). "Atypical Neuroleptics Have Low Affinity for Dopamine D2 Receptors or Are Selective for D4 Receptors." Neuropsychopharmacology **16**(2): 93-110.
2. Friesner, R.A.; Murphy, R.B.; Repasky, M.P.; Frye, L.L.; Greenwood, J.R.; Halgren, T.A.; Sanschagrin, P.C.; Mainz, D.T., "Extra Precision Glide: Docking and Scoring Incorporating a Model of Hydrophobic Enclosure for Protein-Ligand Complexes," *J. Med. Chem.*, **2006**, *49*, 6177–6196.