New Orally Active Diphenylmethyl-based Ester Analogues of Dihydroartemisinin: Synthesis and Antimalarial Assessment against multidrug-resistant *Plasmodium Yoelii Nigeriensis* in mice

Sandeep Chaudhary, Niraj K. Naikade, Mohit K. Tiwari, Lalit Yadav, Bharti Rajesh K. Shyamlal, Sunil.K. Puri

PII: S0960-894X(16)30122-6
DOI: http://dx.doi.org/10.1016/j.bmcl.2016.02.019
Reference: BMCL 23570

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 8 January 2016
Revised Date: 3 February 2016
Accepted Date: 8 February 2016

Please cite this article as: Chaudhary, S., Naikade, N.K., Tiwari, M.K., Yadav, L., Shyamlal, B.R.K., Puri, Sunil.K., New Orally Active Diphenylmethyl-based Ester Analogues of Dihydroartemisinin: Synthesis and Antimalarial Assessment against multidrug-resistant *Plasmodium Yoelii Nigeriensis* in mice, *Bioorganic & Medicinal Chemistry Letters* (2016), doi: http://dx.doi.org/10.1016/j.bmcl.2016.02.019

New Orally Active Diphenylmethyl-based Ester Analogues of Dihydroartemisinin: Synthesis and Antimalarial Assessment against multidrug-resistant *Plasmodium Yoelii Nigeriensis* in mice

Sandeep Chaudhary, [a, b, c, *] Niraj K. Naikade,[c] Mohit K. Tiwari, [a] Lalit Yadav, [a] Bharti Rajesh K. Shyamlal[a] and Sunil. K. Puri,[d,*]

[a]*Department of Chemistry &* [b]*Materials Research Centre, Malaviya National Institute of Technology, Jawaharlal Nehru Marg, Jaipur-302017, India*

[c]*Division of Medicinal and Process Chemistry and* [d]*Division of Parasitology, CSIR-Central Drug Research Institute, Sector 10, Jankipuram Extension, Sitapur Road, Lucknow-226031, India*

This is where the receipt/accepted dates will go; Received Month XX, 2000; Accepted Month XX, 2000 [BMCL RECEIPT]

Abstract— A new series of ester analogues of artemisinin **8a-f**, incorporating diphenylmethyl as pharmacologically privileged substructure, and **8g-j** have been prepared and evaluated for their antimalarial activity against multidrug-resistant (MDR) *Plasmodium yoelii nigeriensis* in Swiss mice via oral route. These diphenylmethyl-based ester analogues **8a-f** were found to be 2-4 folds more active than the antimalarial drugs *β*-arteether **4** and artesunic acid **5**. Ester **8a**, the most active compound of the series, provided complete protection to the infected mice at 24 mg/kg × 4 days as well as 12 mg/kg × 4 days, respectively. In this model *β*-arteether provided 100% and 20% protection at 48 mg/kg × 4 days and 24 mg/kg × 4 days, respectively.

The discovery of artemisinin **1**, as the active principle of the Chinese traditional drug against malaria, *Artemisia annua*, is a major breakthrough in malaria chemotherapy.[1] The derivatives of artemisinin, e.g. dihydroartemisinin **2**, artemether **3**, arteether **4**, and artesunic acid **5** (figure.1), are more active than the parent compound, and are currently the drugs of choice for the treatment of malaria caused by multidrug-resistant *P. falciparum*.[2, 3]

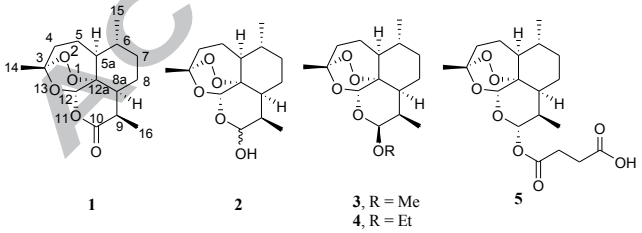


Figure 1. Artemisinin and its clinically useful derivatives.

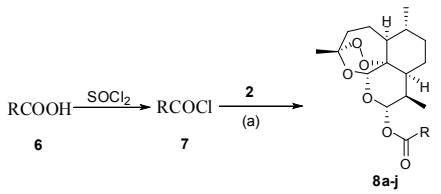
While these compounds show high efficacy when administered by systemic routes, they are comparatively less active when given by oral route. In recent years, several efforts have been made to improve the antimalarial activity of artemisinin derivatives by oral route.[6] However, these new derivatives are only marginally more active than artemether and artesunic acid. Therefore, the search for the next generation artemisinin analogues continues to define an active area of scientific research.

We recently reported the synthesis of lipophilic ether and ester derivatives of dihydroartemisinin, incorporating pharmacologically privileged substructures such as biphenyl, adamantane and flourene, most of which showed high order of antimalarial activity against multidrug-resistant (MDR) *P. yoelii nigeriensis* in Swiss mice by oral route.[4] In these studies, we noticed quite unique observation that *α*-isomers (in the case of ether derivatives) and the ester derivatives (which are formed exclusively as *α*-isomers[5]) were found to show promising antimalarial activity in comparison to their *β*-isomers. Similar observations were also obtained on synthetic antimalarial 1, 2, 4-trioxanes, wherein molecules built around adamantane, biphenyl and flourene scaffolds show high

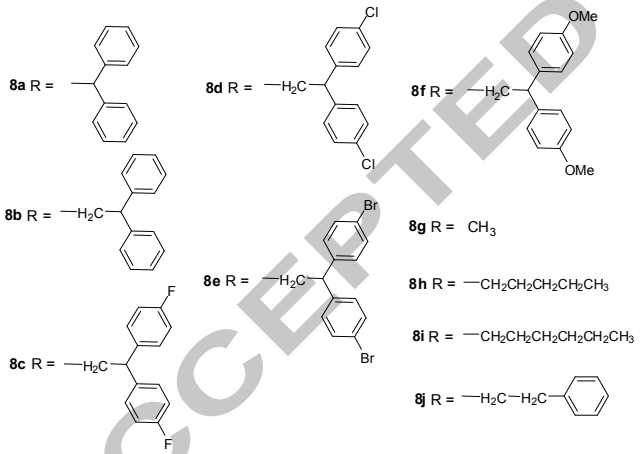
Keywords: Dihydroartemisinin; Arteether; Antimalarial; Multi-drug resistant; 1, 2, 4-trioxanes
*Corresponding author. Tel.: +91-0141-2713319; fax: +91-141-2529029; e-mail: schaudhary.chy@mnit.ac.in, sk_puri@cdri.res.in

order of antimalarial activity by oral routes.[6] Furthermore, several reports are available in the literature wherein compounds having these pharmacologically privileged substructures as part of molecular architecture show promising biological activities.[7]

Chemical literature reveals that, compounds build around diphenylmethyl scaffold also show promising biological activities.[8] Inspired by its promising role in improving biological activity, we prepared ester derivatives **8a-f**, incorporating diphenylmethyl group as pharmacologically privileged substructures and evaluated them for their antimalarial activity against multidrug-resistant *P. yoelii nigeriensis* in Swiss mice. Herein, we report the synthesis and antimalarial activity of a new series of ester derivatives of dihydroartemisinin **8a-f**, some of which were found to be orally 2 to 4-folds more active than β-arteether. We also report, for the first time, *in vivo* antimalarial activity of some previously reported esters **8g-j** which were assessed against multidrug-resistant *P. yoelii nigeriensis* in Swiss mice via oral route. These known esters were earliar assessed against chloroquine-sensitive *P. berghei* strain.

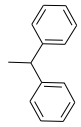
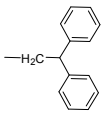
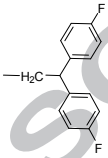
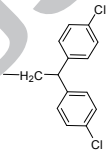
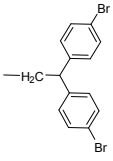
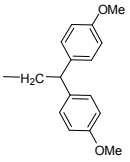
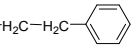


Scheme 1 *Reagents and conditions*: (a)Triethylamine , Dry CH_2Cl_2 , 0^oC, 2h.

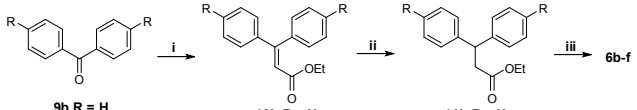


Dihydroartemisinin **2** was prepared from artemisinin **1** using the literature procedure.[9] The acid chlorides RCOCl **7a-j** were prepared from the corresponding carboxylic acids **6a-j** by heating with thionyl chloride at 50 °C-60 °C for 2-3 h and then reacted in situ with dihydroartemisinin **2** in the presence of Et_3N in dry CH_2Cl_2 at 0 °C for 2h to furnish ester derivatives **8a-j** in 48-94% yields (scheme 1, Table 1).[10] The known ester derivatives **8a**[10a], **8g**[10b,c], and **8h-j**[10d], were also prepared in a similar way (scheme 1, Table 1).

Table 1: Ester derivatives **8a-j.**

Compd. No.	R =	m.p. (in ^{0}C)	% yield
8a		70-71	59
8b		72-73	61
8c		68-70	51
8d		81-83	48
8e		83-85	54
8f		65-67	55
8g	CH_3	99- 101	94
8h	$-CH_2CH_2CH_2CH_2CH_3$	Oily	59
8i	$-CH_2CH_2CH_2CH_2CH_2CH_3$	Oily	60
8j		Oily	62

For the synthesis of ester derivatives **8b-f**, the synthesis of carboxylic acid **6b-f** was carried out using the literature procedure (Scheme 2).[11]



Scheme 2. Reagents and conditions: (i) Triethylphosphonoacetate, NaH, dry THF, 0 °C-rt, 10 h. (ii) H_2, 10% Pd/C, MeOH, rt, 2 h. (iii) LiOH, CH_3CN:H_2O (1:1), rt, 3 h. (iv) $SOCl_2$, reflux, 2 h. (v) Et_3N, dry DCM, 0 °C-rt, 3 h.

Antimalarial drugs *β*-arteether and artesunic acid, when given orally at 48 mg/kg × 4 days provide 100% protection to the mice infected with multidrug-resistant *P. yoelii nigeriensis*. At 24 mg/kg × 4 days, while artesunic acid does not provide any protection, *β*-arteether provides only

20% protection. Since the aim of the present study was to select compounds having activity profile better than that of *β*-arteether and artesunic acid, all the prepared ester derivatives **8a-j** were initially screened against multidrug-resistant *P. yoelii nigeriensis* in Swiss mice at 48 mg/kg × 4 days by oral route.[12] All these esters provided 100% protection at this dose except ester **8g** and therefore all these active compounds were further screened at 24 mg/kg × 4 days. Compounds **8a-f** which showed 100% protection at 24 mg/kg × 4 days were further tested at 12 mg/kg × 4 days. Compounds **8a**, **8c** and **8f** which showed 100% or partial protection at 12 mg/kg × 4 days were further tested at 6 mg/kg × 4 days. The results are summarized in Table 3.

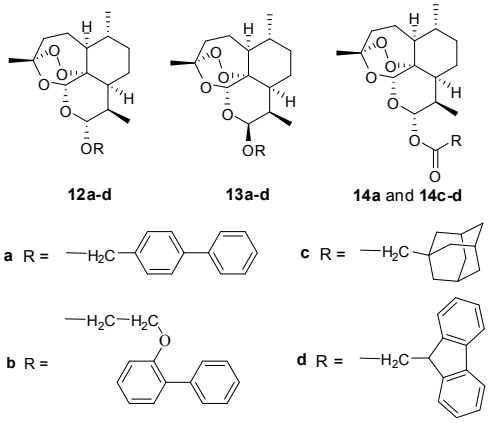


Figure 2. Structure of active ether derivatives of dihydroartemisinin **12a-d** and **13a-d** and ester derivatives of dihydroartemisinin **14a** and **14c-d**.

In search for new artemisinin derivatives having high efficacy and greater bioavailability by oral route, we had recently reported a series of ether and ester derivatives of dihydroartemisinin, incorporating adamantane, biphenyl and fluorene moieties. Several of these lipophilic derivatives **12-14** were found to be 2-4 times more active than *β*-arteether by oral route (Figure 2, Table 2).[4, 5, 6] In that study, we had observed earliar that the *α*-isomers i.e. **12a-d** of these ether derivatives were significantly more active than the corresponding *β*-isomers **13a-d**. Similarly, among ester derivatives, fluorene-based ester **14d** was found significantly more active than **14a** and **14c** (Figure 2). This observation was found fully in compliment with the Janssen et al. model; that increased lipophilicity is accompanied by increase in oral bioavailability and hence increased in antimalarial activity.[4b]

This unique observation has, however, suggested us that a bulkier group on the α-face of the molecule has beneficial effect on antimalarial activity.[4c] Thus, to give insight into this observation; we initially prepared simple non-bulky esters **8g-j** and assessed them for their antimalarial activity (Table 3). The ester **8g**, the acetate of dihydroartemisinin having Log P value of 3.37, was found to be less potent than β-arteether and artesunic acid. We then prepared straight chain containing ester derivatives **8h** (Log P =5.28) and **8i** (Log P =5.70) having greater lipophilicity than **8g**; both were found to be equally potent as β-arteether and artesunic acid.

Table 2. Blood schizontocidal activity of esters **12-14** against multidrug-resistant (MDR) strain *P. yoelii nigeriensis* in Swiss mice via oral route[12] (Data taken from ref. **4a-e**)

Compd.	Log P	Dose (mg / kg × 4 days)[a]	% suppression Of Parasitaemia on day 4[b,c]	Cured / Treated
12a	6.91	48	100	5/5
		24	100	10/10
		12	100	10/10
		6	86.33	0/5
12b	6.85	48	100	5/5
		24	100	10/10
		12	100	10/10
		6	64.44	0/5
12c + 13c	6.02	48	100	5/5
		24	100	7/10
		12	100	3/5
12d	6.75	48	100	5/5
		24	100	5/5
		12	100	1/5
13a	6.91	48	100	5/5
		24	100	6/10
		12	100	2/5
13b	6.85	48	100	0/5
		24	100	0/5
13d	6.75	48	100	5/5
		24	100	5/5
		12	100	2/5
		6	92.95	0/5
14a	6.89	48	100	5/5
		24	100	3/5
14c	5.99	48	100	5/5
		24	100	5/5
		12	100	1/5
14d	6.79	48	100	5/5
		24	100	5/5
		12	100	0/5
β-arteether	3.84	48	100	5/5
		24	100	1/5
α-Arteether	3.84	48	100	0/5
		24	100	0/5
Artesunic acid	3.04	48	100	5/5
		24	100	0/5

[a]The drug dilutions of compounds were prepared in ground oil and administered to a group of mice at each dose, from day 0-3, once daily. [b]Percent suppression= [(*C*- *T*) / *C*] × 100; where *C*= parasitaemia in control group, and *T*= parasitaemia in treated group. [c]100% suppression of parasitaemia means no parasites were detected in 50 oil immersion fields during microscopic observation.[13]

Subsequently, to understand the effect of aromatic ring on antimalarial activity of artemisinin, we prepared ester **8j**. This compound was also found to be as equally potent as *β*-arteether and artesunic acid. These results suggest us that non-bulky substituent at C-10 position of artemisinin derivatives do not significantly improve antimalarial activity. Then, we prepared bulky ester derivatives **8a-f** (Log P 6.90-8.27) incorporating diphenylmethyl group which were more lipophilic than that of the active ether derivatives **12a-d** (Log P 5.51-6.91) and the ester derivatives **14a** and **14c-d** and screened them against multi-drug resistant *P.yoelii* via oral route.[4]

Table 3. Blood schizontocidal activity of esters **8a-j** against multidrug-

resistant (MDR) strain *P. yoelii nigeriensis* in Swiss mice via oral route.[12]

Compd.	Log P	Dose (mg / kg × 4 days)[a]	% suppression Of Parasitaemia on day 4[b,c]	Cured / Treated
8a	6.97	48	100	5/5
		24	100	5/5
		12	100	10/10
		6	100	0/5
8b	7.15	48	100	5/5
		24	100	5/5
		12	100	0/5
8c	7.47	48	100	5/5
		24	100	5/5
		12	100	8/10
		6	100	0/5
8d	8.27	48	100	5/5
		24	100	5/5
		12	96	0/5
8e	8.81	48	100	5/5
		24	100	5/5
		12	100	0/5
8f	6.90	48	100	5/5
		24	100	5/5
		12	100	8/10
		6	100	0/5
8g	3.37	48	100	2/5
		24	99	0/5
8h	5.28	48	100	5/5
		24	100	0/5
8i	5.70	48	100	5/5
		24	100	1/5
8j	5.63	48	100	5/5
		24	100	1/5
β-arteether	3.84	48	100	5/5
		24	100	1/5
α-Arteether	3.84	48	100	0/5
		24	100	0/5
Artesunic acid	3.04	48	100	5/5
		24	100	0/5

[a]The drug dilutions of compounds were prepared in ground oil and administered to a group of mice at each dose, from day 0-3, once daily. [b]Percent suppression= [(*C*- *T*) / *C*] × 100; where *C*= parasitaemia in control group, and *T*= parasitaemia in treated group. [c]100% suppression of parasitaemia means no parasites were detected in 50 oil immersion fields during microscopic observation.[13]

As can be seen from Table 3, all these compounds provided 100% protection at 48 mg/kg × 4 days and therefore all these derivatives are at least as effective as β-arteether which provided 100% and 20% protection at 48 mg/kg × 4 days and 24 mg/kg × 4 days, respectively. Since the present work on ester derivatives is an extension of our previous studies,[4] it is worthwhile to compare the biological activities of these two series. The most active fluorene derivative **14d**, provided 100% protection at 24 mg/kg. At 12 mg/kg × 4 days, it showed 100% clearance of parasitaemia on day 4 but none of the treated mice survived beyond day 28. Whereas the diphenylmethyl-based ester **8a**, the most active compound of the series, provides 100% protection at both 24 mg/kg × 4 days as well as 12 mg/kg × 4 days and was found to be four times more active than *β*-arteether and artesunic acid. Even at 6 mg/kg × 4 days, it shows 100% suppression of parasitaemia on day 4 but none of the treated mice survived beyond day 28. The next most active ester **8c** and **8f**, showed 100% suppression of parasitaemia at 24 mg/kg × 4 days and 12 mg/kg × 4 days and provided 100% and 80% protection, respectively to the treated mice. Even at 6 mg/kg × 4 days, it shows 100% suppression of parasitaemia on day 4 but none of the treated mice survived beyond day 28. Ester **8b, 8d** and **8e**, the next most active ester showed complete clearance of parasitaemia at 24 mg/kg × 4 days and 12 mg/kg × 4 days and provided 100% and 80% protection, respectively to the treated mice. At 12 mg/kg × 4 days, **8b, 8d** and **8e** showed 100%, 96% and 100 %, respectively suppression of parasitaemia on day 4 but none of the treated mice survived beyond day 28.

In conclusion, we have prepared a new series of highly active lipophilic ester derivatives of dihydroartemisinin **8a-f** incorporating diphenylmethyl group as pharmacologically privileged substructures and evaluated them for their antimalarial activity against multidrug-resistant *P. yoelii nigeriensis* in Swiss mice via oral route, all of which show better activity profile than that of *β*-arteether and artesunic acid. For the first time, we also report the *in vivo* antimalarial activity of some previously reported esters **8g-j** which were assessed against multidrug-resistant *P. yoelii nigeriensis* in Swiss mice via oral route. Compound **8a**, the most active compound of the series, was found to be four times more active than *β*-arteether and artesunic acid. This study justifies that introduction of more bulky lipophilic group on the *α*-face of the dihydroartemisinin significantly enhance antimalarial activity. Hence, the easy preparation of these artemisinin compounds with high order of antimalarial activity qualifies these compounds for further developmental studies.

Acknowledgement

S.C. thanks MNIT Jaipur for providing Seed Grant. S.C. and N.K.N are thankful to the Council of Scientific and Industrial Research (CSIR), New Delhi for the award of Senior Research Fellowship. B.R.K.S. is thankful to the University Grant Commission (UGC), New Delhi for the award of Junior Research Fellowship. L.Y. is thankful to the Department of Science and Technology (DST), New Delhi for the award of Junior Research Fellowship (Project No. CS-067/2013). S.C. is thankful to Dr. Chandan Singh, CSIR-Central Drug Research Institute, Lucknow for providing necessary chemicals and lab facilities. M.K.T. is thankful to MNIT Jaipur for providing institute fellowship. S.C. thanks SAIF, CSIR-CDRI, Lucknow and Materials Research Centre, MNIT Jaipur for providing analytical facilities.

References and Notes

1. Lin, J. M.; Ni, M.-Y.; Tou, Y.-Y.; Wa, Z.-H.; Wu Y.-L.; Chou, W. S. *Acta Chim. Sinica*, **1979**, *37*, 129.
2. For reviews on artemisinin and its analogues see: (a) Klayman, D. L. *Science* **1985,** *228*, 1049-1055. (b) Luo, X. D.; Shen, C. C. *Med.*

Res. Rev. **1987**, *7*, 29-52. (c) Cumming, J. N.; Ploypradith, P.; Posner, G. H. *Adv. Pharmacol.* **1997**, *37*, 253-297. (d) Bhattacharya, A. K.; Sharma, R. P. *Heterocycles* **1999**, *51*, 1681-1745. (e) Borstnik, K.; Paik, I.; Shapiro, T. A.; Posner, G. H. *Int. J. Parasitol.* **2002**, *32*, 1661-1667. (f) Ploypradith, P. *Acta Trop.* **2004**, *89*, 329-342. (g) O'Neill, P. M.; Posner, G. H. *J. Med. Chem.* **2004**, 47, 2945-2964. (h) Tang, Y.; Dong, Y.; Vennerstrom, J. L. *Med. Res. Rev.* **2004**, *24*, 425-448. (i) Jefford, C. W. *Curr. Opin. Invest. Drugs* **2004**, *5*, 866-872. (j) Jefford, C.W. *Drug Discovery Today* **2007**, *12*, 487-494.

3. (a) Asthana, O. P.; Srivastava, J. S.; Valecha, N. *J. Parasitic Diseases* **1997**, *211*, 1-12. (b) Jambou. R.; Legrand, E.; Niang, M. Khim, N.; Lim, P.; Volney, B.; Therese Ekala, M.; Bouchier, C.; Esterre, P.; Fandeur, T.; Mercereau-Puijalon, O. *Res. Lett.* **2005**, *366*, 1960-1963.
4. (a) Chaudhary, S.; Puri, S. K. and Singh, C. *Med. Chem. Res.*, **2004**, *12* (*6/7*), 362. (b) Singh, C.; Chaudhary**,** S.; Puri, S. K. *J. Med. Chem.*, **2006**, *49 (24)*, 7227-7233. (c) Singh, C.; Chaudhary, S.; Puri, S. K. *Bioorg. Med. Chem. Lett.*, **2008**, *18*, 1436-1441 and references cited therein. (d) Singh, C.; Chaudhary, S.; and Puri, S. K. *Indian Patent,* **2010**, *Patent No.* A 20100326 *(IN2004DE00209)*. (e) Singh, C.; Chaudhary, S.; and Puri, S. K. *Indian Patent,* **2012**, *Patent No.* **253045** A1 20120622 *(IN2006DE00391)*. (f) Singh, C.; Kanchan, R.; Chaudhary, S. and Puri, S. K. *J. Med. Chem.* **2012**, *55(3)*, 1117-1126 and references cited therein.
5. Haynes, R. K.; Chan, H. –W.; Cheung, M.-K.; Lam, W. –L.; Soo, M, -K.; Tsang, H.-W.; Voerste, A.; Williams, I. D. *Eur. J. Org. Chem*, **2002**, 113-132.
6. (a) Singh, C.; Kanchan, R.; Puri, S. K. *Indian Patent Appl. No.* 1554 DEL 99, 1999. (b) Singh, C.; Tiwari, P.; Puri, S. K. U.S. Patent 6,737,438 B2, 2004. (c) Singh, C.; Kanchan, R.; Sharma, U.; Puri, S. K. *J. Med. Chem.*, **2007**, *50 (3)*, 521-527.
7. (a) Craig, P. N. Drug Compendium. In *Comprehensive Medicinal Chemistry*, 1st Ed., Vol. 6.; Hansch, C.; Sammes, P. G.; Taylor, J. B., Eds.; Pergamon Press.; Oxford, UK, **1990**; pp 237-965. (b) Vennerstrom, J. L.; Arbe-Barnes, S.; Brun, R.; Charman, S. A.; Chiu, F. C. K.; Chollet, J.; Dong, Y.; Dorn, A.; Hunziker, D.; Matile, H.; McIntosh, K.; Padmanilayam, M.; Santo Tomas, J.; Scheurer, C.; Scorneaux, B.; Tang, Y.; Urwyler, H.; Wittlin S.; Charman, W. N. *Nature* **2004**, 430, 900-904. (c) Augeri, D. J.; Robl, J. A.; Betebenner, D. A.; Magnin, D. R.; Khanna, A.; Robertson, J. G.; Wang, A.; Simpkins, L. M.; Taunk, P.; Huang, Q.; Han, S. -P.; Abboa-Offei, B.; Cap, M.; Xin, L.; Tao, L.; Tozzo, E.; Welzel, G. E.; Egan, D. M.; Marcinkeviciene, J.; Chang, S. Y.; S. A.; Biller, Kirby, M. S.; Parker, R. A.; Hamann, L. G. *J. Med. Chem.* **2005**, 48, 5025 – 5037. (d) Lund, B. W.; Piu, F.; Gauthier, N. K.; Eeg, A.; Currier, E.; Sherbukhin, V.; Brann, M. R.; Hacksell, U.; Olsson, R. *J. Med. Chem.* **2005**, 48, 7517 – 7519. (e) Griesbeck, A.G.; El-Idreesy, T. T.; Hoinck, L. –O.; Lexa, J.; Brun, R.; *Bioorg. Med. Chem. Lett.* **2005**, *15*, 595--597. (f) Nguyen, C.; Kasinathan, G.; Leal-Cortijo, I.; Musso-Buendia, A.; Kaiser, M.; Brun, R.; Ruiz-Pérez, L. M.; Johansson, N. G.;, González-Pacanowska, D.; Gilbert, I. H. *J. Med. Chem.* **2005**, *49(19)*, 5942 – 5954. (g) Stern, E.; Muccioli, G. G.; Millet, R.; Goossens, J. -F.; Farce, A.; Chavatte, P.; Poupaert, J. H.; Lambert, D. M.; Depreux, P.; Hénichart, J. -P. *J. Med. Chem.* **2006**, *49(1)*, 70-79. (h) Roberti, M.; Pizzirani, D.; Recanatini M.; Simoni, D.; Grimaudo, S.; Cristina, A. D.; Abbadessa, V.; Gebbia, N.; Tolomeo, M.; *J. Med. Chem.* **2006**, *49(10)*, 3012 – 3018. (i) Qiao, L.; Baumann, C. A.; Crysler, C. S.; Ninan, N. S.; Abad, M.C.; Spurlino, J. C.; DesJarlais, R. L.; Kervinen, J.; Neeper, M. P.; Bayoumy, S. S. *Bioorg. Med. Chem. Lett.* **2006**, *16(1)*, 123-128. (j) Leban, J.; Kralik, M.; Mies, J.; Baumgartner, R.; Gassen M.; Tasler, S. *Bioorg. Med. Chem. Lett.* **2006**, *16(2)*, 267-270. (k) Xiang, J. S.; Hu, Y.; Rush, T. S.; Thomason, J. R.; Ipek, M.; Sum, P.-E.; Abrous, L.; Sabatini, J. J.; Georgiadis, K.; Reifenberg, E. *Bioorg. Med. Chem. Lett.* **2006**, *16(2)*, 311-316. (l) Chaudhary, S.; Sharma, V.; Jaiswal, P. K.; Gaikwad, A. N.; Sinha, S. K.; Puri, S. K.; Sharon, A.; Maulik, P. R.; Chaturvedi, V. *Org. Lett.*, **2015,** *17 (20)*, 4948-4951.
8. (a) (i) Greaves, M.W.; Tan, K. T. *Clin Rev Allergy Immunol* **2007**, *33 (1-2)*, 134-143. (ii) Katagiri, K.; Arakawa, S.; Hatano, Y.; Fujiwara, S. *The Journal of Dermatology* **2006**, *33 (2)*, 75. (b) Chakraborty, P.; Roy, S. S.; Hossain, S. K.U.; Bhattacharya, S. *Free Radical Res.* **2010**, *45 (2)*, 177-187. (c) Tep-Areenan, P; Sawasdee, P. *International Journal of Pharmacology*, **2011**, *7 (11)*, 119-124.
9. Brossi, A.; Venugopalan, B. ; Dominquez, G. L. ; Yeh, H. J. C. ; Flippen, A. J. L.; Buchs, P.; Wo, X. D.; Milhous, W.; Peters, W. *J. Med. Chem.* **1988**, *31*, 645.
10. The compound **8g**, **8h**, **8i**, **8j** were prepared earliar: (a) Li, Y.; Yu, P.-L.; Chen, I- H.; Chi, J.-Y. *Yao Hsueh Tung Pao* **1980**, *15 (12)*, 38. (b) Li, Y.; Yu, P.; Chen, Y.; Ji, R. *HuaXue XueBao* **1982**, *40(6)*, 557-61. (c) Li, Y.; Yu, P.-L.; Chen, Y. – X.; Li, L.-Q.; Gai, Y.-Z.; Wang, D.- S.; Zheng, Y. –P. *Acta Pharm. Sin.* **1981**, *16*, 429. (d) Haynes, R. K.; Lam, W. –L.; Chan, H. –W.; Tsang, H. –W. *European Patent 98305595.5, Dated **14-07-1998***. (a) **General Procedure for Esterification of Dihydroartemisinin (Compound 8b as representative)**: To a solution of dihydroartemisinin (0.50 g, 1.75 mmol) and Biphenyl-4-carbonyl chloride (1.14 g, 3 eq., 5.25 mmol) dissolved in dry dichloromethane (30 mL) was added triethylamine (0.73 ml, 3 eq., 5.29 mmol) dropwise at 0^0C. The mixture was stirred at the same temperature for 2h. The reaction mixture was then quenched with saturated sodium bicarbonate solution (25 mL) and extracted with dichloromethane (3 x 25 mL). The organic layer was washed with 10% aqueous HCl solution (2 x 20 mL), then with water, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product on column chromatography over silica gel using ethylacetate/hexane (1:25) as eluant gave pure **8b** (465 mg, 57%) as a white solid. (b) **Selected Spectral Data**: **8a**: White solid; FT-IR (KBr, cm^{-1}): 2929.5, 2875.4, 1749.5, 1453.5, 1142.1, 1116.2, 752.2; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.58 (d, 3H, *J*= 7.0 Hz, CH_3), 0.94 (d, 3H, *J*= 4.8 Hz, CH_3), 1.25-2.06 (m, 10H), 1.43 (s, 3H, CH_3), 2.29-2.56 (m, 2H), 5.12 (s, 1H, benzylic H), 5.43 (s, 1H, C_{12}-H), 5.82 (d, 1H, *J*= 9.8 Hz, C_{10}-H), 7.31 (m, 10H, Aromatic H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.22 (CH_3), 20.64(CH_3), 22.37 (CH_2), 24.99 (CH_2), 26.36 (CH_3), 30.13 (CH_2), 32.32 (CH), 34.47 (CH_2), 36.59 (CH_2), 37.65 (CH), 45.65 (CH), 51.92 (CH), 57.19 (CH), 80.53 (C), 91.91 (CH), 92.97 (CH), 104.85 (C), 127.60 (CH), 127.76 (CH), 128.78 (CH), 129.07 (CH), 129.33 (CH), 138.59 (C), 138.86 (C), 171.76 (C); ESMS (m/z): 501 $[M + Na]^+$; Anal. Calcd for ($C_{29}H_{34}O_6$): C 72.78 H 7.16; Found C 73.03 H 6.96. **8b**: White solid; FT-IR (KBr, cm^{-1}) 2929.9, 2877.2, 1747.2, 1653.9, 1529.6, 1450.4, 1350.9, 1275.6, 1216.2, 1145.2, 1097.4, 1014.1, 755.9; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.84 (d, 3H, *J* = 7.1 Hz, CH_3), 0.98 (d, 3H, *J* = 5.3 Hz, CH_3), 1.25-2.08 (m, 10H), 1.45 (s, 3H, CH_3), 2.31-2.38 (m, 1H), 2.53-2.63 (m, 1H), 3.14-3.23 (m, 2H, $CO\underline{CH_2}$), 4.62 (t, 1H, *J* = 8.1 Hz, benzylic H,), 5.50 (s, 1H, C_{12}-H), 5.92 (d, 1H, *J* = 9.8 Hz, C_{10}-H), 7.28-7.41 (m, 4H), 7.51-7.58 (m, 2H), 7.75 (d, 2H, *J* = 7.4 Hz), , ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.61 (CH_3), 20.65 (CH_3), 22.46 (CH_2), 25.03 (CH_2), 26.38 (CH_3), 32.11 (CH), 34.53 (CH_2), 36.63 (CH_2), 37.72 (CH), 39.10 (CH_2), 43.77 (CH), 45.68 (CH), 51.98 (CH), 80.55 (C), 91.90 (CH), 92.77 (CH), 104.90 (C), 120.30 (CH), 120.42 (CH), 124.77 (CH), 124.94 (CH), 127.68 (CH), 127.88 (CH), 128.01 (CH), 141.20 (C), 146.41 (C), 146.66 (C), 171.88 (C); ESMS (m/z): 508 $[M + NH_4]^+$, 513 $[M + Na]^+$; Anal. Calcd for ($C_{30}H_{34}O_6$): C 73.45 H 6.99; Found C 73.30 H 6.95. **8c:** White solid; mp 68-70 ºC; FT-IR (KBr, cm^{-1}) 1748.9, 1602.9, 1508.1, 1227.4, 1016.3, 756.4; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.51 (d, 3H, *J* = 7.1 Hz), 0.86-2.57 (m, 12H), 0.95 (d, 3H, *J* = 5.4 Hz), 1.43 (s, 3H), 3.09 (d, 2H, *J* = 8 Hz), 4.56 (t, 1H, *J* = 8 Hz), 5.39 (s, 1H), 5.68 (d, 1H, *J* = 9.9 Hz), 6.91-7.26 (m, 8H, Ar); ^{13}C NMR (75 MHz, CDCl3) δ 10.14 (CH_3), 18.71 (CH_3), 20.46 (CH_2), 23.06 (CH_2), 24.41 (CH_3), 30.10 (CH), 32.51 (CH_2), 34.73 (CH_2), 35.76 (CH), 39.12 (CH_2), 43.74 (CH), 44.06 (CH), 50.04 (CH), 78.59 (C), 89.99 (CH), 90.71 (CH), 102.98 (C), 127.28 (4 × CH), 127.50 (4 × CH), 131.08 (C), 139.58 (C), 139.95 (C), 168.51 (C); ESI-MS (m/z) 529.0 $[M+H]^+$; Anal. Calcd for $C_{30}H_{34}F_2O_6$: C, 68.17, H, 6.48; found: C, 68.21, H, 6.49. **8d:** White solid; mp 81-83 ºC; FT-IR (KBr, cm^{-1}) 1750.8, 1604.6, 1509.4, 1227.9, 1014.0, 830.9; ^{1}H (300 MHz, $CDCl_3$) δ 0.56 (d, 3H, *J* = 7.1 Hz), 0.93-2.06 (m, 10H), 0.97 (d, 3H, *J* = 5.6 Hz), 1.45 (s, 3H), 2.34-2.53 (m, 2H), 3.11 (d, 2H, *J* = 8 Hz), 4.56 (t, 1H, *J* = 8 Hz), 5.40 (s, 1H), 5.69 (d, 1H, *J* = 9.9 Hz), 7.14-7.29 (m, 8H, Ar); ^{13}C NMR (75 MHz, CDCl3) δ 10.34 (CH_3), 18.91 (CH_3), 20.67 (CH_2), 23.29 (CH_2), 24.67 (CH_3), 30.38 (CH), 32.76 (CH_2), 34.91 (CH_2), 35.99 (CH), 39.37 (CH_2), 43.94 (CH), 44.26 (CH), 50.24 (CH), 78.80 (C), 90.20 (CH), 90.93 (CH), 103.19 (C), 127.58 (4 × CH), 127.80 (4 × CH), 131.38 (C), 139.88 (C), 140.15 (C), 168.82 (C); ESI-MS (m/z) 583.1 $[M + Na]^+$;

Anal. Calcd for $C_{30}H_{34}Cl_2O_6$: C, 64.17, H, 6.10; found: C, 63.89, H, 6.34. **8e:** White solid; mp 83-85 ºC; FT-IR (KBr, cm^{-1}) 1751.4, 1605.3, 1512.8, 1228.5, 1014.9, 831.7; ^{1}H (300 MHz, $CDCl_3$) δ 0.57 (d, 3H, *J* = 7.1 Hz), 0.90-2.06 (m, 10H), 0.99 (d, 3H, *J* = 5.6 Hz), 1.47 (s, 3H), 2.33-2.54 (m, 2H), 3.13 (d, 2H, *J* = 8 Hz), 4.59 (t, 1H, *J* = 8 Hz), 5.41 (s, 1H), 5.71 (d, 1H, *J* = 9.9 Hz), 7.16-7.31 (m, 8H, Ar); ^{13}C NMR (75 MHz, CDCl3) δ 10.35 (CH_3), 18.93 (CH_3), 20.68 (CH_2), 23.30 (CH_2), 24.69 (CH_3), 30.40 (CH), 32.78 (CH_2), 34.93 (CH_2), 36.01 (CH), 39.39 (CH_2), 43.96 (CH), 44.29 (CH), 50.26 (CH), 78.81 (C), 90.22 (CH), 90.95 (CH), 103.21 (C), 127.60 (4 × CH), 127.82 (4 × CH), 131.40 (C), 139.89 (C), 140.17 (C), 168.84 (C); ESI-MS (m/z) 671.0 $[M + Na]^+$; Anal. Calcd for $C_{30}H_{34}Br_2O_6$: C, 55.40, H, 5.27; found: C, 55.44, H, 5.29. **8f:** White solid; mp 65-67 ºC; FT-IR (KBr, cm^{-1}) 1748.2, 1609.8, 1507.7, 1232.5, 1019.0, 834.7; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.50 (d, 3H, *J* = 7.1 Hz), 0.92-2.04 (m, 10H), 0.94 (d, 3H, *J* = 5.6 Hz), 1.43 (s, 3H), 2.37 (dt, 1H, *J* = 14.2 and 3.8 Hz), 2.45-2.49 (m, 1H), 3.07-3.10 (m, 2H), 3.74 (s, 3H), 3.76 (s, 3H), 4.49 (t, 1H, *J* = 8 Hz), 5.38 (s, 1H), 5.68 (d, 1H, *J* = 9.9 Hz), 6.78-7.26 (m, 8H, Ar) ^{13}C NMR (75 MHz, CDCl3) δ 11.79 (CH_3), 20.39 (CH_3), 22.16 (CH_2), 24.78 (CH_2), 26.16 (CH_3), 31.93 (CH), 34.28 (CH_2), 36.42 (CH_2), 37.46 (CH), 41.53 (CH_2), 45.44 (CH), 45.48 (CH), 51.76 (CH), 55.42 (2 × CH_3), 80.32 (C), 91.67 (CH), 92.17 (CH), 104.63 (C), 114.08 (2 × CH), 114.15 (2 × CH), 128.66 (2 × CH), 128.72 (CH), 128.83 (CH), 135.95 (C), 136.20 (C), 158.32 (C), 158.37 (C), 170.87 (C); ESI-MS (m/z) 553.4 $[M+H]^+$; Anal. Calcd for $C_{32}H_{40}O_8$: C, 69.54, H, 7.30; found: C, 69.59, H, 7.34.

11. (a) Tao, Y. T.; Saunders, W. H. Jr. *J. Am. Chem. Soc*. **1983**, *105*, 3183-3188. (b) Klemm, L. H.; Bower, G. M. *J. Org. Chem*. **1958**, *23*, 344-8. (c) Jagadale, A. R.; Sudalai, A. *Tetrahedron Lett*. **2007**, 48, 4895-4898.
12. (a) Peters, W. In *Chemotherapy and drug resistance in malaria*; Academic Press: London, **1970**; pp 64-136. (b) **In vivo antimalarial efficacy test**: The blood schizontocidal activity of the test compounds was evaluated in rodent model using multidrug-resistant strain of *Plasmodium yoelii nigeriensis*. Multidrug-resistant *Plasmodium yoelii nigeriensis* used in this study is resistant to chloroquine, mefloquine and halofantrine. The colony bred Swiss mice of either sex (20 ± 2 g) were inoculated intraperitoneally with 1×10^5 *P. yoelii* (MDR) parasites on day zero, and treatment was administered to group of five mice at each dose, from day 0 to 3, once daily. The drug dilutions of all compounds were prepared in groundnut oil so as to contain the required amount of the drug (0.6 mg/kg for a dose of 48 mg/kg, 0.3 mg for a dose of 24 mg/kg, 0.15 mg for a dose of 12 mg/kg and 0.075 mg for a dose of 6 mg/kg) in 0.1 mL and administered orally for each dose. Parasitaemia level were recorded from thin blood smears on day 4 and subsequently twice a week till day 28. The animals which did not develop patent infection till day 28 were recorded as cured.[14] Mice treated with β-arteether served as positive control.
13. (a) 100% suppression of parasitemia means no parasites were detected in 50 oil immersion microscopic fields (parasites if at all present, were below the detection limit). The parasites present below the detection limit can multiply and eventually can be detected during observation on subsequent days. In such cases though the drug is providing near 100% suppression of the parasitaemia on day 4 but will not provide full protection to the treated mice in the 28 day survival assay. (b) 100% protection means none of the treated mice developed patent infection during the 28 days observation period and hence were recorded as cured. Similarly 60% protection means only 3 out of 5 mice were cured.
14. Puri, S. K.; Singh, N. *Expl. Parasitol*. **2000**, *94*, 8-14.

Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

New Orally Active Diphenylmethyl-based Ester Analogues of Dihydroartemisinin: Synthesis and Antimalarial Assessment against multidrug-resistant *Plasmodium Yoelii Nigeriensis* in mice

Leave this area blank for abstract info.

Sandeep Chaudhary, [a, b,c,]* Niraj K. Naikade,[c] Mohit K. Tiwari,[a] Lalit Yadav, [a] Bharti Rajesh K. Shyamlal[a] and Sunil. K. Puri,[d,*]

[a]*Department of Chemistry and* [b]*Materials Research Centre, Malaviya National Institute of Technology, Jawaharlal Nehru Marg, Jaipur-302017, India*

[c]*Division of Medicinal and Process Chemistry and* [d]*Division of Parasitology, CSIR-Central Drug Research Institute, Sector 10, Jankipuram Extension, Sitapur Road, Lucknow-226031, India*