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Design, Synthesis, and In-silico Evaluation of Quinazoline Derivatives as Anti-Inflammatory Agents

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ABSTRACT

Researchers are now investigating quinazoline derivatives, which are a group of chemicals with diverse biological effects, in order to find powerful anti-inflammatory drugs. Developing and analysing novel quinazoline compounds that precisely target the 4JQA protein—a critical component of the inflammatory response—is the main goal of this study. The study will involve designing and synthesising these compounds, as well as evaluating their effectiveness using computer simulations. A number of quinazoline derivatives were synthesised by employing rational drug design ideas and synthetic chemistry methods many spectroscopic methods, such as NMR, were used to confirm the structures of the synthesised molecules.

Afterward, the anti-inflammatory capabilities of these compounds were assessed using molecular docking experiments against the 4JQA protein. The docking investigations demonstrated that a number of the synthesized quinazoline derivatives had robust binding affinities and advantageous interactions with the active region of the 4JQA protein. Significant interactions with amino acid residues essential for the protein's activity were detected, indicating a potential mode of action for these chemicals as anti-inflammatory drugs.

The encouraging findings from the computational docking studies establish a strong basis for subsequent laboratory and animal experiments, facilitating the progress toward creating innovative quinazoline-based medicines with anti-inflammatory properties. This study emphasizes the potential benefits of integrating computational and experimental approaches in developing new drugs, namely in the search for and development of innovative therapeutic drugs that target pathways linked with inflammation.

Keywords: Quinazoline, anti-inflammatory, Docking studies, etc.

1. INTRODUCTION

1.1 Quinazoline

Heterocyclic compounds are a prevalent category of organic chemical compounds. They are characterized by the presence of rings in their molecular structure, where at least one element, other than carbon, is included. The term "heterocyclic" signifies that the chemical possesses a ring structure, while the word "hetero" denotes the presence of noncarbon atoms, known as heteroatoms, within the ring**.[1]** However, the presence of heteroatoms in heterocyclic compounds gives them unique physical and

chemical properties that are different from those of cyclic compounds consisting solely of carbon atoms(Rani *et al*., 2004). Nitrogen, oxygen, and sulphur are confirmed components of heterocyclic rings. Approximately 50% of the known chemicals, which amount to around 20 million, are classified as heterocyclic. Heterocyclic compounds make a substantial impact in the fields of biology and industry, as well as in enhancing the quality of life and biological processes**.[2]** Heterocyclic rings are present in a diverse array of medications and physiologically active chemicals that exhibit a multitude of beneficial qualities, including anticancer, antibiotic, anti-inflammatory, antidepressant, antiviral, antimalarial, anti-HIV, antimicrobial, antibacterial, antifungal, antidiabetic, herbicidal, fungicidal, and insecticidal effects. In addition, several heterocyclic compounds are employed as additives and modifiers in various industrial applications, including cosmetics and polymers. Of all these compounds, heterocycles containing nitrogen as a heteroatom are particularly intriguing to the scientific community because of their wide range of uses. **[3]** Antipyrine, developed in 1887, was the inaugural synthetic medication employed for fever treatment. The use of sulfapyridine as an antibiotic commenced in 1938. Sumatriptan is the inaugural medicine used to treat migraines, whereas omeprazole has the ability to reduce stomach acid secretion, making it effective in preventing ulcers. Quinazoline and its derivatives are well researched and documented heterocyclic chemicals under the category of nitrogen-containing heterocycles glutathione S-transferase (GST), heat shock proteins, NADPH, P450s, and cyclooxygenase-2 (COX-2). **[4]**

1.2. Quinazoline

Quinazoline derivatives are currently attracting significant attention in the field of chemistry due to their intriguing biological properties and their potential applications in medicine as anticonvulsants, anti-inflammatory agents, and anticancer drugs.**[5]** Similarly, triazoles, oxazoles, and thiazoles have also been extensively studied from both chemical and biological perspectives, and physiological activities.**[6]** Quinazoline is an organic molecule represented by the chemical formula C8H6N2. With a bicyclic structure made up of two fused six-membered aromatic rings, one of which is a pyrimidine ring, it is a fragrant heterocycle. **[7]**

It is a soluble pale yellow crystalline solid. Quinazoline, often referred to as 1,3-diazanaphthalene, is named as such because it is a derivative of quinoline with an aza group. While the original quinazoline molecule is not frequently discussed independently in technical literature, modified derivatives have been created for medical applications, such as developing anti-inflammation, antimalarial and anticancer medicines. **[8,9]** Quinazoline exhibits planarity. It shares the same molecular formula but has a different arrangement of atoms compared to the other diazanaphthalenes of the benzodiazepines subgroup, namely cinnoline, quinoxaline, and phthalazine. More than 200 physiologically active quinazoline and quinoline alkaloids have been found. **[10]**

Fig.1.1 2D, 3D and structure of Quinazoline

Chemistry's domain of heterocyclic molecules is very complex. In addition to being widely found in

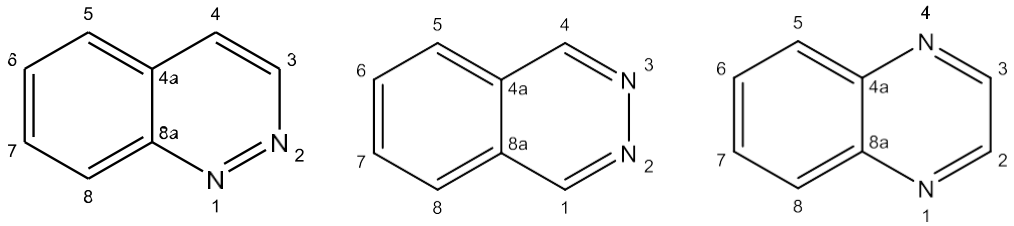
nature, heterocyclic compounds may also be made intentionally. They significantly affect how biological processes are regulated. Antibiotics, vitamins, and alkaloids all have a heterocyclic structure. **[11]** Heterocyclic compounds have wide-ranging uses in the pharmaceutical, co-polymer, dye, and chemotherapeutic industries. **[12]**

Quinazoline Structure And Properties

These isomers, also known as diazanaphthalenes, are identified by the position of N in the heterocy- clic ring. The class of bicyclic aromatic ring structure, which consists of a benzene ring linked two nitrogen-containing two ring, such as pyridazine, pyrimidine, and pyrazine, is known in four isomers with the structural formula as shown in figure. The chemical quinazoline is composed of two fused rings with six members.**[13,14]**

Quinazoline

A benzene ring is connected to two nitrogen-containing rings, such as pyridazine, pyrimidine, and pyrazine, to form the class of bicyclic aromatic ring structures. These structures are known as diazanaphthalenes and are found in four isomers, as the image illustrates.**[15]** The location of the nitrogen atom inside the heterocyclic ring separates the isomers. Quinazoline is a heterocyclic compound made up of two joined rings with six mmbers. **[16]**



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1.2.2 Quinazoline based drugs available in the market

The frequency of pharmacological adverse effects and the quick development of drug resistance both set restrictions on the therapeutic agent. The use of antimicrobial drugs is in crisis as a result of these conditions. The limited efficacy of available drugs forces scientists to develop new antibacterial agents with a broad range of antimicrobial activity. Quinazoline-based medicines are generally acknowledged as an important class of therapeutic agents. In addition, it is essential to address the problem of the growth in microbial resistance to conventional antimicrobial agents and to lessen the side effects of present drugs. **[17]** As a result, several quinazoline molecules have been synthesised and evaluated for their various biological purposes. The rapid advancement indicates that more quinazoline derivatives will be subjected to clinical trials in the near future. In the near future, these molecules should prove to be more effective than the existing organic-based treatments. Methaqualone is a well-known quinazoline-based drug that has been used for its sedative-hypnotic effects since 1951. There are already a sizable number of patented quinazoline derivatives available on the market as potential medications for a variety of illnesses. Many quinazoline medications that are sold commercially and used to treat various illnesses are included in the table below**[18]**. Two quinazolinone-based medications, idelalisib and fenquizone, have shown a variety of antibacterial, anticancer, antifungal, and cytotoxic properties. Quinazoline-4-(3H)-one derivatives have attracted a great deal of attention from medicinal and synthetic chemists owing to their extraordinary variety in biological activity. Lapatinib has shown to be effective in combination therapy for breast cancer. This is shown by the large number of approved drugs that use quinazoline as the primary pharmacophore

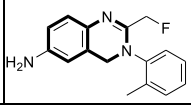
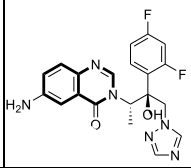
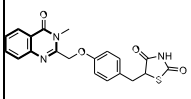
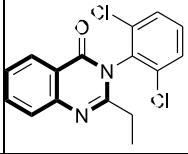
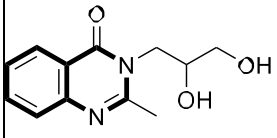
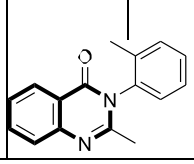
unit on the market. **[19]**

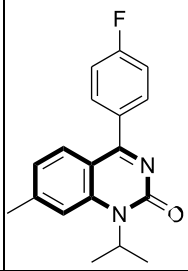
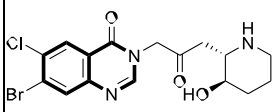
Methaqualone, a well-known quinazoline-based medication, has been utilised for its sedative-hypnotic properties. Currently, there is a significant quantity of patented quinazoline derivatives that are commercially accessible as possible pharmaceuticals for a range of diseases. **[20]** The table below enumerates many quinazoline medicines that are commercially available and utilised for the treatment of different diseases.

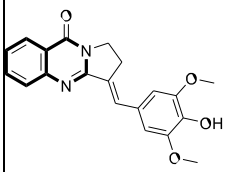
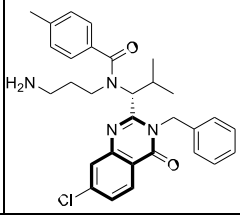
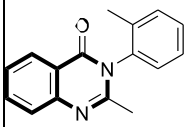
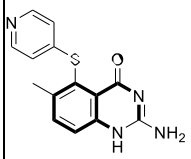
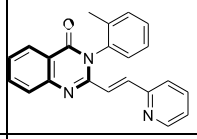
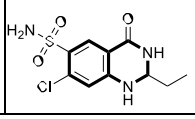
Idelalisib and fenquizone, both quinazolinone-based medicines, have demonstrated a wide range of antibacterial, anticancer, antifungal, and cytotoxic effects. Lapatinib has demonstrated efficacy in combination treatment for breast cancer.

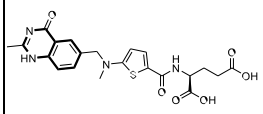
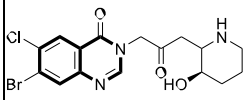
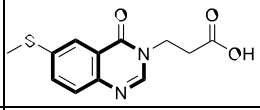
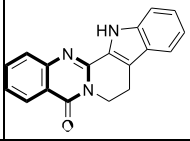
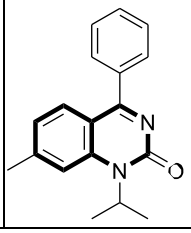
Quinazoline-4-(3H)-one derivatives have garnered significant interest from medicinal and synthetic chemists due to their remarkable diversity in biological activities. This is evidenced by the presence of numerous licensed medications in the market that include quinazoline as the major pharmacophore unit. **[21]**

Table 1.1 Quinazoline Marketed Drugs

S N.	Drug	IUPAC name	Structure	Activity
1	**Afloqualone**	6-amino-2(flouromethyl)-3- (2-methylphenyl) quinazoline		Sedative, Hypnotic, Anticancer, Anti-anxiety agent
2	**Albaconazole**	7-chloro-3-[(2R,3R)-3-(2,4-diflourophenyl)-3-hydroxy- 4-(1,2,4-triazol—1-yl)butan- 2-yl] quinazoline-4-one		Antifungal
3	**Balaglitazone**	5-[[4-(3,4-dihydro-3-methyl- 4-oxo-2-quinazolinyl)methoxy]phenyl]methyl]-2,4- thiazolidinedione		Peroxisome proliferator-activated receptor (PPAR) gamma agonist Anti-diabetic
4	**Chloroqualone**	3-(2,6-dichlorophenyl)-2-ethylquinazolin-4(3H)-one		Sedative and Antitussive
5	**Diproqualone**	3-(2,3-dihydroxypropyl)-2-methyl-quinazoline-4-one		Anxiolytic, Analgesic, Antihistamines rheumatoid arthritis
6	**Etaqualone**	3-(2-ethylphenyl)-2-methyl-quinazoline-4-one		Nervous system depressant properties

7	**Flouproquazone**	4-(4-fluorophenyl)-7methyl-1-propan-2-ylquinazoline-2-one		Antipyretic avtivity, NSAID
8	**Halofuginone**	7-bromo-6 chloro-3-[3-[(2S, 3R)-3-hydroxy-2-piperidinyl]- 2-oxopropyl]-4-quinazoline		Coccidiostat, antitumor, auto-immune disorders

9	**Isaindigotone**	3-[(3,5-dimethoxy-4-oxycyclohexa-2,5-dien-1-ylidiene)methyl]-2,4-duhydro-1H-pyrollo[2,1-b] quinazoline-9-one		Acetylcholinesterase and butyrylcholinesterase
10	**Ispinesib**	N-(3-aminopropyl)-N- [(1R)-[7- chloro-3,45-dihydro-4-oxo-3- (phenylmethyl)-2-quinazolinyl]-2-methylpropyl]-4-methyl benzamide		Anticancer
11	**Methaqualone**	2-methyl-3-o-tolyl-4(3H)-quinazolinone		Hypnotic
12	**Nolatrexed**	2-amino-6-methyl-5-(4-pyridylthio)-1H-quinazoline-4-one		anticancer
13	**Piriqualone**	3-(2-methylphenyl)-2-[(E)-2-pyridin-2-ylethenyl]quinazoline-4-one		Anticonvulsants
14	**Quinethazone**	7-chloro-2-ethyl-4-oxo-1,2,3,4-tetrahydroquinazoline-6-sulfonamide		Antihypertensive

15	**Raltitrexed**	N-[(5-{methyl[)2-methyl-4-oxo-1,4-dihydroquinazoline-6-yl)methyl]amino}-2-thienyl)carbonyl]-L-glutamic acid		Anticancer
16	**Tempostatin**	7-bromo-6-chloro-3-(3-((3R)-3-hydroxypiperidin-2-yl)-2-oxopropyl)quinazolin-4(3H)-one		Inhibiting the deposition of collagen
17	**Tiacrilast**	(E)-3-[6-(methylthio)-4-oxoquinazoline-3(4H)-yl]propionic acid		Antiallergic
18	**Rutaecarpine**	8,13-dihydroindolo[2',3':3,4]pyrido[2,1-b]quinazoline- 5(7H)-one		gastrointestinal disorders
19	**Proquazone**	1-isopropyl-7-methyl-4-phenyl-2(1H)-quinazoline		Non-steroidal, anti-inflammatory potential

MATERIALS AND METHODS

2.0. Materials and methods. Material:

- All TLC was performed on precoated TLC plates **(**Silica Gel 60 F254, Merck, Germany**)**, and visualization done under UV light**.**
- All chemicals are bought from Sigma Aldrich, Tokyo Chemical Industries **(**TCI**)**, and Avra chemicals are used as such**.**
- All ^{1}H NMR spectra were recorded in Bruker spectrophotometer AMX-400 **(**400 MHz**)**, Bruker Optik **(**Germany**)** in $CDCl_3$ using TMS as an internal standard**.**
- We utilized Schrodinger software for the *in-silico* studies.

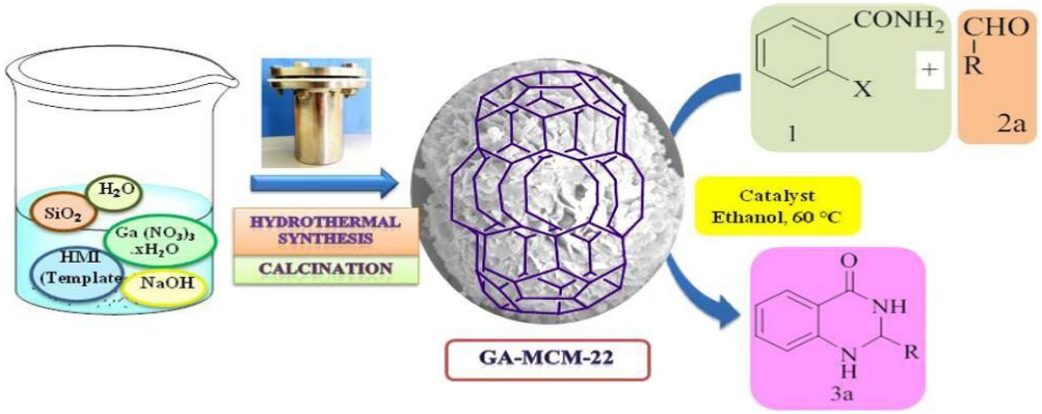
Method:

Experiment

2.1 Synthesis of Ga-MCM22 catalyst

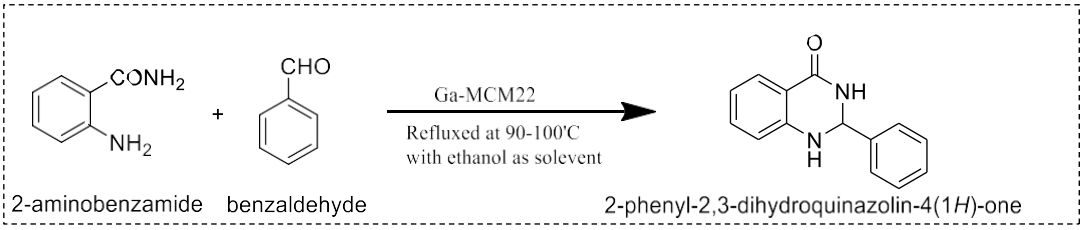
There are two steps involved in the catalysts' synthesis. The synthesis of the catalysts is done in two phases. The first step is to continuously mix a sodium hydroxide (NaOH) and colloidal silica (SiO2) solution in Millipore water. The following step involves adding a gallium nitrate solution (Ga(NO3)3xH2O, Alfa Aesar, 99.9% metal base). The gel was matured at 180 °C in a preheated oven before being moved to a stainless steel autoclave coated with Teflon. Additionally, the mixture was chilled and combined with hexamethyleneimine and a NaOH solution. After that, the solution was transferred to the autoclave made of stainless steel coated with Teflon and stored in a hot oven at 155 °C

for 168 hours. In addition, the resultant gel was allowed to reach room temperature, filtered, cleaned with Millipore water, and allowed to dry at 80 °C for a whole night. The sample was then calcined for six hours at 550 °C with a 50–100 mL/min airflow. Using the calcined sample, protons were removed from the catalyst by ion exchange with a 1 M ammonium acetate solution.



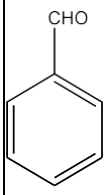
2.2 PROCEDURE

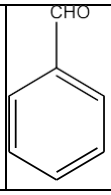
2.2.1 Synthesis of first derivative quinazoline (Q1)



A condenser-equipped two-necked round-bottom flask was used to perform the reaction. Usually, ethanol in the RB flask was mixed with a catalyst known as Ga-MCM22, which was heated to (120 °C for 30) minutes. After that, the mixture was cooked in an oil bath while being constantly stirred. Following a five-minute standard run, a solution containing one millimolar (mM) of 2-aminobenzamide (anthranilamide) was added. Stirring was then required to add benzaldehyde (1.2 mM). TLC was used to monitor the reaction's progress. The catalyst was easily isolated from the end product by filtering it after the reaction was finished, and it was then dried and recrystallised using ethanol.

Table 1: Physical properties of synthesized 2-phenyl-2,3-dihydroquinazolin-4(1H)-one

S.NO	R	Mol. Wt	%Yield	M.P.	Catalyst
1		224.09	78%	268.28°C	Ga- MCM22
2		224.09	32%	268.28°C	N/A

2.2.2 Synthesis of quinzaoline derivative (Q2)

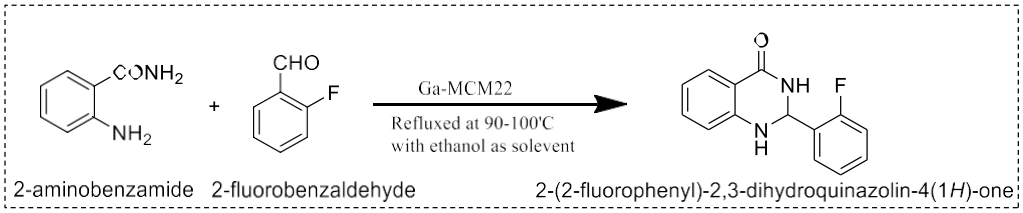
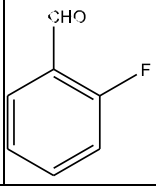
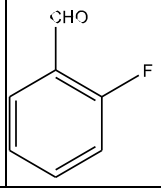


Table 2: Physical properties of synthesized 2-(2-fluorophenyl)-2,3-dihydroquinazoline-4(1H)-one

S.NO	R	Mol. Wt	%Yield	M.P.	Catalyst
1		242.09	71%	281.59°C	Ga- MCM22
2		242.09	29%	281.59°C	N/A

2.2.3 - Synthesis of quinazoline derivative (Q3)

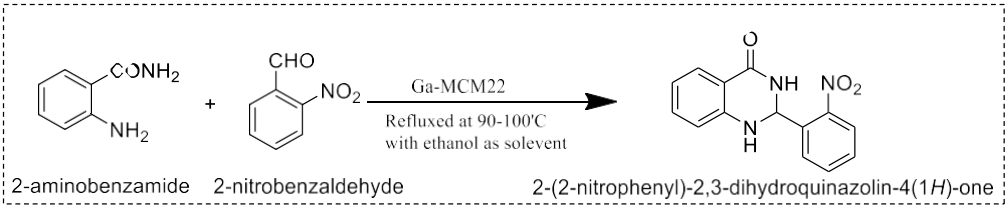
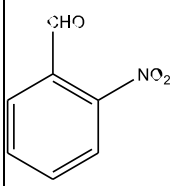
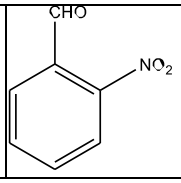


Table 3: Physical properties of synthesized 2-(2-nitrophenyl)-2,3-dihydroquinazoline-4(1H)-one

S.NO	R	Mol. Wt	%Yield	M.P.	Catalyst
1		269.26	78%	N/A	Ga- MCM22
2			33%	N/A	N/A

		269.26			

2.2.4 Synthesis of quinazoline derivative (Q4)

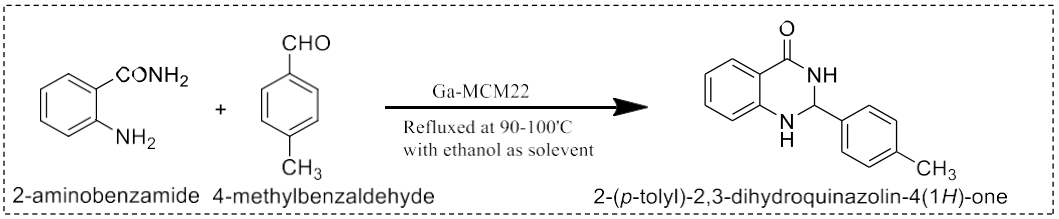
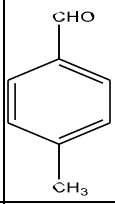
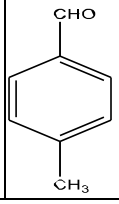


Table 4: Physical properties of synthesized 2-(p-tolyl)-dihydroquinazoline-4(1H)-one

S.NO	R	Mol. Wt	%Yield	M.P.	Catalyst
1		238.11	69%	293.27°C	Ga- MCM22
2		238.11	21%	293.27°C	N/A

2.2.5 Synthesis of quinazoline derivative (Q5)

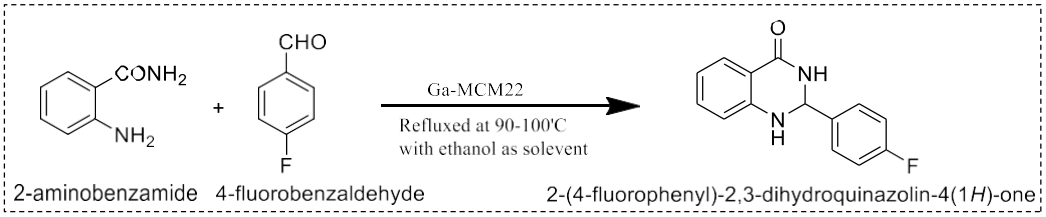
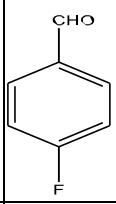
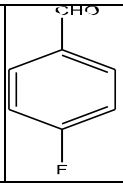


Table 5: Physical properties of synthesized 2-(4-flourophenyl)-2,3-dihydroquinazoline-4(1H)-one

S.NO	R	Mol. Wt	%Yield	M.P.	Catalyst
1		242.09	75%	281.57°C	Ga- MCM22
2					

		242.09	**19%**	**281.57°C**	**N/A**

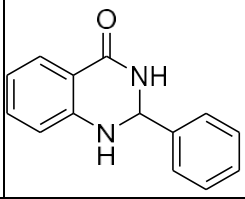
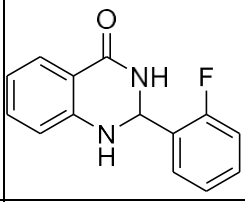
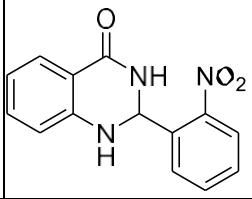
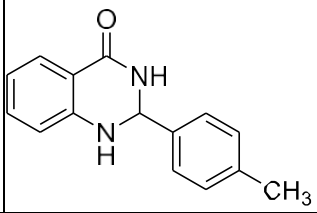
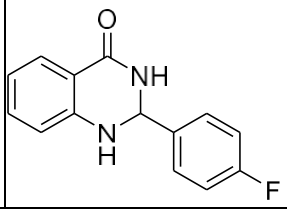
S.No.	Structure	IUPAC Name
Q1.		2-phenyl-2,3-dihydroquinazolin-4(1H)- one
Q2.		2-(2-fluorophenyl)-2,3-dihydroquinazolin-4(1H)- one
Q3.		2-(2-nitrophenyl)-2,3-dihydroquinazolin-4(1H)- one
Q4.		2-(p-tolyl)-2,3-dihydroquinazolin-4(1H)- one
Q5.		2-(4-fluorophenyl)-2,3-dihydroquinazolin-4(1H)- one

Table 01 Table of all Derivatives of compound

Preparation of zeolite Ga-MCM-22 catalyst

We looked into the zeolite Ga-MCM-22 sample's catalytic capability for the production of 2,3-dihydroquinazoline4(1H)-ones. This sample shows altered acidic properties. The Lewis acid catalyst may be used for these processes. Initially, we mixed benzaldehyde (2a) and anthranilamide (1a) in ethanol at 80 °C without the use of a catalyst. Thin-layer chromatography was used to observe the reaction (TLC). The reaction yielded unsatisfactory amounts of 2,3-dihydroquinazoline-4(1H)-ones after 24 hours. Then, for six hours, a combination of 1a and 2a was exposed to a reaction in ethanol under reflux conditions with a little amount of active Ga-MCM-22 catalyst (10 M%). After 2,3-dihydroquinazoline4(1H)-one 3a was successfully synthesised, we looked into the effects of Ga-MCM-22 in ethanol at different catalytic concentrations under reflux conditions.

3. RESULTS AND DISCUSSION

The synthesised molecule was subjected to elemental analysis, both quantitative and qualitative. Using chloroform D as the solvent, the broker DRX-400 spectrophotometer running at 400 MHz was used to get the NMR spectra. The reference component is tetramethyl silane (TMS), and chemical shifts are reported in parts per million (PPM).

Qualitative Analysis

Table 5.0: Solubility profile of the synthesized compound

a. Solubility: The solubility of the synthesized compound are shown in table

S.No	Cool water	Hot water	methan ol	Ethan ol	Hot ethanol	DMF	Chloroform
Q1	-	-	++	+	++	+++	_
Q2	-	-	++	+	++	+++	_
Q3	-	-	++	+	++	+++	_
Q4	-	-	++	+	++	+++	_
Q5	-	-	++	+	++	+++	_

Where = (-) Practically insoluble, (+) Slightly soluble, (++) Soluble, (+++) Freely soluble

b. Test for elements (Lassaigne's test): The sodium fusion extract of each compounds were prepared and it was tested for nitrogen.

c. TLC profile: Using n-Hexane and ethylacetate in varying ratios as a solevent system on silica gel G plates and iodine as visualising agents, the reaction's progress was tracked using TLC

3.1 Spectral analysis of the synthesized compounds: All synthesized compounds were studied by NMR spectra. The spectral analysis was interpreted with the help of an appropriate spectral chart.

- **Data No. Q1**

Molecular Formula = C14H11N2O1 Molecular weight = 224.09

^{1}H NMR (600 MHz)

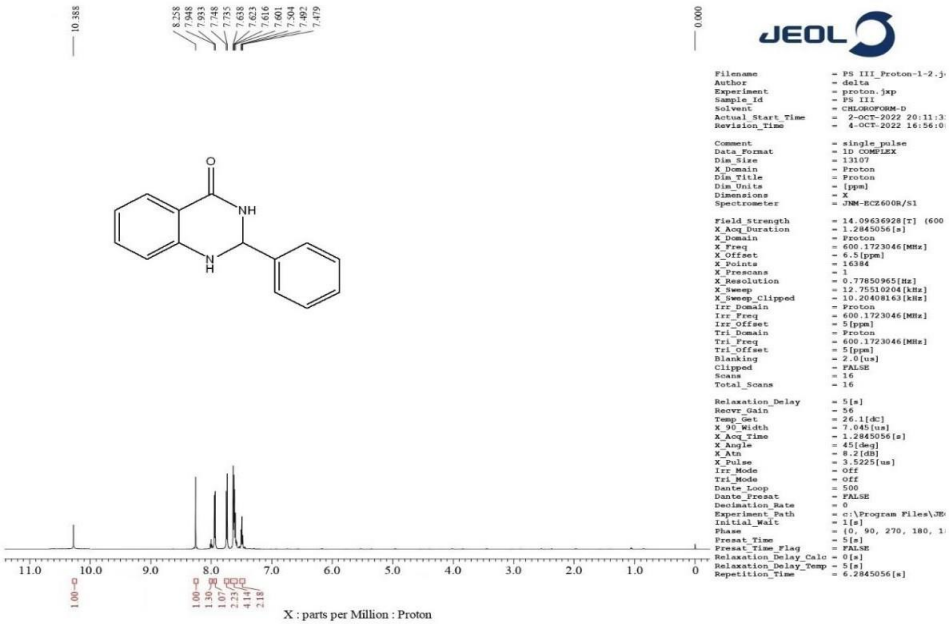


Fig. 3.1 PMR spectrum of 2-phenyl-2,3-dihydroquinazolin-4(1H)-one

Chemical Shift (ppm)	Signal due to
10.388	S, 1H, Ar-NH
8.258	S, 1H, Ar-NH
7.948	D, J=7.5Hz, 1H-Ar-H
7.748	D, J=6.5Hz, 1H-Ar-H

- **Data No. Q2**

Molecular Formula = C14H10N2O1F1 Molecular Weight = 242.09

^{1}H NMR (600 MHz)

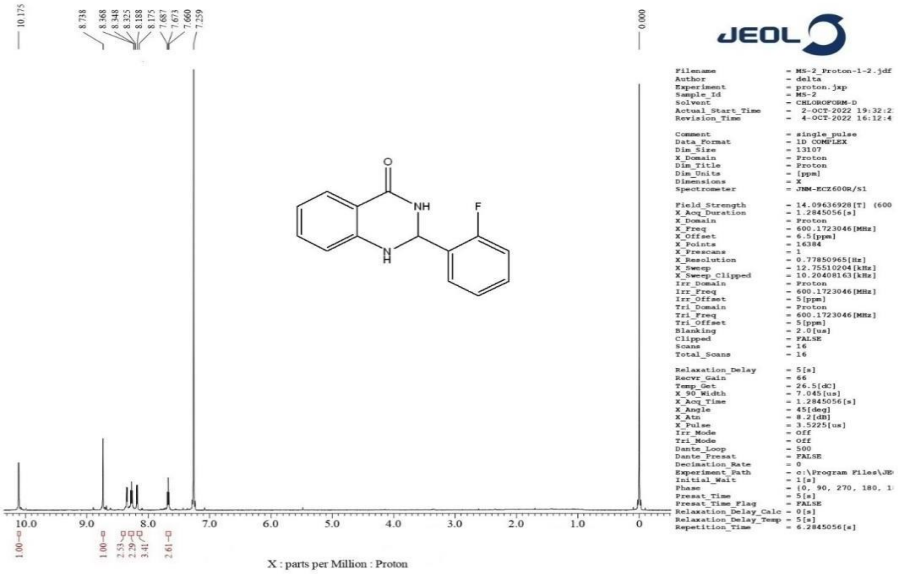


Fig. 3.2 PMR spectrum of 2-(2-flourophenyl)-2,3-dihydroquinazoline-4(1H)-one

- **Data No. Q3**

Molecular Formula = C14H10N3O3 Molecular Weight = 269.26

1H NMR (600 MHz)

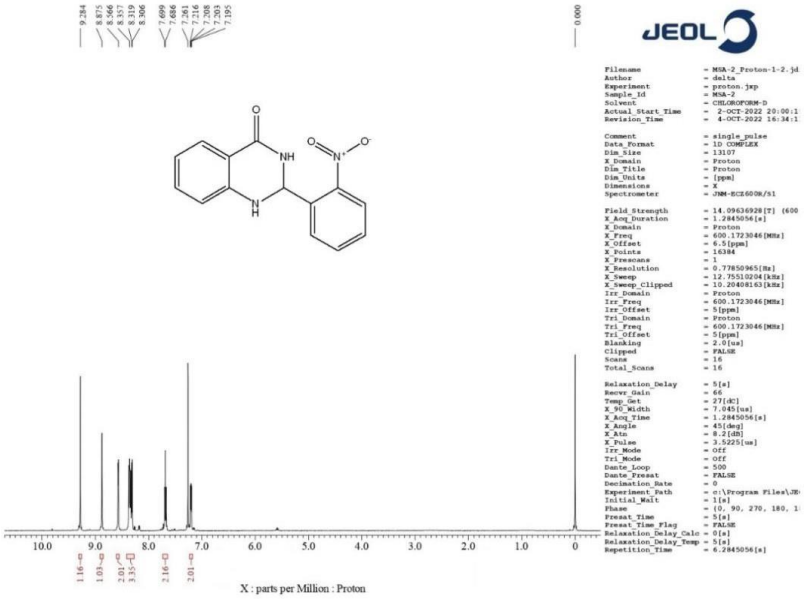


Fig. 3.3 PMR spectrum of 2-(2-nitrophenyl)-2,3-dihydroquinazoline-4(1H)-one

- **Data No. Q4**

Molecular Formula = C15H13N1O1 Molecular Weight = 238.04
1H NMR (600 MHz)

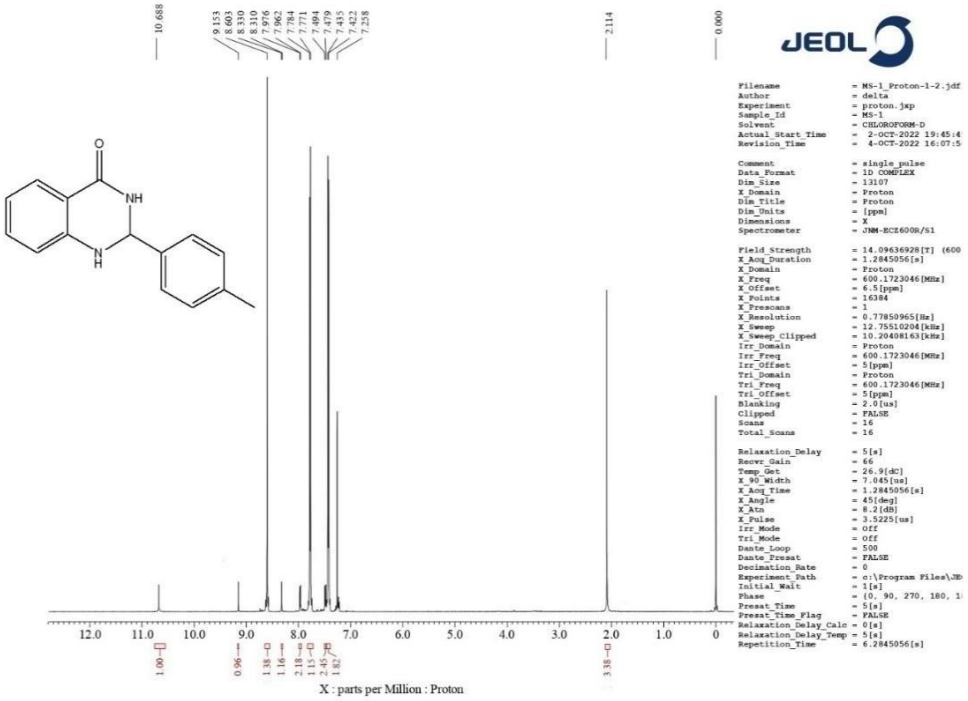


Fig. 3.4 PMR spectrum of 2-(p-tolyl)-dihydroquinazoline-4(1H)-one

- **Data No. Q5**

Molecular Formula = C14H10N2O1F1 Molecular Weight = 242.09
1H NMR (600 MHz)

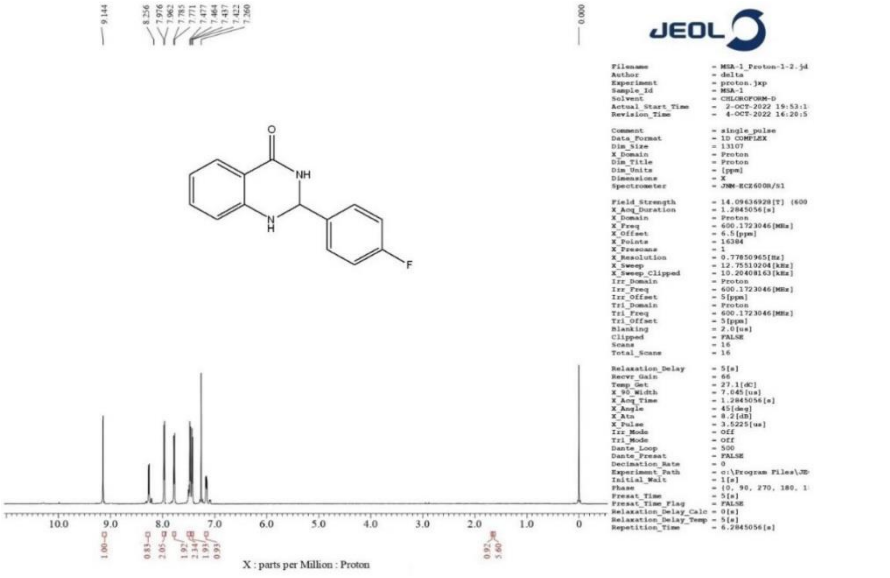


Fig. 3.5 PMR spectrum of 2-(4-fluorophenyl)-2,3-dihydro quinazoline-4(1H)-one

3.2 .Molecular docking and its result

After the synthesis and characterization of N-heterocyclic compounds such as quinazoline derivatives, compounds were investigated for molecular docking studies.**[22]** Due to its ability to reduce inflammation,

as shown by earlier studies. The protein known as AKR1C2 (aldo-keto reductase family 1 member C2) has been chosen because it has anti-inflammatory properties.[**23**] The protein structure was obtained as 4AJQ from the PDB data library.

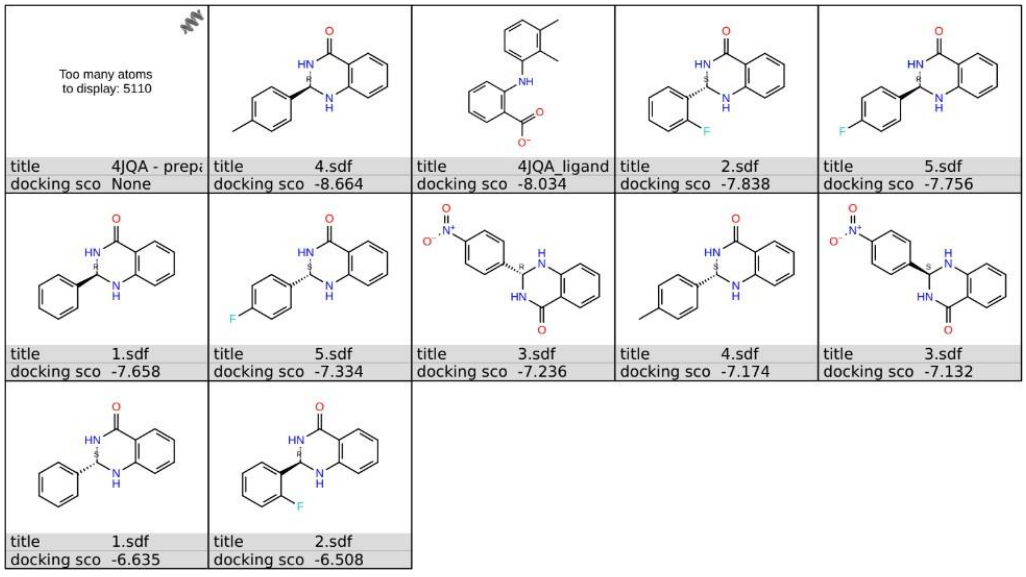
3.3. Scereninig for antiInflammation potential

As Quinazoline and its derivative based scaffolds possess anti-inflammation potential reflected in previous reports, We chose the AKR1C2 protein which is responsible for the anti-inflammatory activity, and investigated the anti-inflammatory activities of these molecules against 4JQA, which is responsible for the anti-inflammatory activity, because quinazoline and its derivative-based scaffolds possess anti-inflammatory potential, as shown in previous reports **[24].**

The protein structure was recived from the pdb data bank in the form of 4JQA, which was prepared by using the protein preparation wizard of Maestro software (Schrodinger). The synthesized compounds were drawn in the sdf format by using ChemDraw 16.0 and a database was prepared for the virtual screening. which was prepared by using the protein make Wizard of Maestro software (Schrodinger).**[25]** The synthesized compounds were drawn in the sdf format by using ChemDraw 16.0 and a database was prepared for the virtual screening. The ligand database was prepared with the help of LigPrep tool of Schrondinger under default settings. **[26,27]** Next, the receptor grid was generated in the maestro software by specifying the internal ligand (mefenamic acid) inside the active pocket of the protein. XP docking was performed for the synthesized ligand against 4AJQ protein within the active binding site AKR1C2 protein.

Docking results show the promising anti-inflammatory potential against the target protein in comparison of mefenamic acid. Compounds **Q4, Q2, and Q5** were found to be the most effective against 4AJQ protein among all . The docking scores for **Q4, Q2, and Q5** were found to **be -8.664, -7.838, and -7.756** respectively, while mefenamic acid has shown a docking score of **-8.034**. Different derivatives and their docking score – Table 2. Docking score of synthesized compounds

Docking Schore



Docking results show the anti-inflammatory potential targeted on 4JQA.

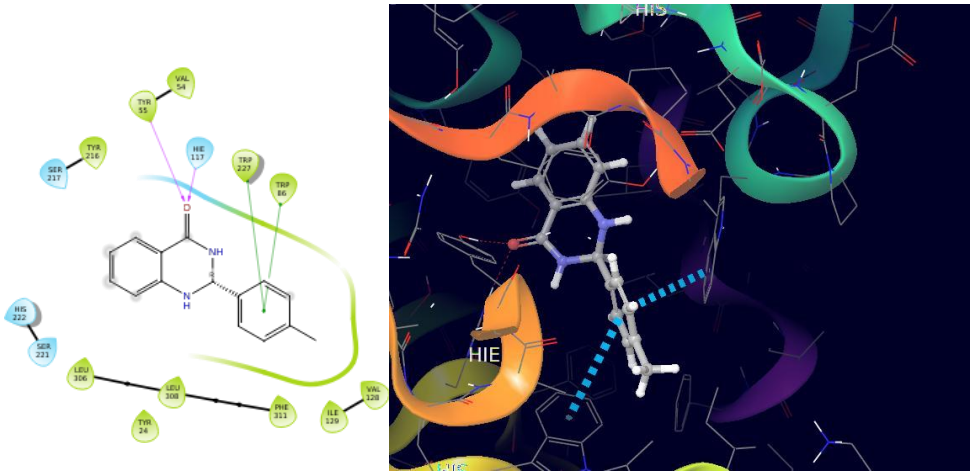


Fig.3.6 2D, 3D Interaction of the 2-(4-Methylphenyl)-2,3-dihydro quinazoline-4(1H)-one

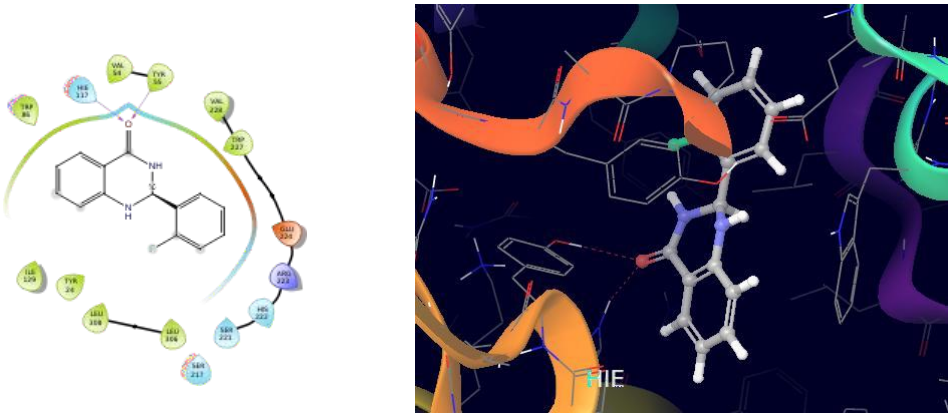


Fig.3.7 2D, 3D Interaction of the 2-(2-flurolphenyl)-2,3-dihydro quinazoline-4(1H)-one

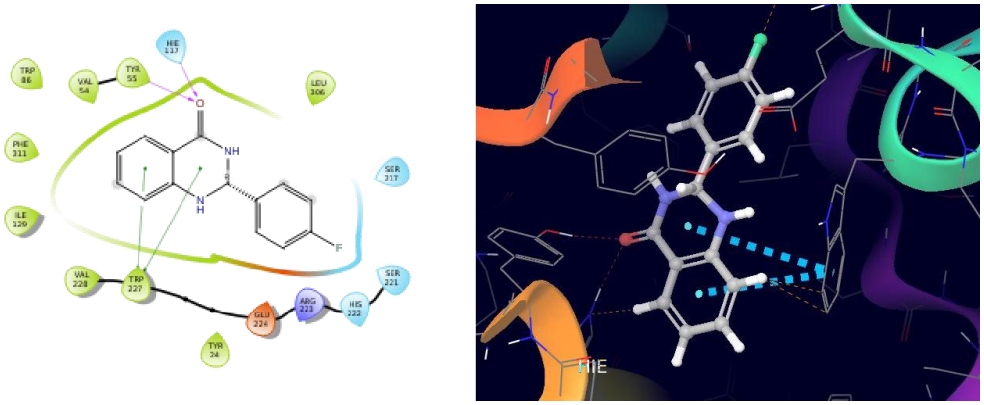


Fig.3.8 2D, 3D Interaction of the 2-(4-flurolphenyl)-2,3-dihydro quinazoline-4(1H)-one

The oxygen of quinazoline derivatives has shown two hydrogen-bonding interactions with the TYR55, HIE117, and additionally two π- π interaction with TRP227& TRP86 was also observed between of quinazoline. **Q4.** (**Fig. 3.6**). Similarly,two hydrogen-bonding interaction with the HIE227 and TYR55 residues are observed between the Oxygen. **Q2** (**Fig. 3.7**)**.** In case of **Q5** Similarly,two hydrogen-bonding interaction with the HIE227 and TYR55 and **Q5** with TRP227 residues of protein are respectectivily (**Fig. 3.8**).

Overall, docking analysis gave three promising molecules (**Q4, Q2, and Q5**), which have good binding potential with the 4AJQ protein. That is potent as an anti-inflammation oxidoreductase inhibitor of AKR1C2 complex with mefenamic acid. Further, these hits can be investigated for *in-vitro* and *in-vivo* activity to validate the computational results.

4. CONCLUSION

We have synthesized a library of quinazoline derivative derivatives. Initially. The study began with the preparation of various indoline derivatives by synthesized 2-(2-nitrophenyl)-2,3-dihydroquinazoline-4(1H)-one isolated product and further reaction to form the desired quinazoline derivatives. Characterization of the synthesized compounds was carried out using various spectroscopic techniques e.g.TLC, MS, NMR, etc. confirming the creation of the target quinazoline derivative structures.

The oxygen of quinazoline derivatives has shown two hydrogen-bonding interactions with the TYR55, HIE117, and additionally two π- π interaction with TRP227& TRP86 was also observed between of quinazoline. **Q4**. (Fig. 3.6). Similarly,two hydrogen-bonding interaction with the HIE227 and TYR55 residues are observed between the Oxygen. **Q2** (Fig. 3.7). In case of **Q5** Similarly,two hydrogen-bonding interaction with the HIE227 and TYR55 and **Q5** with TRP227 residues of protein are respectectivily (Fig. 3.8).

Overall, docking analysis gave three promising molecules **(Q4, Q2, and Q5**), which have good binding potential with the 4AJQ protein. That is potent as an anti-inflammation oxidoreductase inhibitor of AKR1C2 complex with mefenamic acid. Further, these hits can be investigated for in-vitro and in-vivo activity to validate the computational results. In conclusion, we have successfully synthesized a library of quinazoline substrates. Moreover, the synthesized compounds were also inspected for ant-inflammatory and anticancer potential via *in-silico* studies.

Overall, docking analysis gave three promising molecules (**Q4, Q2, and Q5**), which have good binding potential with the 4AJQ protein.In comparison to mefenamic acid and quinazoline substrates derivatives have good binding potential with the 4AJQ protein better than mefenamic acid.

5. FUTURE ASPECTS

It would be a great change towards allopathic medicines to counter and control the development. Moreover, the synthesized compounds were also inspected for ant-inflammatory via *in-silico* studies. Overall, docking analysis gave three promising molecules (**Q4, Q2, and** and **Q5**), which have good binding potential with the 4AJQ protein as compare mefenamic acid . It may also be refined that its production would be reasonable in terms of cost with relatively strong usefulness. It would be great deal for stability of formulation as it comes from a natural source. It suggests these hits can be investigated for *in-vitro* and *in-vivo* activity to validate the computational results

6. REFERENCE

1. Abbas ES, Awadallah MF, Ibrahim AN et al. New quinazolinone–pyrimidine hybrids:Synthesis, anti-infl ammatory, and ulcerogenicity studies . Eur J Med Chem 2012 ; 53 : 141 – 149.
2. Aly, a. A: synthesis of novel quinazoline derivatives as antimicrobial agents, department of chem-istry, faculty of science, ben ha university, be&, Egypt, chine5e journal of chemistry 2003, 21, 339-346.
3. Aziza MA (1997) Synthesis and anticonvulsant testing of some new 2-phenyl-6-iodo-3- substituted- 4-

(3H)-quinazolinone derivatives. Az J Pharm Sci 19:129–135.
4. Balbaa M, Abdel-Megeed M, Diab T et al. Inhibition of mammalian aspartate transcarbamylase by quinazolinone derivatives. J. Enzyme Inhib Med Chem 2008; 23: 483 – 492.
5. C. Sharma, P., Kaur, G., Pahwa, R., Sharma, A., & Rajak, H. (2011). Quinazolinone analogs as potential therapeutic agents. *Current medicinal chemistry*, *18*(31), 4786-4812.
6. Patinote, C., Cirnat, N., Bonnet, P. A., & Deleuze-Masquéfa, C. (2021). Fused Azolo-Quinoxalines: Candidates for Medicinal Chemistry. A Review of their Biological Applications. *Current Medicinal Chemistry*, *28*(4), 712-749.
7. Sharma, S., Sharma, K., Pathak, S., Kumar, M., & Sharma, P. K. (2020). Synthesis of medicinally important quinazolines and their derivatives: A review. The Open Medicinal Chemistry Journal, 14(1).
8. Gheidari, D., Mehrdad, M., & Maleki, S. (2022). Recent advances in synthesis of quinazoline-2, 4 (1H, 3H)-diones: Versatile building blocks in N-heterocyclic compounds. *Applied Organometallic Chemistry*, *36*(6), e6631.
9. K Subran, S., & Paira, P. (2017). Synthesis and pharmacological applications of certain quinoxaline analogues: A review. *Current Bioactive Compounds*, *13*(3), 186-212.
10. Faisal, M., & Saeed, A. (2021). Chemical insights into the synthetic chemistry of quinazolines: Recent advances. *Frontiers in chemistry*, *8*, 594717.
11. Rusu, A., Moga, I. M., Uncu, L., & Hancu, G. (2023). The role of five-membered heterocycles in the molecular structure of antibacterial drugs used in therapy. *Pharmaceutics*, *15*(11), 2554.
12. Safaei, M., & Shishehbore, M. R. (2021). A review on analytical methods with special reference to electroanalytical methods for the determination of some anticancer drugs in pharmaceutical and biological samples. *Talanta*, *229*, 122247.
13. Selvam, T. P., & Kumar, P. V. (2015). Quinazoline marketed drugs. *Research in Pharmacy*, *1*(1).
14. El-Sherief, H. A., Mahmoud, A. M., & Esmaiel, A. A. (1984). Quinazoline derivatives from 2-phenyl-4-quinazolinylhydrazine. *Bulletin of the Chemical Society of Japan*, *57*(4), 1138-1142.
15. Hunston, R. N., Parrick, J., & Shaw, C. J. G. (1964). Pyridazines, Cinnolines, Benzocinnolines and Phthalazines. In *Rodd's Chemistry of Carbon Compounds* (pp. 1-153). Elsevier.
16. Albini, A. (2019). *Heterocyclic N-oxides*. Routledge.
17. Bhanot, A. (2023). *Exploration of anti-malarial chemical space and bisquinolines and quinazoline hybrids as potential anti-tubercular and anti-malarial agents* (Doctoral dissertation, BITS Pilani, Pilani Campus).
18. Cernicchi, G., Felicetti, T., & Sabatini, S. (2021). Microbial efflux pump inhibitors: A journey around quinoline and indole derivatives. *Molecules*, *26*(22), 6996.
19. Shaik, T. B., Malik, M. S., Routhu, S. R., Seddigi, Z. S., Althagafi, I. I., & Kamal, A. (2020). Evaluation of anticancer and anti-mitotic properties of quinazoline and quinazolino-benzothiadiazine derivatives. *Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents)*, *20*(5), 599-611.
20. Tiwari, B. K. (2016). Studies on antiproliferative and antibacterial properties of some quinazoline- 4 (3H)-ones and their dimers.
21. Auti, P. S., George, G., & Paul, A. T. (2020). Recent advances in the pharmacological diversification of quinazoline/quinazolinone hybrids. *RSC advances*, *10*(68), 41353-41392.
22. Kong, X., Xing, E., Wu, S., Zhuang, T., Li, P. K., Li, C., & Cheng, X. (2022). Computational

modeling studies reveal the origin of the binding preference of 3-(3, 4-di hydroisoquinolin-2 (1H)-ylsulfonyl) benzoic acids for AKR1C3 over its isoforms. *Protein Science*, *31*(12), e4499.

23. Pippione, A. C., Carnovale, I. M., Bonanni, D., Sini, M., Goyal, P., Marini, E., ... & Lolli, M. L. (2018). Potent and selective aldo-keto reductase 1C3 (AKR1C3) inhibitors based on the benzoisoxazole moiety: application of a bioisosteric scaffold hopping approach to flufenamic acid. *European Journal of Medicinal Chemistry*, *150*, 930-945.
24. Gupta, S. S., Kumar, A., Shankar, R., & Sharma, U. (**2021**). *In silico* approach for identifying natural lead molecules against SARS-COV-2. *Journal of molecular graphics and modeling*, *106*, 107916
25. Shankar Mani, A Over View On Molecular Docking, American Journal Of Biological And Pharmaceutical Research, **2016**; 3(2):83-89
26. Kitchen D, De cornez H, Furr J, Bajorath J. (**2004**). Docking and scoring in virtual screening for drug discovery: methods and applications. International Journal of pharma and bioscience, 3(11), 95-97.
27. Torres, P. H., Sodero, A. C., Jofily, P., & Silva-Jr, F. P. (**2019**). Key topics in molecular docking for drug design. *International journal of molecular sciences*, *20*(18), 4574.