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Target Based Computational Drug Repositioning for Astrocytoma

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ABSTRACT
Drug reposition is innovative method as it provides new ways to measure drug kinetics, multiplexed assays and others. In drug repositioning already approved drugs are used due to which time is not wasted on initial clinical trials. Market attainment cost for repositioned drugs is far less than the market attainment cost for new drugs. The secondary indications of most of the approved drugs and the availability of approved drug databases can provide an efficient way of searching safer drugs for new indications. Drug repositioning can provide an alternative method to explore the safe anti-cancer agents. Astrocytoma is the one type of Brain tumor. There are four types of Astrocytoma which arise in different part of the brain. The type IV that is Glioblastoma is very aggressive form of it. Many genes are involved in spreading of this disease but it is normally caused by Tp53. Mutations in the Tp53 gene are identified in about 28% of *de novo* GBM and 65% of secondary , thus indicating that Tp53 abnormalities are common in the progression of disease. The structure for Tp53 protein was obtained from RCSB PDB: RCSB Protein Data Bank. For repositioning Drugs are randomly selected from Drug Bank. Those drugs which have fewer side effects as compared to the drugs for Glioblastoma are selected as a candidate compounds for docking. Patch Dock server was used to perform molecular docking. Then among all selected drugs, some drugs are reposition on the basis of significant binding interactions with target protein TP53.

***Key Words*:** Drug repositioning, Patch Dock server, Molecular docking, Drug Bank, Tp53, Anti-cancer.

INTRODUCTION

Astrocytoma is the type of glyoma which is the tumor that arises from the supportive tissue or glial cell, of the brain. Astrocytomas are originated from astrocytes that are star-shaped cells causing the tumor. According to the degree of abnormality Astrocytomas are graded into I to IV classes. These divisions are Pilocytic Astrocytomas (PA), Diffuse Astrocytoma, Anaplastic Astrocytomas (AA) and Glioblastoma Multiformeor (GBM).

Pilocytic Astrocytomas are generally low paced, non-infiltrative pediatric tumors (Beni-Adani *et al.*, 2000) and rarely fatal. Pilocytic astrocytoma appears most commonly in pre-aged adults and children, with most cases (75%) stipulating in the first 2 half's of life (McComb, 2000; Wallner *et al.*, 1988; Koeller & Rushing, 2004). Diffuse Astrocytoma may be coming up-forth anywhere in the brain, but are mainly indicated in the cerebral hemispheres, the brain part that is responsible for thinking and reasoning (Yung *et al.*, 2014). Anaplastic Astrocytomas (AA) is malignant type of astrocytomas. Alternative methodology for curing were used e.g. surgical treatment, adjuvant radiation therapy etc. (Burdett & Stewart, 2003).

Glioblastoma Multiformeor (GBM) account for about half of all astrocytic tumors. GBM is accountable for death within a period of one year in most of the sufferers (Vescovi, Galli, & Reynolds, 2006), (Markert, 2003). Grade IV astrocytoma is of two types i.e. Primary and secondary tumors , as the primary tumors are very aggressive and the most common form of astrocytoma grade IV (Ohgaki *et al.*, 1996) and the secondary tumors are those which originate as a lower-grade tumor and develop into a grade IV tumor. It is distinguished histopathologically from diffuse lower-grade astrocytomas by the presence of necrosis or micro vascular proliferation (Louis *et al.*, 2007). Among several tumor suppressor genes, tp53 reveal to play a key role in the pathogenesis of many prevalent malignancies (Prives & Manfredi, 2005) including brain cancer. Tp53 has been displayed to exert tumor suppressor activity by impelling apoptosis, initiating the cell cycle (Levine, 1997), stimulating cell differentiation (Almog & Rotter, 1998), and being involved in DNA regeneration pathways (Akyuz *et al.*, 2002).

Mutations in the p53 gene are specified in about 28% of *de novo* GBM and 65% of secondary (Ohgaki, 2005), thus indicating that p53 abnormalities are common in the progression from a low grade lesion to a high grade lesion (Sarkar *et al.*, 2004). Doctors can rely on a number of tools, for preventing cancer. Among the most frequently used medical devices, one of the active small molecules, the drugs. However, for the utilization in clinics, a candidate drug has first to go through series of phases which takes many years and can cost up to a billion dollars (DiMasi, 2001). This process involves many different people, from biologists to law attorneys. Therefore, drug repositioning, the process of finding new utility of existing drugs, has been gaining popularity in recent years. A variety of computational drug repositioning approaches have been established to identify old drug with new tricks (Keiser *et al.*, 2009). Docking many drugs to one protein has been utilized as a sensible methodology. During this method the approved drugs were selected, analyzed and then Docked with protein structure described in figure 1. The results provide insightful clues for meaningful alternative indications.

MATERIALS AND METHODS

The structure for Tp53 protein was obtained from RCSB PDB: RCSB Protein Data Bank. The drugs which are available for glioblastoma in existing market were taken from Therapeutic Target Database (TTD). Their side effects were examined in Drugs.com (http://www.drugs.com).

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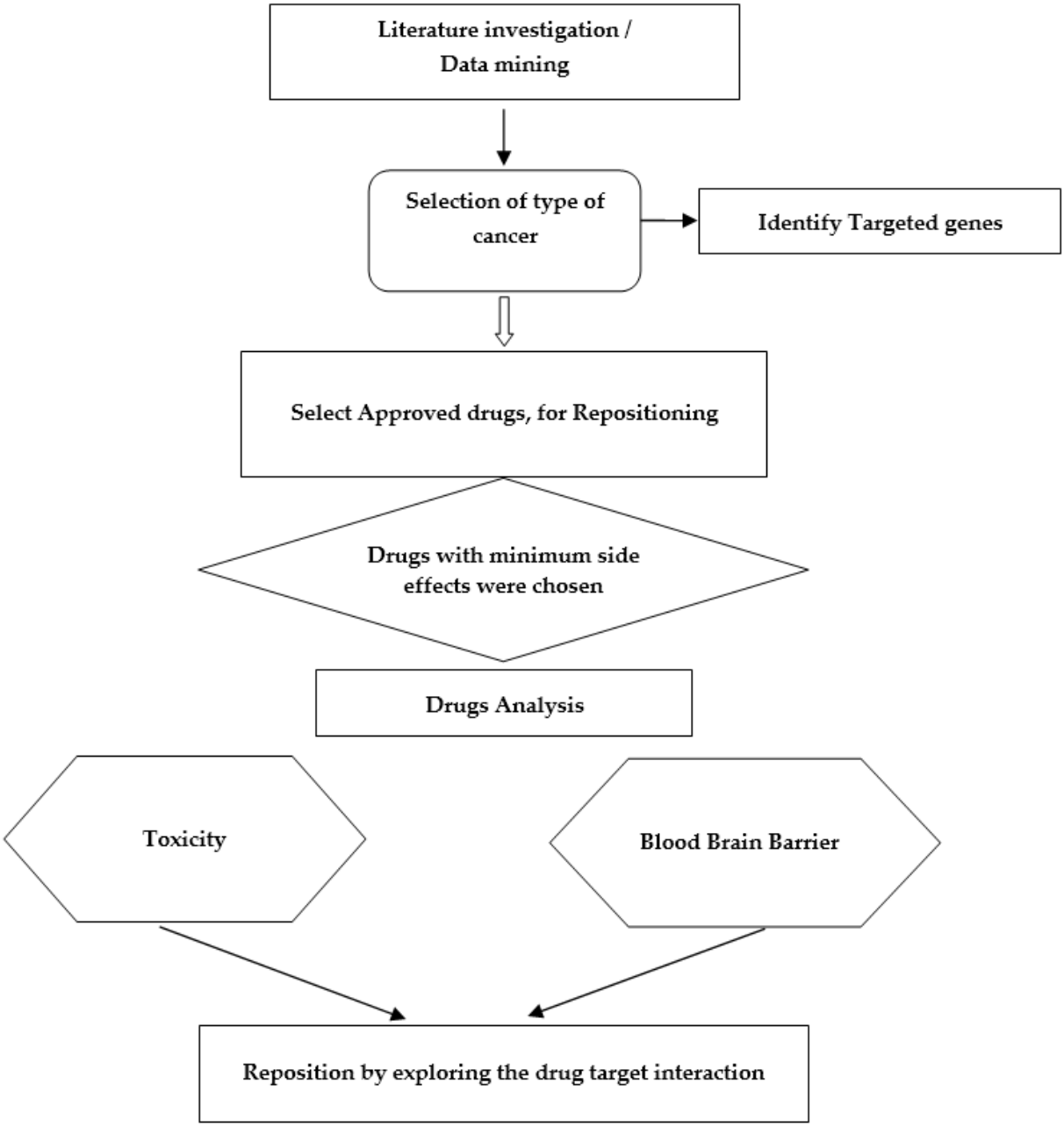


Figure 1: Drug repositioning with structural bioinformatics.

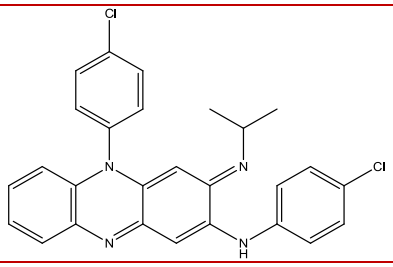
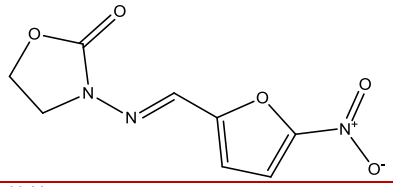
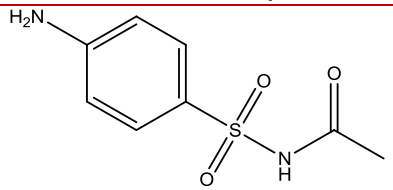
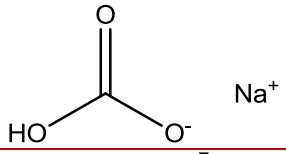
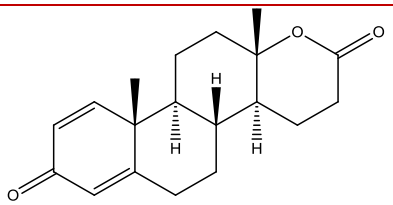
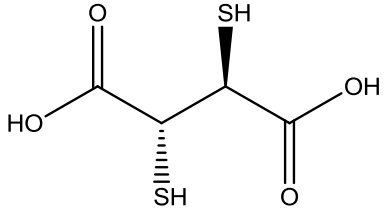
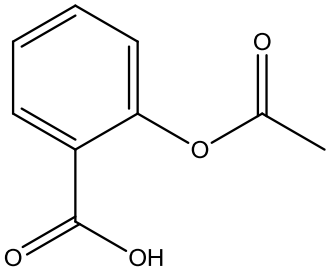
After performing high throughput screening a list of drugs were selected. For repositioning Drugs are randomly gathered from Drug Bank (http://www.drugbank.ca). The undesirable effects of these drugs were compared with drugs available for Astrocytoma, to cure mutation in tp53 and drugs have fewer side reactions compared to the drugs for Glioblastoma are elected as a candidate compounds for docking. The ADMET properties and toxicity ratio for drugs were also calculated. The information related to Blood Brain Barrier (BBB) for different drugs were procured from admet SAR @ LMMD.

The obtained drugs were used for interaction with tp53. Drug target interaction was predicted by using Docking technique. Patch Dock server was used to perform molecular docking. For case study of appointed drugs, some drugs are reposition on the basis of significant binding interactions with target protein. Sulfacetamide, sodium bicarbonate, Testolactone and succimer demonstrated interaction with tp53 protein.

RESULTS AND DISCUSSION

Drug molecules are not solely influence their planned macromolecule targets however additionally to different targets also, drug macromolecule interactions prompt the revelation of latest therapeutic targets and pathways (Munir *et al.*, 2015). Drug repositioning, creates different uses of medicine outside their original indication, has the potential

Table 1: Drugs characteristics.

Drugs	Structure	BBB	Toxicity class
Clofazimine		+	V
Furazolidone		+	I
Sulfacetamide		+	VI
Sodium Bicarbonate		+	III
Testolactone		+	III
Succimer		+	V
Acetylsalicylic acid		+	III

to drastically offset drug development prices (Daminelli *et al.*, 2012).Given the exorbitant and tedious procedure and high wearing down rates in drug revelation and advancement, drug repositioning is considered as a reasonable system both to renew the drying out drug pipelines and to surmount the development crevice (Wu *et al.*, 2013). The expenses for putting up repositioned drugs for sale to the public are ~60% lower than the improvement of a novel drugs, which costs about one billion US dollars (Haupt &

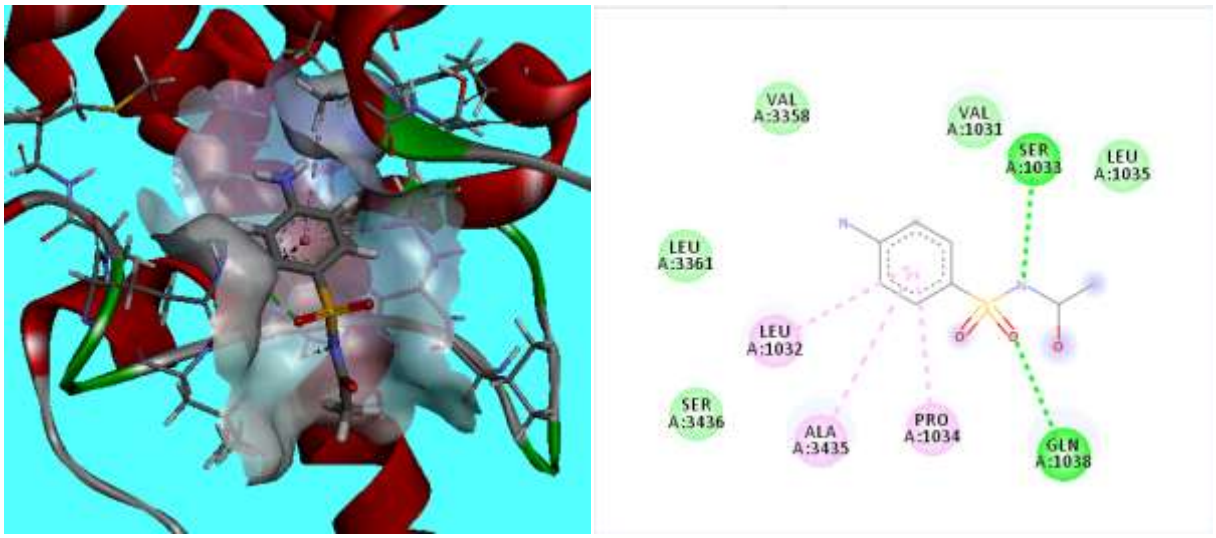


Figure 2: 3D and 2D representation of Sulfacetamide docked complex using Discovery Studio.

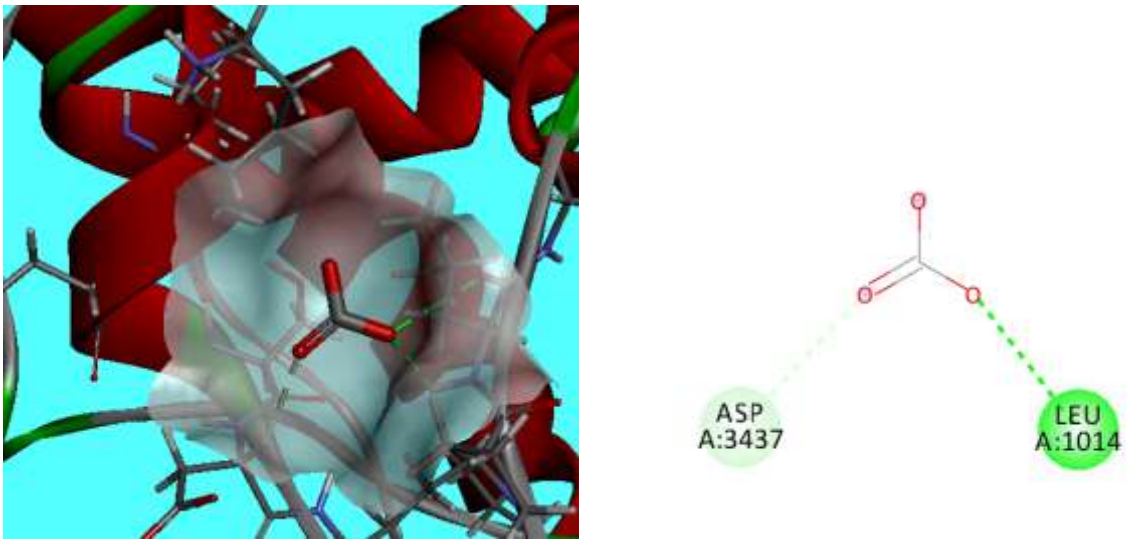


Figure 3: 3D and 2D representation of Sodium bicarbonate docked complex using Discovery Studio.

Schroeder, 2011). One of the benefit of reexamining established drugs is that they have already been endorsed and, subsequently, they can possibly be re-marketed in a quicker and more cost-effective route by skipping Phase I clinical trial (Iorio *et al.*, 2013).

Target-based drug-repositioning methods were performed that comprises high-throughput and/or high-content screening (HTS/HCS) of drugs for a protein of interest.Twenty six drugs were randomly obtained from Drug Bank, Therapeutic Target Database and STITICH ("search tool for interaction of chemicals"). Some of these Drugs have been used for infectious diseases, many of them used as a cancerous medicines and others for varied purposes e.g. for malaria, sepsis and for hypertension etc.

Recorded adverse drug reactions have been acquired from Drugs.com and SIDER4.1. On the basis of available information, drugs with fewer side effects were selected from twenty six drugs. It was noted that drugs Bleomicin, Clofazimine, Furazolidone, Idoxurine, Leucovorine, Sulfacetamide, Sodiumbicarbonate, Testolactone, Succimer, Natamycin and Acetylsalicylic acid have less adverse reactions.

The main issue in drug transport to brain is the existence of the Blood Brain Barrier (BBB). Drugs that are effective against diseases in the Central Nervous System must penetrate the BBB. The BBB is a unique membranous barrier that shields the brain from the circulating blood. The information related to BBB for different drugs were obtained from admet SAR @ LMMD**.** Among twenty six drugs, only six drugs show positivity for the acquired result. The BBB and ADMET property of these six drugs are shown in table 1.

Those six drugs then docked with tp53. Among six drugs four drugs Sulfacetamide, Sodium bicarbonate, Testolactone and Succimer were given appropriate results. Ten conformations were obtained for each drug from Patch Dock Server. In all conformations the best were chosen. 3D and 2D of drug receptor complex of each molecule are described in figures 2, 3, 4 and 5, respectively. In 3D representation, hydrophobic surface is generated which

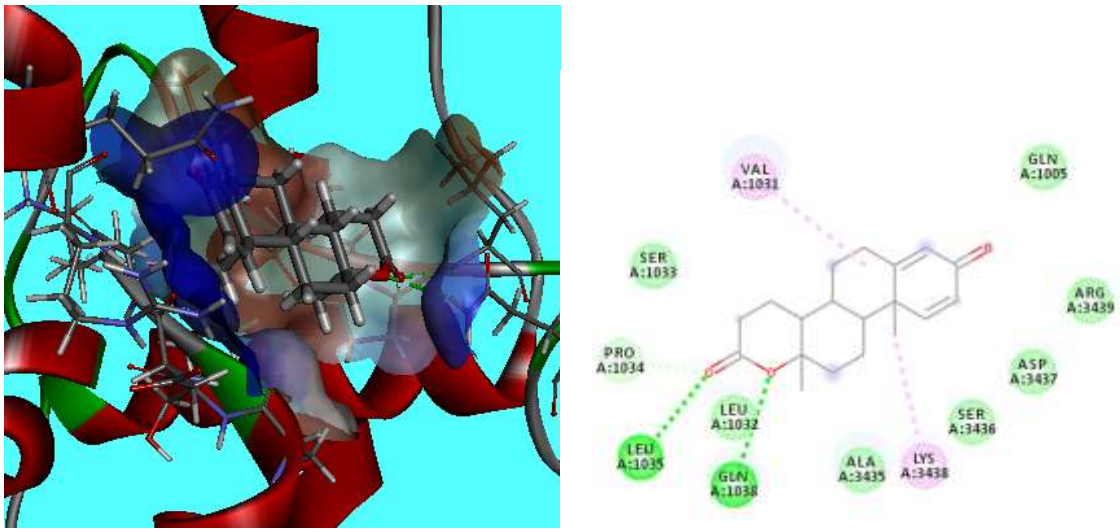


Figure 4: 3D and 2D representation of Testolactone docked comples using Discovery Studio.

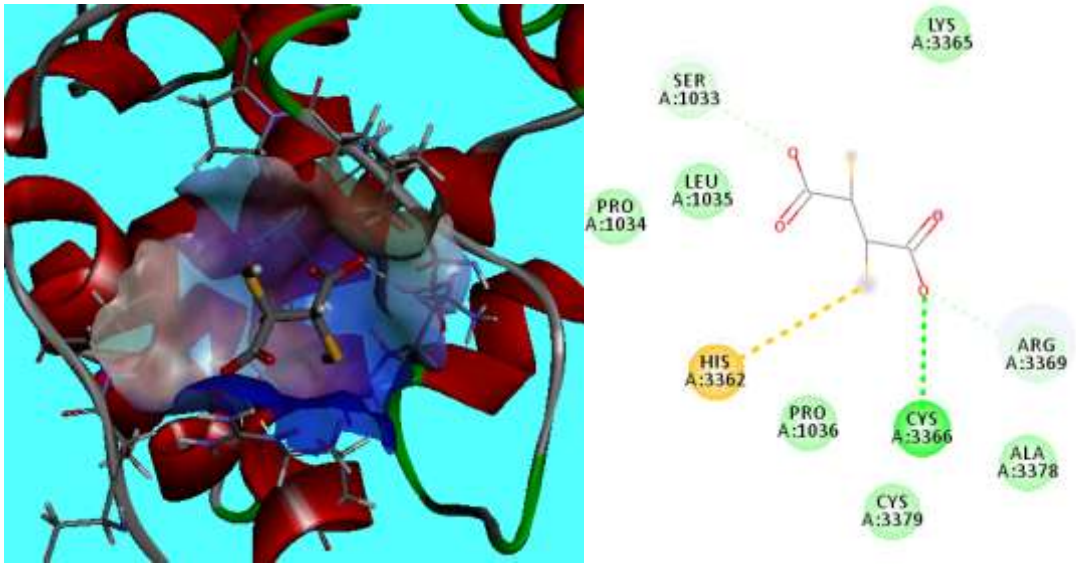


Figure 5: 3D and 2D representation of succimer docked complex using Discovery Studio.

shows the favorable binding pockets, and the ligand interaction in this pocket. In 2D representation, the different color circles represent the receptor different residues and their features. Dotted lines indicate interactions and in the hub, drug molecule is indicated.

By using Discovery Studio®, the interaction of the active conformation of drug and the target protein have been identified. The saved conformation for drug receptor complex of each molecule was subjected to detailed interaction analysis. Type of interaction, residues involved in interaction and the distance has been mentioned for each bond.

Sulfacetamide made two hydrogen bonds with target protein and residues involved in hydrogen bonding are SER1033 and GLN 1038 which form hydrogen bonding with N and O of molecule, respectively. Vander Waals and Pi-Alkyl interactions were also observed. The distance of all bonds is greater than 2.

Sodium Bicarbonate made two hydrogen bonds with target and residue involved in hydrogen bonding are ASP3437 and LEU1014 which form hydrogen bonding with O and O of molecule, respectively. The distance of all bonds is greater than 2.

Testolactone made three hydrogen bonds with target protein and residues involved in hydrogen bonding are LEU1035, PRO1034 and GLN 1038 which form hydrogen bonding with O and O of molecule, respectively. Vander Waals interactions were also observed. The distance of all bonds is greater than 2.

Succimer made three hydrogen bonds with target protein and residues involved in hydrogen bonding are CYS3366, ARG3369 and SER1033. Vander Waals and Pi-Sulfur interactions were also observed. The distance of all bonds is greater than 2.

CONCLUSION AND FUTURE DIRECTION

In our research work we took TP53 and performed its interaction with Sulfacetamide, Sodium bicarbonate, Testolactone, succimer, Clofazimine and furazolidone. All These drugs have fewer side effects. Sulfacetamide, Sodium bicarbonate, Testolactone and succimer demonstrated good interaction with TP53 protein. On the basis of this outcome we suggest that these drugs can be reposition to cure glyoblastoma/Astrocytoma.

This work will lead to construct more complete target-drug interaction networks. Extension of interaction networks improves the process of network based drug repositioning. The outcome of this work is further used as clinical trials. For Clofazimine, furazolidone, sulfacetamide, sodiumbicarbonate, Testolactone and succimer, other predicted targets were also obtained. The interactions of these drugs with other target will open new areas to drug repositioning.

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