www.ijrps.pharmascope.org

ISSN: 0975-7538
Research Article

Synthesis, characterization and biological screening of some 3-phenyl indole derivatives

S.Muthu Kumar*[1], D. Selva Kumar[3], Rajpati yadav[2], Shiv Prakash Pandey[2], Sanjay kumar gupta[2]

[1]Karpagam University, Coimbatore, Tamil Nadu, India
[2]Kamla Nehru Institute of Management and Technology, Sultanpur (U.P), India
[3]AVN Ayurveda Formulations Private Limited, Madurai, Tamil Nadu, India

ABSTRACT

In an attempt to search for new and alternative antimalarial agents, a series of 2-(4-amino sulfonyl phenyl) 3-phenyl indole substituted amine derivative -2-(4-amino sulfonyl phenyl) 3-phenyl-5 chloro indole and 2-(4-amino sulfonyl phenyl) 3-phenyl -5 fluoro indole derivatives were synthesized and their chemical structures confirmed by Elemental, 1H NMR, IR and mass spectrophotometric analysis. The in vitro antimalarial activities of these compounds were evaluated against the chloroquine-sensitive (D10) and the chloroquine-resistant (RSA11) strains of Plasmodium falciparum. The 2-(4-amino sulfonyl phenyl) 3-phenyl -5 chloro indole derivatives increased in vitro activity when compared to the unsubstituted analogues, which are all devoid of activity. The presence of the 5-chloro, fluoro, amine, mehoxy, hydroxy group in the indole ring system leads to compounds with diminished anti malarial activity when compared to the corresponding unsubstituted analogues. The compounds associate with ferriprotoporphyrin.

Keywords: Antimalarial activity**;** Antibacterial activity**;** Anti-inflammatory activity**;** Indole**;** Plasmodium falciparum**;** ferriprotoporphyrin 3-phenyl Indole derivatives.

I. Introduction

Medicinal chemistry is a chemistry-based discipline, involving aspects of biological, medical and pharmaceutical science. It is concerned with the invention, discovery, design, identification and preparation of biologically active compounds, the interpretation of their mode of action at the molecular level and the construction of the relationship between chemical structure and pharmacological activity (J.S. Biradar et al 2010).

The main objective of medicinal chemistry is the design and the production of compounds that can be used as medicine for the prevention, treatment and cure of human or animal diseases. Medicinal chemistry is the application of chemical research techniques to the synthesis of pharmaceuticals. During the early stage of medicinal chemistry development, scientists were primarily concerned with the isolation of medicinal agents found in plants. Today, scientists in the field are also equally concerned with the creation of new synthetic drug compounds. Medicinal chemistry is almost always geared towards drug discovery and development. Medicinal chemists apply their chemistry training to the process of synthesizing new pharmaceuticals (Peter Cosmos et al 2007).

The 2-(4-amino sulfonyl phenyl) 3-phenyl indole aroused considerable interest as a result of their broad spectrum of antibacterial, antifungal and antiparasitic activities. The majority of the2-(4-amino sulfonyl phenyl) 3-phenyl -5 fluoro indole are active in vitro against a variety of viruses including several strains of rhinovirus. Since they are purine analogues, it is expected that they should exert their pharmacological effects by interfering with the DNA metabolism. Recent hypotheses seem to suggest that the quinoline-type antimalarial drugs coordinate to the malaria parasite's endogenous antimalarial agent, Ferriprotoporphyrin IX (FP), thus disrupting the conversion of haematin to haemozoin (malaria pigment). A free FP as a toxic substance to the malaria parasites, serves as a receptor for the accumulation of antimalarial drugs in the food vacuoles. The parasites which are lacking in haem oxygenase are unable to detoxify the free FP by metabolism, but the malaria parasites have evolved an autocatalytic detoxification process in which FP is oxidized to haematin (Kazuhiro Kobayashi et al 2007).

It is also possible that both the free FP and its complex with chloroquine- type drugs inhibit proteases, which are essential for the degradation of haemoglobin, and thus affect the growth of the parasite. The binding of the quinoline-type antimalarial drugs may also stabilize the l-oxo dimer relative to the monomers, shifting the

* Corresponding Author
Email: smuthupharma81@gmail.com
Contact: +91-
Received on: 01-06-2011
Revised on: 25-06-2011
Accepted on: 12-07-2011

dimerization equilibrium to the right and reducing the amount of haematin monomers available for incorporationinto the growing haemozoin.Since the discovery of the non-phototoxic, but highly effective quinoline-methanol antimalarial agent, mefloquine the trifluoromethyl group has aroused considerable interest as a pharmacophore. Halofantrine also containing a trifluoromethyl group compares favourably with mefloquine, both compounds being effective against multidrug-resistant Plasmodium falciparum, including strains, which are highly resistant to chloroquine (Joseph L et al 2005 & Carola Huthmacher 2010).

The emergence of multidrug-resistant strains of Plasmodia has created a near-desperate situation, where the need for new and inexpensive antimalarials to circumvent the parasite's resistance mechanism has become vital. Chloroquine resistance is associated with reducedconcentrations of the drug from the acid food vacuoles of the parasite due to increased efflux of the drug from the cell. In this paper, in a search for alternative agents to the quinoline antimalarial compounds, we report the synthesis and the exploratory evaluation of the in vitro antimalarial activities of a series of derivative -2-(4-amino sulfonyl phenyl) 3-phenyl-5 chloro indole and 2-(4-amino sulfonyl phenyl) 3-phenyl -5 floro indole derivatives, together with their characteristic interactions with ferriprotoporphyrinIX to ascertain their mode of antimalarial action**.** Indole is an aromatic heterocyclic organic compound (E. Elisabetsky1 et al 2006).

It has a bicyclic structure, consisting of a six-membered benzene ring fused to a five-membered nitrogen-containing pyrrole ring. Indole is a popular component of fragrances and the precursor to many pharmaceuticals. Compounds that contain an indole ring are called indoles. Notably, the indolic amino acid tryptophan is the precursor of the neurotransmitter serotonin. Indole is a solid at room temperature. Indole can be produced by bacteria as a degradation product of the amino acid tryptophan. It occurs naturally in human feces and has an intense fecal odor. At very low concentrations, however, it has a flowery smell, and is a constituent of many flower scents (such as orange blossoms) and perfumes. It also occurs in coal tar (CS Mitaine-Offer et al 2002).

1. a) Synthesis of indoles

Indole is a major constituent of coal-tar, and the 220-260°C distillation fractions are the main industrial source of the material. Indole and its derivatives can also be synthesized by a variety of methods. The main industrial routes start from aniline.

Illustrative of such large-scale syntheses, indole (and substituted derivatives) forms via vapor-phase reaction of aniline with ethylene glycol in the presence of catalysts:

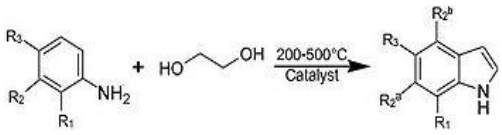

Figure 1: Synthesis of indoles

Reactions are generally conducted between 200 and 500 °C. Yields can be as high as 60%. Other precursors to indole include formyltoluidine, 2-ethylaniline, and 2-(2-nitrophenyl) ethanol, all of which undergo cyclizations. Many other methods have been developed that are applicable.

One of the oldest and most reliable methods for synthesizing substituted indoles is the Fischer indole synthesis developed in 1883 by Emil Fischer. Although the synthesis of indole itself is problematic using the Fischer indole synthesis, it is often used to generate indoles substituted in the 2- and/or 3-positions. Indole can still be synthesized however using the Fischer indole synthesis by reacting phenyl hydrazine with pyruvic acid followed by decarboxylation of the formed indole-2-carboxylic acid. This has also been accomplished in a one-pot synthesis using microwave irradiation (Joana Dumc et al 2002).

Malaria is one of the most successful parasites ever known to mankind. After thousands of years, it remains the world's most pervasive infection, affecting at least 91 different countries and some 300 million people. The disease causes fever, shivering, joint pain, headache, and vomiting. In severe cases, patients can have jaundice, kidney failure, and anemia, and can lapse into a coma (E.O. Ajaiyeoba et al 1999 & Andrew Net al 2005).

It is ever-present in the tropics and countries in sub-Saharan Africa, which account for nearly 90 percent of all malaria cases. The majority of the remaining cases are clustered in India, Brazil, Afghanistan, Sri Lanka, Thailand, Indonesia, Vietnam, Cambodia, and China. Malaria causes 1 to 1.5 million deaths each year, and in Africa, it accounts for 25 percent of all deaths of children under the age of five (Jingyong Sun et al 2008 & Apurba Ket al 2004).

1. b) Parasite lifecycle

Malaria parasites spread by successively infecting two types of hosts: female Anopheles mosquitoes and humans.

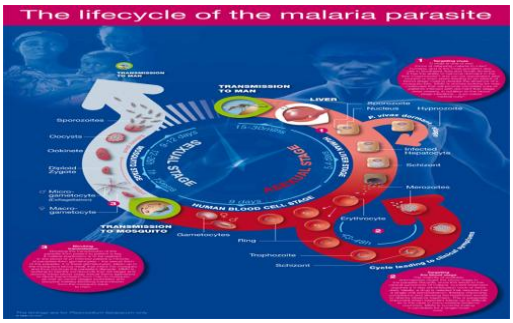

Figure 2: Parasite lifecycle

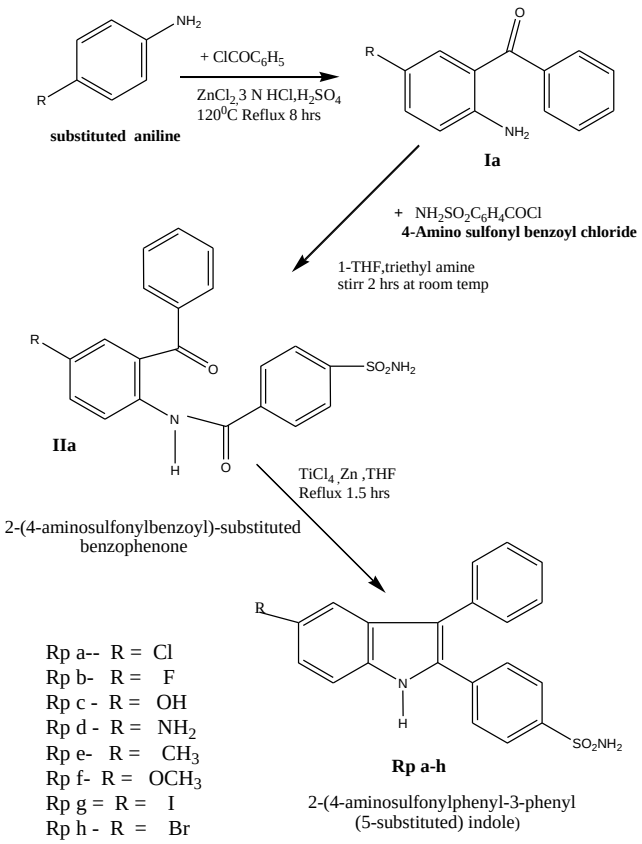

Figure 3: Scheme of synthesis of 2-(4-aminosulfonylphenyl-3-phenyl (5-substituted) indole)

Table 1: Physicochemical properties of some 3-phenyl indole derivatives

S.No	Compound	R	Mol.Formula	M.Wt	Yield (%)	M.P	Rf value
1	Rp a	-Cl	$C_{20}H_{15}SO_2N_2Cl$	383	45.7%	297°C-299°C	0.715
2	Rp b	-F	$C_{20}H_{15}SO_2N_2F$	365	53.5%	302°C-304°C	0.681
3	Rp c	-OH	$C_{20}H_{16}SO_3N_2$	364	67.0%	241°C-243°C	0.521
4	Rp d	$-NH_2$	$C_{20}H_{17}SO_2N_3$	363	57.5%	216°C-218°C	0.645
5	Rp e	CH_3	$C_{21}H_{18}SO_2N_2$	362	77.5%	242°C-244°C	0.554
6	Rp f	$-OCH_3$	$C_{21}H_{18}SO_3N_2$	346	72.0%	280°C-282°C	0.745
7	Rp g	-I	$C_{20}H_{15}SO_2N_2I$	474	62.4%	306°C-308°C	0.880
8	Rp h	-Br	$C_{20}H_{15}SO_2N_2Br$	427	55.5%	310°C-312°C	0.744

Five species

Malaria is caused by protozoan parasites of the genus ***Plasmodium*** – single-celled organisms that cannot survive outside of their host(s).

Plasmodium falciparum is responsible for the majority of malaria deaths globally and is the most prevalent species in sub-Saharan Africa. The remaining species are not typically as life threatening as *P. falciparum.*

Plasmodium vivax, is the second most significant species and is prevalent in Southeast Asia and Latin America. *P. vivax and* ***Plasmodium ovale*** have the added complication of a dormant liver stage, which can be reactivated in the absence of a mosquito bite, leading to clinical symptoms.

P. ovale and ***Plasmodium malariae*** represent only a small percentage of infections.

A fifth species ***Plasmodium knowlesi*** – a species that infects primates – has led to human malaria, but the exact mode of transmission remains unclear.

2. RESULTS AND DISCUSSION

2. a) Chemistry

We have synthesized the series of the indole anologues with different substitutient (R_5) at the para position of the 3- phenyl ring such as hydrogen,halogen;methyl,methoxy and other (R_P a-h) Sulfonamide leading thus to the desired series of compounds (R_Pa-h) We have chosen the various substituents of the 3-phenyl group of indoles ar 4^{th} position (R_Pa-h) by considering both the limited available space within the hydrophobic pocket of the enzyme active site, as discussed above, as well as general medicinal chemistry considerations, for example, moieties that may increase lipo-or hydro solubility of the new compounds, and eventually also interacting in a positive

Table 2: *In vitro* IC50 (µ M) of the 2-(4 amino sulfonyl phenyl)-3 phenyl indole derivatives

Compound	R	CHLOROQUINE SENSITIVE	CHLOROQUINE RESISTANT
Rp a	Cl	256.00 +_10	26.00 +_4
Rp b	F	35.00 +_ 5	20.00 +_ 5
Rp c	OH	45.00+_ 6	15.00+_ 3
Rp d	NH_2	150.00 +-10	10.00 +-2
Rp e	CH_3	56.00 +-5	ND
Rp f	OCH_3	80.00 +- 10	1 8.00 +- 4
Rp g	I	60.00 +- 5	15.00 +- 2
Rp h	Br	75.00 +-8	10.00 +-2

Table 3: Biological Activity of the Compounds

SAMPLE CODE	R	Zone Of Inhibition					
		ANTI MICROBIAL ACTIVITY 500 µgm/ml				ANTIFUNGAL ACTIVITY 500 µgm/ml	
		S.aureus	*B.subtilis*	*E.coli*	*P Vulgaris*	*C.albicans*	*A. Nigra*
Rp a	Cl	20	30	17	16	23	15
Rp b	F	25	35	22	13	20	NS
Rp c	OH	35	18	15	20	30	NS
Rp d	NH_2	15	22	19	26	28	NS
Rp e	CH_3	10	20	15	18	25	18
Rp f	OCH_3	14	25	16	20	23	NS
Rp g	I	23	15	10	15	19	NS
Rp h	Br	30	20	14	20	25	NS
A	Norfloxacin	20	20	32	32	--	--
B	fluconazole	--	--	--	--	25	28

manner with amino acid residues present in the active site region where this moiety of the inhibitors. Thus, we have incorporated 5-substituted phenyl groups possessing methyl-, halogeno- and methoxy- functionalities ensued by the presence of the additional functionality in the 3-phenyl ring may lead to diverse interactions of compounds 8 with amino acid residues within the various isoforms active sites cavity. The main interest in this class of compounds is that of detecting derivatives with a more isoform-selective profile as compared to the clinically used sulfonamides.

2. b) Materials and Methods

All starting materials were from different manufactured company like (sd.fine chemicals, Merck, Lobachem etc.) And all the materials used without further purification all reactions were monitored by thin- layer-chromatography using TLC sheet coated with silica gel GF254 spots were visualized with UV light.

3. EXPERIMENTAL PROTOCOLS

3. a) Chemistry

Buffers and chemicals were from sd.fine chemicals, Merck, Lobachem of highest purity available, and were used without further purification. All the synthesized 3 phenyl indole derivatives produced and purified in laboratory as described earlier. Melting points are recorded in open capillary one ended tubes and are uncorrected. The IR spectra (KBr) were recorded on a SHIMADZU FTIR-8300, spectrophotometer. The 1H-NMR spectra were recorded on a Bruker Advance-400 MHz spectrometer

3. a) a)- 2-amino-5-chloro-4-chloro-benzophenone

A mixture of 31.5 g (0.135 mol) of p-chlorobenzoic acid (6) and 30mL of thionyl chloride was heated under reflux to give a clear solution. Removal of the excess of thionyl chloride under reduced pressure obtained white solid and immediately used for the next reaction. To the benzoyl chloride heated to 120 _C was added in portions with stirring 9.6 g (0.05 mol) of 4-chloroaniline. The mixture was heated to 180 _C and 12.5 g (0.063 mol) of ZnCl2 was added. The temperature was gradually increased to about 205 _C and kept there for 2 h. After cooling to 120 _C, 90mL of 3N HCl was added and the mixture stirred and heated to reflux. The hot acid layer was decanted and this procedure repeated two or three times. The water-insoluble residue was dissolved in 120mL of 70% sulfuric acid and reflux for 8 h and then, after cooling poured into a large amount of ice water. The reaction mixture was neutralized with aqueous ammonia hydroxy and extracted with ethyl acetate, dried over Na2SO4.

3. a) b) 2-N-(4-aminosulfonylbenzoyl)-amide-benzophenone

To a solution of 3.0 g (0.010 mol) of 2-aminobenzophenone (3a), 2.6mL (0.011 mol) of triethylamine in 30mL of dry THF under nitrogen was added a solution of 3.0 g (0.010 mol) of 4-aminosulfonylbenzoyl chloride in 15mL of dry THF. The

reaction mixture was stirred at room temperature for 2 h, and filtered. The filtrate was concentrated and the residue was purified by column chromatograph on silica gel (eluent: petroleum ether–ethyl acetate, 1:1) to give the title compound as white needle crystal,

3. a) c) 2-(4-aminosulfonylphenyl)-3-phenyl-indole .

2-N-(4 - aminosulfonylbenzoyl) - amide – benzophenone (4a) (1.04 g, 3 mmol), 1.5 g (12 mmol) of 90% Zn was suspended in 20mL dry THF. To the mixture 1.0mL (6.2 mmol) of TiCl4 was added dropwise and heated toreflux for 1.5 h. The solvent was removed in vacuo and the residue was purified by column chromatography using petroleum ether–ethyl acetate (3:1) as elutant.

R_P a. 2-(4-aminosulfonylphenyl)-3-phenyl-5-chloro indole The litil compound was obtained was white crystal yield 45.7% mp297-299^{0}C IR (KBr) v max in cm^{-1} 3417 (N=N), 3321 (N-H), 1688(C=O), 2872(C-H) 763 (C-Cl) ^{1}H NMR (300 MH_Z, DMSO) $^\delta$ 3.24 ($_S$ 2H, SO_2NH_2),7.02-7,91($_M$ 12H.Ar-H),11.94 ($_S$ 1H,N-H,)anal;calcd for, C $_{20}$H $_{15}$ClN$_2$SO$_2$,C 62.72 H 3.95,N 7.32, found C 62.59,H 4.08,N 7.30

R_P b. 2-(4-aminosulfonylphenyl)-3-phenyl-5-floro indole The litil compound was obtained was white crystal yield 53.5% mp302-304^{0}C IR (KBr) v max in cm^{-1} 3410 (N=N), 3318 (N-H), 1667(C=O), 2894(C-H) 1231 (C-F) ^{1}H NMR (300 MH_Z,DMSO)$^\delta$ 3.35($_S$ 2H, SO_2NH_2),7.01-7,79($_M$ 12H.Ar-H),11.84 ($_S$ 1H,N-H,)anal;calcd for, C $_{20}$H $_{15}$ FN$_2$SO$_2$,C 65.56 H 3.84,N 7.65, found C 65.46,H 4.16,N 7.43

R_P c. 2-(4-aminosulfonylphenyl)-3-phenyl-5-Hydroxy indole The litil compound was obtained was white crystal yield 67% mp241-243^{0}C IR (KBr) v max in cm^{-1} 3423 (N=N), 3308 (N-H), 1643(C=O), 2862(C-H) 1565 (C-OH) ^{1}H NMR(300 MH_Z,DMSO)$^\delta$ 3.62($_S$ 2H, SO_2NH_2),6.80-7,77($_M$ 11H.Ar-H),9.43 ($_S$ 1H,OH,) 11.56 anal;calcd for, C $_{20}$H $_{16}$ N$_2$SO3 ,C 56.92 H 4.43,N 6.69, found C 56.82,H 4.34,N 7.47

R_P d. 2-(4-aminosulfonylphenyl)-3-phenyl-5-amino indole The litil compound was obtained was white needle crystal yield 57.5% mp216-218^{0}C IR (KBr) v max in cm^{-1} 3437 (N=N), 3313 (N-H), 1653(C=O), 2851(C-H) 1529 (C-NH_2) ^{1}H NMR (300 MH_Z, DMSO)$^\delta$ 3.62($_S$ 2H, SO_2NH_2),6.80-7,77($_M$ 11H.Ar-H),9.43 anal;calcd for, C $_{20}$H $_{17}$ N$_3$SO2 ,C 63.15 H 4.24,N 7.36, found C 63.37,H 4.37,N 7.44

R_P e. 2-(4-aminosulfonylphenyl)-3-phenyl-5-methyl indole The litil compound was obtained was white crystal yield 77.5% mp242-244^{0}C IR (KBr) v max in cm^{-1} 3418 (N=N), 3304 (N-H), 1673(C=O), 2855(C-H) ^{1}H NMR(300 MH_Z,DMSO)$^\delta$ 3.32 ($_S$,3H,CH_3) ($_S$ 2H, SO_2NH_2),7.01-7,77($_M$ 12H.Ar-H),9.11.57($_S$ 1H,N-H,) 3.32 anal;calcd for, $C_{21}H_{18}N_2SO2$,C 56.92 H 4.43,N 6.69, found C 56.82,H 4.34,N 7.47

R_P f. 2-(4-aminosulfonylphenyl)-3-phenyl-5-methoxy indole The litil compound was obtained was white crystal yield 72.5% mp280-282^{0}C IR (KBr) v max in cm^{-1} 3423 (N=N), 3307 (N-H), 1652(C=O), 2868(C-H) 1872 (C-OCH_3) ^{1}H NMR(300 MH_Z,DMSO)$^\delta$ 3.32 $_S$,3H,OCH_3)6.97-7.78 ($_S$ 2H, SO_2NH_2),3.79($_M$ 12H.Ar-H),9.11.57 ($_S$ 1H,N-H,) 3.32 anal;calcd for, $C_{21}H_{18}N_2SO_3$,C 66.65 H 4.43,N 6.69, found C 56.82,H 4.79,N 7.40 N 6.86.

R_P g. 2-(4-aminosulfonylphenyl)-3-phenyl-5-iodine indole The litil compound was obtained was white crystal yield 62.5% mp305-307^{0}C IR (KBr) v max in cm^{-1} 3413 (N=N), 3304 (N-H), 1673(C=O), 2858(C-H) 928 (C-I) ^{1}H NMR(300 MH_Z,DMSO)$^\delta$ 3.42 ($_S$,3H,I) 7.97-8.78 ($_S$ 2H, SO_2NH_2),3.79($_M$ 12H.Ar-H),21.59($_S$ 1H,N-H,) 4.32 anal;calcd for, $C_{20}H_{15}IN_2SO_3$,C 56.65 H 4.43,N 6.69, found C 66.82,H 4.59,N 7.40 ,

R_P h. 2-(4-aminosulfonylphenyl)-3-phenyl-5-bromo indole The litil compound was obtained was white crystal yield 55.5% mp310-312^{0}C IR (KBr) v max in cm^{-1} 3419 (N=N), 3313 (N-H), 1675(C=O), 2856(C-H) 524 (C-Br) ^{1}H NMR(300 MH_Z,DMSO)$^\delta$ 3.31 ($_S$ 2H, SO_2NH_2),7.29-7.78 ($_M$ 12H.Ar-H),.11.94($_S$ 1H,N-H,) 3.32 anal;calcd for, $C_{20}H_{15}N_2BrSO_3$,C 56.33 H 3.54,N 6.56, found C 56.45,H 3.76, N 6.60.

CONCLUSION

In conclusion, we have synthesized some 3 phenyl indole derivatives (Rp a-h) and evaluated these ompounds for their inhibition of renin activities. Most of them demonstrated a broad spectrum of Anti microbial activities. The simple 3 phenyl indole derivatives Rp b, Rpf and Rp g were concluded as most potent derivatives in all the cases.

REFERENCES

Andrew N. Boa Shane P. Canavan, Paul R. Hirst, Christopher Ramsey, Andrew M. W. Steadb, and Glenn A. McConkey “Synthesis of brequinar analogue inhibitors of malaria parasitedihydroorotate dehydrogenase. Bioorganic & Medicinal Chemistry” 13 (2005); 1945–1967.

Apurba K. Bhattacharjee , Mark G. Hartell, Daniel A. Nichols, Rickey P. Hicks, Benjamin Stanton, John E. van Hamont,Wilbur K. Milhous. “Structure-activity relationship study of antimalarial indole quinazoline-6, 12-diones (tryptanthrins). Three dimensional pharmacophore modelling and identification of new antimalarial candidates” European Journal of Medicinal Chemistry. 39 (2004); 59–67.

Carola Huthmacher, Andreas Hoppe, Sascha Bulik, Hermann-Georg Holzhütter “Antimalarial drug targets in Plasmodium Palciparum predicted by stage-specific metabolicnetwork Analysis” BMC Systems Biology. 2010, 4:120.

CS Mitaine-Offer, M. Sauvain, A. Valentin, J. Callapa, M. Mallié and M. Zèches- Hanrot “Antiplasmodial activi-

ty of *Aspidosperma* indole alkaloids Phytomedicine" 2002 Vol. 9; 142–145.

E. Elisabetsky1 and L. Costa-Campos "The Alkaloid Alstonine: A Review of Its Pharmacological Properties" Advance1 Access Publication. 16 January 2006.

E.O. Ajaiyeoba U.I. Abalogu H.C. Krebs b, A.M.J. Oduola "In vivo antimalarial activities of *Quassia amara* and *Quassia undulata* plant extracts in mice" Journal of Ethnopharmacology. 67 (1999) 321–325.

J.S. Biradar, B.S. Sasidhar, R. Parveen "Synthesis, antioxidant and DNA cleavage activities of novel indole derivatives" European Journal of Medicinal Chemistry. 45 (2010); 4074 4078.

Jingyong Sun , Hongxiang Lou , Shengjun Dai , Hui Xu, Feng Zhao, Ke Liu "Indole alkoloids from Nauclea officinalis with weak antimalarial activity" Phytochemistry. 69 (2008); 1405–1410.

Joana Dumc, Vytas Martynaitis,a Wolfgang Holzer, Sven Mangelinckx, Norbert De Kimpec and Algirdas S kus. "Synthesis and ring transformations of 1-amino-1, 2, 3, 9a-tetrahydroimidazo [1, 2-a] indol-2(9H)-ones" Tetrahedron 62 (2006); 3309–3319.

Joseph L Kgokong,a, Peter P. Smithb and Gilbert M. Matsab "1,2,4-Triazino-[5,6b]indole derivatives: effects of the trifluoromethyl group on in vitro antimalarial activity" Bioorganic & Medicinal Chemistry. 13 (2005); 2935–2942.

Kazuhiro Kobayashi, Yasutoshi Himei, Shuhei Fukamachi, Miyuki Tanmatsu,Osamu Morikawa and Hisatoshi Konishi "Synthesis of 9-arylamino- and (Z)-9-arylimino-9H-pyrrolo-[1,2-a]indoles by reactions of 2-(pyrrol-1-yl)-benzaldehydes with aryl amines" Tetrahedron 63 (2007); 4356–4359.

Peter Cosmos, Lajos Fodor, Istv_an M_anditya and G_abor Bern_ath. "An efficient route for the synthesis of 2-arylthiazino [5, 6-b]indole derivative" .Tetrahedron 63 (2007); 4983–4989.