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DOCKING STUDIES OF QUINAZOLINONES FUSED IMIDAZOLONES AS ANTICANCER AGENTS

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ABSTRACT:
A series of quinazolinones were synthesized in 2017 and characterised by IR, NMR, mass spectra and elemental analysis. All the compounds were evaluated for *in vitro* cytotoxicity against HeLa cell line (cervical cancer), MCF-7 (breast cancer), HL-60 (leukemia cells), and hepatocellular carcinoma (HepG2). Almost all compounds showed reliable results in comparison to reference cisplatin. In the present work, *in silico* study was performed on synthesized compounds taken from literature to support experimental findings or to accomplish preliminary confirmation of the observed *in-vitro* cytotoxicity using PDB ID-(1TUB) & PDB ID- (1MI7) by Molegro virtual docker 4.0.2. All the compounds showed effective binding with 1TUB in comparison to 1M17. Although these compounds have much resemblance in structure to Raltitrexed and Thymitaq which inhibit its EGFR tyrosine kinase by binding to the adenosine triphosphate (ATP)-binding site of the enzyme. But these are found to bind effectively with tubulin heterodimer (1TUB).

KEYWORDS: ITUB, IM17, Molegro virtual Docker, Quinazolinones, Docking**.**

INTRODUCTION:

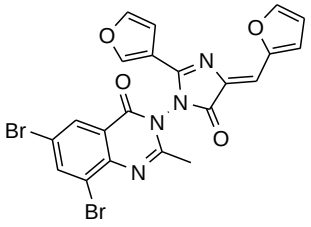
Cancer is a disease characterized by irregular unlimited growth and proliferation of abnormal cells, as well as imbalance of apoptosis. Cases of death from cancer are expected to rise by 11 million in 2030 according to WHO Cancer Fact sheet no. 297.2. So, it is essential to develop a safe and effective drug to save the lives. Quinazolinones, member of heterocyclic nitrogen-based compound were found to have broad spectrum of biological functions as antifungal, anti tumour, antimalarial, anticonvulsant, anti-inflammatory, antimicrobial, antihyperlipidemic[i]. Interest in quinazolinones as anticancer has aroused since discovery of Raltitrexed (a) and Thymitaq (b) as thymidylate enzyme inhibitors [ii].

Compounds containing imidazole were also found to have wide range of biological activites like anticancer, anti- inflammatory, cardioactivity, angiotensin II receptor antagonistic activity[iii]. Based on these findings, in 2017 we synthesized novel quinazolinone fused imidazolone derivatives and evaluate for its anticancer activities against various cell lines[iv]. In the present study, fourteen quinazolinones derivatives were taken from literature[iv] were docked into two different receptors (PDB ID-1TUB) & (PDB ID-1M17) to explore the mechanism of action of quinazolinone derivatives. These quinazolinones were closely resemble in structure with thymitaq, raltitrexed which inhibits EGFR tyrosine kinase by binding to adenosine trisphosphate (ATP). Based upon the objectives of docking simulations [v, vi], there are various kinds of molecular docking procedures such as flexible ligand docking (target as rigid molecule), rigid docking (both the target and ligand as rigid molecules) and flexible docking (both interacting molecules as flexible). Various search algorithms are employed such as genetic algorithm, fragment-based algorithms, Monte Carlo algorithms and molecular dynamics algorithms for carrying out docking process.

Binding affinity between two molecules can be predicted by the knowledge of preferred orientation. Preferred orientation of small molecule ligands to the appropriate target binding site can be predicted by molecular docking which is one of the most frequently used method in structure based drug design. Based on binding behaviour it is possible to design novel drugs and also helpful in explaining fundamental biological processes. [vii] Thus it can be used to develop more potent, discriminating and efficient drug candidates[viii]. To find out potent drug candidate, docking in combination with scoring function can be used to evaluate large databases [ix].

EXPERIMENTAL

Placing molecule in appropriate configurations to interact with receptor is known as Molecular Docking. Docking is *in-silico* approach to determine possible modes of ligand to active site of receptor. Docking studies has been performed with a group of fused imidazolone and quinazolinone derivatives taken from literature using Molegro virtual docker 4.0.2 [x] on (PDB ID -1TUB and 1M17) accessed from protein data bank [xi].



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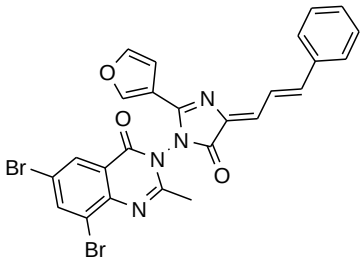

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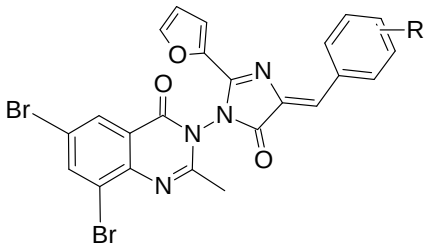
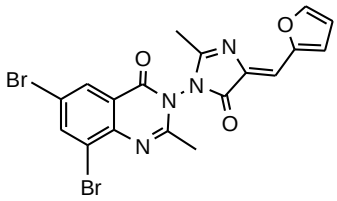


(3-10)

Compound No.	R
3	H
4	2-Cl
5	4-Ome
6	4-N(Me)$_2$
7	3-Cl
8	2-OH
9	3-OCH$_3$
10	3-NO$_2$



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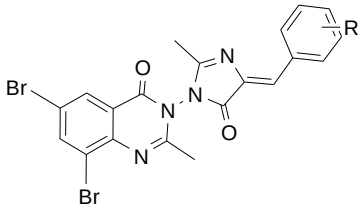

(12-14)

Compound No.	R
12	H
13	2-Cl
14	3-Cl

LIGAND PREPARATION: Structures of ligands were drawn using chem draw ultra8.0. Energy minimization was done using MMFF94force field. Energy minimization is done to help docking programme for identifying the bioactive conformer from the local minima.

PROTEIN PREPARATION: 3D crystal structure of both receptors were taken from protein data bank as (PDB ID-1TUB, 1M17). PDB were imported in Molegro virtual docker space and prepared using protein preparation. In this step, removal of water takes place. Standard

Molegro algorithm was utilized for rendering missing charge, protonation state and assigning of polar hydrogen to receptor.

DOCKING: The construction of the binding site, as you described, involves including all residues that have at least one atom within 3.5 Å of any atom in the co-crystallized inhibitor. This gives a good representation of important residues in binding pocket for protein target. To determine binding, ligands were docked into receptor using docking wizard. Compounds were ranked after docking according to their mol dock score and were visualized inside the pocket to view their affinity. Molegro docking studies also revealed nature of interaction between compound and its active site to obtain reliable results.

RESULTS AND DISCUSSION:

Docking score were analyzed for effective binding. Almost all ligands showed better interaction with tubulin heterocyclic dimer in comparison to EGFR tyrosine kinase as shown in table I and II and Fig. 1 to Fig.8. Compound 6 was found to have highest mol dock score (-207.173) when bind with tubulin(1TUB) with three hydrogen bond interaction while same compound when docked into EGFR tyrosine kinase (PDB ID- 1M17) showed only one hydrogen interaction with Mol dock score (-128.094). Except compound 10 which when docked into 1TUB showed mol dock score (-195.601) with three hydrogen bond interaction and when docked into 1M17 showed mol dock score (-126.806) with four hydrogen interaction but still its docking score is less when bind in pocket of 1M17 as compare to when bind with 1TUB.

Table I-Docking results of compounds using PDB ID(1TUB)

Compound No.	R	Mol Dock score	No. Of H-bond interaction	Ligand atom	PDB atom	Distance Annotation (°A)
1.	-	-192.95	4	1. -O of furan 2. =O of imidazolone 3. =O of quinazolinone 4. =O of quinazolinone	1. N of Asn 101 2. N of Ser 178 3. O of Ser 178 4. O of Tyr 224	2.60 3.53 2.60 2.41
2	-	-190.405	3	1. =O of quinazolinone 2. =O of quinazolinone 3. =O of imidazolone	1. O of Tyr 224 2. O of Ser 178 3. N of Ser 178	2.60 2.58 3.46
3	-H	-179.159	3	1. =O of quinazolinone 2. =O of quinazolinone 3. -O of furan	1. O of Tyr 224 2. O of Ser 178 3. O of Tyr 224	2.39 2.70 3.33
4	2-Cl	-181.244	3	1. N-1 of quinazolinone 2. O- of furan	1. O of Ser 140 2. O of Tyr 224 3. O of Tyr 224	2.58 3.24

				3. N-4 of imidazolone		2.46
5	4-OMe	-190.599	5	1. =O of quinazolinone 2. =O of quinazolinone 3. -O of furan 4. -O of 4-OMe 5. -O of 4- OMe	1. O of Tyr 224 2. O of Ser 178 3. O of Tyr 224 4. N of Asn 101 5. N of Lys 254	2.60 2.63 3.17 2.94 2.82
6	4-$N(Me)_2$	-207.173	3	1. =O of quinazolininone 2. =O of quinazolinone 3. -O of furan	1. O of Tyr 224 2. O of Ser 178 3. O of Tyr 224	2.58 2.60 3.10
7	3-Cl	-186.276	2	1. =O of quinazolinone 2. =O of quinazolinone	1. O of Tyr224 2. O of Ser 178	2.60 2.60
8	2-OH	-182.464	4	1. =O of quinazolinone 2. =O of quinazolinone 3. -O of 2-OH 4. -O of 2-OH	1. O of Ser 178 2. O of Tyr 224 3. N of Asn 101 4. N of Lys 254	2.80 2.46 2.78 2.98
9	3-OCH_3	-190.72	4	1. =O of quinazolinone 2. =O of quinazolinone 3. -O of 3- OMe 4. -O of 3- OMe	1. O of Tyr 224 2. O of Ser 178 3. N of Lys 254 4. N of Asn 101	2.60 2.65 2.76 2.99
10	3-NO_2	-195.601	3	1. =O of quinazolinone 2.=O of 3-NO_2 3. –O of furan	1.O of Ser 140 2.O of Tyr 224 3. O of Tyr 224	3.12 3.08 3.26
11	-	-169.961	3	1. -O of furan 2. =O of quinazolinone 3. =O of quinazolinone	1. N of Asn 101 2. O of Ser 178 3. O of Tyr 224	3.10 2.74 2.25
12	-H	-164.69		1. =O of quinazolinone 2. =O of quinazolinone	1. O of Ser 178 2. O of Tyr 224	2.83 2.28
13	2-Cl	-171.63	2	1.=O of quinazolinone 2.=O of quinazolinone	1. O of Ser 178 2. O of Tyr 224	2.81 2.28

14	3-Cl	-178.022	3	1. =O of imidazolone 2. =O of quinazolinone 3. =O of quinazolinone	1. -O of Tyr 224 2. -O of Ser 178 3. -O of Tyr 224	3.31 2.78 2.26

Table II- Docking Results of Compounds 1-14 using (PDB ID-1M17)

Compound No.	R	Mol dock score	No. Of Hydrogen bonding Interaction	Ligand Atom	PDB atom	Distance Annotation (°A)
1	-	-142.0976	1	1. O of furan	1. N of Gln 958	3.17
2	-	-133.502	2	1. O of furan 2. =O of quinazolinone	1. N of leu785 2. N of Gly 959	3.37 2.94
3	H	-120.265	1	1.O of furan	1. N of Gln 958	3.19
4	2-Cl	-131.912	-	-	-	-
5	4-OMe	-126.304	1	N-1 of quinazolinone	N of Gln 958	3.03
6	4-$N(Me)_2$	-128.094	1	N-1 of quinazolinone	N of Gln 958	3.19
7	3-Cl	-143.137	No	-	-	-
8	2-OH	-139.916	2	1. -O of 2-OH 2. -O of furan	1. N of Lys 782 2. N of Gln 952	2.93 3.56
9.	3-OCH_3	-134.916	2	1. -O of 3-OCH_3 2.-O of 3-OCH_3	1. N of Glu 961 2. N of Asp 960	3.00 3.07
10.	3-NO_2	-126.806	4	1. -N-1 of quinazolinone 2. -O of Furan 3. -N of NO_2 4. -O of NO_2	1. N of Glu 958 2. N of Gly 959 3. N of Arg 784 4. N of Arg 784	3.10 3.38 2.94 3.32
11.	-	-123.113	-	-	-	-
12.	H	-118.584	-	-	-	-
13.	2-Cl	-119.859	-	-	-	-
14.	3-Cl	-123.447	-	-	-	-

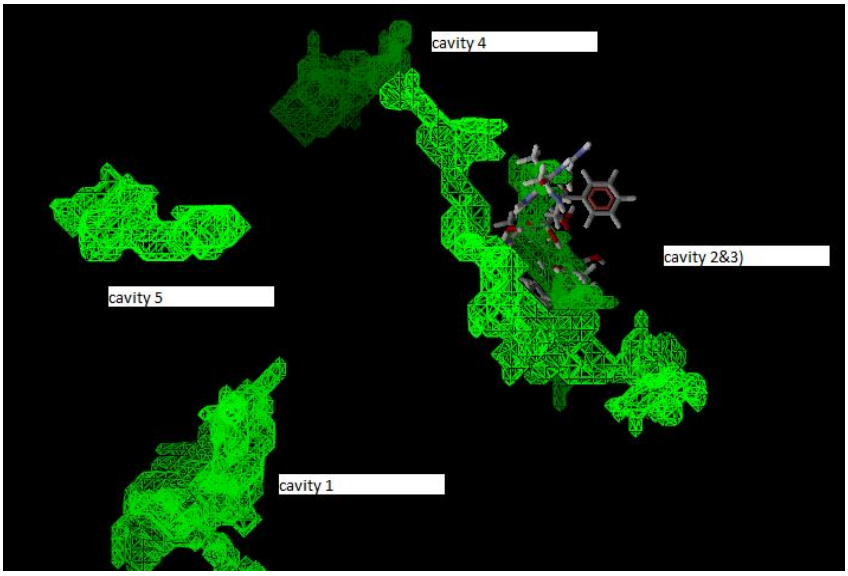

Fig.1: Binding of reference ligands in pocket of PDB ID (1TUB)

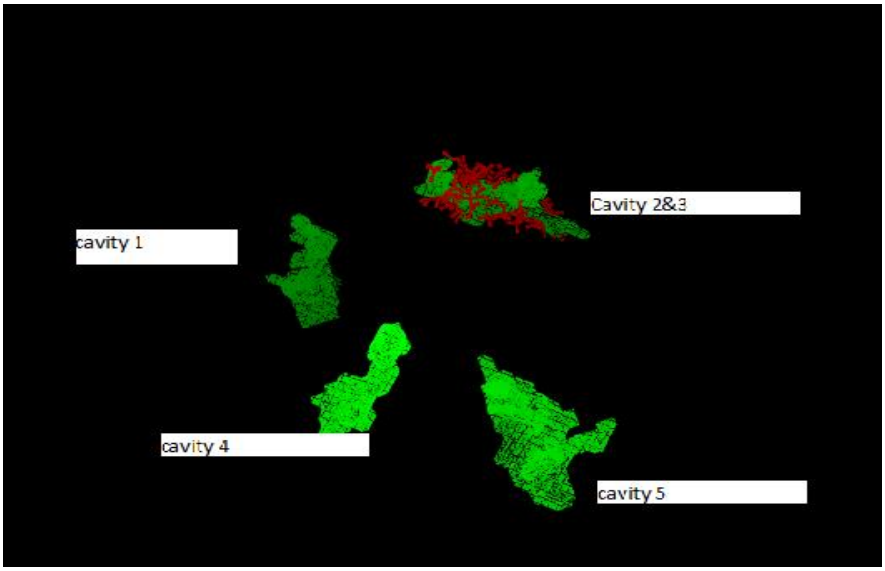

Fig 2: Binding of all poses in binding pocket of PDB ID(1TUB)

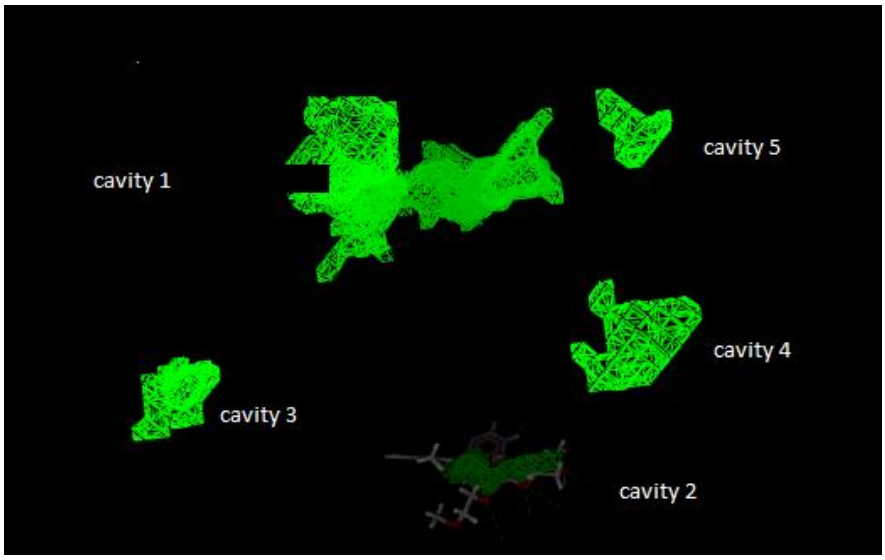

Fig 3: Binding of reference ligand in cavity 2 of PDB ID (1M17)

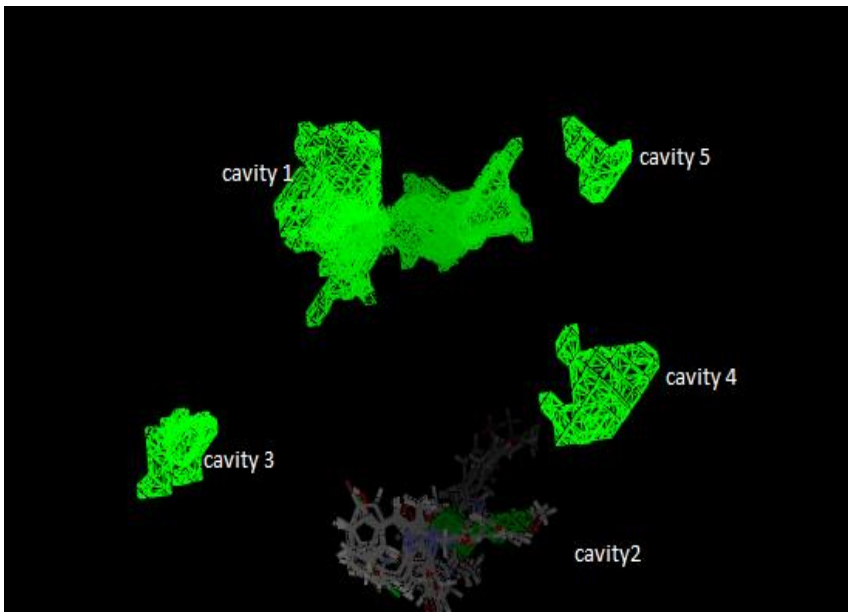

Fig 4: Binding of all ligands in binding pocket (cavity 2) of PDB ID(1M17)

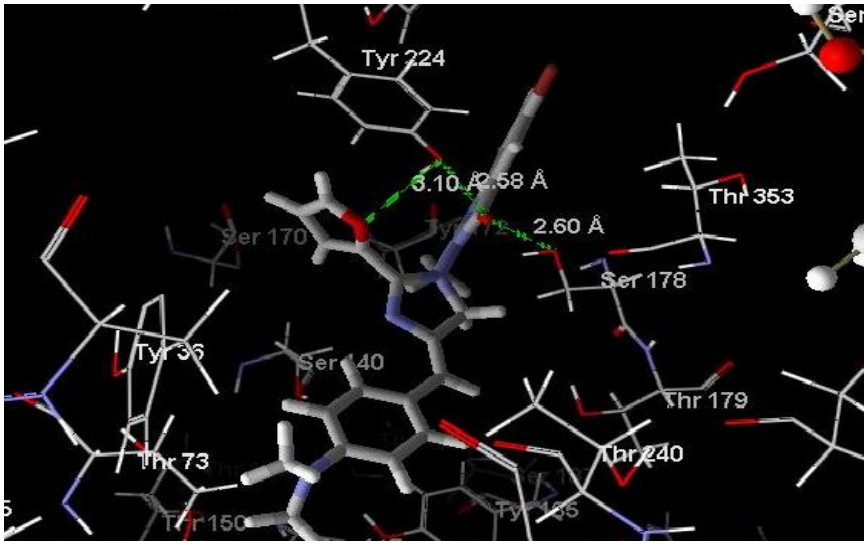

Fig 5: Binding of compound 6 having highest Mol dock score (207.173) in PDB ID(1TUB) with three hydrogen bonded interaction as shown by green dotted lines

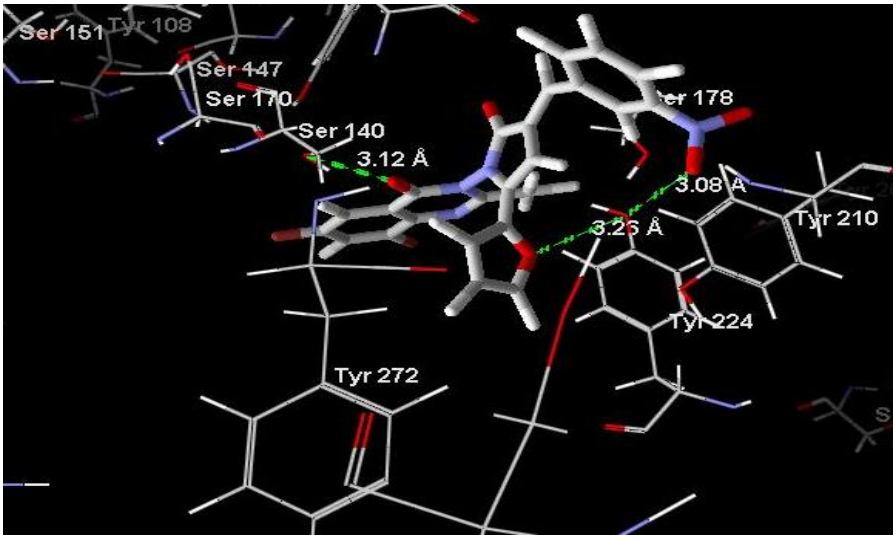

Fig 6: Binding of compound 10 in binding pocket of PDB ID(1TUB)

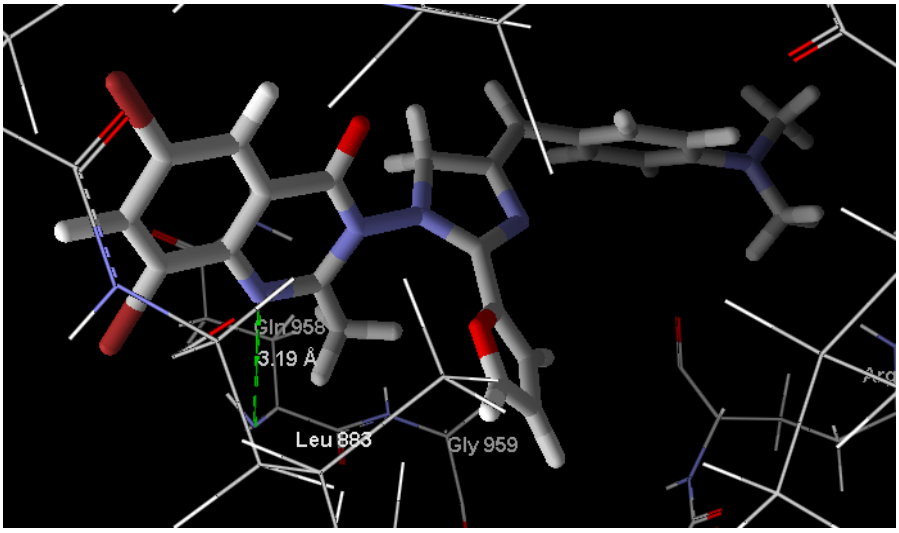

Fig 7: Binding of compound 6 in PDBID(1M17) with only one hydrogen bond interaction

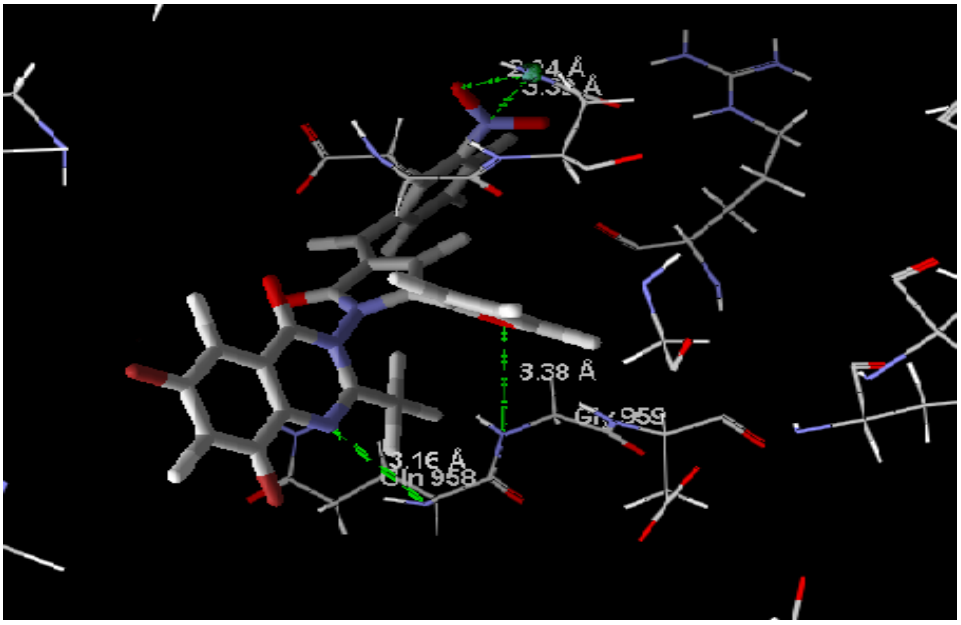

Fig 8: Binding of compound 10 in binding pocket of PDB ID(1M17)

CONCLUSION:

As all the quinazolinone compounds showed effective binding with receptor 1TUB in comparison to receptor 1M17. Even these compounds have much resemblance in structure to Raltitrexed and Thymitaq which inhibit its EGFR tyrosine kinase by binding to the adenosine triphosphate (ATP)-binding site of the enzyme. But these are found to act by binding to tubulin heterodimer thus show its action.

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