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Repurposing of Modified Alpidem and Propoxyphene to Cure AURKA, BCAS1, GNAS and MLH1 Gene Mutations in Colorectal Cancer

Anum Munir[1-3]*, Shumaila Azam[1-3], Sartaj Ali[3], Azhar Mehmood[1,3], Abbas Hussain Shah[5], M Saad Khan[2], Rabbiah Manzoor[2,4], Maria Sana[2], Shakeel Ahmed Mufti[2] and Sahar Fazal[2]

[1]*Bioinformatics International Research Club, Abbottabad, Pakistan*
[2]*Department of Bioinformatics and Biosciences, Capital University of Science and Technology, Islamabad, Pakistan*
[3]*Department of Bioinformatics, Government Post Graduate College Mandian, Abbottabad, Pakistan*
[4]*Department of Medical Sciences, Wah Medical College, Wah Cantt, Pakistan*
[5]*Department of Botany, Government Post Graduate College Mansehra, Pakistan*

Abstract

Background: Colorectal cancer is a varied illness with an expected heritability of 25–30%. Many CRC disorders occur because of solid family history, a high penetrance of the infection, and developing various tumors at an early age. A few novel genes are recognized that shows associations with CRC, such as AURKA, BCAS1, GNAS and MLH1.

Material and methods: In this research work FDA rejected Alpidem and Propoxyphene were selected. Drugs were changed on the basis of side effects; modified drugs were docked with AURKA, BCAS1, GNAS and MLH1 proteins and QSAR analysis was performed.

Results: Docked and QSAR results demonstrated the better interaction of both modified Alpidem and Propoxyphene along with proteins of CRC causing genes. The toxicity value and side-effects of modified Alpidem and modified Propoxyphene are less than original drugs.

Conclusion: The fewer side effects and docking results of both modified Alpidem and Propoxyphene suggest that both the drugs can be used to cure mutations of genes in colorectal cancer as both modified drugs have fewer side-effects and toxicity, as compared to original drugs, both drugs have demonstrated greater interactions with the amino acid residues lying in the pockets of mutated proteins that demonstrates their stability and soundness.

Keywords: Alpidem; CRC; Docking; Propoxyphene; QSAR; Repurposing; Side-effects; Toxicity

Introduction

Colorectal cancer (CRC) is a varied illness with an expected heritability of 25–30%. Around 5–10% of CRC cases are occurs because of germ-line transformations in genes, many CRC disorders occur because of solid family history, a high penetrance of the infection, and developing various tumors at an early age, while 10% of the heritability of CRC might be shown by a developing large number of low-penetrant hazard variables [1]. In spite of advances in screening procedures, diagnosis and treatment, colorectal malignancy are the third most common cancer and the fourth driving reason for the tumor demise around the world. Neurotic arranging is the only prognostic characterization utilized as a part of clinical practice to choose patients for adjuvant chemotherapy [2].

The genomic occasions representing gain and loss of chromosomes, uni-parental disomy, loss of heterozygosity, and so on are understood to have a solid connection with CRC. A few novel genes are recognized that shows associations with CRC, for example, Aurora Kinase (AURKA), Breast Carcinoma Amplified Sequence 1 (BCAS1), guanine nucleotide antisense arrangement (GNAS), Mutl homolog 1 (MLH1) genes and several others. The recognizable proof of an expanding number of tumor genes is basically opening up new techniques in CRC genetics [3,4].

AURKA is a cell cycle-directed kinase require in the spindle formation and chromosomal isolation, AURKA is situated on chromosome 20q, a genomic region that is as often as possible enhanced in CRC, that has been connected with adenoma-to-carcinoma movement and is a pointer of poor prognosis. AURKA overexpression drives harmful conduct and shows that AURKA might be a prognostic biomarker for CRC [5]. BCAS1 locates in a region at 20q13 which is enhanced with an assortment of different types of tumor and connected with more forceful tumor phenotypes. Significant down-regulations in expressions of BCAS1 gene result in CRC [6].

GNAS is a known Oncogene. GNAS codon 201 transformations are especially common. About 51% of GNAS mutant cases additionally bear mutations in KRAS. GNAS transformations in colon cancers may likewise regularly be joined by mutations in KRAS and/or BRAF [7]. Germ-line mutations in one of the DNA-mismatch repair (MMR) genes MSH2 or MLH1 are distinguished in colorectal tumor. Basically, every single colorectal tumor from MSH2 or MLH1 change transporters results in microsatellite instability, which reflects the deformity in DNA-mismatch repair, and removal of expressions of the MMR gene [8].

The aim of this research work was to repurpose several drugs for the treatment of AURKA, BCAS1, GNAS and MLH1 gene mutations

***Corresponding author:** Anum Munir, Bioinformatics International Research Club, Abbottabad, Pakistan, Tel: +923348958178; E-mail: anummunir786@yahoo.com

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in colorectal cancer. Repurposing commonly alludes to concentrating on medications that are affirmed to treat one infection or condition, to check whether they are protected and successful for treating different illnesses. Numerous drugs endorsed for different uses, now have been tried in human. Because repurposing based upon past innovative work endeavors, new candidate drugs could be prepared for clinical trials rapidly, speeding the survey by the Food and Drug Administration and, if affirmed, they are integrated into human health care services [9,10].

Material and Methods

Information about the AURKA, BCAS1, GNAS and MLH1 genes, associated with colorectal cancer was obtained through literature [3]. Mutated protein ids of AURKA, BCAS1, GNAS and MLH1 proteins were downloaded through Research collaboratory for structural Bioinformatics (RCSB) protein database (PDB). RCSB PDB is mainly a database that comprises X-ray crystallographic and nuclear magnetic resonant three-dimensional structures of nucleic acids and proteins. It is available at https://www.rcsb.org [11]. The 3D structures of proteins are shown in Figure 1.

Chemical structures of Alpidem with chemical name 2-[6-Chloro-2-(4-chlorophenyl) imidazole [1, 2-a] pyridin-3-yl]–N, N-dipropyl acetamide and Propoxyphene with chemical name (2R, 3S)-4-(Dimethyl amino)-3-methyl-1, 2-diphenyl-2-butanyl propionate, were obtained through PubChem database. PubChem is an open database of the compound structures and organic test results, available at http://pubchem.ncbi.nlm.nih.gov [12]. The chemical structures of Alpidem and Propoxyphene obtained through PubChem are shown in Figure 2.

Alpidem has withdrawn from the market worldwide due to increased rate of hepatotoxicity, while propoxyphene has withdrawn worldwide due to increased rate of heart attack and stroke. Quantitative structural activity relationships (QSAR) were determined, both

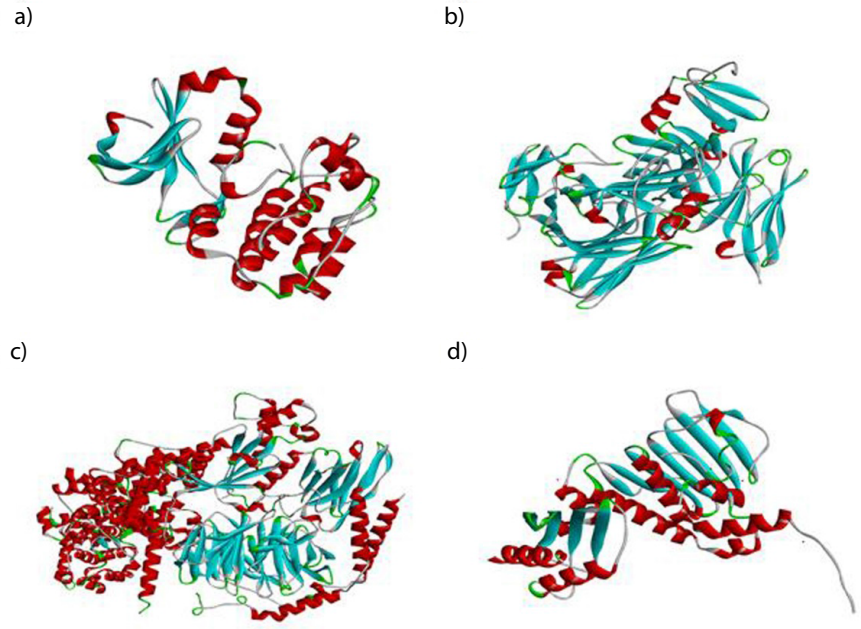

Figure 1: Mutated protein ids of AURKA, BCAS1, GNAS and MLH1 genes, a) 3D structure of mutated protein of AURKA gene b) mutated protein of BCAS1 gene c) mutated protein 3D structure of GNAS gene and d) mutated protein 3D structure of MLH1 gene.

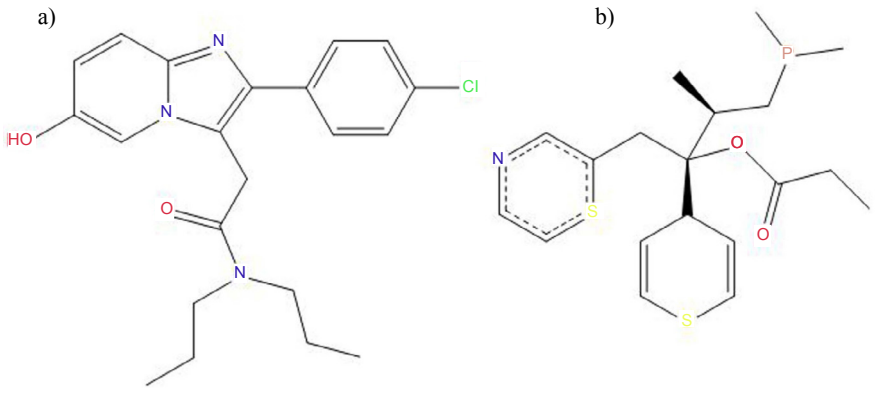

Figure 2: Chemical structures of original Alpidem and Propoxyphene downloaded through Pubchem database, a) Alpidem b) propoxyphene.

Alpidem and Propoxyphene were checked for their toxicity values by the use of Protox server. Protox is a webserver used for the prediction of oral toxicity values of small drug compounds in the rodents. It is available at https://www.tox.charite.de/ [13]. Probability of side effects and genotoxicity hazards of both the drugs were analyzed through ACD Labs server, available at https://ilab.acdlabs.com/. The ACD Labs server is usually used for the In Silico Prediction of Physicochemical, ADME and Toxicity Properties of drug candidates. It allows scientists to understand QSAR relationships and to explain the behavior of novel drug candidates.

After the calculation of side effects ratios, both the Alpidem and Propoxyphene were modified to lessen the side effects and new compounds were designed in discovery studio software with reduced side effects and toxicity. After modification, the new chemical structures of both the Alpidem and Propoxyphene were checked for toxicity and side effects from the same servers that were used before, on the basis of better results both the Alpidem and Propoxyphene were docked with the downloaded 3D structure of mutated proteins through the patch dock server [14]. On the basis of results, it is suggested that both the modified Alpidem and Propoxyphene can be used to treat mutations of colorectal cancer-causing genes.

Results

It was observed that, before modifications in the chemical structures of Alpidem and Propoxyphene, the toxicity value of Alpidem in lethal doses (LD_{50}) was 200 mg/ kg, which was not reliable and considered to be hazardous. The Electrophilic vinyl and carbonyl halogenides (excluding fluorides) present in Alpidem induce DNA damage by various mechanisms. The toxicity value of Propoxyphene in LD_{50} was 84 mg/kg, which was quite toxic and lethal and both the compounds were lying in the toxicity category of classes. Toxic doses are frequently given as LD50 values in mg/kg of the body weight. The LD50 is the average deadly dose, implies the dose at which 50% of test subjects die upon contact to a compound. The modified Alpidem and Propoxyphene are shown in Figure 3.

The presence of a Cl atom along with the aromatic ring was a cause of genotoxicity, therefore; the Cl atom was replaced with O atom, which results in the reduction of toxicity. Similarly to make the propoxyphene non toxic in nature, the P atom and two S atoms were added in the aromatic rings. There are several classes of toxicity according to the globally harmonized system of classification of labelling of chemicals (GHS), the compounds lying in the class 1 and 2 are considered to be fatal, the compounds present in class 3 are toxic in nature whereas the compounds lying in the class 4-6 are non toxic in nature. After modification, the toxicity value of the Alpidem lies in LD_{50} 1050 mg/kg and that of modified Propoxyphene lies in the LD_{50} 5000 mg/kg. Both the compounds were lying in the nontoxic classes. In the screening process of drug molecules, the determination of LD_{50} is crucial to determine the toxicity level of compounds, the greater the LD_{50} values safer is the drug compound [15]. The probability of side effects of modified Alpidem obtained through ACD Labs is shown in Table 1.

Table 1 demonstrated that the modified Alpidem has fewer side effects in several organs of the body as compared to original Alpidem so, it is less toxic in nature, it will show better results in the treatment of colorectal cancer, being non toxic in nature. The probability of side effects of modified Propoxyphene obtained through ACD Labs is shown in Table 2.

Table 2 demonstrated that the modified Propoxyphene has much

Probability of side effects of modified Alpidem		Probability of side effects of Original Alpidem	
Organs	**Ratio**	**Organs**	**Ratio**
Blood	0.71	Blood	0.86
Cardio-vascular system	0.69	Cardio-vascular system	0.83
Gastro-intestinal System	0.79	Gastro-intestinal System	0.99
Kidneys	0.32	Kidneys	0.56
Liver	0.28	Liver	0.42
Lungs	0.57	Lungs	0.84

Table 1: Comparison between the probability ratios of side effects of modified Alpidem and original Alpidem.

Probability of side effects of modified Propoxyphene		Probability of side effects of Original Propoxyphene	
Organs	**Ratio**	**Organs**	**Ratio**
Blood	0.04	Blood	0.6
Cardio-vascular system	0.47	Cardio-vascular system	0.87
Gastro-intestinal System	0.22	Gastro-intestinal System	0.92
Kidneys	0.03	Kidneys	0.65
Liver	0.08	Liver	0.32
Lungs	0.09	Lungs	0.87

Table 2: Comparison between the probability ratios of side effects of modified Propoxyphene and original Propoxyphene.

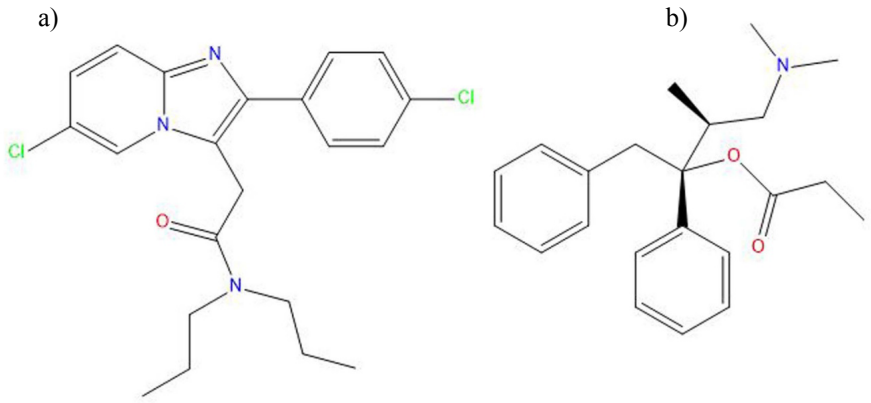

Figure 3: Modified Alpidem and Propoxyphene a) Modified Alpidem in which one Cl from the ring is replaced by O to make it less toxic in nature b) Modified Propoxyphene in which one P and two S atoms were added by the replacement of C atom in the structure that made the structure less toxic.

fewer side effects in several organs of the body as compared to original Propoxyphene so, it is non-toxic in nature, it will show better results in the treatment of colorectal cancer. Usually; drug revelation projects based the scanning for lead structures. However; Virtual screening and molecular docking constitutes extraordinary options so as to discover hit compounds. Novel disease targets can likewise be characterized and utilized together with molecular docking tools used in drug discovery programs [16]. The docked results of modified Alpidem and Propoxyphene with AURKA, BCAS1, GNAS and MLH1 proteins are shown in Figures 4 and 5.

The interacting amino acid residues in each docked complex of modified Alpidem and Prpoxyphene are shown in Figures 6 and 7.

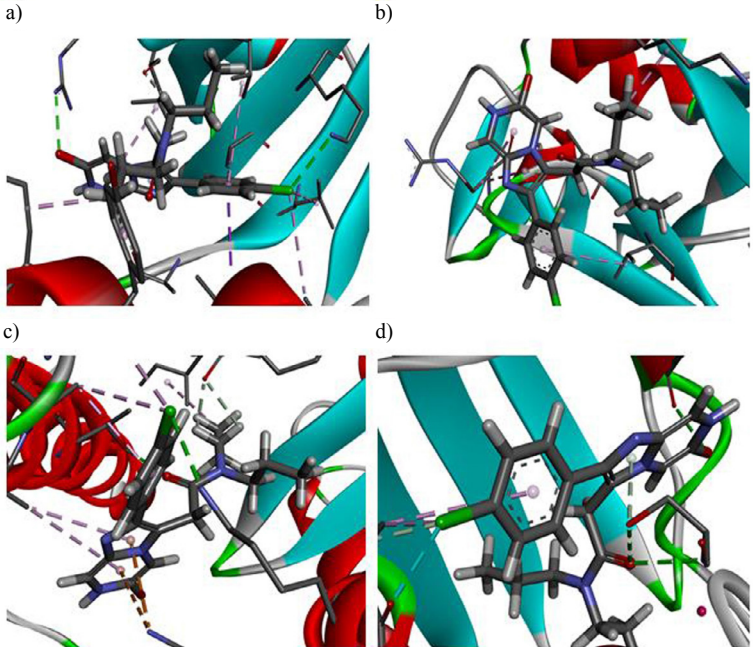

Figure 4: Docked complexes of modified Alpidem along with AURKA, BCAS1, GNAS and MLH1 genes a) Docking result of Modified Alpidem and mutated AURKA protein b) Docking result of Modified Alpidem and mutated BCAS1 protein c) Docking result of Modified Alpidem and mutated GNAS protein d) Docking result of Modified Alpidem and mutated MLH1 protein.

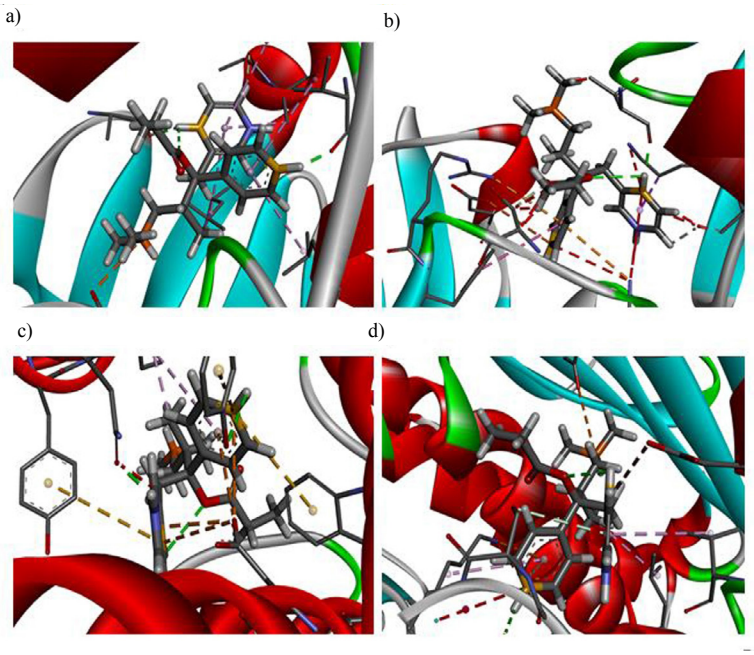

Figure 5: Docked complexes of modified Propoxyphene along with AURKA, BCAS1, GNAS and MLH1 genes a) Docking result of Modified Propoxyphene and mutated AURKA protein b) Docking result of Modified Propoxyphene and mutated BCAS1 protein c) Docking result of Modified Propoxyphene and mutated GNAS protein d) Docking result of Modified Propoxyphene and mutated MLH1 protein.

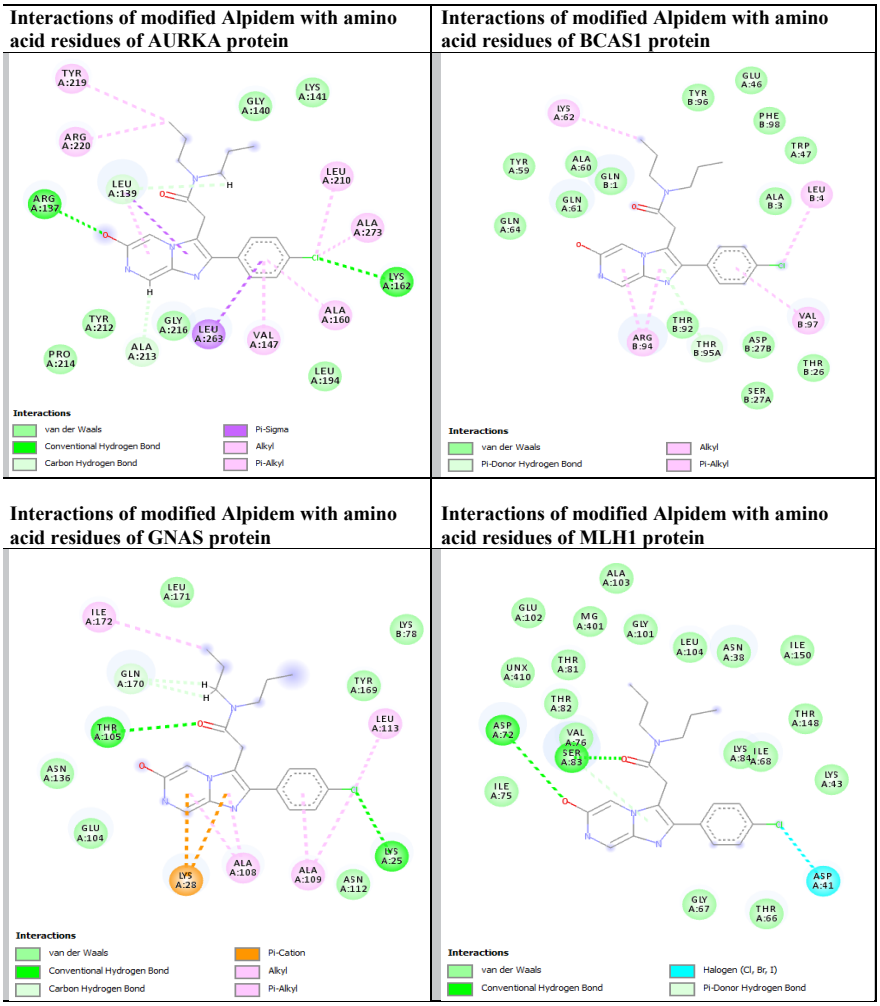

Figure 6: Interactions of modified Alpidem with several amino acid residues, within the binding pockets of AURKA, BCAS1, GNAS and MLH1 proteins.

The fewer side effects and docking results of both modified Alpidem and Propoxyphene suggests that both the drugs can be used to cure mutations of genes in colorectal cancer as both modified drugs have fewer side effects and toxicity values. As compared to original drugs, both drugs demonstrated greater interactions with the amino acid residues lying in the pockets of mutated proteins that demonstrates their stability and soundness. The greater the interactions, the more better are the compounds as a drug candidate.

Discussion

Cancer treatment fundamentally; focuses on drug repurposing systems for two reasons. As a matter of first importance, repurposing of affirming and surrendered drugs for cancer represents a chance to quickly progress to patients promising medication treatments by benefiting from existing information and experience. The same procedure remains constant for abandoned or "retired" medications, whose development was suspended due to non-safety–related reasons [17,18]. In this research project, the same approach is used to repurpose abandoned drugs by making some modification in compounds to make the drug compound useful in the treatment of colorectal cancer.

The FDA likewise endorsed new biologic CRC medicines in 2004. These new biologic operators—bevacizumab, cetuximab, and panitumumab—are regularly alluded to as monoclonal antibodies. In fact; these antibodies encourage immune responses against quickly multiplying cancer cells [19]. Drug repurposing has several advantages and the endeavors have been driven by a few imperative components including; the access to expanding measures of experimental information, better comprehension of compound poly pharmacology and biological information mining. *In silico* strategies, either receptor-based or ligand-based, have been adapted to drug repurposing ventures. Recently repurposing approaches are utilized for large scale testing of drug actions on side effect targets [20,21].

Here the approach is used to measure side effects probability of drugs on several organs of the body and on the basis of side effects both the Alpidem and Propoxyphene were modified and then docked with proteins to determine their suitability as drug candidates. Alpidem was previously used for the treatment of anxiety while the propoxyphene was used as the pain reliever. Several medicines used in the treatment of CRC produce severe side effects such as Bevacizumab and $FLFOX_4$ causes cardiac ischemia, hypertension, vomiting, CNS bleeding leads to hemorrhage, bowel perforation [22]. Cetuximab; an IgG monoclonal antibody is used in the treatment of EGFR mutations in colorectal cancer it causes rash involving the face and trunk, hypersensitivity, edema, fatigue, anorexia, confusion, etc. [23].

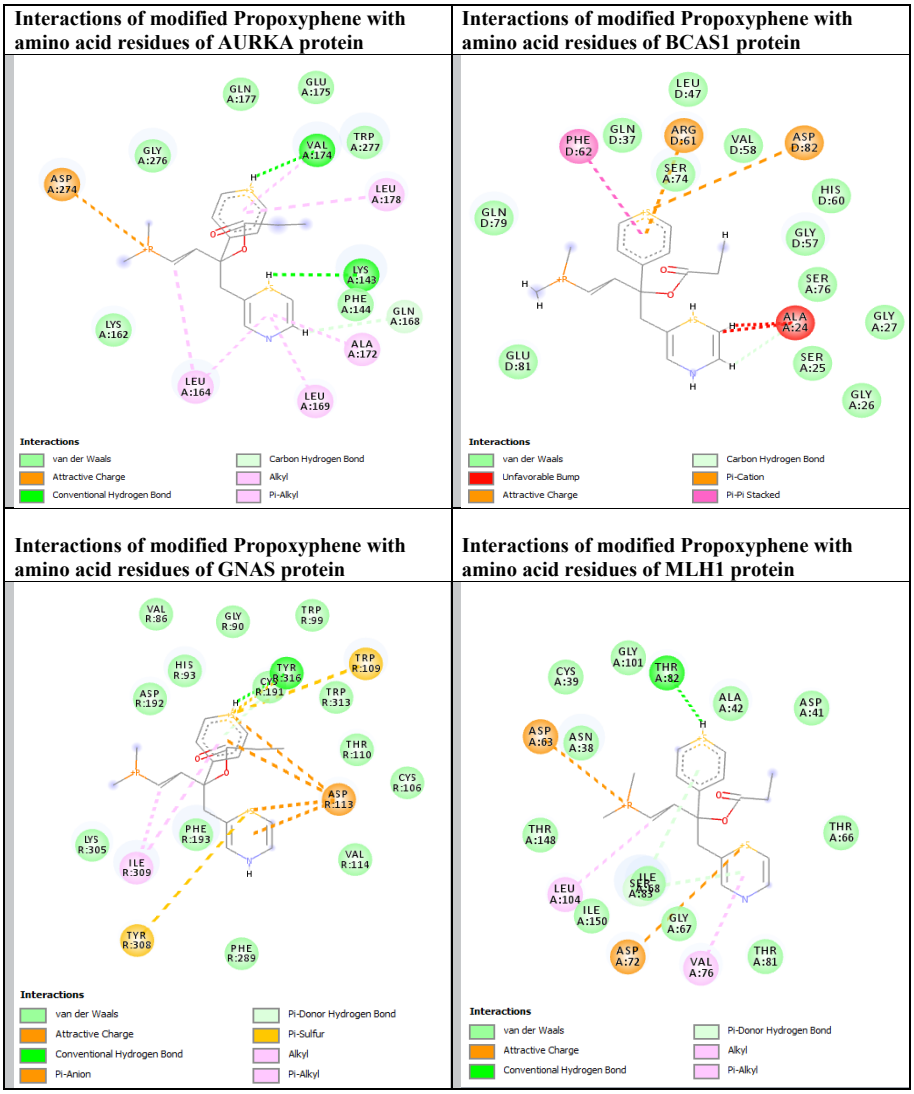

Figure 7: Interactions of modified Propoxyphene with several amino acid residues, within the binding pockets of AURKA, BCAS1, GNAS and MLH1 proteins.

Oxaliplatin, Fluorouracil, and Leucovorin cause anemia, fever, Vomiting, thrombocytopenia, nausea, diarrhea and neutropenia when used in the treatment of colorectal cancer [24-26]. The repurposing of both modified Alpidem and Propoxyphene will be fruitful to cure the effects of colorectal cancer, as both these drugs have fewer signs than the drugs commonly available as better treatment of cancer.

In silico techniques, both the receptor-based or ligand-based, have been connected to tranquilize repurposing ventures. Keiser et al. anticipated and approved 23 novel medication target interactions utilizing two-dimensional compound likeness approach [27]. Nowadays, this approach is utilized for a substantial scale prediction and testing of medication side effects on the targets [28]. Ligand-based quantitative structure-activity relationship models have been utilized by Yang et al. to foresee signs for 145 sicknesses utilizing the reactions as features [29]. With structure-based systems, inverse docking can additionally be utilized for drug repurposing [30,31]. Therefore; in this project repurposing approach was used on the basis of QSAR properties.

Conclusion

The probability of side effects of modified Alpidem and Propoxyphene is less than original Alpidem and Propoxyphene. In docked complexes and QSAR analysis, both drugs have demonstrated greater interactions with the amino acid residues lying in the pockets of mutated proteins that demonstrates their stability and soundness. The fewer side effects and docking results of both modified Alpidem and Propoxyphene suggest that both the drugs can be used to cure mutations of genes in colorectal cancer as both modified drugs have less side effects and toxicity as compared to original drugs.

In future, this research work can be used as a part of clinical trials to check its competence and social importance.

Acknowledgement

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Conflict of Interest

This research work is unique and has not been submitted to any other journal. None of the authors have any challenged conflicts of interest.

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