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MOLECULAR DESIGN AND DOCKING STUDY OF NOVEL QUINOXALINE-CONTAINING COMPOUNDS AS PI3K/MTOR DUAL INHIBITOR

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Keywords:

PDB, mTOR, Pi3k, Signaling Pathway, Molecular docking, Dual inhibitors

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ABSTRACT: The PI3K-AKT-mTOR signaling pathway is widely used in cancer therapy as it is a signaling pathway that is frequently disrupted in human cancers. Increasingly, inhibitors develop against key proteins in signaling pathways, such as PI3K and mTOR. Dual inhibitors targeting PI3K and mTOR are more potent than one inhibitor targeting only a single protein. This study used to design and molecular docking analysis to investigate the precise binding positions and interaction forces of quinoxaline-containing compounds within the active site of PI3Kγ and mTOR with the help of freely available software for virtual screening of compounds, docking, and drug interaction result analysis. And also proposed the development of new potent drug candidates which works as dual inhibitors against cancer diseases; thus it could be concluded that Quinoxaline-containing derivatives might be used as a template for destiny improvement thru change or derivatization to lay out stronger healing agents.

INTRODUCTION: Cancer is an epidemic worldwide, a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020, or nearly one in six deaths. The most common cancers are breast, lung, colon, rectum, and prostate cancers [1]. With the worldwide devastation the sickness is wreaking, the call for brand-new and powerful drugs is inexhaustible. The position of the PI3K-AKT-mTOR signaling pathway is an essential boom signaling pathway, advancing our knowledge that its ongoing activation in numerous cancers kinds is rising as a fascinating goal for most cancers therapy [2-5].

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In recent years, there have been growing attempts to increase new inhibitors towards key signaling proteins in signaling pathways, including PI3K, AKT and Mtor [6-11] Phosphatidylinositol-4,5-bisphosphate-3-kinase (PI3K) is a lipid and member of the serine/threonine kinase family. Produces β-triphosphate (PIP3). PI3K regulates cellular metabolism and cellular proliferation by phosphorylating downstream effectors and adapters *via* the second messenger, PIP3 [12].

However, consistent activation and/or over-expression of PI3K reasons disruption of mobile characteristics main to most cancers [13-17]. PI3Ks are categorized into 3 groups [3], I, II and III, primarily based totally on their collection and substrate specificity [18-19]. Class I PI3Ks are the maximum implicated in most cancers [20] and are similarly divided into Class IA and IB categories, primarily based on their regulatory subunits and activation mechanisms. Class IA PI3Ks incorporate

regulatory and catalytic subunits, particularly p85 and p110. Class IA p110 subunits are located in 4 isoforms α, β, γ, and δ. All p110 catalytic subunits proportion a not unusual place fundamental shape with a C2 area, a helical area, and a catalytic area [21] All p110 elegance IA subunits are activated via way of means of receptor tyrosine kinases (RTKs) [22] Persistent activation of sophistication 1A PI3K *via* way of means of mutation is regularly detected in numerous human cancers. The cytosolic serine-threonine kinase mTOR is a member of the PI3K-associated kinase family (PIKK) [24].

mTOR stands for "mammalian goal of rapamycin" and turned into so name as it turned into first observed because the mammalian homologue of a yeast protein referred to as TOR, an acronym for "goal of rapamycin "[25, 26].

The kinase area of mTOR (approximately 550 residues) includes an N-terminal lobe (N-lobe) and a bigger C-terminal lobe (C-lobe) with an ATP-binding or catalytic webpage within side the cleft among them [27, 28]. mTOR is an appropriate drug goal for numerous forms of most cancers as it regulates cellular metabolism and cellular boom [29, 30].

Rapamycin, the primarily regarded inhibitor of mTOR, pals with its intracellular receptor FKBP12 and allosterically inhibits mTOR [31, 32]. The FKBP12-rapamycin complicated at once interacts with the FKBP12-rapamycin binding area (FRB) to inhibit mTOR characteristics. Rapamycin binds handiest to at least one mTOR complicated, mTORC1, and inhibits handiest mTORC1-related signaling features [33]. This brought about the invention of ATP-aggressive mTOR inhibitors [34] that bind to each mTORC1 and mTORC2 and inhibit the kinase-based features of mTOR [35].

Quinoxaline and its derivatives are a crucial magnificence of heterocyclic compounds, they have got attracted large interest through the years thanks to their very thrilling pharmaceutical and organic homes including insecticidal, antifungal, anthelmintic, anticancer, antibacterial and antiviral [36, 37] and it's far formerly suggested that the quinoxaline moiety is a famous and promising scaffold with its far a crucial heterocyclic nucleus with a huge spectrum of organic activities, and these days an awful lot interest has been located on anticancer drug recognized anticancer homes.

MATERIAL AND METHOD:

To Generate the Combinatorial Library of Compounds: For the technology of the Combinatorial Library of compounds, the concept is taken from the Previously pronounced compound and picks the R1 and R2 role with specific substituents to generate the brand new compounds [38].

The 9 substituents have been taken into consideration for R1 possibility from the preceding stated PI3K/mTOR inhibitors **Fig. 1**. Whereas five small substituents including `-O-CH3`, `-OH`, `-NH2`, `-F`, and `-Br` have been used for R2 possibility **Fig. 2** and **Fig. 3**. These R1 and R2 replacements generate a library of favored forty compounds used on this have a look at for digital displaying with inside the course of PI3Kγ and mTOR. The compounds generated have been named as sequential numbers from 1 to twenty within the order of systematic substitution of R1 and R2 Position **Table 1 and 2.**

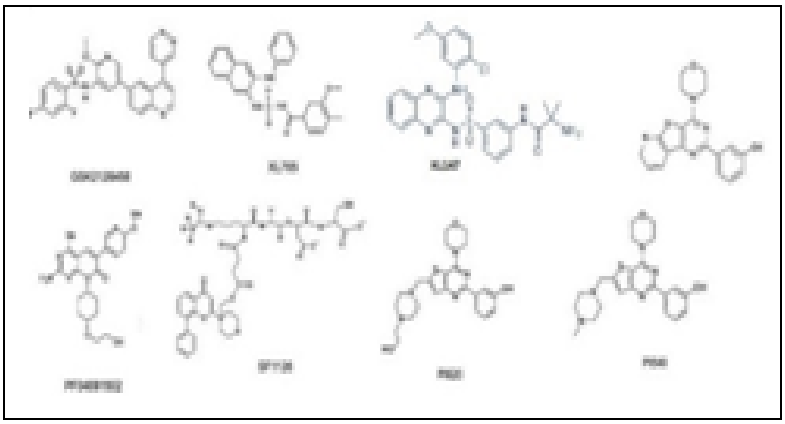


FIG. 1: STRUCTURES OF PREVIOUSLY REPORTED DUAL MTOR/PI3K INHIBITORS

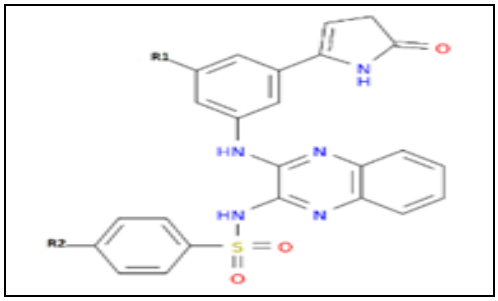
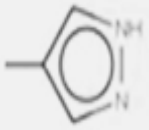
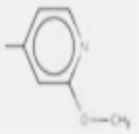
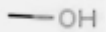
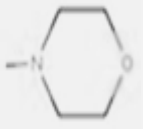
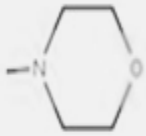
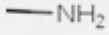
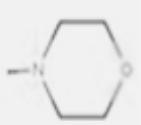
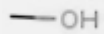
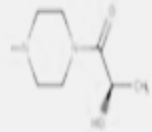
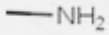
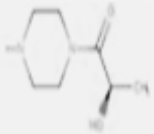
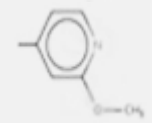
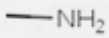
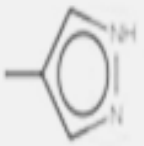
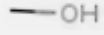
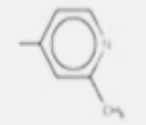
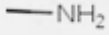
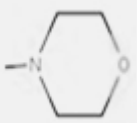
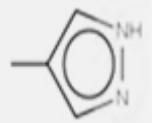
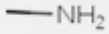
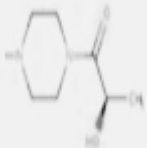
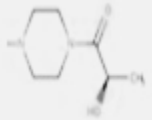
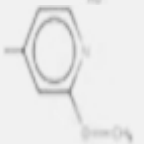
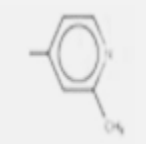
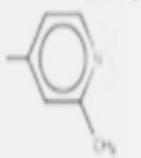
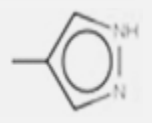
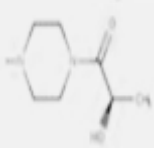
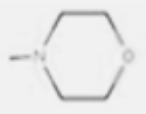


FIG. 2: TO GENERATE COM1 -COM 20

TABLE 1: STRUCTURES OF R_1 AND R_2 TO DESIGNED COM1 TO 20

Compd.	R_1	R_2	Compd	R_1	R_2
Com 1			Com 11		
Com 2			Com 12		
Com 3			Com 13		
Com 4			Com 14		
Com 5			Com 15		
Com 6			Com 16		
Com 7			Com 17		
Com 8			Com 18		
Com 9			Com 19		
Com 10			Com 20		

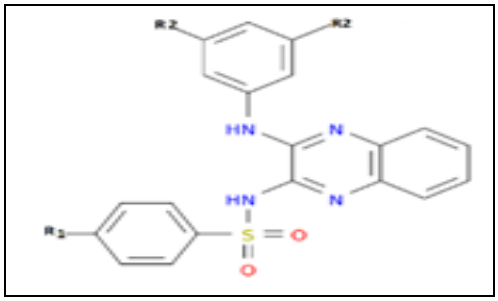


FIG. 3: TO GENERATE MOL1-MOL 20

TABLE 2: STRUCTURES OF R_1AND R_2 TO DESIGNED MOL1 TO 20

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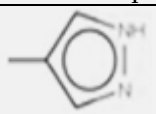
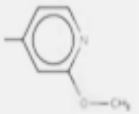
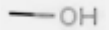
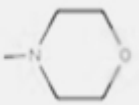
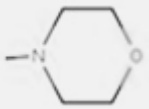
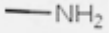
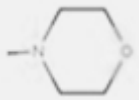
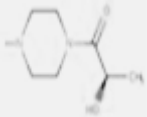
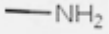
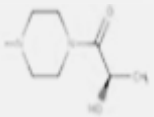
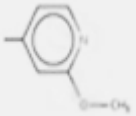
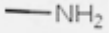
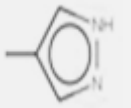
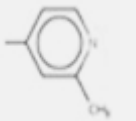
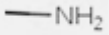
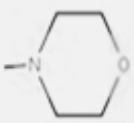
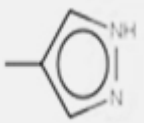
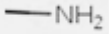
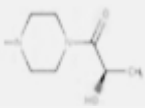
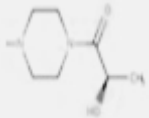
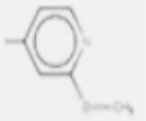
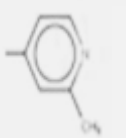
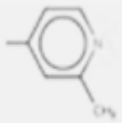
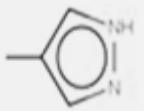
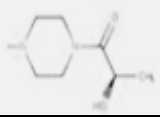
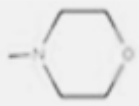
Mol 1			Mol 11		
Mol 2			Mol 12		
Mol 3			Mol 13		
Mol 4			Mol 14		
Mol 5			Mol 15		
Mol 6			Mol 16		
Mol 7			Mol 17		
Mol 8			Mol 18		
Mol 9			Mol 19		
Mol 10			Mol 20		

Data Procurement: The 3-dimensional structure of selected drugs designed from the freely available site Novoprolabs https://www.novoprolabs.com/ while the systems of proteins had been retrieved from Protein Data Bank (PDB): PI3Kγ p110 with PDB Id, 3L54 and mTOR with PDB Id, 4JT6 respectively. The kinase area of mTOR (residues from 1867 to 2436) was taken into consideration with inside the have a look at and used for all analyses. The retrieved systems had been co-

complicated systems with certain ligands (PI3Kγ with certain LXX, mTOR with certain PI-103), and those certain ligands had been used as clues for catalytic grid era in molecular docking [44].

Molecular Docking and Structure Generation: All the molecular docking simulations were carried out through Auto Dock veena v.2.1 [39, 40]. The pre-processing of proteins and ligands, which are referred to as shape preparation, required as enter for docking, was carried out through Chimera v.1.6.2 [41].

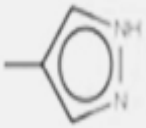
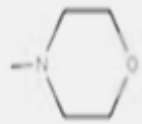
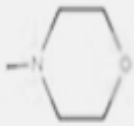
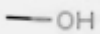
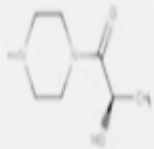
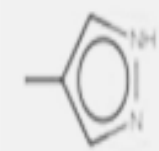
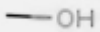
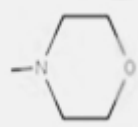
First, we used the Chimera to remove all HOH molecules from the protein, assign hydrogen polarities, and add Colman charges and polar hydrogen atoms. A Gas tiger charge was also applied to the generated proteins, and the protein structure file PDB was converted to PDBQT. The chemical substances had been changed the usage of Marvin Sketch v.18.4, Che Maxon https://chemaxon.com/marvin and chem-doodle.

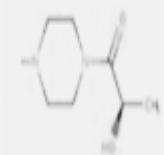
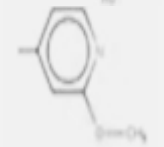
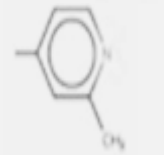
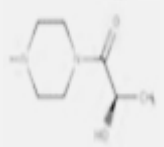
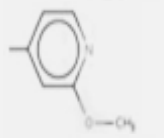
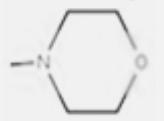
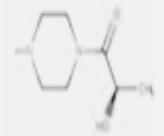
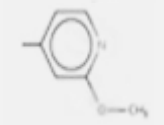
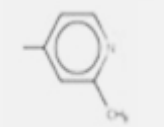
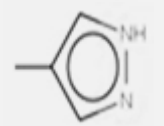
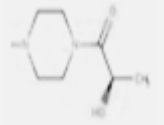
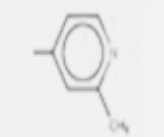
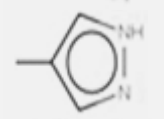
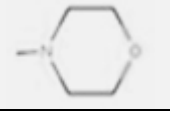
Analyses of Docked Protein-ligand Interaction: The docked complexes of protein and ligand had been visually analyzed through PyMOL v.1.three[42,] and illustrations had been prepared. The molecular interactions among the proteins and ligands had been analyzed and illustrated through Biovia discovery studio [43].

RESULTS AND DISCUSSION:

Virtual Screening of Generated Combinatorial Library: The combinatorial library of all the 40 compounds (20 compounds generated from schem1 and other 20 compounds generated from scheme 2) used for virtual screening and their dock scores for PI3Kγ and mTOR is provided in **Table 3.** The eight compounds (highlighted in bold in table 3) were common among top scoring compounds of PI3Kγ and mTOR **Fig. 3**. Generally, these eight compounds have better dock scores and binding energy. These compounds were proposed as potential dual PI3K/mTOR inhibitors.

TABLE 3: VIRTUAL SCREENING OF ALL THE LIGANDS AND THEIR DOCK SCORES FOR PI3KΓ AND MTOR

Mol.	R_1	R_2	Docking Score for mtor (Kcal/mol)	Docking Score for Pi3k (Kcal/mol)	Compd	Docking Score for mtor (Kcal/mol)	Docking Score for Pi3k (Kcal/mol)
Mol 1			-7.6	-5.2	Com 1	-8.0	-8.3
Mol 2			-8.0	-8.3	Com 2	-6.4	-4.2
Mol 3			-5.2	-4.6	Com 3	-5.3	-3.7
Mol 4			-10.2	-6.4	Com 4	-9.3	-6.4
Mol 5			-5.3	-6.4	Com 5	-6.4	-3.6
Mol 6			-6.4	-3.6	Com 6	-3.4	-3.4

Mol 7		—O—CH$_3$	-4.3	-3.4	Com 7	-1.2	-1.2
Mol 8		—O—CH$_3$	-5.6	-4.2	Com 8	-4.8	-4.3
Mol 9		—O—CH$_3$	-4.6	-4.8	Com 9	-3.4	-3.4
Mol 10		—OH	-5.5	-6.5	Com 10	-6.2	-4.6
Mol 11		—OH	-6.4	-6.2	Com 11	-5.8	-1.3
Mol 12		—NH$_2$	-7.2	-3.4	Com 12	-5.4	-3.4
Mol 13		—NH$_2$	-6.3	-1.2	Com 13	-7.4	-5.1
Mol 14		—NH$_2$	-10.2	-6.6	Com 14	-10.1	-8.4
Mol 15		—NH$_2$	-3.4	-3.4	Com 15	-4.4	-3.4
Mol 16		—NH$_2$	-1.2	-1.2	Com 16	-5.2	-1.2
Mol 17		—F	-4.8	-4.8	Com 17	-4.8	-4.8
Mol 18		—Br	-3.4	-3.4	Com 18	-3.4	-3.4
Mol 19		—Br	-6.1	-5.9	Com 19	-8.4	-7.6
Mol 20		—Br	-5.8	-3.5	Com 20	-6.8	-4.3

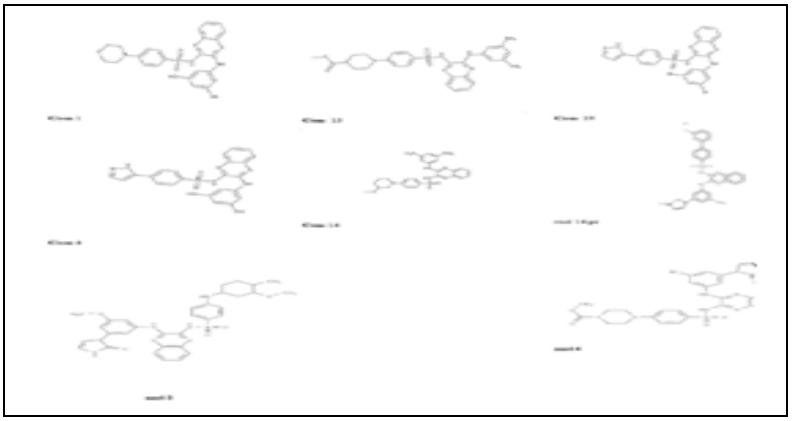


FIG. 4: STRUCTURE REPRESENTATION OF EIGHT COMPOUNDS WAS PROPOSED AS A POTENTIAL DUAL PI3K/MTOR INHIBITOR

Molecular Docking Results Analysis of Eight Proposed Dual Inhibitors Interactions with Mtor: During target docking of all eight compounds, all compounds were observed to form conventional hydrogen bonds with the minimum bond length>3, and of them Com 14 and Mol 14 was observed to form the most hydrogen bonds. However, binding energies, hydrogen bond length, and the interacting residue for all eight compounds were determined, as shown in **Table 4.** Interestingly, Com 14 and Mol 14 exhibited the lowest binding energy of -10.1 kcal/mol and -10.2, respectively and the most common interacting residue is LYS-890. However, the binding energies shown in the table are mainly due to the chemical interactions shown in **Fig. 4**. Basically, chemical interactions form bonds such as covalent, alkyl, pi, and hydrogen bonds that affect the stability of protein-ligand bonds. All the compounds have 6-10 no of interactions, reflecting that the docked compound's binding poses ensure favorable and valid potential binding modes with Mtor.

TABLE 4: DOCKING RESULT ANALYSIS OF EIGHT PROPOSED COMPOUNDS FOR MTOR

S. no.	Compound	Docking Score (Kcal/mol)	Hydrogen bond	Hydrogen bond distance(Å)	Interacting Residue
1	Com 1	-8.0	1	3.01 LYS-890	ALA-885, LYS-890, MET-804, MET-953 ASP-964, PRO-810, ILE-963, ILE-831 and TYR-867
2	Com 4	-9.3	2	1.09 VAL-882 2.09 ASP-964	VAL-882, ASP-964, ALA-885, LYS-833, MET-953 ASP-964, ILE-963, ILE-881, ILE-831 and ILE-879
3	Com 13	-7.4	2	2.84 LYS-890 2.0 8 ASP-964	LYS-890, ASP-964, ASP-950, ILE-963, MET-953, TYR-867 AND VAL-1091
4	Com 14	-10.1	4	2.36 LYS-890 2.48 ASP-964 2.95 ASP-950 2.53 VAL882	LYS-890, LYS-833ASP-964, ASP-950, ILE-963, MET-953, TYR-867 and VAL-882, SER-806, ILE-831 and ILE-879
5	Com 19	-8.4	3	2.27 LYS-833 2.61 ASP-964 2.96 ASN-951	LYS-833ASP-964, ASP-950, ILE-831, PRO-810, SER-806, MET-804, ASN-951, HIS-967 and LEU-1090
6	Mol 2	-8.0	2	2.32 ALA-805 2.76 LYS-890	MET-953, MET-804, TRP-812, ILE-831, ILE-879, ILE-953, ALA-805, TRP-812, LYS-890, ASP-964, TYR-867, MET-953, ILE-963, and PRO-810
7	Mol4	-10.2	3	2.32 ALA-885 2.56 LYS-833 2.32 LYS-890	ALA-885, LYS-833, LYS-890, MET-953, MET-804, ILE-953, ILE-831, PRO-810, ASP-964, TYR-867 and PHE-961
8	Mol 14	-10.2	4	2.41 LYS-833 3.09 ASP-964 2.54VAL-882 2.43SER-806	LYS-833,ASP-964, ASP-950, VAL-882, SER-806, TYR-867, LYS-807, LYS-808, MET 953, ASN-951, TRP-812 and ILE-831, ILE-881

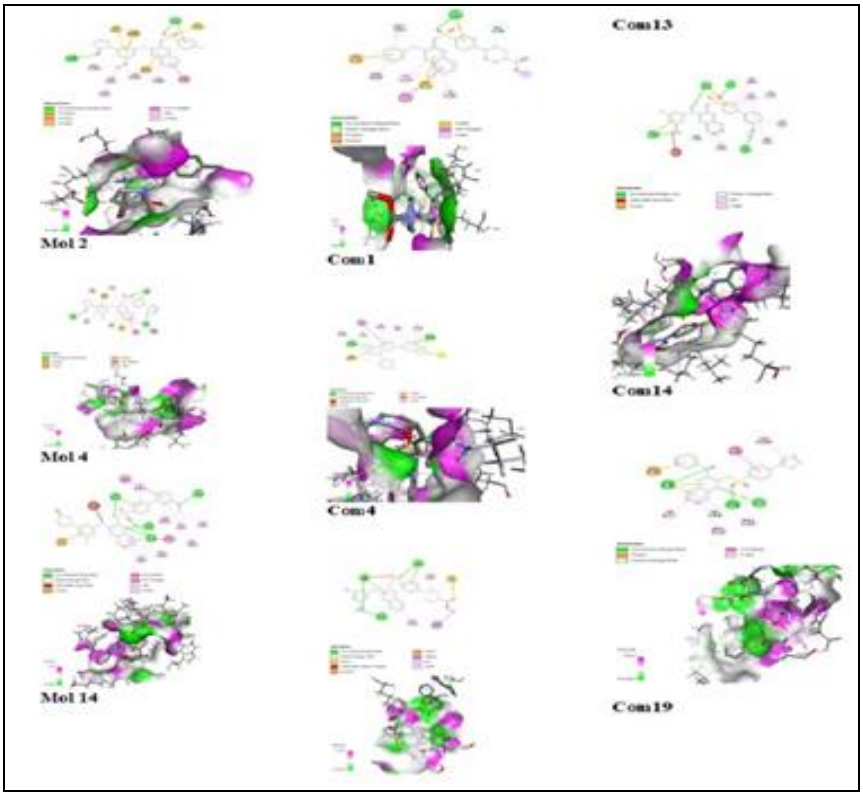


FIG. 5: 2D AND 3D INTERACTIONS OF EIGHT PROPOSED COMPOUNDS WITH MTOR

Molecular Docking Results Analysis of Eight Proposed Dual Inhibitors Interactions with Pi3k: During target docking of all eight compounds, all compounds were observed to form conventional hydrogen bonds with a minimum bond length >2, and among them, Mol2 and Mol4 were found to form the most hydrogen bonds it Observed. However, the binding energies, hydrogen bond lengths, and interacting residues were determined for all eight compounds, as shown in **Table 5**. Interestingly, Com 14 and Mol 2 show the lowest binding energies of −8.4 kcal/mol and −8.3 kcal/mol, respectively, and the highest covalent interaction residue is met-494. However, the binding energies shown in the table are primarily due to the chemical interactions shown in **Fig. 5**. Basically, chemical interactions form bonds such as covalent, alkyl, pi, and hydrogen bonds that affect the stability of protein-ligand bonds. All compounds exhibit 3–10 interactions, reflecting that the binding positions of the docked compounds ensure favorable and effective potential binding modes with Pi3k.

TABLE 5: DOCKING RESULT ANALYSIS OF EIGHT PROPOSED COMPOUNDS FOR PI3K

S. no.	Compound	Docking Score (Kcal/mol)	Hydrogen bond	Hydrogen bond distance (Å)	Interacting Residue
1	Com 1	-6.8	2	2.62 LEU-459, 2.69 SER-463	LEU-459, SER-463, MET-494
2	Com 4	-6.3	1	2.19 lys-204	LEU-490, ILE-310, MET-494, VAL-307, ASP-489, VAL-328 and LYS-204
3	Com 13	-5.1	1	2.82 Gly-542	VAL-338, LEU-306, ALA-302, LEU-343, ARG-546, PRO-277 and GLY-542
4	Com 14	-8.4	1	2.19 ASP-489	ILE-310, VAL-307, GLU, 493, VAL-338, ASP-489 and LEU-490
5	Com 19	-7.6	1	2.27 Glu-332	MET-473, MET-336, ARG-466, SER-333, TRP-335 and GLU-332
6	Mol 2	--8.3	5	3.1 leu-273 2.31 tyr-397 2.73 Lys-401 2.70 His-279 3.01 glu-274	TYR-397 LYS-401, HIS-279, MET-336, 3.01 GLU-274, PRO-277, GLU-305, VAL-280 and HIS-39

7	Mol 4	-6.4	3	1.95Ser-409 2.55 Arg-466 2.81 His-498	SER-408, SER-409, ARG-466, HIS-498, GLU-337, MET-403, LEU-462 and LEU-459
8	Mol 14	-6.6	2	Pro-275 Trp-348	ARG-546, GLU-305, GLU-275, TRP-348, HIS-279 LEU-481, SER-933, PRO-275and SER-409

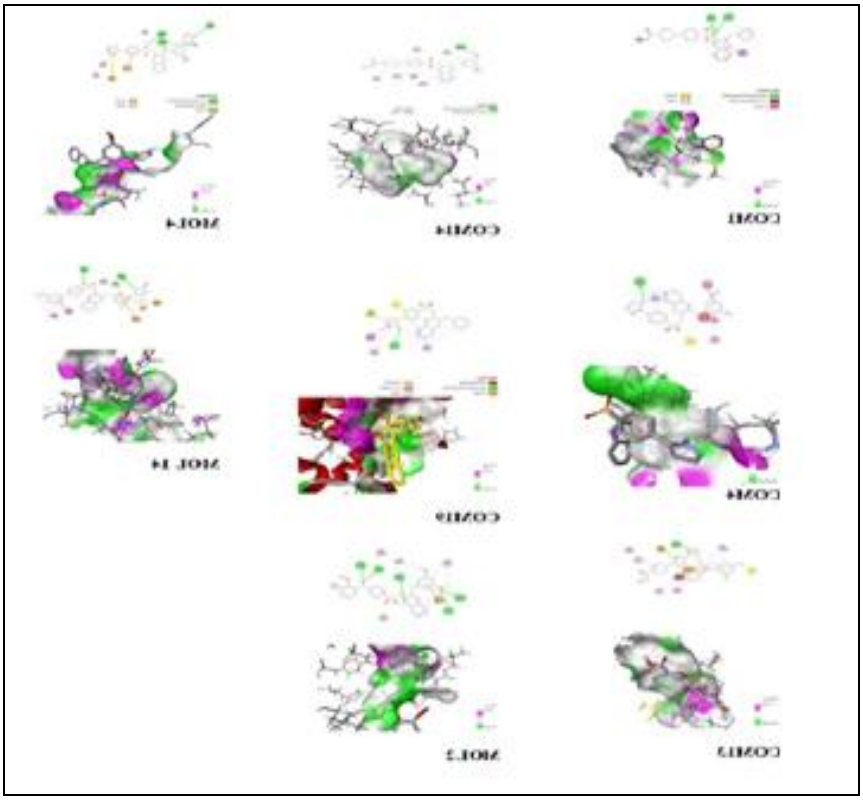


FIG. 6: 2D AND 3D INTERACTIONS OF EIGHT PROPOSED COMPOUNDS WITH PI3K

CONCLUSION: The drug designing and molecular docking have a look at Quinoxaline containing derivatives with Mtor and pi3k twin inhibitors and discovered that Quinoxaline containing derivatives have correct interplay in a beneficial pose with Mtor and pi3k twin inhibitors, which become defined through the lowest binding energy, sturdy bond duration and 3-10 no of interactions with the energetic site. Thus it could be concluded that Quinoxaline-containing derivatives might be used as a template for destiny improvement thru change or derivatization to lay out stronger healing agents. Compounds synthesized if well modified into a healing agent may be used as an anticancer agent.

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REFERENCES:

1. Abbass EM, Khalil AK, Mohamed MM, Eissa IH and El-Naggar A: M. Design, efficient synthesis, docking studies, and anticancer evaluation of new quinoxalines as potential intercalative topo ii inhibitors and apoptosis inducers. bioorg. Chem. 2020; 104: 104255.doi:10.1016/j.bioorg.2020.104255.
2. Abo Elmaaty, Hamed A, Ismail MIA, Elkaeed MIB, Abulkhair ES and Khattab HM: Computational Insights on the Potential of Some NSAIDs for Treating COVID-19: Priority Set and Lead Optimization. Molecules 2021; 26(12): 3772.
3. Agoni C, Olotu FA, Ramharack P and Soliman ME: Druggability and Drug-Likeness Concepts in Drug Design: Are Biomodelling and Predictive Tools Having Their Say. J Mol Model 2020; 26(6): 1–11.

4. Alnajjar R, Mostafa A, Kandeil A and Al-Karmalawy AAJH: Molecular Docking, Molecular Dynamics, and In Vitro Studies Reveal the Potential of Angiotensin II Receptor Blockers to Inhibit the COVID-19 Main Protease 2020; 6(12): 05641.
5. Garces AE and Stocks ME: Class 1 PI3K clinical candidates and recent inhibitor design strategies: a medicinal chemistry perspective. J Med Chem 2019; 10: 1021;
6. Rehan M: An Anti-Cancer Drug Candidate OSI-027 and its Analog as Inhibitors of mTOR: Computational Insights into the Inhibitory Mechanisms. J Cell Biochem 2017; 118(12): 4558-4567. doi: 10.1002/jcb.26117.
7. Mohd Rehan: A structural insight into the inhibitory mechanism of an orally active PI3K/mTOR dual inhibitor, PKI-179 using computational approaches. J Mol Graph Model 2015; 62(11): 226-234. doi: 10.1016/j.jmgm.2015.10.005.
8. Rehan M: Anticancer compound XL765 as PI3K/mTOR dual inhibitor: A structural insight into the inhibitory mechanism using computational approaches. PloS One 2019; 14(6): 0219180..
9. Jamal MS, Parveen S, Beg MA, Suhail M, Chaudhary AG, Damanhouri GA, Abuzenadah AM and Rehan M: Anticancer compound plumbagin and its molecular targets: a structural insight into the inhibitory mechanisms using computational approaches. PLoS One 2014; 9(2): 87309. doi:10.1371/journal.pone.0087309.
10. Lv X, Ying H, Ma X, Qiu N and Wu PB: Design, synthesis and biological evaluation of novel 4-alkynyl-quinoline derivatives as PI3K/mTOR dual inhibitors. Eur J Med Chem 2015; 99: 36–50.
11. Xu M, Xu L, Wang Y, Dai G, Xue B, Liu YY, Zhu J and Zhu J: BRD4 inhibition sensitizes renal cell carcinoma cells to the PI3K/mTOR dual inhibitor VS-5584. Aging (Albany NY) 2020; 12(19): 19147.
12. Campbell IG, Russell SE, Choong DY, Montgomery KG, Ciavarella ML, Hooi CS, Cristiano BE, Pearson RB and Phillips WA: Mutation of the PIK3CA gene in ovarian and breast cancer. Cancer Res 2004; 64(21): 7678-81. doi: 10.1158/0008-5472.CAN-04-2933.
13. Hung MC, Wang WP and Chi YH: AKT phosphorylation as a predictive biomarker for PI3K/mTOR dual inhibition-induced proteolytic cleavage of mTOR companion proteins in small cell lung cancer. Cell & Bioscience 2022; 12(1): 1-5.
14. Tian YF, Wang HC, Luo CW, Hung WC, Lin YH, Chen TY, Li CF, Lin CY and Pan MR: Preprogramming therapeutic response of PI3K/mTOR dual inhibitor via the regulation of EHMT2 and p27 in pancreatic cancer. American Journal of Cancer Research 2018; 8(9): 1812.
15. Bertacchini J, Frasson C, Chiarini F, D'Avella D, Accordi B, Anselmi L, Barozzi P, Forghieri F, Luppi M, Martelli AM and Basso G: Dual inhibition of PI3K/mTOR signaling in chemoresistant AML primary cells. Advances in Biological Regulation 2018; 68: 2-9.
16. Barra F, Evangelisti G, Ferro Desideri L, Di Domenico S, Ferraioli D, Vellone VG, De Cian F and Ferrero S: Investigational PI3K/AKT/mTOR inhibitors in development for endometrial cancer. Expert Opinion on Investigational Drugs 2019; 28(2): 131-42.
17. Hu Y, Zhang K, Zhu X, Zheng X, Wang C, Niu X, Jiang T, Ji X, Zhao W, Pang L and Qi Y: Synergistic inhibition of drug-resistant colon cancer growth with PI3K/mTOR dual inhibitor BEZ235 and nano-emulsioned paclitaxel via reducing multidrug resistance and promoting apoptosis. International Journal of Nanomedicine 2021; 16: 2173.
18. Guertin DA, Sabatini DM. Defining the role of mTOR in cancer. Cancer Cell 2007; 12(1): 9-22. doi: 10.1016/j.ccr.2007.05.008.
19. Kim MY, Kruger AJ, Jeong JY, Kim J, kyung Shin P, Kim SY, Cho JY, Hahm KB and Hong SP: Combination Therapy with a PI3K/mTOR Dual Inhibitor and Chloroquine Enhances Synergistic Apoptotic Cell Death in Epstein–Barr Virus-Infected Gastric Cancer Cells. Molecules and Cells 2019; 42(6): 448.
20. Yang H, Rudge DG, Koos JD, Vaidialingam B, Yang HJ and Pavletich NP: mTOR kinase structure, mechanism and regulation. Nature 2013; 497(7448): 217-23. doi: 10.1038/nature12122.
21. Zoncu R, Efeyan A and Sabatini DM: mTOR: from growth signal integration to cancer, diabetes and ageing. Nat Rev Mol Cell Biol 2011; 12(1): 21-35. doi: 10.1038/nrm3025.
22. Wang W, Liao L, Wang Y, Li H, Suo Z, Long K and Tang P: Preclinical evaluation of novel PI3K/mTOR dual inhibitor SN202 as potential anti-renal cancer agent. Cancer Biology & Therapy 2018; 19(11): 1015-22.
23. Kim HJ, Gong MK, Yoon CY, Kang J, Yun M, Cho NH, Rha SY and Choi YD: Synergistic antitumor effects of combined treatment with HSP90 inhibitor and PI3K/mTOR dual inhibitor in cisplatin-resistant human bladder cancer cells. Yonsei Medical Journal 2020; 61(7): 587.
24. Zaytseva YY, Valentino JD, Gulhati P and Evers BM: mTOR inhibitors in cancer therapy. Cancer Lett 2012; 319(1): 1-7. doi: 10.1016/j.canlet.2012.01.005.
25. Ning C, Liang M, Liu S, Wang G, Edwards H, Xia Y, Polin L, Dyson G, Taub JW, Mohammad RM and Azmi AS: Targeting ERK enhances the cytotoxic effect of the novel PI3K and mTOR dual inhibitor VS-5584 in preclinical models of pancreatic cancer. Oncotarget 2017; 8(27): 44295.
26. Wu P, Su Y, Liu X, Yang B and He Q: Discovery of novel 2-piperidinol-3-(arylsulfonyl) quinoxalines as phosphoinositide 3-kinase α (PI3Kα) inhibitors. Bioorg Med Chem 2012; 20: 2837–2844.
27. Wu P, Su Y, Liu X, Zhang L and Ye Y: Synthesis and biological evaluation of novel 2-arylamino-3-(arylsulfonyl) quinoxalines as PI3Kα inhbitors. Eur J Med Chem 2011; 46: 5540–5548.
28. Liu YN, Wan RZ and Liu ZP: Recent developments of small molecule PI3K/mTOR dual inhibitors. Mini Rev Med Chem 2013; 13(14): 2047-59. doi: 10.2174/13895575113136660105.
29. Herschbein L and Liesveld JL: Dueling for dual inhibition: Means to enhance effectiveness of PI3K/Akt/mTOR inhibitors in AML. Blood Reviews 2018; 32(3): 235-48.
30. Ning C, Liang M, Liu S, Wang G, Edwards H, Xia Y, Polin L, Dyson G, Taub JW, Mohammad RM and Azmi AS: Targeting ERK enhances the cytotoxic effect of the novel PI3K and mTOR dual inhibitor VS-5584 in preclinical models of pancreatic cancer. Oncotarget 2017; 8(27): 44295.
31. Pettersen EF, Goddard TD, Huang CC, Couch GS, Greenblatt DM, Meng EC and Ferrin TE: UCSF Chimera-a visualization system for exploratory research and analysis. J Comput Chem 2004; 25: 1605–1612.
32. Fourneaux B, Chaire V, Lucchesi C, Karanian M, Pineau R, Laroche-Clary A and Italiano A: Dual inhibition of the PI3K/AKT/mTOR pathway suppresses the growth of leiomyosarcomas but leads to ERK activation through mTORC2: biological and clinical implications. Oncotarget 2017; 8(5): 7878.

33. Yokota T, Bendell JC, LoRusso P, Tsushima T, Desai V, Kenmotsu H, Watanabe J, Ono A, Murugesan BG, Silva J and Naito T: A call for global harmonization of phase I oncology trials: Results from two parallel, first-in-human phase I studies of DS-7423, an oral PI3K/mTOR dual inhibitor in advanced solid tumors conducted in the United States and Japan 2017; 2536-2536.
34. Huang HY, Li KN, Lau HC, Hsueh CY, Cong N and Zhang M: Dual inhibition of autophagy and PI3K/mTOR pathway as a potential therapeutic strategy against laryngeal squamous cell carcinoma. Translational Cancer Research 2022; 11(5): 1076.
35. Tang, Wenbo: "WX390, a high-potent PI3K-mTOR dual inhibitor, first-in-human (FIH) phase I study in advanced relapsed or refractory solid tumor, and lymphoma 2021; 3106-3106.
36. Li L, Zhang S, Xie D, Chen H, Zheng X and Pan D: Dual inhibitor of PI3K and mTOR (NVP-BEZ235) augments the efficacy of fluorouracil on gastric cancer chemotherapy. Onco Targets and Thera 2018; 20: 6111-8.
37. Choi SY, Jung J, Han JH, Shin J, Moon JW, Song SH, You D and Hwang JJ: Kim cs. pd32-08 synergistic anticancer effect of combination treatment with mek inhibitor and pi3k/mtor dual inhibitor in castration-resistant prostate cancer *in-vivo* and *ex-vivo*. The Journal of Urology 2016; 195(4S): 763-.
38. Lv Y, Du T, Ji M, Wang C, Lin S, Xue N, Jin J, Xu H and Chen X: A novel PI3K/mTOR dual inhibitor XH002 exhibited robust antitumor activity in NSCLC. Journal of Drug Targeting 2019; 27(4): 451-9.
39. Cheng H, Orr STM, Bailey S, Brooun A and Chen P: Structure-Based Drug Design and Synthesis of PI3Kα-Selective Inhibitor (PF-06843195). J Med Chem 2021; 64(1): 644-661. doi:10.1021/acs.jmedchem.0c01652.
40. Pagadala NS, Syed K and Tuszynski J: Software for molecular docking: a review. Biophysical Reviews 2017; 9: 91-102.
41. DeLano WL: ThePyMOL Molecular Graphics System. San Carlos, CA. DeLano Scientific 2002.
42. Fan J, Fu A and Zhang L: Progress in molecular docking. Quantitative Biology 2019; 7: 83-9.
43. https://www.3ds.com/products-services/BIOVIA/products/molecular-modeling-simulation/BIOVIA-discovery-studio/visualization. (n.d.).

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