ijlpr 2022; doi 10.22376/ijlpr.2023.13.1.SP1.L1-15

International Journal of Life science and Pharma Research

ISSN 2250-0480

Research Article

Antimalarials: A Patents Landscape Study (2015-Present)

Narender Yadav[1&*], Mukesh Kumar Kumawat[1&*], Gufran Ajmal[1], and Manoj Kumar Sharma[1]

[1]School of Pharmaceutical Sciences, Apeejay Stya University, Sohna-Palwal Road, Sohna, Gurugram, Haryana-122001.

Abstract: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and *P. knowlesi* are five Plasmodium species that cause malaria, a life-threatening parasitic disease. In the developing world, the rapid development of *Plasmodium falciparum* resistance to currently available treatments has become a serious health concern. This work reports a patent landscape analysis of patent documents related to antimalarial. The patent search was conducted using the commercially available CAS SciFinder database and the open-source patent database, The Lens. Seven hundred ninety-seven patents from The Lens and 1172 patent Sci-finder were exported using the antimalarial drug as a keyword. After the initial screening, 58 patent documents were shortlisted for in-depth analysis. After analysis, it was found that most of the top applicants come from the United States and Switzerland, which shows that market protection is more important in these two countries. The top applicants come from private companies, universities, and public-private partnerships. The United States, Europe, China, Canada, and the Republic of Korea lead the patent race in this area. The most-recorded IPC code is A61P33/06, related to the chemical substances or pharmaceutical formulations showing antimalarials activity. Most of the time, antimalarial drugs were made from quinine, artemisinin, trioxolane, naphthoquinones, and isoquinoline derivatives. Quinine and artemisinin are well-established classes of antimalarials with the maximum number of antimalarial drugs in the market. The research and innovations disclosed in most patents were focused on exploring or evaluating the new scaffolds and their mechanism of action against the normal and resistant malarial parasite. In conclusion, it has been found that various scaffolds are needed to be explored further in search of new antimalarial compounds.

Keywords: *Plasmodium*, Antimalarial Agents, Trioxolanes, Quinolines, Artemisinin, Triazine, Naphthylisoquinolone,

***Corresponding Author**

Narender Yadav , School of Pharmaceutical Sciences, Apeejay Stya University, Sohna-Palwal Road, Sohna, Gurugram, Haryana-122001.

Received On 18 October 2022

Revised On 06 December 2022

Accepted On 13 December 2022

Published On 01 January 2023

This research did not receive any specific grant from any funding agencies in the public, commercial or not for profit sectors.

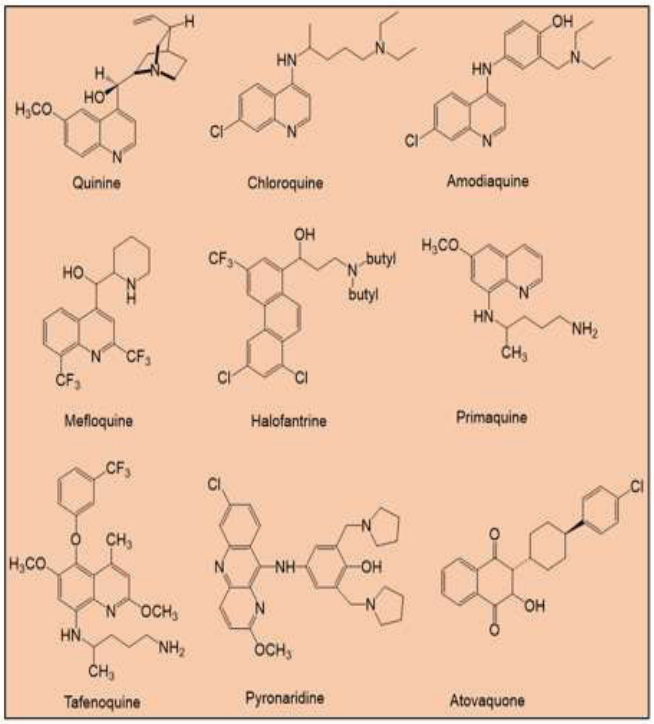
Citation Narender Yadav, Mukesh Kumar Kumawat, Gufran Ajmal, and Manoj Kumar Sharma , Antimalarials: A Patents Landscape Study (2015-Present).(2023).Int. J. Life Sci. Pharma Res.13(1), L1-15 http://dx.doi.org/10.22376/ijlpr.2023.13.1.SP1.L1-15

1. INTRODUCTION

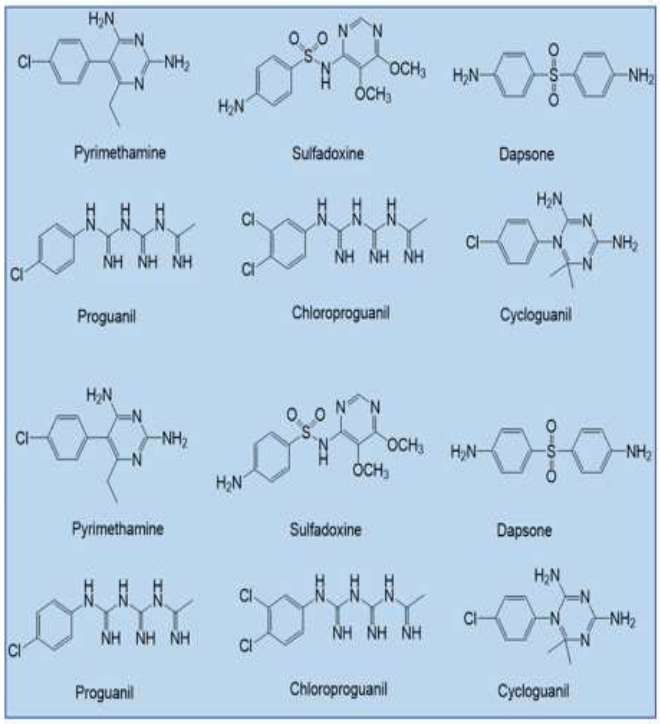
Malaria is a life-threatening parasitic disease transmitted by Anopheles mosquitoes. Plasmodium, a parasitic worm genus, causes human malaria. Plasmodium is divided into five species. The most common causes of death are *P. falciparum* and *P. vivax*, while *P. ovale* and *P. malariae* induce a milder form of malaria that is seldom fatal. *P. knowlesi*, a Southeast Asian zoonotic species that causes malaria in macaques but can also infect humans[1, 2]. 1.7 billion Malaria infections and 10.6 million malaria deaths were averted globally between 2000 and 2020, according to the WHO report 2021. Most of the cases (82%) and fatalities (95%) were prevented in the WHO African region, with the WHO South-East Asia region second (cases 10% and deaths 2%)[3]. In addition to malaria interventions, other factors that affect malaria transmission or illness, such as socioeconomic status, malnutrition, infrastructure, housing, and urbanization, could have helped to prevent cases and fatalities. In addition to malaria interventions, other factors that affect malaria transmission or illness, such as socioeconomic status, malnutrition, infrastructure, housing, and urbanization, could have prevented cases and fatalities. Artemisinin-based combination therapy (ACTs) is indicated in all locations where falciparum malaria is endemic. Antimalarial drugs (ACTs) have played a critical role in malaria management during the last 20 years, with artemether-lumefantrine being the most widely used ACT in Africa. However, artemisinin-resistant *Plasmodium falciparum* parasites have expanded throughout Southeast Asia, limiting the efficacy of several ACTs. Worse, artemisinin-resistant parasites are growing in Africa, according to recent research from Rwanda and northern Uganda. If artemisinin activity is reduced, the action of partner drugs such as lumefantrine is hampered; the loss of both components of ACTs might have severe consequences across the continent. It's become critical to create new therapeutic strategies to combat the spread of artemisinin-resistant parasites[4]. Despite major delays in malaria services during the COVID-19 pandemic, it is expected that by 2020, 170 million cases and 938000 deaths will have been prevented, compared to the estimated burden if case incidence and fatality rates remained unchanged from 2000. WHO has authorized the RTS, S malaria vaccine to prevent *P. falciparum* malaria in children living in moderate to high transmission areas. This is the first human parasite vaccination to receive a WHO recommendation and the WHO advises governments to consider it when choosing the optimum subnational mix of interventions for maximum impact[3]. The following are the most often used antimalarial drugs for treatment and prophylaxis

1.1 Quinoline-based antimalarials

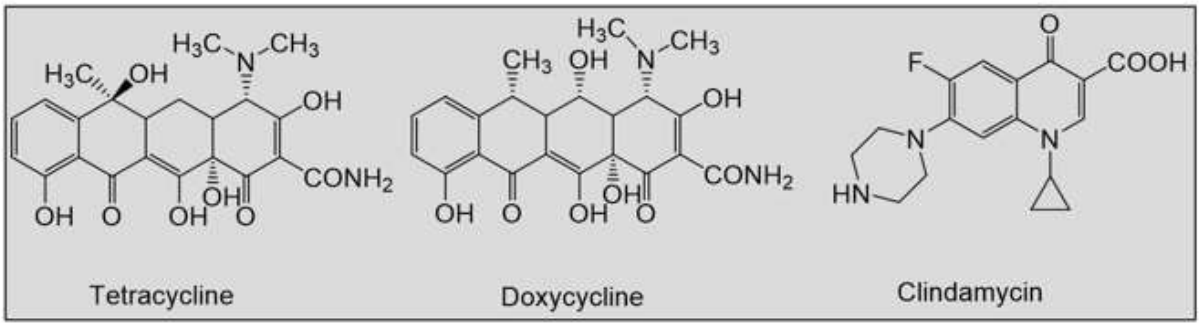
Antimalarials based on quinine (Figure 1A) are structural derivatives of quinine used in the treatment and chemoprophylaxis of simple or acute *falciparum* and *vivax* malaria. They have been proven to be successful in the treatment of acute and severe instances of chloroquine or multidrug-resistant *P. falciparum* infection when used in conjunction with other drugs of the same category or with other treatments[5, 6].



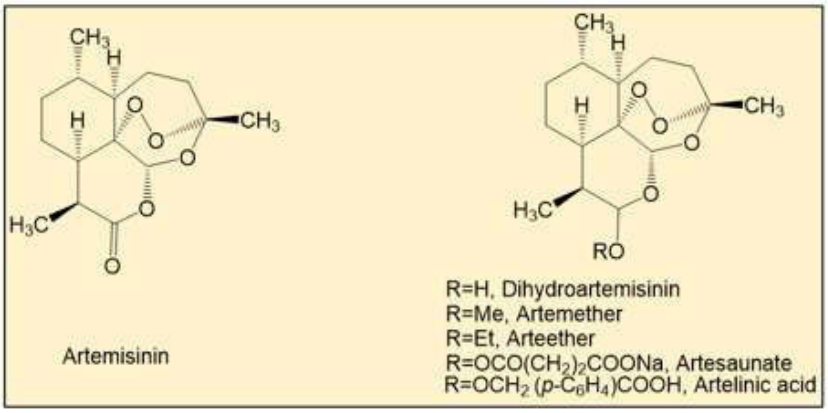
A. Quinoline-based Antimalarial Drugs



B. Folate Antagonists



C. Antibiotics as an Antimalarial



D. Artemisinin and Its Derivatives

Fig 1: Structure of antimalarial drugs A. Quinoline-based antimalarial drugs, B. Folate Antagonists, C. Antibiotics as an Antimalarial, D. Artemisinin and its Derivatives

1.2 Folate antagonists

These compounds prevent the synthesis of parasitic pyrimidines and thus the production of parasitic DNA. There are two types of antifolates ((Figure 1B)): (i) inhibitors of dihydrofolate reductase (DHFR), which include diaminopyrimidines and biguanides such as pyrimethamine, trimethoprim, proguanil and chlorproguanil, and (ii) inhibitors of dihydropteroate synthase (DHPS), which include sulphonamides and sulfones such as sulfadoxine, sulfalene, and dapsone[7].

1.3 Antibiotics

Antibiotics are also crucial in the treatment and prevention of malaria. Antimalarial drugs like tetracycline and chloramphenicol are well-tolerated and effective. Prophylactic drugs against *P. falciparum* include tetracycline and its equivalents, such as doxycycline, azithromycin, and clindamycin (Figure 1C). They obstruct translation by reversibly binding to the 30S subunit and distorting it so that the charged tRNA anticodons do not align properly with the tRNA codons[5, 7, 8]. Artemisinin and its derivatives: Artemisinin, a fast-acting medication against multidrug-resistant *P. falciparum* strains, is the active ingredient in *Artemisia annua* (sweet wormwood). Artemisinin-based drugs (and their variants) are now widely recognized as the most important new antimalarials (Figure 1D) and are used to treat severe malaria. Artemisinin derivatives include dihydroartemisinin (DHA), artemether, arteether (oil-soluble ethers), artesunate (water-soluble hemisuccinate), and artelinic acid. All of these substances are sesquiterpene lactones or cyclic endoperoxides[8]. The aim of the study is present patent landscape analysis to identify novel scaffolds and new antimalarial agents with promising activities against resistant malaria. This study, in the form of a patent landscape, illustrates state-of-the-art by describing antimalarial compounds patented between 2015 and 2021. The study's objective is to present a detailed qualitative and quantitative analysis of retrieved patent documents. For quantitative analysis, detailed charts based on year-wise publication, patent technical characteristics using IPC classifications, inventors, applicants, geographical and jurisdictions are presented with valuable technical insights. In addition, screening of extracted patent documents is done to find relevant patents. A qualitative analysis was done for relevant granted patents and patent applications demonstrating antimalarial discovery's invention and advancement. It helps in finding the most promising scaffold for the antimalarial drug candidate.

2. MATERIALS AND METHODS

2.1 *Resources and Research Methods*

The patent search was conducted using two databases. One is CAS SciFinder, which is commercially available. The second is The Lens, an open-source patent database[9]. Patent documents were searched in title, abstract, and claims using various keywords related to antimalarials. Seven hundred ninety-seven patents (The Lens) and 1172 (Sci-finder) were retrieved for search keywords containing antimalarial. The search results were then narrowed to patent publications published between January 1, 2015, and December 31, 2021.

2.2 Analysis of the Patentability of Antimalarial Agents

Seven hundred ninety-seven patent documents (396 Simple INPADOC Family) were identified due to the search. This typically included patent applications and granted patents. Regarding antimalarial drugs, the retrieved patent documents

include 568 patent applications and 229 granted patents. Following this, a review of the current state-of-the-art will be presented, beginning with an overview of novel antimalarial agents that have been patented. Next, a comprehensive patentability study will be presented, emphasizing the types of scaffolds and mechanisms of action of disclosed antimalarial agents. Additionally, detailed charts based on publication year, patent classifications, inventors, applicants, and jurisdictions are also presented with clear insight.

3. RESULTS AND DISCUSSION

3.1 Application, Publication, Granted Patents Year-Based Trend Analysis

The year a patent application was first published and made available to the general public is referred to as the "publication year"[10]. Between 2015 and 2021, we found 795 patent documents related to antimalarial agents. There were 568 patent applications and 227 granted patents found in the results. The highest number of patent applications (124) was recorded in the year 2021, followed by 2015 (93), 2019 (90) and 2020 (72). In 2016, the highest number of awarded patents (472) was reported (Figure 2).

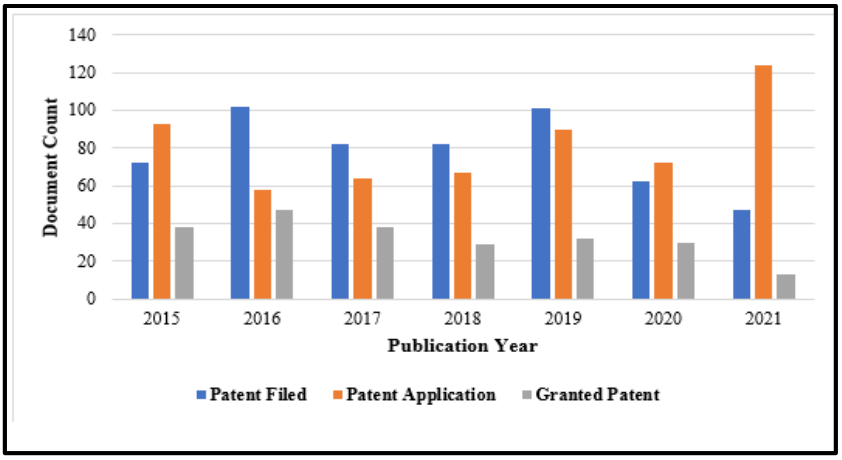


Fig 2: Application, Publication, Granted Patents Year Based Trend Analysis between 2015 and 2021.

3.2 International Patent Classification-Based Trend Analysis to Highlight the Technological Characteristics

The International Patent Classification (IPC) is a global hierarchical system based on codes that provide standard data for classifying inventions and evaluating their technological variations. The IPC classification is accepted worldwide[11-13]. Figure 3 shows the top 20 IPC codes for antimalarial agents between 2015 and 2021. The most-recorded IPC code corresponds to A61P33/06, which includes chemical substances or pharmaceutical formulations that display antimalarial activity. This subgroup alone recorded 203 patent documents. The second and third most recorded IPC code corresponds to A61K45/06 and C07D471/04. A61K45/06 is a group of medicinal preparations containing a mixture of active ingredients without chemical characterization, e.g. antiphlogistics and cardiaca C07D471/04 includes *ortho*-condensed heterocyclic compounds containing only nitrogen as ring hetero atoms in the condensed system. It should have at least one ring, be a six-membered ring with one nitrogen atom. These groups have 136 and 66 recorded patent documents. For more details concerning these top 20, a description of each IPC code is shown in Table 1.

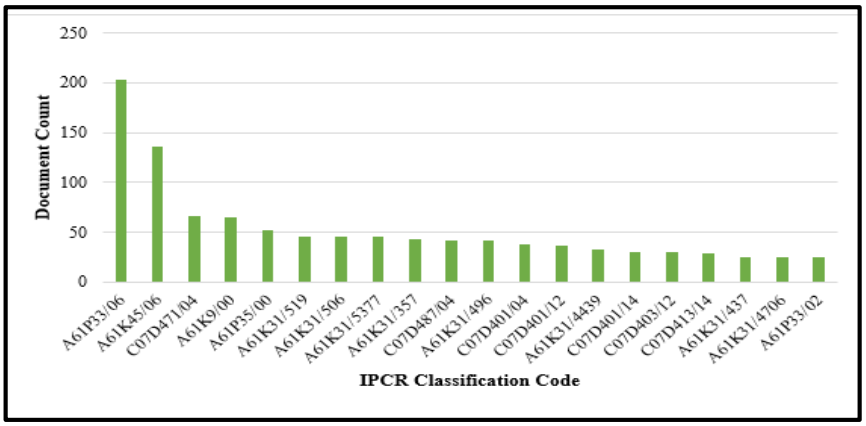


Fig 3: International Patent Classification (IPC) (Top 20) Based The trend between 2015 and 2021.

Table 1: Meaning of IPC codes concerning the resultant patents of probiotic-based cosmetics[13].

IPC code	Description
A61P33/06	Antimalarial therapeutic activity of chemical compounds or medicinal preparations.
A61K45/06	Medicinal preparations containing a mixture of active ingredients without chemical characterization, e.g.antiphlogistics and cardiaca.
C07D471/04	The *ortho*-condensed heterocyclic compounds contain only nitrogen as ring hetero atoms in the condensed system. It should have at least one six-membered ring with one nitrogen atom.
A61K9/00	Special physical forms characterize medicinal preparations.
A61P35/00	Subclass cover antineoplastic agents.
A61K31/519	Medicinal preparations have active ingredients with *ortho*- or *peri*-condensed with heterocyclic rings.
A61K31/506	Medicinal preparations have active ingredients without a condensed ring system and contain heterocyclic rings.
A61K31/5377	Medicinal preparations have active ingredients without a condensed ring system and, further, contain heterocyclic rings, e.g. timolol.
A61K31/357	Medicinal preparations have active ingredients with two or more oxygen atoms in the same ring, e.g. crown ethers or guanadrel.
C07D487/04	Heterocyclic compounds containing nitrogen atoms as the only ring hetero atoms in the o*rtho*-condensed system.
A61K31/496	Medicinal preparations have active ingredients with non-condensed piperazines containing heterocyclic rings, e.g.rifampin, thiothixene.
C07D401/04	Heterocyclic compounds contain two or more hetero rings, having nitrogen atoms as the only ring hetero atoms. It should have at least one six-membered ring with one nitrogen atom. The ring is directly linked by a ring-member-to-ring- member bond.
C07D401/12	Heterocyclic compounds contain two or more hetero rings, having nitrogen atoms as the only ring hetero atoms. It should have at least one six-membered ring with one nitrogen atom direct. Ringlinked by a chain containing hetero atoms as chain links.
A61K31/4439	Medicinal preparations have active ingredients containing a five-membered ring with nitrogen as a ring hetero atom, e.g. omeprazole.
C07D401/14	Heterocyclic compounds contain three or more hetero rings, having nitrogen atoms as the only ring hetero atoms. It should have at least one six-membered ring with one nitrogen atom.
C07D403/12	Heterocyclic compounds contain two or more hetero rings, having nitrogen atoms as the only ring hetero atoms. It should have at least one six-membered ring with one nitrogen atom. Ring linked by a chain containing hetero atoms as chain links.
C07D413/14	Heterocyclic compounds contain three or more hetero rings, at least one ring having oxygen and sulfur atoms as the only ring hetero atoms.
A61K31/437	Medicinal preparations have active ingredients containing a heterocyclic ring system containing a five-membered ring having nitrogen as a ring hetero atom, e.g. indolizine, beta-carbolin.
A61K31/4706	Medicinal preparations having active ingredients containing 4-Aminoquinolines; 8-Aminoquinolines, e.g. chloroquine, primaquine
A61P33/02	Chemical compounds or medicinal preparations having antiprotozoal activity against parasites include leishmaniasis, trichomoniasis, and toxoplasmosis.

3.3 Inventors-Based Trend Analysis

An inventor is an individual named in a patent application who discovered the technology[14]. Concerning antimalarial agents, the top 20 inventors between 2015 and 2021 are presented in Figure 4. Floyd D. from the United States is ranked as the first inventor with 19 patent documents. The inventor, Matthews D. from Switzerland, for second place with 17 patent documents. The inventors, Charman S. A., Yuthavong Y. and Goodman B. from Switzerland and United States, respectively, tied for third place with 16 patent documents each. Out of 795 patent documents, these are the major inventors, contributing 289 to the total. Goodman B. filed 14 patent documents in a single year in 2019. All patent documents by the above five inventors concern Rutgers the State University of New Jersey (New Jersey, United States), Medicines for Malaria Venture MMV (Geneva, Switzerland), and Evelo Biosciences INC (Massachusetts, United States) as applicants (Figures 3). Medicines for Malaria Venture MMV is one of the core companies working in antimalarial drugs, with almost 11 compounds in clinical development. It has many antimalarial products marketed products such as Coartem® *Dispersible*, Artesun®, Larinate® 60 mg, Eurartesim®, Pyramax® tablets or granules, ASAQ Winthrop®, SPAQ-CO™; Supyra®, 100 mg Artesunate Rectocaps, 10: Artecap™, Kozenis or Krintafel (trademarks owned or licensed by GSK), etc. It also partners with more than 150 active partners, including many prominent pharmaceutical companies such as Novartis, Pfizer, Sanofi, GSK, and IPCA[15]. Evelo Biosciences is a biotechnology company in the clinical stage. It makes product candidates that can be taken orally and are intended to act on the minor intestinal axis. SINTAXTM, a technology developed by Evelo Biosciences and in Phase 2 clinical trials, has the potential to revolutionize the global treatment of inflammatory diseases such as psoriasis[16].

Publication Year → Inventors ↓	2015	2016	2017	2018	2019	2020	2021	Grand Total
Abla N.	0	0	0	0	2	4	2	8
Aissaoui H.	6	4	4	1	0	0	0	15
Andahazy W. J.	0	0	2	0	5	1	3	11
Beasley F. C.	0	0	2	0	5	1	3	11
Boss C.	6	4	4	1	0	0	0	15
Burrows J.	6	3	1	0	1	0	2	13
Charman S. A.	5	3	1	2	2	1	2	16
El-Ahmad Y.	8	3	1	1	0	1	0	14
Filoche-Romme B.	8	3	1	1	0	1	0	14
Floyd D.	5	2	4	4	1	1	2	19
Ganzhorn A.	9	3	1	1	0	1	0	15
Goodman B.	0	0	0	0	14	2	0	16
Kamchonwongpaisan S.	2	3	0	0	7	1	1	14
Marciniak G.	9	3	1	1	0	1	0	15
Matthews D.	4	4	0	1	8	0	0	17
Muzet N.	9	3	1	1	0	1	0	15
Ronan B.	9	3	1	1	0	1	0	15
Siegrist R.	6	4	4	1	0	0	0	15
Vivet B.	9	3	1	1	0	1	0	15
Yuthavong Y.	2	3	2	0	7	1	1	16
Grand Total	103	51	31	17	52	19	16	289

Fig 3: Inventors Based Trend Analysis for top 20 inventors between 2015 and 2021

3.4 *Applicants-Based Trend Analysis*

In the context of patent applications, an applicant is the individual/organization/ legal entity that has submitted the application[13,17-19]. Regarding antimalarial drugs, the top 20 applicants between 2015 and 2021 in terms of the number of patent families are presented in Figure 4 and Table 2. Most of the top applicants come from the United States and Switzerland, which shows that market protection is more important in these two countries. The top applicants come from private companies, universities, and public-private partnerships. Regarding this top 20, all applicants are considered as people or organizations (companies and universities). As a legal entity, the pharmaceutical company Medicines for Malaria Venture MMV (Geneva, Switzerland) was top-ranked as the first applicant with 62 patent documents. The applicant, the Department of Health and Human Services (Washington, US), was in second place with a recorded patent document of 26, followed by the big pharma company Novartis (Basel, Switzerland) with 22, and Sanofi SA (Paris, France) with 20. Out of 795 patent documents, these are the top 20 applicants, contributing 313 to the total. Evelo Biosciences INC (Massachusetts, United States) filed the maximum number of patents (14) in a single calendar year in 2019, followed by Medicines for Malaria Venture MMV (13) in 2016.

Publication Year → Applicants ↓	2015	2016	2017	2018	2019	2020	2021	Grand Total
Actelion Pharmaceuticals LTD	6	4	3	0	0	0	0	13
Almirall SA	1	1	4	1	1	3	1	12
Amgen INC	0	2	1	1	1	1	0	6
Carna Biosciences INC	0	1	0	1	3	2	0	7
Centre Nat Rech Scient	2	4	2	0	1	0	2	11
Council Scient Ind Res	2	2	0	2	3	1	7	17
Evelo Biosciences INC	0	0	0	0	14	2	0	16
Genmab AS	2	1	2	0	0	1	1	7
Helperby Therapeutics LTD	0	1	3	0	3	0	0	7
Medicines for Malaria Venture MMV	10	13	9	10	10	5	5	62
Merck Patent Gmbh	3	0	0	1	3	4	4	15
Merck Sharp & Dohme	0	0	2	1	1	1	8	13
Novartis AG	3	1	1	6	4	2	5	22
Pfizer	2	2	2	1	1	0	0	8
Premier Dental Products Co	0	0	0	0	3	4	2	9
Sanofi SA	12	3	2	2	0	1	0	20
Scripps Research Inst	1	0	1	0	4	1	3	10
Sio2 Medical Products INC	2	0	3	1	1	4	3	14
Univ Washington	6	5	1	2	3	1	0	18
US Health Depart.	1	6	1	4	5	2	7	26
Grand Total	53	46	37	33	61	35	48	313

Fig 4: Applicants Based Trend Analysis for top 20 applicants between 2015 and 2021,

The top assignees among companies possessed a few patent families but many patent documents. By contrast, representative players of academic institutions from India have a small patent family size, which implies that India pays less attention to international patent portfolio strategy.

Table 2. Top assignees of antimalarial drugs

Rank	Assignee	Patent Documents	Patent Family	Average Number of Patents per family	Assignee Type
1	Medicines for Malaria Venture Mmv (Switzerland)	62	16	3.8	PPP
2	Us Health (US)	26	6	4.3	C
3	Novartis Ag (Switzerland)	21	6	3.5	C
4	Sanofi Sa (France)	17	1	17.0	C
5	University of Washington (US)	17	5	3.4	A&G
6	Council of Scientific & Industrial Research (India)	16	7	2.3	A&G
7	The University of Texas (US)	16	7	2.3	A&G
8	Evelo Biosciences INC (US)	15	12	1.3	C
9	Sio2 Medical Products INC (US)	15	7	2.1	C
10	Merck Patent Gmbh (Germany)	14	3	4.7	C
11	Actelion Pharmaceuticals LTD (Switzerland)	13	3	4.3	C
12	Almirall Sa (Spain)	12	8	1.5	C
13	Centre National de la Recherche Scientifique (France)	10	5	2.0	A&G
14	Merck Sharp & Dohme (US)	10	5	2.0	C
15	Premier Dental Products Co (US)	9	3	3.0	C

16	Pfizer (US)	8	3	2.7	C
17	Sbi Pharmaceuticals Co LTD (Japan)	8	2	4.0	C
18	The Scripps Research Institute (US)	8	2	4.0	A&G
19	Drexel University (US)	8	3	2.7	A&G
20	Walter and Eliza Hall Institute of Medical Research (Australia)	8	3	2.7	A&G

Abbreviations: C: Company; A&G: Academia and Government; PPP: Public-Private Partnership. The average number of patents per family = the number of patent documents / the number of patent families

3.5 Geographical Distribution and Jurisdictions-Based Trend Analysis

A patent application can be submitted to the appropriate patent office within the jurisdiction of which the applicant typically resides, has his domicile, or maintains a place of business; alternatively, it can be submitted to the office in the location from which the invention was conceived. Related patent applications may be submitted in a number of different jurisdictions depending on the case[20]. We then analyzed the nationalities of patent inventors. We looked at the inventors rather than the applications to trace the locus of knowledge production, a common approach in innovation studies. As shown in Figure 5, countries with the most inventors include the United States (314 patents), EPO (European Patent Office (93 patents), The Republic of China (71 patents), Canada (18 patents), and The Republic of Korea (17 patents).

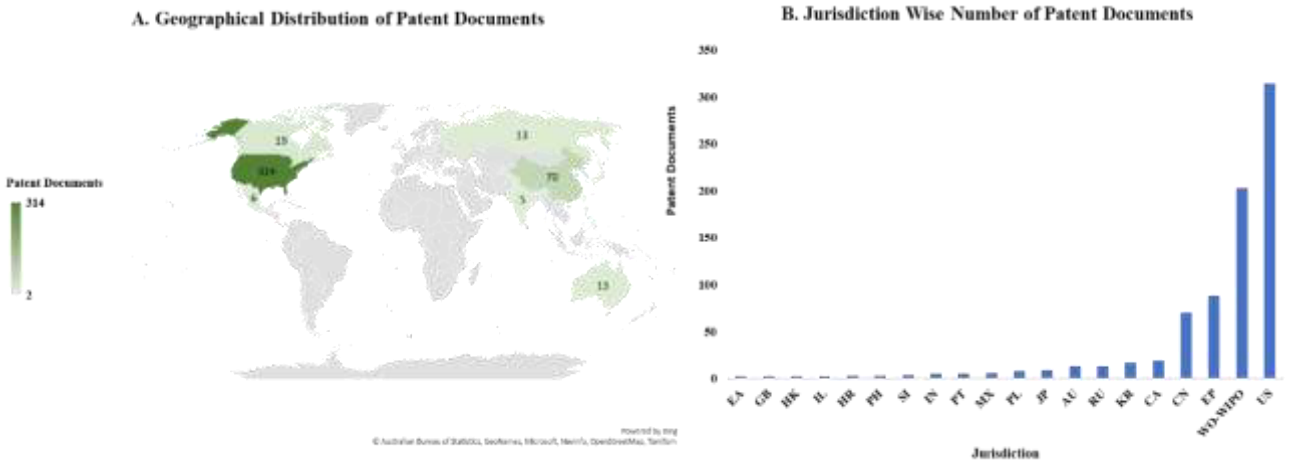


Fig 5: A. Geographic distribution by nationalities of patent inventors.

The colour intensity denotes the frequency of patent families. B. Geographic distribution by nationalities of jurisdictions (based on patent documents) Regarding antimalarials, the top 20 jurisdictions between 2015 and 2021 are presented in Figure 6. The United States, through the USPTO (United States Patent and Trademark Office), encompassed 314 patent documents with a higher patent contribution per total of ~39%; the global system for filing patent applications, known as the Patent Cooperation Treaty (PCT) and administered by WIPO, encompassed 207 patent documents with a patent contribution per total of ~26%; the EPO (European Patent Office), through which patent applications are filed regionally (Europe), encompassed 93 patent documents with a patent contribution per total of ~12%; The Republic of China, through the CNIPA (China National Intellectual Property Administration), encompassed 71 patent documents with a patent contribution per total of ~9%; The Republic of Canada, through the CIPO (Canadian Intellectual Property Office), encompassed 18 patent documents with a patent contribution per total of ~2%; finally, the Republic of Korea, KIPRIS (Korea Intellectual Property Rights Information Service) encompassed 17 patent documents with a patent contribution per total of ~2%. The chart also demonstrates that patent filed through the USPTO is maximum throughout the years, followed by WIPO, EPO, CNIPA, CA and KIPRIS. The geographical distribution of year-wise patent application filings shown in Figure 6 also indicates that patent filing in antimalarial areas has been consistent over the last six years. That means antimalarial will also maintain dominance in their segment in the coming years.

Jurisdiction→ Publication Year ↓	AU	CA	CN	EA	EP	GB	HR	HU	IN	JP	KR	MX	PH	PL	PT	RU	SG	SI	US	WO	Grand Total
2015	3	1	10	1	16	0	1	0	5	1	5	2	3	1	1	2	1	1	48	26	128
2016	3	1	6	1	15	0	0	1	0	0	3	1	0	1	1	5	0	1	49	20	108
2017	1	5	6	0	11	2	1	1	0	4	1	1	0	3	2	2	0	1	34	29	104
2018	3	1	7	0	12	0	0	1	0	0	1	1	0	2	0	0	0	0	46	23	97
2019	2	4	14	0	14	0	1	1	0	1	0	1	0	1	1	0	1	1	47	36	125
2020	1	3	14	0	13	0	0	0	0	2	1	0	0	0	0	3	1	0	42	26	106
2021	2	3	14	0	12	0	0	0	0	0	6	0	0	0	0	1	0	0	48	47	133
Grand Total	15	18	71	2	93	2	3	4	5	8	17	6	3	8	5	13	3	4	314	207	801

Fig 6: Jurisdictions Based Trend Analysis for top Twenty jurisdictions between 2015 and 2021.

3.6 Scientific Implications

P. falciparum has developed resistance to almost all currently available antimalarial drugs. The cost of medicine to combat drug-resistant malaria is also an important consideration. Therefore, resistance to antimalarial medications is rising, and new, effective treatments are urgently needed. Various government and non-government organizations have launched many initiatives against malaria. The WHO has also launched the Global Malaria Programme to control, prevent and eradicate multiple types of malaria from mild to severe. The present study presents the current scenario in developing new scaffolds with a novel mechanism of action as antimalarial drug candidates. After patent analysis, we have found that various public-private partnerships, private companies, and Academia and government research organization are in the top assignee list from the United States, Switzerland, Germany, and India. Medicines for Malaria Venture (MMV) from Switzerland was the principal applicant with about sixty innovations related to malaria and discovered patent documents. Since 1999, when MMV started, it has built the richest pipeline of malaria drugs in history. Right now, 14 antimalarials are being used to treat people. In the last 20 years, these medicines have helped save the lives of almost 3 million people. From the study, we have found about fifteen scaffolds disclosed for antimalarial activity. Amongst them, the derivatives of quinoline, artemisinin, and peroxides like trioxane and tetraoxanes were the most used as antimalarial agents. This study gives an overview of the novel antimalarial compound and their mechanism of action that have a high potential to be antimalarial agents. More research can be done in future.

3.7 Analysis of Relevant Patents

The recent antimalarial drug patents are discussed in this overview. Compound patents that disclose the new antimalarial drugs considered for the study. Various types of new antimalarial agents with different scaffolds disclosed in patents filed between 2015 and 2021 are shown in Figure 7. Quinine, artemisinin, trioxolane, naphthoquinones, and isoquinoline derivatives were used chiefly as antimalarial agents. Quinoline and artemisinin are well-established classes of antimalarials with the maximum number of antimalarial drugs in the market. The patent documents shortlisted (58 patents) for the study disclosed many next-generation antimalarials with increased activity and market potential, as shown in Table 3.

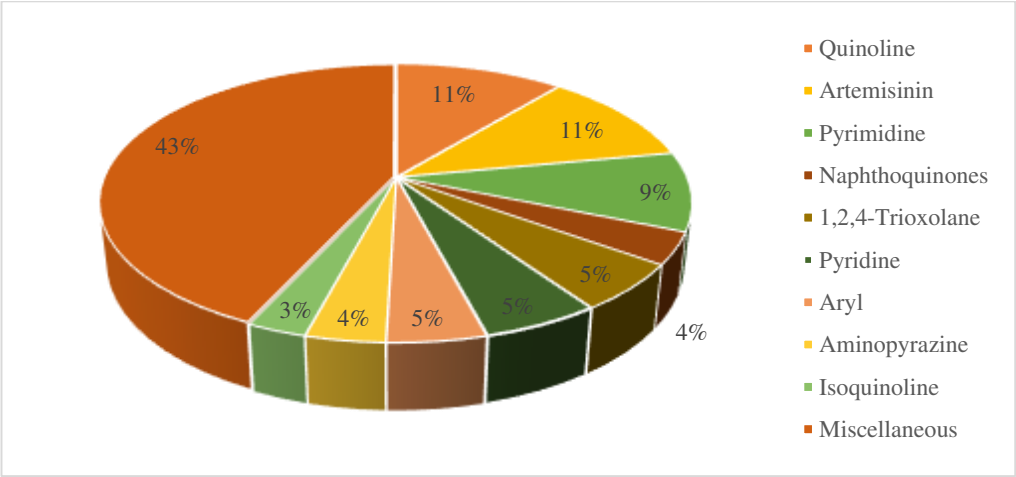


Fig7: New antimalarial agents with different scaffolds disclosed in patents filed between 2015 and 2021.

The analyzed patents focused on newer antimalarial agents, crystal forms composition, and compounds or formulation preparation methods. The relevant patent documents were selected based on the countries that patent antimalarial the most, patenting rates in those countries and disclosing new chemical entities (Figure 8). The most relevant patents are discussed in detail. Antimalarial drug agents are classified based on the scaffold, and in-depth analysis was done.

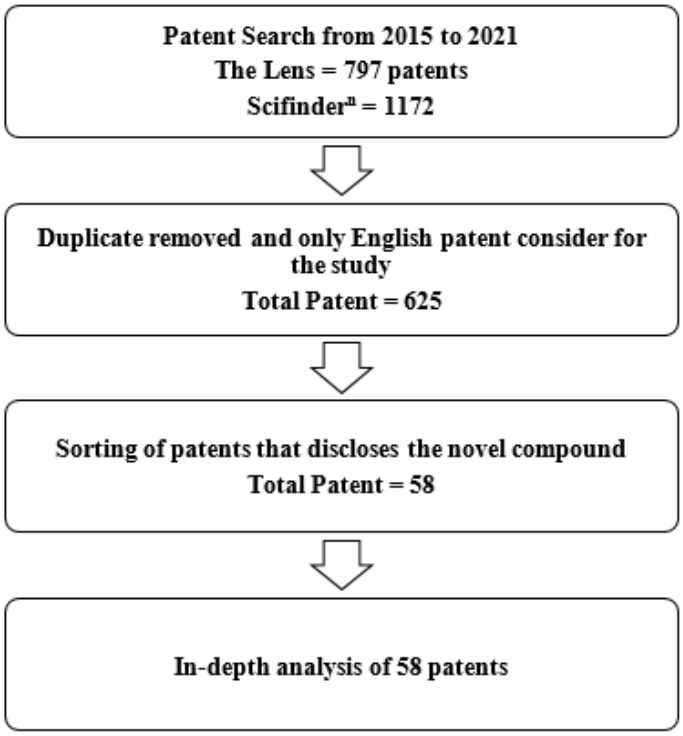


Fig 8: Stepwise method for shortlisting relevant patents.

3.8 *Quinoline and Isoquinoline Derivatives*

Several patents disclose the novel antimalarial agents having quinoline-based scaffolds such as quinolone, 4-aminoquinoline, 8-aminoquinoline, dihydro isoquinoline, tetrahydroisoquinoline, pyrroloquinoline, etc. In patent US9206131B2, Riscoe M. K. *et al.* disclose the development of quinoline and quinolone-based antimalarial agents against chloroquine-resistant and multidrug-resistant strains of *Plasmodium* parasites. The patent document also describes the use of novel compounds for prophylactic treatment against chloroquine-resistant or multidrug-resistant malaria[21]. In US9493420B2, David H. P. *et al.* describe the novel Reversed Chloroquines (RCQs) antimalarial compounds highly potent against chloroquine-resistant and chloroquine-sensitive malaria parasites. RCQs are hybrid compounds with two moieties. One is an antimalarial quinoline analogue (such as chloroquine) that inhibits the parasite, while another inhibits chloroquine efflux via transporters in the resistant malaria parasite's digestive vacuole membrane[22]. Higuchi T. *et al.* describes novel asymmetrical 4-aminoquinoline-based compounds for prophylaxis and treatment of malaria. Compounds disclosed act by interfering with the malaria heme toxicity avoidance mechanism of malaria[23]. Chakrabarti D. *et al.* (WO2020/206252A1) describe novel 2-substituted4-aminoquinoline derivatives for treating malaria[24]. In patents US2021/0087187A1 and US2015/0336947A1, Mhaske S. B. *et al.* describe the development of pyrroloquinoline scaffold containing compounds including analogues of natural alkaloids such as marinoquinazolinone A-F and aplidiopsamine A as potential antimalarial agents[25, 26]. Geiger W.E. *et al.* invented organometallic compounds containing chloroquinoline moiety for prophylaxis and treatment of malaria. The compounds disclosed in the invention mainly contain manganese or rhenium as a ligand[27]. The patent documents EP3892332A1 and US9416124B2 describe the novel dihydro isoquinoline and tetrahydroisoquinoline derivatives for preventing or treating malaria[28, 29].

Table 3. Top Relevant Patent documents on antimalarial drugs.

S. No.	Patent Number	Publication Date	Scaffold Disclosed in Patent	Title
1	US9206131B2	08-12-2015	Quinoline, quinolone	Compounds having antiparasitic or anti-infectious activity
2	US9399625B2	26-07-2016	Acridone	Acridone compounds
3	US9409879B2	09-08-2016	Naphthoquinones	Total synthesis of redox-active 1,4-naphthoquinones and their metabolites and their therapeutic use as antimalarial and schistosomicidal agents
4	US9938321B2	10-04-2018	Peptoid Oligomers	Cyclic peptoid oligomers, pharmaceutical compositions and methods of using the same
5	WO2021123266A1	24-06-2021	Pyrrole	Anti-malarial agents
6	EP3450549A1	06-03-2019	Artemisinin	Artemisinin derivatives, methods for their preparation and their uses as antimalarial agents

7	US9090549B2	28-07-2015	Naphthoquinones	1,4-naphthoquinones derivatives and therapeutic use thereof
8	EP3546452A1	02-10-2019	Aminopyrimidine	Antimalarial compounds with flexible side-chains
9	US9926314B2	27-03-2018	Pyrazolo[1,5-A]Pyridine	Compounds and compositions for the treatment of parasitic diseases
10	WO2016151521A1	29-09-2016	Triazolopyrimidine	New substituted triazolopyrimidines as anti-malarial agents
11	US9637473B2	02-05-2017	Acrylamide	Acrylamide derivatives as antimalarial agents
12	EP3892332A1	13-10-2021	Dihydroisoquinoline	New anti-malarial agents
13	US9493420B2	15-11-2016	Quinoline	Quinoline derivatives and uses thereof
14	US9416124B2	16-08-2016	Tetrahydroisoquinoline	Substituted 2-alkyl-1-oxo-n-phenyl-3-heteroaryl-1,2,3,4-tetrahydroisoquinoline-4-carboxamides for antimalarial therapies
15	US8962657B2	24-02-2015	Aryl	Aryl derivatives and uses thereof
16	WO2021191882A1	30-09-2021	Aryl	Antimalarial agent, methods and uses thereof
17	US10154974B1	18-12-2018	Abscisic Acid	Use of abscisic acid for the prevention and treatment of malaria
18	WO2018060423A1	05-04-2018	Naphthalene Diimide	Naphthalene diimide compounds for the treatment of diseases
19	WO2017142825A2	24-08-2017	Iminopyrimidinones	N3-substituted iminopyrimidinones as antimalarial agents
20	EP3907227A1	10-11-2021	Trilobine	Trilobine derivatives and their use thereof in the treatment of malaria
21	WO2021033159A1	25-02-2021	Quinazoline	Pyrazino [1,2-b]quinazoline-3,6-diones derivatives, their production, and uses thereof
22	WO2016207869A1	29-12-2016	Aryl	Antimalarial agent, methods and uses thereof
23	EP3118198A1	18-01-2017	Aminopyrazine	Anti-malarial agents
24	US9464057B2	11-10-2016	Pyrazole	Anti-malarial agents
25	WO2020263191A1	30-12-2020	Aminopyrazine	Compounds having antimalarial activity
26	WO2015133280A1	11-09-2015	Quinoline	A compound having antimalarial activity, and antimalarial drug
27	US9266842B2	23-02-2016	Aminopyrazine	Anti-malarial agents
28	US20150210652A1	30-07-2015	Triazines	Substituted triazines for malaria treatment and chemoprophylaxis
29	WO2016063301A2	28-04-2016	Aryl	Anti-malarial compounds and process for preparation thereof
30	WO2019050850A1	14-03-2019	Biguanidine	Biguanidine derivatives of therapeutic agents and methods of preparation and use thereof
31	WO2016063848A1	28-04-2016	Peroxide	Antimalarial
32	WO2021186348A1	23-09-2021	Dihydro-Spiro[Indoline-3:1'-Isoquinolin]-2-Ones	Dihydro-spiro[indoline-3:1'-isoquinolin]-2-ones as antimalarial agents
33	WO2017143964A1	31-08-2017	Aminopyrazine	Novel high-efficiency antimalarial drug, quisinostat
34	WO2016175264A1	03-11-2016	Triazine, Pyrimidine	Novel heteroaryl derivative having antimalarial activity
35	US20190112267A1	18-04-2019	Indole Compounds	Small molecule N-(alpha-peroxy) indole compounds and methods of use
36	WO2016203488A1	22-12-2016	1,2,4- Triazole	Preparation of novel deferasirox analogues for antimalarial activity
37	WO2020209932A1	15-10-2020	Aryl	Compounds with antimalarial activity
38	WO2020206252A1	08-10-2020	Quinoline	Antimalarial compounds
39	WO2021081500A1	29-04-2021	Naphthoquinones	Mitochondria-targeted atovaquone: a more potent and more effective antitumor, antimicrobial, and antimalarial drug
40	WO2021195603A1	30-09-2021	Carbazole	Anti-malarial compounds and uses thereof
41	EP2526090B1	19-08-2015	Aminopyridine	New anti-malarial agents
42	WO2021149692A1	29-07-2021	Aminopyridine	Novel antimalarial agent containing heterocyclic compound

43	US9000003B2	07-04-2015	Aminopyrimidine	Antifolate antimalarials with dual-binding modes and their preparation
44	US20210087187A1	25-03-2021	Pyrroloquinoline	Antimalarial heterocyclic compounds and a process for the preparation thereof
45	EP3093020A1	16-11-2016	Pyridine	Anti-malarial agent
46	US20150336947A1	26-11-2015	Pyrroloquinoline	Pyrroloquinoline alkaloids as antimalarial agents and process for the preparation thereof
47	WO2017052479A4	26-05-2017	Aminopyrimidine	2,4-diamino-6-methyl pyrimidine derivatives with antimalarial activities against plasmodium falciparum
48	US20160353789A1	08-12-2016	Amino Acid	Nutrition composition suppressing the growth of protozoan parasites of blood cells
49	US20190091216A1	28-03-2019	Macrolide	Macrolide compounds and their use in liver stage malaria and related disease
50	WO2021200934A1	07-10-2021	Benzimidazole	Antimalarial drug
51	US20190054074A1	21-02-2019	Pyridine	Anti-malarial agent
52	US10744119B1	18-08-2020	Benzimidazole	Inhibitors of the malarial GST
53	US20200377483A1	03-12-2020	Trioxolane	New anti-malarial agent
54	US20180214457A1	02-08-2018	Quinoline	Use of cymanquine compounds as antimalarial agents
55	EP3137455B1	15-08-2018	Aminopyrimidine	Triaminopyrimidine compounds are useful for preventing or treating malaria
56	US20200369616A1	26-11-2020	Alkoxycarbonate Ester Prodrug	Alkoxycarbonate ester prodrugs for use as antimalarial agents
57	US20210121476A1	29-04-2021	Furan fused quinoline	Inhibitors of the plasmodial surface anion channel as antimalarials
58	EP2638902B1	24-02-2016	Alaremycin	Antimalarial drug comprising aureomycin or derivative thereof as the active ingredient

3.9 Artemisinin Derivatives

Several types of artemisinin derivatives, such as thioether, sulfoxide, and sulfone derivatives of dihydroartemisinin, dihydroartemisinin pyrimidine derivatives, and artesunate heparin derivatives, have been disclosed in various patents. Most patents disclosing artemisinin-based compounds belong to China. In patent EP3450549A1, Fasan R. *et al.* reveal the development of 6a, 7 and 10 substituted derivatives of artemisinin for treating a disease caused by infection with a parasite of the genus Plasmodium[30]. Yang D. *et al.* describe the novel dihydroartemisinin pyrimidine derivatives and thioether, sulfoxide and sulfone derivatives of dihydroartemisinin derivatives as antimalarial drugs, leishmanial drugs, anti-angiogenesis drugs, antitumor drugs, hypolipidemic drugs and WNT signal pathway agonists[31,32]. Li X. *et al.* describe artesunate heparin derivatives where artesunate is connected with heparin by ester bond and its use for treating or preventing malaria[33]. In patent CN112585142A, Bhattacharya A. describes novel artemisinin-dipeptidyl vinyl-based compounds for treating drug-resistant malaria[34].

3.10 Naphthaquinone Derivatives

In patents US9409879B2 and US9090549B2, Davioud-Charvet E. *et al.* describe the synthesis of naphthoquinones, azanaphthoquinones and benxanthones, as antimalarial or antischistosomal agents. It also disclosed the therapeutic use of these compounds as antimalarial and schistosomicidal agents[35, 36]. In patent WO2021/081500A1, Kalyanaraman B. *et al.* describe the novel mitochondria-targeted Atovaquone derivatives as an effective antitumor, antimicrobial, and antimalarial drug[37].

3.11 1,2,4-Trioxolane Derivatives

In patents US20200377483A1 and CA2702256C, Vennerstrom J. L. *et al.* describe new spiro or dispiro1,2,4-trioxolane derivatives to treat malaria, schistosomiasis, and cancer[38,39]. 1,2,4-trioxolanes compounds have a spiroadamantane group on one side of the trioxolane group and a spirocyclohexyl on the other side of the trioxolane group is disclosed in the patent document CA2702256C. This compound is structurally simple, easy to synthesize, nontoxic, and potent against malarial parasites compared to artemisinin semisynthetic derivatives. Also, this compound claims to provide a single-dose cure and prophylactic activity against malaria.

3.12 Pyrimidine Derivatives

Several types of pyrimidine derivatives such as aminopyrimidine, triazolopyrimidine, iminopyrimidinones, etc., have been disclosed in various patents. In patent US9000003B2, Tarnchompoo B. *et al.* describe novel diaminopyrimidine derivatives as antifolate antimalarials with dual-binding modes activity. These compounds inhibit wild-type mutant enzymes, double (C59R+SIOSN), triple (N51 + C59R + SIOSN, C59R + S1 OSN + 1164L) and quadruple (N51+C59R+S108N+1164L) mutant enzymes with high inhibition constants. The chemicals are effective against both wild-type (Tm4/S.2) and mutant (K1CB1, W2, Cs1-2, and V1/S) malaria parasites[40]. In patent WO2016/151521A1, Phillips M. *et al.* describe novel triazolopyrimidine derivatives as antifolate antimalarials with dual-binding modes activity[41]. In patent WO2017/142825A2, Khan T. A. *et al.* describe novel

triazolopyrimidine derivatives as antifolate antimalarials with dual-binding mode activity[42].

3.13 Aminopyrazine Derivatives

In the last five years, several patent documents (EP3118198A1, WO2020263191A1, US9266842B2 and WO2017143964A1) discuss aminopyrazine derivatives for the treatment of malaria[43-46]. For example, in patent WO2017143964A1, Jiang L. *et al.* described a novel highly potent quisinostat's analogues antimalarial drug. The disclosed quisinostat shows better plasmodium-killing effects than artemisinin in mice[46].

3.14 Pyridine Derivatives

Several types of pyridine derivatives, such as pyrazolo[1,5-a]pyridine, pyrazolo[3,4-b]pyridines, aminopyridine, tris(2-pyridylmethyl)amine, etc., have been disclosed in various patents. In patents US20190054074A1 and EP3093020A1, Wada A. *et al.* describe metal chelators such as tris(2-pyridylmethyl)amine for treating malaria[47,48]. In patent US9926314B2, Chatterjee A. K. *et al.* describe Pyrazolo[1,5-a]pyridine derivatives for treating malaria in combination with any one of the existing antimalarial drugs[49]. The patent documents EP2526090B1 and WO2021/149692A1 disclosed aminopyridine derivatives for treating or preventing malaria[50, 51].

3.15 *Aryl Derivatives*

Various aryl-based compounds, such as biphenyl, 3-phenylacrylate, aminopyridine, phenethyl cinnamate, etc., have been disclosed in multiple patents. For example, the patent document WO2021191882A1 describes 3-phenyl acrylate for treating malaria[52]. In patent US8962657B2, Heffernan G. D. *et al.* describe biphenyl derivatives for treating malaria in a combination of any of the existing antimalarial drugs[53].

3.16 5.9 *Miscellaneous*

Other antimalarial agents include acridone derivatives, peptide derivatives, abscisic acid, trilobine derivatives, triazines, biguanidine, carbazole, macrolide, alaremycin, etc. In patent US20190091216A1, Sullivan D. *et al.* describe macrolide-based compounds acting as liver-stage antimalarial therapeutic molecules[54]. In patent WO2016203488A, Havaldar F. H. *et al.* describe 1,2,4- Triazole based deferasiroxan analogues as antimalarial agents[55]. In patent US20150210652A1, Sciotti R. J. *et al.* describe substituted triazines for the prophylaxis and treatment of malaria[56]. In patent EP3907227A1, Nardella F. *et al.* describe trilobine derivatives for treating drug-resistant malaria[57]. In patent US10154974 B1, Luckhart S. *et al.* describe abscisic acid and its analogues for therapeutic and prophylactic treatment of malaria. It effectively reduces parasitemia and gametocytemia and reduces transmission of *Plasmodium* by a mosquito vector[58].

4. CONCLUSION

This study provided a patent analysis of novel antimalarial agents described in patents published between 2015 and 2021. The publication year, 2021, had the highest patent registration, with 124 patent documents, followed by 2015 (93) and 2019 (90). The United States is ranked first with 314 patent documents. Based on the IPC codes, all filed patents concerned antimalarial agents for the prevention and treatment of malaria. Many patents also disclose the development of antimalarial with novel scaffolds against multiple drug-resistant malaria. This study also indicated that the inventions shown in the patents are related to the synthetic method and formulation method. In addition, research has found numerous unexplored scaffolds where new potential antimalarial agents can be developed.

5. ACKNOWLEDGMENT:

The authors acknowledge Apeejay Stya University for access to the commercially available CAS Sci-Finder^{n} database and the Cambia Institute for The Lens patent data set used in this study.

6. AUTHOR CONTRIBUTION STATEMENT

N.Y. conceived and planned the study. N.Y., M.K.K., G.A., and M.K.S. were responsible for data collection, model analysis and manuscript writing. N.Y. took the lead in writing the manuscript. N.Y. and M.K.K. were responsible for research design, manuscript revision and project management. All authors provided critical feedback and helped shape the research, analysis and manuscript.

7. CONFLICT OF INTEREST

Conflict of interest declared none.

8. REFERENCES

1. Casteel DA. Antimalarial agents. In: Burger's medicinal chemistry and drug discovery. 6th ed. Volume 5: Chemotherapeutic Agents. New York: A John Wiley & Sons, Inc. [publication]; 2003: 920-31.
2. White NJ. Plasmodium knowlesi: the fifth human malaria parasite. Clin Infect Dis. 2008;46(2):172-3. doi: 10.1086/524889, PMID 18171246.
3. Available from: http://www.who.int assessed on 23.05.2022.
4. Jagannathan P, Kakuru A. Malaria in 2022: increasing challenges, cautious optimism. Nat Commun. 2022;13(1):2678. doi: 10.1038/s41467-022-30133-w, PMID 35562368.
5. Robert A, Benoit-Vical F, Dechy-Cabaret O, Meunier B. From classical antimalarial drugs to new compounds based on the mechanism of action of artemisinin. Pure Appl Chem. 2001;73(7):1173-88. doi: 10.1351/pac200173071173.
6. O'Neill PM, Bray PG, Hawley SR, Ward SA, Park BK. 4-aminoquinolines: past, present and future: a chemical perspective. Pharmacol Ther. 1998;77(1):29-58. doi: 10.1016/s0163-7258(97)00084-3, PMID 9500158.
7. Bloland PB. Drug resistance in malaria. Geneva: WHO. World Health Organization/CDS/CSR/DRS/2001.4; 2001. p. 1-20.
8. Chiang PK, Bujnicki JM, Su X, Lanar DE. Malaria: therapy, genes and vaccines. Curr Mol Med.

2006;6(3):309-26. doi: 10.2174/156652406776894545, PMID 16712477.
9. Cambia Institute. The lens patent data set. Version 8.0.14 [cited Mar 30 2022]. Available from: https://www.lens.org.
10. European Patent Office. Espacenet glossary. Version 1.24.1 [cited Mar 5 2022]. Available from: https://worldwide.espacenet.com/patent.
11. World Intellectual Property Organization. IPC publication. Version 2022.01 [cited Mar 5 2022]. Available from: https://www.wipo.int/classifications/ipc/en/.
12. World Intellectual Property Organization. Guide to the international patent classification (IPC) [cited Mar 5 2022]. Available from: https://www.wipo.int/edocs/pubdocs/en/wipo_guide_ipc_2020.pdf.
13. International Patent Classification (IPC) [cited Mar 10 2022]. Available from: https://ipcpub.wipo.int/.
14. PCT glossary, World Intellectual Property Organization. Guide to the international patent classification (IPC) [cited Mar 5 2022]. Available from: https://www.wipo.int/pct/en/texts/glossary.html.
15. Medicines for Malaria Venture. MMV – Company Profile [cited Jan 05 2022]. Available from: https://www.mmv.org/.
16. Evelo Biosciences INC. Company Profile [cited Mar 05 2022]. Available from: https://evelobio.com/.
17. World Intellectual Property Organization. What is intellectual property? Frequently asked questions: patents [cited Mar 28 2022]. Available from: https://www.wipo.int/patents/en/faq_patents.html.
18. United States Patent and. Trademark office. Manual of patent examining procedure: ownership/assignability of patents and applications [cited Mar 28 2022]. Available from: https://www.uspto.gov/web/offices/pac/mpep/mpep-0300.html.
19. World Intellectual Property Organization. Legal status [cited Feb 22 2022]. Available from: https://www.wipo.int/edocs/mdocs/aspac/en/wipo_it_ip_tyo_17/wipo_it_ip_tyo_17_t6.pdf.
20. WIPO intellectual property handbook [cited Mar 10 2022]. Available from: https://www.wipo.int/edocs/pubdocs/en/wipo_pub_489.pdf.
21. Riscoe MK, KJX, Winter RW, Hinrichs DJ, Smilkstein MJ, Nilsen A et al. Compounds having antiparasitic or anti-infectious activity. Patent US9206131B2. USA; December 08, 2015.
22. Peyton DH, Burgess S. Quinoline derivatives and uses thereof. Patent US9493420 B2. USA; November 15, 2016.
23. Higuchi T, Kato N, Umezawa N. Compound having antimalarial Activity, and antimalarial Drug. Patent WO2015/133280A. Vol. 1. Seattle: Pet Care Trust; September 11, 2015.
24. Chakrabarti D, Yuan Y, Huang G, Solano C. Antimalarial compounds. Patent WO2020/206252A. Vol. 1. Seattle: Pet Care Trust; October 08, 2020.
25. Mhaske SB, Mahajan JP, Dhanasekaran S. Antimalarial heterocyclic compounds and a process for the preparation thereof. Patent US2021/0087187A. Vol. 1. USA; March 25, 2021.
26. Mhaske SB, Lande JR. Pyrroloquinoline alkaloids as antimalarial agents and process for the preparation thereof. Patent US2015/0336947A. Vol. 1. USA; December 08, 2016.
27. Geiger WE, Lam K, Bergman LW. Use of Cymanquine compounds as antimalarial agents. Patent US2018/0214457A. Vol. 1. USA; August 02, 2018.
28. Guy RK, Hammill JT, Floyd D, Burrows J, Brand S. New antimalarial agents. Europe. Patent EP3892332A1. 2021;13 October.
29. Guy RK, Zhu F, Guiguemde WA, Floyd D, Knapp S, Stein P et al. Substituted 2-Alkyl-1-Oxo-N-Phenyl-3-Heteroaryl-1,2,3,4-Tetrahydroisoquinoline-4-Carboxamides for antimalarial therapies. Patent US9416124 B2. USA; August 16, 2016.
30. Fasan R, Zhang K-D. Artemisinin derivatives, methods for their preparation and their Useas antimalarial agents. Patent EP 3450549. Europe. March 06, 2019;A1.
31. Yang D, Liu J, Fan L, Zhang S, Tang X. Application of dihydroartemisinin derivative of Antimalarial Drug. Patent CN110448552 A. China; November 15, 2019.
32. Yang D, Zhang S, Fan L, Liu J, Tang X, Meng R. Thio ether, sulfoxide and sulfone derivatives of dihydroartemisinin, and applications thereof. Patent CN110642869 A. China; January 03, 2020.
33. Li X, Si M. Artesunate heparin derivative as well as pharmaceutical composition and application thereof. Patent CN109481692A. China; March 19, 2019.
34. Bhattacharya A, Aratikatla EK, Malhotra P, Mohmmed A. Novel antimalarial compounds, process for preparation and their use for drug resistant malaria. Patent CN112585142A. China; March 30, 2021.
35. Davioud-Charvet E, Lanfranchi DA, Johann L, Williams DL, Cesar RE. Total synthesis of redox-active 1.4-naphthoquinones and their metabolites and their therapeutic use as antimalarial and schistomicidal agents. Patent US9409879 B2. USA; August 09, 2016.
36. Davioud-Charvet E, Muller T, Bauer H, Schirmer RH. 1,4-Naphthoquinones derivatives and therapeutic use thereof. Patent US9090549 B2. USA; July 28, 2015.
37. Kalyanaraman B, Cheng G, Hardy Micael J. Mitochondria-targeted atovaquone: A more potent and more effective antitumor, antimicrobial, and antimalarial Drug. Patent WO2021/081500A. Vol. 1. Seattle: Pet Care Trust; April 29, 2021.
38. Vennerstrom JL, Charman SA. New antimalarial agent. Patent US2020/0377483A. Vol. 1. USA; December 03, 2020.
39. Vennerstrom JL, Dong Y, Charman SA, Wittlin S, Chollet J, Creek DJ et al. Dispiro 1,2,4-trioxolane antimalarials. Patent CA2702256C. Canada; September 26, 2017.
40. Tarnchompoo B, Chitnumsub P, Kamchonwongpaisan S, Shaw PJ, Rattanajak R, Poen S et al. Antifolate antimalarials with dual-binding modes and their preparation. Patent US9000003B2. USA; April 07, 2019.
41. Phillips M, Charman SA, Rathod PK, Matthews D, Waterson D. New substituted triazolopyrimidines as antimalarial agents. Patent WO2016/151521. Vol. A1. Seattle: Pet Care Trust; September 29, 2016.
42. Khan TA, Cumming JN, Olsen DB, Boddey JA, Cowman AF, Sleebs BE. N3-substituted Iminopyrimidinones as antimalarial agents. Patent WO2017/142825. Vol. A2. Seattle: Pet Care Trust;

August 24, 2017.
43. Waterson D, Witty MJ, Chibale KY, Street L, Gonzalez CD, Paquet T. Antimalarial agents. Patent EP3118198A1. Europe; January 18, 2017.
44. Donald TWJ, Rainer PP, Hong TC. Compounds having antimalarial Activity. Patent WO2020/263191. Vol. A1. Seattle: Pet Care Trust; December 30, 2020.
45. Younis Y, Chibale K, Witty MJ, Waterson D. Antimalarial agents. Patent US9266842B2. USA; February 23, 2016.
46. Jiang L, Haung Z. Novel high-efficiency antimalarial Drug, quisinostat. Patent WO2017/143964. Vol. A1. Seattle: Pet Care Trust; August 31, 2017.
47. Wada A, Hayase H, Watanabe N, Osada H, Shimizu T, Wierzba K. Antimalarial agent. Patent US2019/0054074A. Vol. 1. USA; February 21, 2019.
48. Wada A, Hayase H, Watanabe N, Osada H, Shimizu T, Wierzba K. Antimalarial agent. Patent EP3093020A1. Europe; November 16, 2016.
49. Chatterjee AK, Nagle AS, Paraselli P, Kondreddi RR, Leong SY, Mishra PK et al. Compounds and Compositionsa or the treatment of parasitic diseases. Patent US9926314 B2. USA; March 27, 2018.
50. Witty MJ, Hardick D. New antimalarial agents. Patent EP2526090B1. Europe; August 19, 2015.
51. Horii T, Suzuki S, Roupany AJA, Mui JJB, Lewis-Marshall JP, Devan FA et al. Novel antimalarial agent containing heterocyclic compound. Patent WO2021/149692A. Vol. 1. Seattle: Pet Care Trust; July 29, 2021.
52. Freitas Da Costa MS, Monginho BMDF, De Jesus RPPMF, Mendes VMI, Mendes FPE, Martins CCS. Antimalarial agent, methods and uses thereof. Patent WO2021/191882. Vol. A1. Seattle: Pet Care Trust; September 30, 2021.
53. Heffernan GD, Jacobus DP, Schiehser GA, Shieh HM, ZW. Aryl derivatives and uses thereof. Patent US8962657 B2. USA. Vol. 24(February); 2015.
54. Sullivan D, Kaludov N, Liu Y, Martinov M. Macrolide compounds and their use in liver stage malaria and related disease. Patent US2019/0091216. Vol. A1. USA; February 21, 2019.
55. Havaldar FH, Dabholkar BV, Mule GB. Preparation of novel deferasirox analogues for antimalarial activity. Patent WO2016/203488. Vol. A1. Seattle: Pet Care Trust; December 22, 2016.
56. Sciotti RJ, Reichard GA, Pannone KM, Zottig VE. Substituted triazines for malaria treatment and chemoprophylaxis. Patent US2015/0210652. Vol. A1. USA; July 30, 2015.
57. Nardella F, Halby L, Haitham H, Menard D, Scherf A, Arimondo PB. Trilobine derivatives and their use thereof in the treatment of malaria. Patent EP 3907227. Europe. November 10, 2021;A1.
58. Luckhart S, Glennon EKK. Use of abscisic acid for the prevention and treatment of malaria. Patent US10154974 B. USA; December 18, 2018.