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A review on quinazoline containing compounds: Molecular docking and pharmacological activites

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Abstract

Molecular docking is a routinely employed tool in computer-aided structure-based rational drug design. It evaluates how well the ligands, or small molecules, and the target molecule fit together. In order to predict how minute molecules will interact with a target protein whose 3D structure is known, a programme called Auto Dock Tools (ADT) was developed. In this docking study, the ligand position within the enzyme binding site and the binding energy may both be visualised. It can be utilised to create novel medications and comprehend how binding works. The heterocyclic nitrogen-containing compound quinazoline, which is a constituent of many synthetic molecules, can be produced via a variety of synthetic methods. Quinazoline and quinazolinone scaffolds have caught the interest of medicinal chemists for the development of novel medications or therapeutic prospects due to their distinct pharmacological features. In addition to its diverse applications, quinazoline has anticancer, antimicrobial, anticonvulsant, and antihyperlipidemic properties. The pharmacological activity and molecular docking studies of quinazoline scaffolds are summarised in this article. The review also helps to hasten the drug development process by identifying the potential contribution of these hybridised pharmacophoric traits to the manifestation of various pharmacological actions.

1. Introduction

The organic substance quinoline has the molecular formula $C_8H_6N_2$. It has one bicyclic structure made up of two fused, six-membered aromatic rings, a ring of benzene and a ring of pyrimidine which is an aromatic heterocycle. It is a crystalline material that dissolves in water and has a faint yellow hue. It is a planar substance. Quinazoline is a quinoline-aza derivative also known as 1,3-diazanaphthalene. Despite the fact that substituted forms of the molecule have been developed for pharmacological reasons, such as antimalarial and anticancer drugs, the basic quinazoline molecule is rarely investigated on its own in scholarly literature. Members of the diazanaphthalene benzodiazine subgroup that it shares isomers which include cinnoline, quinoxaline, and phthalazine. The physiological effects of 200 quinazoline are known and also the physiological effects of quinoline alkaloids are recognized (Lian *et al.*, 2023)

To forecast the direction of the ligand when it binds to a protein receptor or enzyme, modern drug research frequently uses the protein-ligand or protein-protein docking technique. We discuss the electrostatic interactions and the structure of the ligand. When hydrogen bonds are formed, Van der waals interactions are just as crucial as coulombic interactions. The likelihood of binding is expressed using the docking score, which effectively sums up all of these interactions.

2. Molecular docking

2.1 The fundamental concepts of molecular docking

Molecular docking can predict and determine the binding affinity and interactive mode between ligand and receptor by modelling the optimum conformation in accordance with complementarity and pre-organisation (Alberg and Schreiber,1993).

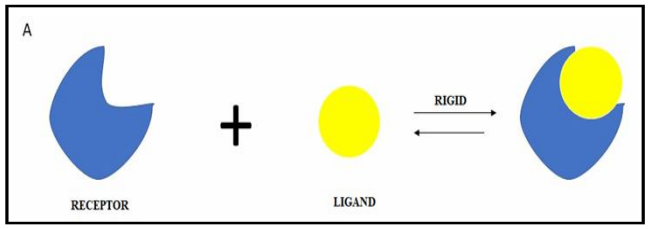

Figure 1: The lock and key model.

By illustrating the "lock-and-key model" (Morris and Lim-Wilby, 2008*)* in its original context and emphasizing the significance of geometric complementarity, this approach highlights the arduous docking of receptors and ligands to determine the ideal orientation for the "key" to unlock the "lock." As shown in Figure 1.

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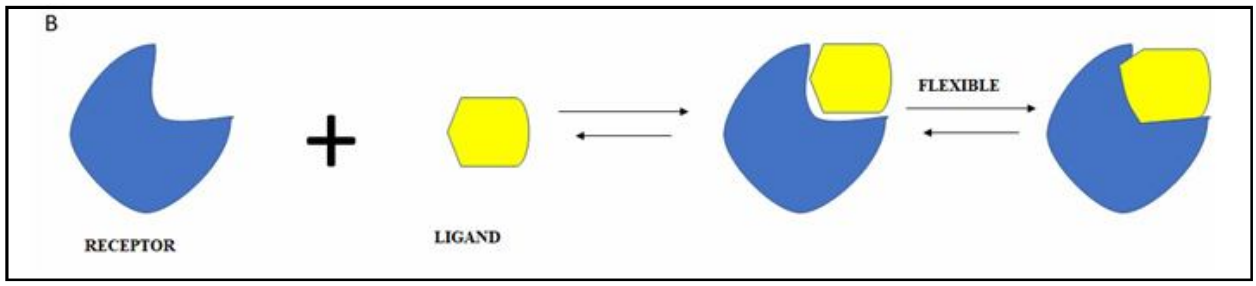


Figure 2: The induced fit model.

The afore mentioned illustration shows how the docking procedure itself is flexible, enabling receptors and ligands to change how they interact with one another. An "induced fit model" in light is shown in Figure 2. Because of pre-organisation and geometric complementarity-based energy complementarity, receptors and ligands are able to attain the lowest free energy with the most stable structure.

2.2 Molecular docking strategies

The three primary categories of molecular docking approaches are shown in the flowchart below. The use of flexible-rigid docking is common. However, study in this field has lately increased since flexible docking is typically more precise. The flexibility of proteins and ligands is typically taken into account by docking systems using one of the three methods described below:

i. Since the ligand is believed to be a rigid body with no internal degrees of freedom and the protein is believed to be stiff, only the ligand's translational and rotational degrees of freedom are investigated.

ii. The degrees of freedom for conformation, translation, and rotation are looked at with the protein conceptualized as stiff.

iii. All levels of ligand freedom are evaluated, regardless of whether the protein is fully flexible or merely partially. Bond lengths and angles are maintained despite the fact that sp^3 bonds can spin since the majority of algorithms take the ligand's flexibility and the protein's rigidity for granted.

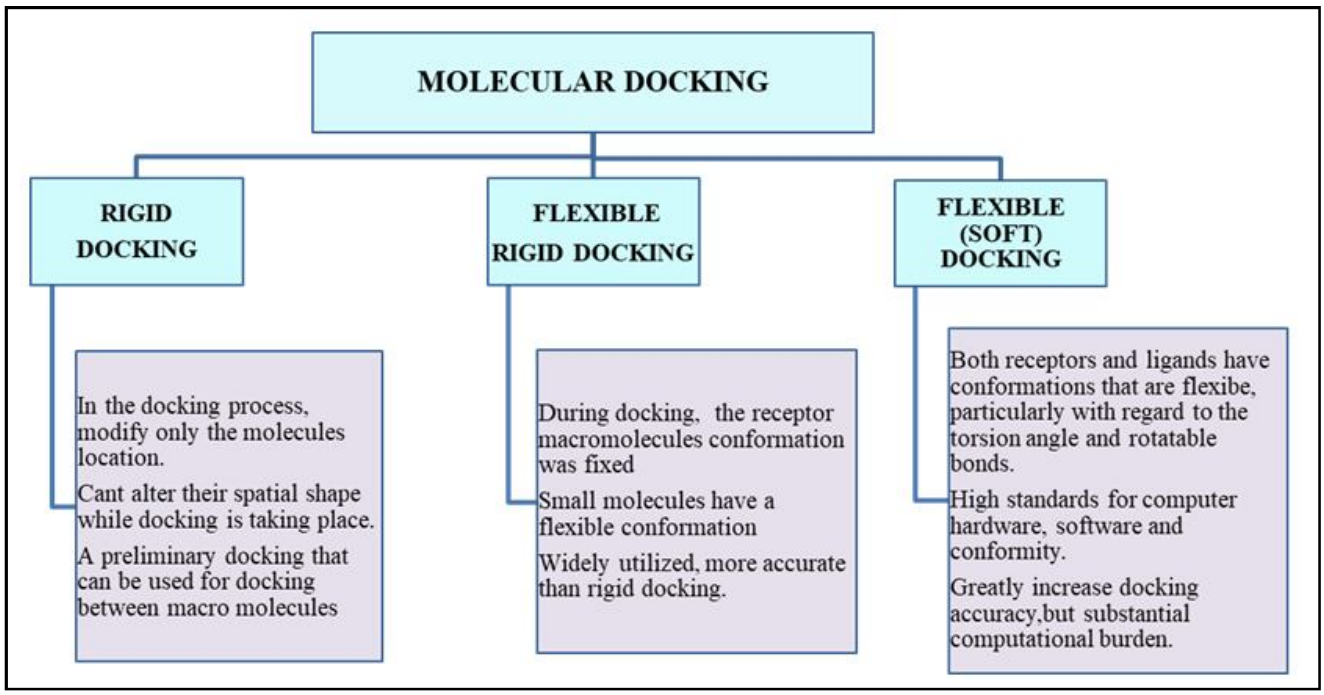


Figure 3: Types of molecular docking.

The ligand has been sought *via* a six-dimensional rotational or translational space to fit in the binding site in the most basic rigid-body systems and acts as the lead chemical for drug development. (Nataraj *et al.,* 2017*;* Alberg and Schreiber,1993). According to Nataraj and Schreiber, bound complexes have a noticeably higher docking accuracy than simple structures when utilising a rigid-body technique. Even if the structural distinctions between the bound and free forms are just marginally different, the accuracy gap raises the possibility that the rigidity assumption may not be totally supported. Additionally, using straight forward scoring criteria like the assessment of surface complementarity (Katchalski-Katzir *et al.,*1992), surface area accessible to solvent (SASA) burial, solvation-

free energy, electrostatic interaction energy, or total molecular dynamics energy, it is impossible to distinguish between structures that are close to native and those that are far from it. (Shoichet *et al.,*1991). So, by allowing for flexibility in receptor and ligand, a number of groups were able to enhance docking procedures.

2.3 Technical advances in docking algorithms

In order to study the free energy landscape and find the best ligand locations, search techniques were applied in the molecular docking process. The experimentally determined receptor-ligand conformation, or the native binding mode, will be comparable to the global minimum of the energy landscape, while local minima will correspond to alternative binding modes if the energy function accurately models the thermodynamics of the system, that is, the enthalpic and entropic effects. Since it is difficult to account for entropic effects, current docking approaches rely on approximations. As a result, it is difficult to say for sure if the global minimum related to the energy landscape examined by docking methods fits the native binding mode. The shortcomings in conformational sampling and scoring have led to the development of new software and molecular docking techniques. Along with efforts to enhance well-known docking programmes like AutoDock, DOCK, Prodock/ Ecepp, FLOG, FlexX, GREEN,GOLD, LUDI, Pro_LEADS, ICM, QXP, and SLIDE (Shoichet *et al.,* 1993; Walters *et al.,* 1998; Abagyan and Totrov, 2001), new docking programmes like the EUDOC algorithm (Pang *et al.,* 2001), SEED (Majeux *et al.,* 2001), SEEDS (Honma *et al.,* 2001) and MM (David *et al.,* 2001) have also been introduced in the past few years.

The two methodological challenges continue to be adequate ligand-receptor configuration, sampling and precise complementarity assessment. Most docking techniques used today consider ligand conformations. Reliable complementarity assessment is still very challenging in receptor flexibility treatment (Guedes *et al.,* 2001*;* Abagyan *et al.,* 2001). Most docking techniques used today consider ligand conformations. Increased receptor flexibility may actually worsen docking computations if the receptor configuration being sampled is a high-energy conformation and this is not taken into account when computing, according to claims that growing receptor flexibility is still very difficult to treat (Morrison *et al.,* 2006).

The kinetics and equilibria of molecules in solution must be taken into account in any attempt to hasten this process. An explanation of the impacts that will be taken into account and the approximations that will be employed must come before each approach. As a result, there are many different schools of thought regarding the appropriate theories and methods for molecular docking of the impacts that will be taken into account and the approximations that will be employed must come before each approach. (Medhat Farag *et al.,* 2022). An explanation of the impacts that will be taken into account and the approximations that will be employed must come before each approach. There are numerous schools of thought, and as a result, there is disagreement regarding the right presumptions and methods for molecular docking. These methods span a wide range of models and are constrained by the lock-and-key and induced fit theories for ligand binding. In this article, we shall look at two of these techniques and the scoring improvements that make them even more useful as models for molecular docking research. It is impossible to exaggerate the importance of this aspect of docking complexity, especially in light of what we have achieved with the combinatorial problem (Koshland *et al.,* 2010). Our ability to characterize the physical mechanism of molecular recognition and, in turn, our understanding of what an ideal configuration is will be directly impacted by how effectively we rank docked complexes. To fully benefit from a molecular docking analysis, including the potential for drug development and the capacity to understand thermodynamic binding processes, proper ranking is essential. For thermodynamic calculations, precise absolute affinity measurements and relative rankings of different binding modes may be required. Whether or not we are able to predict with any degree of accuracy how strongly one molecule will bind to another is the main problem that has to be answered in the field of structure-based drug design (Audie and Scorlata, 2007).

3. Quinazoline and its pharmacological activities

The pharmacological properties of quinazolines include acaricide, anticancer, antimicrobial, antifungal, antiviral, anti-inflammatory, diuretic, muscle relaxant, antitubercular, CNS depressive, anti-convulsant, and weedicide, to name just a few. Quinolines are also noteworthy in pharmaceutical chemistry (Ranjeeta Verma and Shweta Verma, 2022). The only three licenced drugs with a quinazoline composition on the market are prazosin hydrochloride, doxazosine mesylate, and terazosine hydrochloride (Arun *et al.,* 2011).

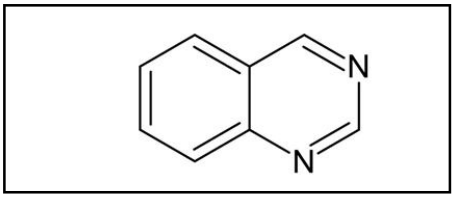
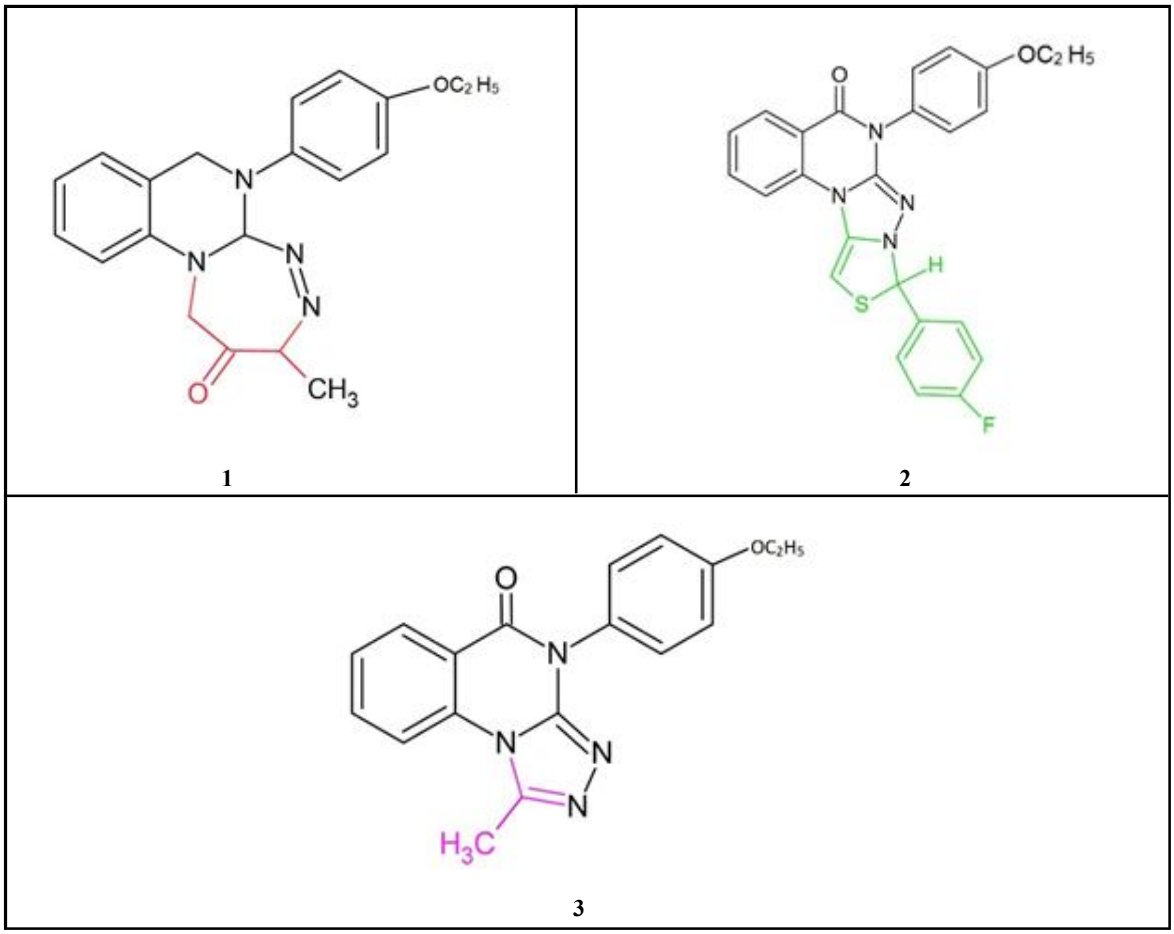


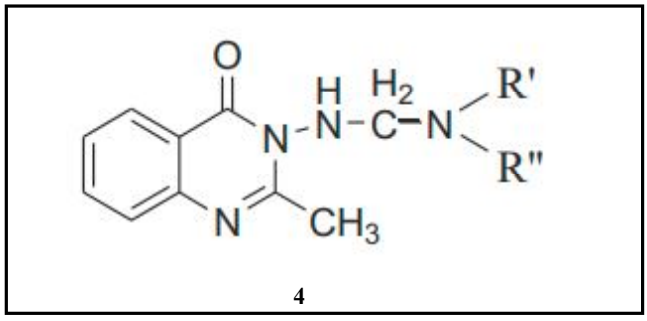
Figure 4: Quinazoline structure.

3.1 Antimicrobial activity

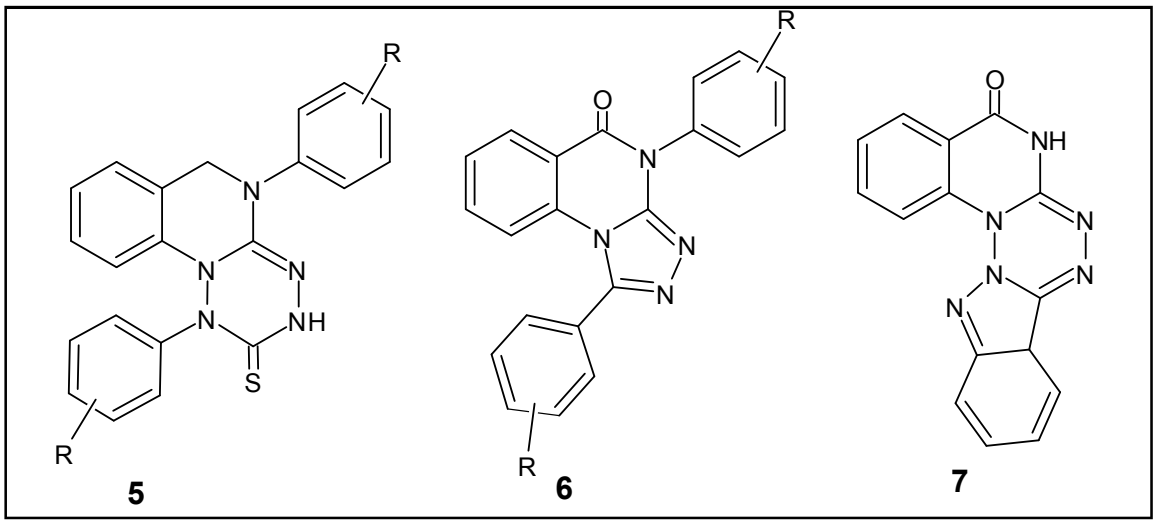
Sarvesh Kumar Pandey *et al.* (2021) studied the synthesis, biological analysis, and molecular docking studies of novel quinazolinones as antibacterial medicines. With quinzolinone, a variety of distinctive hybrids have been created. The physiological consequences of the target compounds on bacterial and pathogen strains were studied *in vitro*. According to the results of the bioassays, some of the compounds displayed antibacterial activity that was noticeably more potent than that of conventional medications evaluated in analogous circumstances. Compounds 1 and 3 were proven to be equally efficient against ciprofloxacin; however, compound 3 was superior against the pathogenic bacterium *S. aureus*. Compounds 1, 2, and 3 all showed strong inhibitory action against *P. aeruginosa* at their lowest inhibitory doses (MIC). Through, molecular docking experiments, the chemicals' inhibitory actions were clarified. Due to their strong binding affinities and high binding energies inside the active pocket, the compounds may operate as efficient inhibitors of some targets.



Antibacterial and antifungal activities in synthetic materials have been demonstrated by condensing the active hydrogen atom of the amino group of 3-amino. Alagarsamy *et al*. (2007) created 2-methyl-3-(substituted methylamino)-(3H)-quinazolin-4-ones 4. The antimicrobial activity of the test compounds was assessed against three pathogenic fungi (*C. albicans, A. niger*, and *M. audou*) using the agar dilution method. The least amount of agent resistance was present in the tested bacteria and fungi. Further research was done into the test compounds' potential to prevent HIV-I (IIIB) and HIV-II (ROD) reproduction in MT-4 cells. Only a small number of compounds, exhibit 25% anti-HIV-I (IIIB) and anti-HIV-II (ROD) action.

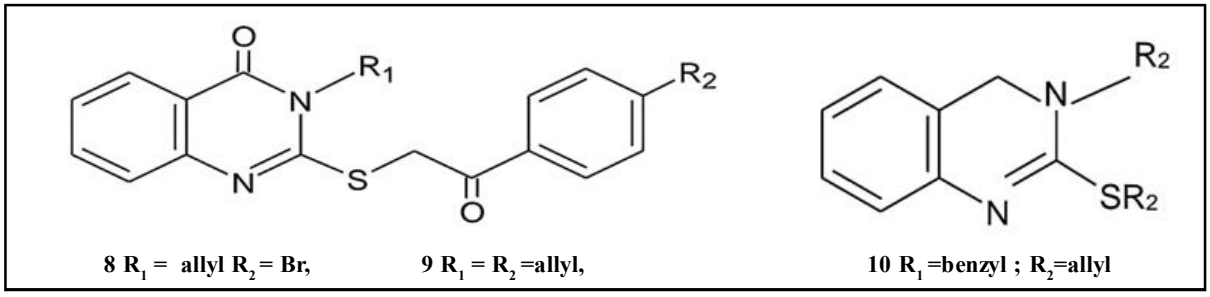


Pandey *et al.* (2008) found that active quinazolinones are either C-2 or N-3 mono- and/or disubstituted derivatives. Fused indole, 1,2,4-triazole, and 1,2,4-triazine and 1,2,4,5-tetrazine nuclei in between the N-1 and C-2 locations of the quinazolinone ring in figures in order to obtain unique fused systems, triazolo[4,3-a].-quinazolin-7- ones, tetrazino[4,3-a]-quinazolin-8-ones and indolo[2,3-c][1,2,4]- triazino[4,3-a]- quinazolin-8-ones. In order to test the antibacterial properties of named compounds in vitro against: (i) gram-positive bacteria such as *Streptococcus pneumoniae* and *Bacillus subtilis* and (ii) gram-negative bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa* by using the disc diffusion method, preliminary studies were carried out. The results of the antimicrobial screening revealed that triazolo[4,3-a] was the most effective agent. Quinazolin-7-ones compound 5 proved to be more potent than tetrazino [4,3-a]-quinazolin-8- ones compound 6 and indolo[2,3-c][1,2,4]-triazino[4,3- a]-quinazoline-8-ones compound 7. The data also showed that the presence of a triazole moiety at positions N1 and C-2 had a greater impact on the antibacterial profile than did the presence of triazine and tetrazine moieties in the compound. It is possible to draw the conclusion that the presence of a triazole nucleus at position N1 and C-2 of the quinazolinone ring contributes more effectively to the antibacterial activity of this series of compounds than the presence of other nuclei does. In addition, antifungal activity against *Candida albicans, Aspergillus fumigatus, Aspergillus flavus, and Aspergillus niger* was investigated for each of the sixty compounds that were given titles. These series of compounds demonstrate moderate to good antifungal activity, according to the screening data of antifungal activity that was performed on them.



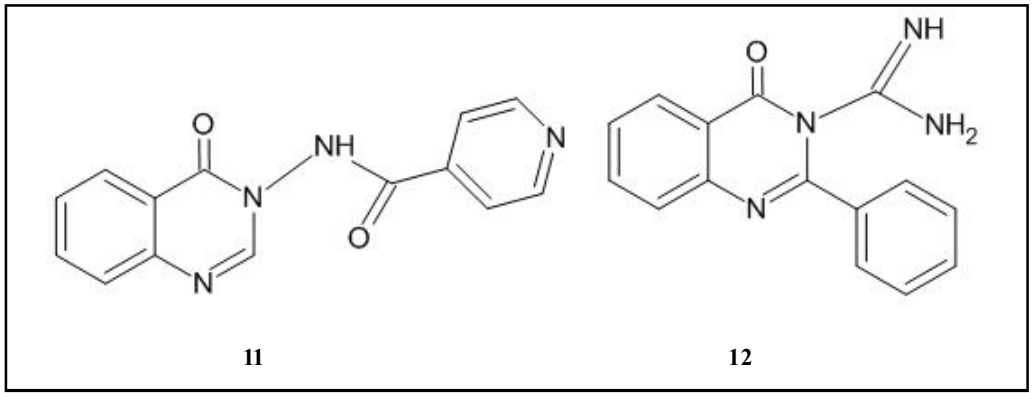
3.2 Antitubercular activity of quinazoline

Several 2-alkylthio-6-iodo-3 substituted quinazolin-4-one derivatives were created and tested by Al-Deeb and Alafeef (2008). They created them in an effort to emulate those that have been proposed as promising anti-tubercular treatments in their search for drugs that are biologically effective as shown is dtuctures. At a concentration of 6.25 g/ml, experiments revealed that compounds 8, 9, and 10 significantly reduced the rate of reaction initiation by 96%, 97%, and 94%, respectively. According to SAR analyses, the electron-withdrawing group on the sulphur atom at position 2 and the allyl and/or benzyl moiety at position 3 are both said to be responsible for the antitubercular effect.



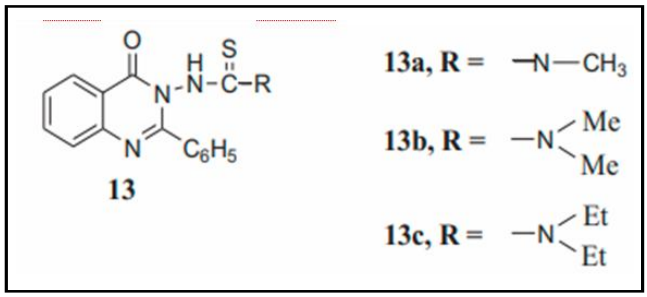
8 R_1 = allyl R_2 = Br, **9 R_1 = R_2 =allyl,** **10 R_1 =benzyl ; R_2=allyl**

Rajasekhar *et al*. (2009) researched the derivatives of 2,3-disubstituted quinazolinone for their antitubercular and antibacterial activity, characterization, and molecular docking. Strong antibacterial and antitubercular effects have been demonstrated for the physiologically varied quinozolinone derivatives. Compounds 5a-e and 8a-c's lowest inhibitory concentrations against *Mycobacterium tuberculosis* ranged from 6.25 to 100 g/ml. Among two-methylated or two-phenylated quinazolinones are these 14 compounds, chemicals 11 and 12; however, significantly inhibited the growth of *Streptococcus pyogenes and Staphylococcus albus*. It is well known that quinazolinone can be modified to have stronger antitubercular effects by modifying the 3-position with thioamido, amido, imidamido, N,N-dimethyl guanidinyl, or N-pyridoyl. According to Autodock Vina, the 2-phenyl series is anticipated to have a higher binding affinity Kushwaha *et al*. (2022). This could be as a result of additional hydrophobic interactions in the enoyl-acyl carrier protein reductase's binding region.

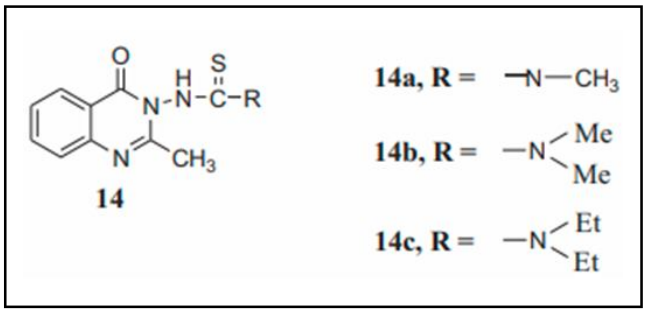


3.3 Anti-inflammatory activity of quinazoline

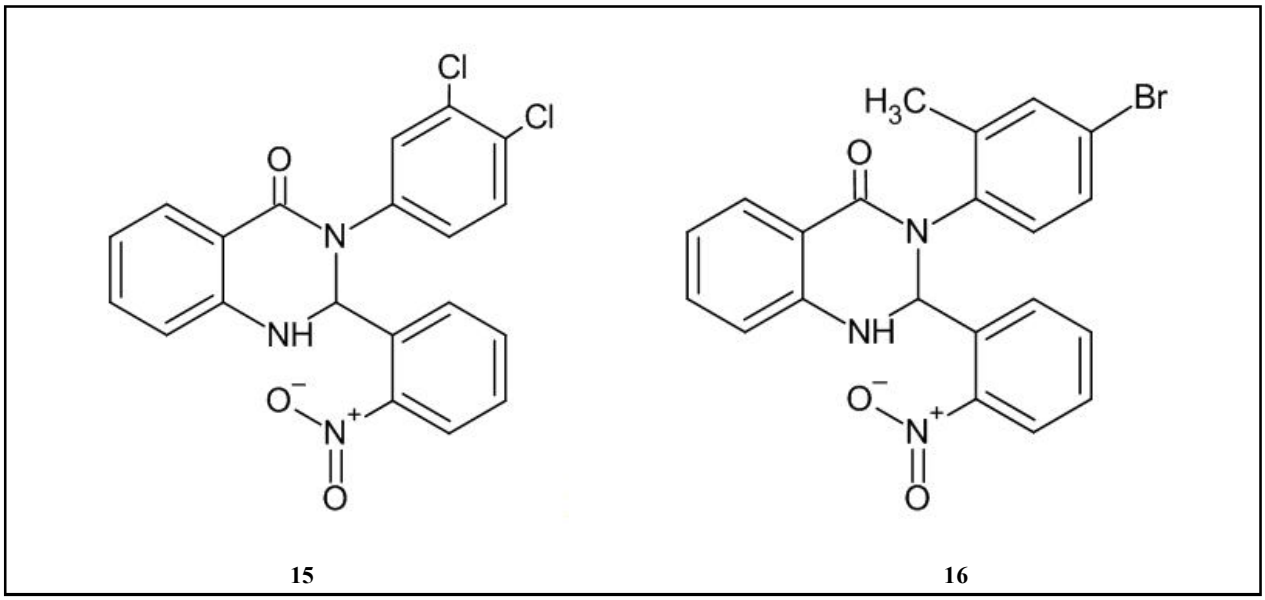
Alagarsamy *et al*. (2002) discoveries made it possible to synthesise 2-phenyl-3-substituted quinazolin-4(3H)-ones by reacting methyl-N-(2-phenyl quinazolin-3-yl-4(3H)-one)dithiocarbamate with a range of amines. Anthranilic acid was used as the initial raw material to make dithiocarbamate. The compounds' were examined for anti-inflammatory, antibacterial, and analgesic activities. The dimethyl group of compound 13b, which possessed increased lipophilicity, allowed the methyl substitution molecule 13a to display potent analgesic action. Both the analgesic's effectiveness and lipophilicity (diethyl group) increased in 13c. When alicyclic amines were added, the activity was reduced. More heteroatoms at alicyclic amine sites resulted in a notable rate of activity reduction. Drugs with an aliphatic open-chain substitution frequently have a better analgesic effectiveness. There was no further aromatization. Each drug considerably reduced inflammation, (Mamta Arya *et al.,* 2022). The medications demonstrated moderate to good efficiency in tests against the typhimurium virus, *P. aeruginosa, S. paratyphi B. Proteus vulgaris, E. tarda* and *Bacillus subtilis*.

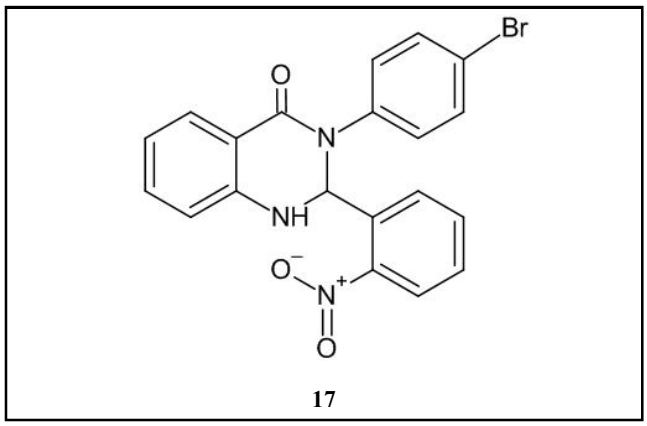


Alagarsamy *et al*. (2003), the anthranilic acid was transformed to its parent molecule, dithio carbamate, by the anthranilic acid's methyl ester, 2-methyl-4-oxo-3H-quinazolin-3-yl dithio carbamic acid. Similar to this, numerous more unique quinazolin-4-(3H)-ones have also been made, *P. vulgaris, B. Subtilis,* tarda. Researchers examined the compounds' anti-inflammatory, analgesic, and antibacterial effects. The methyl-substituted drug 14a has shown efficient analgesic effects in contrast to compound 14b, which has stronger activity and a higher lipophilicity (dimethyl group). The 14c molecule's diethyl group increased its lipophilicity, which increased its analgesic potency. An alicyclic amine is added to continue the reaction. More heteroatoms at alicyclic amine sites resulted in a notable rate of activity reduction. Testing for anti-inflammatory properties revealed that previously reported 2-phenyl-3-substituted quinazolines efficiently reduced inflammation brought on by carrageenan in rats. It was investigated how well *S. aureus, Typehi murium*, P. and *E. coli,* and other bacteria fought against infections. By converting the C-2 phenyl group to a C-2 methyl group, *Bacillus subtilis* and tarda enhanced the analgesic and anti-inflammatory properties of 2-phenyl-3-substituted quinazolines.



Bhimrao Ghodge *et al*. (2020) and associates developed and provided a description of 2,3-disubstituted quinazoline-4(1H)-one. They also examined the substance's anti-inflammatory capabilities. Mass, ^{1}HNMR, and FTIR spectra were used to produce and study a wide range of 2,3-disubstituted quinazolin-4(1H)-one derivatives. The anti-inflammatory properties of the synthesised compounds were tested *in vitro* using an egg albumin protein denaturation assay, *in vivo* with carrageenan-induced rat paw edoema, and in a granuloma pouch model employing cotton pellets. Both *in vitro* and *in vivo* tests reveal that the synthetic chemicals 15, 16 and 17 have stronger anti-inflammatory effects. Future therapeutic strategies must take into account the harmful interactions between inflammation and the immune system of the body.





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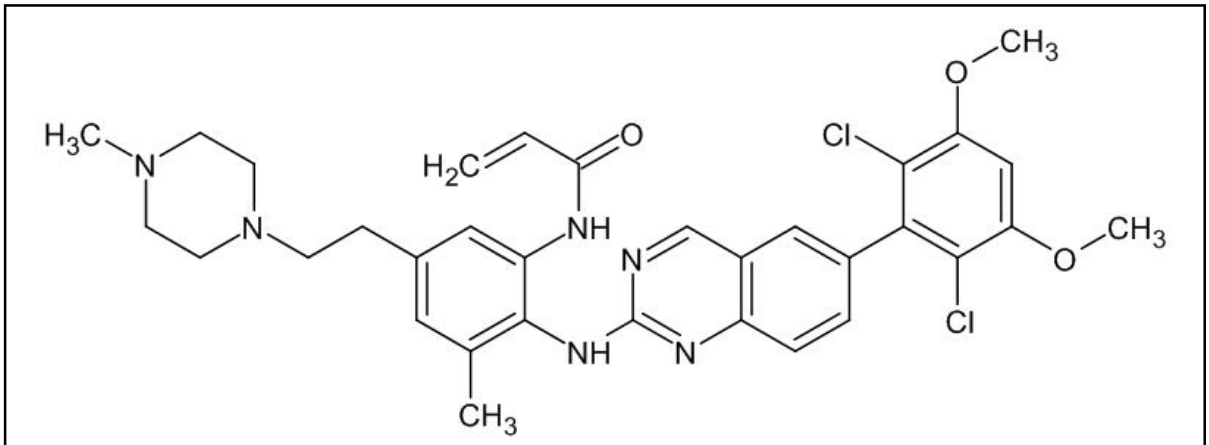
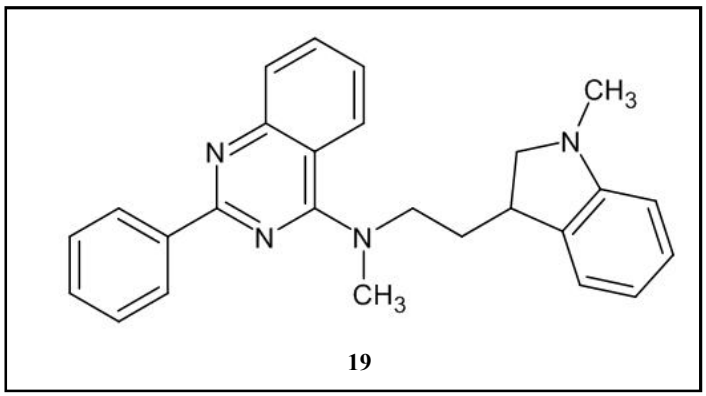
3.4 Anticancer activity

Zheng Lian *et al.* (2023) set out to produce new quinazolines for usage in 3D and 2D-QSAR research as well as the docking of chemicals that are targets for osteosarcoma. The CoMSIA methodology in SYBYL, the GEP (gene expression programming) algorithm, and heuristic methods were used to build the first 2D and 3D QSAR models. The use of 2D and 3D QSAR analysis led to the creation of 200 novel quinazoline molecules. The autodock 4.2 tool was used to select compounds for molecular docking that had high prediction values (Shobhit Srivastava *et al.,* 2022). The FGFR4 target related to osteosarcoma was docked using the ligands 18. The capacity of 10 to create hydrogen bonds with the residues ASP630, ALA553, ASN557, and LYS471, plus its potent target binding capabilities, make it possible to successfully treat osteosarcoma.



18

Novel quinazoline analogues have been shown to dramatically activate NF-B and exhibit anticancer activities by Lu Xu and Wade A. Russu (2003). The NF-kB p50 subunit has a high affinity for the autodock 4.2 tool, which was used for molecular docking. Quinazoline's position 2 phenyl substitution group of compounds reduced NF-kB activity the most. Compound 19 suppresses the development of numerous cancer cell lines with a mean GI50 of 2.88 M against the NCI-60 cell line.



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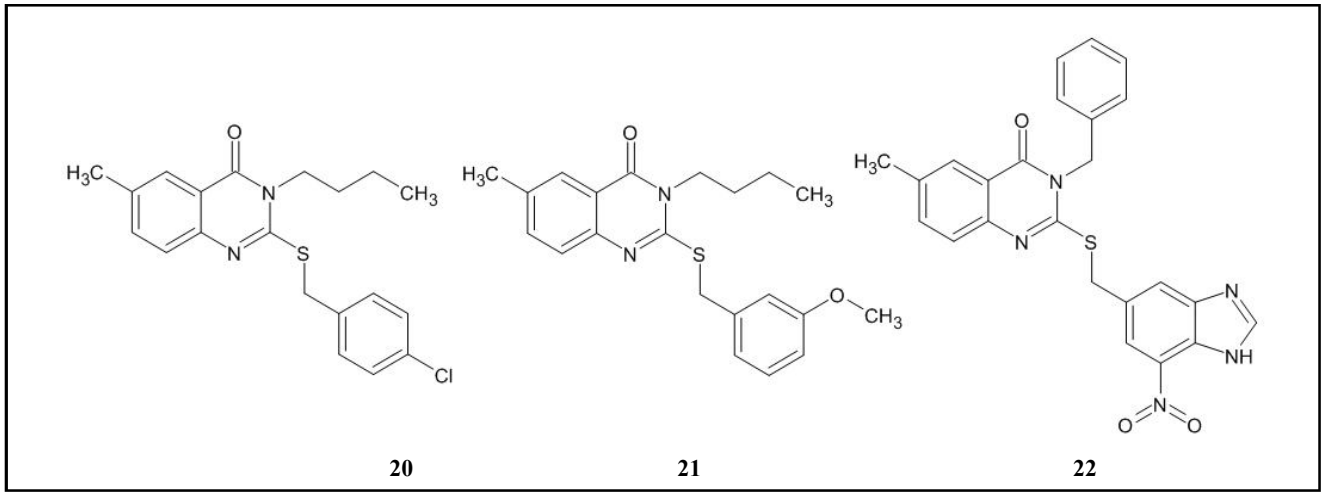
3.5 Anticonvulsant activity

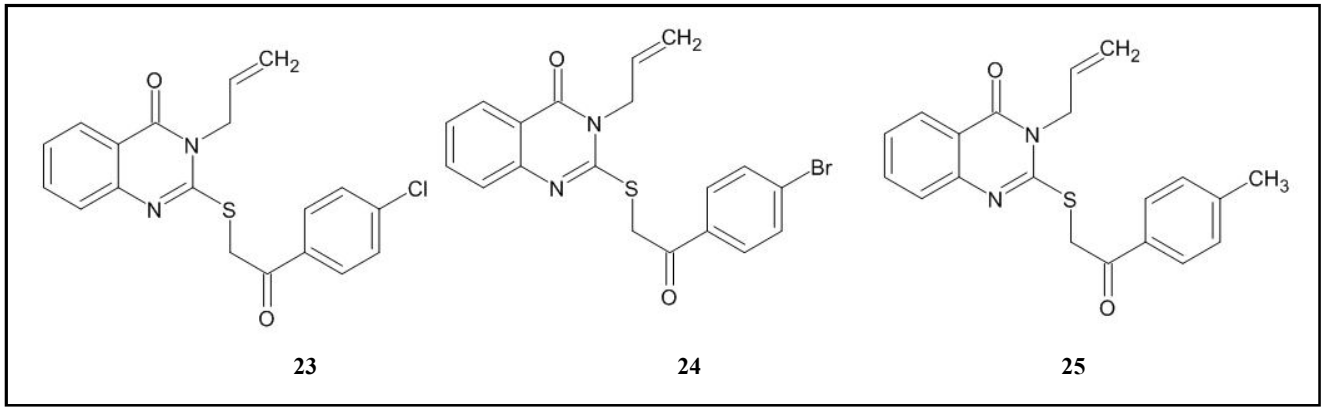
Newly synthesised quinazoline derivatives molecular docking and anticonvulsant properties were studied by Hatem A. Abuelizz *et al*. (2017). There have been 24 quinazoline compounds found. The existence of these chemicals' anticonvulsant properties is being investigated. The best active defence (100%) against PTZ-induced convulsions is provided by compounds 20, 21, and 22 out of the twenty-four compounds. These three compounds perform better than ethosuximide. The enzyme human carbon anhydrase II (HCA

II) was subjected to molecular docking. Arun Kumar *et al.* (2022), the quinazoline analogues were more successful at lowering the seizure threshold and stopping the propagation of epileptic discharge thanks to the butyl substitution at position 3 in the compound.



20 **21** **22**

Novel 2-substituted -3-allyl-4(3H)-quinazolinone derivatives were synthesised, biologically tested, and molecularly docked as anticonvulsant medications by Hamada S. Abulkhair *et al.* (2016). In this research, they investigated the ability of novel 2-substituted-3-allyl-4(3H)-quinazoline derivatives to inhibit pentylenetetrazole (PTZ)-induced epileptic episodes. To compare results, baseline medications sodium valproate and methaqualone were used. Every synthetic medication makes a physical docking connection with the GABA-A receptor. The compounds 23, 24, and 25 showed the greatest anticonvulsant effects on experimental mice while having the least neurotoxicity and toxicity, according to biological tests. Their GABA-A receptor binding affinities were also the lowest. The results of biological screening and molecular docking revealed great agreement.



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4. Conclusion

In medicine, substituted quinazoline derivatives are extensively used because of their bioactivities against bacteria, fungus, inflammation, and tuberculosis. Several bioactivities are reviewed in this article. To better understand the connection between the target and pharmacophore, the study reverses the order; this could be useful for the development of novel medications. By analyzing the structure and electrostatic interactions between the protein and the ligand, a procedure known as protein-ligand docking is used, When a ligand attaches to an enzyme or protein receptor, it is feasible to predict the direction of the ligand. By these strategies new quinazoline derivatives for different activities were explored which gives better idea for the current researchers. Further research and clinical trials can explore other pharmacological activities and their interactions and its level of toxicity with other compounds may help researchers in medicinal chemistry to select the proper nucleus and functions when creating quinazoline hybrids that are effective against a variety of disorders.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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