

Comparative Modeling and Electronic Molecular Investigation for Designing Potential Inhibitor for Schizencephaly

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Abstract: Schizencephaly (SCH) is congenital brain malformation whose hallmark is the presence of one or more cleft spanning the pial surface and ependymal of one or both cerebral hemispheres associated with Homeobox protein EMX2. In current study, hybrid approach of comparative modeling and molecular docking were followed. An inhibitor (C12H15N3O2S) scrutinized from PubChem showed maximum binding affinity against EMX2. Docking studies revealed that Asn-66, Phe-71, Ala-72, Glu-73, Leu-108, Phe-109, Ala-110, Ser-111, Gln-112, Gln-113 and Tyr-127 are critical residues for receptor-ligand interaction. Comparative modeling approach coupled with docking energies and drug likeness rules illustrated that selected inhibitor protein kinase are potential inhibitor compound for targeting EMX2. This study suggests that selected inhibitor might be potent molecule based on the binding energy values and drug score. Further analysis of this inhibitor could be helpful for exploring the details of binding sites. Overall, findings of current effort may be helpful in designing the novel therapeutic targets to cure SCH.

Keywords: Schizencephaly, Bioinformatics, Modeling, Docking, EMX2, Computer-aided drug designing.

Introduction

Schizencephaly or “Cleftbrain” (SCH) is an inborn brain malformation and orphan disease whose hallmark is the presence of more or one cleft spanning the ependymal and pial surface of both or one cerebral hemispheres [3, 14, 15]. SCH clefts are present in the perisylvian region and lined poorly with heterotopias, polymicrogyria and laminated grey matter. SCH is also linked with septo-optic dysplasia, hydrocephalus, microcephaly and other malformations in some cases [2, 9, 18].

SCH is characterized by full thickness cleft spanning from the ventricular wall to the surface of pial. This surface lined by cortex abnormality revealing the polymicrogyria pathological

changes. The cleft can be closed with largely separated walls (Type II) or closed with adjacent walls touching (Type I). Mostly, the clefts are present in the parietal or posterior frontal regions of the cortical mantle [2, 4].

SCH is linked with various clinical features of varying severity including motor deficits, epilepsy, mental retardation and developmental delay [1, 2, 8, 9, 18]. The malformation of brain is rare among the general population with an estimation of approximation of 1.54 per 100 000 individuals [8].

SCH can also arise from several environmental factors comprising in utero vascular accidents in monozygotic twins, viral infection, maternal trauma substance abuse and other vascular disruptions [2, 8, 10, 16, 21, 23, 27, 28].

Numerous reports associated the Homeobox Protein (EMX2) transcription factor as a causative gene for SCH [6, 7, 13]. SCH is an orphan disease. Many proteins of cerebral hemisphere may be replaced and absent by cerebro-spinal fluid. Bioinformatics is emerging field of science. This approach merges all disciplines of biological sciences. Bioinformatics has been used for *in silico* analysis of biological queries using statistical and mathematical techniques with employing computational approaches. This revolutionary science is used to analyze different genetically inherited diseases. Present study illustrates the inhibitor against SCH. The experimentally three dimensional structure of EMX2 by X-ray crystallography and NMR is not available yet. The 3D structure of EMX2 was predicted by applying NMR structure of the homeodomain transcription factor Gbx1 from Homo sapiens [PDB ID 2M34]. The employed *in silico* analysis may provide framework for novel drug designing and targeting potential drugs against SCH.

Materials and methods

In current study, structure prediction and molecular docking were performed on Core-I-5 HP workstation. The EMX2 amino acid sequence (252 residues) was retrieved in FASTA format for comparative modeling from Uniprot Knowledge Base having accession number Q04743. The EMX2 sequence subjected to protein-protein blast against Protein Data Bank (PDB) [5] for suitable template. The automated protein modeling program MODELLER 9v14 [12] was used to predict 3D structure of EMX2. The structure was evaluated by MolProbity [26] and poor rotamers and ramachandran outliers were corrected by employing WinCoot [11] tool. The protein kinase inhibitor was searched from PubChem having ID CID 3540. The number of rotatable bonds, H-bond acceptors and H-bond donors were obtained using PubChem. The Osiris Property Explorer was employed to estimate their possible tumorigenic, reproductive or mutagenic risks and to calculate the drug like properties of inhibitor. The geometry optimization of three dimensional structures of inhibitor was performed by Vega ZZ [20] and ChemDraw Ultra [19]. The molecular docking analysis was done and interactions were elucidated by using PatchDock. Results were analyzed by using Chimera 1.6 [17].

Results and discussion

The objective of this study under consideration was based on EMX2 relation with SCH and its bioinformatics analysis for designing, identifying and evaluating inhibitor. The top two optimally aligned templates with total scores, e-values, maximum identity and query coverage were utilized for three dimensional structure prediction. Consequently, effective evaluation results are obtained through 2M34 template having 24% query coverage and 56% identity. The EMX2 3D structure (Fig. 1) was built by using NMR structure of 2M34 as a homologous template.

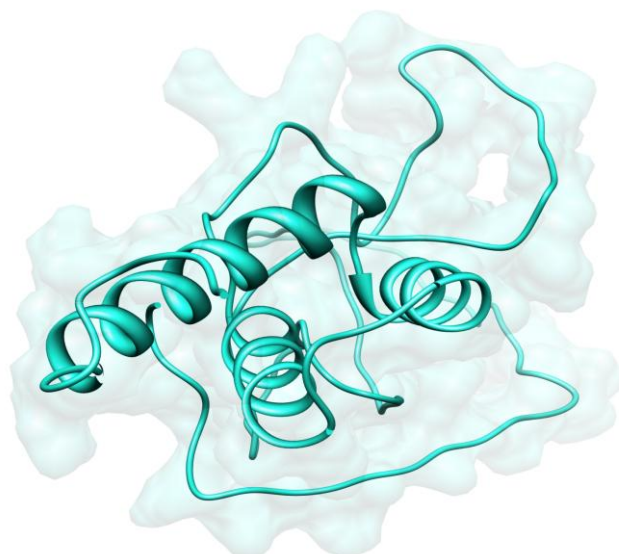


Fig. 1 Three dimensional structure of EMX2

Evaluation tools showed the efficacy and reliability of EMX2 predicted structure. 93.20% residues were detected in favored region of Ramachandran plot. Only 3 residues out of 252 were observed in the outlier region. Subsequently, outliers and all the poor rotamers were corrected to refine the predicted model of EMX2.

Table 1. Inhibitor properties and binding residues

Ligand properties	CID: 3540
Molecular weight	265.3314
Hydrogen bond acceptor	5
Hydrogen bond donor	2
Rotatable bonds	5
ClogP	0.43
Solubility	-1.77
Drug likeness	2.09
Drug score	90%
Global energy	-43.77
Molecular formula	$C_{12}H_{15}N_3O_2S$
Interacting residues	Asn-66, Phe-71, Ala-72, Glu-73, Leu-108, Phe-109, Ala-110, Ser-111, Gln-112, Gln-113, Tyr-127

Patch Dock docking online tool was employed to explore how the ligand binds to the respective protein, best structural information, functionally interacting residues and the binding conformation. The ligand retrieved for EMX2 (Fig. 2) from PubChem is described in Table 1. About 100 protein-ligand complexes were generated by the software and the one with the lowest binding energy was selected. The post docking analysis of protein-ligand docked complex and amino acids found in binding pocket of protein were identified by Chimera 1.4 (Fig. 3). Reliable results are explored in docking analysis of used EMX2 inhibitor. In an endeavor to inspect, It was observed that Asn-66, Phe-71, Ala-72, Glu-73, Leu-108, Phe-109, Ala-110, Ser-111, Gln-112, Gln-113, Tyr-127 residues exhibit good

binding interactions with inhibitor. It was also analyzed and observed that the inhibitor bind at the binding residues between Asn-66 to Tyr-127.

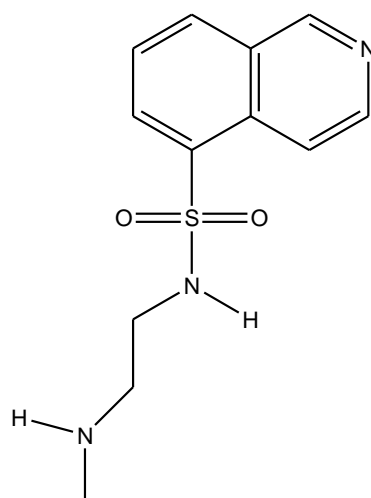


Fig. 2 Two dimensional structure of inhibitor (CID 3540)

In present work, computational approaches like comparative modeling and molecular docking analysis were carried out. Researchers designed novel inhibitors for different diseases by bioinformatics approaches. Tahir et al. [24-25] methodology was utilized to predict the three dimensional structure of protein for reliable comparative modeling analysis that are not generated by X-ray crystallography and NMR techniques. Novel inhibitor was designed for neurological disorder schizophrenia and proposed approach followed for better results in this study [22]. The generated 3D structure of EMX2 showing reliability, especially focusing at binding pocket of protein. The molecular docking analysis was conducted by online docking tool PatchDock. A detailed molecular docking analysis of EMX2 interactions with inhibitor have pointed out the complex having least global energy. The docking results suggests that inhibitor showed least global binding energy, good drug score and drug likeness and inhibitor is proven as a potential compound for SCH by targeting EMX2. Docking analysis also explored that the mutational studies of identified binding residues could be highly effective in further research.

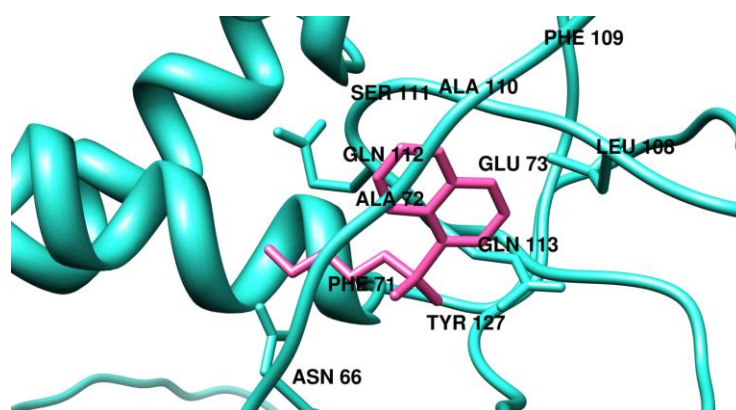


Fig. 3 Interacting residues of SCH protein with inhibitor

The inhibitor in this study has the tendency to be a candidate for SCH treatment by targeting EMX2.

Conclusion

In conclusion, the comparative modeling and molecular docking analysis of inhibitor are efficacious in SCH treatment. Through various computational approaches and docking analysis, it seems to be justified to conclude that inhibitor may be the good option for the treatment of SCH. Further analysis and synthesis of other inhibitors considering these findings can cure the SCH.

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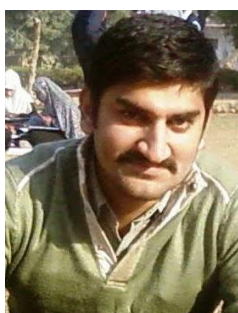
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