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Docking Studies of Some Novel Hetrocyclic Compound as Acat Inhibitors: A Meta Analysis

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ABSTRACT

We use molecular modelling and pharmacological testing to identify TCM compounds that may suppress SQS activity. By utilising previously established SQS inhibitors, ten HipHop pharmacophore models were developed. Finally, we used active medicines to explore other potential anti-hyperlipidemia targets in HepG2 cells and establish whether or not the lipid-lowering effect was due to SQS inhibition. As a potential treatment for hyperlipidemia, this research seeks to identify TCM SQS inhibitors. The rings in a heterocyclic compound are each made up of atoms from a different chemical element. Pyridine, thiophene, pyrrole, and furan are the building blocks for quinoline, benzothiophene, indole, benzofuran, benzthiazole, benzimidazole, and benzoxazole, respectively.

***Keywords*-** Hyperlipidemia, Biological assay, quinoline, docking studies.

I. INTRODUCTION

One of the major risk factors for atherosclerosis and visceral obesity [1] is hyperlipidemia, which is defined by abnormally increased levels of cholesterol in the blood. Reducing cholesterol levels can be attained by blocking cholesterol production [2]. Statins and other inhibitors of human HMG-CoA reductase (hHMGR) are the most effective drugs for lowering cholesterol levels to date. Myotoxicity, hepatotoxicity, and even rhabdomyolysis are all possible side effects of statins [3]. To a large extent, these negative effects can be attributed to the inhibition of HMG-CoA reductase, which disrupts the production of several nonsteroidal isoprenoid compounds that are essential for a wide variety of cellular processes [4]. Squalene synthase (SQS), a critical downstream enzyme in the cholesterol synthesis pathway, is viewed as an attractive target for anti-hyperlipidemia [5]. Since SQS is the first enzyme involved in the synthesis of steroids, blocking it can block the manufacture of cholesterol without affecting isoprenoid production [6]. Inhibitors of SQS are prospective medications for the treatment of hyperlipidemia because of the pathway's advantageous positioning. It is currently very costly and time-consuming to find SQS inhibitors by using chemical

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synthesis [7] or genetic engineering techniques [8]. There are few negative side effects and inexpensive treatment costs associated with using traditional Chinese medicine (TCM) to treat hyperlipidemia. [9,10]. Despite TCM's significant contribution to the development of new medicines, TCM has a strong history of using natural resources for the treatment of hyperlipidemia, although there are currently very few studies focusing on the finding of SQS inhibitors from TCM. Consequently, it is crucial to identify TCM compounds that may suppress SQS. Molecular docking and virtual screening techniques were used to investigate SQS inhibitors by the authors of [11], however the study lacked confirmation from biological experiments.

In this article, we present a dependable method for finding putative SQS inhibitors in TCM by combining molecular modelling techniques with biological testing. The first step was to create ten HipHop pharmacophore models based on existing SQS inhibitors. To find putative SQS inhibitors in the Traditional Chinese Medicine Database, we queried the database using the pharmacophore model that performed best in four validation indices (TCMD, Version 2009). To fine-tune the pharmacophore model hits and examine the protein-ligand binding mechanisms, molecular docking was used. The stability of the chemicals' binding to the protein was then verified using MD simulations. Based on the fitvalue, docking score, and interactions produced between the ligands and SQS, the possible SQS inhibitors were chosen. The compounds were also tested for their ability to reduce lipid levels in sodium oleate-induced HepG2 cells. Finally, the active compounds were used to determine whether or not the lipid-lowering action was related to the inhibition of SQS by doing a reverse-target-identification study in HepG2 cells. This research intends to identify TCM substances with the capacity to inhibit SQS, which can then be used as candidate drugs in the clinical management of hyperlipidemia.

The atoms in the rings of a heterocyclic compound come from two separate chemical families. Homocyclic compounds, as well as rights made up of a single element, are analogous to heterocyclic compounds. In most situations, it has been observed that heterocyclic compounds are inorganic, with a single carbon atom remaining present in the majority of these molecules. Heteroatoms are atoms that are neither carbon nor hydrogen and are used to substitute carbon atoms in organic chemistry. There is a system for categorising heterocyclic compounds based on their electrical structure. Saturated heterocyclic derivatives function like their acyclic counterparts. This means that tetrahydrofuran and piperidine are unconventional amines and ethers with modified atomic profiles. Therefore, the majority of applications and studies in heterocyclic chemistry include unconstrained rings with 5–6 members, and the vast majority of the study focuses on unsaturated derivatives. Thiophene, pyridine, furan, and pyrrole are all components of this. The benzene ring system is another important family of ring-fused heterocycles. Names for pyridine, thiophene, pyrrole, and furan are quinoline, benzothiophene, indole, benzofuran, benzthiazole, benzimidazole, and benzoxazole. Two benzene rings can also fuse to create the large chemical family of acridines, dibenzothiophenes, carbazoles, and dibenzofurans. A method for categorising unsaturated rings is based on the presence or absence of heteroatom involvement in the pi-system. They are more reactive because Heterocycles have a ring strain of three atoms. One-heteroatom compounds are far more stable than their two-heteroatom counterparts. Two-heteroatom compounds tend to be more reactive than one-heteroatom compounds. Aziridine, azirine, oxirane, oxirene, thiirane, thiirene, etc. are all examples of 3-membered heterocycles that contain only one heteroatom.

II. MATERIAL & METHODS

We search from different web source like Scopus, web of science, pubmed, publon, mdpi etc. we found the basic building block of most commercially available medicines is the heterocycle. In 2021, four of the top five selling small molecule drugs in the United States are either entirely heterocyclic or contain significant heterocyclic components in their overall structure (Figure 1). These four drugs generate an astounding $27.4 million in retail sales annually, or nearly 80% of the total revenue generated by the top five prescription drugs.

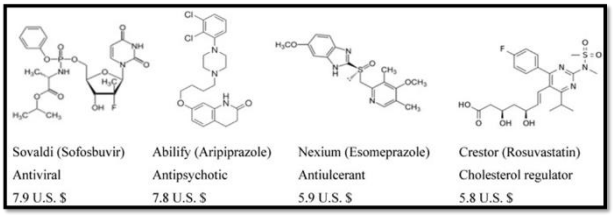

Fig. 1: US top five prescription medications using heterocycle molecules and retail sales

Drug design's rationale and engineering are inextricably linked to the calculated use of heterocyclic-like fragments with targeted physicochemical features. Pharmaceutical medications can have their potency and selectivity fine-tuned by bioisosteric substitutions, lipophilicity, polarity, and aqueous solubility in an effort to obtain molecularly targeted agents. Despite their adaptability and promise, these compounds face the same challenges as any other type of pharmaceutical in terms of market penetration and research and development. Among the fields where this is most apparent is oncology, in part because of the inherent limits of chemotherapy in terms of its main therapeutic routes, associated side effects, and toxicity to healthy tissues. By passively or actively targeting distribution

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into malignant cells, it may be possible to avoid these side effects. Some key figures in the chemotherapeutic field have argued that the success of "molecularly focused medicines" like imatinib are lucky outliers, and that the actual number of successes in this area is quite low. New therapeutic approaches and alternate methods of drug delivery have emerged as a result of recent developments in the interdisciplinary field of nanobiotechnology, capitalising on the architectural brilliance of systems based on nanoscale devices specifically tailored to deliver drugs to a selected tissue. Nanoparticles, and the nanomedicine tools that go along with them, are quickly becoming the most promising solution to chemotherapy's issues, such as poor drug solubility, degradation, rapid clearance rates, and nonspecific toxicity.

Three heterocyclic compounds (HL, CH3L, and NO2L) have been analysed computationally to determine their structural properties. Density functional theory was used in this computation, which was performed using the Gaussian 09 programme [27]. (DFT). The Lee Yang Parr (B3LYP) correlation function with the polarised basis set 6-31G has been chosen as the computational approach (d,p). CPCM (conductor-like polarizable contimum) model without imaginary frequency [30] was used in ethanol for the computations. The Gaussian input file and the optimised structure were both visualised using the Chemcraft tool [32] and the Gauss view software [31]. The optimised compounds' infrared spectra and ultraviolet-visible (UV-vis) characteristics were measured and estimated using the same level of DFT theory. After optimization with the gauge-including-atomic-orbital (GIAO) approach, spectra were analysed using 1H and 13C NMR spectroscopy. Following the UV–VIS analysis, the time-dependent density functional theory (TD-DFT) approach [33] was used to verify the various electronic transitions in the heterocyclic ligands. The stability and reactivity of the optimised structures were determined by estimating several quantum chemical parameters. Since topological analysis can aid in the discovery of atomic interactions at the structure's surface, it was given some thought. In order to learn more about electrophilic and nucleophilic binding sites, the concept of molecular electrostatic potential (MEP) was implemented. Benzimidazole is an essential structural motif seen in a wide variety of natural and pharmacologically active compounds [1], and non covalent interaction analysis utilising reduced density gradient (NCI-RDG) was investigated to assist illustrate the types of intramolecular interactions present. Antiulcer [2, 3], antioxidant [4, 5], HIV-RT inhibitor [4, 6], anticancer [5, 6], antihelmintic [7, 8], antimicrobial [8, 9], antihistamine [10, 11], and many other selective drugs have been synthesised using privileged scaffolds based on the benzimidazole ring, making it an urgent pharmacophore in the modern medical field. Veliparib (a), glasdegib (b), liarozole (c), crenolanib (d), abemaciclib (e), pracinostat (f), bendamustine (g), and nocodazole (g) are just few of the commercially available medications that include a benzimidazole component (Fig.2)

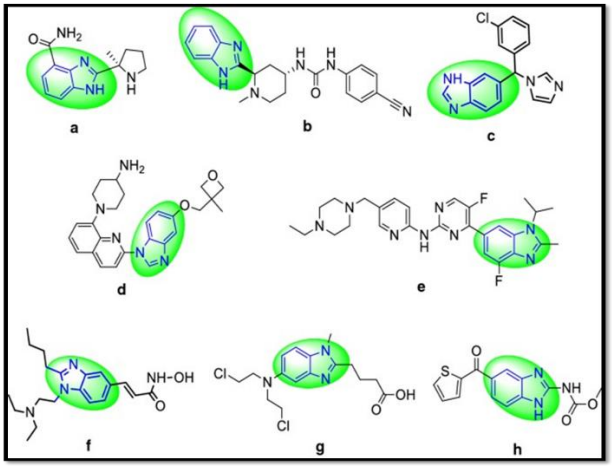

Fig. 2: Selected benzimidazole-containing medications now available on the market.

Current chemotherapy drugs work by inhibiting DNA replication and transcription, slowing the spread of tumours. However, the last decade of research into new curative anticancer drugs has shown unique molecular alterations in tumour cells that can be targeted for therapy. Small biologically active compounds with significant action and no harm from conventional chemotherapy are the major focus of the new strategy [9]. One of the proteins responsible for acute lymphoblastic leukemias is CDKs, a component of the human RNA polymerase.

Association with regulatory subunits (cyclins) and CDK inhibitor proteins, as well as their phosphorylation state and ubiquitin-mediated proteolysis, all play roles in regulating CDK activity. Due to the fact that unchecked cell proliferation is a defining feature of cancer, it is hypothesised that blocking cyclin-dependent kinases (CDKs) will be a useful strategy for halting the progression of tumours and influencing cancer treatment. Numerous groups have investigated CDK inhibition, and various structural templates with differing degrees of selectivity and activity [10] have been developed and used to accomplish CDK inhibition.

By using Western blotting analysis, researchers were able to show that three of the hits specifically target CDK8 in HCT 116 colorectal cancer cells. These findings demonstrate the utility of virtual screening cascades for the identification of CDK8-targeted scaffolds amenable to further development into a drug discovery programme. The cyclin-dependent kinase CDK8 is an integral component of the Mediator complex, which controls RNA polymerase II transcription. Multiple studies have demonstrated that CDK8 regulates the transcriptional output of many oncogenic control transcription factors. The Wnt/-

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catenin pathway, Notch, p53, and transforming growth factor- are only a few examples of these elements. Colon cancer is associated with an amplification and overexpression of CDK8. CDK8 has been identified as an oncogene in colon cancer. RNAi-mediated inhibition of CDK8 and the use of a kinase dead mutant CDK8 have been crucial to understanding CDK8's role in cellular signalling and colon cancer. In order to better understand CDK8's role in colon cancer, we set out to create a highly specific and effective small chemical inhibitor of CDK8 [11].

As a heterodimeric kinase protein, CDK-8 controls cell cycle progression, transcription, and other processes. CDKs can't function without cyclin, a protein that offers essential extra sequences for the enzyme to do its job. The N-terminal portion of each CDK (1, 4, 5, 7, 8, 9, and 11) is built of beta sheets, while the C-terminal portion is made up of -helices [12, 13]. Human breast cancer cannot begin or progress without oestrogen signalling. Anti-estrogen therapy was the first targeted therapy for human cancer and was made possible by decades of research into the mechanisms of this crucial signalling system in breast cancer. A wide variety of tissues and physiological processes rely on oestrogen for their growth and maintenance [14, 15]. Molecular docking is an example of a computational method utilised in contemporary drug discovery [16]. There are a number of reasons why a drug molecule might not make it through development, but researchers have shown that poor pharmacokinetic: ADME characteristics is a common cause of failures [17]. When a drug is taken off the market, one of the main reasons is because of its toxicity. As a result, ADME characteristics are the most important predictors of pharmacological efficacy in humans [18]. These days, the ADME profile of a substance is determined using computer-based drug design. As a result of their high-throughput nature and low cost, ADME models have garnered the interest of pharmaceutical researchers for drug discovery [19].

Researchers used the Maestro docking module by Schrödinger Inc. HIV-RT inhibitors rilpivirine and elvitegravir were considered the gold standard (PDB ID: 4I2P). Because of its superior binding affinity and docking score with the protein compared to other pyrimidine-containing NNRTIs, the synthesised compounds were docked against rilpivirine. This protein structure in a complex with a rilpivirine (TMC278)-based analogue was chosen because the resolution of the structure was high (2.30). We have redocked the cocrystallized ligand, (2E)-3-[4-(6-[(4-methoxyphenyl)amino]-7H-purin-2-ylamino)-3,5-dimethylphenyl]prop-2-enenitrile, within the same constraints as where it was crystallised with 4I2P, and we have recorded both the docking score and the RMSD value. The RMSD value was 0.559, and the docking score was the same as what was calculated beforehand (–11.63 Kcal/mol), demonstrating the accuracy of the process.

All of the proposed ligands had high docking scores, indicating that they bound to the reverse transcriptase with high specificity and strength, as shown by the docking profile. Elvitegravir's 2D and 3D interaction diagrams (Figure 3) reveal that the standard inhibitor binds to the target site, demonstrating hydrogen bonding interaction with LYS 101, ILE-180, and LEU-100 and a docking score of 0.9. (–8.57). Hydrogen bonds were also observed between rilpivirine, a commonly used drug, and LYS 101 (docking score = -8.56, literature value = -7.51) [33]. The compounds were optimised for use in the HIV reverse transcriptase's allosteric site. Docking scores for compounds 4–8 were higher than those for reference medications (rilpivirine and elvitegravir), whereas scores for compounds 11–13 were on par with those for reference pharmaceuticals. Hydrophobic interactions with TRP229 and hydrogen bond interactions with LYS 101 led to the best docking scores (-10.67, -10.38, and -10.23, respectively) for compounds 4, 5, and 7 in series 1. Docking scores were somewhat high for compounds 6 and 8, both of which include a phenyl ring fused to a phenyl amino group (–10.19 and –9.96, respectively). Hydrophobic interactions were observed between compound 6 and TYR 188 and PHE 227, and between compound 8 and TYR 188 exclusively. Compound 6 had a lower docking score than compound 8 because the p-Br-phenyl moiety substituted for the p-tolyl moiety in the fourth position of the pyrimidine ring. Compound 14, the sole member of series 2 to have hydrophobic interactions with TYR 188 and TRP 229, had the best docking score (–9.34), lower than that of both standard medicines. Compound 11 docked at a lower score (–8.76) than any reference drug, indicating that it had pi-pi interactions.

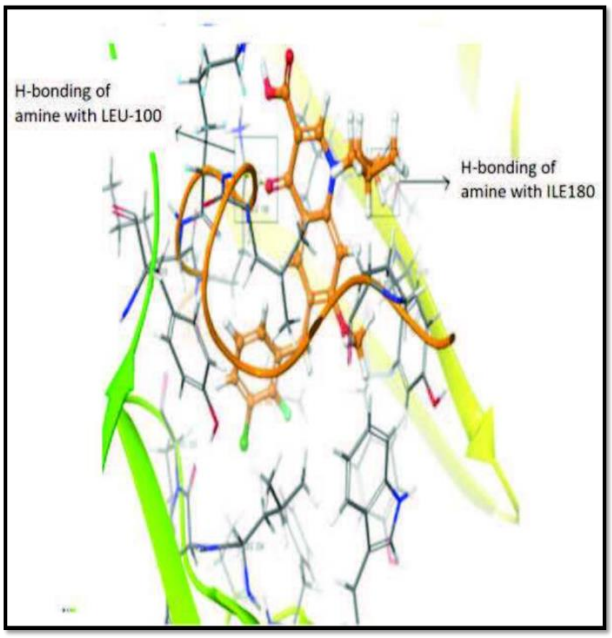

Fig. 3: 3D elvitegravir-reverse transcriptase protein interaction (4I2P).

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Built EGFR inhibitors from chalcones and 4,5-dihydropyrazoles based on quinoline (Figure 4). The IC50 value for compound 40 in an EGFR inhibitory experiment was 37 nanomolar. The results of testing the anti-proliferative activity of the synthesised adducts against the three human cancer cell lines MCF-7, DLD1, and HeLa showed that the anti-proliferative activity was enhanced by the substitution of pyrazole NH with a 4-arylthiazolyl moiety and the placement of a 4-p-tolyl ring at the pyrazole ring. The IC50 values for compound 41, a 4-p-tolyl derivative, against the cell lines used and displayed were in the nanomolar to low micromolar range, indicating that it is a powerful cytotoxic agent.

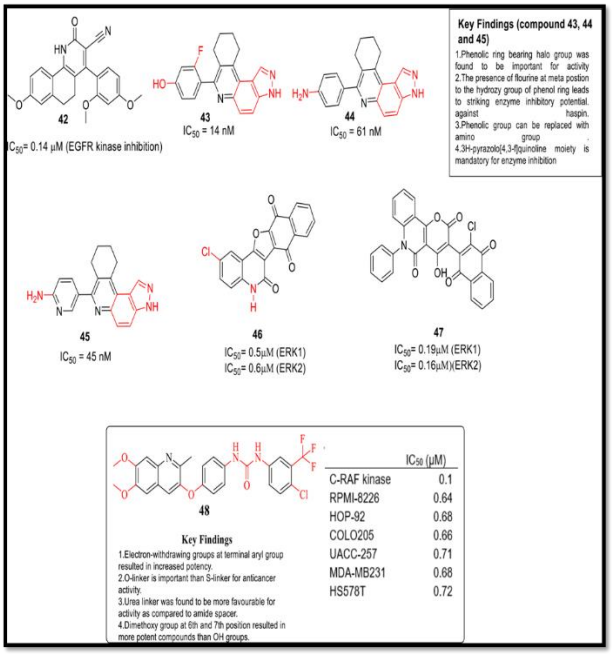

Fig. 4: Kinase inhibitor

To determine whether or not they could limit the replication of SARS CoV and MERS CoV 3CLpro, a series of 5-pyrazolone derivatives were developed and tested. Using Dabcyl-KTSAVLQSGFRKME-Edans as a peptide substrate for either 50 nM SARS CoV 3CLpro or 300 nM MERS CoV 3CLpro, in vitro fluorometric studies revealed that compound 30 had the most potential, with IC50 values of 5.8 M and 7.4 M. The structure-activity relationship analysis shown that the inhibitory capability of the pyrazolone moiety is lost when the bulky phenyl substituent at position 3 is replaced with smaller groups such as methyl or CF3. Also, the carboxylate group was removed from compound 30 to create derivatives that had no inhibitory function. Increased activity was also seen after the p-position of the phenyl ring at the N1 position of the pyrazolone was substituted with a lipophilic group. Docking study of the ligand within the active site of SARS CoV 3CLpro (PDB: 2ALV) using the iGemdock v2.1 tool provided further confirmation of the in vitro assay results.

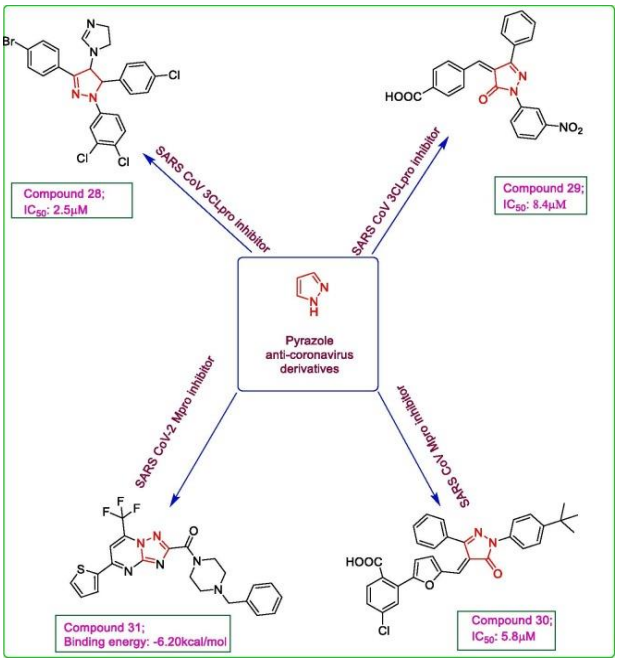

Fig. 5. Pyrazole compounds that inhibit SARS-CoV-2.

Compound 30 docked well into the active site, with the carboxylate moiety sitting in the S1 site and making hydrogen bonds to Gly 143, Ser 144, and Cys 145, and the furan moiety engaging with the hydrophobic S1′ site. Compound 30's inhibitory activity was boosted by the contact between its lipophilic tert-butyl group and the hydrophobic S2 site. Furthermore, the catalytic dyad at the active site of SARS CoV 3CLpro is stabilised by hydrogen bond formation between His 41 and the carbonyl group of the pyrazolone moiety [48]. With the hope of locating effective inhibitors of SARS CoV-2 major protease, the ZINC database was screened through the RASPD web server. Two hit compounds were chosen based on their high RASPD scores, and these were then evaluated for drug-like properties using the SwissADME and Molinspiration servers. The results showed that both ligands had a high bioactive score and favourable pharmacokinetics. Therefore, the ParDOCK server was used to examine the binding affinities of these two ligands with the SARS CoV-2 major protease (PDB: 6LU7). The results of the docking study demonstrated a good fit between both ligands and the active site of the protease, with compound 31 exhibiting a higher binding affinity than ligand N3 (Binding energy: 6.20 kcal/mol), both of which involved -alkyl interactions with the histidine residue of the main protease. Through the use of microwave irradiation, a novel class of benzimidazole, 1,2,4-triazole, and 1,3,5-triazine derivatives was developed and synthesised. All of the novel analogues were tested for their cytotoxic activity against four different human cancer cell lines (HepG-2, PC-3, MCF-7, and A-549) and normal peripheral blood mononuclear cells (PBMCs), with doxorubicin and

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erlotinib serving as reference medicines. Evidence was found that indicated that some of the tested compounds exhibited high levels of specific cytotoxicity against MCF-7 and A-549 cell lines. N-phenyl-1,2,4-triazole analogues 6a-c shown the highest cytotoxic activity against MCF-7 cells, with IC50 values ranging from 1.29 to 4.30 M, clearly close to those of the reference drugs (doxorubicin and erlotinib) of 4.17 and 4.16 M, respectively. Moreover, compared to doxorubicin, A-549 cancer cells were 1.3–2.6-fold more sensitive to the latter derivatives, with IC50 values ranging from 3.18 to 5.80 M, while IC50 values for doxorubicin and erlotinib were 8.20 and 3.76 M, respectively. However, IC50 values ranging from 4.18 to 5.42 M and 7.43 to 12.30 M were observed for the 1,2,4-triazole analogues 5a–c and the 1,3,5-triazinone 7 in MCF-7 and A-549 cell lines, respectively, compared to the reference medicines. Among the 1,3,5-triazin-2-thione derivatives 8, IC50 values for MCF-7 and A-549 cell lines ranged from 10.31 to 25.46 M and 37.21 to 25.46 M, respectively, whereas compounds 8c and 8d were as powerful as doxorubicin against the A-549 cell line. Additionally, the compounds showed moderate to weak antiproliferative action against hepatocellular carcinoma (HepG-2) and prostate cancer (PC-3) cell lines. All of the derivatives put to the test showed modest cytotoxicity against the normal PBMC cell line (IC50 values 100 M), substantiating the new compounds' margin of safety.

Finally, in vitro EGFRWT and EGFRT790M inhibitor evaluations were performed using the new target compounds 5, 6, and 7 that showed the most promising anticancer activity compared to the reference drugs erlotinib and AZD9291. Overcoming the EGFR-TKI resistance issue is facilitated by the target derivatives' promising inhibitory effect against EGFRWT and EGFRT790M, with more potency against the mutant form EGFRT790M. The most effective suppression effect against EGFRWT and EGFRT790M was demonstrated by derivative 6b. The oncogenic parameter p53 ubiquitination was also down-regulated by compounds 5–7, and their suppression potency was comparable to that of the reference diphenyl imidazole (DPI). Promising inhibitors 5–7 were subjected to a docking simulation research, with results showing energy scores of 11.40 and 12.66 kcal/mol and RMDS values of 0.91 and 1.02, respectively. Compound 6b was used to illustrate the differences in binding modalities between wild-type (WT) and mutant (EGFRT790M) EGFR. Its 1,2,4-triazole scaffold and the phenolic ring linked via the NH group formed diverse hydrophilic and hydrophobic contacts in the active pocket of wild EGFRWT and its mutant variant EGFRT790M, suggesting promising binding interactions with the active sites of the examined proteins. This study provides preliminary evidence that 6b is a novel potent anticancer drug with a favourable safety profile against normal cells and a promising inhibitory impact against EGFRWT and EGFRT790M.

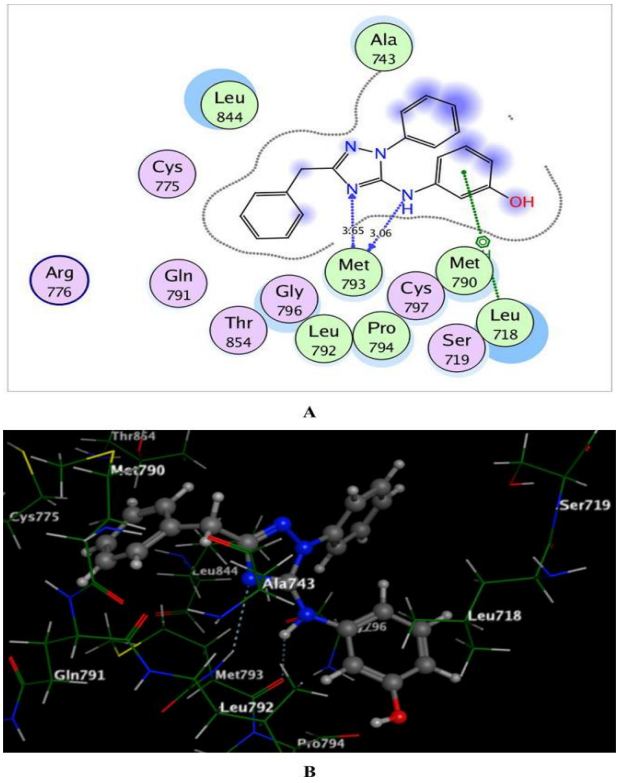

Fig. 6: 2D and 3D binding schematics of chemical 6b into EGFRT790M (PDB code: 6JX0) using MOE software.

III. CONCLUSION

Six-b is a novel, effective anticancer medication with a benign profile against normal cells and a possible inhibitory impact against EGFRWT and EGFRT790M. These advantages suggest that 6b could be a useful lead chemical in the research and development of new anticancer medicines that target EGFR. According to the results of the docking study, both ligands fit well within the active site of the protease, however compound 31 binds more tightly than ligand N3 (Binding energy: 6.20 kcal/mol), due to the presence of -alkyl contacts with the histidine residue of the primary protease. Derivatives of benzimidazole, 1,2,4-triazole, and 1,3,5-triazine were produced by microwave irradiation. Four human cancer cell lines (HepG-2, PC-3, MCF-7, and A-549) and normal peripheral blood mononuclear cells (PBMCs) were used to examine all novel analogues in comparison to doxorubicin and erlotinib. Selective cytotoxicity was seen against MCF-7 and A-549 cells by a number of substances. To combat the 3CLpro of SARS CoV and MERS CoV, 5-pyrazolone derivatives were created. Compound 30 showed its greatest potential with IC50 values of 5.8 M and 7.4 M, respectively, in an in vitro fluorometric study using Dabcyl-KTSAVLQSGFRKME-Edans as a peptide substrate for either 50 nM SARS CoV 3CLpro or 300 nM MERS CoV 3CLpro. According to the results of a structure-

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activity study, the inhibitory capability of pyrazolone is diminished when the phenyl substituent at position 3 is replaced with methyl or CF3. Deactivated derivatives were obtained by removing the carboxylate group from compound 30.

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