ISSN No:-2456-2165

Design, Synthesis and Characterization of Anti-Malarial Agent (ethyl 6-methoxy-4-(naphthalen-2-yloxy) quinoline-3-carboxylate)

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Abstract:- The malaria parasite is a Plasmodium protozoan species, which evolved with time differentiating into four distinct species: P. falciparum, P. vivex, P. malarae and P. ovale, well defined for people. A few other related animal categories including P. berghii and P. yeolii are intended for different gatherings of the mammalian class. The World Health Organization (WHO) revealed the event of 214 million cases overall in 2015, and the passing of 438,000 individuals, generally youngsters in the African area. Our work was Synthesis of molecules with minimum cost and high degree of efficacy. Synthesis of the drug molecules with having least side effects. The synthesized compound was characterized with different spectroscopic techniques i.e. ^{1}HNMR, ^{13}CNMR and HRMS.

Keywords:- *Treatment, ^{1}HNMR. ^{13}CNMR and HRMS.*

I. INTRODUCTION

➢ *Malaria*

Intestinal sickness is a mosquito-borne infection of people brought about by parasitic protozoans of the Plasmodium variety [1]. Plasmodium falciparum, P. vivax, P. ovale, and P. malariae are the critical types of the protozoal parasite causing human intestinal sickness. P. falciparum and P. vivax represent 95% or a greater amount of the malarial diseases overall [2]. Among the various species of *Plasmodium, P. falciparum* is the most lethal one causing the most virulent form of human jungle fever; bringing about 200-300 million contaminations and 1-3 million passings, every year [3]. Jungle fever is related with side effects like weakness, fever, migraines and heaving, and in serious cases it might cause yellow skin, seizures, extreme lethargies or even passing [4]. It has been accounted for to contaminate human populaces for north of 50,000 years [5]. The principal proof of Plasmodium was accounted for in a fossilized Culex mosquito in a piece of golden, very nearly 30 million years of age [6].

As of now, a few medications like chloroquine (CQ), amodiaquine, pyrimethamine, proguanil, mefloquine, atovaquone, primaquine, and so on. (Fig. 1) are accessible in market for the treatment of jungle fever. The fundamental objective of a large portion of the antimalarial drugs is the erythrocytic phase of malarial contamination. From the most recent twenty years, the obstruction of P. falciparum strains to CQ and the antifolate mix of sulfadoxine/pyrimethamine prompted artemisinin mix treatment (ACT), [7] which is presently an overall treatment of straightforward jungle fever[8].

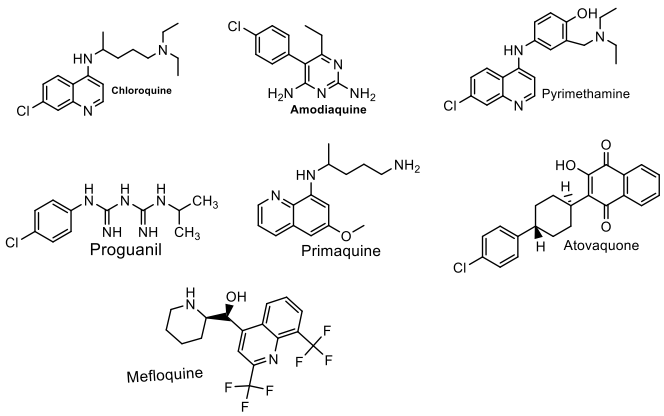

Fig 1:- Some of the market available antimalarial

Malaria has been described as a global epidemic disease that has been known in China, Mesopotamia and Egypt since 2700, 2000 and 1570 BCs, respectively [9]. Resent scenario witness's malaria as one of the main causes of human sufferings in terms of increasing morbidity and mortality, and arresting intellectual and economic growth [10]. Malaria stands as one of the most shattering diseases worldwide and affects about 225 million people annually with deaths of about 780,000.patients.[11].

The World Health Organization and the World Bank rank malaria as the largest single component of the disease burden in Africa, causing an annual loss of 35 million future life-years from disability and premature mortality. In Africa, malaria is responsible for about 20-30% of hospital admissions and about 30-50% of outpatient consultations. Malaria is also a major public health problem in parts of Asia, Latin America, the Middle East, Eastern Europe and the Pacific. In India, epidemics of malaria are frequently reported from areas that previously were not associated with malaria. In Bangladesh, the malaria situation has been steadily deteriorating since the late 1980s. The number of cases increased fivefold between 1988 and 1994. In Latin America, Brazil is worst affected with over 50% of all malaria cases in

ISSN No:-2456-2165

the Americas. Malaria is mostly a disease of hot climate.[4]. The existence cycle [12] of jungle fever parasite P. falciparum is perplexing that integrates different intra and extra cell conditions. It incorporates three sub-cycles, one happening in the vector called sporogonic cycle and two in the human host called exo-erythrocytic cycle and erythrocytic cycle. Human jungle fever is brought about by four unique types of Plasmodium falciparum, Plasmodium malariae, Plasmodium ovale and Plasmodium vivax[13]. Different side effects shown by patients impacted by jungle fever are Running nose, hack and different indications of respiratory disease, Diarrhea/looseness of the bowels, Burning micturition or potentially lower stomach pain, Skin rash/contaminations, Abscess, Painful expanding of joint, Ear discharge[14].

➢ *Treatment*

Intestinal sickness is treated with antimalarial meds; the ones utilized relies upon the kind and seriousness of the illness. While prescriptions against fever are ordinarily utilized, their consequences for results are not satisfactory [15].Uncomplicated intestinal sickness might be treated with oral drugs. The best treatment for P. falciparum contamination is the utilization of artemisinins in mix with different antimalarials (known as artemisinin-mix treatment, or ACT), which diminishes protection from any single medication part [12]. To treat jungle fever during pregnancy, the WHO suggests the utilization of quinine in addition to clindamycin right off the bat in the pregnancy (first trimester), and ACT in later stages (second and third trimesters) [7]. Contamination with P. vivax, P. ovale or P. malariae is typically treated without the requirement for hospitalization. Treatment of P. vivax requires both treatment of blood stages (with chloroquine or ACT) and freedom of liver structures with primaquine [13].Recommended treatment for extreme jungle fever is the intravenous utilization of antimalarial drugs. For serious jungle fever, artesunate is better than quinine in the two kids and grown-ups [11].

➢ *Medicines*

Drugs to treat jungle fever have been around for millennia. Maybe the most popular of the customary cures is quinine, which is gotten from the bark of the cinchona tree. Commodity of quinine to Europe, and later the United States, was a rewarding business until World War II slice off admittance to the world stockpile of cinchona bark. During the 1940s, a concentrated exploration program to find options in contrast to quinine led to the assembling of chloroquine and various other synthetic mixtures that turned into the trailblazers of current antimalarial drugs. Chloroquine was the third most generally involved drug on the planet until the mid-1990s. It is modest to make, simple to give, and doesn't create issues for a great many people. Sadly, chloroquine-safe intestinal sickness parasites have created and have spread to mostareas of the world. From the 1950s to the present, chloroquine opposition continuously spread to virtually all P. falciparum jungle fever endemic locales.

During the 1960s, many specialists treating individuals in Asia were utilizing one more new group of medications in light of the parent drug artemisinin, a concentrate of the Chinese natural cure qinghaosu.

Sadly, jungle fever parasites in numerous geographic areas have become impervious to elective medications, a significant number of which were found exclusively over the most recent 30 years. Indeed, even quinine, the extensive backbone of jungle fever treatment, is losing its adequacy in specific regions. To address the problem of drug-resistant malaria [14], researchers are leading examination on the hereditary systems that empower Plasmodium parasites to keep away from the harmful impacts of jungle fever drugs. Understanding how those systems work ought to empower researchers to foster new meds or change existing ones to make drug obstruction more troublesome.

Jungle fever parasites attack different tissues like skin, blood, liver, stomach, and salivary organs of human and mosquito has, which means the parasites must be able to attach to a diverse array of molecules or receptors on the outside of host cells. By deciding the three-layered designs of these receptors, researchers desire to decide precisely the way that the parasites target specific sorts of cells, which might uncover new focuses for antimalarial drugs. NIAID scientists are also working to understand how P. falciparum has adapted to survive and grow within RBCs. They may be able to configuration channel blockers that slow down the parasite's capacity to procure required supplements. These blockers might end up being novel and valuable medications for treating intestinal sickness.

II. DESIGN OF MOLECULES

➢ *What is PfPMT?*

- Plasmodium falciparum
- Phosphoethanolamine Methyltransferase (PfPMT) is S-adenosyl methamine (SAM) subordinate methyl transferase that catalyzes
- phosphoethanolamine (pEa) to phosphocoline.
- PfPMT is fundamental for the ordinary development and endurance of the Plasmodium which isn't found in people is a feasible objective.

➢ *PfPMT Inhibitors*

- The inhibitor or chemical inhibitor is a particle that ties to the dynamic site of a compound and diminishes its movement. Since impeding a chemical's action can kill a microorganism or right a metabolic lopsidedness. many medications are protein inhibitors.

➢ *Docking Protocol*

The docking and scoring of ligands with PfPMT. Proteins are achieved utilizing pardock module of sanjeevini drug plan suite which depends on physic-substance descriptors. We involved docking module for the planning of reference protein mind boggling as an info record. Docking of ligand particle at the dynamic site cavity of PfPMT was finished by utilizing all molecule energy based Monte Carlo calculation which limits and scores the docked complex. The molecule was designed and docked with freely accessible software called ParDOCK, available at IIT, Delhi. The crystal structure of protein is ***PfPMT*** which is docked with synthesized compound. The PDB ID of ***PfPMT*** is 3UJB.

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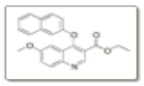
Name of compound	Synthesized Compound	Free energy value (kcal/mol)	logP
ethyl 6-methoxy-4-(naphthalen-2-yloxy)quinoline-3-carboxylate		-8.74	5.72

Table 1:- Binding free energy and logP value of the docked compound by Pardock

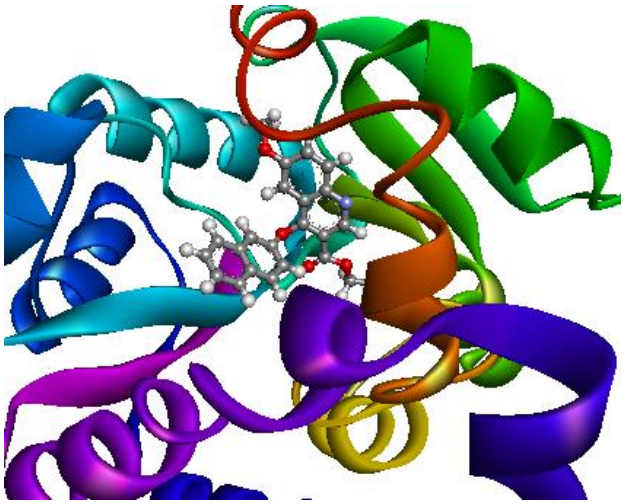


Fig 2:- Docked view of ethyl 6-methoxy-4-(naphthalen-2-yloxy)quinoline-3-carboxylate with *Pf*PMT.

The free energy value of 5 docked with *Pf*PMT is -8.74 kcal/mol.

➢ *Result and Discussion*

➢ *Chemistry*

The combination of target particle was accomplished by multistep responses which are illustrated in **Scheme1**. First of all, diethyl ethoxymethylenemalonate was treated with different aniline at ambient temperature in presence of benzene to obtain compound 3. Secondly,$POCl_3$ was added to the compound 3 and and refluxed for 18 h for the cyclization of the compound called, Vilsmeier-Haack reaction to get the compound 4. Finally compound 4 undergo nucleophilic aromatic substitution reaction with p-toludine and p-anisidine to give the desired final compound as 5. Finally, all the newly synthesized compound was verified by different spectroscopic methods I.e.^{1}H NMR, ^{13}C NMR and HRMS.

➢ *Objectives of Work*

- To design and synthesize drugs molecules with high potency than the previously reported ones.
- Synthesis of molecules with minimum cost and high degree of efficacy.
- Synthesis of the drug molecules with having least side effects.

➢ *Methodology*

- Synthesis of the designed compounds using organic protocol.
- Spectral techniques *viz.* ^{1}HNMR, ^{13}CNMR and HRMS has been used for the characterization of newly synthesized compound.

III. EXPERIMENTAL SECTION

➢ *Experimental Protocol*

➢ *Materials and methods*

Melting point of the synthesized compounds were determined in pyrex capillaries using a basic melting apparatus and were uncorrected. All required chemicals were purchased from Spectrochem and Sdfine chemicals Pvt. Ltd. India, and were used as received. Precoated aluminium sheet (silica gel 60 F254, Merck Germany) were used for thin layer chromatography (TLC) and spots were visualized under UV light. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker spectrospin DPX 400 MHz using DMSO and $CDCl_3$ as solvent and TMS as an internal standard.

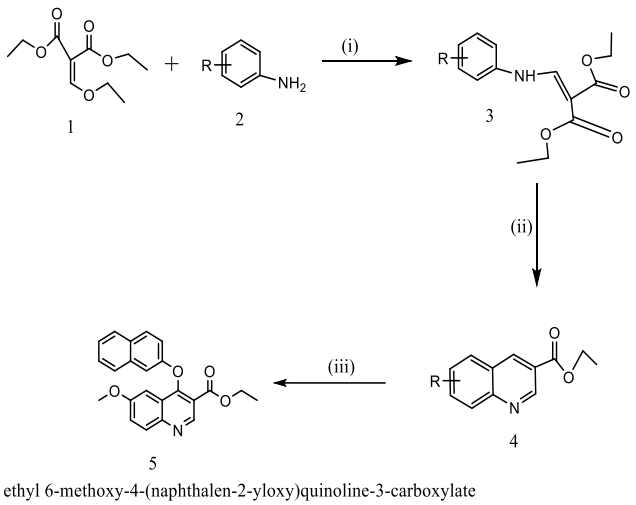


Fig 3:- Scheme for the synthesis of ethyl 6-methoxy-4-(naphthalen-2-yloxy)quinoline-3-carboxylate

Reagents and conditions: 1= Diethyl ethoxymethylenemalonate, R= p-anisidine, p-toluidine; (i) Benzene, 83 °C; (ii) $POCl_3$, 110 °C; (iii) β-Naphthol, DMF, t-BuO^-K^+, 120-130 °C.

➢ *Procedure:*

Methods for the preparation of compound 3 Diethyl (ethoxymethylene) malonate (25 mmol) and subbed aniline (25 mmol) were blended in identical extents at surrounding temperature, bringing about an exotherm of 18 ^{0}C. Benzene (6.5 ml) was added and the subsequent arrangement warmed under reflux (83 ^{0}C) for 1.5 h. The arrangement was amassed in vacuo to get an oil, which was solidified on standing. The unrefined item was slurried in hexane, separated off and air dried to give the compound 3 (m.p. 47-50 ^{0}C).

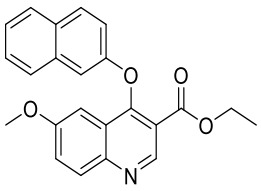
➢ *Methods of preparation of compound 4*

An answer of 3 (85 mmol) in POCl3 (1.34 mol) was warmed under reflux for 18 h. The cooled arrangement was amassed in vacuo and the subsequent earthy colored oil apportioned between dichloromethane (500 ml) and water (250 ml). Natural concentrates were dried over Na2SO4 and gathered in vacuo to give an earthy colored oil, which was refined by section chromatography eluted with 17% EtOAc/Hexane to get compound4.

- *Synthesis of ethyl 6-methoxy-4-(naphthalen-2-yloxy)quinoline-3-carboxylate.*

A combination of compound 4 (1.2 equiv.), β-naphthol (1.0 g) and t-BuO-K (1.2 equiv.) in anhydrous DMF was added to the room temperature and was reflux at 120-130 °C for 8-10 hrs. After the culmination of response observed by TLC, the response blend was cooled to room temperature. Water was added to the response blend and separated with ethyl acetic acid derivation (2×75). The joined natural layers were washed with saline solution, dried over Na2SO4, and vanished to yield the rough item, which was decontaminated by segment chromatography and eluted with EtOAc/hexane to give compound 5 as strong smooth white; yield: 73%; mp: 270-280 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.09 (1H), 8.11 (1H), 8.09 (1H), 7.98 (1H), 7.96 (1H), 7.90 (1H), 7.88 (3H), 7.71 (1H), 7.41 (1H), 4.0 (2H), 3.75 (3H, p-Anisidine), 0.92 (3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.66, 157.35, 156.32, 150.63, 149.84, 138.02, 134.63, 133.72, 130.06, 129.32, 129.19, 127.61, 126.96, 126.74, 124.62, 122.50, 121.44, 117.72, 115.87, 109.45, 61.11, 21.28, 13.56. HRMS (TOF) Calcd. for $C_{23}H_{19}NO_4Na$ $[M+Na]^+$, 396.1212; found, 396.1212.

IV. CHARACTERIZATION



ethyl 6-methoxy-4-(naphthalen-2-yloxy)quinoline-3-carboxylate

Fig 4:- Synthesized compound are characterized by ^{1}H NMR, ^{13}C NMR and HRMS Spectral studies

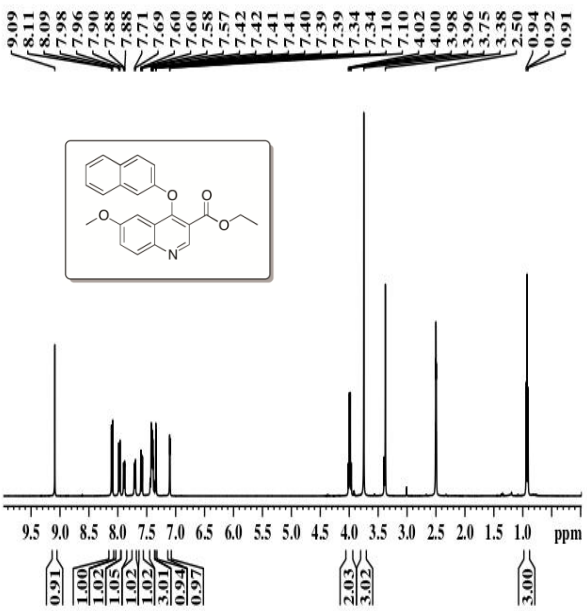


Fig 5:- ^{1}H NMR of ethyl 6-methoxy-4-(naphthalen-2-yloxy)quinoline-3-carboxylate.

Off white solid; yield: 73%; mp: 270-280 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.09 (1H), 8.11 (1H), 8.09 (1H), 7.98 (1H), 7.96 (1H), 7.90 (1H), 7.88 (3H), 7.71 (1H), 7.41 (1H), 4.0 (2H), 3.75 (3H, p-Anisidine), 0.92 (3H, CH_3).

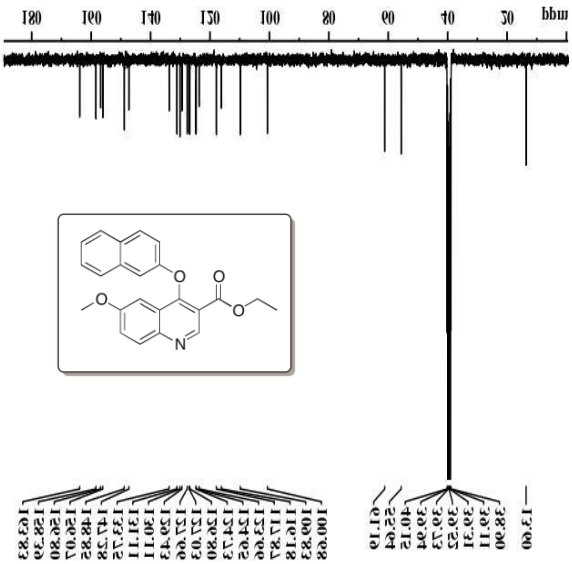


Fig 6:- ^{13}C NMR of ethyl 6-methoxy-4-(naphthalen-2-yloxy)quinoline-3-carboxylate.

^{13}C NMR (100 MHz, DMSO-d_6) δ 163.66, 157.35, 156.32, 150.63, 149.84, 138.02, 134.63, 133.72, 130.06, 129.32, 129.19, 127.61, 126.96, 126.74, 124.62, 122.50, 121.44, 117.72, 115.87, 109.45, 61.11, 21.28, 13.56.

ISSN No:-2456-2165

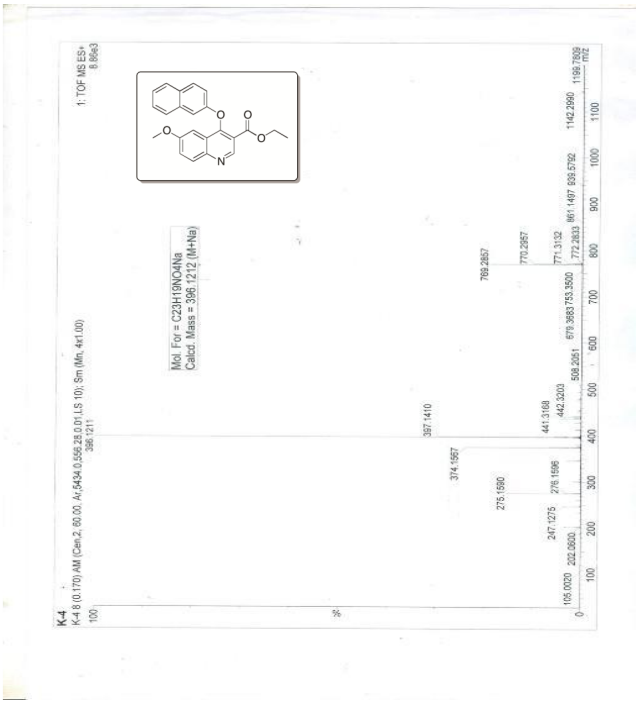


Fig 7:- HRMS of ethyl 6-methoxy-4-(naphthalen-2-yloxy)quinoline-3-carboxylate

HRMS (TOF) Calcd. for $C_{23}H_{19}NO_4Na$ $[M+Na]^+$, 396.1212; found, 396.1212.

V. CONCLUSION

- Quinoline based compounds were designed and synthesized via feasible synthetic route.
- Compounds were designed and docked with ParDOCK, IIT Delhi.
- The binding free energy value of the synthesized compound i.e. A docked with *Pf*PMT is -8.74kcal/mol.
- The synthesized compounds were characterized with different spectroscopic techniques i.e. ^{1}HNMR, ^{13}CNMR and HRMS.

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