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COMPUTATIONAL DRUG DISCOVERY OF POTENT ANTIMALARIAL XANTHONES: A SYSTEMATIC REVIEW AND ADMET-GUIDED IDENTIFICATION OF A LEAD CANDIDATE

Joanne Theophilia Winata[1], Komang Dian Aditya Putra[1], Yosi Bayu Murti[2], Akhmad Kharis Nugroho[3*]

[1]Master in Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Gadjah Mada, Jl. Sekip Utara, Sleman, Yogyakarta 55281, Indonesia
[2]Department of Pharmaceutical Biology, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, 55281, Indonesia
[3]Department of Pharmaceutics, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, 55281, Indonesia

Corresponding author email: a.k.nugroho@ugm.ac.id

ABSTRACT

Background: Artemisinin resistance mediated by Kelch13 mutations threatens malaria elimination efforts. Xanthones from Garcinia mangostana present a promising alternative scaffold for antimalarial drug development. **Objective:** This study systematically identified potent xanthones reported in the literature and evaluated their pharmacological potential using computational methods. **Methods:** A comprehensive systematic review was conducted across PubMed, Scopus, and Wiley Online Library (through September 2025) following PRISMA 2020 guidelines, searching for "Xanthone" combined with "Antimalarial" or "Plasmodium". Selection criteria included original research reporting IC50 values against Plasmodium falciparum. **Results:** Among 165 identified compounds from 46 studies, 18 demonstrated potent activity (IC50 < 1 µM). Structure-Activity Relationship analysis revealed that synthetic xanthones with alkylamino side chains were substantially more efficacious than natural isolates. Compound 117 (3-(3-(dimethylamino)propoxy)-6,8-dihydroxy-2-methoxy-7-(3-methylbut-2-en-1-yl)-9H-xanthen-9-one) emerged as the lead candidate with IC50 of 0.1 µM. In silico ADMET profiling predicted superior intestinal absorption (>90%), compliance with Lipinski's Rule, and a favourable-toxicity profile (non-mutagenic, non-hepatotoxic) compared to the natural prototype α-mangostin. **Conclusion:** This integrated systematic review-cheminformatics approach, strengthened by transparent multi-criteria prioritization, identified Compound 117 as a promising pre-clinical candidate requiring further biological evaluation, including in vivo efficacy in rodent malaria models, in vitro cytotoxicity profiling, and experimental validation of predicted CYP interactions before advancing toward clinical translation.

Keywords: ADMET; Antimalarial; Lipinski's Rule of Five; Systematic Review; Xanthone

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INTRODUCTION

Despite ongoing global efforts, malaria remains a significant public health challenge, with an estimated 263 million cases and 597,000 deaths reported in 2023[1]. In response, the World Health Organization's Global Technical Strategy for Malaria 2016-2030 aims to reduce global malaria incidence and mortality rates by at least 90% by 2030, emphasizing universal access to prevention, diagnosis, and treatment. However, eradication efforts are hindered by rising artemisinin resistance and *hrp2/hrp3* gene deletions, which can lead to false-negative results in HRP2-based rapid diagnostic tests and increase the risk of incomplete case detection and control[2-4]. The persistence of malaria cases is partly driven by resistance to first-line antimalarial drugs, notably artemisinin, highlighting the urgent need for alternative therapeutic agents[5]. However, the development of new antimalarial drugs remains slow and resource-intensive. Cheminformatic analysis of previously reported bioactive compounds offers a strategic approach to accelerate drug discovery at a lower cost[6]. Among the promising candidates, xanthone and its derivatives have attracted considerable attention due to their diverse pharmacological properties, including antimalarial potential[7-8].

Xanthone, an aromatic oxygenated heterocycle with a dibenzo-γ-pyrone scaffold ($C_{13}H_8O_2$), originates from acetate and shikimic acid biosynthetic pathways in higher plants, and its derivatives exhibit structural diversity based on the type and position of substituents on the fused benzene rings[9]. Notably, many natural and synthetic xanthones have demonstrated antimalarial potential from in vitro studies[10-12]. This study addresses this gap through a dual-pronged strategy. First, we employed a PRISMA-guided systematic review to filter the vast library of natural and synthetic xanthones reported up to 2025, identifying derivatives with superior potency (IC50 < 1 μM). Second, we applied advanced in silico ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiling to "de-risk" these hits early in the discovery phase. By systematically prioritizing compounds that balance molar potency with favorable drug-likeness and safety profiles, this study highlights the compound that was rationally selected as the lead candidate, offering a specific blueprint for the development of next-generation synthetic xanthones.

METHODS

The systematic review was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. Special attention was paid to the specific challenges of synthesizing *in vitro* data, incorporating guidelines for preclinical data reliability and reporting to ensure the robustness of the findings.

1. Protocol registration and reporting

This systematic review was not prospectively registered in PROSPERO or other systematic review registries. The decision not to register was based on the study design, which focuses on comprehensive data collection and compilation of antimalarial activity data for xanthone compounds rather than synthesizing qualitative evidence from heterogeneous in vitro and in vivo studies. The primary objective is to establish a curated database of xanthone antimalarial properties for subsequent cheminformatics analysis, which falls outside the typical scope of protocol-driven clinical or intervention reviews. However, to ensure methodological transparency and reproducibility, this review was conducted in accordance with the PRISMA 2020 statement, with all

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methodological elements documented prior to data collection.

2. Search strategy and data sources

A comprehensive search was executed across three primary electronic databases: PubMed, Scopus, and Wiley Online Library. The search covered the literature from inception through September 17, 2025. The search strategy employed a combination of Medical Subject Headings (MeSH) and free-text keywords connected by Boolean operators to maximize sensitivity: ("xanthone" OR "xanthones") AND ("antimalarial" OR "malaria" OR "plasmodium" OR "antiplasmodial"). The protocol was designed in accordance with the PRISMA 2020 statement.

3. Eligibility criteria and selection process

We included original research articles published in English that reported in vitro (IC50 values) or in vivo (parasite suppression) antimalarial activity of natural or synthetic xanthones. Exclusion criteria included: (1) Review articles, book chapters, and conference proceedings; (2) Studies focusing solely on non-malaria parasites; (3) Studies lacking quantitative efficacy data; and (4) Purely computational docking studies without biological validation.

Citations were exported to Rayyan AI for duplicate removal and systematic screening. Two independent reviewers (JTW and KDAP) performed title and abstract screening in a blinded fashion, followed by full-text review of potentially eligible studies. Disagreements at each screening stage were documented and resolved through consensus-based discussion. When consensus could not be reached, a third senior reviewer (AKN) adjudicated the final inclusion decision. The entire disagreement resolution process was documented, including the number of conflicts at each stage and the rationale for final decisions.

4. Data extraction and compound categorization

Data were extracted into a standardized logbook, capturing: compound name/structure, source (natural/synthetic), Plasmodium strain (e.g., 3D7, K1, W2), assay method (e.g., HPIA, LDH), and potency (IC50). Potency was classified based on Batista et al.[14]: Highly Potent (IC50 < 1 µM), Promising (1–20 µM), Moderate (20–100 µM), Weak (100–200 µM), and Inactive (> 200 µM). Only "Highly Potent" compounds were selected for advanced in silico profiling.

5. Quality and Risk of Bias Assessment

To ensure the reliability of the included in vitro data, a Customized Quality Assessment Tool was developed for this study. This tool was adapted from principles outlined in the CRIS Guidelines (Checklist for Reporting In-vitro Studies) and the ToxRTool, but tailored specifically to address the nuances of antimalarial drug discovery assays. The assessment framework comprises 8 key domains, scored on a binary scale (Yes=1, Partial=0.5, No=0), resulting in a maximum possible score of 8 points. Quality rating: >7 points (high quality), 5-6 points (moderate quality), <5 points (low quality).

6. In silico ADMET and drug-likeness profiling

The chemical structures of the selected potent compounds were converted to Canonical SMILES format using ChemDraw Professional 16.0. These SMILES were submitted to the pkCSM web server (http://biosig.unimelb.edu.au/pkcsm/) to predict ADMET properties [13]. Key parameters analyzed included: Absorption (water solubility, Caco-2 permeability, and

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human intestinal absorption), Distribution (CNS permeability and volume of distribution), Metabolism (Cytochrome P450 3A4 and 2D6 inhibition/substrate potential), and Toxicity (AMES mutagenicity, hepatotoxicity, and hERG inhibition). Drug-likeness was assessed using Lipinski's Rule of Five (MW < 500, LogP < 5, H-bond donors < 5, H-bond acceptors < 10).

RESULTS AND DISCUSSION

1. Literature search, study selection, and collecting compounds

The screening process conducted in this study is illustrated in Figure 1. A total of 165 compounds were collected from 46 selected articles. Detailed data extracted from each article are presented in Table 1.

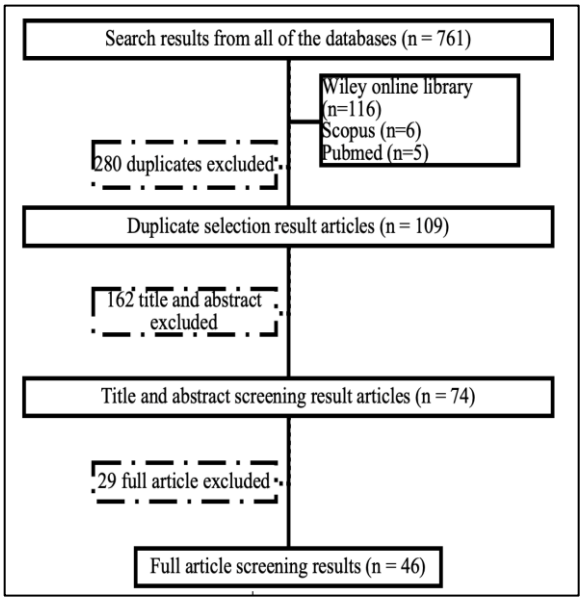

Figure 1. Flowchart for selecting articles

Compounds were identified, and antimalarial efficacy was evaluated based on the half-maximal inhibitory concentration (IC_{50}) of each test compound. According to the classification proposed by Batista et al. [14], compounds were categorized as highly potent ($IC_{50} < 1$ μM), promising (1 μM < $IC_{50} \leq 20$ μM), moderately active (20 μM < $IC_{50} \leq 100$ μM), weakly active (100 μM < $IC_{50} \leq 200$ μM), or inactive ($IC_{50} > 200$ μM). For in vivo assessments, antimalarial performance was determined by the percentage of parasitemia suppression, following the criteria outlined by Upegui et al.[15]: Chemosuppression above 80% was considered highly effective, between 50-80% as moderate, and below 50% as low efficacy.

2. Antimalarial activities from xanthone compounds, ADMET, and Lipinski rule of five by pkCSM

Malaria is caused by the Plasmodium protozoa, transmitted by female Anopheles mosquitoes, which inject sporozoites into the host's skin during a blood meal, initiating their journey to the liver via the bloodstream[58]. Among the five Plasmodium species infecting humans (P. *falciparum, P. vivax, P. malariae, P. ovale,* and *P. knowlesi*), *P. falciparum* predominates in Africa, while *P. Vivax* is most common in South America and Southeast Asia[59]. Although global malaria cases have declined in recent years[60], the disease remains prevalent in developing countries due to socio-economic and demographic factors that accelerate its transmission[61]. Its elimination remains suboptimal, partly due to the emergence of resistance to first-line therapies[5],[62-63].

The discovery of new antimalarial agents with proven efficacy, favorable pharmacokinetics, and acceptable toxicity profiles is crucial to support malaria eradication efforts. This study focuses on selecting xanthone derivatives with potent antimalarial activity based on in vitro and in vivo evaluations, followed by ADMET profiling to identify promising candidates for clinical development.

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Table 1. Antimalarial activity based on selected compounds

No	Compound	Sources	Assay	Organism	IC_{50}	Unit	Concl.	Ref
1	Xanthyl laurate	synthetic	HPIA	-	24.87	µM	moderate	[16]
2	Xanthyl myristate				33.46		moderate	
3	Xanthyl palmitate				24.24		moderate	
4	Xanthyl stearate				87.57		moderate	
5	Xanthyl oleate				46.66		moderate	
6	1-hydroxy-5,6,7 trimethoxyxanthone (dosis 1 mg)	Isolation of dried *Mammea siamensis* flower	In vivo 4-day suppressive test	*Pb* ANKA	21.91 ± 2.25	%	low	[17]
	1-hydroxy-5,6,7 trimethoxyxanthone (dosis 3 mg)				17.79 ± 2.31		low	
	1-hydroxy-5,6,7 trimethoxyxanthone (dosis 10 mg)				8.62 ± 1.21		low	
	1-hydroxy-5,6,7 trimethoxyxanthone		pfLDH	*Pf* K1	9.57 ± 1.59	µM	promising	[18]
7	xanthenol	synthetic	HPIA	-	35.97	µM	moderate	[19]
8	xanthene				55.011		moderate	
9	xanthone				581.63		inactive	
10	cochinchinone D	isolation of *Cratoxylum sumatranum* stem bark	pfLDH	*Pf* 3D7	4.79	µM	promising	[20]
11	cochinchinoxanthone				4.41		promising	
12	Cratoxyarborenone E	isolation of *C. glaucum* Korth leaves	pfLDH	*Pf* 3D7	5.82 ± 0.04	µM	promising	[21]
13	2-hydroxyxanthone	synthetic	Microscopic (candle jar method)	*Pf* 3D7	2.08	µM	promising	[22]
		isolation of dried *M. siamensis* flowers	pfLDH	*Pf* K1	74.97 ± 0.88	µM	74.97 ± 0.88	[18]
14	3,6-dihydroxy-4-methyl-9H-xanthen-9-one	synthetic	Parasite Culture Assay	*Pf* 3D7	0.71	µM	potent	[23]
15	3,4,6-trihydroxy-9H-xanthen-9-one				0.11		potent	
16	Mckeanianone A	isolation of *Garcinia mckeaniana* leaves	HIA	*Pf* TM4	6.2±0.4	µM	promising	[24]
				Pf K1	5.2±0.4		promising	
17	MckeanianoneB			*Pf* TM4	6.7±0.6		promising	
				Pf K1	6.4±0.5		promising	
18	Mckeanianone C			*Pf* TM4	6.0±1.1		promising	

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No	Compound	Sources	Assay	Organism	IC_{50}	Unit	Concl.	Ref
				Pf K1	6.6±0.7		promising	
19	(Z)-2-methyl-4-(5,8,9-trihydroxy-2,2-dimethyl-12-(3-methylbut-2-en-1-yl)-6-oxo-2H,6H-pyrano[3,2-b]xanthen-7-yl)but-2-en-1-yl acetate			*Pf* TM4	8.5±1.2		promising	
				Pf K1	3.6±1.7		promising	
20	(Z)-5,8,9-trihydroxy-7-(4-hydroxy-3-methylbut-2-en-1-yl)-2,2-dimethyl-12-(3-methylbut-2-en-1-yl)-2H,6H-pyrano[3,2-b]xanthen-6-one			*Pf* TM4	8.3±0.9		promising	
				Pf K1	7.3±1.2		promising	
21	Mckeanianone D	isolation of *G. mckeaniana* branches		*Pf* TM4	15.1±3.9		promising	
				Pf K1	14.3±1.8		promising	
22	Mckeanianone E			*Pf* TM4	27.7±3.4		moderate	
				Pf K1	25.7±2.3		moderate	
23	1,3,6-trihydroxy-2 (3-methylbut-2-enyl)-7-methoxy-8-(3-methylbut-2- enyl)xanthen-9-on	isolation of *G. parvifolia* (Miq) Miq Stem Bark	HPIA	-	453.61	µM	inactive	[25]
24	5-hydroxysterigmatocystin	isolation of scale insect fungus *Aschersonia coffeae* Henn.	GFP	*Pf* K1	25.12	µM	moderate	[26]
25	5-hydroxy-3-methoxyxanthone	isolation of *Hypericum lanceolatum* stem bark	pfLDH	*Pf* W2mef	3.26 ± 0.08	µM	promising	[27]
				Pf SH4	1.43 ± 0.48		promising	
26	3-Hydroxy-5-methoxyxanthone			*Pf* W2mef	33.84 ± 0.20		moderate	
				Pf SH4	34.09 ± 0.12		moderate	
27	gerontoxanthone I	isolation of *C. maingayi* and *C. Cochinchinense*	HIA	*Pf* K1	4.237	µM	promising	[28]
28	macluraxanthone				3.422		promising	
		isolation of *G. bancana* Miq. stem bark	pfLDH	*Pf* 3D7	4.28 ± 0.10		promising	[8]
29	formoxanthone C	isolation of *C. maingayi* and *C. Cochinchinense*	HIA	*Pf* K1	3.001		promising	[28]
30	fuscaxanthone E				7.938		promising	
31	Vismione B				1.862		promising	
32	Vismione F				4.758		promising	
33	Vismione E				10.970		promising	

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No	Compound	Sources	Assay	Organism	IC_{50}	Unit	Concl.	Ref
34	1,5-dihydroxy-3-methoxy 4-isoprenylxanthone	isolation of *Chrysochlamys tenuis* leaves	fluorometric method	*Pf* W2	30.7±8.7	µM	moderate	[29]
35	6,11-dihydroxy-3,3-dimethyl-5-(3-methylbut-2-en-1-yl)-7a,11a-dihydro-3H,7H-pyrano[2,3-c]xanthen-7-one				41.0±16.8		moderate	
36	2,6,8-trihydroxy-5,7-bis(3-methylbut-2-en-1-yl)-4a,9a-dihydro-9H-xanthen-9-one				19.7±1.8		promising	
37	4,6,8-trihydroxy-5,7-bis(3-methylbut-2-en-1-yl)-4a,9a-dihydro-9H-xanthen-9-one				19.7±1.8		promising	
38	5,10-dihydroxy-2,2-dimethyl-12-(3-methylbut-2-en-1-yl)-6a,10a-dihydro-2H,6H-pyrano[3,2-b]xanthen-6-one				15.9±3.7		promising	
		isolation of *Pentadesma butyraceae* stem bark	HIA	*Pf* FcB1	7,63	µM	promising	[30]
39	gerontoxanthone C	isolation of *G. bancana* Miq. stem bark	pfLDH	*Pf* 3D7	5.52 ± 0.10	µM	promising	[31]
40	isojacareubin				11.45 ± 0.30		inactive	
41	α-Mangostin	isolation of *G. mangostana pericarp*	pfLDH	*Pf* K1	2.2	µM	promising	[34]
		synthetic	SYBR green assay	*Pf* 3D7	17.9		promising	[10]
				Pf K1	9.7		promising	
		synthetic	pfLDH	*Pf* D6	11.40±0.00		promising	[11]
				Pf W2	10.20±2.00		promising	
		isolation of *Allanblackia monticola* leaves	HIA	*Pf* F32	6.4		promising	[33]
				Pf FcM29	5.3		promising	
		synthetic	HIA	*Pf* K1	17 ± 1		promising	[34]
		isolation of *A. monticola* STANER L.C. stem bark	Parasite Culture Assay	*Pf* F32	5.36	µM	promising	[36]
				Pf FcM29	6.33		promising	
			fluorometric method	*Pf* 3D7	36.10±4.9	µM	moderate	[15]
				Pf FCR3	0.20±0.01		potent	

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No	Compound	Sources	Assay	Organism	IC_{50}	Unit	Concl.	Ref
		isolation of *G. mangostana* pericarp	In vivo (100 mg 1x7 days)	*Pb*	25.2±8.5	%	low	
42	caloxanthone C	isolation of *Calophyllum caledonicum*	HIA	*Pf* FcB1	3.439	µM	promising	[37]
43	demethylcalabaxanthone				2.381		promising	
44	calothwaitesixanthone				2.24		promising	
45	calozeyloxanthone				11.63		promising	
46	dombakinaxanthone				4.26		promising	
47	6-deoxy-g-mangostin				2.10		promising	
48	pancixanthone A	isolation of *G. vieillardii*			5.12		promising	
49	isocudraniaxanthone B				9.35		promising	
50	isocudraniaxanthone A				7.01		promising	
51	2-deprenylrheediaxanthone B				10.22		promising	
52	1,4,5-trihydroxyxanthone				14.33		promising	
53	1,3,5-trihydroxyxanthone	synthetic			65		moderate	
54	Ravenelin	isolation of fungus *E. rostratum*	SYBR green assay	*Pf* 3D7	3.4±0.4	µM	promising	[12]
55	9-hydroxycalabaxanthone (5,9-Dihydroxy-8-methoxy-2,2-dimethyl-7-(3-methyl-2-butenyl) 2H,6H-pyranol[-,2-b] xanthen-6-6one)	synthetic	SYBR green assay	*Pf* 3D7	1.5	µM	promising	[10]
				Pf K1	1.2		promising	
56	β-Mangostin	synthetic	pfLDH	*Pf* D6	7.42±0.49	µM	promising	[11]
				Pf W2	4.71±0.67		promising	
57	3-Isomangostin			*Pf* D6	7.88±1.88		promising	
				Pf W2	6.15±2.41		promising	
		isolation of *P. butyracea* stem bark	HIA	*Pf* FcB1	7,56	µM	promising	[30]
58	1,5-dihydroxy-3,6-dimethoxy-2,7-diprenylxanthone	isolation of *G. griffithii* stem bark	pfLDH	*Pf* Ghana	7.25	µM	promising	[38]
59	3b-hydroxy-23-oxo 9,16-lanostadien-26-oicacidorgarcihombronane D				7.71		promising	
60	3,6-Bis--(N,N-diethylamino) ethoxyxanthon	synthetic	HIA	*Pf* D6	2.2±0.5	µM	promising	[39]

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No	Compound	Sources	Assay	Organism	IC_{50}	Unit	Concl.	Ref
61	3,6-Bis--(N,N-diethylamino) propoxyxanthone				1.5±0.7		promising	
62	3,6-Bis--(N,N-diethylamino) butoxyxanthone				0.65±0.08		potent	
63	3,6-Bis-ε-(N,N-diethylamino) amyloxyxanthone				0.10±0.05		potent	
				Pf W2	0.12±0.07		potent	
				Pf F86	0.11±0.06		potent	
64	3,6-Bis--(N,N-diethylamino) hexyloxyxanthone			*Pf* D6	0.07±0.02		potent	
				Pf W2	0.07±0.03		potent	
				Pf F86	0.07±0.02		potent	
65	3,6-Bis--(N,N-diethylamino) octyloxyxanthone			*Pf* D6	0.07±0.02		potent	
66	1-Hydroxy-7-methoxyxanthone	isolation of *M. ferrea* roots	pfLDH	*Pf* K1	345.56 ± 3.51	µM	inactive	[40]
67	1-Hydroxy-5-methoxyxanthone				163.75 ± 1.71		low	
68	1,6-Dihydroxyxanthone				226.13 ± 1.32		inactive	
		isolation of dried *M. siamensis* flowers			47.94 ± 5.16		moderate	[18]
		synthetic	Parasite Culture Assay	*Pf* 3D7	71.78±0.31		moderate	[41]
				Pf FCR3	81.77±5.78		moderate	
		isolation of *G. vieillardii* stem bark	HIA	*Pf* FcB1	18.42	µM	promising	[37]
69	1,5-Dihydroxyxanthone	isolation of *M. ferrea* roots	pfLDH	*Pf* K1	106.98 ± 4.41	µM	low	[40]
70	Rheediachromenoxanthone				106.98 ± 4.41		low	
71	1,5-Dihydroxy-3-methoxyxanthone				198.27 ± 2.43		low	
72	2,5-Dihydroxy-1-methoxyxanthone				46.30 ± 1.65		moderate	
73	Griseoxanthone C	isolation of *Dacryodes edulis* leaves and stem bark	SYBR green assay	*Pf* 3D7	91.91	µM	moderate	[42]
				Pf Dd2	91.91		moderate	

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No	Compound	Sources	Assay	Organism	IC_{50}	Unit	Concl.	Ref
74	3,6-bis-(x N,N-diethylaminoamyloxy)-4,5-difluoroxanthone	synthetic	fluorometric method	*Pf* D6	0.093	µM	potent	[43]
				Pf W2	0.15		potent	
75	1,3,8-trihydroxy-6-methylxanthone (dosis 20 mg/kg.day)	synthetic	In vivo 4-day suppressive test	*Pb* ANKA	17.0	%	promising	[44]
76	1,3,6-trihydroxy-8-methylxanthone (norlichexanthone) (dosis 20 mg/kg.day)				15.0		promising	
77	1,3-dihydroxy-xanthone (dosis 20 mg/kg.day)				22.9		moderate	
78	1,3,6,8-tetrahydroxyxanthone (dosis 20 mg/kg.day)				8.0		promising	
79	7-0-Methylgarcinone E	isolation of *G. cowa* Roxb. stem bark	HIA	NA	5.23	µM	promising	[45]
80	cowanin				6.28		moderate	
81	cowanol				3.24		inactive	
82	cowaxanthone				3.65		promising	
83	4,5-Dihydroxy-3-methoxylxanthone	isolation of dried *M. siamensis* flowers	pfLDH	*Pf* K1	68.55 ± 2.54	µM	moderate	[18]
84	4-Hydroxyxanthone				41.67 ± 2.23		moderate	
85	1,7-Dihydroxyxanthone				45.00 ± 3.51		moderate	
		isolation of *G. dulcis* bark	HIA	NA	17,02	µM	promising	[46]
86	3,4,5-Trihydroxyxanthone	isolation of dried *M. siamensis* flowers	pfLDH	*Pf* K1	15.48 ± 2.63	µM	promising	[18]
		synthetic	HIA	*Pf* D6	45 3		moderate	[47]
87	5-Hydroxy-1-methoxyxanthone	isolation of dried *M. siamensis* flowers	pfLDH	*Pf* K1	29.32 ± 4.44	µM	moderate	[18]
88	1,5-Dihydroxy 6-methoxyxanthone				22.27 ± 1.67		moderate	
89	1,8-Dihydroxy-3,7-dimethoxyxanthone	isolation of *Andrographis paniculata* roots	pfLDH	*Pf* FSG	111.11	µM	low	[48]
			Parasite Culture Assay		52.08		moderate	
90	4,8-Dihydroxy-2,7-dimethoxyxanthone		pfLDH		111.11		low	
			Parasite Culture Assay		31.25		moderate	

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No	Compound	Sources	Assay	Organism	IC_{50}	Unit	Concl.	Ref
91	1,2-Dihydroxy-6,8-dimethoxyxanthone		pfLDH		13.89		promising	
			Parasite Culture Assay		10.42		inactive	
			In vivo 4-day suppressive test (30 mg/kg)	*Pb* NK65	62.1	%	moderate	
92	3,7,8-Trimethoxy-8-hydroxyxanthone		pfLDH	*Pf* FSG	105,61	µM	low	
			Parasite Culture Assay		151,82		low	
93	MDN-0185	isolation of *Micromonospora* sp	pfLDH	*Pf* 3D7	0.009	µM	potent	[49]
94	Tovophyllin A	isolation of *A. monticola* leaves	HIA	*Pf* F32	5.0	µM	promising	[33]
				Pf FcM29	5.6		promising	
95	Allanxanthone C			*Pf* F32	5.5		promising	
				Pf FcM29	6.8		promising	
			Parasite culture Assay	*Pf* F32	6.9		promising	[36]
				Pf FcM29	5.6		promising	
96	1,7-Dihydroxy-3-methoxy-2 (3-methylbut-2-enyl)xanthone		HIA	*Pf* F32	5.8		promising	(33)
				Pf FcM29	8.0		promising	
97	gaboxanthone	isolation of *Symphonia globulifera* seed shells	Parasite Culture Assay	*Pf* W2	3.53	µM	promising	[50]
98	Symphonin				1.29		promising	
99	Globuliferin				3.86		promising	
100	2,5-dihydroxyxanthone	synthetic	HIA	*Pf* D6	53±10	µM	moderate	[47]
101	4,5-dihydroxyxanthone				28±6		moderate	
102	2,3,4-trihydroxyxanthone				36±7		moderate	
103	3,4,6-trihydroxyxanthone				35±4		moderate	
104	2,3,4,5-tetrahydroxyxanthone				9.0±1.0		promising	
105	2,3,4,6-tetrahydroxyxanthone				30±15		moderate	
106	3,4,5,6-tetrahydroxyxanthone				1.3±0.7		promising	
107	2,3,4,5,6-pentahydroxyxanthone				0.7±0.5		Potent	

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No	Compound	Sources	Assay	Organism	IC_{50}	Unit	Concl.	Ref
108	1,3,5,6,7-pentahydroxyxanthone				6.5±0.5		Promising	
109	1,2,3,5,6,7-hexahydroxyxanthone				54		moderate	
110	2,3,4,5,6,7-hexahydroxyxanthone				0.2±0.1		potent	
111	garciniaxanthone I	isolation of *G. dulcis* barks	HIA	NA	2,13	µM	promising	[46]
112	smeathxanthone A	isolation of *G. polyantha* roots	Parasite Culture Assay	*Pf* NF54	2.5 - 4.1	µM	promising	[51]
113	smeathxanthone B							
114	chefouxanthone							
115	3-(2-(diethylamino)ethoxy)-6,8-dihydroxy-2-methoxy-7-(3-methyl-3l5-buta-2,3-dien-1-yl)-1-(3-methylbut-2-en-1-yl)-9H-xanthen-9-one	synthetic	HIA	*Pf* K1	0.3 ± 0.02	µM	potent	[34]
116	3-(2-(dimethylamino)ethoxy)-6,8-dihydroxy-2-methoxy-7-(3-methyl-3l5-buta-2,3-dien-1-yl)-1-(3-methylbut-2-en-1-yl)-9H-xanthen-9-one				0.6 ± 0.03		potent	
117	3-(3-(dimethylamino)propoxy)-6,8-dihydroxy-2-methoxy-7-(3-methyl-3l5-buta-2,3-dien-1-yl)-1-(3-methylbut-2-en-1-yl)-9H-xanthen-9-one				0.1 ± 0.01		potent	
118	3-(3-(diethylamino)-2-hydroxypropoxy)-6,8-dihydroxy-2-methoxy-7-(3-methyl-3l5-buta-2,3-dien-1-yl)-1-(3-methylbut-2-en-1-yl)-9H-xanthen-9-one				0.05 ± 0.005		potent	
119	3-(3-(dimethylamino)-2-hydroxypropoxy)-6,8-dihydroxy-2-methoxy-7-(3-methyl-3l5-buta-2,3-dien-1-yl)-1-(3-methylbut-2-en-1-yl)-9H-xanthen-9-one				0.6 ± 0.03		potent	
120	1-hydroxy-3,6-bis(2-hydroxy-3-(isopropylamino)propoxy)-7-methoxy-2,8-bis(3-methylbut-2-en-1-yl)-9H-xanthen-9-one				0.6 ± 0.03		potent	

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No	Compound	Sources	Assay	Organism	IC_{50}	Unit	Concl.	Ref
121	(E)-2-(3,7-dimethylocta-2,6-dien-1-yl)-1,3,6-trihydroxy-7-methoxy-8-(3-methylbut-2-en-1-yl)-9H-xanthen-9-one	isolation of *P. butyraceae* stem bark	HIA	*Pf* FcB1	6.28	µM	promising	[30]
122	5,8,9-trihydroxy-2,2-dimethyl-7,10-bis(3-methylbut-2-en-1-yl)-2H,6H-pyrano[3,2-b]xanthen-6-one				5.84		promising	
123	2,5,9,11-tetrahydroxy-3,3-dimethyl-6,10-bis(3-methylbut-2-en-1-yl)-2,3-dihydropyrano[3,2-a]xanthen-12(1H)-one				NA		NA	
124	(E)-3,6,8-trihydroxy-1-(7-hydroxy-3,7-dimethyloct-2-en-1-yl)-2-methoxy-9H-xanthen-9-one				23.36		moderate	
125	5,9-dihydroxy-8-methoxy-2,2-dimethyl-7-(3-methylbut-2-en-1-yl)-2H,6H-pyrano[3,2-b]xanthen-6-one				4.66		promising	
126	(E)-1-(3,7-dimethyloct-2-en-1-yl)-3,6,8-trihydroxy-2-methoxy-9H-xanthen-9-one				8.25		promising	
127	garcinone E				6.03		promising	
		isolation of *P. butyraceae* pericarp		*Pf* W2	0.41	µM	potent	[52]
128	5,9,11-trihydroxy-3,3-dimethyl-6,10-bis(3-methylbut-2-en-1-yl)-2,3-dihydropyrano[3,2-a]xanthen-12(1H)-one	isolation of *P. butyraceae* stem bark		*Pf* FcB1	6.03	µM	promising	[30]
129	pentadexanthone	isolation of *P. butyraceae* pericarp	HIA	*Pf* W2	3.0	µM	promising	[52]
130	cratoxylone				2.89		promising	
131	1,5,6-trihydroxy-3-methoxy-7-geranylxanthone	isolation of *Rheedia acuminata* trunk bark	HIA	*Pf* FcB1	10.5	µM	promising	[53]
132	12b-hydroxy-des-D-garcigerrin A				15.1		promising	
		isolation of *G. dulcis* bark		NA	6.67	µM	promising	
133	5,12,14-trihydroxy-2,2,10,10-tetramethyl-2H,6H,10H-dipyrano[3,2-b:2',3'-i]xanthen-6-one	isolation of *R. acuminata* trunk bark		*Pf* FcB1	11.4	µM	promising	

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No	Compound	Sources	Assay	Organism	IC_{50}	Unit	Concl.	Ref
134	Chaetoxanthone A	isolation of the marine-derived fungus *Chaetonium* sp.	HIA	*Pf* K1	9.45	µM	promising	[54]
135	Chaetoxanthone B				1.41		promising	
136	Chaetoxanthone C				10.24		promising	
137	6,11-Dihydroxy-3-methyl-3-(4-methylpent-3-enyl)pyrano[2,3-c] xanthen-7(3H)-one	isolation of *G. livingstonei* root bark	pfLDH	*Pf* Ghana	52±17	µM	moderate	[55]
138	4[(E)-3,7-Dimethylocta-2,6-dienyl]-1,3,5-trihydroxy-9H-xanthen 9-one				59.0±8.7		moderate	
139	1,4,5-Trihydroxy-3-(3-methylbut-2-enyl)-9H-xanthen-9-one				10.0±0.1		promising	
140	Garcilivin A				6.7±1.5		promising	
141	Garcilivin C				>64		moderate	
142	1-O-methylsymphoxanthone	isolation of *G. dulcis* bark	HIA	NA	7.31	µM	promising	[46]
143	symphoxanthone				11.43		promising	
144	norcowanin	isolation of *A. monticola* STANER L.C. stem bark	Parasite Culture Assay	*Pf* F32	7.07	µM	promising	[36]
				Pf fcM29	22.47		moderate	
145	1,6,8-Trihydroxyxanthone	synthetic	Parasite Culture Assay	*Pf* 3D7	6.10±2.01	µM	promising	[41]
				Pf FCR3	6.76±2.38		promising	
			HPIA	-	2854	µM	inactive	
146	1,5,6-Trihydroxyxanthone		Parasite Culture Assay	*Pf* 3D7	27.64±0.19	µM	moderate	
				Pf FCR3	64.09±5.08		moderate	
147	1-Hydroxy-5-chloroxanthone			*Pf* 3D7	85,30±0.87		moderate	
				Pf FCR3	89.85±7.69		moderate	
148	1,6-Dihydroxy-5-methylxanthone			*Pf* 3D7	46.69±0.29		moderate	
				Pf FCR3	59.73±0.78		moderate	
149	gamma-mangostin	isolation *G. mangostana* pericarp	fluorometric method	*Pf* 3D7	12.40±1.0	µM	promising	[35]
				Pf FCR3	>121.20±1.0		low	
			In vivo (100 mg 1x7 days)	*Pb*	22.4±6.9	%	moderate	
150	6-chloro-1-{[2-(diethylamino) ethyl]amino}-9H-xanthen-9-one	synthetic	Parasite Culture Assay	*Pf* 3D7	3.7±0.5	µM	promising	[56]
				Pf Dd2	3.9±0.3		promising	

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No	Compound	Sources	Assay	Organism	IC_{50}	Unit	Concl.	Ref
151	6-chloro-1-((2-(diethylamino)ethyl)amino)-9H-xanthen-9-one			*Pf* 3D7	2.4±0.2		promising	
				Pf Dd2	13.5±0.9		promising	
152	3,4,5,6-tetrachloro-1-((2-(diethylamino)ethyl)amino)-9H-xanthen-9-one			*Pf* 3D7	4.4±0.7		promising	
				Pf Dd2	25.8±1.12		moderate	
153	4,5,6-trichloro-1-((2-(diethylamino)ethyl)amino)-9H-xanthen-9-one			*Pf* 3D7	9.9±0.8		promising	
				Pf Dd2	13.6±1.0		promising	
154	3,5,6-trichloro-1-((2-(diethylamino)ethyl)amino)-9H-xanthen-9-one			*Pf* 3D7	2.8±0.5		promising	
				Pf Dd2	33.3±0.3		moderate	
155	3,4,6-trichloro-1-((2-(diethylamino)ethyl)amino)-9H-xanthen-9-one			*Pf* 3D7	1.7±0.5		promising	
				Pf Dd2	66.4±0.7		moderate	
156	3,4,5-trichloro-1-((2-(diethylamino)ethyl)amino)-9H-xanthen-9-one			*Pf* 3D7	7.1±0.8		promising	
				Pf Dd2	9.7±0.2		promising	
157	4,6-dichloro-1-((2-(diethylamino)ethyl)amino)-9H-xanthen-9-one			*Pf* 3D7	18.1±1.3		promising	
				Pf Dd2	38.3±0.6		moderate	
158	3,5-dichloro-1-((2-(diethylamino)ethyl)amino)-9H-xanthen-9-one			*Pf* 3D7	2.25±0.7		promising	
				Pf Dd2	46.6±2.3		moderate	
159	3,6-dichloro-1-((2-(diethylamino)ethyl)amino)-9H-xanthen-9-one			*Pf* 3D7	12.5±0.8		inactive	
				Pf Dd2	13.7±0.3		inactive	
160	5,6-dichloro-1-((2-(diethylamino)ethyl)amino)-9H-xanthen-9-one			*Pf* 3D7	3.7±0.5		inactive	
				Pf Dd2	8.1±0.6		inactive	
161	5-chloro-1-((2-(diethylamino)ethyl)amino)-9H-xanthen-9-one			*Pf* 3D7	4.1±0.7		inactive	
				Pf Dd2	5.9±0.3		promising	
162	5-O-methylcelebixanthone	isolation of *C. cochinchinense* (LOUR.) BLUME roots	HIA	*Pf* K1	8.99	µM	promising	[57]
163	celebixanthone				14.33		promising	
164	cochinchinone A				16.06		promising	
165	cochinchinone C				6.34		promising	

Abbreviation: HPIA = Heme polymerization inhibitory assay, Pb = *Plasmodium berghei*, pfLDH = *Plasmodium falciparum* lactate dehydrogenase, Pf = *Plasmodium falciparum*, HIA = Hypoxanthine inhibitory assay, GFP = Green fluorescent protein, NA: not available in the article.

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This review identified 121 xanthone derivatives from both natural isolates and synthetic sources, with most originating from the genus *Garcinia* (*Clusiaceae)*[64]. Xanthones are widely distributed across various plant parts, including leaves, stems, roots, flowers, and fruit pericarps, as well as particular fungi, highlighting their diverse biological sources and potential for antimalarial drug development. Structurally, xanthones are plant-derived phenolic compounds with a C6-C1-C6 tricyclic backbone, comprising two aromatic rings formed via distinct biosynthetic pathways: the acetate-derived A-ring (carbons 1-4) and the shikimate-derived B-ring (carbons 5-8) [65]. Their structural diversity, driven by various substituents, allows xanthones to be classified into several subgroups: simple xanthones, xanthone glycosides, prenylated xanthones, xanthonolignoids, bisxanthones, and miscellaneous xanthones[66].

Various in vitro assays have been employed to assess the antimalarial activity of xanthone derivatives, including heme polymerization inhibition assay (HPIA), hypoxanthine incorporation assay (HIA), parasite lactate dehydrogenase (pfLDH) assay, green fluorescent protein (GFP) tagging, fluorometric and SYBR Green I assays, as well as traditional parasite culture and microscopic examination. HPIA targets the parasite's heme detoxification pathway by blocking the conversion of toxic heme into inert hemozoin, leading to parasite death[67]. HIA measures parasite proliferation by tracking the incorporation of radiolabeled hypoxanthine into nucleic acids[68]. The pfLDH assay evaluates parasite viability by monitoring lactate production, a key step in ATP generation [69]. SYBR Green I, GFP, and fluorometric methods detect parasite DNA within infected red blood cells using fluorescence-based quantification[70]. Meanwhile, parasite culture assays rely on Giemsa-stained blood smears observed microscopically to determine parasitemia [71]. For in vivo evaluation, the 4-day suppressive test is commonly used, in which the efficacy of compounds is assessed by measuring parasitemia reduction in *Plasmodium berghei* ANKA-infected mice following administration of test compounds [72].

Several *Plasmodium falciparum* strains have been widely used in in vitro antimalarial research, including 3D7, D6, Dd2, F32, F86, FcB1, FcM29, FCR3, FSG, Ghana, K1, NF54, SH4, SHF4, W2, W2mef, and TM4. Among these, the 3D7 strain is the most frequently employed for evaluating the antimalarial activity of xanthone derivatives (30 compounds), owing to its known sensitivity to chloroquine. This sensitivity is reflected in its low inhibitory concentrations and is attributed to mutations that significantly reduce glutathione reductase activity, thereby impairing the parasite's ability to counter oxidative stress[73]. Other strains such as NF54, D6, F32, and TM4 are classified as chloroquine-sensitive, whereas Dd2, FcB1, and FcM29 exhibit chloroquine resistance, and K1, W2, FCR3, and W2mef are recognized as multidrug-resistant strains[74]. In vivo, *Plasmodium berghei* is commonly used due to its rodent-specific infection profile, making it a safe and practical model for investigating malaria pathogenesis and therapeutic efficacy[75].

Eighteen xanthone derivatives were identified as potent antimalarial candidates based on various assay methods and *Plasmodium* strains. Compounds **14, 15**, and **114** were tested in parasite culture assays against the 3D7 and NF54 strains, both known for their chloroquine sensitivity (23),(51). Compound **9** showed intense activity in the pfLDH assay against 3D7[49].

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Compound **41** (α-mangostin) was uniquely profiled across multiple methods and strains, including fluorometric, pfLDH, SYBR Green, HIA, and parasite culture assays, showing consistent potency against resistant strains such as FCR3, K1, FcM29, and moderate activity in 3D7 [10-11],[15],[32-34],[36]. Compound **74** was evaluated fluorometrically against D6 and W2[43]. Several compounds **62, 63, 64, 65, 107**, and **115–120** were tested using the hypoxanthine incorporation assay (HIA) across strains including D6, W2, F86, and K1 [34],[47],[76]. Compound **127** (garcinone E) was assessed via HIA against W2 and FcB1, with promising results despite FcB1 being less commonly used[30],[52]. Overall, compounds **41** and **127** stood out for their broad-spectrum activity across multiple strains and assay platforms.

3. Toxicity, pharmacokinetics, and Lipinski rule of five by pkCSM

Potent antimalarial compounds were collected, and their corresponding SMILES notations were retrieved using PubMed or ChemDraw (Table 2). The toxicity profiles, pharmacokinetic parameters, and compliance with Lipinski's Rule of Five for each compound, as predicted by pkCSM, are summarized in Table 3.

To be successfully developed into a therapeutic agent, an active compound must exhibit favorable pharmacokinetic properties, as these are key determinants of its efficacy and safety[77]. In recent years, in silico ADMET prediction methods have gained prominence in drug discovery due to their cost-effectiveness and ability to rapidly evaluate pharmacokinetic profiles without the need for extensive laboratory resources [78]. A wide array of in silico ADMET tools is now available, ranging from commercial platforms such as CASE ULTRA, DEREK, META-PC, METEOR, PASS, and GUSAR to freely accessible online servers like ADMETlab, admetSAR, pkCSM, and SwissADME, each offering rapid profiling capabilities to support early-stage decision-making[79]. In this study, pkCSM was selected as the ADMET screening platform due to its accessible web-based interface and robust predictive models, which assist medicinal chemists in optimizing the balance between potency, safety, and pharmacokinetic performance (http://structure.bioc.cam.ac.uk/pkcsm)[13].

This study evaluates the drug-likeness of xanthone derivatives using 22 pharmacokinetic and toxicity-related parameters, including molecular weight, LogP, hydrogen bond acceptors and donors, Caco-2 permeability, solubility, human intestinal absorption, volume of distribution (VDss), blood–brain barrier (BBB) and central nervous system (CNS) permeability, CYP450 substrate and inhibition profiles (CYP2D6, CYP3A4, CYP1A2, CYP2C19, CYP2C9), total clearance, renal OCT2 substrate status, AMES toxicity, rat acute toxicity, and hepatotoxicity. These parameters reflect both Lipinski's Rule of Five and comprehensive ADMET profiling. A total of 18 xanthone-based compounds with reported antimalarial activity were selected from previous literature and screened against these criteria (Table 2). The most promising candidate was identified based on its compliance with Lipinski's rules, favorable absorption characteristics, and absence of AMES toxicity and hepatotoxicity.

The "Rule of Five" serves as a predictive guideline for assessing the oral bioavailability of biologically active compounds[80]. According to this principle, a substance is more likely to be effectively absorbed through the gastrointestinal tract if it adheres to specific physicochemical thresholds.

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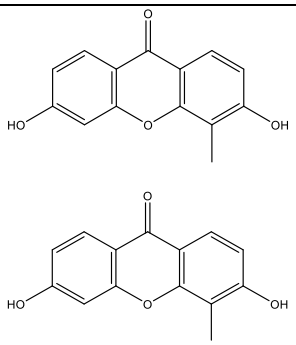
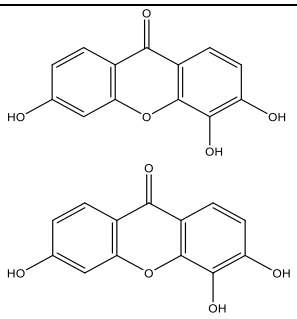
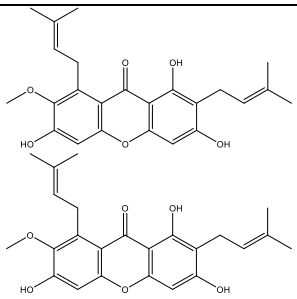
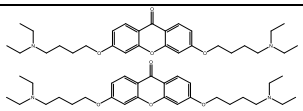
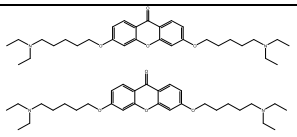
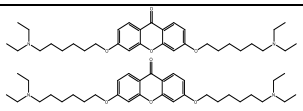
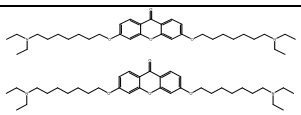
Table 2. List of potent antimalarial xanthone derivatives

No	Compound	CID	IUPAC name	Structure	SMILES
14	3,6-dihydroxy-4-methyl-9H-xanthen-9-one	-	3,6-dihydroxy-4-methylxanthen-9-one		O=C1C2=C(OC3=C1C=CC(O)=C3)C(C)=C(O)C=C2
15	3,4,6-trihydroxy-9H-xanthen-9-one	-	3,4,6-trihydroxy-9H-xanthen-9-one		O=C1C2=C(OC3=C1C=CC(O)=C3)C(O)=C(O)C=C2
41	α-mangostin	5281650	1,3,6-trihydroxy-7-methoxy-2,8-bis(3-methylbut-2-enyl)xanthen-9-one		CC(=CCC1=C(C2=C(C=C1O)OC3=C(C2=O)C(=C(C(=C3)O)OC)CC=C(C)C)O)C
62	3,6-Bis--(N,N-diethylamino) butoxyxanthone	-	3,6-bis(4-(diethylamino)butoxy)-9H-xanthen-9-one		O=C1C2=CC=C(OCCCCN(CC)CC)C=C2OC3=CC(OCCCCN(CC)CC)=CC=C31
63	3,6-Bis-ε-(N,N-diethylamino) amyloxyxanthone	-	3,6-bis((5-(diethylamino)pentyl)oxy)-9H-xanthen-9-one		O=C1C2=CC=C(OCCCCCN(CC)CC)C=C2OC3=CC(OCCCCCN(CC)CC)=CC=C31
64	3,6-Bis--(N,N-diethylamino) hexyloxyxanthone	-	3,6-bis((6-(diethylamino)hexyl)oxy)-9H-xanthen-9-one		O=C1C2=CC=C(OCCCCCCN(CC)CC)C=C2OC3=CC(OCCCCCCN(CC)CC)=CC=C31
65	3,6-Bis--(N,N-diethylamino) octyloxyxanthone	-	3,6-bis((7-(diethylamino)heptyl)oxy)-9H-xanthen-9-one		O=C1C2=CC=C(OCCCCCCCN(CC)CC)C=C2OC3=CC(OCCCCCCCN(CC)CC)=CC=C31

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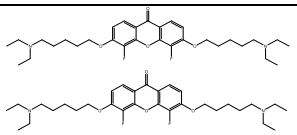
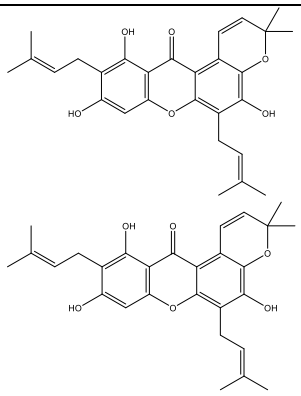
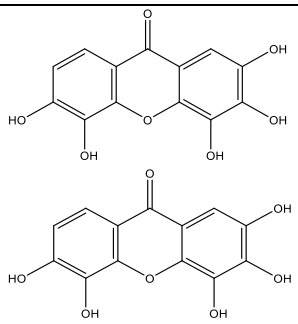
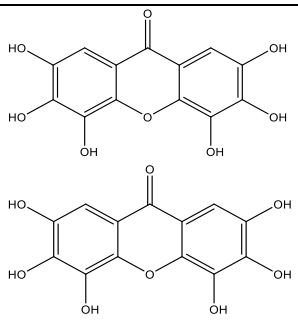
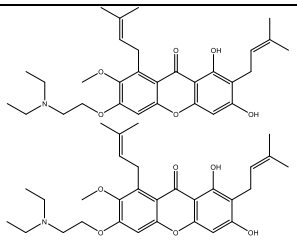
No	Compound	CID	IUPAC name	Structure	SMILES
74	3,6-bis-(x N,N-diethylaminoamyl oxy)-4,5-difluoroxanthone	-	3,6-bis((5-(diethylamino)pentyl)oxy)-4,5-difluoro-9H-xanthen-9-one		O=C1C2=C(C(F)=C(OCCCCCN(CC)CC)C=C2)OC3=C(F)C(OCCCCCN(CC)CC)=CC=C31
93	MDN-0185	139590076	(2R,11S,13R,20S,21R,25R)-2,21,28-trihydroxy-7-methyl-14,16,19-trioxa-6-azaheptacyclo[15.11.1.02,11.04,9.013,29.018,27.020,25]nonacosa-1(29),4(9),7,17,22,27-hexaene-3,5,10,26-tetrone		CC(=CCC1=C(C2=C(C=C1O)OC3=C(C(=C4C(=C3C2=O)C=CC(O4)(C)C)O)CC=C(C)C)O)C
107	2,3,4,5,6-pentahydroxyxanthone	9993573	2,3,4,5,6-pentahydroxyxanthen-9-one		C1=CC(=C(C2=C1C(=O)C3=CC(=C(C(=C3O2)O)O)O)O)O
114	2,3,4,5,6,7-hexahydroxyxanthone	9838994	2,3,4,5,6,7-hexahydroxyxanthen-9-one		C1=C2C(=C(C(=C1O)O)O)OC3=C(C(=C(C=C3C2=O)O)O)O
115	3-(2-(diethylamino)ethoxy)-6,8-dihydroxy-2-methoxy-7-(3-methyl-3l5-buta-2,3-dien-1-yl)-1-(3-methylbut-2-en-1-yl)-9H-xanthen-9-one	-	3-(2-(diethylamino)ethoxy)-6,8-dihydroxy-2-methoxy-1,7-bis(3-methylbut-2-en-1-yl)-9H-xanthen-9-one		OC1=C(C/C=C(C)/C)C(O)=CC2=C1C(C3=C(C/C=C(C)/C)C(OC)=C(OCCN(CC)CC)C=C3O2)=O

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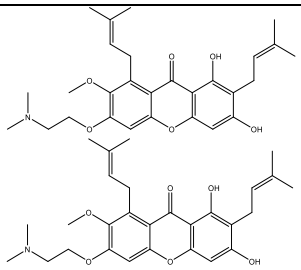
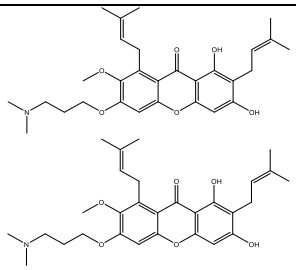
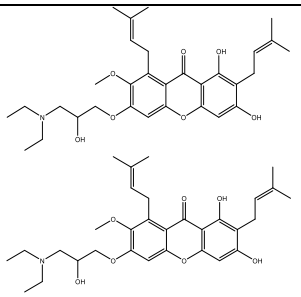
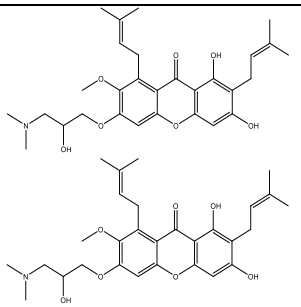
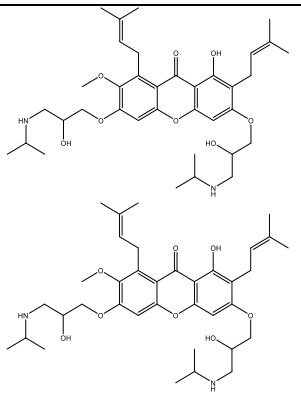
No	Compound	CID	IUPAC name	Structure	SMILES
116	3-(2-(dimethylamino)ethoxy)-6,8-dihydroxy-2-methoxy-7-(3-methyl-3l5-buta-2,3-dien-1-yl)-1-(3-methylbut-2-en-1-yl)-9H-xanthen-9-one	-	3-(2-(dimethylamino)ethoxy)-6,8-dihydroxy-2-methoxy-1,7-bis(3-methylbut-2-en-1-yl)-9H-xanthen-9-one		OC1=C(C/C=C(C)/C)C(O)=CC2=C1C(C3=C(C/C=C(C)/C)C(OC)=C(OCCN(C)C)C=C3O2)=O
117	3-(3-(dimethylamino)propoxy)-6,8-dihydroxy-2-methoxy-7-(3-methyl-3l5-buta-2,3-dien-1-yl)-1-(3-methylbut-2-en-1-yl)-9H-xanthen-9-one	-	3-(3-(dimethylamino)propoxy)-6,8-dihydroxy-2-methoxy-1,7-bis(3-methylbut-2-en-1-yl)-9H-xanthen-9-one		OC1=C(C/C=C(C)/C)C(O)=CC2=C1C(C3=C(C/C=C(C)/C)C(OC)=C(OCCCN(C)C)C=C3O2)=O
118	3-(3-(diethylamino)-2-hydroxypropoxy)-6,8-dihydroxy-2-methoxy-7-(3-methyl-3l5-buta-2,3-dien-1-yl)-1-(3-methylbut-2-en-1-yl)-9H-xanthen-9-one	-	3-(3-(diethylamino)-2-hydroxypropoxy)-6,8-dihydroxy-2-methoxy-1,7-bis(3-methylbut-2-en-1-yl)-9H-xanthen-9-one		OC1=C(C/C=C(C)/C)C(O)=CC2=C1C(C3=C(C/C=C(C)/C)C(OC)=C(OCC(O)CN(CC)CC)C=C3O2)=O
119	3-(3-(dimethylamino)-2-hydroxypropoxy)-6,8-dihydroxy-2-methoxy-7-(3-methyl-3l5-buta-2,3-dien-1-yl)-1-(3-methylbut-2-en-1-yl)-9H-xanthen-9-one	-	3-(3-(dimethylamino)-2-hydroxypropoxy)-6,8-dihydroxy-2-methoxy-1,7-bis(3-methylbut-2-en-1-yl)-9H-xanthen-9-one		OC1=C(C/C=C(C)/C)C(O)=CC2=C1C(C3=C(C/C=C(C)/C)C(OC)=C(OCC(O)CN(C)C)C=C3O2)=O
120	1-hydroxy-3,6-bis(2-hydroxy-3-(isopropylamino)propoxy)-7-methoxy-2,8-bis(3-methylbut-2-en-1-yl)-9H-xanthen-9-one	-	1-hydroxy-3,6-bis(2-hydroxy-3-(isopropylamino)propoxy)-7-methoxy-2,8-bis(3-methylbut-2-en-1-yl)-9H-xanthen-9-one		OC1=C(C/C=C(C)/C)C(OCC(O)CNC(C)C)=CC2=C1C(C3=C(C/C=C(C)/C)C(OC)=C(OCC(O)CNC(C)C)C=C3O2)=O

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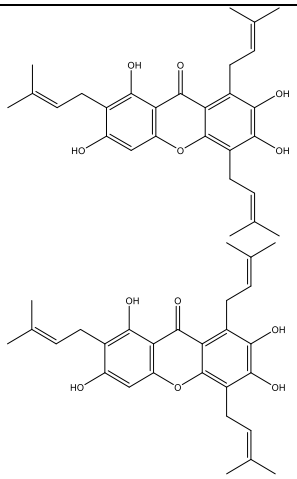
No	Compound	CID	IUPAC name	Structure	SMILES
127	garcinone E	10298511	2,3,6,8-tetrahydroxy-1,4,7-tris(3-methylbut-2-enyl)xanthen-9-one		CC(=CCC1=C(C2=C(C=C1O)OC3=C(C(=C(C(=C3C2=O)CC=C(C)C)O)O)CC=C(C)C)O)C

Abbreviation: "–" in the CID column indicates the compound is not in PubChem; SMILES was derived from literature-reported structures

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Table 3. Drug likeness of potent antimalarial xanthone derivatives

Compound	Rule of Five				Absorption			Distribution			Metabolism							Excretion			Toxicity	
	Molecular Weight	LogP	#Acceptors	#Donors	Caco2 Permeability log Papp in 10^{-6} cm/s	Solubility log mol/L	Intes Final absorption (human) %absorbed	VDss (human) log L/kg	BBB permeability log BB	CNS permeability log PS	CYP 2D6 substrate	CYP 3A4 substrate	CYP 1A2 inhibitior	CYP 2C19 inhibitior	CYP 2C9 inhibitior	CYP 2D6 inhibitior	CYP 3A4 inhibitior	Total Clearance log mL/min/kg	Renal OCT2 substrate	AMES toxicity	Rat Acute Toxicity LD_{50} mol/kg	Hepa To toxicity
1	242.23	266.582	4	2	-3.424	1.103	94.6	-0.063	-0.078	-1.943	N	N	Y	Y	Y	N	N	0.52	N	Y	1.818	N
2	2.442.002	2.063	5	3	-2.918	1.165	95.415	-0.152	-0.9884	-2.265	N	N	Y	N	N	N	N	0.463	N	Y	1.865	N
3	410.466	5.089	6	3	-4.067	-0.048	93.647	-0.282	-1.075	-1.984	N	Y	Y	Y	Y	N	N	0.43	N	Y	1.949	N
4	482.665	59.478	6	0	-5.322	1.346	91.454	2.564	-0.498	-2.694	Y	Y	N	N	N	Y	N	1.266	N	Y	2.651	Y
5	510.719	6.728	6	0	-5.534	0.943	89.038	2.416	-0.588	-2.679	Y	Y	Y	N	N	N	Y	1.38	N	Y	2.574	Y
6	538.773	75.082	6	0	-5.572	0.961	87.905	2.319	-0.599	-2.671	Y	Y	N	N	N	N	N	1.383	N	N	2.494	Y
7	566.827	82.884	6	0	-5.36	0.951	87.246	2.135	-0.657	-2.662	Y	Y	N	N	N	N	N	1.479	N	N	2.409	Y
8	546.699	70.062	6	0	-4.834	1.053	88.82	1.427	-0.694	-2.718	N	Y	N	N	N	N	Y	1.324	N	N	2.526	Y
9	462.542	62.646	6	3	-5.062	0.289	99.653	-0.052	-1.044	-1.6	N	Y	N	Y	Y	N	Y	-0.285	N	Y	1.829	Y
10	276.2	14.742	7	5	-2.935	-0.298	63.936	1.75	-1.427	-3.154	N	N	Y	N	N	N	N	0.284	N	Y	2.303	N
11	292.199	11.798	8	6	-2.973	-0.109	68.557	0.923	-1.589	-3.625	N	N	Y	N	N	N	N	0.196	N	N	2.322	N
12	509.643	6.104	7	2	-5.95	0.691	82.518	1.146	-1.166	-2.345	N	Y	N	Y	N	N	Y	0.787	N	N	2.471	Y
13	481.589	53.238	7	2	-5.532	0.715	81.068	1.028	-1.063	-2.329	N	Y	N	Y	N	N	Y	0.664	Y	Y	2.458	Y
14	495.616	57.139	7	2	-5.702	0.701	81.93	0.952	-1.131	-2.313	N	Y	N	N	N	Y	Y	0.759	N	N	2.46	N
15	539.669	54.649	8	3	-5.676	0.524	77.53	0.79	-1.368	-3.168	N	N	N	Y	N	N	Y	0.754	N	N	2.415	Y
16	511.615	46.847	8	3	-5.395	0.579	71.082	0.725	-1.265	-3.191	N	N	N	Y	N	N	Y	0.595	N	N	2.377	Y
17	640.818	51.532	10	5	-3.576	-0.523	62.163	1.004	-1.516	-3.361	N	Y	N	N	N	N	Y	0.669	N	N	2.457	Y
18	464.558	62.947	6	4	-4.176	-0.234	90.397	-0.792	-1.137	-1.827	N	Y	N	Y	Y	N	N	-0.045	N	Y	2.079	Y

Abbreviation: BBB=blood brain barrier, CNS=central nervous system, CYP= cytochrome P450, OCT2= Organic cationic transporter2, Y=Yes, N=No

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A molecular mass under 500 Daltons, no more than 10 hydrogen bond acceptors, a maximum of five hydrogen bond donors, and a LogP value below 5, indicating moderate lipophilicity[81]. Typically, a compound is regarded as a viable candidate for oral administration when it breaches no more than two of these parameters [82]. Among the 18 screened compounds, only compound **120** was found to violate Lipinski's Rule of Five.

The pkCSM platform evaluates compound absorption using predictive metrics such as permeability across Caco-2 cell layers, water solubility, and human intestinal absorption (%HIA)[13]. Among these, %HIA is particularly informative as it reflects the extent of passive diffusion of neutral species in aqueous environments, offering a broader physiological relevance compared to membrane-specific Caco-2 data [83]. While Caco-2 permeability and solubility thresholds (e.g., >0.9 and –5 to –1 log mol/L, respectively) are useful for preliminary screening, %HIA exceeding 70% is considered a more decisive indicator of good intestinal uptake within the pkCSM framework[13]. In this study, compound selection prioritized %HIA to ensure retention of candidates with favorable absorption profiles, even if other parameters were suboptimal. Based on %HIA alone, compounds **14, 15, 41, 62–65, 74, 93, 115-119,** and **127** demonstrated good intestinal absorption. Among these, compounds 14, 15, and 74 also met all three absorption criteria, including Caco-2 permeability and solubility thresholds.

Understanding drug distribution is essential in antimalarial development. A high steady-state volume of distribution (Vdss) indicates tissue over plasma localization, while high BBB and CNS permeability suggest potential brain access[13]. In severe cases such as cerebral malaria, CNS distribution becomes critical, as Plasmodium-infected erythrocytes can adhere to brain endothelium and form rosettes with uninfected cells[84]. This leads to microvascular obstruction, reduced perfusion, and oxygen deprivation, which may contribute to blood-brain barrier disruption and vascular leakage[85]. High tissue distribution is defined as log Vdss > 0.45, while BBB and CNS permeability are considered favorable when logBB > 0.3 and logPS > -2. Compounds **62-65, 74, 107,** and **114-120** exhibited high tissue distribution. Although none showed strong BBB penetration, three compounds (**14, 41,** and **93**) were predicted to cross the CNS barrier, making them promising candidates for cerebral malaria applications.

Metabolism primarily occurs in the liver with the help of cytochrome P450 (CYP) enzymes, which catalyze diverse reactions that significantly influence the biological activity of both xenobiotics, such as drugs and environmental chemicals, and endobiotics like fatty acids, steroids, prostaglandins, and bile acids[86]. The pkCSM platform predicts whether compounds act as substrates or inhibitors of key CYP isoforms, including CYP2D6 and CYP3A4 (substrates), as well as CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4 (inhibitors). Most compounds in this study showed minimal interaction as CYP2D6 substrates or inhibitors, while several were predicted to inhibit CYP1A2, CYP2C19, and CYP2C9. Notably, compounds **63, 74, 93**, and **115-120** exhibited CYP3A4 inhibition, which may affect metabolic clearance and raise the potential for drug–drug interactions.

The pkCSM platform assesses excretion profiles by estimating total clearance and

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interactions with the Organic Cation Transporter 2 (OCT2). Clearance values among xanthone derivatives range from 1.818 to 2.651 log mL/min/kg, indicating varying elimination rates that directly affect drug half-life and dosing frequency [87]. OCT2, a membrane transporter located in hepatocytes, enterocytes, and renal proximal tubule cells[80], plays a key role in mediating the uptake and excretion of cationic compounds[88]. Its influence on drug disposition depends on whether a compound serves as a substrate or inhibitor[13]. In this study, only compound **116** was predicted to interact with OCT2 as a substrate.

The toxicity profile of xanthone derivatives was assessed using three key parameters: the Ames test, oral acute toxicity in rats (LD_{50}), and hepatotoxicity prediction [13]. LD_{50} values ranged from 1.818 to 2.651 mol/kg, indicating a moderate level of acute toxicity across the compounds. The Ames assay, a widely accepted bacterial reverse mutation test, is commonly employed to identify mutagenic potential through short-fragment DNA damage[89]. Hepatotoxicity evaluation was included due to the high incidence of drug-induced liver injury (DILI), a leading cause of clinical trial failure and discontinuation of drug development[90]. Among the tested compounds, only **114** and **117** satisfied both mutagenicity and hepatotoxicity safety criteria.

Taken together, these findings emphasize that clinically meaningful thresholds such as $IC_{50} < 1$ μM provide a rational benchmark for prioritizing candidates, while safety-critical predictions, including hepatotoxicity and CYP3A4 inhibition, remain decisive filters in early development. Synthetic derivatives bearing alkylamino side chains consistently outperformed natural prototypes like α-mangostin, underscoring the value of structural modification in balancing potency and tolerability. Although pkCSM offers reliable first-pass insights, its predictive scope is inherently limited and requires experimental validation to confirm pharmacokinetic and toxicity outcomes [14]. Importantly, the strong intestinal absorption and Lipinski compliance predicted for Compound 117 link favorable pharmacokinetics directly to drug-likeness, supporting its designation as a promising lead for further optimization.

CONCLUSION

This study successfully integrated a systematic review with computational profiling to filter the xanthone chemical space. Compound 117 was identified as the premier candidate, supported by high-quality primary data and a superior in silico safety profile. The use of a customized, stringent quality assessment tool ensures that this recommendation is based on the most reliable evidence available. Compound 117 represents a prioritized scaffold for immediate in vivo optimization.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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