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POTENTIAL EFFECTIVENESS OF VITRAKVI (LAROTRECTINIB) FOR TREATING TYPES OF SOLID TUMORS CARRYING NTRK GENES AND THE IMPACT OF TRKC MUTATIONS

Eficacia de *vitrakvi* (larotrectinib) para el tratamiento de tumores sólidos portadores de genes *ntrk* y el impacto de las mutaciones *trkc*

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Abstract

Vitrakvi is a cancer treatment that targets solid tumors with NTRK gene fusion. NTRKs are rare genetic effects that can arise in tumors from several organs, including the lungs, thyroid glands, and intestines. This study sought to identify the position at which Vitrakvi binds to tropomyosin receptor kinases (TRKs) as well as the effects of TRKC mutations on the fusion site. Materials and PubChem were used to obtain the chemical structure of Vitrakvi. The 3D structure of TRKs was derived from the PDB. Docking was implemented via AutoDock Vina. Docking, visualization, and sequence reconstruction were completed via the PyMol, BIOVIA, and PyRx programs. The fusion of Vitrakvi with TRKA and TRKB is altered if they are combined with their respective stimulators (BDGF and NT-4/5). TRKC combines with Vitrakvi in the same chain in which it is coupled to its stimulator (NT-3), but the fusion site shifts away from the triple mutation site. Even though clinical trials of TRK inhibitors have just started, there is reason to be hopeful for people with TRK mutations and the field of molecularly targeted medicines.

Keywords: Vitrakvi, TRK, Solid cancer, NT-3, Mutation, Docking.

Resumen

Vitrakvi es un tratamiento oncológico dirigido a tumores sólidos que presentan fusiones génicas del gen NTRK. Las alteraciones en los genes NTRK constituyen efectos genéticos poco comunes que pueden manifestarse en tumores originados en diversos órganos, incluidos los pulmones, las glándulas tiroideas y el intestino. El objetivo de este estudio fue identificar el sitio de unión de Vitrakvi a las quinasas del receptor de tropomiosina (TRK), así como evaluar los efectos de las mutaciones en TRKC sobre el sitio de fusión. Para obtener la estructura química de Vitrakvi se utilizaron recursos como PubChem, y la estructura tridimensional de las TRK se obtuvo del Protein Data Bank (PDB). El acoplamiento molecular (docking) se llevó a cabo mediante el programa AutoDock Vina. Las simulaciones de acoplamiento, visualización y reconstrucción de las secuencias se realizaron utilizando los programas PyMol, BIOVIA y PyRx. La fusión de Vitrakvi con TRKA y TRKB se ve modificada cuando estas quinasas se combinan con sus respectivos estimuladores (BDGF y NT-4/5). En el caso de TRKC, la unión con Vitrakvi ocurre en la misma cadena que se acopla a su estimulador (NT-3); sin embargo, el sitio de fusión se desplaza respecto al sitio de la triple mutación. Aunque los ensayos clínicos con inhibidores de TRK se encuentran en fases iniciales, existen fundamentos prometedores para la esperanza tanto en pacientes con mutaciones en TRK como en el campo de las terapias dirigidas molecularmente.

Palabras clave: Vitrakvi, TRK, Cáncer sólido, NT-3, Mutación, Docking.

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1 Introduction

Vitrakvi, also known as larotrectinib, is a tyrosine kinase inhibitor that can be used to treat adults and children who have solid tumors that have one of the following characteristics: a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without acquired surgical resection that is likely to result in severe morbidity, metastatic resistance mutation, no satisfactory alternative therapies, or post treatment progression. The FDA authorized Vitrakvi on November 26, 2018. The total response rate and length of response data were used as the primary justification for the expedited approval of larotrectinib ($C_{21}H_{22}F_6NO_2$) (Loxo Oncology, 2018; US Food and Drug Administration, 2018).

Because carcinomas of tropomyosin receptor kinase (TRK) fusion are uncommon, there is no homeostasis in tumor tissue where standard therapies are unavailable or recommended therapies exist but fail to provide documented and relevant clinical benefit, and patient transfer is possible; randomized controlled trials to demonstrate improvement are neither feasible nor appropriate(Wyatt et al., 1999).
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There are many different types of primary tumors, each with its own unique natural history, making it impossible to conduct a single randomized study on all of them. However, the data from the Vitrakvi trials were pooled to provide evidence of the efficacy and safety of each regulatory request (Amatu et al., 2016; Lange and Lo, 2018).

The overall response rate has been demonstrated to be a positive indicator of the efficacy of Vitrakvi in treating select groups of tumors. Quantitative differences in effects are possible on the basis of cancer type and additional genetic changes (Burris et al., 2015).

Vitrakvi is unlike many other cancer drugs since it is designed to attack tumors with a specific gene arrangement regardless of where they may be located in the body. Preliminary data demonstrate that it successfully reduces tumor size in patients. In addition, the rapidity with which tumors can be reduced is crucial for providing symptom relief to patients (Doebele et al., 2015; Laetsch et al., 2018).

Vitrakvi appears to be safe, and any potential harm from it seems to be minimal. Therefore, the European Medicines Agency decided that the benefits outweigh the dangers and that it has approved for use in the European Union (Figure 1).

Vitrakvi pills or liquid (20 mg/ml) can be used orally (25 and 100 mg). If the malignancy is stable and the side effects are acceptable, adults should take 100 mg twice a day. Weight determines the child's dose (US Food and Drug Administration, 2018).

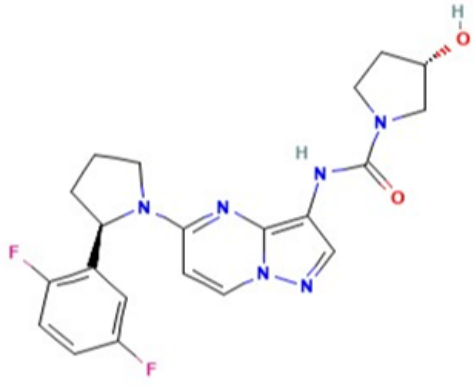

Figure 1. Chemical structure of Larotrectinib (Vitrakvi).

The primary objective of this study is to evaluate the molecular interactions between Vitrakvi (larotrectinib) and TRKs (TRKA, TRKB, and TRKC), particularly focusing on the impact of TRKC mutations on drug binding and efficacy.

1.1 Mechanism of action

TRKs are proteins that are found in human neural tissue. They become active as a result of the action of neurotrophins, which allows them to play a significant role in the physiological processes that underlie the development of the nervous system as well as its functions. The optimal levels of neuronal development, differentiation, and survival are regulated by the TRKs TRKA, TRKB, and TRKC when they engage in a dynamic interaction with neurotrophic autoligands (Yang et al., 2022). The genes NTRK1, NTRK2, and NTRK3 encode TRKA, TRKB, and TRKC, respectively.

Fusion proteins have been identified as a result of chromosomal rearrangements such as in-frame fusion of these genes with a variety of partners, translocations in the TRK domains, mutations in the TRK binding area, NTRK amplification, and the production of TRK splice variants. Activated TRK chimeras that can act as tumor inducers enhance cancer cell line proliferation and survival (Ardini et al., 2016; Tacconelli et al., 2004).

Gene fusions result in the synthesis of chimeric TRK proteins, which either have inherent kinase activity or overexpress the kinase domain. This changed state, which can be induced by point mutations, chromosomal rearrangements, gene fusions, or deletions, results in spontaneous ligand-independent dimerization, which activates the signal transduction pathway (Arevalo et al., 2000). To date, it has been established that all of the known mechanisms for oncogenic TRKA activation involve truncation of the extracellular domain (Bové et al., 2021).

According to one study, the expression of the gene encoding a neurotrophin's cognate TRK receptor is regulated by the physiological levels of the neurotrophin in vivo, although this mechanism of regulation only occurs in a portion of the cells that express the receptor (Raedler, 2019).

Vitrakvi has shown anticancer effects in *in vitro* and *in vivo* tumor models, with constitutive activation of TRK proteins caused by gene fusion, protein regulatory domain loss, or overexpression of the TRK protein. Vitrakvi has demonstrated little efficacy in cell lines harboring TRKA kinase domain point mutations, including the clinically characterized acquired resistance mutation. F617L, G623R, and G696A are point mutations in the TRKC domain associated with clinically recognized acquired resistance to Vitrakvi (Vaishnavi et al., 2013; Hashimoto et al., 2005).

Like other receptor tyrosine kinases, TRK proteins are activated when a ligand binds to the receptor's extracellular domain. Initially identified and classified as proteins that promote sympathetic and sensory neuronal growth and survival, neurotrophins are proteins that are secreted and act as ligands for TRK proteins (Coppola et al., 2004).

For every kinase, the individual ligands are denoted by the acronym NGF, which stands for nerve growth factor. The brain-derived growth factor (BDGF) is for the TRKA receptor, whereas NT-4/5 and NT-3 are, respectively, for the TRKB and TRKC receptors. There is a ligand-binding region, a transmembrane region, and an intracellular domain that includes a kinase domain. It regulates the latter stages of cell division, axon and dendrite growth, and branching. They also perform more nuanced roles that have nothing to do with the neurological system (Ferrer et al., 1999; Dwivedi et al., 2003).

NGF stimulation of TRKA has been connected to the modulation of pain, itch, and inflammation in addition to its function in the growth and maintenance of cholinergic, sympathetic, and sensory neurons (Ernst et al., 2009). TRKB is triggered by BDNF and has been proven to improve neuronal plasticity and survival. TRKB inhibition as a therapeutic target may result in unpleasant side effects such as ataxia, lethargy, anhedonia, and depression (Ivanov et al., 2013).

NGF binding to the TRKA receptor activates the Ras/MAPK pathway, resulting in increased proliferation and cellular growth via extracellular kinase (ERK) signaling. Other pathways, such as phospholipase C (PLC) and phosphatidylinositol-3 kinase (PI3K), are also active (Nakagawara, 2001; Boulle et al., 2012).

Neurotrophin-3 (NT-3) is a growth factor that affects some nerve cells. It promotes the creation and differentiation of new neurons and synapses, as well as the survival of existing neurons (Chaldakov et al., 2004). NT-3 stimulates cell migration via TRKC. Inhibitors such as K252a and Vitrakvi prevent this effect from occurring. Hirschsprung's disease is characterized by gastrointestinal issues and the absence of neurons in the muscular plexus and submucosa. TRKC mutations that result in an inactive protein have been identified as a cause of Hirschsprung's disease, which is defined by these characteristics (Keeler et al., 2017).

Some malignancies with TRKA protein expression may have a better prognosis than others do. In the case of neuroblastoma, for example, TRKA expression is associated with a favorable prognosis because TRKA and NGF signaling may play a tumor suppressor role by inducing differentiation, growth arrest, and angiogenesis in neuroblastoma cells. The expression and signaling of TRKC are related to a neuroblastoma phenotype that is more aggressive and invasive, whereas higher TRKA expression is associated with favorable clinical characteristics. The clinical characteristics of TRKC and TRKB are more aggressive, indicating that this hopeful outlook may apply exclusively to TRKA.

TRKB promotes angiogenesis and resistance to anticancer treatments by promoting autocrine and paracrine signaling in cancer cells. Despite the fact that this feature has been observed only in neuroblastoma, it is likely that it applies to other types of cancer as well. Furthermore, NTRK1 rearrangement in papillary thyroid carcinomas is associated with a poorer prognosis than that in patients without this fusion gene. On the other hand, the invention and improvement of kinase inhibitor medicines, targeted tumor methods, and scarcity of clinical resistance mechanisms may make NTRK genes that affect malignancies more treatable (Lange and Lo, 2018; Vaishnavi et al., 2015).

2 Materials and methods

The chemical structure of Vitrakvi was retrieved from PubChem and molecular docking was conducted using AutoDock Vina. The three-dimensional structures of TRKA, TRKB, and TRKC were obtained from the PDB database, and docking visualizations were performed using PyMol, PyRx, and BIOVIA software. Mutagenic models of TRKC (F617L, G623R, and G696A mutations) were constructed to analyze the effects of these mutations on binding efficacy. The chemical structure of Vitrakvi was obtained from PubChem via the identifier CID (46188928). TRKs with the following PDB IDs were selected: TRKA (4F0I), TRKB (4ASZ), and TRKC (6KZD). The most essential aspect is that these receptor kinases can be activated by combining them with other ligands. We used Vitrakvi for the molecular docking of these combination kinases.

Brain-derived growth factor (BDGF) is coupled with TRKA under PDB ID (1WWW). TRKB is coupled with neurotrophin-4/5 under ID (1HCF). Neurotrophin-3 (NT3), the NKRC receptor, was acquired from PDB under the ID (1B8K). Using AutoDock Vina, molecular docking between Vitrakvi and TRKs was performed. To accomplish docking tasks, we used the BIOVIA Discovery Studio 2021 Visualizer and the Python package PyRx. Each molecule docking was viewed in three dimensions with PyMol. The 3-point mutations in TRKC were built via the PyMol molecular modeling program.

3 Results

Molecular docking results demonstrated high binding affinity between Vitrakvi and wild-type TRKA, TRKB, and TRKC, with binding energies of -9.4, -8.8, and -9.9 kcal/mol, respectively. However, TRKC mutants exhibited significant conformational shifts at the binding site, specifically in the F617L mutant, indicating a potential mechanism of drug resistance. Furthermore, when TRKs interacted with their respective ligands (BDGF, NT-4/5, and NT-3), the binding affinity of Vitrakvi decreased, highlighting competitive binding dynamics. TRKs consist of three subunits: TRKA, TRKB, and TRKC.

Molecular docking of proteins with Vitrakvi was subsequently conducted, and the proteins were subsequently assembled into the TRK structure. Figure 2 shows the constituents of the natural TRKs that interact with Vitrakvi. Table 1 displays the interaction energy, also known as the binding affinity, as well as the relative mean square deviation

(RMSD) of the atoms between the protein and ligand. When the RMSD between models was zero, it was chosen as the best interaction with high affinity.

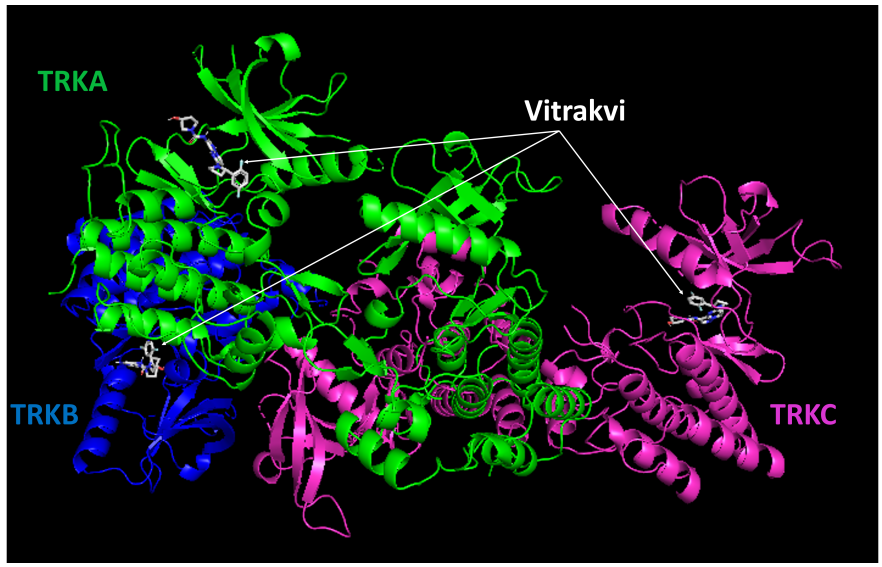

Figure 2. Molecular docking of Vitrakvi with normal TRKA (green), TRKB (blue) and TRKC (violet).

3.1 TRKA-Vitrakvi interaction poses:

The interaction poses between TRKA and Vitrakvi are illustrated in Figure 3. The types of bonds and residues used were as follows: conventional hydrogen bonds (ARG591 and SER671), carbon hydrogen bonds (MET591, ARG592 and GLY516), fluorine bonds (ARG653), alkyl and pi-alkyl bonds (LEU515), pi-sigma bonds (ILE674) and pi-sulfer bonds (MET670).

3.2 TRKB-Vitrakvi interaction poses:

The interaction poses included conventional hydrogen bonds (ASP710), carbon hydrogen bonds (GLU604 and GLY709), fluorine interactions (HIS690), alkyl and pi-alkyl interactions (LEU608, PHE633 and ILE616), and amide pi-stacking interactions (ILE708).

3.3 TRKC-Vitrakvi interaction poses:

The interaction poses included conventional hydrogen bonds (ASP624 and ARG683), carbon hydrogen bonds (LEU544 and MET620), alkyl and pi-alkyl interactions (ALA570 and LEU686), pi-sigma interactions (VAL552), and pi-pi T-shapes (PHE698).

The anticancer activity of Vitrakvi has been demonstrated in both *in vitro* and *in vivo* tumor models, namely, in cells whose TRK proteins are constitutively activated as a result of gene fusion or deletion of the protein's regulatory region. The point mutations G623R, G696A, and F617L in the TRKC domain confer resistance to Vitrakvi. The alterations were uploaded to the molecular fusion prototype between TRKC and Vitrakvi. A study of the fusion data revealed that the attachment region has a definite effect and that there is a considerable difference between the wild-type fusion model and the mutagenic model (Figure 4).

The second type of molecular docking occurs when kinases and Vitrakvi form complexes with NGFs. When TRKA combines with BDGF, it docks with Vitrakvi at two residues (HIS353 and VAL354). When TRKB interacts with NT-4/5, it forms a fusion with the ASN325, ILE330, MET354, and ASN355 residues. Various types of bonds are observable because of these interactions (Figure 5).

Table 1. The best docking models with high affinity and degree of RMSD.

Interaction	Binding affinity	RMSD/Lower bond	RMSD/Higher bond
TRKA-Vitrakvi	*-9.4*	*0*	*0*
=	-9	37.952	40.5
=	-8.9	31.582	34.651
=	-8.9	38.86	40.942
=	-8.8	2.959	4.916
=	-8.8	20.467	23.779
=	-8.8	3.334	6.68
=	-8.7	39.125	41.494
=	-8.6	34.193	38.61
TRKB-Vitrakvi	*-8.8*	*0*	*0*
=	-8.3	3.949	5.795
=	-8.2	11.7	14.007
=	-8.2	3.016	3.988
=	-8.2	3.818	6.713
=	-8.1	13.205	15.731
=	-8	15.184	17.403
=	-7.9	2.873	4.3
=	-7.5	14.745	17.109
TRKC-Vitrakvi	*-9.9*	*0*	*0*
=	-9.8	60.896	62.482
=	-9.7	61.139	62.664
=	-9.4	59.204	61.71
=	-9.4	3.145	5.358
=	-9.4	4.198	6.607
=	-9.3	2.309	3.632
=	-9.3	3.498	6.198
=	-9.2	4.166	7.191

Table 2 contains both the binding affinity and the RMSD of the atoms that are found between the ligand and the protein. The best interaction model with high electrostatic affinity energy when the RMSD is equal to zero.

Notably, the situation is different in the case of TRKC, which has the ability to fuse with a ligand (NT-3). For the first two types of kinases (TRKA and TRKB), the interaction between the ligand and the kinase was dependent on the chains that the Vitrakvi did not directly connect with. With respect to TRKC, the ligand and Vitrakvi are fused together in the same chain.

NT-3 (1B8K) is considered an inhibitor of TRKC's current activity in the presence of another drug; thus, the docking operation was performed on TRKC, NT-3, and Vitrakvi, as illustrated in Figure 6. The docking site of TRKC appears at the LYS49, TYR51, and ARG87 residues. The results of the triple fusion clearly revealed that the Vitrakvi fusion site shifted from its initial position. The binding affinities and RDDs are presented in Table 3.

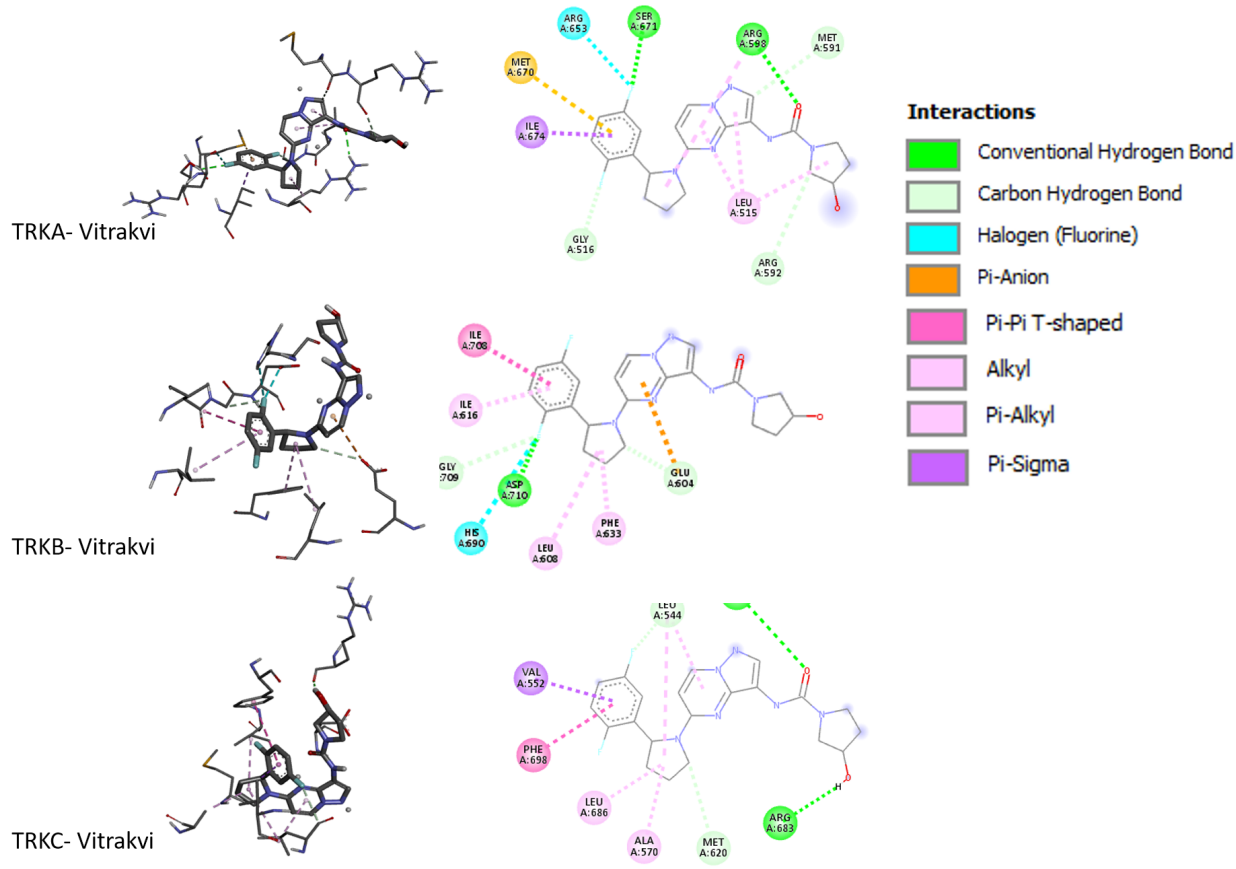

Figure 3. Pose interactions between TRKs and Vitrakvi with a variety of bonds.

4 Discussion

This study elucidates the intricate relationship between Vitrakvi's binding mechanisms and TRK mutations, providing critical insights into the role of molecular docking in predicting drug efficacy and resistance. The observed shifts in binding affinity and conformation for TRKC mutants underscore the importance of targeting specific mutations to enhance the therapeutic efficacy of Vitrakvi. The development of molecular diagnostic methods has led to the identification of an increasing number of neoplastic abnormalities, such as gene activation, point mutations, insertions, frame-shift deletions, and amplifications or rearrangements, which has had a significant impact on the treatment of solid tumors in recent years. A significant change in the way solid tumors are treated has resulted from the identification of an increasing number of neoplastic abnormalities, such as gene activation point mutations, insertions, in-frame deletions, and amplifications or rearrangements, with the development of molecular diagnostics (De Braud et al., 2014; Federman and McDermott, 2019).

By using these mutations as predictive biomarkers, precision medicine aims to provide tailored care. Molecular alterations resulting in constitutively active fusion proteins have recently come to the forefront as targets for cancer therapy. TRK proteins are examples of targets exploited in cancer treatment. In addition, methods of sequencing of the future generation are helpful for discovering gene fusions in an objective manner, which helps to increase research in this area (Hong et al., 2020).

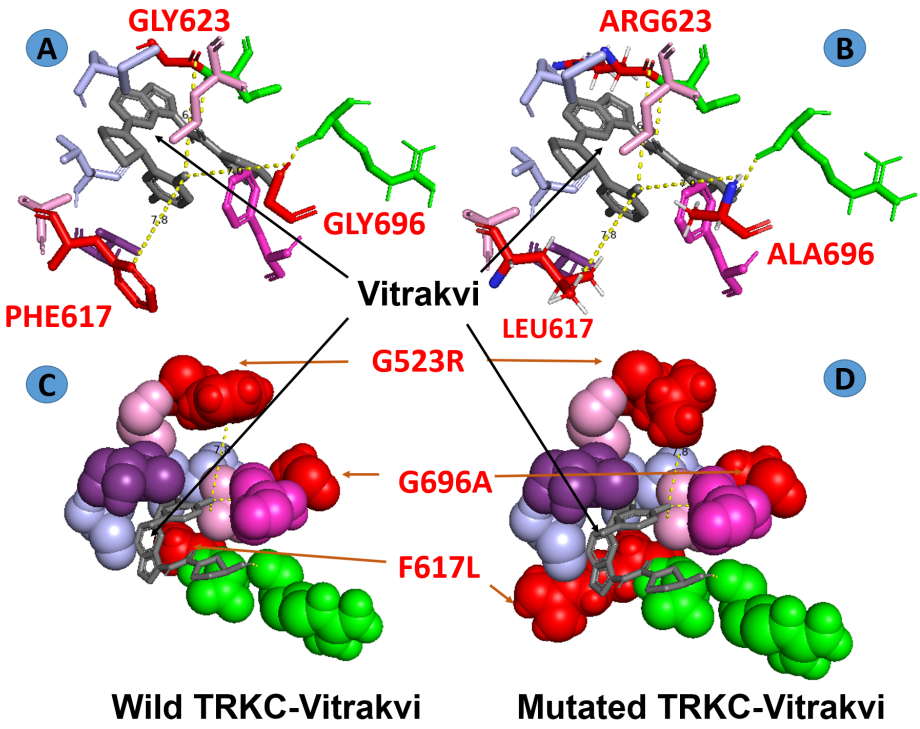

Figure 4. Molecular docking of TRKC-Vitrakvi in wild-type and mutated TRKC. A: Licorice wild docking image showing the interaction poses and residues (PHG617, G623 and G696). B: Licorice mutation docking image showing the mutated residues (LEU617, ARG623 and ALA696). C: Wild-type Spheres docking with the red residues of interest. D: Sphere mutation docking results in different red residue forms.

Tumorigenicity occurs when several distinct neoplastic tissues are brought together with a shared tumor driver. There is a growing need to normalize data from studies of novel medicines to data reported for historically accessible therapies across tumor tissues as more tumor-agnostic studies are conducted. There is currently no foolproof method for gauging the clinical efficacy of these treatments in individual tumor types. The data will likely show historical and within-patient comparisons across subsequent treatment lines, and several methods are anticipated to play crucial roles in understanding these data across tumor tissues (Laetsch and Hong, 2021; Cocco et al., 2019).

TRK fusion cancer is traditionally treated with a combination of chemotherapy, biologic therapy, or immunotherapy, which is based mostly on tumor histology. Vitrakvi is a drug that has been approved in the US and Japan as the first and only way to treat solid tumors in adults and children over 12 years of age that have an NTRK gene fusion (Megan et al., 2021). Vitrakvi was purposefully developed as an ATP-competitive and selective RTK inhibitor to prevent the activity of off-target kinases (Drilon et al., 2022).

In three clinical trials including 55 adults and children with solid tumors and an NTRK gene fusion without a resistance mutation, Vitrakvi proved effective. These patients had cancer that advanced after treatment or had no effective alternatives. Vitiligo responds to 75% of solid tumors. These reactions were persistent, with 73% lasting at least six months and 39% lasting a year or more at the time of the outcome analysis (Doz et al., 2022).

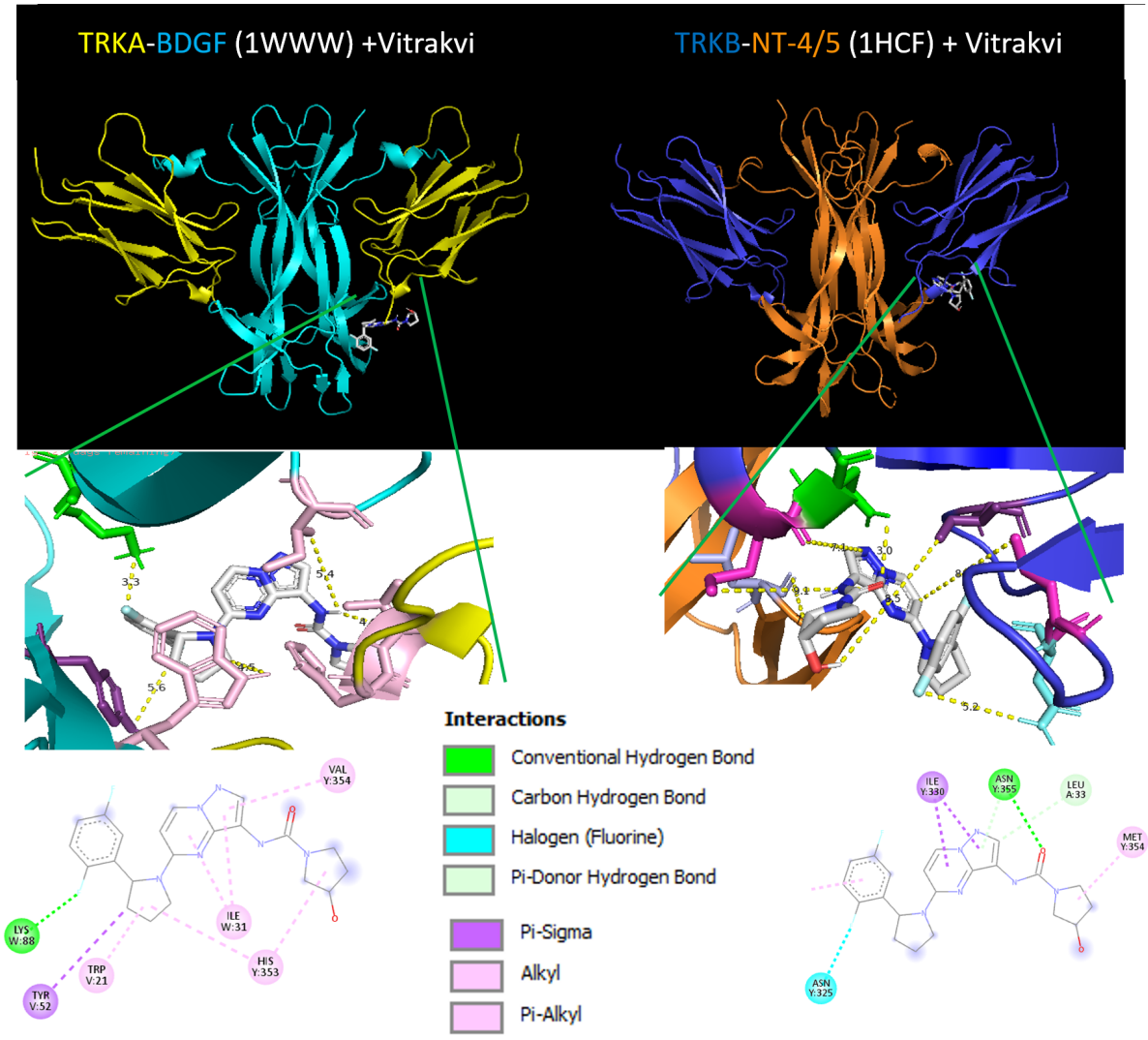

Figure 5. Molecular interactions between kinases and Vitrakvi when their favorite ligands are combined. Left: TRKA+BDGF (1 WWW). Vitrakvi is in contact with TRKA in HIS353 and VAL354, whereas it contacts BDGF in TRP21, ILE33, TYR52, and LYS88. Right: TRKB+NT-4/5 (1HCF). Vitrakvi is in contact with TRKB in ASN325, ILE330, MET354, and ASN355, whereas it contacts NT-4/5 in LEU33.

In the present study, complete fusion was carried out between the TRK proteins. Vitrakvi was docked to each component of kinases (TRKA, TRKB, and TRKC). When the RMSD was equal to zero, the optimal model with high binding affinities for each kinase was determined: -9.4, -8.8, and -9.9, respectively. Fusions have revealed several forms of bonds, with typical hydrogen bonds occurring most commonly.

Viktrakvi is an effective anticancer drug that acts by either blocking the activity of fusion kinases or deleting the regulator protein domain in cells that overexpress kinases. Both of these mechanisms work together to combat cancer. However, research has shown that specific point mutations in TRKC (F617L, G623R, and G696A) can confer resistance to Vitrakvi (Vaishnavi et al., 2013). The wild-type TRKC and Vitrakvi successfully docked with each other.

The three-dimensional structure of the mutated TRKC carrying the triple mutation was subsequently reconstructed. As a consequence of the action of the medication, differences in the configuration of the anchoring site were found between the wild-type kinase and the mutant kinase that was being evaluated. The most significant alteration in the shape of the fusion was observed in the F617L mutant in the sphere view, where the residues underwent a distinct conformational change that influenced the result of the fusion.

The kinases can also act with other growth factors; hence, we docked the receptor to the activator in addition to Vitrakvi. To stimulate, it is well known that TRKA is paired with BDGF and that TRKB is combined with NT-4/5. Complexes of (1WWW) and (1HCF) were selected for docking with Vitrakvi. For each docking, a distinct set of bonds is established. Once TRKA and TRKB were docked with Vitrakvi, the binding affinity scores were recorded to a lesser degree than before. The binding energy was -8.9 for TRKA-BDGF and -7.4 for TRKB-NT-4/5. These data showed for the first time that docking Vitrakvi with TRKA or TRKB is superior to docking with TRKA-BDGF or TRKB-NT-4/5.

In the present work, the binding of Vitrakvi to TRKA or TRKB alone differed from the docking site when both kinases were coupled with BDGF or NT-4/5, respectively. The problem is slightly different for TRKC because the location where the mutations take place is in the same region of fusion with Vitrakvi. In contrast to several other types of kinases (TRKA and TRKB), the TKRC activator, also known as NT-3, combines with the same chain. Figure 5 shows that in the association of Vitrakvi with TRKC, the location of the intercalation fusion changed in the direction of neurotrophin-3, away from the location where the mutation took place. This helps to explain why the mechanism changed the direction of the intercalation from its original docking area in the event that there were triple mutations. In addition, the binding energy between TRKC alone and Vitrakvi was greater when TRKC was paired with NT-3.

Table 2. The best docking models with high affinity and degree of RMSD between 1WWW and 1HCF with Vitrakvi.

Interaction	Binding affinity	RMSD/Lower bond	RMSD/Higher bond
1WWW- Vitrakvi	*-8.9*	*0*	*0*
=	-8.8	5.023	3.039
=	-8.4	16.653	14.031
=	-8.3	18.73	16.162
=	-8.2	3.112	1.677
=	-8	17.109	14.566
=	-7.7	16.675	13.961
=	-7.7	16.51	13.609
=	-7.7	7.245	4.608
1HCF- Vitrakvi	*-7.4*	*0*	*0*
=	-7.3	14.887	12.102
=	-7.3	37.06	34.562
=	-7.1	2.325	1.746
=	-7.1	29.87	26.509
=	-7	36.186	34.368
=	-7	15.02	12.533
=	-7	22.616	19.816
=	-6.9	36.138	32.961

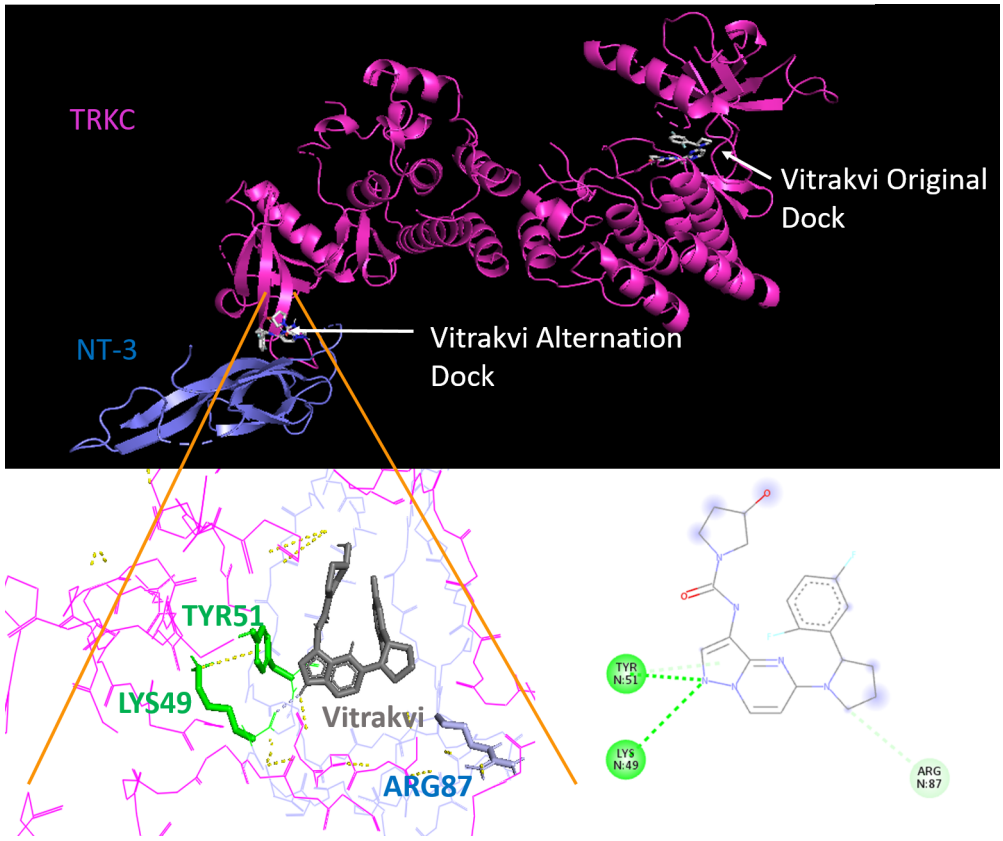

Figure 6. Changes in the molecular interaction of the original position docking between TRKC and Vitrakvi on the right. New fusion of Vitrakvi with TRKC when a kinase is combined with NT-3 (1B8K) is shown on the left. Two conventional hydrogen bonds are present in the LYS49 and TYR51 residues of TRKC. Carbon–hydrogen bonds appear in the ARG87 residue of TRKC.

Both humans and rodents express Neurotrophin-3 as well as its corresponding receptor TRKC. The level of NT-3 expression decreases as people age. The expression of NT-3 is most commonly detected in blood vessels that are in charge of irrigating adipose tissue, whereas the expression of TRKC is equivalent in both isolated adipocytes and total tissue (Bové et al., 2021).

Virakvi is approved for individuals with solid tumors, and this biomarker is not a suitable alternative treatment for their progressing metastatic condition. Vitrakvi is an innovative step forward in both the field of precision medicine and the development of oncology drugs because it is a tissue-agnostic treatment that has been shown to be safe and to produce long-lasting effects in this patient population (Vaishnavi et al., 2013).

Since the overexpression of NTRK genes contributes to carcinogenesis and progression, TRK inhibitors may be beneficial for treating malignancies with abnormal NTRK signaling. Mutations in NTRK genes are found in a range of cancer tissues; hence, research and investment in TRK inhibitors may be novel and effective treatments for many cancers (Lange and Lo, 2018).

However, the development and improvement of kinase inhibitor therapies, in conjunction with the identification of an oncogenic target and the relatively restricted expression of clinical resistance mechanisms, may prove to be effective in making cancers caused by NTRK gene changes more manageable.

Table 3. The best docking models with high affinity and degree of RMSD between TRKC+ NT-3 and Vitrakvi.

Interaction	Binding affinity	RMSD/Lower bond	RMSD/Higher bond
(TRKC+NT-3)- Vitrakvi	*-7.3*	*0*	*0*
=	-7	5.217	2.451
=	-6.9	5.903	2.368
=	-6.8	6.165	3.599
=	-6.7	4.974	2.856
=	-6.7	5.678	2.898
=	-6.7	6.751	3.876
=	-6.5	18.278	16.808
=	-6.5	1.994	1.759

5 Conclusions

By clearly connecting the research objective, methodology, and results, this study highlights the potential of molecular docking simulations to unravel mechanisms of drug interaction and resistance, paving the way for more effective targeted therapies in precision oncology. Multiple cancers have been linked to abnormal TRK protein signaling. Opportunities for therapeutic intervention have been revealed following the discovery of mutated NTRK genes as oncogenic factors.

Drugs such as Vitrakvi, which have demonstrated promising early clinical results, could make the target rather than the tumor organ crucial when deciding on a treatment. As a result of technical improvements, more data on gene rearrangements are becoming available, which enables more precise planning of therapeutic interventions to target oncogenic factors. There is reason to be positive for persons who have TRK mutations as well as those in the field of molecularly targeted medications, although clinical trials of TRK inhibitors have just begun.

Author Contributions

A.A.D.: Conceptualization, formal analysis, research, validation, visualization, writing-original draft, writing-review, and editing.

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