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In-silico molecular docking study based on a computational drug design of Jatrorrhizine against 6RA5 of main group of protein Traf2 and Nck interacting serine protein kinase (TNIK) for treatment of Breast Cancer

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Abstract: A chronic lethal breast cancer over-expressed in mammary carcinoma cells or breast cancer cell lines, MDA-MB-231 and MCF-7, the activity of 6RA5 of the major group of proteins Traf2 and Nck interacting serine protein kinase (TNIK) was amended, which was linked to poor prognosis. During molecular docking, jatrorrhizine of the isoquinoline group inhibited the multiplication and mutation of breast cancer cells without a malignant state. We retrieved Canonical SMILES of Jatrorrhizine (JATH) medication from pub-chem compound database under National Center for Biotechnology information for this exertion, and we also revealed various proteins, including 1YCS, 1KZY, 2PCX, 2ADY, 3IGL, 5BUA, and 6RA5. The ADMET analysis, pharmacokinetics analysis thermodynamic properties analysis, ligand-protein binding, homologous displaying of ligand were implemented in this study. The energy minimization and modification of drug and its derivatives using Chem3D-12 pro software were executed with substituting the functional group, -CF3, Naphthalene, Benzene in different bio-active position following Structure Activity Relationship (SAR). The autodock vina docking protocol method of PyRx for ligand-protein binding excluded the different binding affinity with different group. In comparison to the parent drug, which had a binding energy of -8.5 kcal/mol with protein 6RA5 of Traf2 and Nck interacting serine protein kinase (TNIK), the JATH-(Naphthalene+CF3) after modification had the best binding energy of -10.3 kcal/mol with protein 6RA5 of Traf2 and Nck interacting serine protein kinase (TNIK). The redesigned JATH medication containing Naphthalene and the –CF3 group could be a possible antagonist of 6RA5 of Traf2 and Nck interacting serine protein kinase (TNIK) in the treatment of breast cancer.

Keywords

Jatrorrhizine, Traf2 and Nck interacting serine protein kinase (TNIK), CADD, ADMET, Molecular docking, Pharmacokinetics, Hydrophobicity.

INTRODUCTION

Fatal breast cancer has turned out to be a prominent health dilemma for women and exists in the second foremost reason of mankind ruination around the world [1]. From statistical data, about 231,840 new cases of invasive breast cancer death among human body and also 40,290 deaths were recorded among both US black and white women in 2015 [2]. The estimated 2.1 million women in 2018 by breast cancer were affected which conveyed to one new case every 18 seconds [11] and approximately 15% of women died from breast cancer [1]. The mortality rate of breast cancer was reduced by 36%, resulting in 249,000 fatalities in all ethnic groups except Americans, Indians, and Alaska natives. However, this condition is currently being upraised dramatically, with 271,270 new cases and 42,260 deaths recorded in the United States [2]. Intriguingly, it was discovered that black women's death rates were 42 percent higher than white women's, despite lower breast cancer rates in Al or AN, Hispanic, and API women [2].

Tinospora cordifolia, also known as Geduchi, Giloy, or Armita, is a natural herbal plant that belongs to the moonseed family Menispermaceae [15] and is used to cure a variety of ailments, including breast cancer cell lines, MDA-MB-231 [3] [4] [14] [23] [26].

Table-01: Chemical Constituents of Tinospora cordifolia

Active components	Compounds	Uses
Terpenoids [30,31,32]	"ATinosporide, Furanolactone diterpene, Furanolactone clerodane diterpene, furanoid diterpene, Tinosporaside, ecdysterone makisterone and several glucosides isolated as poly acetate, phenylpropene disaccharides cordifolioside A, B and C, cordifoliside D and E, Tinocordioside, cordioside, palmatosides C and F, Sesquiterpene glucoside tinocordifolioside, Sesquiterpene tinocordifolin" [30,31,32].	"Infections of the respiratory tract; Skin problems; Snake bite and scorpion sting antidote; Anti-hyperglycemic (anti-hyperglycemic) properties; Boost your immune system Property of being anti-carcinogenic [30, 31, 32]".
Alkaloids [33,34]	"Tinosporine, (S), Magnoflorine, (S), Berberine, (S), Choline, (S), Jatrorrhizine, (S), 1,2-Substituted pyrrolidine(S), Alkaloids, viz. jatrorrhizine, palmatine, beberine, tembeterine, choline"[33,34].	"It has anti-neoplastic properties; Antioxidant properties; Activity that is anti-tumour or anti-cancer [33, 34]".
Lignans [35, 36]	"3(a, 4-dihydroxy-3-methoxybenzyl)-4-(4-hydroxy-3-methoxybenzyl), (S)" [35, 36].	"Snake bite and scorpion sting antidote; Neuropharmacological and analgesic actions; Diabetis, rheumatoid arthritis, gout, cancer, and excessive cholesterol levels are all symptoms of diabetes;

		Treatment for asthma and chronic cough; Antipyretic [35, 36]".
Steroids [37]	"Giloinsterol, (S), ß-Sitosterol, (S), 20aHydroxy ecdysone, (S)" [37].	Anti-stress activity [37].
Others [38]	"Tinosporidine, Heptacosanol, Octacosanol, sinapic acid, Tinosponone, two phytoecdysones, an immunologically active arabinogalactan, Giloin, Tinosporan acetate, Tinosporal acetate, Tinosporidine, Heptacosanol, Octacosanol, sinapic acid, Tinosponone, two phytoecd" [38].	Anti-inflammatory activity [38]

Jatrorrhizine chemical constituents [29] from Tinospora cordifolia significantly suppressed the proliferation, migration, and invasion of MCF-7 cells [17] [23] in Epithelial–mesenchymal transition related genes regulated with increased transcription of E-cadherin [8] [22] [24] in the human breast adenocarcinoma cell line MCF-7 [16]. A wide range of components have been identified from various portions of T.cordifolia, including alkaloids, diterpenoid lactones, steroids, glycosides, aliphatic compounds, and polysaccharides [9] [10]. An antihypercholesterolemic and bacterial affects of Jatrorrhizine having anti-tumour or anticancer property [12] attributes the effective cleaning therapy. By activating the epithelial-mesenchymal transition (EMT) and boosting the ZEB1-mediated transcriptional suppression of E-cadherin in breast cancer cells, jatrorrhizine reduced the formation, growth, and progression of breast malignancies. [5] [13].

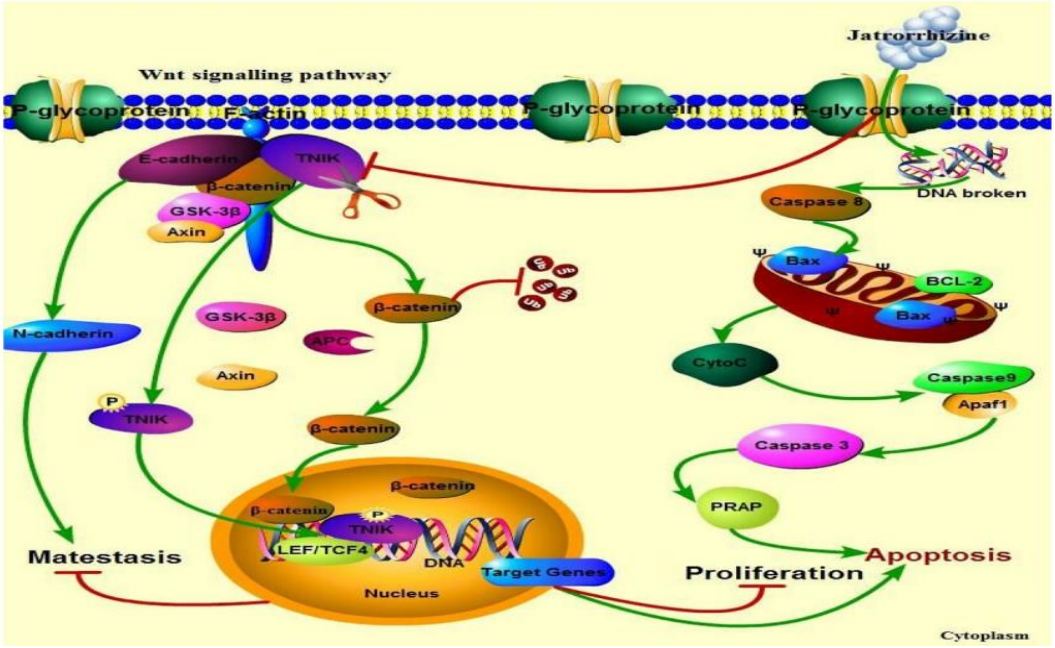


Figure-01: In memory carcinoma cells, a schematic model of jatrorrhizine's antitumor process is shown [1].

We identified p155 as Traf2- and Nck-interacting kinase (TNIK), a protein with an N-terminal kinase domain that is similar to STE20, the Saccharomyces cerevisiae mitogen activated protein kinase, and a C-terminal regulatory region known as the citron homology (CNH) domain. TNIK stopped cells from spreading activating the C-Jun N-terminal kinase (JNK) pathway in a unique way. TNIK is a germinal center kinase that has 1360 amino acids and an N-terminal kinase domain as well as a middle domain called TNIK [6] [7]. TNIK triggers the c-Jun N-terminal kinase (JNK) pathway, which causes F-actin structure to be disrupted, preventing cell spreading. TNIK interacted with Rap2 via its CNH domain but did not network with Rap1, according to our findings. The complete effector region and GTP-bound conformation of Rap2 were required for TNIK interaction with Rap2 [21]. TNIK colocalized with Rap2 in cultivated cells, whereas a mutant TNIK missing the CNH domain did not. Rap2 significantly improved TNIK's inhibitory activity against cell spreading, but not for the mutant TNIK lacking the CNH domain. Rap2 did not improve TNIK-induced JNK activation, but it did boost autophosphorylation and TNIK translocation to the detergent-insoluble cytoskeletal fraction. These findings imply that TNIK is a Rap2 effector that regulates the actin cytoskeleton [6] [7]. Wnt signaling pathways are involved in a variety of developmental processes as well as elements of adult homeostasis [1] [19]. Wnt signaling activity that is abnormal has also been linked to a variety of cancers. Through a thorough proteomic analysis in human colorectal cancer cell lines, we have identified Traf2- and Nck-interacting kinase (TNIK) as a novel stimulator of Wnt signaling. TNIK is a T-cell factor-4 (TCF4) activating kinase that is required for -catenin-TCF4 transactivation and colorectal cancer progression [20] [21] [25].

METHODOLOGY

Drugs or Ligands selection

We had designated a drug for our research purpose on the basis of characteristics of any that should have the properties of drug. We retrieved the Jatrorrhizine chemical from Tinospora cordifolia that has antitumor or anticancer properties maintaining the toxicity analysis, drug likeness analysis, Lipinski's Rules using Preadmet, Admetsar, swissadme, medchem designer software indulge with an outlook for selecting compounds that can qualify for properties of drugs. In Table-02, the altered medications and their parent drug names are summarized.

Proteins preparation and optimization

The protein data bank was used to retrieve the three-dimensional crystal structures of recombinant human TNIK in pdb format. PyMOl was used to remove heteroatoms, lipids, contaminants, and water molecules from the crystal structure prior to docking. Protein crystal structures of 1YCS, 1KZY, 2PCX, 2ADY, 3IGL, 5BUA and 6RA5 were retrieved for Jatrorrhizine by Swiss Target Predictor, Pass prediction, RCSB PDB, Uniprot ID as PDB files.

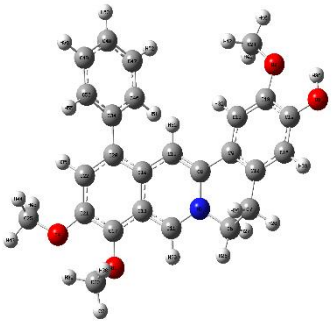
Ligands preparation and minimization

The three-dimensional geometry of JATH chair forms was obtained using Gaussian view 09 and the Chem3D Pro12.0 program. The amendment of main drug, JATH was occurred with altering CH_3, C_6H_6, $C_{10}N_8$, $C_{10}H_8$+CH_3, and C_6H_6+CF_3 functional groups according to change of these

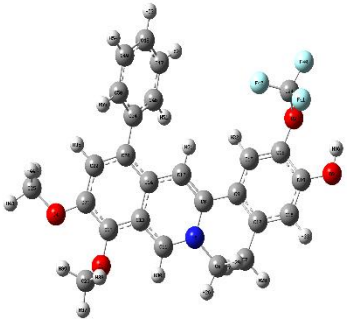
functional groups in the position of Carbon. On the BIOVIA Drawer, the molecules were sketched. Then, using Becke's exchange functional combined with Lee, Yang, and Parr's (LYP) correlation functional, 3D structures were created by fully optimizing with DFT. 'Following optimization, vibrational frequency calculations were carried out to ensure that the stationary spots corresponded to potential energy surface minima. Each compound's electronic energies, enthalpies, Gibbs free energies, dipole moments, and partial charge analysis were premeditated'.

Table-02: Drugs or ligands preparation and minimization

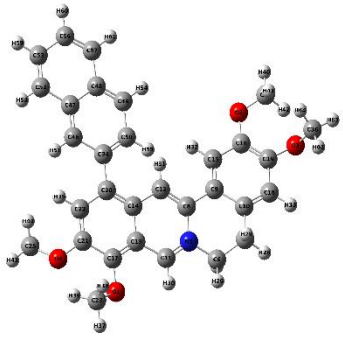
Structural Drugs Name	Rename of drugs
Jatrorrhizine	JATH
D-Benzene(C-20)	D-1
D-Benzene(C-20)+OCF_3(C-18)	D-2
D-Naphthalene(C-20)+CH_3(C-19)	D-3
D-Naphthalene(C-20)	D-4



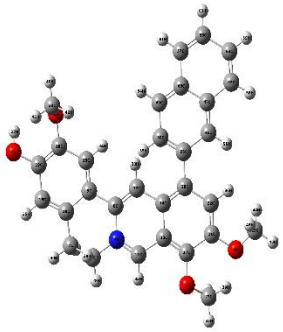
D1



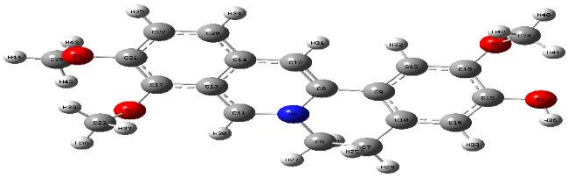
D2



D3



D4



JATH

Figure-02: All developed analogues' most stable optimal structures, together with their parent molecule

Minimization of the retrieved proteins

To minimize poor connections between protein atoms, the model was subjected to energy minimization using the steepest descent and conjugate gradient techniques. The GROMOS96 parameters were established, and the Swiss-PDB Viewer was used to carry out the computations in vacuo. The crystal structure's geometry and energy minimization were performed using Swiss-PDB Viewer (version 4.1.0) and the GROMOS96 force field 12.

Pharmacokinetic parameters study

The admetSAR server was used to calculate the pharmacokinetic parameters and toxicity of the rehabilitated and parent drugs. The pharmacokinetics parameters relating to drug absorption, distribution, metabolism, excretion, and toxicity of the parent drug and its developed analogues were evaluated using the admetSAR online database. AdmetSAR forecasts the most up-to-date and thorough data for a wide range of compounds related with established ADMET profiles. The admetSAR tool was utilized for ADMET analysis, and 96,000 distinct compounds with 45 different types of ADMET-related qualities, proteins, species, or animals were meticulously selected from a vast number of different literatures.

RESULTS AND DISCUSSION

Identification of IR and NMR spectrums of the ligands

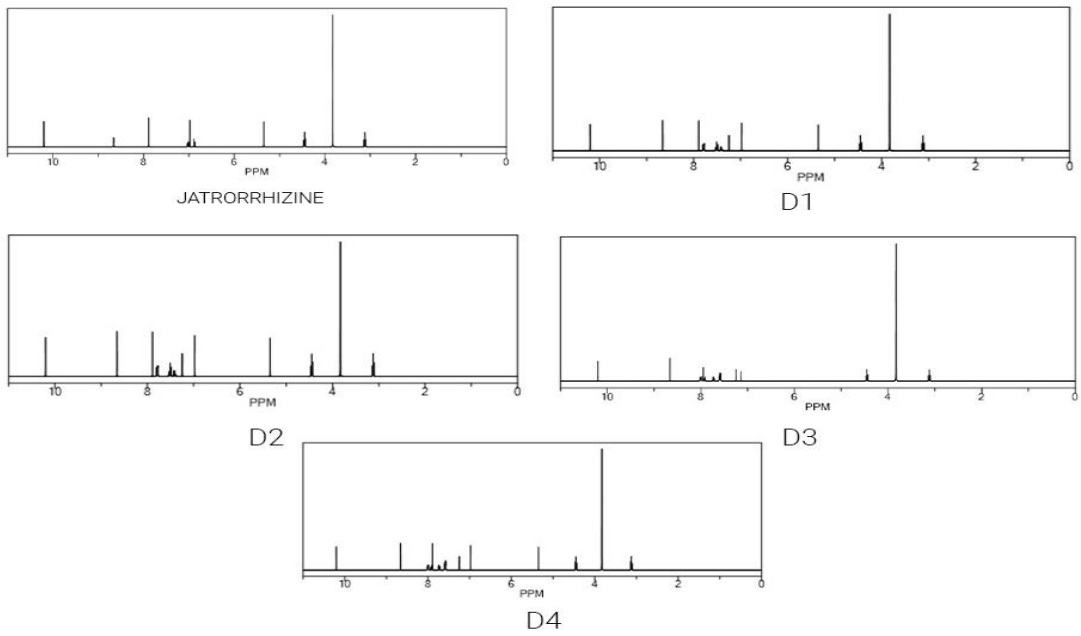
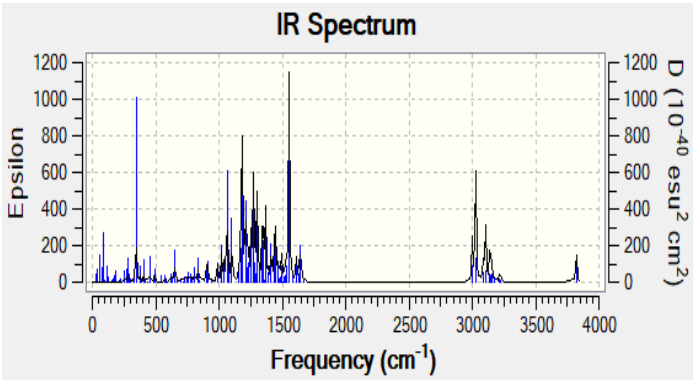
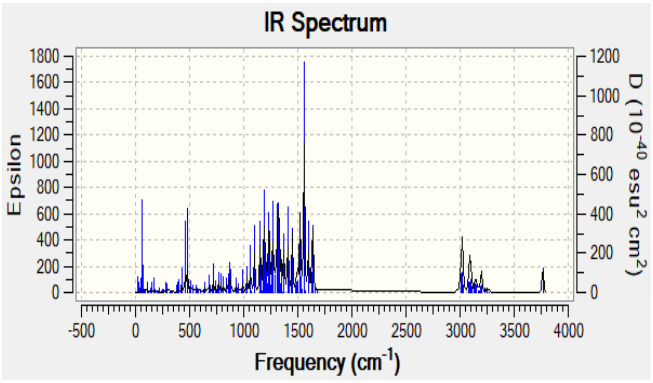


Figure-03: Identification of ligands by Chem NMR H-1 estimation.

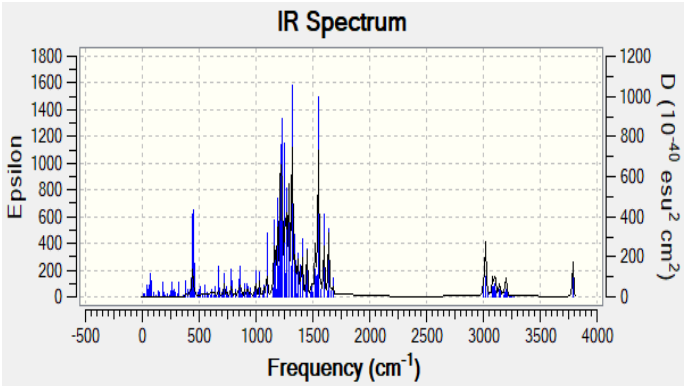
The IR and NMR spectra of the ligands were identified. The figures 03 and 04 show how 1H NMR was used to identify the specific altered drug molecule and parent ligand, and how IR was estimated using Gaussian view, respectively.



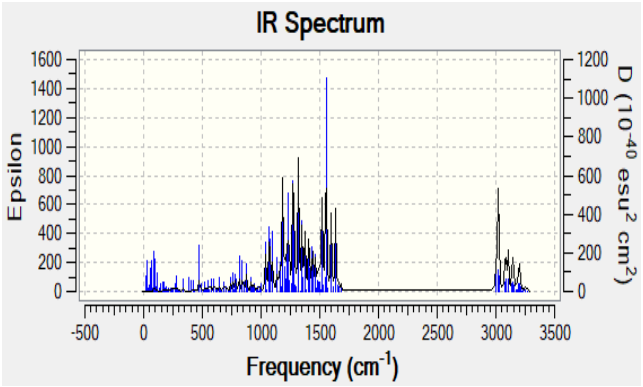
JATH



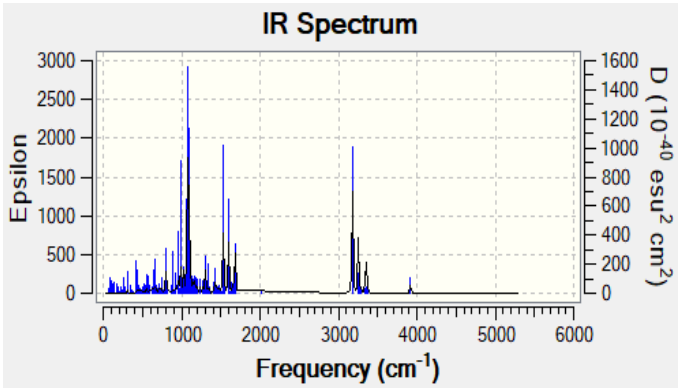
D1



D2



D3



D4

Figure-04: Identification of IR spectrum of the ligands by Gaussian view (v5.0).

Admet Analysis of the Identified Compounds

ADME/T analysis that was implemented to inspect whether the altered conglomerates bring about any toxicity or improved pharmacokinetic profile where high through virtual screening (HTVS) and MedChem Designer, admetSAR@LMMD, PreADMET softwares were used for absorption, distribution, metabolism, and excreation and toxicity analysis of the halogen-modified derivatives. A variety of pharmacokinetic and pharmacodynamic characteristics were investigated, including human intestinal absorption, blood–brain barrier penetration, cytochrome P450 inhibition, inhibition of human ether-a-go-go-related genes, acute oral toxicity, and rat acute toxicity.
Lipophilicity is defined as the logarithm of the partition coefficient P (logP) between octanol and water (buffer), which depicts the partition of the unionized (neutral) form of the compound, whereas logD depicts the overall partition of both the ionized and unionized forms of the compound. Drugs with logp values more than 5 are lipophilic, whereas JATH and its equivalents D-1, D-2, D-3, and D-4 have logp values less than 5, suggesting that they are hydrophilic. MlogP (Moriguchi octanol-water partition Coefficient) is a well-known parameter that has been employed in QSAR model structure analysis for a long time. It characterizes a compound's lipophilicity, which reveals how well it penetrates lipid-rich zones from aqueous solutions. With a logP (MLogP) larger than 4.15, Moriguchi's logP (MLogP) predicts that the sole constituent D-4 would be the least assimilated of all the deduced analogues. In addition, changes to JATH resulted in a P-glycoprotein non-inhibitor. D-1, D-2, and D-3 were discovered to be possible compounds of the human ether a-go-go-related gene. All of the compounds have a comparable oral toxicity profile, although D-3 has the greatest LD50 value in rat acute toxicity, indicating that it is non-toxic when compared to parent JATH. In furthermore, D-1, D-2, D-3, and D4 ADME/T predictions were made and compared to the D-3 equivalent. Various functional groups of D-(C10H8+CH3) indicated different values. The modified, anticipated drugs, P-glycoprotein inhibitors to be safe for use are capable of crossing the blood-brain barrier (BBB), and the bioavailability of these drugs was predicted to optimize drug metabolism and intestinal permeability, as well as the pharmacokinetic parameters and toxicity of some drugs. Table 5 depicts the AdmetSAR values for various agonists. Except for D-4, all compounds have a designed MLogP of less than 4.15, indicating that they will be solubilized represented in Table 3. The ADMET assessment of the following picked had also been performed using PreADMET

Table-03: MedChem designer admet values of Ligands.

Factors	JATH	D-1	D-2	D-3	D-4
MlogP	2.562	3.620	3.921	3.877	4.197
S+logP	0.388	1.706	2.119	3.231	2.926
S+logD	-0.763	0.128	0.795	3.231	1.231
MWt	338.386	414.484	468.455	478.572	464.545

Table-04: Toxicity analysis by PreADMET Values of Ligands.

Factors	JATH	D-1	D-2	D-3	D-4
algae at	0.0585699	0.0211391	0.00496146	0.00566403	0.00568338
daphnia_at	0.190163	0.0248441	0.00202716	0.00564413	0.00747619

medaka_at	0.0645766	0.00151936	1.21597e-005	0.000104476	0.000177713
minnow_at	0.0972814	0.00889953	0.000136521	0.00150261	0.00184392

Analysis of pharmacokinetic properties of JATH and amended ligands

The ADMET@SAR online database looked into increased bioavailability and blood brain barrier, as well as reduced carcinogenicity and toxicity. Table-05 shows the results of the analyses of the parent drug and amended analogues.

Table-05: Analysis of pharmacokinetic parameters by ADMET@SAR Values of the Ligands.

Factors	JATH	D-1	D-2	D-3	D-4
Blood brain barrier	(+)	(+)	(+)	(+)	(+)
	0.9060	0.9060	0.9663	0.9060	0.9103
Human intestinal absorption	(+)	(+)	(+)	(+)	(+)
	0.7947	0.7947	0.8492	0.7947	0.8002
Caco-2 permeability	(+)	(+)	(-)	(+)	(+)
	0.9270	0.6871	0.5527	0.5298	0.6283
P-glycoprotein inhibitor	(-)	(+)	(+)	(+)	(+)
	0.5595	0.8776	0.8044	0.9250	0.9690
Human ether a-go-go-related(hERG) gene inhibition	(-)	(-)	(+)	(+)	(+)
	0.6374	0.4128	0.7104	0.6578	0.8974
Acute oral toxicity (c)	III	III	III	III	III
	0.7143	0.6918	0.6157	0.6918	0.7389
Hepatotoxicity	(-)	(+)	(+)	(+)	(+)
	0.7000	0.7500	0.6500	0.6750	0.7500
Aqueous solubility	(-)	(-)	(-)	(-)	(-)
	2.7364	2.9461	3.8277	2.9461	3.2299
Carcinogenicity	0.5946	0.5856	0.5990	0.5856	0.5560
Rat Acute Toxicity	2.6103	2.6883	2.7577	2.6883	2.6834
CYP450 2C9	0.9122	0.8222	0.6658	0.8222	0.8012

Molecular docking analysis

Molecular docking simulations with Autodock Vina were used to check the binding mechanisms of changed molecules. Molecular docking is one of the most popular methodologies in structure-based drug discovery for analyzing the atomic level interaction between a tiny molecule and a protein. AutodockVina was used for docking analysis, with AutoDock Tools (ADT) from the PyRx software package utilized to convert pdb into pdbqt format for protein and ligand input. For a

negative score, kcal/mole was used as a metric to measure ligand binding affinity. The root mean square deviation (RMSD) of the docked conformation with respect to the experimental conformation, as the threshold for effective docking approach, indicates the docking protocol's dependability. After that, using comparable optimized docking conditions, all developed analogues were docked into the same binding site pocket of TNIK. The docking research revealed that all compounds, including the parent molecule, have binding affinities of -8.5 to -10.3 kcal/mol. Table 5 demonstrated that when compared to the parent molecule, JATH, all modified analogues had high binding affinities, with D-3 having the highest binding affinity. These findings showed that adding a water molecule to JATH boosted binding affinity, although adding functional groups such -CH_3, -C_6H_6, -$C_{10}N_8$, -$C_{10}H_8$+CH_3, and -C_6H_6+CF_3 caused minor oscillations in binding affinities; nevertheless, adding naphthalene and benzene rings elevated binding affinity. The derivative D-3 counterpart has the strongest binding affinity. According to the results of the post docking study, all compounds had π-alkyl interactions with the PAS residues LEU160, VAL31, VAL39, and VAL170 in the enzyme's active site. D-3 interacts with LEU160, VAL31, VAL39, VAL170, and ALA52 residues to generate supportive π-alkyl bonds. Moreover, changes to JATH boosted the π-engagements with the kinase domain, whilst elevating their polarity resulted in the development of hydrophobic interactions associations. The D-3 molecule formed the strongest H-bonds with the five -alkyl contacts of LEU160, VAL31, VAL39, VAL170, and ALA52 residues. D-1, D-2, and D-4, on the other hand, established H-bonds with the LEU160, VAL31, VAL39, and VAL170 residues. Despite having varied bonding distances, D-1 and D-4 had similar binding conformations. Along with LEU160, D-1, D-2, D-3, and D-4 showed the highest number of π- π- interactions, indicating a strong binding to the active site. According to reports, LEU160 is the most vital ingredient of the PAS, regulating the adaptability of metabolites to the catalytic site as well as allosterism, and aromatic interactions with the LEU160 residue attenuate the bacteriostatic axioms for some TNIK kinases that act as indispensable activators.

Table-06: Free energy of binding values (kcal/mol) for the ligands and proteins

DRUG / PDB ID	Resolution (Å)	JATH	D-1	D-4	D-3	D-2
6RA5	2.90 Å	-8.5	-9.3	-9.9	-10.3	-9.3
5BUA	1.81 Å	-7.4	-7.8	-8.4	-8.9	-8.4
3IGL	1.80 Å	-6.5	-6.9	-7.8	-7.7	-7.9
2PCX	1.54 Å	-6.6	-7.1	-7.6	-7.5	-7.3
2ADY	2.50 Å	-6.2	-7	-7.4	-7.3	-6.9
1YCS	2.20 Å	-5.9	-6.6	-8.3	-7	-7.1
1KZY	2.50 Å	-6.8	-6.7	-8.3	-7.5	-6.9
1GZH	2.60 Å	-6.5	-7	-7.8	-7.5	-7.1

Homo-Lumo, Gap, Hardness and Softness Analysis

The energies (ε) of frontier HOMOs (highest occupied molecular orbitals) and LUMOs (lowest unoccupied molecular orbitals) were accustomed to determine the hardness and softness of all

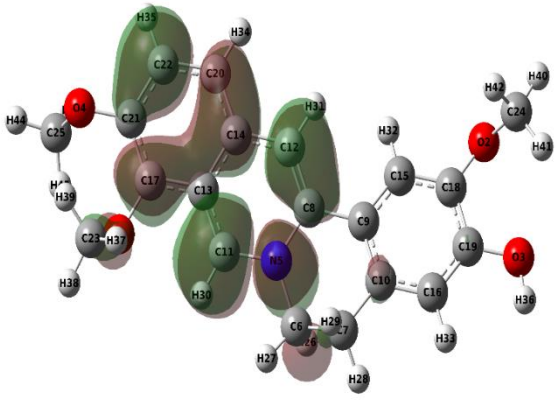
compounds[39]. The following equation was used to compute the hardness (H) and softness (S) of the medications using the Parr and Pearson interpretation of DFT and the Koopmans theorem and represented the views in Figure-05.

$$\eta = \frac{\varepsilon_{HOMO} - \varepsilon_{LUMO}}{2}$$

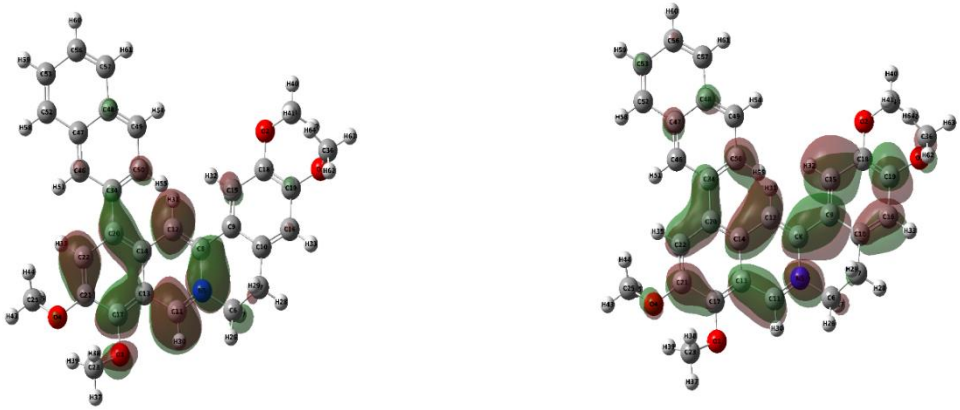
$$s = \frac{1}{\eta}$$

Table-07: HOMOs, LUMOs, Gaps, Hardness, and Softness

Molecules (chair)	εHOMO	εLUMO	Gap	H (Hardness, Gap/2)	S (Softness, 1/Hardness)
JATH	-0.10792	-0.03480	0.07312	0.03656	27.352298
D-1	-0.17380	-0.03283	0.14097	0.070485	14.187416
D-2	-0.17994	-0.04110	0.13884	0.06942	14.405071
D-4	-0.18255	-0.05527	0.12727	0.063635	15.714623
D-3	-0.11548	-0.05026	0.06522	0.03261	30.66544



HOMO JATH LUMO



HOMO D3 (JATH-$C_{10}H_8$-CH_3) LUMO

Figure-05: Frontier molecular orbitals of JATH and D-3

Binding Site and Docking Analysis

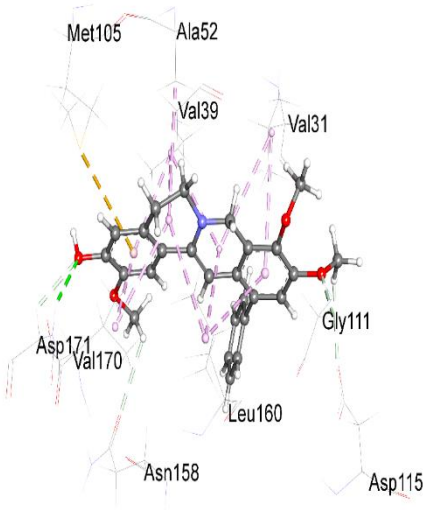
Computed Atlas of Surface Topography of proteins (CASTP) anticipated the energetic requisite concise of JATH. The CASTP reduced the binding site for JATH were used for grid generation. The deducted highest binding free energy conformer with the particular protein that was carefully chosen for analysing using PyMOL Molecular Graphics System [40]. The Discovery Studio 2016 designated overall view in Figure-06.

Table-08: The stoichiometry, electronic energy, enthalpy, Gibbs free energy

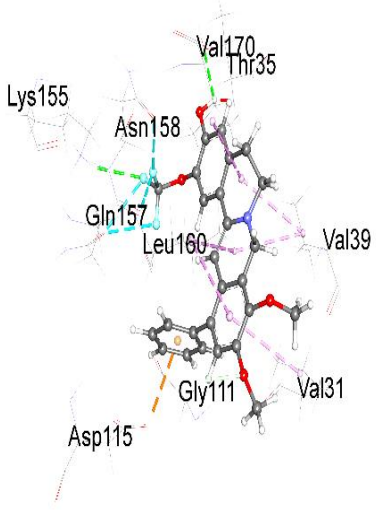
Name of Compounds	Stoichiometry	Electronic Energy (Hartree)	Enthalpy (Hartree)	Gibbs Free Energy (Hartree)	Dipole Moment (Debye)
JATH	$C_{20}H_{20}NO_4$	-1129.391748	-1129.390804	-1129.466937	5.0041
D-1	$C_{26}H_{24}NO_4$	-1513.679270	-1513.678326	-1360.463141	1.9585
D-4	$C_{30}H_{26}NO_4$	-1513.679270	-1513.678326	-1513.752931	1.5964
D-2	$C_{26}H_{21}F_3NO_4$	-1658.126774	-1658.125830	-1658.218854	1.4022
D-3	$C_{31}H_{28}NO_4$	-1553.240938	-1553.239993	-1553.337125	4.4084

Non-bonding interactions between chair ligands D-1, D-2, D-3 and D-4 with 6RA5 attained through the analysis accompanying with discovery studio

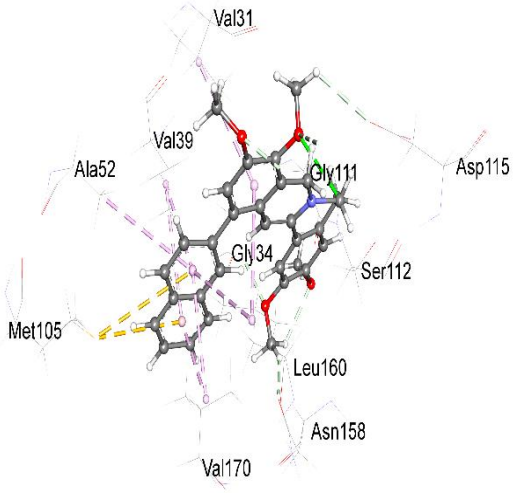
The hydrogen bond was perceived in the imitative of D-3 that might be compulsory for DNA configuration. It was revealed that the binding affinity was intensified in hydrogen bond distance. The strong hydrogen bonds were investigated in a conventional type bond with SER112 (2.96909 Å) bond distance and a carbon hydrogen type bond with ASN158 (2.97076 Å) bond distance existing in D-3-6RA5 compared to JATH-6RA5 where a conventional type bond with LYS54 (2.8236 Å) and a carbon hydrogen type bond with CYS108 (2.9386). A number of hydrophobic bonds were also twisted in the D-3-6RA5 conformer. Bonding interacting amino acid, LEU160 attributing bonding distance 5.38841Å in Alkyl bond demonstrated that better binding dependability of D-3-6RA5 analogue and respective protein as well as others bonds was also observed that expelled the most prominent binding interaction. Others Pi-Sulfur bond also demonstrated interacting amino acid, MET105 attributing bonding distance 5.13989Å demonstrating better dependability for interaction of D-3-6RA5 analogue rather than other analogues as well as parent drug. The binding site of ligand-proteins has been represented in Figure-06.



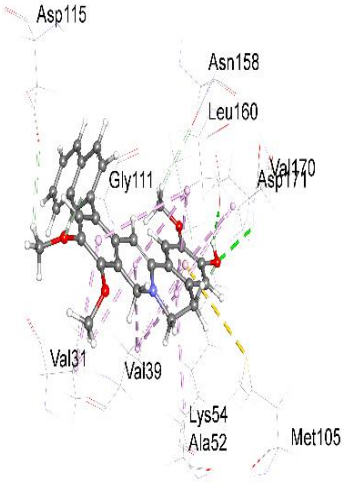
D1



D2



D3



D4

Figure-06: Active Binding sites of ligands-protein

Table-09: Nonbonding interaction data with Binding affinity (kcal/mol) of maternal drug JATH and derived compounds

.

Compounds	Binding Affinity (kcal/mol)	Hydrogen Bonds			Hydrophobic Bonds			Others		
		Bonding Types	Interacting Amino Acid	Distance (Å)	Bonding Types	Interacting Amino Acid	Distance (Å)	Bonding Types	Interacting Amino Acid	Distance (Å)
Jatrorrhizine	-8.5	Conventional	LYS54	2.82326	Alkyl	LEU160	5.27878	Pi-Sulfur	MET105	5.05038
						VAL39	4.8527			
		Carbon Hydrogen bond	GLU69	2.6195		LEU160	4.92069			
						VAL170	4.76318			
			CYS108	2.9386	Pi-Alkyl	VAL31	5.41001			
			LYS54	2.81921		LEU160	5.13659			
			GLY111	2.6871		VAL39	4.65413			
			ASP171	2.64856		VAL170	3.73636			
D-1	-9.3	Conventional	ASP171	2.66149	Alkyl	LEU160	4.81745	Pi-Sulfur	MET105	4.94595
		Carbon Hydrogen bond	ASP115	2.82641		VAL31	5.05454			
						VAL39	4.94379			
			ASN158	2.99467		LEU160	4.46649			
						VAL39	4.33083			
			GLY111	2.61758		ALA52	4.52659			
			ASP171	2.63224		VAL170	4.48438			
					Pi-Alkyl	VAL39	4.41739			
						VAL170	3.95784			
						VAL31	4.87193			
						LEU160	5.31446			
D-3	-10.3	Conventional	SER112	2.96909	Alkyl	LEU160	5.38841	Pi-Sulfur	MET105	5.13989
									MET105	4.51464
		Carbon Hydrogen bond	ASP115	2.97076	Pi-Alkyl	VAL31	4.87626			
			ASN158	2.32759		LEU160	4.71361			
						VAL39	4.10805			
			UNK1	2.62012		ALA52	5.26104			
						LEU160	5.01762			
			GLY34	2.48968		VAL170	4.30107			
						VAL39	4.78621			
			GLY111	2.37164		VAL170	3.89768			
			GLY111	2.87524						
D-4	-9.9	Conventional	ASP171	2.75739	Alkyl	LEU160	4.8143	Pi-Sulfur	MET105	4.99751
						VAL31	5.0001			
			ASP171	2.7126		VAL39	4.98467			
		Carbon Hydrogen bond	ASP115	2.85349		LEU160	4.47312			
			ASN158	3.04499		VAL39	4.31375			
			LYS54	2.81012		ALA52	4.50504			
			GLY111	2.60191		VAL170	4.5383			
					Pi-Alkyl	VAL39	4.37415			
						VAL170	3.98949			
						VAL31	4.82572			
						LEU160	5.35434			

Compounds	Binding Affinity (kcal/mol)	Hydrogen Bonds			Hydrophobic Bonds			Halogen Bonds			Others		
		Bonding Types	Interacting Amino Acid	Distance (Å)	Bonding Types	Interacting Amino Acid	Distance (Å)	Bonding Types	Interacting Amino Acid	Distance (Å)	Bonding Types	Interacting Amino Acid	Distance (Å)
D-2	-9.3	Conventional	THR 35	2.78692	Alkyl	VAL39	4.46959	Halogen (Fluorine)	GLN157	3.69256	Pi-Anion	ASP 115	3.87974
						LEU160	4.80722		GLN157	3.11532			
									GLN157	3.15823			
			LYS 155	2.90942		VAL39	4.237178		ASN158	2.8987			
						VAL170	4.48684						
		Carbon Hydrogen bond	GLY 111	2.28431	Pi-Alkyl	VAL31	4.7436						

CONCLUSION

The overview of total research revealed some functional groups directed Serine/threonine kinase inhibitors developed by modifying a known inhibitor, JATH. Alteration of JATH along with −($C_{10}H_8$+CH_3) replacement by means of aromatic ring and −CH3 although decreased the dipole moment but increased the aptitude of π-π interlinkage of the derived component. Furthermore, as they demonstrated the lower HOMO–LUMO gaps these reformed amalgams were supplementary sensitive than JATH. Moreover, ADMET analyses proposed that amended conformers were fewer lethal and have enhanced pharmacokinetic profiles than the maternal drug.

In this computational study, the derivative of D-($C_{10}H_8$+CH_3) demonstrated binding energy -10.3 (kcal/mol) with 6RA5 macromolecule compared to the maternal medicament JATH that demonstrated binding energy -8.5 (kcal/mol) with the equivalent macromolecule through significant altered pharmacokinetics, HOMO-LUMO, thermodynamics properties. From these outcomes further long-established the aptitude of ($C_{10}H_8$+CH_3)-directed analogues due to binding capability simultaneously to the energetic positions of 6RA5 and so they were potentiated as prospective medicaments for the therapy of breast cancer disease.

Finally, JATH-($C_{10}H_8$+CH_3)-6RA5 might be the potential medicament as the target of the treatment of breast cancer in future perspective applications.

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AUTHORS' CONTRIBUTION

Idea generation, simulation of Drug and report writing, Anthology of information and concoction, Conceptualization, Methodology, Supervision and Data analysis were implemented, read and finally approved the paper by all researchers and authors.

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