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Design, Synthesis, Molecular Docking Study of Novel Quinolines as Potential Anti malarial Drugs

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ABSTRACT: Quinoline moiety is the most important scaffold in the field of drug discovery and drug development with a wide range of pharmacological activities. In the present study we have designed and synthesized the molecules containing quinoline derivatives as antimalarial agents. 5 compounds were synthesized and characterized by IR, swiss ADME. The synthesized compounds were also docked on the binding site (PDB 3L4B, 2XOI, 2LNL, 5LWE, 7EOA). Most of the compounds showed good binding interaction with the active domino of the receptor. The highest docking score was -6.3kcal /mol then quinoline.

KEYWORDS: Quinoline, Antimalarial activity, Lipinski rule of five, Molecular docking.

I. INTRODUCTION QUINOLINE:

One of the most significant N-based heterocyclic aromatic chemicals is quinoline. Researchers have recently become interested in quinolines due to their vast range of functions and, of course, their wide uses. Friedlieb Ferdinand Runge first determined quinoline from coal tar in 1834. The main source of commercial quinoline is still coal tar. (1)

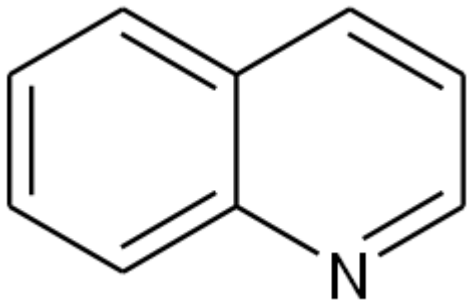

Fig.1 shows Quinoline structure

They possess pharmacological properties including anti-inflammatory, anti-tumour, anti-cancer, and anti-bacterial properties. Quinoline can be obtained from a variety of natural sources, including animals, flowers, and microorganisms (2). Its distinctive double-ring structure, with the chemical formula C9H7N, consists of a benzene ring joined to a pyridine moiety. Quinoline is a crucial component of both organic and inorganic molecules. Quinoline compounds have demonstrated remarkable outcomes through a variety of mechanisms of action, including growth inhibitors by cell cycle arrest, apoptosis, suppression of modulation, cell migration disruption,and angiogenesis. (3)

In general, it is acknowledged that quinoline derivatives have a variety of applications in industrial, medicinal, bioorganic, and synthetic organic chemistry. Their derivatives have been found to have a wide range of biological effects, including anti-malarial, anti-bacterial, anti-fungal, anti- asthmatic, anti-hypertensive, anti-inflammatory, and anti-platelet activity. They also have immune- suppressing and anti-tubercular effects. Some quinoline-ringed compounds, such as pamaquine, chloroquine, tafenoquine, bulaquine, quinine, and mefloquine, as well as amodiaquine, which has antimalarial and anti-inflammatory effects, are demonstrating potential as antimalarial drugs. An- aryl quinoline derivatives selectively bind to the estrogen receptor b (ER b), which is essential for the development, maintenance, and functionality of the mammalian reproductive system as well as in non-sexual tissues (4).A weak tertiary base is a quinoline. With acids, it can produce salt and exhibits reactions akin to those of pyridine and benzene. Both nucleophilic and electrophilic substitutionreactions are demonstrated. Intake of it is harmless for peopleboth inhalation and absorption. (10)

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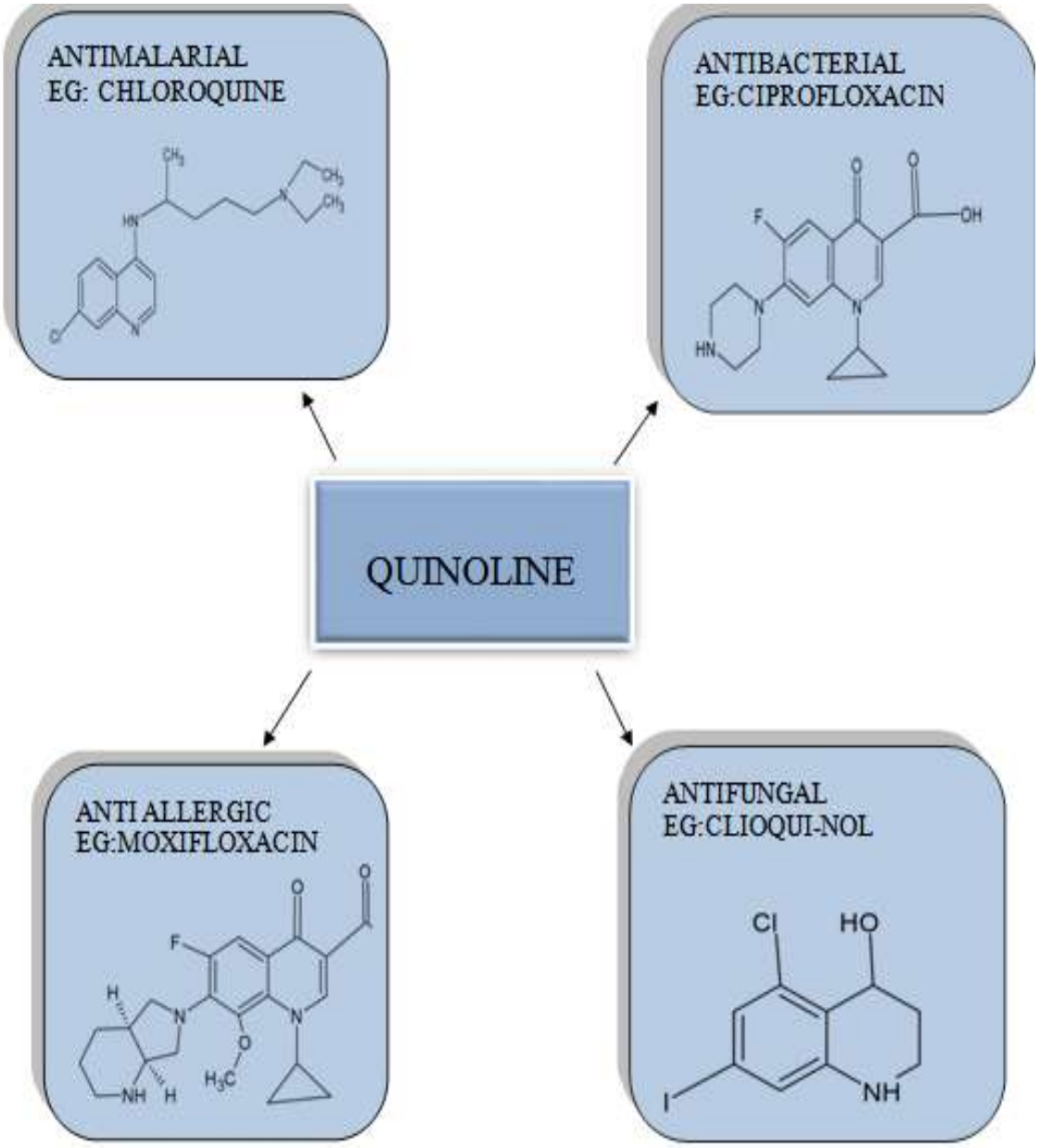

Fig 2 :Showing the different pharmacological actions along with their structures.

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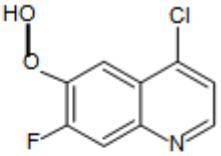
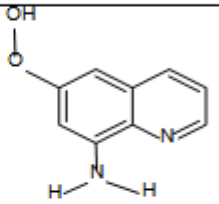
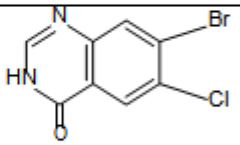
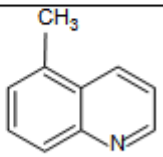
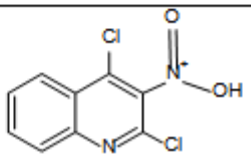
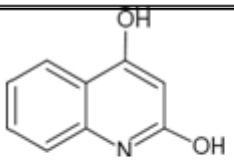
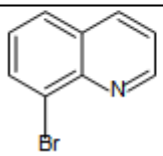
II. QUINOLINE DERIVATIVES

Table-1: Showing the quinoline derivatives

S.NO	DERIVATIVE	STRUCTURE
1	4-Chloro-7-fluoro-6-methoxy quinolone	
2	8-Amino-6-methoxy quinolone	
3	7-Bromo-6-chloroquinazolin-4(3H)-one	
4	5-Methylquinoline	
5	2,4-Dichloro-3-nitroquinoline	
6	2,4-Dihydroxyquinoline	
7	8-Bromoquinoline	

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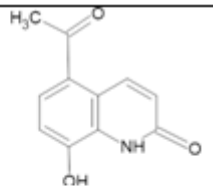
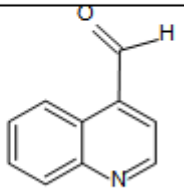
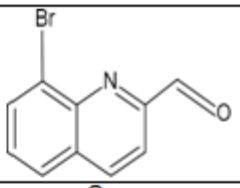
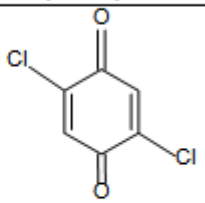
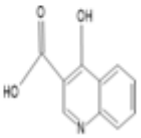
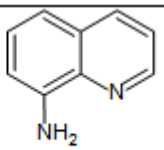
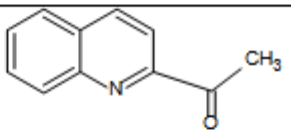
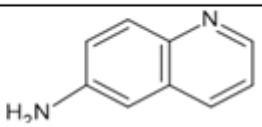
8	5-acetyl-8-hydroxy-1H-quinolin-2-one	
9	4-Quinolinecarboxaldehyde	
10	8 Bromoquinoline 2 formaldehyde	
11	2,5-Dichloro-p-benzoquinone	
12	3carboxy4 hydroxyquinoline	
13	8-Aminoquinoline	
14	2-Quinolinecarboxaldehyde	
15	6-Aminoquinoline	

SOME EXAMPLES AND THEIR USES OF QUINOLINE :

Numerous quinoline derivatives have been created and reported for use in a variety of applications. Quinoline derivatives are often employed in the synthesis of molecules having therapeutic properties as "parental" compounds particularly when it comes to anti-malarial and anti-microbial properties. The antibacterial, anticancer, antifungal, hypotensive, anti-HIV, analgesic, and anti-inflammatory properties of quinoline and its derivatives are well documented.

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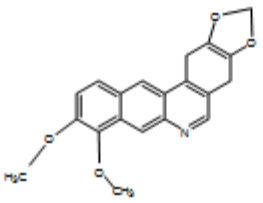
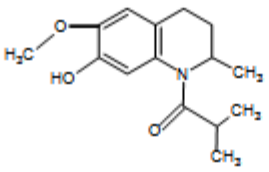
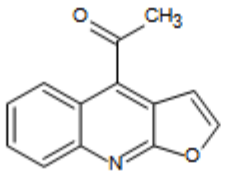
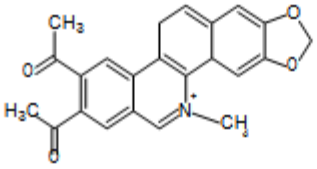
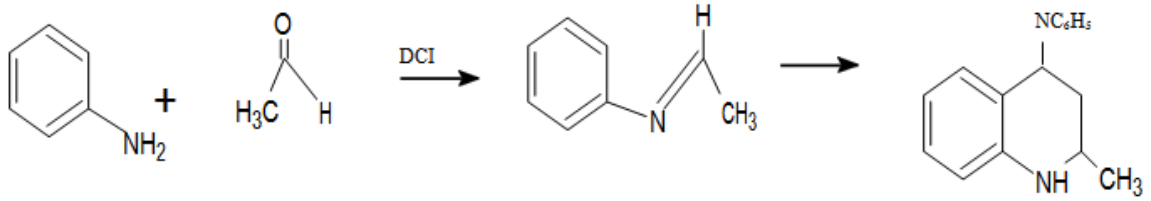
Table-2: Showing some examples of quinoline showing different pharmacological actions.

COMPOUNDS	STRUCTURE	USES
Berberine		Colon cancer
Lophocerine		Anti tumor antibiotic
Dictamine		Cytotoxicity to HepG2 cells
Nitidine		Topoisomerase inhibitor

III. EXPERIMENTATION METHODS:

Synthesis of quinolines:

1. Denmark etal , had done the experiment by treating aniline with acetaldehyde, Dauphinee and Forrest extracted imine, that the self-condensation process results in the synthesis of quinoline is followed by cyclization of a Schiff base.(9)



ANILINE ACETALDEHYDE QUINOLINE

Scheme 1

2. Prajapati et al,synthesized quinoline by reacting Amino acetophenone and phenylacetylene with Zn(OTf)2 acting as an efficient catalyst under microwave irradiation.(10)

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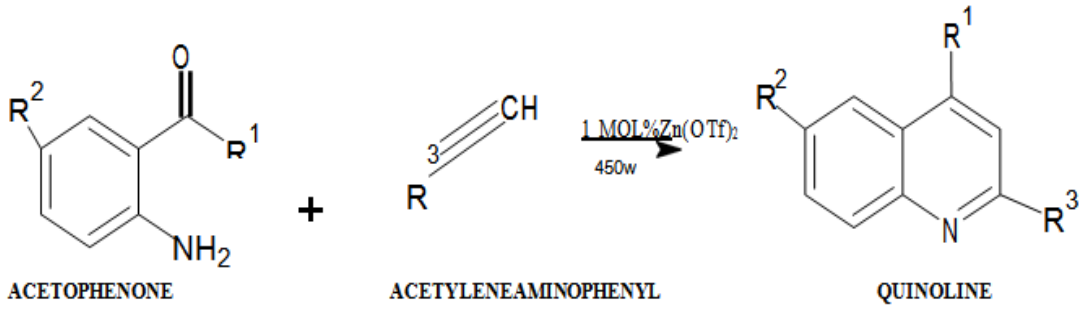

ACETOPHENONE ACETYLENEAMINOPHENYL QUINOLINE

Scheme 2

DERIVATIVES OF QUINOLINES :

A) 2,4 dihydroxy quinoline

Fig 3: showing the 2D & 3D of structure 2,4 dihydroxy quinoline.

The molinspiration image showing red colour indicates hydroxyl group and blue colour indicatesnitrogen group.

SYNTHESIS :

The most popular technique for making 2,4-dihydroxyquinoline involves treating N-acetylanthranilic acidic ester using sodium metal in toluene.Whenisatin and chloroacetyl chloride were combined, N- (chloroacetyl)-isatin was produced. This compound was then refluxed with aqueous potassium hydroxide and acidified with hydrochloric acid to precipitate 2,4-dihydroxyquinoline while simultaneously evaporating carbon dioxide (13).

Showing the physical properties of 2,4 dihydroxy quinoline

MOLECULAR FORMULA: C9H7NO2, MOLAR MASS: 161.16, DENSITY: 1.2480, WATER SOLUBILITY: INSOLUBLE IN WATER, APPERANCE: POWDER, COLOUR: VERY LIGHT BROWN

IRVALUES:1603.30(c=c),1530.43(c-N),1493.99(c=c),1080.08(c-OH)1055.33(c-o),904.90(c-o),

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B) 3 carboxy 4 hydroxyquinoline

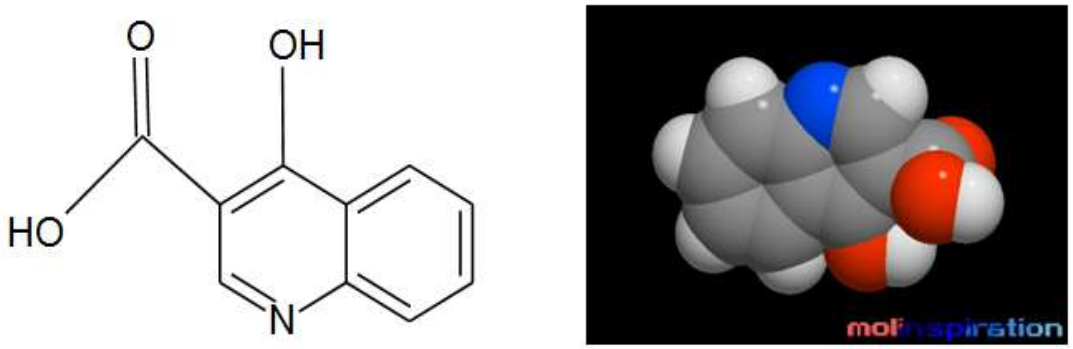

Fig 4:Showing the 2D & 3D structure of 3 carboxy 4 hydroxyquinoline

The molinspiration image showing red colour indicates hydroxyl group and blue colour indicatesnitrogen group

SYNTHESIS:

The combination of 56.5 g (0.2 mole) of the crude ester and 395 ml of 10% sodium hydroxide solution was refluxed. Petroleum ether was used to remove any remaining diphenyl ether once the solution hadcooled to room temperature (b. p. 85-110). With 10% hydrochloric acid, the aqueous solution was made somewhat acidic, and the precipitate was filtered out of the cooled solution. The acid was cleaned withwater and dried at 80 inches, weighing 48 grammes (95%).(14)

Showing the Physical properties of 3 carboxy 4 hydroxyquinoline

MOLECULAR FORMULA: C10H7NO3, MOLAR MASS: 189.17, DENSITY: 1.54, WATER SOLUBILITY:SOLUBLE DENSITY LE IN WATER,APPERANCE: SOLID, COLOUR: WHITE TO PALE BROWN.

IRVALUES:1658.48(c=O),1592.64(C=N),1578.79 (C=N),1477.55(C=C),1441.74(C=C),1395.36(NO2) ,1345.29 (NO2),1210.53(CO),1174.61(C-O),1127.89(C-F),1076.52(C-F),1057.83(C-O),1023.08(C-O),998.91(C-H),977.17(CH),929.63(C-H),875.37(CHH),800.01(C-CL),770.18(C-CL),760.07(C-CL),718.17(C-I),697.02(C-CI),681.63(C-CL),641.73(C-CCI).

C)6 aminoquinoline

Fig5: Showing the 2D &3D structure of 6 aminoquinoline.

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The molinspiration image showing blue colour indicates nitrogen group.

SYNTHESIS:

Upon carefully heating for 1 hour, the 6-nitroquinoline derivative (0.1 g) was added slowly while stirring to 1.0 g of stannous chloride in 5 mL of 6 mol/L hydrochloric acid. The precipitate was extractedwith CH2Cl2 (4–20 mL) after the reaction mixture had been neutralised with aqueous ammonia. With anhydrous MgSO4, the mixed CH2Cl2 layer was dried. Chromatographing and evaporating the extraction produced the desired pure 6-aminoquinoline.

Showing the physical properties of 6 aminoquinoline

MOLECULAR FORMULA: C9H8N2, MOLAR MASS: 144.17, DENSITY: 1.1148, WATER SOLUBILITY: INSOLUBLE IN WATER. SOLUBLE IN METHANOL, CHLOROFORM, ETHANOL AND BENZENE, APPERANCE: SOLID, COLOUR: PALE BROWN TO BROWN.

IRVALUES:1495.99(C=C),1441.41(C=C),1395.52(C-F),1346.41(C-F),1219.39(C-O), 1141.89(C-O),1075.43(C-O),1058.17(C-OH),1021.57(C-OH)977.65(C-H),928.28(C-H),817.09(C-H),801.37(C- H),762.60(C-CL), 730.11(C-CL),695.81(C-CL),620.55(C-CL).

D) 8 Bromoquinoline 2 formaldehyde

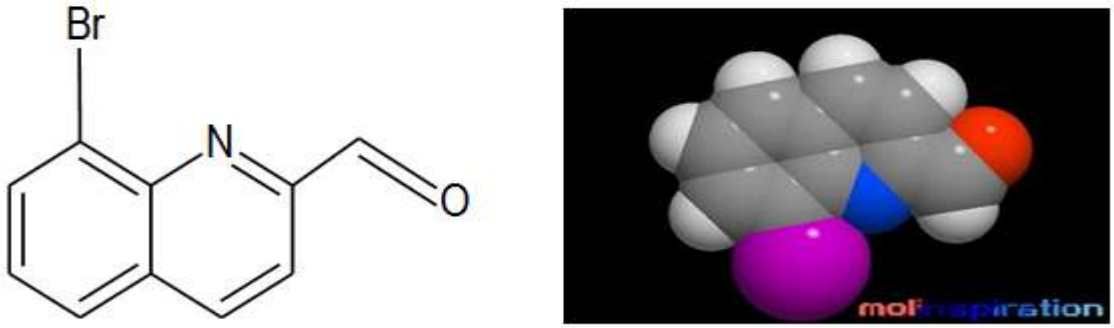

Fig6: Showing the 2D &3D structure of 8 Bromoquinoline 2 formaldehyde.

The molinspiration image showing red colour indicates oxygengroup , pink colour indicates bromine molecule and blue colour indicates nitrogen group.

SYNTHESIS :

Bromo-for 60g of 8-2-toluquinoline is added to 500ml of tetrahydrofuran (THF), along with 92g of tin anhydride. After 3 hours of reflux stirring, cooling, filtering, collecting filtrate, water, and extraction into an ethyl acetate separatory, the \ product 36g of 8-bromoquinoline-2-formaldehyde is obtained.

Showing the physical properties of 8 Bromoquinoline 2 formaldehyde:

MOLECULAR FORMULA: C10H8BrN, MOLAR MASS: 222.08, DENSITY: 1.488, WATER SOLUBILITY: SOLUBLE IN WATER, APPEARANCE: CRYSTALLINE POWDER, COLOUR: ORANGE

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E) 5-acetyl-8-hydroxy-1H-quinolin-2-one

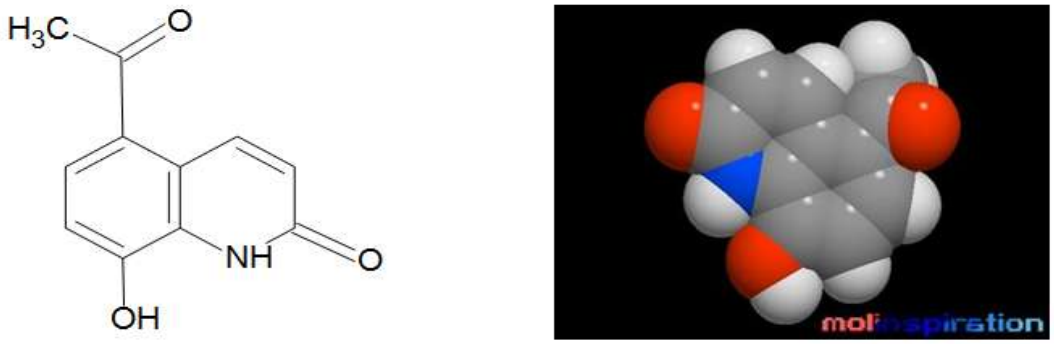

Fig 7: Showing the 2D &3D structure of 5-acetyl-8-hydroxy-1H-quinolin-2-one

The molinspiration image showing red colour indicates hydroxyl group and blue colour indicatesnitrogen group

SYNTHESIS :

Introduce 8-hydroxyquinoline (3 g, 20 mmol) to an acetyl chloride (1.62 g, 20 mmol) in nitrobenzene (3-5 mL) solution to get a yellow precipitant. With steady shaking, 5 g of aluminium chloride and titanium chloride were added to the reaction mixture mentioned above. The precipitate vanished, leaving behind a transparent semi-solid as a result. In a flask containing a calcium chloride tube, it wasmaintained at 70 oC for 12 hours. After cooling, the mixture was mixed with some crushed ice and 100 mL of 10% HCl, and the separated nitrobenzene was then blown out with steam. The 5-acetyl-8- hydroxyquinoline hydrochloride was filtered after standing overnight.When sodium acetate was added after it had been dissolved in water, the free base separated. After recrystallization, it was recrystallized from hotwater; (55% of the theoretical).

Showing the physical properties of 5-acetyl-8-hydroxy-1H-quinolin-2-one :

MOLECULAR FORMULA: C11H9O3, MOLAR MASS: 203.19, DENSITY: 1.336, WATER SOLUBILITY: INSOLUBLE IN WATER,SOLUBLE IN ETHANOL, APPERANCE: NEEDLE SHAPED CRYSTAL, COLOUR: PALE YELLOW.

DOCKING:

An increasingly crucial technique for drug development is molecular docking.There are more and morenew therapeutic targets available for drug discovery as a result of the completion of the human genome project. The development of nuclear magnetic resonance spectroscopy, crystallography, and high- throughput protein purification methods has also led to the understanding of several structural features of proteins and protein-ligand complexes. These developments enable computational methodologies, such virtual screening (VS) tools for hit detection and lead optimisation, to pervade many facets of drug discovery today. VS is a more straightforward and logical method to drug discovery than conventional experimental high-throughput screening (HTS), and it has the benefit of being both inexpensive and effective. The two types of VS are ligand-based and structure-based.

The use of ligand-based approaches, such as pharmacophore modelling and quantitative structure- activity relationship (QSAR) methodologies, is possible when a collection of active ligand molecules is known and little to no structural information about targets is available. The most popular approach for structure-based drug creation, molecular docking, has been in use since the early 1980s.

The molecular docking method may be used to simulate the atomic-level interaction between a tiny molecule and a protein, allowing us to characterise how small molecules behave at the binding site of target proteins and to better understand basic biological processes. Prediction of the ligand structure as well as its placement and orientation inside these sites (often referred to as pose) and evaluation of the binding affinity are the two fundamental processes in the docking process. These two actions have an impact on sample techniques and scoring systems, which will be

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covered in the theory section. The efficiency of docking procedures is greatly improved by knowing the location of the binding site prior to docking actions.

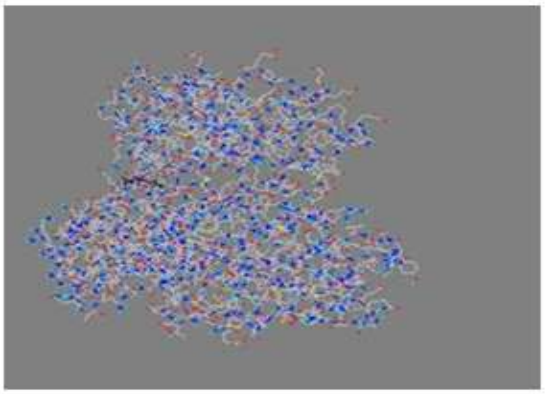
The lock-and-key idea, put out by Fischer, in which the ligand fits into the receptor like a lock and key, is an early explanation for the ligand-receptor binding mechanism. This notion served as the foundation for the earliest known docking techniques, which considered the ligand and receptor as rigid things. The "induced-fit" idea put out by Koshland then advances the "lock-and-key" theory by asserting that interactions with the ligands cause the protein's active site to be continuously altered. According to this hypothesis, while docking, the ligand and receptor should be viewed as flexible. As a result, it could better capture the binding events than the rigid treatment.(18)

IV. OBSERVATIONS AND RESULTS:

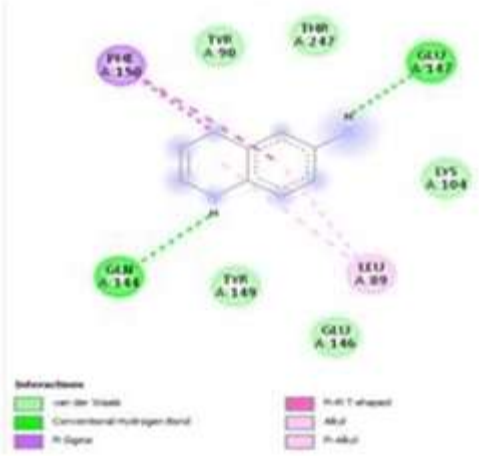
COMPOUND :1

Table 3: showing the binding affinities of Compound 1

DERIVATIVES	LIGAND	BINDING AFFINITIES
2,4 Dihydroxy quinolines	Tyrosine protein kinase SRC	-6.3kcal/mol



Docked (8a) Binded(8b)



Discovered(8c)

Fig :8a,8b,8c shows the docked, binded and discovered images repectively.

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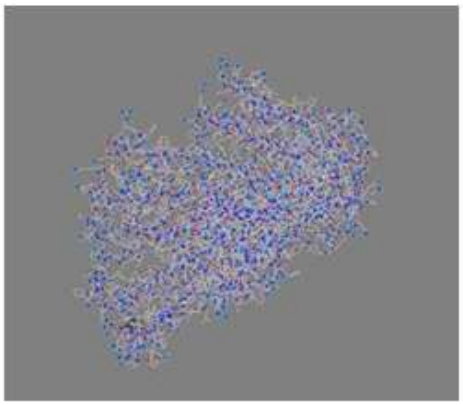
Amino acid interaction with the PHE:150,TYR A:90,THR A:247'GLUA:147,LYS A:104,LEU A:89,GLUA:146,TYR A:149,GLNA:144.

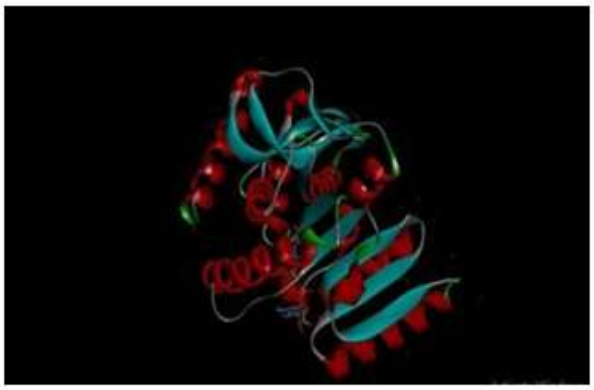
COMPOUND 2

Table 4: showing the binding affinities of Compound 2

DERIVATIVES	LIGAND	BINDING AFFINITIES
3 carboxy 4hydroxyquinoline	Malate dehydrogenase mitochondria	-7.0kcal/mol



Docked(9a)



Binded(9b)

Discovered(9c)

Fig :9(a),9(b),9(c) shows the docked, binded and discovered images repectively.

Amino acid interaction with VAL A:227,ALA A:98,ALA A:55,ASP A:53,LEU A:58,ALA A:29,HOH A:2038, THR A:97, HOH A:2036, ALA A:245, THR A:246, PRO A:250,SO A:42000, LEU A:167,GLY A:164, HIS A:195,MET A:142,MET A:163, HOH A:2027,VAL A:138,ASN A:140,THR A:139, LEU A:100, VAL A:32,ALA A:101, HOH A:2037, GLY A:28, GLY A:30, GLY A:33, GLY A:99,ILE A:119,ILE A:54, TYR A:85,ILE A:123,HOH A:2015.

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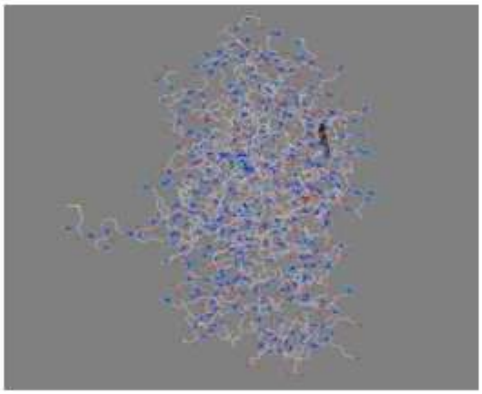
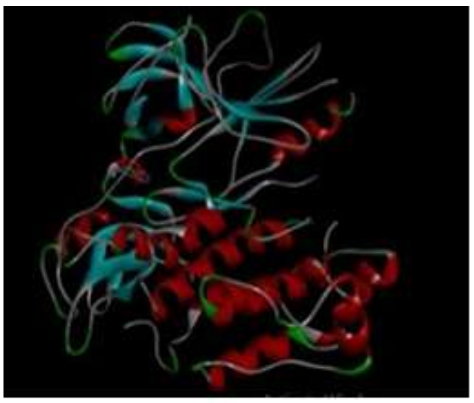
COMPOUND 3

Table 5: showing the binding affinities of Compound 3

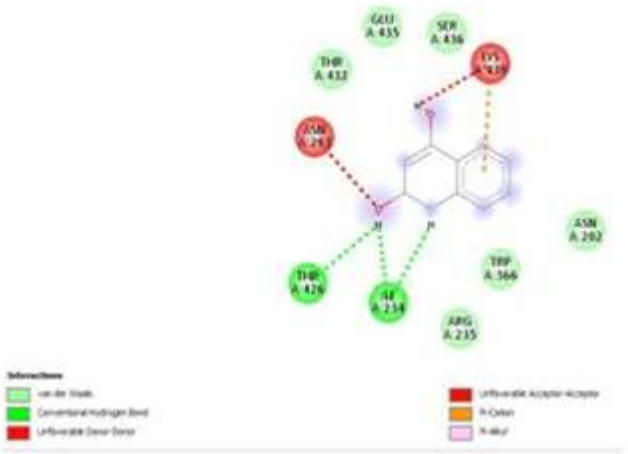
DERIVATIVES	LIGAND	BINDING AFFINITIES
6 aminoquinoline	Nitric oxide synthase inducable	-6.9kcal/mol



Docked (10a)



Binded(10b)



Discovered(10c)

Fig :10(a),10(b),10(c) shows the docked, binded and discovered images repectively.

Amino acid interaction with the GLU A:435,SER A:436,LYS A :439,ASN A:202,TRP A:366,ARG A:235,ILEA:234,TARA:426,ASN A:233,THR A :432.

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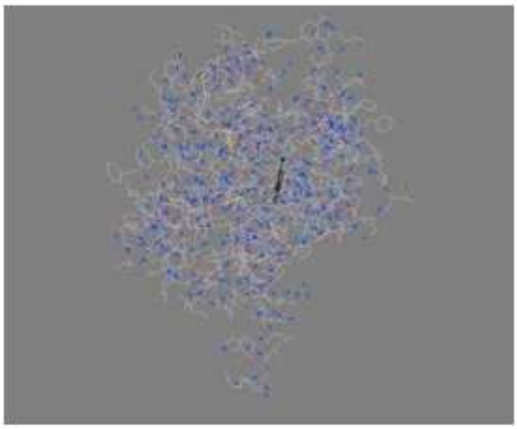
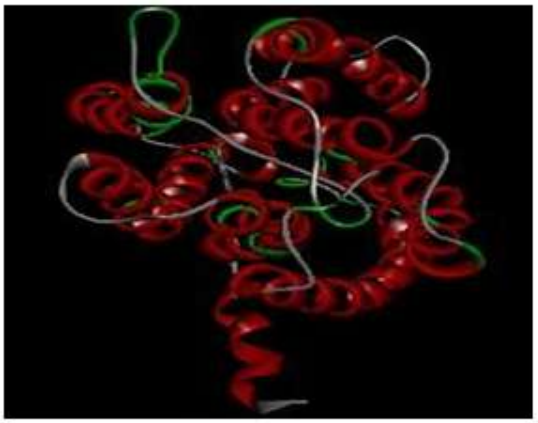
COMPOUND 4

Table 6: showing the binding affinities of Compound 4

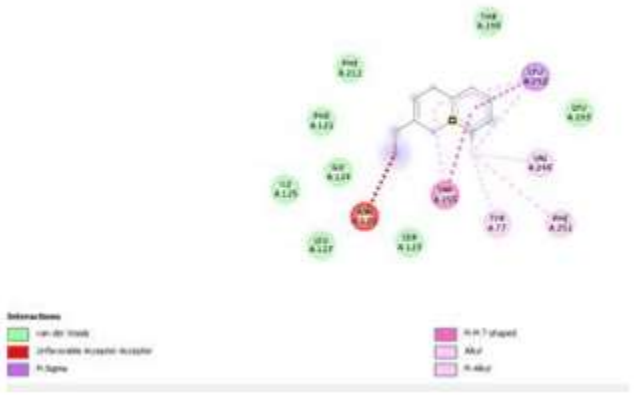
DERIVATIVES	LIGAND	BINDING AFFINITIES
8 Bromoquinoline2 formaldehyde	C-C Chemokine receptor type 1	-7.3kcal/mol



Docked 11(a)



Binded(11b)



Discovered(11c)

Fig :11(a),11(b),11(c) shows the docked, binded and discovered images repectively.

Amino acid interaction withTHRA:290,LEUA:252,LEUA:295,VLAA:245,PHE A :251,TYR A:22,THP A:255,PHA A:211,PHE A:122,GLU A:224, ASN A:120,SER A:123,ILE A:125,LFUA:227.

COMPOUND 5

Table 7: showing the binding affinities of Compound 5

DERIVATIVES	LIGAND	BINDING AFFINITIES

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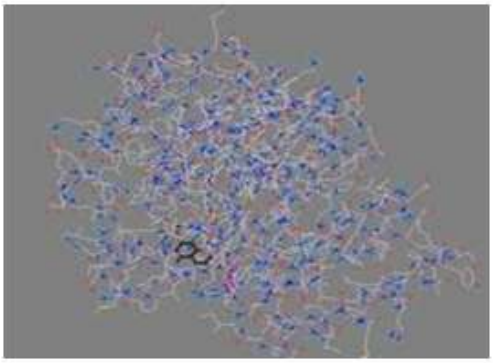
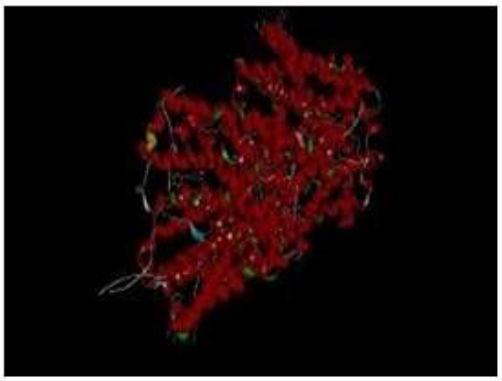
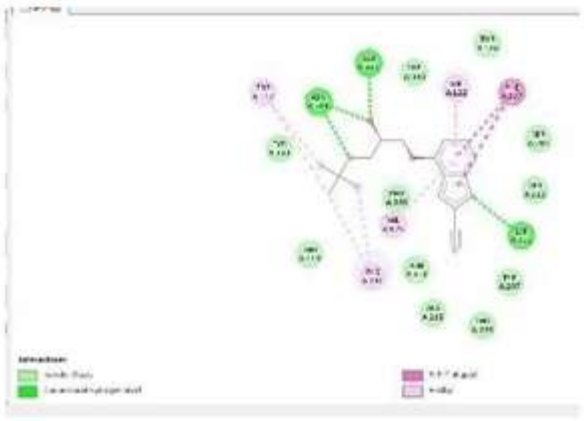
5-acetyl-8-hydroxy-1H-quinolin-2-one	Beta 1 andregenic receptor	-6.9 kcal /mol





Docked (12a) Binded 12(b)



Discovered 12(c)

Fig :12(a),12(b),12(c) shows the docked, binded and discovered images repectively.

Amino acid interaction with the TRP A:117,TYR A:333,THR A:118,PHEA:201,AS A:310,ALA A:208, VAL A:125,PHE A:306, ASN A:329,ASPA:121,TRP A:303, VLA A:122, THR A:126,PHE A:307, SER A:215,SERA:212,SER A:211,TYR A:207, THRA A:203.

Table 8: Showing the Physiochemical properties of 5 compounds :

DERIVATIVES	H-ACCEPTOR	H-DONOR	M.WT	MOLAR REFRACTIVITY	ROTATABLE BONDS
2,4 Dihydroxy quinolines	3	2	161.16g/mol	45.79	0

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3 carboxy4hydroxyquinoline	4	2	189.17g/mol	50.73	1
6 aminoquinoline	1	1	144.17g/mol	46.15	0
8 Bromoquinoline2 formaldehyde	2	0	236.6g/mol	54.83	1
5-acetyl-8-hydroxy-1H-quinolin-2-one	3	2	203.19g/mol	56.79	1

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