REVIEW

DISCOVERY AND DEVELOPMENT OF ANTIPLASMODIAL COMPOUNDS IN THAILAND DURING THE 21ST CENTURY

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Abstract. This review describes research conducted in Thailand from 2000 to 2013 on the discovery of new compounds from local flora and fauna, including those of marine organisms from coastal regions, which have antiplasmodial activity against *Plasmodium falciparum* growth in culture. These antiplasmodials comprised alkaloids, angucyclinones, anthraquinones, azaanthraquinone, azaphilones, benzoquinones, bioxanthracenes, carbazomycins, chalcones, chromone, clerodane, coumarins, cyclomarin, cyclopeptides, cytochalasins, depsidones, depudecin, flavaglines, flavonoids, furans, isoflavonoids, limonoids, macrolides, nucleoside, oxepin, peptides, phloroglucinol, polylactone, polypropionate, preussomerins, prodigiosin, pterocarpans, pyrenocines, pyridones, pyrrolidines, quassinoids, quinone, stilbenes, styryl lactones, terpenoids, tetramic acids, tetronic acids, trinorcadalenes, tropolones, xanthones, and a variety of miscellaneous molecules (a total of 293 compounds). The review also describes the screening and synthesis of novel chemicals targeted against parasite enzymes, (carbonic anhydrase, cytochrome *bc*1, dihydrofolate reductase and orotidine 5′-monophosphate decarboxylase), which have the potential of being developed into antimalarial drugs. Possible future trends in antimalarial drug research in Thailand are discussed.

Keywords: antimalarial development, antiplasmodial discovery, flora and fauna antimalarials, marine antimalarials, Thailand

INTRODUCTION

Malaria still remains a major public health problem, especially in sub-Saharan Africa. In 2011 WHO reported 219 million new cases of malaria, with 800,000 deaths, mainly in children in sub-Saharan Africa (WHO, 2013). Although a new attenuated sporozoite vaccine holds promise (Seder *et al*, 2013), treatment of malaria still continues to depend on the use of antimalarial drugs. However, human malaria parasites, in particular *Plasmodium falciparum,* the most virulent of the five plasmodial parasites (*P. vivax*, *P. malariae*, *P. ovale* and most recently *P. knowlesi*) infecting humans have become resistant to all currently used antimalarials, including the Chinese drug artemi-

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sinin (also known as qinghaosu) and its analogs [dihydroartemisin (the active form), arteether, artmether and artesunate (water soluble form)] (Dorndorp *et al*, 2009). New antimalarials in clinical use are mainly artemisinin combination therapies (ACTs), of which there are five combinations (WHO, 2010), with at least one other combination undergoing multi-center clinical trials in Africa and Asia (Duparc *et al*, 2013).

The successful discovery of artemisinin isolated from the Chinese herbal plant qinghao (sweet wormwood) traditionally used to treat jungle fever (Miller and Su, 2011) has spurred similar efforts to identify compounds from local flora and fauna with antiplasmodial properties, which then could be developed directly or as lead compounds for further chemical modifications to become novel and if possible inexpensive antimalarial drugs. This review has gathered together reports in the literature (from 2000 to 2013) of new chemicals (but not of crude extracts) with inhibitory activities against *P. falciparum*. In addition, reports of research in Thailand on the development of novel compounds directed against *P. falciparum* enzymes with potential for future development as antimalarial drugs are reviewed. However, pharmacological studies and clinical trials conducted in Thailand during the period covered by this article were not included.

Unless indicated otherwise, antiplasmodial inhibition studies employed the Thai parasite isolate, *P. falciparum* K1 (Thaithong and Beale, 1981), resistant to both chloroquine (IC_{50} = 3.6 μg/ml/0.59 μM) and pyrimethamine (IC_{50} = 30 μM), where IC_{50} is defined as the concentration required to inhibit malaria parasite growth in culture by 50%.

DISCOVERY OF NEW ANTIPLASMODIAL COMPOUNDS

During the period of the literature survey there were some 293 new compounds isolated from various species of flora and fauna in Thailand, and those from marine organisms from coastal regions, which show inhibitory activity against *P. falciparum* in culture (summarized in Table 1). The majority of compounds with antiplasmodial activity were discovered during examination of bioactive substances from insect and seed fungi (reviewed earlier by Isaka *et al*, 2005a). The new chemical compounds include alkaloids, angucyclinones, anthraquinones, azaanthraquinone, azaphilones, benzoquinones, bioxanthracenes, carbazomycins, chalcones, chromone, clerodane, coumarins, cyclomarin, cyclopeptides, cytochalasins, depsidones, depudecin, flavaglines, flavonoids, furans, isoflavonoids, limonoids, macrolides, nucleoside, oxepin, peptides, phloroglucinol, polylactone, polypropionate, preussomerins, prodigiosin, pterocarpans, pyrenocines, pyridones, pyrrolidines, quassinoids, quinone, stilbenes, styryl lactones, terpenoids, tetramic and tetronic acids, trinorcadalenes, tropolones, xanthones, and a variety of miscellaneous compounds, but they were not more potent than chloroquine. However, there are some exceptions: metacycloprodigiosin (IC_{50} = 5 ng/ml), and fimbricalyx B, two flavaglines (aglafoline, rocaglamide), a macrolide (bafilomycin A1) and two pyridones (cordypyridones A, B) with IC_{50} values ranging from 20 to 70 ng/ml. However, there have been no reports on the pharmacological and toxicology properties of these promising lead compounds.

Only one study attempted to modify a naturally occurring bioactive compound

(α-mangostin, a xanthone) to generate more active analogs (lowest IC_{50} = 50 nM), but the limited number of analogs synthesized was not sufficient to show a structure-activity relationship (SAR), but did indicate that the presence of a prenyl side chain in the xanthone molecule improves antiplasmodial activity.

The number of compounds isolated from marine organisms off the shores of Thailand with antiplasmodial property was limited to 17: malyngamide X, from *Bursatella leachii*, a marine gastropod mollusc, commonly known as sea hare; coumarin, cytochalasin Q, sesterterpenoids, and tetramic and tetronic acids from marine fungi; and terpenoids and macrolides from marine sponges. A review of the literature from 2006 to 2008 listed 82 natural compounds and synthetic derivatives with antiplasmodial activity from marine and freshwater sources around the world (Gademann and Kobylinska, 2009), and another review of marine antimalarials covering a similar period listed some 60 secondary metabolites with antiplasmodial properties (Fattorusso and Taglialatela-Scafati, 2009). However, reports of Thai antiplasmodial marine natural products in these two reviews were apparently overlooked.

DEVELOPMENT OF NOVEL ANTIPLASMODIAL COMPOUNDS

Compounds screened or developed against *P. falciparum* specific targets were limited to only four enzymes, namely, carbonic anhydrase (CA), cytochrome *bc*1, dihydrofolate reductases (DHFR) and orotidine 5'-monophosphate decarboxylase (OMPDC), mainly involved in pyrimidine biosynthesis (Table 2). This is not unexpected as the malaria parasite lacks pyrimidine salvage pathway and must depend on *de novo* biosynthesis of these precursors of nucleic acids (Gero and O'Sullivan, 1990).

The most extensive work has been carried out on the synthesis and testing of novel compounds directed against *P. falciparum* (*Pf*)DHFR, the target of previously effective antimalarials, pyrimethamine (PYR) and cycloguanil (CG). *Pf*DHFR together with parasite thymidylate synthase (*Pf*TS) and serine hydroxymethyltransferase are involved in dTMP cycle. However through a series of point mutations in *Pfdhfr*, *Pf*DHFR has acquired a highly PYR-resistant quadruple mutant (QM) (N51I, C59R, S108N, and I164L) form. The elucidation of the crystal structures of wild-type bifunctional PfDHFR-TS (in Plasmodia DHFR and TS are synthesized as a single bifunctional enzyme) and QM forms has allowed an understanding of the structural basis for reduced binding of PYR and CG to *Pf*DHFR QM due to a rigid p-chloropheny substituent at the 5-position of PYR resulting in steric clash with the mutated amino acids (Yuvaniyama *et al*, 2003). This has enabled rationale design of compounds based on pyrimidine and triazine scaffolds, which are flexible in order to avoid such steric hindrances with the bulkier mutant amino acid side chains in the *Pf*DHFR binding site. Following synthesis and evaluation of hundreds of such compounds, P218 (2, 4-diamino-6-ethyl-5-(3-(2-(2-carboxyethyl) phenoxy) propoxy) pyrimidine was arrived at, which includes pyrimidine side-chain flexibility and a carboxylate group that makes charge-mediated hydrogen bonds with conserved R122 of *Pf*DHFR and not of human DHFR, providing an explanation of its high selectivity (Yuthavong *et al*, 2012). P218 binds both wild-type and QM *Pf*DHFR tightly almost entirely within the chemical space of DHFR substrate,

Table 1
New antiplasmodial compounds discovered in Thailand from 2000 to 2013.

Compound	IC50[a] (μg/ml)	Source	Reference
Alkaloid			
8-acetonyldihydronitidine	0.34	*Feroniella lucida* (Scheff.) Swingle (Rutaceae) (tree) ("Masung" in Thai)	Sripisut *et al*, 2011
alstonisine	7.6[b]	*Alstonia macrophylla* (Apocynaceae) (tree) ("Tung Fa")	Cheenpracha *et al*, 2013
aporphine ((-)-nordicentrine)	0.3	*Goniothalamus laoticus* (Finet & Gagnep.) Ban (Annonaceae) (tree) ("Khao-lam-dong")	Lekphrom *et al*, 2009
bis-dehydroaporphine (bidebiline C, D)	5.4, 4.1	*Polyalthia debilis* Annonaceae) (herbal plant) ("Kon Krok")	Kanokmedhakul *et al*, 2003
carbozole {clausine H, heptaphylline	5.5-10.7, 3.2-6.4	*Clausena harmandiana* (Pierre) Guillaumin (Rutaceae) (herbal plant)	Yenjai *et al*, 2000
(mukonal, 7-methoxymukonal	3.3, 2.9	*Clausena harmandiana* (Pierre) Guillaumin (Rutaceae) (herbal plant)	Thongthoom *et al*, 2010
O-methylmukonal)}	6.7[c]	*Clausena excavata* Burm. f. (Rutaceae) (herbal plant) ("San Soak")	Sripisut *et al*, 2010
cyclopeptide (hemsine A, nummularine B, H)	7.3[b], 10.3[b], 4.2[b]	*Ziziphus mauritiana* Lam. (Rhamnaceae) ("Phut-sa")	Panseeta *et al*, 2011
dithiodiketopiperazine (6-octenoic acid, 3-hydroxy-2,4,6-trimethyl-5-oxo-, (5*S*,5a*S*, 7a*R*,8*R*,14a*R*)-5,5a,7a,8,14a,15-hexahydro-8, 12-dihydroxy-7a,14a-bis(methylthio)-7,14-dioxo-7*H*,14*H*-oxepino[3'',4'':4',5']pyrrolo[1', 2':4,5]pyrazino[1,2-*a*]indol-5-yl ester, (6*E*))	2.9[b]	*Menisporopsis theobromae* BCC 3975 (seed fungus)	Chinworrungsee *et al*, 2006
hirsutellone F	4.2	*Trichoderma* sp BCC 7579 (seed fungus)	Isaka *et al*, 2006
indole (α-dihydrocadambine)	6.6[b]	*Neonauclea purpurea* (Roxb.) Merr. (Rubiaceae) (tree)	Karaket *et al*, 2012
mauritine M	3.7[b]	*Ziziphus mauritiana* Lam. (Rhamnaceae) ("Phut-sa")	Panseeta *et al*, 2011
oxoaporphine liriodenine	2.8	*Pseuduvaria setosa* (King) J. Sinclair (Annonaceae)	Wirasathien *et al*, 2006a
piperine dimer (chabamide)	2.7	*Piper chaba* Hunter (Piperceae) (herbal plant)	Rukachaisirikul *et al*, 2002
pyrazinedione (5-benzyl-1-hydroxy-3-(hydroxyphenylmethylene)-3*H*-pyrazine-2,6-dione)	28.8[b]	*Menisporopsis theobromae* BCC 3975 (seed fungus)	Chinworrungsee *et al*, 2006
Angucyclinone			
saccharosporone A, B	4.1[b], 3.9[b]	*Saccharopolyspora* BCC 21906 (soil gram-positive bacteria)	Boonlarppradab *et al*, 2013
Anthraquinone			
torrubiellin A, B	3.1, 0.3	*Torrubiella* sp BCC 28517 (leafhopper pathogenic fungus)	Isaka *et al*, 2012
Azaanthraquinone			
marcanine A	2.5	*Goniothalamus marcanii* Craib (herbal plant)	Ichino *et al*, 2006
Azaphilone			
longirostrerone A, B, C	0.6[b], 3.7[b], 0.6[b]	*Chaetomium longirostre* (saprophytic ascomycetes)	Panthama *et al*, 2011

Table 1 (Continued).

Compound	IC50[a] (μg/ml)	Source	Reference
Benzoquinone			
2,6-dimethoxy-1,4-benzoquinone	11.3[b]	*Neonauclea purpurea* (Roxb.) Merr (Rubiaceae) (tree)	Karaket *et al*, 2012
meroterpene, 10-membered ring (alliodorin, cordiachrome B, cordiachrome C, cordiaquinol C, elaeagin, globiferin)	3.1, 1.5, 0.2, 0.3, 3.6, 2.1	*Cordia globifera* W. W. Smith (Boraginaceae) (tree) ("Sak Hin")	Dettrakul *et al*, 2009
racemosol (demethyl racemosol; preracemosol A, B; racemosol)	2.0, 18.0, 3.0, 0.9	*Bauhinia malabarica* Roxb. (Fabaceae) (purple orchid tree)	Kittakoop *et al*, 2000
Bioxanthracene			
11 compounds	1.1-64	*Cordyceps pseudomilitaris* (insect pathogenic fungus)	Jaturapat *et al*, 2001; Isaka *et al*, 2001b
Carbazomycin			
carbazomycin B, C	2.4, 2.1	*Streptomyces* sp BCC 26924	Intaraudom *et al*, 2011
Chalcone			
2′,4′-dihydroxy-3′-(2-hydroxybenzyl)-6′-methoxychalcone	7.1	*Ellipeiopsis cherrevensis* (Pierre ex Finet & Gagnep.) R. E. Fr. (Annonaceae) (herbal plant)	Wirasathien *et al*, 2006b
Chromone			
O-methylalloptaeroxylin	10.5	*Harrisonia perforate* (Blanco) Merr. (Simaroubaceae) (herbal plant)	Tuntiwachwuttikul *et al*, 2006a
Clerodane			
16-hydroxycleroda-3,13(14)Z-dien-15,16-olide	3.6	*Polyalthia viridis* Crib (Anonaceae) (herbal plant)	Ichino *et al*, 2006
Coumarin			
clausarin; dentatin	0.1-0.7, 8.5-12.3	*Clausena harmandiana* (Pierre) Guillaumin (Rutaceae)	Yenjai *et al*, 2000
5-carboxymellein	4	*Halorosellinia oceanica* (marine fungus)	Chinworrungsee *et al*, 2001
dihydroisocoumarin (7-butyl-6,8-dihydroxy-3(*R*)-pent-11-enylisochroman-1-one; 7-butyl-6,8-dihydroxy-3(*R*)-pentylisochroman-1-one	4.7, 2.6	*Geotrichum* sp (endophytic fungus)	Kongsaeree *et al*, 2003
Cyclomarin			
cyclomarin C	0.2	*Streptomyces* sp BCC 26924	Intaraudom *et al*, 2011
Cyclopeptide			
cycloheptapeptide (cordyheptapeptide A)	5.3[b]	*Cordyceps* sp 1788 (insect pathogenic fungus)	Rukachaisirikul *et al*, 2006
cyclohexadepsipeptide (allobeauvericin A, B, C	2.0, 2.4, 1.6	*Paecilomyces tenuipes* BCC 1614 (insect pathogenic fungus)	Nilanonta *et al*, 2002
beauvericin, beauvericin A, B	1.6, 1.8, 2.3	*Paecilomyces tenuipes* BCC 1614 (entomopathogenic fungus)	Nilanonta *et al*, 2000
enniatin B, B4, C, G, H, I	0.3, 0.2, 1.1, 0.5, 1.9, 0.2	*Verticillium hemipterigenum* BCC 1449 (pathogenic fungus)	Nilanonta *et al*, 2002 Nilanonta *et al*, 2003a

Table 1 (Continued).

Compound	IC50[a] (μg/ml)	Source	Reference
enniatin L, M1/M2, N	3.3, 3.4 (1:1 mixture of M1 and M2), 3.4	Unidentified fungus BCC 2629	Vongvilai *et al*, 2004
hirsutatin B	5.8	*Hirsutella nivea* BCC 2594 (insect pathogenic fungus)	Isaka *et al*, 2005c
hirsutellide A	2.8	*Hirsutella kobayasii* BCC 1660 (insect pathogenic fungus)	Vongvanich *et al*, 2002
paecilodepsipeptide A)	4.9[b]	*Paecilomyces cinnamomeus* BCC 9616 (insect pathogenic fungus)	Isaka *et al*, 2007
Cytochalasin			
cytochalasin Q	17	*Halorosellinia oceanica* (marine fungus)	Chinworrungsee *et al*, 2001
19,20-epoxy-cytochalasin Q	0.6	*Xylaria* sp BCC 1067 (wood-decayed fungus)	Isaka *et al*, 2000
Depsidone			
mollicellin B, C, E, J, K, L, M	4.7, 9.1, 3.2, 4.9, 1.2, 3.4, 2.9	*Chaetomium brasiliense* (fungus)	Khumkomkhet *et al*, 2009
Depudecin			
(-)-depudecin	5.8-11.2[b]	*Xylaria* sp BCC 1067 (wood-decayed fungus)	Isaka *et al*, 2000
Flavagline			
aglafoline, rocaglamide	0.054[b,d], 0.061[b,d]	*Aglaia* sp (Meliaceaea) (herbal plant)	Astelbauer *et al*, 2012
Flavonoid			
biflavonoid (3″,4′,4‴,5,5″,7,7″-heptahy droxy-3,8-biflavanone)	1-10[b]	*Garcinia kola* Heckel (Guttiferae) (herbal plant)	Antia *et al*, 2010
chamaaejasmine	2.3	*Enkleia siamensis* (Kurz) Nervling (Thymelaeceae) (herbal plant) (“Po Tao Hai”)	Rajachan *et al*, 2013
artonin F, cycloartobiloxanthone, 7-demethy-lartonol E	2.4, 3.7, 7.9	*Artocarpus rigidus* Blume (Moraceae) (Monkey Jackfruit tree)	Namdaung *et al*, 2006
flavan ((2S)-3′,4′-dihydroxy-5,7-dimethoxyflavan; griffinoid C, D)	9.7[b], 15.7[b], 13.0[b]	*Combretum griffithii* Van Heurck & Müll. Arg. (Combretaceae) (tree)	Moosophon *et al*, 2013
flavanone (abyssinone V, lespedezaflavanone B	7.0, 3.7	*Erythrina subumbrans* Merr. (Leguminosae) (herbal plant)	Rukachaisirikul *et al*, 2008
demethoxymatteucinol	9.5[b]	*Bauhinia purpurea* L. (Leguminosae) (tree) “Chong Kho” or “Siao Dok Daeng”)	Boonphong *et al*, 2007
5-hydroxysophoranone	2.5	*Erythrina stricta* Roxb. (Fabaceae) (tree)	Rukachaisirikul *et al*, 2007
lonchocarpol A)	9.2	*Erythrina fusca* Lour. (Fabaceae) (tree) (“Thong Long”)	Innok *et al*, 2009

Table 1 (Continued).

Compound	IC50[a] (μg/ml)	Source	Reference
Flavone			
5,7,3′,4′-tetramethoxyflavone, 5,7,4′-trimethoxyflavone	4.1, 3.7	*Kaempferia parviflora* (Zingiberaceae) rhizome	Yenjai *et al*, 2004
prenylated flavone (citflavanone, lonchocarpol A, lupinifolin, 8-prenyldaidzein)	5.0, 1.6, 12.5, 3.9	*Erythrina fusca* Lour. (Fabaceae) (tree) (“Thong Long”)	Khaomek *et al*, 2008
Furan			
19-(2-furyl)nonadeca-5,7-diynoic acid, 19-(2-furyl)nonadeca-5,7-diynmethylester	50, 3.7	*Polyalthia evecta* (Pierre) Finet & Gagnep (Annonaceae) (“Nam-tou-lang” or “Tong-lang”)	Kanokmedhakul *et al*, 2006
Isoflavonoid			
isoflavanone (vogelin C)	2.8	*Erythrina subumbrans* Merr. (Leguminosae) (tree)	Rukachaisirikul *et al*, 2008
isoflavanquinone (abruquinone Q)	1.5	*Abrus precatorius* L. (Fabaceae)) (herbal plant)	Limmatvapirat *et al*, 2004
isoflavone (dalparvone	8.2	*Dalbergia parviflora* Roxb. (Leguminosae) (herbal plant)	Songsiang *et al*, 2009
erysubin F)	3.2	*Erythrina subumbrans* Merr. (Leguminosae) (tree)	Rukachaisirikul *et al*, 2007
Limonoid			
6α-acetoxyepoxyazadiradione, azadiradione, dysobinin, epoxyazadiradione, mahonin	6.3, 2.9, 2.1, 3.2, 2.9	*Chisocheton siamensis* Craib (Meliaceae) (tree) (‘‘Ta Suea’’)	Maneerat *et al*, 2008
Macrolide			
bafilomycin A1	0.04	*Streptomyces spectabilis* BCC 4785 (soil fungus)	Isaka *et al*, 2002a
resorcylic (aigialomycin D, hypothemycin)	6.6, 2.2	*Aigialus parvus* BCC 5311 (lignicolous mangrove Ascomycete)	Isaka *et al*, 2002b
samroiyotmycins A, B	3.6, 3.2	*Streptomyces* sp BCC 33756	Dramae *et al*, 2013
trisoxazole (kabiramide B, C, D, J, K	1.7[b], 4.8[b], 1.9[b], 0.3[b], 0.4[b]	*Pachastrissa nux* (sea sponge)	Sirilak *et al*, 2011
kabiramide I, L)	4.5[b], 2.6[b]	*Pachastrissa nux* (sea sponge)	Sirilak *et al*, 2013
Nucleoside			
cordycepin	4.5	*Cordyceps militaris* (entomopathogenic fungus)	Rukachaisirikul *et al*, 2004a
Oxepin			
dihydrobenzoxepin (bauhinoxepin H, bauhinoxepin I, bauhinoxepin J)	11.2[b], 10.8[b], 5.8[b]	*Bauhinia purpurea* L. (Leguminosae) (tree) “Chong Kho” or “Siao Dok Daeng”	Boonphong *et al*, 2007
Peptide			
cysteine knot (psalmopeotoxin II)	2.7[b]	*Psalmopoeus cambridgei* (Trinidad chevron tarantula)	Kamolkijkarn *et al*, 2010
tetrapeptide (hirsutellic acid A)	8.0[b]	*Hirsutella* sp BCC 1528 (insect pathogenic fungus)	Thongtan *et al*, 2006
Phenanthrenone			
9-O-demethyltrigonostemone, 3,6,9-trimethoxyphenanthropolone	2.7, 3.2	*Strophioblachia fimbricalyx* Boerl. (Euphorbiaceae)	Seephonkai *et al*, 2009

Table 1 (Continued).

Compound	IC50[a] (μg/ml)	Source	Reference
Phloroglucinol			
tomentosone A	1.5[b]	*Rhodomyrtus tomentosa* (Aiton) Hassk. (Myrtaceae) (herbal plant)	Hiranrat *et al*, 2012
Polylactone, macrocyclic			
menisporopsin A	4.0	*Menisporopsis theobromae* BCC 4162 (seed fungus)	Chinworrungsee *et al*, 2004
Polypropionate			
spectinabilin	7.8	*Streptomyces spectabilis* BCC 4785	Isaka *et al*, 2002a
Preussomerin			
deoxypreussomerin A, 3'-*O*-demethylpreussomerin I, preussomerin E, F, G, H, I	3.2, 2.4, 2.2, 2.9, 2.7, 2.2, 0.9	*Microsphaeropsis* sp BCC 3050 (lichen fungus)	Seephonkai *et al*, 2002
Prodigiosin			
metacycloprodigiosin	0.005	*Streptomyces spectabilis* BCC 4785 (soil fungus)	Isaka *et al*, 2002a
Pterocarpan			
erstagalin A	3.8	*Erythrina stricta* Roxb. (Fabaceae) (tree)	Rukachaisirikul *et al*, 2007
erybraedin A, erythrabyssin II	3.4, 5.5	*Erythrina subumbrans* Merr. (Leguminosae) (tree)	Rukachaisirikul *et al*, 2007
Pyrenocine			
pyrenocine A, B	7.1, 22	*Verticillium hemipterigenum* BCC 1449 (insect pathogenic fungus)	Nilanonta *et al*, 2003b
Pyridone			
cordypyridone A, B	0.07, 0.04	*Cordyceps nipponica* (insect pathogenic fungus)	Isaka *et al*, 2001c
torrbiellone A	8.1[b]	*Torrbiella* sp BCC 2165 (insect pathogenic fungus)	Isaka *et al*, 2010
Pyrrolidine			
1-piperettyl pyrrolidine, sarmentine	6.5, 18.9	*Piper sarmentosum* Roxb. (Piperaceae) (herbal plant) ("Cha-plu")	Rukachaisirikul *et al*, 2004b
sarentine; sarmentosine	4.5, 3.9	*Piper sarmentosum* Roxb. (Piperaceae) herbal plant) ("Cha-plu")	Tuntiwachwuttikul *et al*, 2006b
Quassinoid			
11-dehydroklaineanone, longilactone, 15β-O-acetyl-14-hydroxyklaineanone, 14,15β-dihydroxyklaineanone, 15β-hydroxyklaineanone	5.3[b,e], 5.5-13.7[b,e], 23.8[b,e], 5.0[b,e], 5.3[b,e]	*Eurycoma longifolia* Jack. (Simaroubaceae) (herbal plant)	Jiwajinda *et al*, 2002
Quinone			
isoflavanquinone (abruquinone B)	1.5	*Abrus precatorius* L. (Fabaceae)) (herbal plant)	Limmatvapirat *et al*, 2004
Stilbene			
prenylated (4-methoxy-2,2-dimethyl-6-(2-(2,4-dihydroxy)phenyl-*trans*-ethenyl) chromene, *trans*-4-isopentenyl-3,5,2 ',4'-tetrahydroxystilbene, *trans*-4-(3-methyl-*E*-but-1-enyl)-3,5,2 ',4'- tetrahydroxystilbene)	9.4, 8.2, 1.7	*Artocarpus integer* Merr. (Moraceae) (tree)	Boonlaksiri *et al*, 2000

Table 1 (Continued).

Compound	IC50[a] (μg/ml)	Source	Reference
Styryl lactone			
(+)-3-acetylaltholactone, (+)-altholactone, goniotriol	2.6, 2.6, 7.9	*Goniothalamus laoticus* (Finet & Gagnep.) Ban (Annonaceae) (tree) ("Khao-lam-dong")	Lekphrom *et al*, 2009
Terpenoid			
diterpenoid acylphenol (malabaricone A)	2.8	*Knema glauca* (Blume) Petermann (Myristicaceae) (herbal plant)	Rangkaew *et al*, 2009
amphilectane (8-isocyanato-15-formamido-amphilect-11(20)-ene; 8-isocyano-15-formamidoamphilect-11(20)-ene; 8-isothiocyanato-15-formamidoamphilect-11(20)-ene)	8.8[b], 0.5[b], 8.1[b]	*Stylissa* cf. *massa* (Carter) (marine sponge)	Chanthathamrongsiri *et al*, 2012
1,11-bisepi-caniojane, caniojane	7.9, 3.3	*Jatropha integerrima* Jacq. (Euphorbiaceae)	Sutthivaiyakit *et al*, 2009
2-hydroxyjatropholone, jatropholone A	4.1, 5.4	*Jatropha integerrima* Jacq. (Euphorbiaceae)	Sutthivaiyakit *et al*, 2009
O-acylated jatrophane diterpenoid (1α,13β,14α-trihydroxy-3β,7β-dibenzoyloxy-9β,15 β-diacetoxyjatropha-5,11 E-diene; 1α,8β,9β,14α,15β-pentaacetoxy-3β-benzoyloxy-7-oxojatropha-5,12-diene; 7,8β,9β,14α,15β-pentaacetoxy-3β-benzoyloxy-1α,5β-dihydroxyjatropha-6(7),12-diene; 1α,7,8β,9β,14α,15β-hexaacetoxy-3β-benzoyloxy-5β-hydroxyjatropha-6(7),12-diene)	4.0, 3.4, 4.3, 4.4	*Pedilanthus tithymaloides* L. (Euporbiaceae) (herbal plant) ("Sa Yaek" or "Sa Yaek Sam Si")	Monkolvisut and Sutthivaiyakit, 2007
oxygenated primarane ((1*R*,2*S*,5*S*,9*S*,-10*S*,11*R*,13*R*)-1,2,11-trihydroxypimara-8(14),15-diene; 1*S*,5*S*,9*S*,10*S*,11*R*,13*R*)-1,11-dihydroxypimara-8(14),15-diene)	8.8, 3.2	*Kaempferia marginata* Carey (Zingerberaceae) (herbal plant) ("Tup Mup")	Thongnest *et al*, 2005
8,9-secokaurane (*ent*-8,9-*seco*-7α,11β-diacetoxykaura-8(14),16-dien-9,15-dione, *ent*-8,9-*seco*-8,14-epoxy-7α-hydroxy-11β-acetoxy-16-kauren-9,15-dione, *ent*-8,9-*seco*-7α -hydroxy-11 β-acetoxykaura-8(14),16-dien-9,15-dione)	2.8, 1.0, 1.0	*Croton kongensis* Gagnep. (Euphorbiaceae) (herbal plant) ("Plao Ngeon" or "Plao Noi")	Thongtan *et al*, 2003
miscellaneous (9α-13α-epidioxyabiet-8(14)-en-18-oic acid; 4-*epi*-triptobenzene L; 12-*O*-deacetyl-6-*O*-acetyl-18- acetyloxycoleon Q; 12-*O*-deacetyl-6-*O*-acetyl-19- acetyloxycoleon Q)	3.0, 4.7, 7.2, 2.9	*Anisochilus hamandii* Doan ex Sudddee & A. J. Paton (Lamiaceae)	Lekphrom *et al*, 2010

Table 1 (Continued).

Compound	IC50a (μg/ml)	Source	Reference
Sesquiterpenoid			
elemophilane ((+)-phaseolinone, (+)-phomenone)	0.5, 0.3	*Xylaria* sp BCC 1067 (wood-decayed fungus)	Isaka *et al*, 2000
germacrolide (5-*epi*-isocentratherin, 5-*epi*-isogoyazensolide, goyazensolide, isocentratherin, isogoyazensolide, lychnophorolide A/centratherin, lychnophorolide B)	3.0, 1.6, 1.2, 2.1, 1.6, 0.3, 0.7	*Camchaya calcarea* Kitamura (Compositae) (weed)	Vongvanich *et al*, 2006
lactone (7β-hydroxy-3,11(13)-eudesmadien-12,8-olide)	2.7	*Xylaria ianthinovelutina* (Mont.) (fungus)	Pittayakhajonwut *et al*, 2009
ophiobolane (halorosellinic acid and acetonide derivative)	13, 19	*Halorosellinia oceanica* BCC 5149 (marine fungus)	Chinworrungsee *et al*, 2001
oxygenated wilfordic acid-containing (9′-deacetoxymekongensine, 7-*epi*-mekongensine, mekongensine, 1-*O*-benzoyl-1-deacetyl-9′-deacetoxymekongensine, 1-*O*-benzoyl-1-deacetylmekongensine)	3.1[b], 3.9[b], 3.1[b], 2.5[b], 3.5[b]	*Maytenus mekongensis* Ding Hou (Celastraceae) (herbal plant) (“Naam Kaan Chaang”)	Lhinhatrakool *et al*, 2011
phomoarcherin B	0.8	*Phomopsis archeri* (endophytic fungus)	Hemtasin *et al*, 2011
pughiinin A	2.4	*Kionochaeta pughii* BCC 3878 (seed fungus)	Pittayakhajonwut *et al*, 2002
Sesterterpenoid			
halorosellinic acid and acetonide derivative	13, 19	*Halorosellinia oceanica* (marine fungus)	Chinworrungsee *et al*, 2001
spirodihydrobenzofuran (stachybotrydial and lactone derivative)	0.8, 0.1	*Stachybotrys nephrospora* BCC 3900 (fungus)	Sawadjoon *et al*, 2004
triquinane (dihydrohypnophilin, panepoxydione, panepoxydone)	3.1, 2.1, 3.4	*Lentinus conatus* BCC 8996 (fungus)	Rukachaisirikul *et al*, 2005
Triterpenoid			
β-acetylolean-12-en-28-olic acid)	5.9	*Prismatomeris fragrans* E.T. Geddes (tree)	Kanokmedhakul *et al*, 2005
ceanothane (zizyberenalic acid)	3.0	*Ziziphus cambodiana* Pierre (Rhamnaceae)	Suksamrarn *et al*, 2006
coumaroyloxyursolic acid/uncarinic acid (mixture)	2.9	*Gardenia saxatilis* Geddes (Rubiaceae) (herbal plant)	Suksamrarn *et al*, 2003
ester (3-*O*-vanillylceanothic acid)	3.7	*Ziziphus cambodiana* Pierre (Rhamnaceae)	Suksamrarn *et al*, 2006
lupine (betulinaldehyde, 2-*O*-*E*-*p*-coumaroylalphitolic acid)	6.5, 0.9	*Ziziphus cambodiana* Pierre (Rhamnaceae)	Suksamrarn *et al*, 2006
messagenic acid A, B	1.5, 3.8	*Gardenia saxatilis* Geddes (Rubiaceae) (herbal plant)	Suksamrarn *et al*, 2003
soyasapogenol B	4.6	*Erythrina stricta* Merr. (Leguminosae) (herbal plant)	Rukachaisirikul *et al*, 2007
tetranortriternenoid (domesticulide B, C, D)	3.2, 2.4, 6.9	*Lansium domesticum* Corr. (Meliaceae) (tree) (“Langsat Khao”)	Saewan *et al*, 2006

Table 1 (Continued).

Compound	IC50a (μg/ml)	Source	Reference
Tetramic acid			
vermelhotin (1:2 *E*/*Z* mixture)	1-10[b,f]	unidentified marine fungus CRI247-01 (Order Pleosporales)	Kasettrathat *et al*, 2008
Tetronic acid			
nodulisporacid A (*E*/*Z* mixture)	1-10[b,f]	*Nodulisporium* sp CRIF1 (marine-derived fungus)	Kasettrathat *et al*, 2008
Trinorcadalene (phytoalexin)			
parvifloral B, F	11.4[b], 6.8[b]	*Decaschistia parviflora* (Kurz) (Malvaceae) (shrub)	Wongsa *et al*, 2013
Tropolone			
cordytropolone	2.2	*Cordyceps* sp BCC 1681 (insect pathogenic fungus)	Seephonkai *et al*, 2001
pycnidione	0.3	*Kionochaeta pughii* BCC 3878 (seed fungus)	Pittayakhajonwut *et al*, 2002
Xanthone			
dimer (ascherxanthone A	0.2	*Aschersonia* sp BCC 8401 (insect pathogenic fungus)	Isaka *et al*, 2005b
phomoxanthone A, B)	0.1, 0.3	*Phomopsis* sp BCC 1323 (teak endophytic fungus)	Isaka *et al*, 2001a
1,3,7-oxygenated (fuscaxanthone E)	3.0	*Cratoxylum cochinchinense* (Lour.) Blume (Clusiaceae) (herbal plant)	Laphookhieo *et al*, 2009
1,3,5,6-oxygenated (formoxanthone C, gerontoxanthone I, macluraxanthone)	1.2, 1.7, 1.3	*Cratoxylum maingayi* (Lour.) Blum (Clusiaceae) (herbal plant)	Laphookhieo *et al*, 2009
prenylated (27 derivatives of α-mangostin)	0.05-17[b]	*Garcinia mangostana* L. (Clusiaceae) (fruit tree) ("mangkhut")	Mahabusarakam *et al*, 2006
miscellaneous (celebixanthone, cochinchinone C, β-mangostin, 5-*O*-methylcelebixanthone	4.9, 2.6, 7.2, 3.2	*Cratoxylum cochinchinense* (Lour.) Blume (Clusiaceae) (herbal plant)	Laphookhieo *et al*, 2006
vismione B, E, F	0.7, 3.9, 2.0	*Cratoxylum cochinchinense* (Lour.) Blume (Clusiaceae) (herbal plant)	Laphookhieo *et al*, 2009
Miscellaneous			
butyrolactone V	7.9	*Aspergillus terreus* BCC 4651	Haritakun *et al*, 2010
diarylpropane (1-(4-hydroxy-3,5-dimethoxy-phenyl)-3- (4-hydroxy-3-methoxyphenyl) propane)	14.4[b]	*Combretum griffithii* Van Heurck & Müll. Arg. (Combretaceae)	Moosophon *et al*, 2013
fimbricalyx B, fimbricalyxanhydride A	0.019[b], 3.9[b]	*Strophioblachia fimbricalyx* Boerl. (Euphorbiaceae) (herbal plant)	Seephonkai *et al*, 2013
malyngamide X	5.4[b]	*Bursatella leachii* (marine gastropod mollusc, commonly known as sea hare)	Suntornchashwej *et al*, 2007
(E)-methyl-3-(4-methoxyphenoxy)propionate	19	*Xylaria* sp BCC 1067 (wood-decayed fungus)	Isaka *et al*, 2000
pterocarpan (phaseollidin)	9.1	*Erythrina fusca* Lour. (Leguminosae) (tree) ("Thong Long")	Innok *et al*, 2009
rugulosone	1.9	*Emericella rugulosa* (Ascomycota) (fungus)	Moosophon *et al*, 2009
scleropycric acid	7.2	*Scleropyrum wallichianum* (Wight & Arn.) (Santalaceae) (tree)	Suksamrarn *et al*, 2005

[a]Concentration required to inhibit parasite growth in culture by 50%; [b]μM; [c]minimum inhibitory concentration; [d]*P. falciparum* isolates from Myanmar (resistant to 4-aminoquinolines, antifolates and mefloquine); [e]ACC Niger *P. falciparum* strain (chloroquine resistant, IC50 = 0.39 μM); [f]*P. falciparum* strain 94 (chloroquine resistant, IC_{50} = 0.29 μM).

Table 2
Drugs developed against *Plasmodium falciparum* targets.

Target	Lead inhibitor	Ki[a] (μM)	Reference
carbonic anhydrase	4-(3,4-dichlorophenyl-ureido) thioureido-benzenesulfonamide	0.18	Krungkrai and Krungkrai, 2011
cytochrome bc1	3-(1,4-dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)-2, 2-dimethylpropyl octanoate; 3-(1,4-dihydro-2-hydroxy-1, 4-dioxonaphthalen-3-yl)-2,2-dimethylpropyl tetradecanoate	0.005, 0.008	Khonkathip *et al*, 2010
dihydrofolate reductase[b]	2, 4-diamino-6-ethyl-5-(3-(2-(2-carboxyethyl)phenoxy) propoxy)pyrimidine (P218)	0.0005	Yuthavong *et al*, 2012
orotidine 5′-monophosphate decarboxylase	4-(2-hydroxy-4-methoxyphenyl)-4-oxobutanoic acid	170	Takashima *et al*, 2012

[a]Concentration required to inhibit enzyme activity by 50%; [b]quadruple mutant (N51I, C59R, S108N and I164L).

which should render it less susceptible to further resistance mutations. The high *in vivo* efficacy in a SCID mouse model of *P. falciparum* malaria, good oral bioavailability, favorable enzyme selectivity, and good safety characteristics bode well for P218 as a potential candidate for pre-clinical development.

The malaria parasite synthesizes pyrimidines *de novo* from bicarbonate ($HCO3^-$), ATP, glutamine, aspartate, and 5-phosphoribosyl-1-pyrophosphate. $HCO3^-$ is formed from the ionization of carbonic acid produced from CO_2 catalyzed by CA. *Pfca* encodes an α-type Zn^{2+}-metalloenzyme possessing catalytic properties distinct from that of the human host CA (reviewed by Krungkrai and Krungkrai, 2011). Screening of a collection of 34 aromatic/heterocyclic sulfonamides, most of which are Schiff's bases derived from sulfanilamide/homosulfanilamide/4-aminoethylbenzene sulfonamides revealed inhibitors specific to *Pf*CA at moderate to low μM and some at sub-μM concentrations. SAR showed that groups substituting the aromatic ureido or aromatic azomethine moieties and variations in the lengths of the parent sulfonamide are critical parameters governing their inhibitory properties. One derivative, 4-(3,4-dichlorophenylureido)thioureido-benzenesulfonamide, is the most effective inhibitor of *Pf*CA activity and is also the most potent in inhibiting *P. falciparum* growth in culture as well as that of *P. berghei in vivo*.

In the *de novo* biosynthesis pathway of pyrimidines, the final two steps of generating uridine 5′-monophosphate (UMP) require addition of ribose 5-phosphate from 5-phosphoribosyl-1-pyrophosphate to orotic acid, catalyzed by orotate phosphoribosyltransferase (OPRT) to form orotidine 5′-monophosphate (OMP),

followed by decarboxylation of OMP by orotidine 5'-monophosphate decarboxylase (OMPDC) to produce UMP. These two enzymes exist as a heterotetrameric $(OPRT)_2(OMPDC)_2$ complex, and inhibition of *Pf*OMPDC is lethal to malaria parasite (Krungkrai *et al*, 2005). *In silico* screening of 156 compounds identified 14 putative inhibitors against *Pf*OMPDC with IC_{50} values ranging from 60 to 250 μM, while further analysis of the crystal structure of *Pf*OMPDC complexed with 4-(2-hydroxy-4-methoxyphenyl)-4-oxobutanoic acid (IC_{50} = 170 μM) revealed that the inhibitor occupies a part of the active site that overlaps with the phosphate-binding region in OMP- and UMP-bound complex and that the space occupied by pyrimidine and ribose rings of OMP and UMP is not blocked by this inhibitor (Takashima *et al*, 2012). The carboxyl group of the inhibitor causes a dramatic movement of two loops (L1 and L2), which play a pivotal role in the recognition of substrate and product, and thus combining parts of the inhibitor with pyrimidine and ribose rings of OMP and UMP represents a promising avenue for further development of these compounds as potential potent antimalarials.

Cytochrome *bc*1 complex (ubiquinol: cytochrome *c* oxidoreductase, respiratory Complex III) catalyzes the transfer of electrons from ubiquinol to cytochrome *c* in the mitochondrial electron-transfer chain and in *P. falciparum* cytochrome *bc*1 can be effectively inhibited by the antimalarial atovaquone, a naphthoquinone, but this drug's current clinical use has been severely curtailed by the appearance of resistant parasites (reviewed by Nixon *et al*, 2013). In an effort to discover alternatives to atovaquone, 26 novel naphthoquinone aliphatic esters derived from rhinacanthin, isolated from *Rhincanthus nasutus* (Acanthacaea) commonly known as snake jasmine and used in Thailand for the treatment of cancer, were synthesized and 24 show significant antiplasmodial activity with IC_{50} values in the range of 0.03-16 μM, and SAR indicates that the length of the aliphatic chain and the presence of C-20 substituents on the propyl chain affect activity (Kongkathip *et al*, 2010). Compounds with 7 (namely 3-(1,4-dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)-2,2-dimethylpropyl octanoate) and 13 (namely 3-(1,4-dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)-2,2-dimethylpropyl tetradecanoate) carbon side chains have promising antiplasmodial activity (0.13 and 0.03 μM against *P. falciparum* K1, respectively) and acceptable *in vitro* therapeutic index (IVTI) (IC_{50} against Vero cell line/ IC_{50} against *P. falciparum*) (> 1,990 and 1,825, respectively); both inhibit *P. falciparum* 3D7 mitochondrial cytochrome bc_1 with IC_{50} value of 5 and 8 nM, respectively, being 3,000-fold more sensitive than against the rat cytochrome bc_1, suggesting that such naphthoquinone ester scaffolds have good potential in being developed into antimalarials. However, it is worth noting that both *P. falciparum* strains employed in the study are atovaquone-sensitive.

CONCLUDING REMARKS

As can be seen from Table 1, the likelihood of discovering from local flora and fauna potent antiplasmodial compounds that have the potential of gaining interest of pharmas to invest in developing them into antimalarials is exceedingly small. A search of 86 Thai medicinal plant samples representing 48 species from 35 genera in 16 families revealed only two new compounds with antiplasmodial activity, namely, marcanine A (azaanthraquinone

from *Polyalthia viridis*) and 16-hydroxycleroda-3,13(14)Z-dien-15,16-olide (clerodane from *Goniothalamus marcanii*) with IC_{50} value of 2.5 and 3.6 μg/ml, respectively (Table 1) (Ichino *et al,* 2006). Learning from the Chinese experience of discovering artemisinin, concerted efforts should be directed to identify a local herbal plant and/or medicinal concoction used traditionally in treating jungle fever, not only colds or flu-like symptoms. A start in this approach is the recent report of antiplasmodial activity of ethanolic extract of *Dracaena loureiri* Gagnep. (Dracaenacae) and "Benjakul" Formulaton 1, composing of 5 dried medicinal plants, namely *Piper chaba* Hunt. (Piperaceae), *Piper interruptum* Opiz. (Piperaceae), *Piper sarmentosum* Roxb. (Piperaceae), *Plumbago indica* Linn. (Plumbaginaceae), and *Zingiber officinale* Rosc. (Zingiberaceae) (IC_{50} values of 1.0-10 μg/ml against *P. falciparum* K1 and 3D7) (Thiengsusuk *et al*, 2013).

A neglected area of antiplasmodial drug research in Thailand is the chemical modifications of promising lead natural products in order to generate SAR that can lead to analogs having more desirable pharmacological properties in terms of specificity, bioavailability and lack of toxicity. For example, Mancini *et al* (2008) have reported the synthesis of a series of analogs, with SAR when possible, derived from natural antiplasmodial compounds of marine organisms (mainly sponges), which include endoperoxides (peroxyplakoric acid methyl esters, plakortin), isonitriles (amphilectane diterpenes, kalihinol A), alkaloids (6-bromoaplysinopsin, cycloprodigiosin, heptylprodigiosin, manzamine A, metacycloprodigiosin) and 2 miscellaneous compounds (aplasmomycin, 15-oxopuupehenol). A more recent example is the synthesis of benzylamine and phenylpropylamine analogs of encecalin, a chromene isolated from *Encelia farinosa* Gray (Asteraceae), known as brittlebush, a common desert shrub of northwestern Mexico and southwestern United States, having IC_{50} value of 0.02 and 0.01 μM, respectively against *P. falciparum* K1, and IVTI (compared with L6 rat skeletal myoblasts) of 6800 and 1800, respectively (Harel *et al*, 2013).

In Thailand, a possible candidate is α-mangostin, a xanthone from *Garcinia mangostana* L. (Clusiaceae), commonly known as mangosteen and "mangkhut", and its fruit is considered among Thais as being the "queen of fruits". Other than their antiplasmodial property, xanthones extracted from mangosteen exhibit a variety of biological activities including antibacterial, antifungal, antiinflammatory, antioxidant, cytotoxic, and potential cancer chemopreventive (Chin and Kinghorn, 2008). However, only a limited number of antiplasmodial SAR studies of xanthone analogs have been undertaken, although by such simple modifications as the addition of alkyl groups containing protonable nitrogen atoms in order to allow accumulation and interaction with heme in the malaria parasite acidic food vacuole for enhancement of inhibition of *P. falciparum* growth in culture are readily achievable (Riscoe *et al*, 2005).

In spite of the fact that target-based rationale-driven drug designs have and will produce clinical efficacious therapeutics, their useful life spans in the field will ultimately be limited by the eventual evolution of drug-resistant malaria parasites. In order to accelerate the drug discovery process, a complementary approach currently advocated is phenotypic screening of large chemical libraries using high throughput techniques, (Butera, 2013 and references therein). A limited number of highly potent (sub nM) novel antiplas-

modial compounds from such screening efforts are now available (known as malaria box) (Guiguemde *et al*, 2012), which should be exploited in screening against *P. falciparum* enzyme and non-enzyme targets studied by Thai researchers, *viz*. DNA β-like polymerase (Nunthawarasilp *et al*, 2007), 3′-5′ DNA helicase (Suntornthiticharoen *et al*, 2006), β-hematin (hemozoin) formation (Auparakkitanon *et al*, 2003), hydroxymethylpterin pyrophosphokinase-dihydropteroate synthase (Rattanachuena *et al*, 2009), plasmepsin II (Sriwilaijaroen *et al*, 2006) and serine hydroxymethyltransferase (Sopitthummakhun *et al*, 2012).

Interestingly, in the past attempts have been made to convert anticancer drugs into antimalarials, *viz*. analogs of amsacrine (Auparakkitanon and Wilairat, 2000) and of rhinacanthin (Kongkathip *et al*, 2010), the reverse process is gaining interest, as demonstrated by the potent antiproliferative abilities of artemisinins, synthetic peroxides and DHFR inhibitors (including P218) against 91 human cancer lines (Hooft van Huijsduijnen *et al*, 2013). A merger of these two pipelines in drug discovery and development should be a win-win situation in the treatment of malaria and cancer.

ACKNOWLEDGEMENTS

The author is grateful to Associate Professor Maliwan Phakpraphai for her careful reading of the manuscript and Professor Prapon Wilairat for proof-reading the final draft.

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