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Organocatalyzed highly atom economic one pot synthesis of tetrahydropyridines as antimalarials

Mridul Misra [a], Swaroop Kumar Pandey [b], Vivek Parashar Pandey [a], Jyoti Pandey [a], Renu Tripathi [b], Rama Pati Tripathi [a,*]

[a] Medicinal and Process Chemistry, Central Drug Research Institute, Lucknow, UP 226001, India
[b] Parasitology Division, Central Drug Research Institute, India

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ABSTRACT

A highly atom economic one pot synthesis of tetrahydropyridines was achieved by L-proline/TFA catalysed multicomponent reaction of β-keto-esters, aromatic aldehydes and anilines. The synthesized compounds were screened against *Plasmodium falciparum* in vitro and one of them showed antimalarial activity with MIC as low as 0.09 μg/mL.

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1. Introduction

Malaria is one of the most important infectious diseases claiming more than 2.7 million deaths and infecting up to 900 million people worldwide each year.[1–3] Currently, there are several drugs known for the treatment of this disease but only limited ones are safe drugs. The recent reports of emerging resistance against existing drugs[3,4] has resulted in great efforts on research and development activities from academic institutes rather than pharmaceutical industries because of limited commercial opportunities. The piperidine subunit is a prominent pharmacophore, occurring in the variety of biologically important synthetic and natural products.[5] This subunit has great chemotherapeutic values as numerous lead molecules with prominent biological activities are clinical candidates for several diseases.[5e] Tetrahydropyridine (THP) derivatives are also useful against several metabolic disorders and human ailments. The prominent biological activities associated with this pharmacophore are antiparasitic, antimicrobial, anticancer, antiviral etc. Further, these are intricately involved in MAO based mechanism in Parkinson's disease[6] and as inhibitors of farnesyl transferase[7] and dihydroorate dehydrogenase[8] and also play key roles in many disease processes. Owing to their importance in bioorganic and medicinal chemistry, several methods including the stereocontrolled syntheses were developed and most of them are associated with many limitations.[9,10] Aza Diels-Alder reaction and several of its modifications has extensively been used to synthesize nitrogen-containing six-membered ring compounds.[11] Towards this endeavor Bruce Pégot et al. have recently developed an elegant diastereoselective synthesis of 2-substituted-2,3-dihydro-4-pyridone derivatives using chiral ionic liquids.[12] Clarke et al.[13] have also reported an $InCl_3$ catalyzed multicomponent synthesis of polysubstituted 1,2,5,6-tetrahydropyridines in moderate to good yields. Organocatalysis, in general, provides the avenues towards green chemistry replacing toxic metal catalysts with degradable organic compounds as catalyst. It has several advantages in developing methods to access compounds in an environment friendly way. On the other hand, the atom economic synthesis[14] offers the most economical method of preparing organic compounds with no loss of the starting material and therefore eco-friendly. Moreover, application of metal catalyst in the synthesis of biologically active compounds is sometimes unwanted as the presence of even minute amount of residual metal would lead to serious consequences. In view of the above, we were interested to develop a nonmetallic, organocatalytic, atom economic method for the syntheses of tetrahydropyridines and evaluate them for different biological activities. In the first instance, the synthesized compounds were evaluated against *Plasmodium falciparum* for their antimalarial activity.

* Corresponding author. Tel.: +91 0522 2612411; fax: +91 522 2623405/2623938/2629504.
E-mail address: rpt.cdri@gmail.com (R.P. Tripathi).

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Our method consists of the reaction of aromatic aldehydes, anilines, and a β-keto ester under the influence of L-proline/TFA as organocatalyst. The choice of L-proline as organocatalyst is based on the facts that it acts as an excellent Lewis acid–base catalyst in a variety of organic reactions.[15]

2. Results and discussion

2.1. Chemistry

The compounds (**1**–**21**) were synthesized by reacting β-keto esters (1.0 equiv.), aromatic aldehydes, and anilines (2.0 equivalents each) in acetonitrile in the presence of L-proline and TFA (20 mol% each) at ambient temperature (Scheme 1).

At first, aniline, 4-methoxy benzaldehyde, and methyl acetoacetate were selected as the model substrates and reacted under different experimental variants (Table 1). We have compared L-proline/TFA with other catalysts including $InCl_3$, silica-sulfuric acid (SSA), *ortho*-phosphoric acid, perchloric acid, and TFA alone to set up standard reaction conditions. The effect of L-proline alone and in combination with TFA, using varying amount of this catalyst-combination in various organic solvents as well as in water were also studied. Among all the experimental variants the reaction with 20 mol% of L-proline and TFA in CH_3CN at ambient temperature (Table 1, entry 10) gave the best result with 72% yield of the required 1,2,6-triphenyl-4-phenylamino-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester (**1**).

The structure of these compounds was established on the basis of their spectroscopic data and microanalysis. The IR spectrum of the compounds, in general, exhibited the absorption band at around 1656–1593 cm^{-1} indicating that the carbonyl group of carbmethoxy or carbethoxy substituents and olefinic bonds are in conjugation. The ESMS (mass spectra) of the compounds showed their respective $[M+H]^+$ peaks. In the ^1H NMR spectrum, the proton at C-2 in the above tetrahydropyridines (**1**–**22**) was observed either as singlet at around *δ 6.18–6.36* ppm or it appeared along with the multiplets of aromatic protons ranging from δ 6.70 to 6.19 ppm. The H-6 in the above compounds was apparent as broad singlet at around δ 5.00 ppm. The two methylene protons of H-5a and H-5b were appeared as two distinct *dd* [at around *δ 2.62–2.76* ppm with coupling constant in the range of 5.0 (J_1) and 15.0 Hz (J_2) and at *δ 2.73–2.91* ppm with coupling constant in the range of 2.0 (J_1) and 15.0 Hz (J_2), respectively] or as doublet [at around δ 2.91 ppm with coupling constant in the range of 5.0 (J)]. The aromatic protons pertaining to the phenyl substituent at C-2 and C-6 and anilinyl moiety at C-4 were observed as mixture of singlets, doublets and multiplets at around *δ 6.26–8.64* ppm. The only exchangeable secondary amine proton (NH) attached at C-4 appeared as br s at around δ 10.20 ppm. The methyl protons of carbmethoxy group appeared as singlet at around δ 3.95 ppm, while the methylene protons of carbethoxy group appeared as quartets or multiplet at around *δ 4.23–4.51* ppm and methyl protons of carbethoxy group were observed as triplet at around *δ 1.42–1.54* ppm, respectively. It is appropriate to mention here that sometimes the quartet pertaining to the methylene protons of carbethoxy substituents appeared with two different chemical shifts due to diastereoisomeric nature of the products. In the ^{13}C NMR spectrum, the C-5 carbon of the above tetrahydropyridines (**1**–**22**) was observed at around *δ 34.0–37.6* ppm while the C-2 carbon was appeared at around *δ 53.0–59.4* ppm. The C-6 and C-3 carbons were observed at around *δ 54.2–61.8* and *δ 96.9–102.3* ppm, respectively. The aromatic carbons (ArCH) were appeared at around *δ 113.4–132.3* ppm while the C-4 and quaternary aromatic carbon were observed in the range of *δ 120.7–164.4* ppm. The quaternary carbon of carbethoxy and carbmethoxy group were observed at around *δ 168.4–172.0* ppm The methyl carbon of carbmethoxy group appeared at around δ 51.0 ppm, while the methylene and methyl carbons of carbethoxy group appeared at around *δ 60.0–64.3* and *δ 15.2–19.1* ppm, respectively.

As evident from Table 2 the aromatic aldehydes with nitro- and benzyloxy substituents did offer only moderate yield of the product, however, other aldehydes gave good yields of the required tetrahydropyridines irrespective of the substituents in benzene ring of the aldehyde. Further, 4-methoxy aniline resulted in better yields of the required tetrahydropyridines compared to either 4-chloro- and 4-bromo aniline.

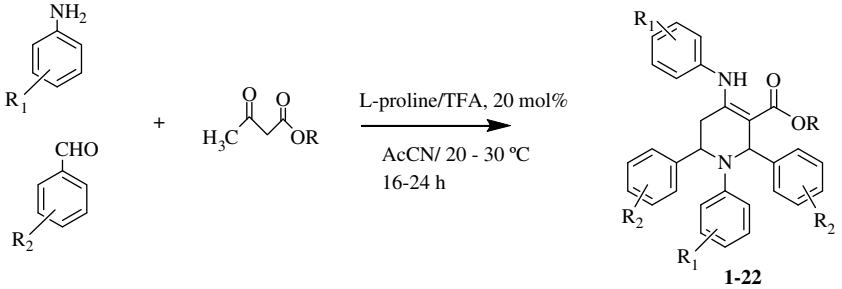
The most probable reaction mechanism (Fig. 1) involves the initial formation of an imine **A** and a Knoevenagel product **C** formed through proline catalysed enamine **B** mediated reaction. Mannich like reaction of aniline with Knoevenagel adducts **C** results an intermediate enamine **D** which undergo Aza Diels-Alder cyclization with imine **A** and results the required tetrahydropyridine **E**. The proposed reaction mechanism is supported by the fact that Knoevenagel adduct (**23**) and imine (**24**) have been isolated during one of such representative reaction of 4-methoxybenzaldehdye, methyl acetoacetate and aniline as shown in Scheme 2.

The relative stereochemistry in the above compound with 2- and 6-substituents being *trans*- to each other was based on the extensive ^1H NMR experiments involving NOESY and NOE experiments. Absence of any NOE between H-2 and H-6 of tetrahydropyridine indicates that they are *trans* to each other, Figure 2. Further, the ^1H NMR and ^{13}C NMR spectra of our compounds were identical to those reported earlier by Clarke et al.[13]

2.2. Biology

2.2.1. Results and discussion

The above compounds **1–21** were assayed for their blood schizontocidal activity against *P. falciparum* 3D7 strain as per earlier reported protocols.[16–18] Initially these compounds were tested at 10.0, 5.0, 2.5, and 1.25 μg/mL concn. Compounds **1**, **3**, **4**, **5**, **6**, **7**, **8**, **9**, **10**, **11**, **12**, **13**, **15**, **16**, **18**, **20**, and **21** displayed 100% schizont inhibition at 10 μg/mL, while compounds **2**, **11**, **17** displayed only 33%, 23%, and 83% schizont inhibition at 10 μg/mL (Table 3).



Scheme 1. Synthesis of tetrahydropyridines from different aromatic aldehydes, anilines, and β-keto esters.

Table 1
Optimization experiments during reaction of 4-methoxy benzaldehyde, aniline, and methyl acetoacetate

Entry	Catalyst	Solvent	Reaction time	% Yields
1	$InCl_3$	CH_3CN	50	25
2	Silica sulfuric acid	CH_3CN	36	10
3	*ortho*-Phosphoric acid	CH_3CN	24	5
4	DBU	CH_3CN	24	Undesired products[a]
5	Glycosylamino acid	CH_3CN	24	Undesired products
6	L-Proline	CH_3CN	24	Undesired products[a]
7	L-Proline + TFA (5 mol% each)	CH_3CN	24	45
8	L-Proline + TFA (10 mol% each)	CH_3CN	24	50
9	L-Proline + TFA (40 mol% each)	CH_3CN	21	72
10	L-Proline + TFA (20 mol% each)	CH_3CN	21	72
11	L-Proline + TFA (20 mol% each)	THF	24	30
12	L-Proline + TFA (20 mol% each)	DMF	24	45
13	L-Proline + TFA (20 mol% each)	DMSO	24	40
14	L-Proline + TFA (20 mol% each)	H_2O	24	10

[a] Among the undesired product the major product was found to be Schiff's base of aldehyde and aniline.

Compounds **1**, **3**, **4**, **8**, **12**, **16**, **18**, and **20** exhibited 100% schizontocidal activity at 1.25 μg/mL. These compounds were further screened for their minimum inhibitory concentration (MIC) at lower dilutions ranging from 0.78 to 0.05 μg/mL. The only compound **4** showed 100% inhibition at 0.09 μg/mL concn, while the compounds **3**, **16**, and **20** showed the 100% schizont inhibition at 0.39 μg/mL concentrations. However, the compounds **1**, **8**, **12**, and **18** exhibited slight inhibition at 0.39 μg/mL concentrations (Table 4).

The effects of various substituents in the phenyl group attached to ring carbons and C-4 nitrogen atom in tetrahydropyridines was examined in order to find out the structure–activity relationship in this series of compounds. As evident from Table 3, the introduction of fluoro- and bromo-substituents at the 4-position and chloro- at the 3-position on to the 2- and 6- phenyl substituents of tetrahydropyridines (compounds **3**, **5**, **13**) did not alter the schizontocidal potential whereas the only compound (**3**) exhibited a moderate enhancement in antimalarial efficacy as compared to compound **1**. However, introduction of *p*-methoxy group in the *N*-phenyl group (compounds **7**, **4**, **21**, and **6**) resulted in marked increase in blood schizontocidal activity as compared to the tetrahydropyridines with unsubstituted *N*-phenyl moiety. In contrast to these results, the incorporation of chloro- and bromo-substituents at the 4-position of the *N*-phenyl substituent (compounds **2**, **8**, and **9**) resulted in loss of activity as compared to compounds **1** and **5** with unsubstituted *N*-phenyl moiety. The introduction of a benzyloxy substituent at the 4-position of the 2- and 6-phenyl substituents (compound **11**) resulted in loss of antimalarial potency as compared to compound **1**. While tetrahydropyridines with thiophenyl and pyridyl groups (compounds **15**, **16**, and **20**) as 2- and 6-substituents resulted in enhancement in schizontocidal activity. Further, replacement of carbmethoxy substituent with carbethoxy group as ester moiety at C-3 in tetrahydropyridines (compounds **14**, **15**, **16**, **17**, **18**, **19**, and **20**) resulted in slight decrease in the blood schizontocidal activity indicating that ester group with smaller alkyl moiety is preferable over larger one.

3. Conclusion

We have developed a metal free, highly atom economic organocatalytic multicomponent synthesis of tetrahydropyridines in moderate to good yields. The compounds have great potential in development of new chemotherapeutics. In the first instance, these compounds displayed antimalarial activity and their biopotential is being investigated in great detail.

4. Experimental

4.1. Chemistry

Commercially available reagent grade chemicals were used as received. All reactions were followed by TLC on E. Merck Kieselgel 60 F254, with detection by UV light and/or spraying a 20% $KMnO_4$ aq soln. Column chromatography was performed on silica gel (230–400 mesh, E. Merck). IR spectra were recorded as thin films or in chloroform soln with a Perkin–Elmer Spectrum RX-1 (4000–450 cm^{-1}) spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Brucker DRX-300 in $CDCl_3$. Chemical shift values are reported in ppm relative to $SiMe_4$ as internal reference, unless otherwise stated; s (singlet), d (doublet), t (triplet), m (multiplet); J in hertz. FAB mass spectra were performed using a mass Spectrometer Jeol SX-102 and ESI mass spectra with Quattro II (Micromass). Melting points were obtained manually by capillary

Table 2
Synthesis of tetrahydropyridines with different aromatic aldehydes, anilines, and β-keto ester

Entry	Aldehyde	Aniline	β-Keto compound	Product	Time (h)	Isolated yield (%)
1	4-Methoxybenzaldehyde	Aniline	Methyl acetoacetate	**1**	18	70
2	4-Bromobenzaledehyde	4-Chloroaniline	Methyl acetoacetate	**2**	18	70
3	4-Fluorobenzaldehyde	Aniline	Methyl acetoacetate	**3**	24	65
4	4-Fluorobenzaldehyde	*p*-Anisidine	Methyl acetoacetate	**4**	18	60
5	4-Bromobenzaldehyde	Aniline	Methyl acetoacetate	**5**	20	65
6	3-Chlorobenzaldehyde	*p*-Anisidine	Methyl acetoacetate	**6**	18	60
7	4-Methoxybenzaldehyde	*p*-Anisidine	Methyl acetoacetate	**7**	19	75
8	4-Methoxybenzaldehyde	4-Chloroaniline	Methyl acetoacetate	**8**	20	70
9	4-Methoxybenzaldehyde	4-Bromoaniline	Methyl acetoacetate	**9**	24	65
10	4-Fluorobenzaldehyde	4-Chloroaniline	Methyl acetoacetate	**10**	21	65
11	4-Benzyloxybenzaldehyde	Aniline	Methyl acetoacetate	**11**	16	55
12	Benzaldehyde	Aniline	Methyl acetoacetate	**12**	17	70
13	3-Chlorobenzaldehyde	Aniline	Methyl acetoacetate	**13**	16	60
14	3-Chlorobenzaldehyde	*p*-Anisidine	Ethyl acetoacetate	**14**	22	70
15	Thiophene-2-carboxaldehyde	4-Chloroaniline	Ethyl acetoacetate	**15**	21	65
16	Thiophene-2-carboxaldehyde	*p*-Anisidine	Methyl acetoacetate	**16**	22	60
17	3-Chlorobenzaldehyde	4-Chloroaniline	Ethyl acetoacetate	**17**	24	65
18	Benzaldehyde	*p*-Anisidine	Ethyl acetoacetate	**18**	18	60
19	Benzaldehyde	4-Chloroaniline	Ethyl acetoacetate	**19**	22	75
20	Pyridine-3-carboxaldehyde	Aniline	Ethyl acetoacetate	**20**	20	55
21	4-Bromobenzaldehyde	*p*-Anisidine	Methyl acetoacetate	**21**	22	65
22	3-Nitrobenzaldehyde	Aniline	Methyl acetoacetate	**22**	28	70

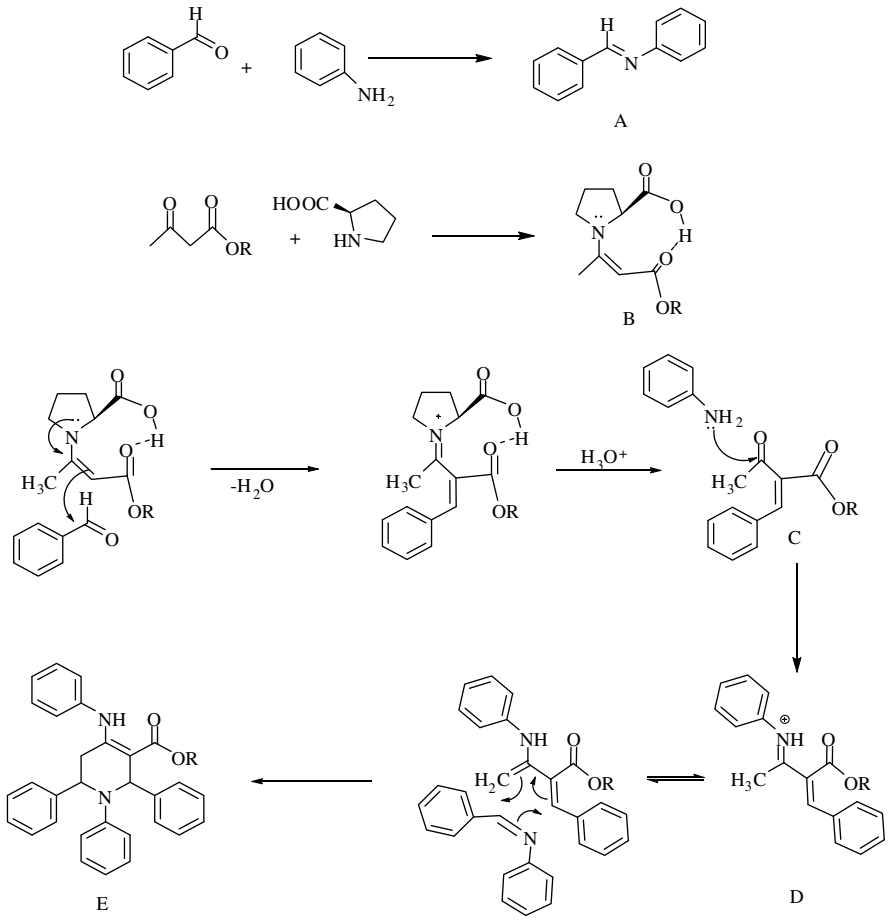
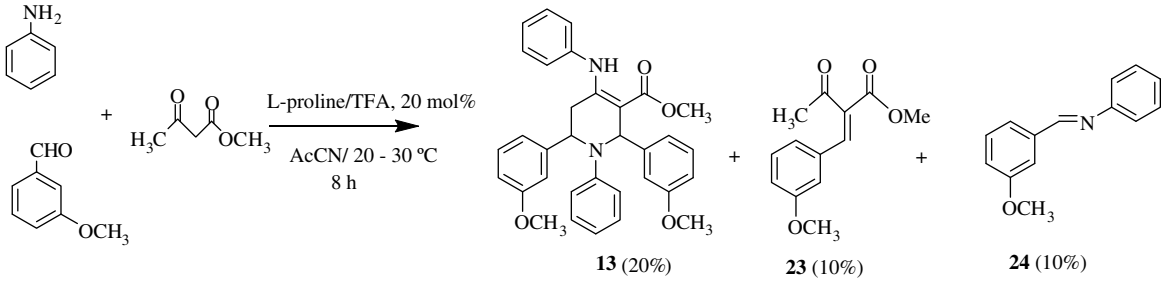


Figure 1. Proposed reaction mechanism for the formation of tetrahydropyridines.



Scheme 2. Synthesis of tetrahydropyridine (13) and reaction intermediates after 8 h.

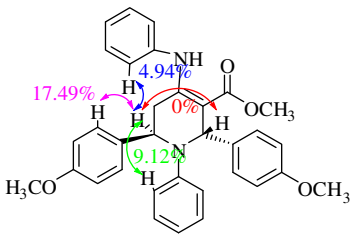


Figure 2. NOE percentage between H-2, H-6, and aromatic protons f or compound **1**.

methods and are uncorrected. Elemental analyses were performed on a Perkin–Elmer 2400 II elemental analyzer.

4.1.1. General procedure for the preparation of compounds 1–22

To a magnetically stirred solution of β-keto ester (8.0 mmol), aromatic aldehyde (14.4 mmol), and aniline (15.6 mmol) in acetonitrile (25.0 mL), L-proline (1.5 mmol), and trifluoroacetic acid (1.09 mmol) were added and the reaction mixture was stirred at ambient temperature. The stirring continued till the disappearance of aldehyde, the reaction mixture was filtered and the solid so obtained was washed with aqueous HCl (10%) followed by water and *n*-hexane sequentially to give colourless powder which was dried under vacuum. For elemental analyses the compound was filtered through a short column of SiO_2. However, if no precipitate appears during reaction, the reaction mixture was evaporated under reduced pressure and extracted with ethyl acetate. The organic layer was washed with aqueous HCl (10%) followed by water and dried (anhydrous Na_2SO_4), evaporated under reduced pressure to give a crude mass. The latter was purified by column chromatography

Table 3
Antimalarial activity of tetrahydropyridines against *P. falciparum* 3D7

Entry	Compound	% Inhibition of Schizonts of *P. falciparum* at different concentrations			
		10 μg/mL	5 μg/mL	2.5 μg/mL	1.25 μg/mL
1	**1**	100	100	100	100
2	**2**	33	00	00	00
3	**3**	100	100	100	100
4	**4**	100	100	100	100
5	**5**	100	100	85	46
6	**6**	100	100	100	33
7	**7**	100	100	90	86
8	**8**	100	100	100	100
9	**9**	100	100	91	25
10	**10**	100	100	100	93
11	**11**	23	02	02	00
12	**12**	100	100	100	100
13	**13**	100	81	81	46
14	**14**	100	92	50	16
15	**15**	100	100	93	86
16	**16**	100	100	100	100
17	**17**	83	66	00	00
18	**18**	100	100	100	100
19	**19**	100	100	92	25
20	**20**	100	100	100	100
21	**21**	100	100	95	33
22	Chloroquine[a]	100	100	97	86
23	Control	38% Schizonts development			

[a] The concentration used are 100, 50, 25, and 12.5 ng/mL.

Table 4
In vitro antimalarial activity of selected compounds (0.78–0.05 μg/mL) against *P. falciparum* 3D7

Entry	Compound	% Inhibition of Schizonts at different concentrations (μg/mL) of test compounds				
		0.78	0.39	0.19	0.09	0.05
1	**1**	94	67	47	45	25
2	**3**	100	100	75	33	16
3	**4**	100	100	100	100	91
4	**8**	95	75	41	33	16
5	**12**	96	90	33	00	00
6	**16**	100	100	75	25	16
7	**18**	66	33	00	00	00
8	**20**	100	100	97	42	42
9	Chloroquine*	100	100	97	86	54
10	Control	46% Schizonts development				

* The concentration used are 100, 50, 25, 12.5, and 6.25 ng/mL.

over SiO_2 (60–120 mesh) in EtOAc: *n*-hexane (40:60) as eluent to give the desired tetrahydropyrdines **1–22**.

4.1.2. Methyl 2,6-*bis*(4-methoxyphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (1)

White solid, mp 180 °C; R_f = 0.5 (ethylacetate/hexane = 1/4); FTIR (KBr): υ 3426, 2922, 2369, 1656, 1597, 1504, 1442, 1251 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 2.76 (dd, *J* = 14.8 and 1.9 Hz, 1H, H-5a), 2.87 (dd, *J* = 14.9 and 5.4 Hz, 1H, H-5b), 3.80 (s, 3H, ArOMe), 3.82 (s, 3H, ArOMe), 3.95 (s, 3H, OMe), 5.10 (br s, 1H, H-6), 6.37–6.39 (m, 3H, 2ArH, and H-2), 6.51–6.54 (d, *J* = 8.3 Hz, 2H, ArH), 6.58–6.63 (t, *J* = 7.1 Hz, 1H, ArH), 6.73–6.84 (m, 4H, ArH), 7.05–7.33 (m, 9H, ArH), 10.31 (br s, 1H, NH) ppm; ^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 34.1 (CH_2, C-5), 51.3 (C, $COOCH_3$), 54.9 (CH, C-2), 55.4 ($ArOCH_3$), 55.5 ($ArOCH_3$), 57.9 (CH, C-6), 98.7 (C, C-3), 113.4, 113.9, 114.4, 116.6, 126.0, 126.2, 127.8, 128.1, 129.3, 129.7 (ArCH), 135.0, 136.2, 138.4, 147.4, 156.6, 158.5, 159.1 (6ArC and C-4), 168.8 (CO); ESMS (*m/z*): $[M+H]^+$, 519.2. Elemental analysis for $C_{33}H_{32}N_2O_4$: Calcd C, 76.13; H, 6.20; N, 5.38. Found: C, 76.14; H, 6.19; N, 5.37.

4.1.3. Methyl 2,6-*bis*(4-bromophenyl)-1-(4-chlorophenyl)-4-(4-chlorophenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (2)

White solid, mp 160–163 °C; R_f = 0.5 (ethyl acetate/hexane = 1/4); FTIR (KBr): υ 3741, 3618, 3020, 2360, 1652, 1614, 1497, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 2.68 (dd, *J* = 15.0 and 1.95 Hz, 1H, H-5a), 2.81 (dd, *J* = 15.2 and 5.6 Hz, 1H, H-5b), 3.95 (s, 3H, OMe), 5.05 (br s, 1H, H-6), 6.26–6.37 (m, 5H, 4ArH, and H-2), 6.98–7.03 (m, 4H, ArH) , 7.11–7.28 (m, 4H, ArH), 7.39–7.44 (m, 4H, ArH), 10.23 (br s, 1H, NH) ppm; ^{13}C NMR (50 Hz, $CDCl_3$ + CCl_4): δ 33.9 (CH_2, C-5), 51.7 (C, $COOCH_3$), 55.3 (CH, C-2), 57.9 (CH, C-6), 98.3 (C, C-3), 114.4 (ArCH), 121.0, 121.7, and 122.5 (3ArC), 127.3, 128.4, 128.6, 129.4, 129.6, 131.9, 132.3 (ArCH), 132.5, 136.5, 141.2, 142.4, 145.2, 155.6 (8ArC and C-4), 168.4 (CO); ESMS (*m/z*): $[M+H]^+$, 663. Elemental analysis for $C_{31}H_{24}Br_2Cl_2N_2O_2$: Calcd C, 67.23; H, 5.13; N, 4.75. Found: C, 67.24; H, 5.12; N, 4.77.

4.1.4. Methyl 2,6-*bis*(4-fluorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (3)

White solid, mp 160 °C; R_f = 0.5 (ethyl acetate/hexane = 1/5); FTIR (KBr): υ 3738, 3681, 3621, 3020, 1652, 1652, 1595, 1504, 1372, 1323, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 2.78 (dd, *J* = 14.9 and 1.56 Hz, 1H, H-5a), 2.87 (dd, *J* = 15.1 and 5.3 Hz, 1H, H-5b), 3.97 (s, 3H, OMe), 5.10 (br s, 1H, H-6), 6.40–6.51 (m, 5H, 4ArH, and H-2), 6.63–6.68 (t, *J* = 7.1 Hz, 1H, ArH), 6.85–7.26 (m, 13H, ArH), 10.32 (br s, 1H, NH) ppm; ^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 34.2 (CH_2, C-5), 51.5 (C, $COOCH_3$), 55.0 (CH, C-2), 57.7 (CH, C-6), 98.2 (C, C-3), 113.4, 115.3, 115.7, 116.1, 117.1, 126.2, 126.4, 128.2, 128.4, 128.5, 128.6, 129.4, 129.5, 129.8 (ArCH), 138.1, 138.5, 139.7, 146.9, 156.4, 159.5, 164.4 (6ArC and C-4), 168.6 (CO); ESMS (*m/z*): $[M+H]^+$, 496.

4.1.5. Methyl 2,6-*bis*(4-fluorophenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4)

White solid, mp 205 °C, R_f = 0.5 (ethyl acetate/hexane = 1/5); FTIR (KBr): υ 3677, 3416, 3062, 2362, 1654, 1607, 1510, 1456, 1243 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 2.62 (dd, *J* = 15.2 and 2.6 Hz, 1H, H-5a), 2.73 (dd, *J* = 15.2 and 5.3 Hz, 1H, H-5b), 3.68 (s, 3H, ArOMe), 3.77 (s, 3H, ArOMe), 3.96 (s, 3H, OMe), 4.97 (br s, 1H, H-6), 6.19 (s, 1CH, H-2), 6.35–6.38 (m, 4H, ArH), 6.61–6.68 (m, 4H, ArH) 6.92–7.01 (m, 4H, ArH), 7.09–7.14 (m, 2H, ArH), 7.19–7.24 (m, 2H, ArH), 10.18 (br s, 1H, NH) ppm; ^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 34.1 (CH_2, C-5), 51.3 (C, $COOCH_3$), 55.6 (CH, C-2), 55.6 ($ArOCH_3$), 55.8 ($ArOCH_3$), 57.6 (CH, C-6), 97.1 (C, C-3), 114.5, 114.9, 115.1, 115.5, 115.6, 116.0, 128.1, 128.4, 128.6, 128.1 (ArCH), 130.9, 139.0, 140.0, 141.5, 151.8, 157.1, 158.3, 159.5, 164.4 (8ArC and C-4), 168.4 (CO); ESMS (*m/z*): $[M+H]^+$, 530.

4.1.6. Methyl 2,6-*bis*(4-bromophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (5)

White solid, mp 140 °C; R_f = 0.5 (ethyl acetate/hexane = 1/4); FTIR (KBr): υ 3685, 3395, 3020, 2361, 1653, 1595, 1500, 1427, 1216, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 2.77 (dd, *J* = 15.0 and 2.25 Hz, 1H, H-5a), 2.86 (dd, *J* = 15.0 and 5.31 Hz, 1H, H-5b), 3.96 (s, 3H, OMe), 5.06 (br s, 1H, H-6), 6.38–6.70 (m, 5H, 4ArH, and H-2), 6.76–6.85 (m, 1H, ArH), 7.02–7.55 (m, 9H, ArH), 7.69–7.71 (d, *J* = 6.99 Hz, 4H, ArH), 10.29 (br s, 1H, NH) ppm; ^{13}C NMR (50 Hz, $CDCl_3$ + CCl_4): δ 34.0 (CH_2, C-5), 51.6 (OCH_3), 55.2 (CH, C-2), 57.8 (CH, C-6), 97.9 (C, C-3), 113.3, 117.2 (ArCH), 120.7, 121.4 (ArC and C-4) 126.2, 126.5, 128.5, 128.9, 129.5, 131.8, 132.1 (ArCH), 138.0, 141.9, 143.3, 146.9, 156.4 (ArC), 168.7 (CO); ESMS

(*m/z*): $[M+H]^+$, 622. Elemental analysis for $C_{31}H_{26}N_2O_2Br_2$: Calcd C, 60.21; H, 4.24; N, 4.53. Found: C, 60.22; H, 4.23; N, 4.52.

4.1.7. Methyl 2,6-*bis*(3-chlorophenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (6)

White solid, mp 160 °C; R_f = 0.5 (ethyl acetate/hexane = 1/5); FTIR (KBr): υ 3781, 3374, 3019, 2361, 1652, 1594, 1511, 1465, 1371, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 2.64 (dd, *J* = 15.0 and 2.37 Hz, 1H, H-5a), 2.75 (dd, *J* = 15.2 and 5.4 Hz, 1H, H-5b), 3.68 (s, 3H, ArOMe), 3.77 (s, 3H, ArOMe), 3.91 (s, 3H, OMe), 4.97 (br s, 1H, H-6), 6.19–6.38 (m, 5H, 4ArH, and H-2), 6.61–6.68 (m, 4H, ArH), 6.92–7.24 (m, 8H, ArH), 10.18 (br s, 1H, NH) ppm; ^{13}C NMR (50 Hz, $CDCl_3 + CCl_4$): δ 33.4 (CH_2, C-5), 50.9 (OCH_3), 55.1 (CH, C-2), 55.2 ($ArOCH_3$), 55.7 ($ArOCH_3$), 57.5 (CH, C-6), 114.0, 114.4, 114.7, 124.8, 124.9, 126.6, 126.9, 127.3, 128.0, 129.8, 130.0 (ArCH), 134.3, 134.5, 140.6, 145.2, 146.4, 151.6, 156.4, 158.1 (ArC and C-4), 167.9 (CO); ESMS (*m/z*): $[M+H]^+$, 562. Elemental analysis for $C_{33}H_{30}N_2O_4Cl_2$: Calcd C,67.23 ; H, 5.13 ; N, 4.75. Found: C, 67.24; H, 5.12; N, 4.76.

4.1.8. Methyl 1,2,6-*tris*(4-methoxyphenyl)-4-(4-methoxyphenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (7)

White solid, mp 158–160 °C; R_f = 0.5 (ethyl acetate/hexane = 1/5); FTIR (KBr): υ 3678, 3437, 3020, 2360, 1649, 1512, 1461, 1217 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 2.64 (dd, *J* = 15.0 and 2.4 Hz, 1H, H-5a), 2.77 (dd, *J* = 15.0 and 5.4 Hz, 1H, H-5b), 3.68 (s, 3H, ArOMe), 3.77 (s, 3H, ArOMe), 3.79 (s, 3H, ArOMe), 3.82 (s, 3H, ArOMe), 3.91 (s, 3H, OMe), 4.98 (br s, 1H, H-6), 6.22 (s, 1CH, H-2), 6.30 (d, *J* = 7.6 Hz, 2H, ArH), 6.43 (d, *J* = 9.0 Hz, 2H, ArH), 6.64 (d, *J* = 7.8 Hz, 4H, ArH), 6.79–6.84 (m, 4H, ArH,), 7.06 (d, *J* = 8.5 Hz, 2H, ArH), 7.17 (d, *J* = 8.5 Hz, 2H, ArH), 10.16 (br s, 1H, NH) ppm; ^{13}C NMR (50 MHz, $CDCl_3 + CCl_4$): δ 34.1 (CH_2, C-5), 51.2 (OCH_3), 55.4 (CH, C-2), 55.5 ($ArOCH_3$), 55.6 ($ArOCH_3$), 55.9 ($ArOCH_3$), 57.8 (CH, C-6), 97.5 (C, C-3), 113.8, 113.9, 114.3, 114.3, 114.8, 128.0, 128.2, 128.5 (ArCH), 131.2, 135.5, 136.5, 141.9, 151.4, 157.4, 158.1, 158.4, 159.0 (8ArC and C-4), 168.9 (CO); ESMS (*m/z*): $[M+H]^+$, 580. Elemental analysis for $C_{35}H_{36}N_2O_6$, 72.39; H, 6.25; N, 4.82. Found: C, 72.36; H, 6.26; N, 4.81.

4.1.9. Methyl-(4-chlorophenyl)-4-(4-chlorophenylamino)-2,6-*bis*(methoxyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (8)

White solid, mp 195 °C; R_f = 0.5 (ethyl acetate/hexane = 1/5); FTIR (KBr): υ 3400, 3020, 2360, 1652, 1603, 1500, 1432, 1216; ^1H NMR (300 MHz, $CDCl_3$): δ 2.71 (dd, *J* = 15.0 and 5.5 Hz, 1H, H-5a), 2.85 (dd, *J* = 15.0 and 2.1 Hz, 1H, H-5b), 3.80 (s, 3H, ArOMe), 3.82 (s, 3H, ArOMe), 3.95 (s, 3H, OMe), 5.06 (br s, 1H, H-6), 6.26–6.32 (m, 3H, ArH, and H-2), 6.44–6.47 (d, *J* = 9.0 Hz, 2H, ArH), 6.82–6.86 (m, 4H, ArH), 7.00–7.20 (m, 8H, ArH), 10.24 (br s, 1H, NH) ppm; ^{13}C NMR (50 Hz, $CDCl_3$): δ 34.0 (CH_2, C-5), 51.6 (OCH_3), 55.1 (CH, C-2), 55.2 ($ArOCH_3$), 55.5 ($ArOCH_3$), 57.9 (CH, C-6), 97.9 (C, C-3), 113.3, 117.2 (ArCH), 120.7, 121.4 (ArC), 126.2, 126.5, 128.5, 128.8, 129.5 (ArCH), 131.8, 132.1, 138.0, 141.8, 143.3, 146.8, 156.4 (ArC and C-4), 168.7 (CO); ESMS (*m/z*): $[M+H]^+$, 588. Elemental analysis for $C_{33}H_{30}N_2O_4Cl_2$: Calcd C, 67.23; H, 5.13; N, 4.75. Found: C, 67.25; H, 5.11; N, 4.78.

4.1.10. Methyl-1-(4-bromophenyl)-4-(4-bromophenylamino)-2,6-*bis*(4-methoxyphenyl)-1,2,5,6-trahydropyridine-3-carboxylate (9)

White solid, mp 178 °C; R_f = 0.5 (ethyl acetate/hexane = 1/5); FTIR (KBr): υ 3781, 3374, 3019, 2361, 1652, 1594, 1511, 1465, 1371, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 2.69 (d, *J* = 14.9 Hz, 1H, H-5a), 2.83 (dd, *J* = 14.9 and 5.4 Hz, 1H, H-5b), 3.78 (s, 3H, ArOMe) 3.81 (s, 3H, ArOMe), 3.96 (s, 3H, OMe), 5.04 (br s, 1H, H-6), 6.26–6.29 (m, 3H, ArH, and H-2), 6.42 (d, *J* = 8.1 Hz, 2H, ArH), 6.80–6.85 (m, 4H, ArH), 6.98–7.17 (m, 8H, ArH), 10.28 (br s, 1H, NH) ppm; ^{13}C NMR (50Hz, $CDCl_3 + CCl_4$): δ 34.0 (CH_2, C-5), 51.6 (OCH_3), 55.1 (CH, C-2), 57.8 (CH, C-6), 61.2 ($2ArOCH_3$), 114.4, 115.4, 115.8, 116.3, 116.5 (ArCH), 122.4 (ArC), 127.2, 128.1, 128.3, 128.4, 128.8, 129.3, 129.5, 129.9 (ArCH), 132.1, 136.6, 137.8, 138.9, 145.3, 155.5, 159.6 (ArC), 164.5 (ArC), 168.2 (CO); ESMS (*m/z*): $[M+H]^+$, 562. Elemental analysis for $C_{33}H_{30}N_2O_4Br_2$: Calcd C, 58.42 ; H, 4.46; N, 4.13. Found: C, 58.51; H, 4.48; N, 4.11.

4.1.11. Methyl-(4-chlorophenyl)-4-(4-chlorophenylamino)-2,6-*bis*(4-fluorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (10)

White solid, mp 176 °C; R_f = 0.5 (ethyl acetate/hexane = 1/5); FTIR (KBr): υ 3697, 3627, 3021, 2360, 1655, 1600, 1499, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 2.70 (dd, *J* = 14.8 and 1.95 Hz, 1 H, H-5a) , 2.82 (dd, *J* = 15.0 and 5.3 Hz, 1H, H-5b), 3.96 (s, 3H, OMe), 5.07 (br s, 1H, H-6), 5.94–6.35 (m, 5H, 4ArH, and H-2), 6.90–7.34 (m, 12H, ArH), 10.29 (br s, 1H, NH) ppm; ^{13}C NMR (50 Hz, $CDCl_{3\ +\ CCl4}$): δ 34.0 (CH_2, C-5), 51.3 (OCH_3), 55.5 (CH, C-2), 57.6 (CH, C-6), 97.1 (C, C-3), 114.4, 114.9, 115.1, 115.5, 115.6, 116.0, 128.1, 128.4, 128.5, 128.6, 128.8 (ArCH), 130.9, 139.0, 139.8, 141.3, 151.9, 156.8, 158.3, 159.4, 164.3 (8ArC and C-4), 168.4 (CO); ESMS (*m/z*): $[M+H]^+$, 565.

4.1.12. Methyl 2,6-*bis*(4-(benzyloxy)phenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (11)

White solid, mp 155 °C; R_f = 0.5 (ethyl acetate/hexane = 1/5); FTIR (KBr): υ 3654, 3450, 3032, 2363, 1656, 1592, 1504, 1453, 1378, 1246 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 2.74–2.79 (m, 1H, H-5a), 2.84–2.91 (dd, *J* =15.0 and 5.2 Hz, 1H, H-5b), 3.97 (s, 3H, OMe), 4.99–5.18 (m, 5H, 2 OCH_2, H-6), 6.38–6.56 (m, 5H, 4ArH, and H-2), 6.63 (t, *J* = 7.1Hz , 1H, ArH), 6.90–6.93 (m, 4H, ArH), 7.09–7.11 (m, 7H, ArH), 7.17–7.28 (m, 2H, ArH), 7.35–7.45 (m, 10H, ArH), 10.31 (br s, 1H, NH) ppm; ^{13}C NMR (50 Hz, $CDCl_3 + CCl_4$): δ 34.1 (CH_2, C-5), 51.3 (OCH_3), 55.0 (CH, C-2), 57.9 (CH, C-6), 70.3, and 70.4 (OCH_2), 98.5 (C, C-3), 113.4, 114.9, 115.4, 116.5, 126.0, 126.2, 127.8, 127.9, 128.1, 128.3, 128.9, 129.2, 129.7 (ArCH), 135.3, 136.4, 137.5, 137.6, 138.3, 147.3, 156.6, 157.8, 158.3 (ArC and C-4), 168.8 (CO); ESMS (*m/z*): $[M+H]^+$, 672. Elemental analysis for $C_{45}H_{40}N_2O_4$: Calcd C, 67.23; H, 5.13; N, 4.75. Found: C, 67.24; H, 5.15; N, 4.73.

4.1.13. Methyl 1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (12)

White solid, mp 194 °C; R_f = 0.5 (ethyl acetate/hexane = 1/4); FTIR (KBr): υ 3859, 3427, 3020, 2360, 1653, 1592, 1498, 1257 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 2.73 (dd, *J* = 15.0 and 2.2 Hz, 1H, H-5a), 2.85 (dd, *J* = 15.0 and 5.4 Hz, 1H, H-5b), 3.91 (s, 3H, OMe), 5.1 (br s, 1H, H-6), 6.25–6.28 (m, 2H, ArH, and H-2), 6.42–6.50 (m, 2H, ArH), 6.54–6.59 (t, *J* = 7.2 Hz, 1H, ArH), 6.99–7.09 (m, 5H, ArH), 7.13–7.29 (m, 10H, ArH), 10.29 (br s, 1H, NH) ppm; ^{13}C NMR (50 Hz, $CDCl_3 + CCl_4$): δ 34.0 (CH_2, C-5), 51.4 (OCH_3), 55.5 (CH, C-2), 58.7 (CH, C-6), 98.5 (C, C-3), 113.4, 116.7, 126.1, 126.2, 126.8, 127.0, 127.6, 128.7, 129.0, 129.2, 129.3, 129.7 (ArCH), 138.3, 143.2, 144.3, 147.3, 156.5 (4ArC and C-4), 168.9 (CO); ESMS (*m/z*): $[M+H]^+$, 460. Elemental analysis for $C_{31}H_{28}N_2O_2$: C, 80.84; H, 6.13; N, 6.08. Found: C, 80.82; H, 6.15; N, 6.06.

4.1.14. Methyl 2,6-*bis*(3-chlorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (13)

White solid, mp 220 °C; R_f = 0.5 (ethyl acetate/hexane = 1/5); FTIR (KBr): υ 3680, 3398, 3020, 2360, 1652, 1593, 1502, 1427,

1261, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 2.82 (dd, J = 15.3 and 2.1 Hz, 1H, H-5a), 2.85 (dd, J =15.2 and 5.3 Hz, 1H, H-5b), 3.97 (s, 3H, OMe), 5.13 (br s, 1H, H-6), 6.39–6.49 (m, 5H, 4ArH, and H-2), 6.65–6.69 (t, J = 7.2 Hz, 1H, ArH), 7.03–7.31 (m, 14H, ArH), 10.29 (br s, 1H, NH); ^{13}C NMR (50 Hz, $CDCl_3 + CCl_4$): δ 34.1 (CH_2, C-5), 51.5 (OCH_3), 55.3 (CH, C-2), 57.9 (CH, C-6), 97.6 (C, C-3), 113.3, 117.4, 125.0, 126.5, 126.6, 126.8, 127.1, 127.9, 129.4, 129.5, 129.8, 130.3 (ArCH), 134.8, 135.0, 137.9, 145.1, 146.5, 146.7, 156.3 (6ArC and C-4), 168.4 (CO); ESMS (m/z): $[M+H]^+$, 530. Elemental analysis for $C_{33}H_{26}N_2O_2Cl_2$: Calcd C, 70.32; H, 4.95; N, 4.61. Found: C, 70.34; H, 4.93; N, 4.62.

4.1.15. Ethyl 2,6-*bis*(3-chlorophenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (14)

Pale yellow solid, mp 167–170 °C, R_f = 0.5 (ethyl acetate/hexane = 1/4); FTIR (KBr): υ 3447, 2987, 2836, 2362, 1646 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$:CCl_4): δ 1.47 (t, J = 7.1 Hz, 3H, $COOCH_2CH_3$), 2.64 (dd, J = 15.1 and 2.7 Hz, 1H, H-5a), 2.77 (dd, J = 15.1 and 5.4 Hz, 1H, H-5b), 3.79 and 3.68 (two s, 6H, 2xOMe), 4.51–4.29 (dq, J = 7.1 H_Z and 3.7H_Z, 2H, OCH_2), 5.01 (br s, 1H, H-6), 6.24–6.41 (m, 5H, 4ArH, and H-2), 6.67–6.71 (m, 4H, ArH), 7.03–7.35 (m, 8H, ArH), 10.17 (br s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3 + CCl_4$): δ 15.2 (CH_3, $COOCH_2CH_3$), 33.9 (CH_2, C-5), 55.7, and 55.9 (OCH_3), 56.1 (CH, C-2), 57.9 (CH, C-6), 60.0 (OCH_2), 96.9 (C, C-3), 114.4, 114.8, 115.0 (ArCH), 125.1, 125.2, 127.0, 127.4, 127.7, 128.4, 129.7 (ArCH), 130.8, 134.7, 134.9, 141.2, 145.6, 147.0, 151.9, 156.8, 158.4 (8ArC and C-4), 168.2 (CO); ESMS (m/z): $[M+H]^+$, 602. Elemental analysis for $C_{34}H_{32}Cl_2N_2O_4$: C, 67.66; H, 5.34; N, 4.64. Found: C, 67.64; H, 5.36; N, 4.63.

4.1.16. Ethyl-(4-chlorophenyl)-4-(4-chlorophenylamino)-2,6-dithiophen-2-yl)-1,2,5,6-tetrahydropyridine-3-carboxylate (15)

White solid, mp 217 °C, R_f = 0.5 (ethyl acetate/hexane = 1/4); FTIR (KBr): υ 3780, 3019, 2926, 2361, 1651 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.42–1.49 (t, J = 7.1 Hz, 3H, $COOCH_2CH_3$), 2.83 (dd, J = 15.2 and 2.5 Hz, 1H, H-5a), 3.1 (dd, J = 15.2 and 5.1 Hz, 1H, H-5b), 4.25–4.49 (m, 2H, OCH_2), 5.3 (br s, 1H, H-6), 6.36 (s, 1H, H-2), 6.44 (d, J = 12.9 Hz, 2H, ArH), 6.63 (d, J = 13.6 Hz, 2H, ArH), 6.81–7.02 (m, 4H, ArH), 7.0–7.26 (m, 6H, ArH), 10.40 (br s, 1H, NH) ppm; ^{13}C NMR (50 MHz, CDC_{l3}): δ 15.3 (CH_3, $COOCH_3$), 34.5 (CH_2, C-5), 53.0 (CH, C-2), 54.2 (CH, C-6), 60.2 (OCH_2), 98.4 (C, C-3), 109.9, 114.8 (ArCH), 122.6 (ArC), 124.1, 124.5, 124.8, 126.9, 127.2 (ArCH), 129.1, 129.6 (ArCH), 131.7, 136.9, 145.0, 147.1, 148.7, 155.7 (ArC and C-4), 168.0 (CO); ESMS (m/z): $[M+H]^+$, 554. Elemental analysis for $C_{28}H_{24}Cl_2N_2O_2S_2$: C, 60.54; H, 4.35; N, 5.04. Found: C, 60.56; H, 4.34; N, 5.03.

4.1.17. Methyl 1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-2,6-*di*-thiophen-2-yl)-1,2,5,6-tetrahydropyridine-3-carboxylate (16)

White solid, mp 210 °C; R_f = 0.5 (ethyl acetate/hexane = 1/5); FTIR (KBr): υ 3694, 3020, 2361, 1655, 1596, 1497, 1437, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): 2.8–3.0 (m, 2H, H-5a, and H-5b), 3.71 (s, 3H, ArOMe), 3.79 (s, 3H, ArOMe), 3.89 (s, 3H, OMe), 5.27 (br s, 1H, H-6), 5.95 (s, 1H, H-2), 6.25–7.27 (m, 14 H, ArH), 10.48 (br s, 1H, NH) ppm; ^{13}C NMR (50 Hz, $CDCl_3 + CCl_4$): δ 33.3 (CH_2, C-5), 51.1 (OCH_3), 54.2 (CH, C-2), 55.6 ($ArOCH_3$), 55.7 ($ArOCH_3$), 57.3 (CH, C-6), 97.4 (C, C-3), 114.5, 114.7, 114.9, 116.6, 119.6, 122.6, 123.8, 124.1, 124.5, 124.7 (ArCH), 125.3 (ArC), 126.4, 126.7, 126.8, 127.3, 128.0 (ArCH), 131.3, 140.9, 148.0, 149.9, 154.1, 156.9 (5ArC and C-4), 168.2 (CO), ESMS (m/z): $[M+H]^+$, 531.2. Elemental analysis for $C_{29}H_{28}N_2O_4S_2$: C, 65.39; H, 5.30; N, 5.26. Found: C, 65.37; H, 5.32; N, 5.24.

4.1.18. Ethyl 1,2,6-*tris*-(4-chlorophenyl)-4-(4-chlorophenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (17)

White solid, mp 190 °C, R_f = 0.5 (ethyl acetate/hexane = 1/5); FTIR (KBr): υ 3780, 3019, 2926, 2361, 1651 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + CD_3OD): δ 1.47–1.54 (t, J = 7.0 Hz, 3H, $COOCH_2CH_3$), 2.76 (dd, J = 15.1 and 2.2 Hz, 1H, H-5a), 2.82 (dd, J = 15.2 and 5.2 Hz, 1H, H-5b), 4.26–4.54 (m, 2H, OCH_2), 5.06 (br s, 1H, H-6), 6.25–6.42 (m, 5H, 4ArH, and H-2), 6.96–7.30 (m, 12H, ArH), 10.25 (br s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$ + CD_3OD): δ 19.1 (CH_3, $COOCH_2CH_3$), 37.6 (CH_2, C-5), 59.4 (CH, C-2), 61.8 (CH, C-6), 64.3 (OCH_2), 102.3 (C, C-3), 118.3 (ArCH), 126.5 (ArC), 128.6, 128.8 (ArCH), 130.2 (C-4), 130.7, 131.0, 131.2, 131.3, 132.0, 132.9, 133.2, 133.4, 133.8, 134.3 (ArCH), 136.2, 138.9, 139.1, 140.3, 148.5, 149.0, 149.8 (ArC), 172.0 (CO); ESMS (m/z): $[M+H]^+$, 611. Elemental analysis for $C_{32}H_{26}Cl_4N_2O_2$: C, 62.76; H, 4.16; N, 4.57. Found: C, 62.78; H, 4.14; N, 4.56.

4.1.19. Ethyl-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (18)

White solid, mp 173 °C, R_f = 0.5 (ethyl acetate/hexane = 1/5); FTIR (KBr): υ 3751, 3447, 3230, 2991, 2362, 1646, 1600, 1511 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 1.41–1.45 (t, J = 7.0 Hz, 3H, $COOCH_2CH_3$), 2.62 (dd, J = 15.2 and 2.2 Hz, 1H, H-5a), 2.76 (dd, J = 15.1 and 5.6 Hz, 1H, H-5b), 3.63 (s, 3H, ArOMe), 3.71 (s, 3H, ArOMe), 4.23–4.48 (m, 2H, OCH_2), 5.02 (br s, 1H, H-6), 6.18–6.21 (d, J = 8.64 Hz, 2H, ArH), 6.29 (s, 1H, H-2), 6.39–6.42 (d, J = 9.0 Hz, 2H, ArH), 6.56–6.63 (m, 4H, ArH), 7.14–7.29 (m, 10H, ArH), 10.30 (br s, 1H, NH) ppm; ^{13}C NMR (50 MHz, CDC_{l3} + CCl_4): δ 15.2 (CH_3, $COOCH_2CH_3$) , 34.0 (CH_2, C-5), 55.6 (CH, C-2), 55.9 ($ArOCH_3$), 56.2 ($ArOCH_3$), 58.7 (CH, C-6), 59.8 (OCH_2), 97.7 (C, C-3), 114.3, 114.6, 114.9, 126.6, 127.0, 127.2, 127.4, 128.2, 128.5, 129.0 (ArCH), 131.2, 141.9, 143.7, 144.7, 151.5, 157.0, 158.2 (6ArC and C-4), 168.2 (CO); ESMS (m/z): $[M+H]^+$, 611. Elemental analysis for $C_{34}H_{34}N_2O_4$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.36; H, 6.43; N, 5.22.

4.1.20. Ethyl 2,6-bis(phenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (19)

Pale yellow solid, mp 202 °C, R_f = 0.5 (ethyl acetate/hexane = 1/4); FTIR (KBr): υ 3446, 3244, 2974, 2361, 1646 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 1.52 (t, J = 7.1 Hz, 3H, $COOCH_2CH_3$), 2.73 (dd, J = 15.0 and 2.0 Hz, 1H, H-5a), 2.89 (dd, J = 15.0 and 5.7 Hz, 1H, H-5b), 4.54–4.34 (dq, J = 7.1 and 3.7 Hz, 2H, OCH_2), 5.13 (br s, 1H, H-6), 6.20–6.43 (m, 3H, ArH, and H-2), 7.00–7.09 (m, 4H, ArH), 7.17–7.35 (m, 10H, ArH), 10.29 (br s, 1H, NH); ^{13}C NMR (50 MHz, CDC_{l3}): δ 15.2 (CH_3, $COOCH_3$), 33.8 (CH_2, C-5), 55.7 (CH, C-2), 58.7 (CH, C-6), 60.2 (OCH_2), 99.2 (C, C-3), 114.4 (ArCH), 121.8 (ArC), 126.7, 126.9, 127.0, 127.3, 127.8, 128.7, 129.1, 129.2, 129.4 (ArCH), 131.8, 136.8, 142.7, 143.6, 145.8, 155.6 (5ArC and C-4), 168.3 (CO); ESMS (m/z): $[M+H]^+$, 543. Elemental analysis for $C_{32}H_{28}Cl_2N_2O_2$: C, 70.72; H, 5.19; N, 5.15. Found: C, 70.71; H, 5.17; N, 5.18.

4.1.21. Ethyl-1-phenyl-4-(phenylamino)-2,6-di(pyridin-3-yl)-1,2,5,6-tetrahydropyridine-3-carboxylate (20)

White solid, mp 178 °C; R_f = 0.5 (methanol/chloroform = 1/2); FTIR (KBr): ν 3368, 3244, 2972, 2362, 1720, 1654 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ 1.46–1.50 (t, J = 7.0 Hz, 3H, $COOCH_2CH_3$), 2.83–2.84 (d, J = 3.8 Hz, 2H, H-5), 4.30–4.50 (m, 2H, OCH_2), 5.20 (br s, 1H, H-6), 6.42–6.48 (m, 5H, 4ArH, and H-2), 6.66 (t, J = 7.2 Hz, 1H, ArH), 7.06–7.28 (m, 7H, ArH), 7.43–7.45 (d, J = 7.7 Hz, 1H, ArH), 7.58–7.61 (d, J = 7.8 Hz, 1H, ArH), 8.43–8.53 (m, 3H, ArH), 8.64 (s, 1H, ArH), 10.38 (br s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ 15.1 (CH_3, $COOCH_3$), 34.1 (CH_2, C-5),

53.9 (CH, C-2), 55.9 (C-6 and OCH_3), 60.4 (OCH_2), 97.6 (C, C-3), 113.5, 117.7, 123.4, 123.7, 126.0, 126.6, 129.0, 129.6, 134.5, 134.6 (ArCH), 137.8, 138.0, 139.6, 146.4 (5ArC and C-4), 148.2, 148.7, 148.9, 149.0 (ArCH), 155.7 (ArC), 168.0 (CO); ESMS (*m/z*): $[M+H]^+$, 477. Elemental analysis for $C_{30}H_{28}N_4O_2$ C, 75.61; H, 5.92; N, 11.76. Found: C, 75.63; H, 5.91; N, 11.74.

4.1.22. Methyl 2,6-*bis*(4-bromophenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (21)

White solid, mp 179 °C; R_f = 0.5 (ethyl acetate/hexane = 1/5); FTIR (KBr): υ 3797, 3421, 3018, 2358, 1650, 1508, 1371, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): 2.61 (dd, *J* = 15.0 and 2.4 Hz, 1H, H-5a), 2.72 (dd, *J* = 15.2 and 5.4 Hz, 1H, H-5b), 3.68 (s, 3H, ArOMe), 3.78 (s, 3H, ArOMe), 3.90 (s, 3H, OMe), 4.95 (br s, 1H, H-6), 6.18 (s, 1CH, H-2), 6.37 (d, *J* = 8.4 Hz, 2H, ArH), 6.64–6.70 (m, 5H, ArH,), 7.00 (d, *J* = 8.1 Hz, 2H, ArH), 7.13 (d, *J* = 8.1 Hz, 2 H, ArH), 7.37–7.42 (m, 5H, ArH), 10.13 (s, 1H, NH) ppm; ^{13}C NMR (50Hz, $CDCl_3 + CCl_4$): δ 34.0 (CH_2, C-5), 51.4 (OCH_3), 55.6 (Ar-OCH_3), 55.8 ($ArOCH_3$), 56.0 (CH, C-2), 57.8 (CH, C-6), 96.8 (C, C-3), 114.5, 114.7, 115.0 (ArCH), 120.6, 121.3 (2ArC), 128.1, 128.7, 129.0 (ArCH), 130.8 (C-4), 131.6, 132.0 (ArCH), 141.2, 142.3, 143.4, 151.9, 156.9, 158.4, 168.5 (CO); ESMS (*m/z*): $[M+H]^+$, 562. Elemental analysis for $C_{33}H_{30}Br_2N_2O_4$: Calcd C, 58.42; H, 4.46; N, 4.13. Found: C, 58.44; H, 4.48; N, 4.11.

4.1.23. Methyl 2,6-*bis*(3-nitrophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (22)

Pale yellow solid, mp 180 °C, R_f = 0.4 (ethyl acetate/hexane = 1/4); FTIR (KBr): υ 3751, 3019, 2954, 2364, 1736, 1669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 2.90 (d, *J* = 3.69 Hz, 2H, H-5), 4.01 (s, 3H, OCH_3), 5.35 (br s, 1H, H-6), 6.41–6.50 (m, 5H, ArH, and H-2), 6.70 (t, *J* = 7.26 Hz, 1H, ArH), 7.08–7.17 (m, 5H, ArH), 7.44–7.51 (m, 3H, ArH), 7.68 (d, *J* = 7.62 Hz, 1H, ArH), 7.96 (s, 1H, ArH), 8.10 (m, 2H, ArH), 8.23 (s, 1H, ArH), 10.32 (br s, 1H, NH); ^{13}C NMR (50 MHz, CDC_{l3}): δ 30.0 (CH_3, $COOCH_3$), 34.1 (CH_2, C-5), 51.8 (CH, C-2), 55.6 (CH, C-6), 57.5 (C, C-3), 113.5, 118.3, 121.8, 121.9, 122.2, 122.8, 126.1, 127.0, 129.5, 129.6, 129.8, 129.9, 132.8 (ArCH), 155.8, 149.1, 146.7, 146.1, 144.8, 137.6 (ArC and C-4), 168.2 (CO); ESMS (*m/z*): $[M+H]^+$, 552. Elemental analysis for $C_{31}H_{27}N_4O_6$: C, 67.50; H, 4.93; N, 10.16. Found: C, 67.45; H, 5.00; N, 10.18.

4.1.24. (*E*)-Methyl 2-(3-methoxybenzylidene)-3-oxobutanoate (23)

Pale yellow viscous mass, R_f = 0.7 (ethyl acetate/hexane = 1/4); FTIR (KBr): υ 3697, 3429, 3020, 2360, 1725, 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 2.34 (d, *J* = 8.40, CH_3), 3.86 (s, 6H, 3xOCH_3), 6.87–6.92 (m, 2 H, ArH), 7.35–7.41 (m, 2H, ArH), 7.51 (d, *J* = 29.4 Hz, 1H, CH); ESMS (*m/z*): $[M+H]^+$, 235.

4.1.25. (*E*)-*N*-(3-Methoxybenzylidene)aniline (24)

Pale yellow solid, mp 65–67 °C; R_f = 0.8 (ethyl acetate/hexane = 1/4); FTIR (KBr): υ 3605, 3020, 2360, 1597 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 8.38 (s, 1H, CH), 7.87 (d, *J* = 8.67 Hz, 2H, ArH); 7.41–7.36 (m, 2H, ArH), 7.24–7.18 (m, 2H, ArH), 7.00 (d, *J* = 8.67, 2H, ArH), 3.89 (s, 3H, CH_3); ESMS (*m/z*): $[M+H]^+$, 212.

4.2. Biology

4.2.1. Determination of antimalarial activity in vitro[16–18]

The antimalarial activity of the compounds and reference drug (chloroquine diphosphate MIC 0.025 μg/mL) were assayed against 3D7 strain of *P. falciparum* by the schizont maturation test. Briefly drug dilutions (100 μL/well) were prepared in complete RPMI 1640 and 10 μL of parasite preparation was added to each well. The final culture suspension had a hematocrit of 3–4% and a 1.0–2.0% infection of parasitized erythrocytes (>95% rings) in culture medium containing 0.5% AlbuMax II and 15 μM hypoxanthine. Micro culture plates were incubated for 30–39 h at 37 °C in an Incubator supplied with 5% CO_2 to allow the development of malaria parasites. After incubation, culture plates were taken out and maximum supernatant medium was removed and thin blood smears of each well content were made and stained with 5% Giemsa stain. These smears were checked for the maturation of schizont relative to the controls. These tests, measure the drug sensitivity of *P. falciparum* following the WHO standard protocol with minor modifications for the assessment of the inhibition of schizont maturation.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2008.11.062.

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