ijlpr 2020; doi 10.22376/ijpbs/lpr.2020.10.5.P102-110

International Journal of Life science and Pharma Research

Research Article

Pharmaceutical Chemistry for Better Medicinal Drug

Molecular Docking studies of N-Methyl- 2, 3 -Disubstituted Quinazolin-4-Ones Scaffold.

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Abstract: In recent days, synthesis of anticancer molecules having both low adverse effects and specific protein targeting are seldom. Synthesis of anticancer molecules having both low adverse effects and specific protein targeting is challenging. The main objective of our study was to develop molecules that can target activated protein kinase P38 alpha and activin receptor (ALK2) kinase for treating carcinoma. P38 alpha is involved in cell differentiation, apoptosis, and autophagy.Activin receptor (ALK2) kinase is responsible for mutations of cancerous cells. The synthesis of N-Methyl - 2, 3 -Disubstituted Quinazolin-4-Ones was carried out by refluxing of 1-methyl-2-(pyridinyl)-1,2-dihydro-4H-3,1-benzoxazin-4-one with 4-substituted phenyl-1,3-thiazol-2-amines. The molecular docking of 1-methyl-3-(4-substituted phenyl-1,3-thiazol-2-yl)-2-(pyridin-3-yl)-2,3-dihydroquinazolin-4(1H)-one (5Da1-5Dk11) and 1-methyl-3-(4-substituted phenyl-1,3-thiazol-2-yl)-2-(pyridin-4-yl)-2,3-dihydroquinazolin-4(1H)-one (5Ea1-5Ek11) derivatives were carried out using Schrödinger Glide (version 2020_1) software. Twenty-two quinazoline-4-one derivatives were docked into selective P38 alpha and ACVR1 (ALK2) kinase with PDB code 3GC7, 6GI6. Based on the docking score, comparison between quinazolin-4-one derivatives, co-crystallized Ligands interaction was evaluated using 5-Fluorouracil as standard. Best activity was found in compounds 5Df6, 5Dd4, 5Ed4 and 5Ef6 with ACVR1 (ALK2) kinase with score of -8.223, -7.936, -8.123, -7.907 and 5Df6, 5Dh8, 5Eb2 and 5Ee5 with P38alpha with score of -7.19, -7.027, -6.698, -6.789 Kcal/mol against enzymes responsible for treatment for cancer compare with reference drug score -5.765 and -6.195. This study will help in the design and development of a drug that gives room for the synthesis of a new selective ACVR1 (ALK2) kinase and P38alpha enzyme inhibitor with predetermined affinity and activity of the compound.

Keywords: Molecular docking, P38alpha Mitogen-activated protein kinase, ACVR1 (ALK2) kinase, anticancer, 1-methyl 2,3-dihydro quinazolin-4(1H)-one.

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Recieved On 08 June 2020
Revised On 20 September 2020
Accepted On 23 September 2020
Published On 04 December 2020

Funding This research did not receive any specific grant from any funding agencies in the public, commercial or not for profit sectors.

Citation ND Nizamuddin, Hindustan Abdul Ahad and Nayakanti Devanna , Molecular Docking studies of N-Methyl- 2, 3 -Disubstituted Quinazolin-4-Ones Scaffold..(2020).Int. J. Life Sci. Pharma Res.10(5), P102-110 http://dx.doi.org/10.22376/ijpbs/lpr.2020.10.5.P102-110

1. INTRODUCTION

Cancer is a significant problem in developed as well as undeveloped countries. In 2018, GLOBOCAN, *International Agency for Research on Cancer (IARC, 2018)* reported 18.1 million as a new cancer case, and 9.6 million people have died due to cancer. Stomach cancer was found as most prevailing cause as any other cancer disease[1]. There are many chemotherapeutic strategies for the cancer treatment that have been proposed and tested. The main procedures of cancer treatments are surgery, irradiation, and chemotherapy[2]. Although chemotherapeutic management has been showing significant results in patients, the continuous research for new anticancer agents remains important[3]. In medicinal chemistry, chemical agents play a crucial role in designing of novel agents. Quinazoline is one such agent for the development of the anticancer drugs[4]. Quinazoline is a framework of fused bicyclic heterocyclic, also known as benzo-1,3-diazanaphthalene. In the early 19th century, the development of drugs was based on trial and error method, so it was time consuming and expensive.. Today, molecular modeling with the aid of computer hardware and software has deducted this risk and the process of discovery is more effective in cost and time. Quinazolines works as an anti-cancer agent through potent inhibition of various enzymes such as cyclic GMP phosphodiesterase, DNA repair proteins[5], epidermal growth factor receptor tyrosine kinase (EGFR-TK), dihydrofolate reductase (DHFR), folate thymidylate synthase[6], tyrosine kinase andaldose reductase[7]. Interest in chemistry of quinazoline-4-one derivatives has significantly grown, primarily due to the discovery of new properties [8]. Derivatives of quinazolinone are found to show a wide range of bioactivities that translate into a broad spectrum of biological effects such as antitubercular[19], anti-inflammatory[9,11], antimicrobial[10], antioxidant[12], and analgesic[13]. Synthesis of quinazolines by adding substituted binding groups such as pyridinyl ring at position 2, and substitution of phenyl thiazole at position 3 to a quinazoline ring leads to an increased inhibitory activity of cancer cells. The purpose of this work is to dock the molecules containing N-Methyl-3-Pridinyl-3-thiazol phenyl-quinazolinone and N-Methyl-4-Pridinyl-3-thiazol phenyl-quinazolinone nucleus to different types of proteins, as mentioned in Table 1.

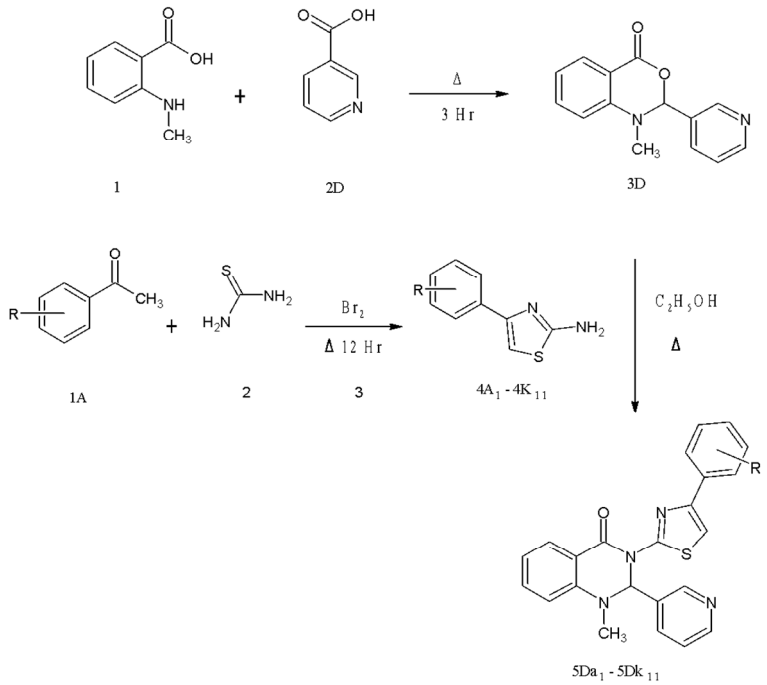
Table 1. ***Details of proteins used for Docking studies***

S. No	Name of the protein	Source	PDB ID	Organism
01	P38alpha-Mitogen-activated protein kinase	RCSB-PDB	3GC7	Homo sapiens
02	ACVR1 (ALK2) kinase	RCSB-PDB	6GI6	Homo sapiens

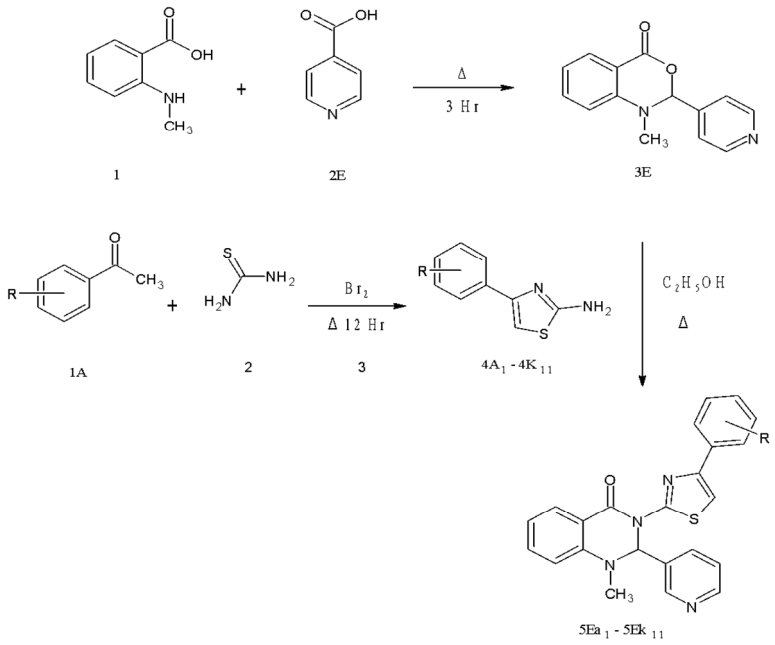
2. MATERIALS AND METHODS

2.1. *Synthesis*

The synthesis of 1-methyl-3-(4-substituted phenyl-1,3-thiazol-2-yl)-2-(pyridinyl)-2,3-dihydro quinazolin-4(1H)-one (5Da1-5Dk11) and 1-methyl-3-(4-substituted phenyl-1,3-thiazol-2-yl)-4-(pyridinyl)-2,3-dihydro quinazolin-4(1H)-one (5Ea1-5Ek11) were achieved through steps outlined in Scheme I & II. The intermediate's 1-methyl-2-(pyridinyl)-1,2-dihydro-4H-3,1-benzoxazin-4-one (3D) and 1-methyl-2-(thiophenyl)-1,2-dihydro-4H-3,1-benzoxazin-4-one (3E) were obtained by reacting N-Methyl Anthranilic acid (1) with Pyridine-3-carboxylic acid (2D) and Pyridine-4-carboxylic acid (2E). The second intermediate 4-substituted phenyl-1,3-thiazol-2-amine (4a1-4k11) was obtained by mixing aromatic ketones (1), and thiourea (2) in ethanol where bromine (3) was added dropwise. Finally, the desired title compounds were obtained by reacting 3D and 3E with 4-substituted phenyl-1,3-thiazol-2-amines (4a1-4k11) in presence of K_2CO_3 and rectified spirit[18, 19]. Good yields were observed during the synthesis of the compounds.



Series I. Scheme 1: synthesis of 1-methyl-3-(4-substituted phenyl-1,3-thiazol-2-yl)-2-(pyridin-3-yl)-2,3-dihydroquinazolin-4(1H)-one (5Da1-5Dk11)



Series II. Scheme II: synthesis of 1-methyl-3-(4-substituted phenyl-1,3-thiazol-2-yl)-2-(pyridin-3-yl)-2,3-dihydroquinazolin-4(1H)-one (5Da1-5Dk11)

2.2. *Molecular docking studies*

The active molecules were subjected to molecular docking studies against various enzymes such as P38alpha mitogen-activated protein kinase[14] and Activin A receptor, type 1 (ACVR1) also known as Activin receptor-like kinase-2[15] (ALK2). The above enzymes were validated as anticancer targets.

2.3. *Software used*

Schrödinger Glide (version 2020-1).

2.4. *Preparation of target protein X-ray structure*

The three-dimensional (3D) structure of proteins used fordocking studies are mentioned in Table 2. It was downloaded from Protein Data Bank (rcsb-PDB). Before docking the Ligand into the protein's active site, the protein was prepared using the protein preparation wizard of Schrödinger molecular docking software[16]. The active site of the protein was defined for generating the grid. The Ligand was docked into the prepared grid, for which "standard precision mode" was selected. No constraints were defined.

Table 2. ***Docking source of active compounds against ACVR1 (ALK2) kinase enzyme & P38alpha Mitogen-activated protein kinase.***

Code	P38alpha Mitogen-activated protein kinase.	Code	ACVR1 (ALK2) kinase
5Df6	-7.19	5Df6	-8.223
5Dh8	-7.027	5Dd4	-7.936
5Eb2	-6.698	5Ed4	-8.123
5Ee5	-6.789	5Ef6	-7.907
3GC7	-10.669	6GI6	-10.518
5-FU	-5.765	5-FU	-6.195

2.5. *Docking*

Docking was carried out using Schrödinger Glide (version_1) (Grid-Based Ligand Docking with Energies) software**.** Glide searches were performed for identification of favorable interactions between ligand molecules and a receptor molecule. A ligand pose refers to the position and orientation of a ligand related to a receptor, along with its conformation in flexible docking[17]. The Ligand Poses Glide and passes through a series of hierarchical filters that evaluate the interaction of the Ligand with the receptor. The inceptive screens, test the spatial fit of the Ligand to the defined active spot and scrutinize the complementary of ligand-receptor communications using a grid-based method, which was patterned after the empirical Chem Score function. These inceptive screens enter the final stage of the algorithm, which involves both evaluation and minimization of a grid approximation to the OPLS-AA non bonded ligand-receptor interaction energy. Final scoring is accomplished on the energy-minimized poses. The results are postulated in Tables 3 & 4, Figures 3 to 13, respectively.

Table 3. ***Structural details and Docking score of 1-methyl-3-(4-substituted phenyl-1,3-thiazol-2-yl)-2-(pyridin-3-yl)-2,3-dihydroquinazolin-4(1H)-one (5Da1-5Dk11).***

Code	R	Docking score of 5Da1-5Dk11			
		P38 alpha mitogen-activated protein kinase	Glide Energy	ACVR1 (ALK2) kinase	Glide Energy
5Da1	-H	-6.621	-47.489	-7.041	-47.488
5Db2	$-3NH_2$	-6.927	-49.201	-7.906	-49.66
5Dc3	$-4NH_2$	-6.832	-49.793	-7.313	-48.045
5Dd4	-2OH	-6.82	-50.36	-7.936	-50.775
5De5	-4OH	-6.935	-49.996	-6.292	-42.791
5Df6	-2,4OH	-7.19	-50.927	-8.223	-50.86
5Dg7	-4Cl	-6.723	-48.675	-6.927	-48.183
5Dh8	-2,4Cl	-7.027	-49.546	-6.538	-47.863
5Di9	$-4CH_3$	-6.823	-48.031	-5.882	-41.789
5Dj10	$-4OCH_3$	-6.391	-49.758	-6.921	-48.203
5Dk11	$-3NO_2$	-6.413	-50.628	-6.945	-49.339
Co Crystal		3GC7	-65.494	6GI6	-50.604
Standard Drug used		5-Fluorouracil	-23.759	5-Fluorouracil	-23.759
Docking Score		-5.765		-6.195	

Table 4. ***Structural details and Docking score of 1-methyl-3-(4-substituted phenyl-1,3-thiazol-2-yl)-2-(pyridin-4-yl)-2,3-dihydroquinazolin-4(1H)-one (5Ea1-5Ek11)***

Code	R	Docking score of 5Ea1-5Ek11			
		P38alpha mitogen-activated protein kinase	Glide Energy	ACVR1 (ALK2) kinase	Glide Energy
5Ea1	-H	-6.523	-46.231	-7.031	-45.735
5Eb2	$-3NH_2$	-6.698	-43.388	-7.732	-47.73
5Ec3	$-4NH_2$	-6.639	-48.881	-6.943	-46.219
5Ed4	-2OH	-6.662	-48.752	-8.123	-48.048
5Ee5	-4OH	-6.789	-49.792	-7.423	-48.773
5Ef6	-2,4OH	-6.669	-49.889	-7.907	-51.466
5Eg7	-4Cl	-6.633	-48.886	-5.551	-42.081
5Eh8	-2,4Cl	-6.659	-48.336	-6.528	-46.553
5Ei9	$-4CH_3$	-6.415	-48.105	-7.004	-46.345
5Ej10	$-4OCH_3$	-6.148	-49.683	-6.906	-46.971
5Ek11	$-3NO_2$	-5.983	-50.525	-6.932	-47.986
Co Crystal		3GC7	-65.494	6GI6	-50.604
Standard Drug used		5-Fluorouracil	-23.759	5-Fluorouracil	-23.759
Docking Score		-5.765		-6.195	

3. RESULTS AND DISCUSSION

3.1. *Molecular Docking*

To incorporate protein in the docking process, virtual screening experiments are the most convenient ways. Molecular docking is used in modern drug design which helps in understanding the interaction of ligands and receptors. Ramachandran plot was obtained from RAMPAGE, which serves as quality assessment tool of prepared macromolecule[20]. In this study, the percentage of residues in the favored region and allowed region was 98.3%, and 1.7% in 3GC7 respectively. The rate of residues in the favored region and allowed area was 97.6% and 2.4% in 6GI6 respectively. Moreover, the number of residues in the outlier region was zero, shown in Figures 1 & 2. The structural analysis and verification server were also used to check and validate the protein structure. The overall standard factor of ERRATA analysis was reported in literature procedure[21]. The docking for 3GC7 and 6GI6 could be 97.9412% and 94.7917% which is as appropriate as high-resolution structures. In general, they produce values around 95% or higher. In the VERIFY3D result: 3GC7, 91.12% of the residues have averaged 3D-1D score ≥ 0.2. This value is higher than the pass value, which is at least 80% of the amino acids with a score of ≥ 0.2 in the 3D-1D profile. 6GI6, 86.91% of the residues have averaged a 3D-1D score of ≥ 0.2. This value is higher than the pass value, which is at least 80% of the amino acids with a score of ≥ 0.2 in the 3D-1D.

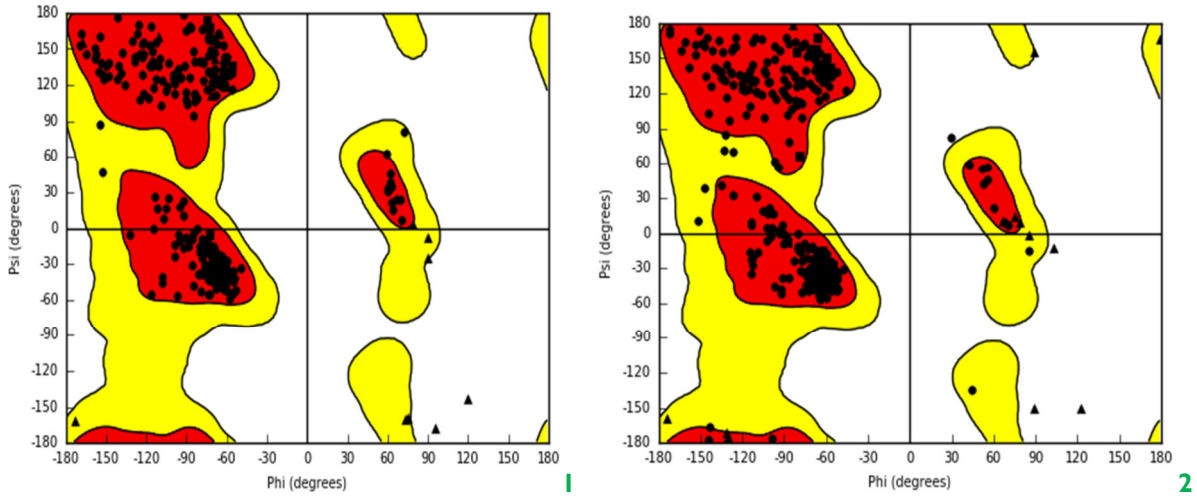


Fig 1 & 2. Ramachandran plot macromolecule prepared for docking for 3GC7 (A) & 6GI6 (B).

Sharma et. al.,[22] reported the molecular docking studies to predict the possible binding mode of this series of compounds, 5Df6, 5Dd4, 5Ed4 and 5Ef6 with ACVR1 (ALK2) kinase (PDB ID: 6GI6). 5Df6, 5Dh8, 5Eb2 and 5Ee5 with P38alpha (PDB ID: 3GC7) the docking study was performed using 5-Fluorouracil as standard. Figures 3 to 13, and Table 1 show that compounds 5Df6, 5Dd4, 5Ed4 and 5Ef6, 5Df6, 5Dh8, 5Eb2 and 5Ee5 are the most active derivative's and were found to have the best fit. These compounds with the best activity and the best docking score of -8.223, -7.936, -8.123, -7.907 and -7.19, -7.027, -6.698, -6.789 Kcal/mol prompted us to look for the possible interactions that formed with Asp293, Tyr219 and Ser290 and Lys53, Gly110 and Leu104. The residues Asp293, Tyr219, Ser290 establish hydrogen bonding interactions with –C=O and –N-H of the derivative compounds. (Figures 3-8).

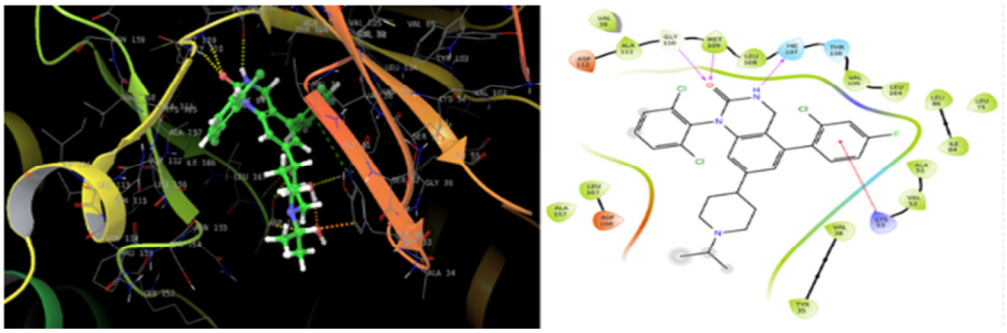


Fig 3. 3D and 2D pose 3GC7

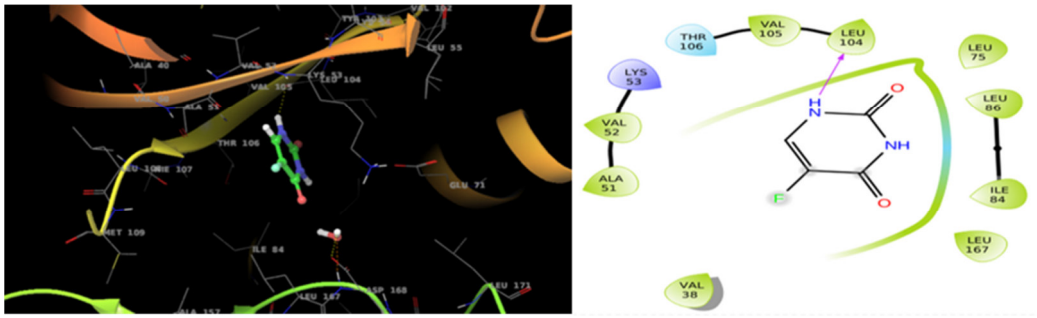


Fig 4. 3D and 2D pose 5-Fluoruracil possible interaction at the binding cleft of P38alpha domain

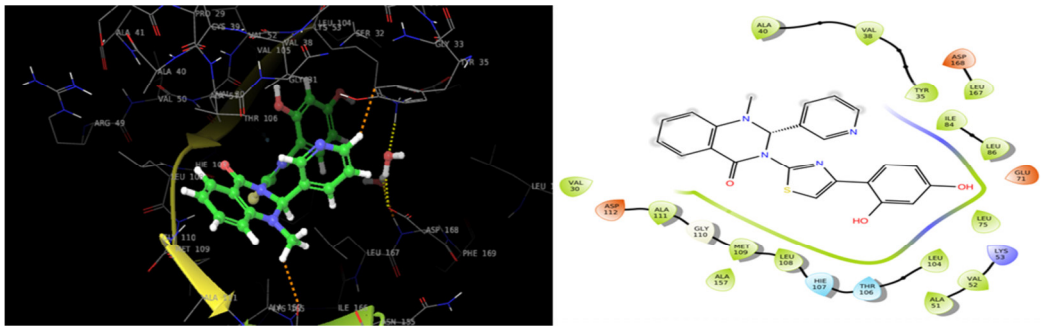


Fig 5. 3D and 2D pose 5Df6 possible interaction at the binding cleft of the P38alpha domain.

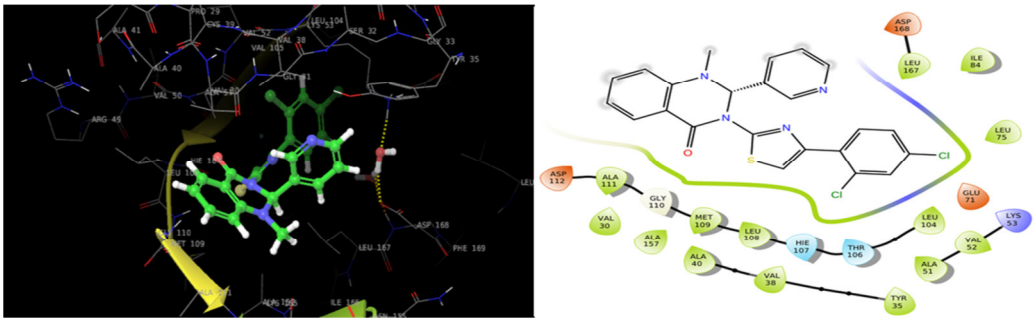


Fig 6. 3D and 2D pose 5Dh8 possible interaction at the binding cleft of the P38alpha domain.

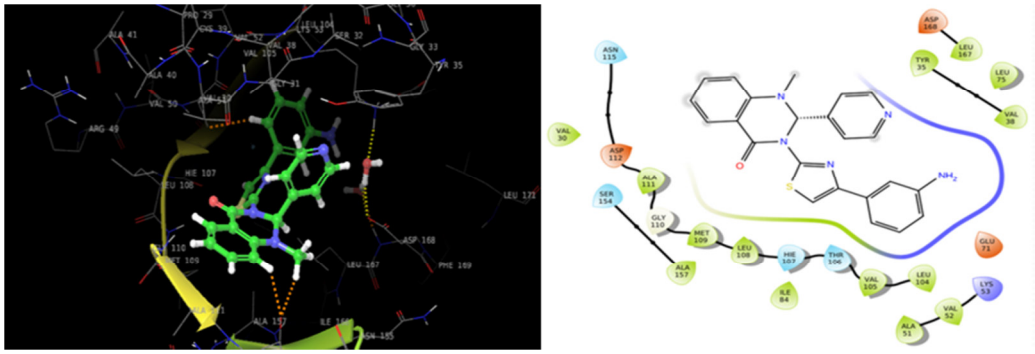


Fig 7. 3D and 2D pose 5Eb2 possible interaction at the binding cleft of the P38alpha domain.

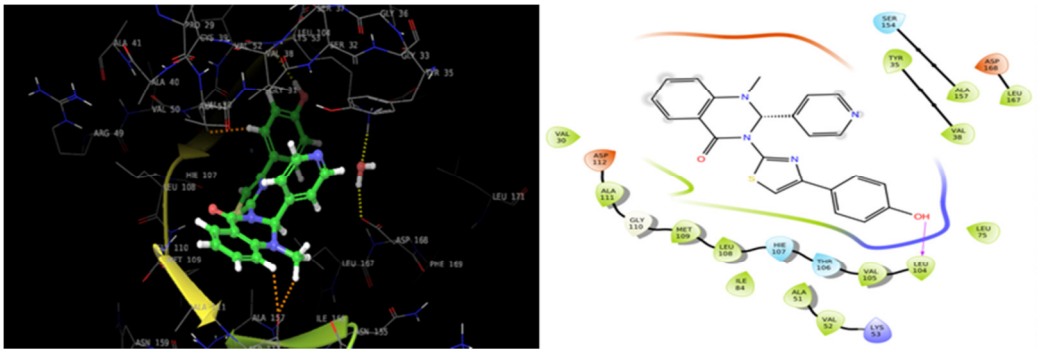


Fig 8. 3D and 2D pose 5Ee5 possible interaction at the binding cleft of the P38alpha domain.

Compounds 5Df6, 5Dd4, 5Ed4 and 5Ef6, and 5-Fluorouracil are favourably fitted into the ACVR1 (ALK2) kinase domain (Figures 9-13). The residue Lys53, Gly110, and Leu104 establish hydrogen bonding interactions with –C=O and –N-H as the interaction of synthesized compounds.

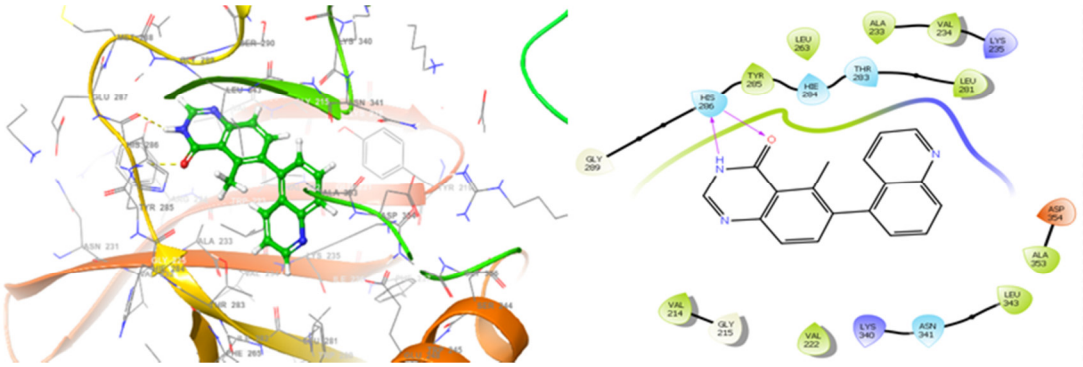


Fig 9. 3D and 2D pose 6GIP

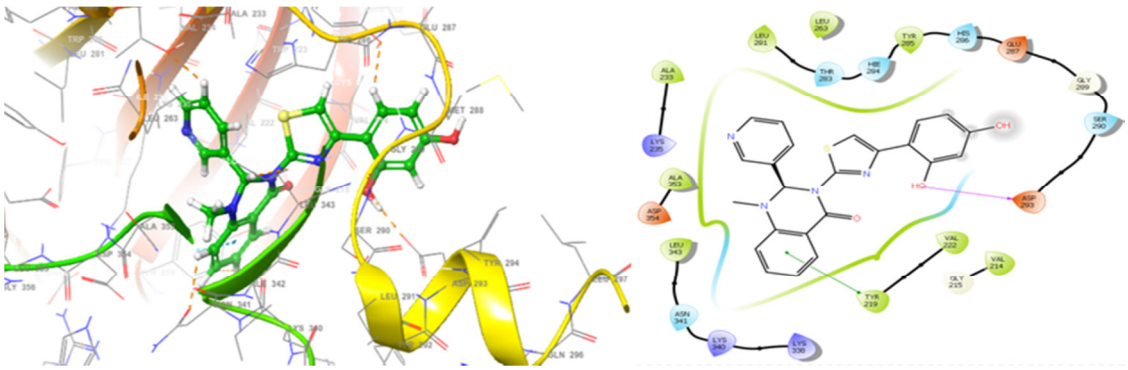


Fig 10. *3D and 2D pose 5Df6 possible interaction at the binding cleft of ACVR1 (ALK2) kinase domain*

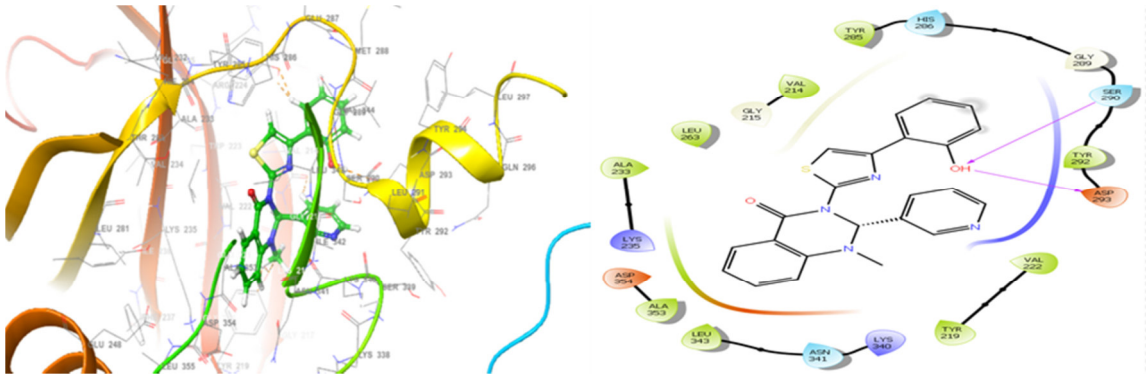


Fig 11. 3D and 2D pose 5Dd4 possible interaction at the binding cleft of ACVR1 (ALK2) kinase domain

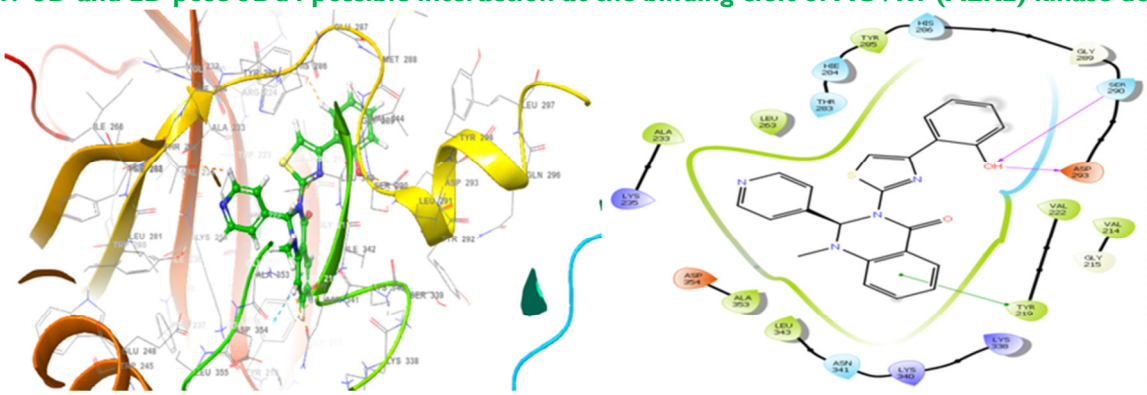


Fig 12. 3D and 2D pose 5Ed4 possible interaction at the binding cleft of ACVR1 (ALK2) kinase domain

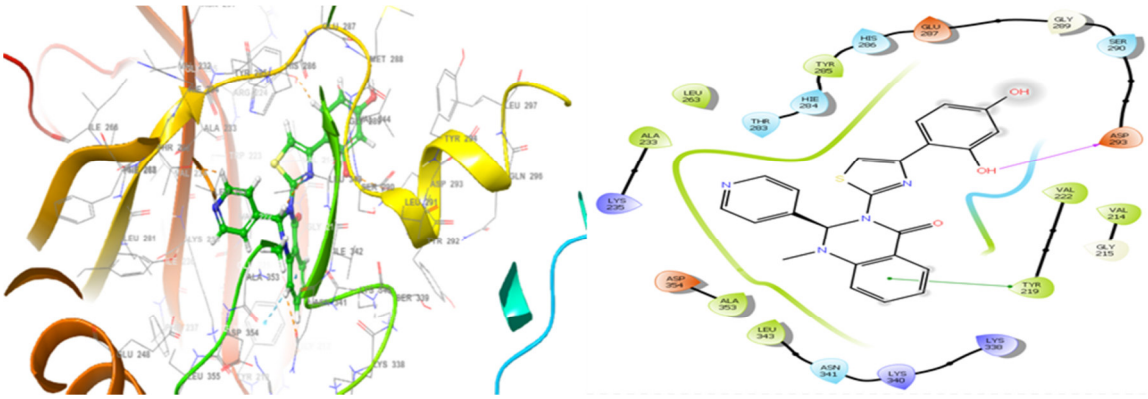


Fig 13. 3D and 2D pose 5Ef6 possible interaction at the binding cleft of ACVR1 (ALK2) kinase domain

Molecules containing functional groups such as Hydroxyl, Amine and Chloride are attached at *Ortho* and *Para* positions to the phenyl thiazole moiety. The above interaction eases the binding of molecules with the targeted proteins *viz.* ACVR1 (ALK2) kinase enzyme and P38alpha enzyme as shown in Figures 3 to 13, respectively.

4. CONCLUSION

In the present study, synthesis of 1-methyl-3-(4-substituted 1-methyl-3-(4-substituted phenyl-1,3-thiazol-2-yl)-2-(pyridin-3-yl)-2,3-dihydro quinazolin-4(1H)-one (4Da1-4Dk11) and 1-methyl-3-(4-substituted phenyl-1,3-thiazol-2-yl)-2-(pyridin-4-

yl)-2,3-dihydro quinazolin-4(1H)-one (5Ea1-5Ek11) was performed. The synthesised compounds were subjected to molecular docking studies. The docking score of 5Df6, 5Dd4, 5Ed4, 5Ef6 with ACVR1 (ALK2) kinase (6GI6) and 5Df6, 5Dh8, 5Eb2, 5Ee5 with P38alpha (3GC7) was -8.223, -7.936, -8.123, -7.907 and -7.19, -7.027, -6.698, -6.789 Kcal/mol against enzymes responsible for treatment for cancer compare with reference drug score -5.765 and -6.195 respectively. This study will help in the design and development of a drug that gives scope for the synthesis of a new selective ACVR1 (ALK2) kinase and P38alpha enzyme inhibitor with predetermined affinity and activity of the compound.

5. ACKNOWLEDGMENT

The authors would like to thank DST - SERB facility of molecular modelling and Drug Discovery division REWARDS – CPR, Raghavendra Institute of Pharmaceutical Education and Research (RIPER Campus), Anantapur-515721, Andhra Pradesh for supporting docking studies.

6. AUTHORS CONTRIBUTION STATEMENT

Mr Nizamuddin N D, designed and performed the work, wrote the manuscript. Dr. Hindustan Abdul Ahad and Prof. Nayakanti Devanna supervised, verified and corrected the manuscript. All authors have read and agreed to the published version of the manuscript.

7. CONFLICTS OF INTEREST

Conflicts of interest declared none.

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