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# SYNTHESIS AND EVALUATION OF THE ANTIMALARIAL ACTIVITY OF CINNAMIC ACIDS DERIVED FROM PIPERIDINE

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## ABSTRACT
The synthesis and antimalarial activity of 1, 4-aminopiperidine derived cinnamic acids are described. Different analogs are prepared from reductive amination reactions and SN1 substitutions. These analogs are tested against chloroquino-sensitive strains 3D7 and chloroquine-resistant W2 *plasmodium falciparum*, cytotoxicity and selectivity are also evaluated. Thus, compound **14a** showed excellent activity against both *plasmodium falciparum* strains [IC50 = 13.18 nM (3D7) and 18.96 nM (W2)] with a CC50> 100 and good selectivity index (> 15.6 (3D7) and> 10.8 (W2)). The molecules are characterized by NMR and mass spectroscopy.

**KEYWORDS:** Antimalarial, *plasmodium falciparum, in vitro*, cinnamic acids.

## INTRODUCTION
Malaria is one of the most lethal diseases, with almost a third of the world's population at risk. It represents a major public health problem due to morbidity and mortality.[1-3]

Despite considerable efforts to control and eliminate malaria in some areas, there is still a public health problem. There is therefore an urgent need to discover new treatments against malaria because of the development of resistance and / or side effects or cost of treatments currently available. The search for a route is continued for the discovery of new antimalarial molecules with fewer side effects, greater speed of action and a better response rate. Thus, in the context of our thesis, we proposed the synthesis and biological evaluation of compounds derived from piperidine. Piperidines are important pharmacophores found in the structure of complex natural products as well as in some recently marketed drugs.[4-5]

Synthetic approaches to this simple ring system have attracted a lot of attention.[6-9]

Cinnamic acid and its phenolic analogues are natural substances. Chemically, cinnamic acids or the 3-phenyl acrylic acids, offer three main reactive sites: substitution on the phenyl ring, addition on the α, β-unsaturation and reactions of the carboxylic acid. Owing to these chemical aspects, cinnamic acid derivatives received much attention in medicinal research as traditional as well as valuable scaffolds in recent synthetic bioactive agents. In the last two decades, there has been huge attention towards various cinnamoyl derivatives and their biological efficacy.[10]

In the process of searching for new small molecules interacting with the strain P. *falciparum*, we have identified the compound **1** of piperidine (Figure 1) as a promising scaffold. In this paper, we describe the synthesis of a new derivatives with as potential antimalarial properties.

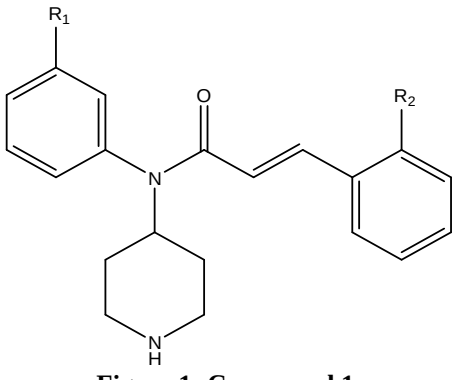


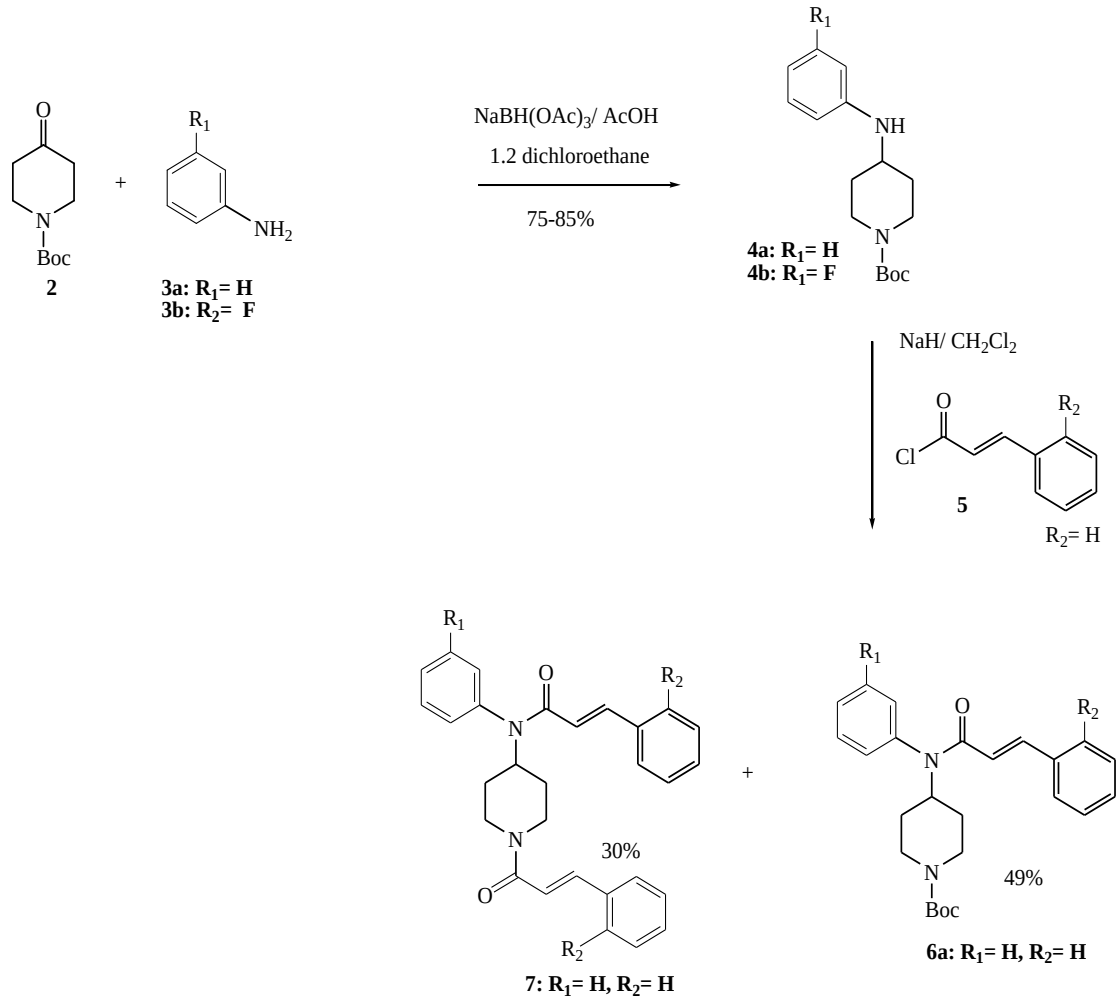

**Figure 1: Compound 1.**

## MATERIALS AND METHODS

### Method of synthesis of the molecules studied

Reductive amination[11-15] of *N*-boc-piperidin-4-one **2** with aniline **3** in $CH_2Cl_2$, gave compound **4** in 75-85% yield. Acylation of the sodium salt of **4** with cynnamoyil chloride **5** in $CH_2Cl_2$ at 0°C furnished compound **6** (49%) and **7** (30%) (Scheme 1). In this reaction we used excess phenoxyacetyl chloride, and we think that this excess probably made the reaction medium acidic which will cause the deprotection of N-Boc.

To avoid this second condensation, we have varied the temperature by increasing it while maintaining constant the amount of acyl chloride.




**2**

**3a: $R_1$= H**
**3b: $R_2$= F**

**4a: $R_1$= H**
**4b: $R_1$= F**

**5**

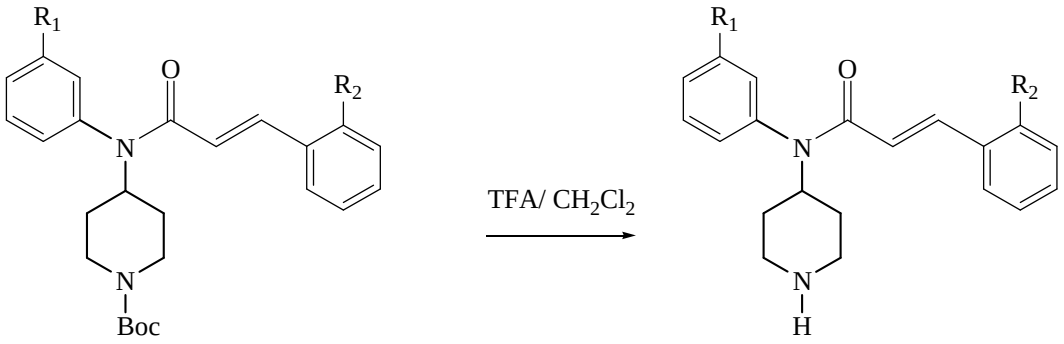
$R_2$= H

**7: $R_1$= H, $R_2$= H**

**6a: $R_1$= H, $R_2$= H**

**Scheme 1: Synthesis compounds 7 and 6a.**

After separarion compounds **7** and **6a,** the molecule **6a** was deprotected[16,17] using trifluoroacetic acid at room temperature provided compound **1a** (45-96%) (Scheme 2).

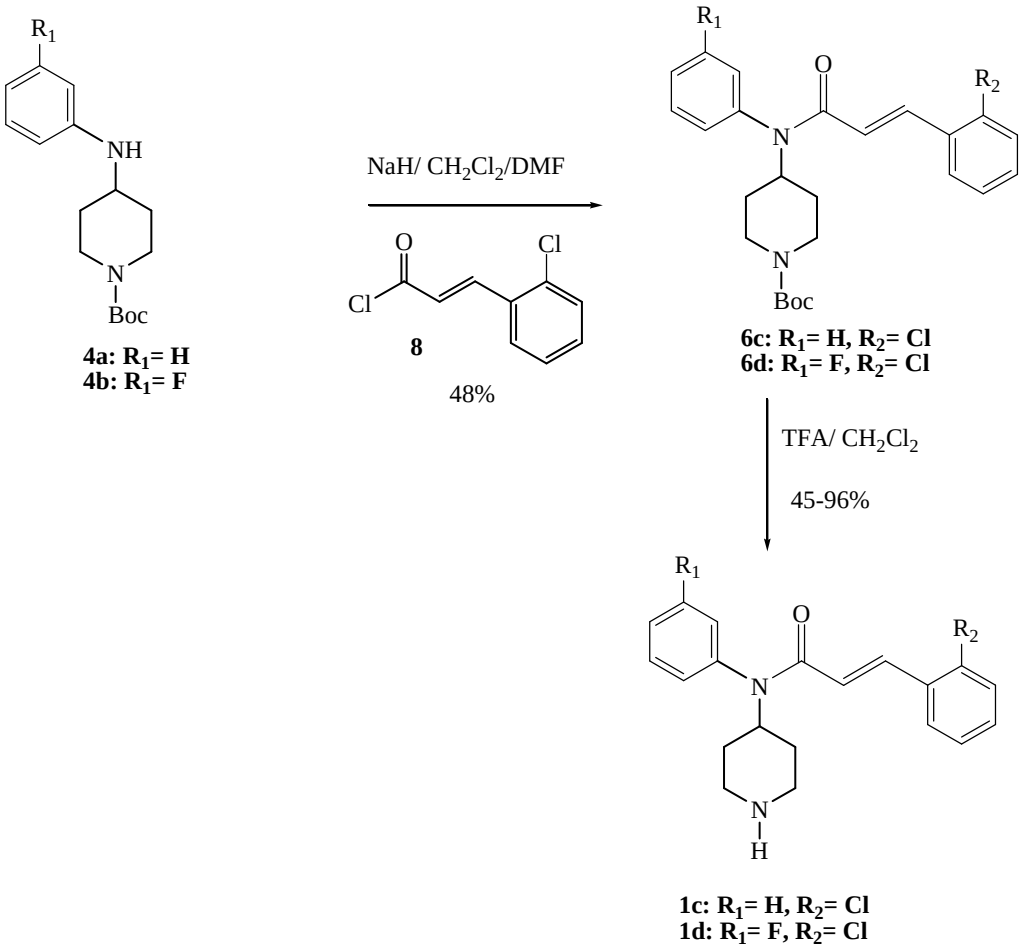



**6a: $R_1$= H, $R_2$= H**

**1a: $R_1$= H, $R_2$= H**

**Scheme 2: synthesis compound 1a.**

The acylation of **4** gave a single compound **6** with a modest yield of 48%. The use of a mixture of $CH_2Cl_2$/DMF is explained by the non-solubility of compound **8** in $CH_2Cl_2$. Final deprotection[16,17] of **6** using trifluoroacetic acid at room temperature provided compound **1** (45-96 %) (Scheme 3, Table 1).

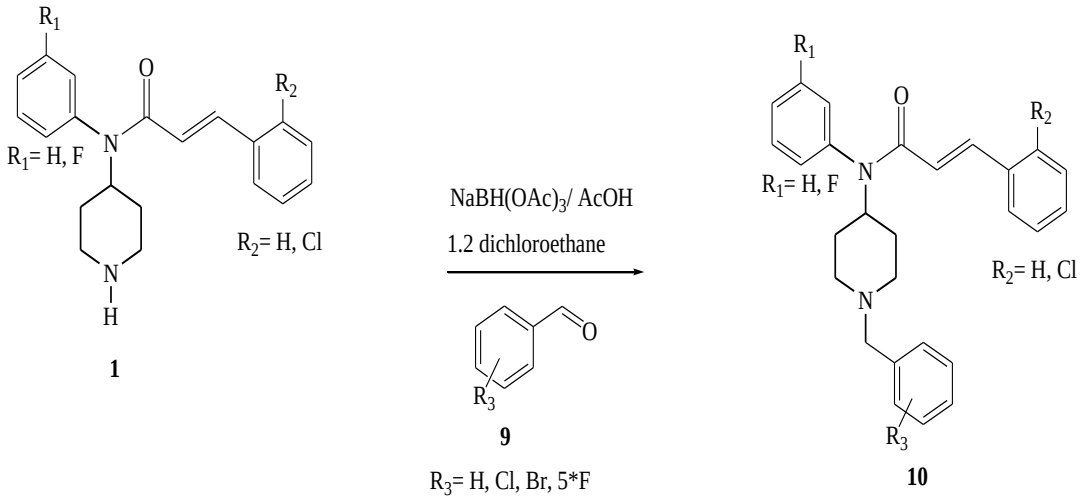



**Scheme 3: Synthesis compounds 1c and 1d.**

**Table 1: The products of the synthesis of 1 recorded.**

| Compounds | $R_1$ | $R_2$ | Yields % |
|---|---|---|---|
| **1a** | H | H | 82 |
| **1c** | H | Cl | 70 |
| **1d** | F | Cl | 55 |

A pharmaco-modulation has been achieved on the parent molecule **1** taking into profit the nucleophilicity of the piperidine nitrogen leading to compounds with good yield. Thus, reductive amination[11-15] of **1** with benzaldehyde derivatives **9** in $(CH_2Cl)_2$, gave compounds **10** (Scheme 4) (Table 2).




**Scheme 4: Synthesis compound 10.**

**Table 2**: **The compounds of reductive amination of 1 with the derivatives benzaldehydes recorded.**

| Compounds | $R_1$ | $R_2$ | $R_3$ | Time (h) | Yields % |
|---|---|---|---|---|---|
| **11a** | H | H | H | 24 | 55 |
| **11c** | H | Cl | H | 24 | 50 |
| **12a** | H | H | Br | 24 | 53 |
| **12c** | H | Cl | Br | 24 | 53 |
| **13a** | H | H | Cl | 24 | 50 |
| **14a** | H | H | 5xF (*o*,*m*,*p*) | 24 | 57 |
| **14c** | H | Cl | 5xF (*o*,*m*,*p*) | 24 | 55 |

**Experimental Details of the Synthesis of Molecules**

**Experimental section**

The $^1H$ and $^{13}C$ spectra were recorded in $CDCl_3$ at ambient temperature on a Bruker AMX 500 spectrometer. Some products secured by DEPT 135, HMQC and HMBC experiments. Chemical shifts are given in δ (ppm) and coupling constants J (Hz) relative to TMS as internal standard; multiplicities were recorded as s (singlet), d (doublet), dd (double doublet), t (triplet), dt (double triple), q (quartet) or m (multiplet). Reactions involving anhydrous conditions were conducted in dry glassware under a nitrogen atmosphere. The infrared spectra have been recorded on a spectrometer Perkin-Elmer 842 (reference: polystyrene). The melting point have been measured on a Tottoli S Bucchi device. The microanalysis has been done on a Perkin-Elmer 2400-CMN apparatus. GC/MS conditions: Analyses were performed using a 5890 gas chromatogram connected to a G 1019 A mass spectrometer (both from Hewlett Packard) operating in the electro spray ionization mode (ESI).

**General procedure for the synthesis of *tert*-Butyl 4-(phenylamino) piperidine-1-carboxylate (4)**

A solution of aniline (1 equiv) in 1,2-dichloroethane (100 mL) containing *t*-butyl-4-oxo-1-piperidine carboxylate (1 equiv), sodium triacetoxyborohydride (1.5 equiv) and acetic acid (1.5 equiv) was stirred for 24 h at 20 °C. 1N NaOH (50 mL, 50 mmol) and 50 mL of ethyl acetate were added. The phases were separated and the aqueous layer was extracted with ethyl acetate (3x25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by crystallization (ether petroleum / ethyl acetate (8/2)).

***Tert-butyl 4-(phenylamino) piperidine-1-carboxylate (4a)***

Aniline (2.8 g, 30.11 mmol) in 1.2-dichloroethane (100 mL) containing *t*-butyl-4-oxo-1-piperidine carboxylate (6 g, 30.11 mmol), sodium triacetoxyborohydride (9.57 g, 45.1 mmol) and acetic acid (2.71 g, 45.16 mmol) gave compound (**4a).**

***Tert-butyl 4-(3-fluorophenylamino) piperidine-1-carboxylate (*4b)**

3-fluoroaniline (3.34 g, 30.11 mmol) in 1,2-dichloroethane (100 mL) containing *t*-butyl-4-oxo-1-piperidine carboxylate (6 g, 30.11 mmol), sodium triacetoxyborohydride (9.57 g, 45.1 mmol) and acetic acid (2.71 g, 45.16 mmol) gave compound (**4b).**

**General Procedure for the coupling with phenoxyacetylchloride (6)**

To an ice-cooled suspension of sodium hydride (60% in mineral oil, 2 equiv) in $CH_2Cl_2$ (10 mL) was added dropwise a solution of compound (**4)** (1 equiv), in $CH_2Cl_2$ (15 mL). After stiring 15 minutes cinamoyl acid **5** (2 equiv) was added. The reaction mixture was stirred for 1 hour at 0°C, and the temperature was raised to room temperature during 24 hours. 20 mL of saturated solution of $NaHCO_3$ was carrefully added. The aqueous

layer was extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic phases were dried over $MgSO_4$, and concentrated in vacuum. The crude product was purified by colonne of chromatographie (ether petroleum / ethyl acetate (8/2)) to fournish compounds (**6)** and (**7).**

***Tert-butyl 4-((E)-N-phenylcinnamamido) piperidine-1-carboxylate (6a)***
Following the general procedure, sodium hydride (60% in mineral oil, 0.610 g, 15.28 mmol) in $CH_2Cl_2$ (10 mL) was added dropwise a solution of compound (**4a)** (2.11 g, 7.64 mmol), in $CH_2Cl_2$ (15 mL). After stiring 15 minutes phenoxyacethylchloride (2.5 g, 15.28 mmol) was added to give compound (**6a).**

***Tert-butyl 4-((E)-3-(2-chlorophenyl)-N-phenylacrylamido) piperidine-1-carboxylate (6c)***
Following the general procedure, sodium hydride (60% in mineral oil, 0.499 g, 20.8 mmol) in $CH_2Cl_2$ (10 mL) was added dropwise a solution of compound (**4a)** (2.3 g, 8.3 mmol), in $CH_2Cl_2$ (15 mL). After stiring 15 minutes cinamoyl chloride (3.5 g, 16.65 mmol) was added to give compound (**6c).**

***Tert-bnylutyl 4-((E)-3-(2-chlorophenyl)-N-(3-fluorophenyl) acrylamide) piperidine-1-carboxylate (6d)***
Following the general procedure, sodium hydride (60% in mineral oil, 0.536 g, 12 mmol) in $CH_2Cl_2$ (10 mL) was added dropwise a solution of compound (**4b)** (2 g, 6.7 mmol), in $CH_2Cl_2$ (15 mL). After stiring 15 minutes cinamoyl chloride (2.7 g, 12 mmol) was added to give compound (**6d).**

***(2E)-N-phenyl-N-(1-((E)-3-phenylacryloyl) piperidin-4-yl) cinnamamide (7)***
Following the general procedure, sodium hydride (60% in mineral oil, 0.610 g, 15.28 mmol) in $CH_2Cl_2$ (10 mL) was added dropwise a solution of compound (**4a)** (2.11 g, 7.64 mmol), in $CH_2Cl_2$ (15 mL). After stiring 15 minutes phenoxyacethylchloride (2.5 g, 15.28 mmol) was added to give compound (**7).**

**General Procedure for deprotection (1)**
1 equiv of compound (**6)** were dissolved in 15 mL of $CH_2Cl_2$, 13 equiv of trifluoroacetique acid were added. After 2 hours of stirring at room temperature, the reaction mixture was concentrated in vacuum. The residual was dissolved in 5 mL of ethyl acetate then neutralized by $NaHCO_3$ (5%). The aqueous layer was extracted with ethyl acetate (4x5mL). The combined organic phases were dried over $MgSO_4$ filtered and concentrated under reduced pressure. The crude product was purified by crystallisation (ether petroleum / ethyl acetate (8/2)).

***(E)-N-phenyl-N-(piperidin-4-yl) cinnamamide (1a)***
Following the general procedure, 1.3 g (3.2 mmol) of compound (**6)** were dissolved in 15 mL of $CH_2Cl_2$, 3.20 mL (41.65 mmol) of trifluoroacetique acid were added.

***(E)-3-(2-chlorophenyl)-N-phenyl-(piperidin-4-yl) acrylamide (1c)***
Following the general procedure, 2.17 g (4.93 mmol) of compound (**6)** were dissolved in 15 mL of $CH_2Cl_2$, 4.937 mL (64 mmol) of trifluoroacetique acid were added.

***(E)-3-(2-chlorophenyl)-N-(3-fluorophenyl)-N-piperidin-4-yl)-acrylamide (1d)***
Following the general procedure, 1.0205 g (2.227 mmol) of compound (**6)** were dissolved in 15 mL of $CH_2Cl_2$, 2.2306 mL (28.95 mmol) of trifluoroacetique acid were added.

**General procedure for reductive amination with benzaldehydes**
A solution of benzaldehyde derivatives (1 equiv) in 1, 2-dichloroethane containing compound (**1)** (1 equiv), sodium triacetoxyborohydride (1.5 equiv) and acetic acid (1.5 equiv) was stirred for 24 h at 20 °C. 1N NaOH (15 mL) and 15 mL of ethyl acetate were added. The phases were separated and the aqueous layer was extracted with ethyl acetate (3x15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum /AcET) (8/2).

***(E)-N-(1-benzylpiperidin-4-yl)-N-phenylcinnamamide (11a)***
Following the general procedure for reductive amination, using benzaldehyde derivatives (**11)** ($R_3$= H) (52 mg, 0.49 mmol); compound (**1a)** (150 mg, 0.49 mmol); sodium triacetoxyborohydride (0.155 mg, 0.735 mmol) and acetic acid (44 mg, 0.735 mmol) in 1,2-dichloroethane (5 mL) gave compound (**13a).**

***(E)-N-(1-benzylpiperdin-4-yl)-3-(2-chlorophenyl)-N-phenylacrylamide (11c)***
Following the general procedure for reductive amination, using benzaldehyde derivatives (**9)** ($R_3$= H) (46 mg, 0.44 mmol); compound (**1c)** (150 mg, 0.44 mmol); sodium triacetoxyborohydride (0.1468 mg, 0.661 mmol) and acetic acid (37.8 mL, 0.661 mmol) in 1,2-dichloroethane (5 mL) gave compound (**11c).**

***(E)-N-(1-bromobenzyl) piperidin-4-yl)-N-phenylcinnamamide (12a)***
Following the general procedure for reductive amination, using benzaldehyde derivatives (**9)** ($R_3$= H) (90 mg, 0.49 mmol); compound (**1a)** (150 mg, 0.49 mmol); sodium triacetoxyborohydride (155 mg, 0.735 mmol) and acetic acid (44.15 mg, 0.735 mmol) in 1,2-dichloroethane (5 mL) gave compound (**12a).**

***(E)-N-(1-(2-bromobenzyl) piperidin-4-yl)-3-(2-chlorophenyl)-N-phenylacrylamide (12c)***
Following the general procedure for reductive amination, using benzaldehyde derivatives (**9)** ($R_3$= H) (81.5 mg, 0.441 mmol); compound (**1c)** (150 mg, 0.441 mmol); sodium triacetoxyborohydride (146.81 mg, 0.661 mmol)

and acetic acid (39.72 mg, 0.661 mmol) in 1,2-dichloroethane (5 mL) gave compound **12c.**

***(E)-N-(1-(2-chlorobenzyl) piperidin-4-yl)-N-phenylcinnamamide (13a)***

Following the general procedure for reductive amination, using benzaldehyde derivatives (**9)** ($R_3$= H) (68.9 mg, 0.49 mmol); compound (**1a)** (150 mg, 0.49 mmol); sodium triacetoxyborohydride (155 mg, 0.735 mmol) and acetic acid (44 mg, 0.735 mmol) in 1,2-dichloroethane (5 mL) gave compound (**13a).**

***(E)-N-(1-(perfluorobenzyl) piperidin-4-yl)-N-phenylcinnamamide (14a)***

Following the general procedure for reductive amination, using benzaldehyde derivatives (**9)** ($R_3$= H) (96.1 mg, 0.49 mmol); compound (**1a)** (150 mg, 0.49 mmol); sodium triacetoxyborohydride (155.8 mg, 0.735 mmol) and acetic acid (44 mg, 0.735 mmol) in 1,2-dichloroethane (5 mL) gave compound (**14a).**

***(E)-3-(2-chlorophenyl)-N-(1-(perfluorobenzyl) piperidin-4-yl)-N-phenylacrylamide (14c)***

Following the general procedure for reductive amination, using benzaldehyde derivatives (**9)** ($R_3$= H) (86.4 mg, 0.441 mmol); compound (**1c)** (150 mg, 0.441 mmol); sodium triacetoxyborohydride (140.2 mg, 0.661 mmol) and acetic acid (39.72 mg, 0.661 mmol) in 1,2-dichloroethane (5 mL) gave compound (**14a).**

**Antiplasmodial assay**

The antimalarial activity of extracts/compounds was evaluated against *P. falciparum* 3D7 and *P. falciparum* W2 strains, using the fluorescence-based SYBR Green I assay approach in 96-well microplates as described by Smilkstein and al.[18] with some modifications. Positive control wells for each assay contained no inhibitor while negative controls contained Chloroquine (CQ). The CQ molecule was provided from World Wide Antimalarial Resistance Network (wwarn Network). Experiments were run in duplicate with both test and control drugs employed at varying concentrations. Stock solutions (extracts) were prepared in dimethyl-sulfoxide (DMSO) and diluted with culture medium to give a maximum DMSO concentration of 0.5% in a final well volume of 200 µL containing 1% parasitemia and 2.5% haematocrit. Extracts and negative control [Chloroquine (CQ)] were prepared by two-fold dilution, in a dose-titration range of 0.098-100 µg / mL, to obtain 11 concentrations each, in duplicate. The concentrations used for CQ were between 0.5 and 1000 nM. After 48 h incubation, the plates were subjected to 3 freeze thaw cycles to achieve complete hemolysis. The parasite lysis suspension was diluted 1:5 in SYBR Green I lysis buffer (10 mM NaCl, 1 mM Tris HCl pH8, 2.5 mM EDTA pH 8, 0.05% SDS, 0,01 mg/mL proteinase K and 10X SYBR Green I). Incorporation of SYBR Green I in parasite DNA amplification was measured using the Master epRealplex cycler® (Eppendorf, France) according the following program to increase the SYBR green incorporation: 90°C for 1 min, decrease in temperature from 90°C to 10°C for 5 min with reading the fluorescence 10°C for 1 min and a new reading at 10°C for 2 min. The $IC_{50}$ was calculated by nonlinear regression using icestimator website 1.2 version: http://www.antimalarial-icestimator.net/MethodIntro.htm.

**Cytotoxicity on HUVEC**

HUVEC cells were cultured in Gibco™ RPMI 1640 medium (Life technologies, France) complemented with 10% Fetal Bovine Serum and 1 mM L-glutamine (Sigma-Aldrich, France) and incubated in 5% $CO_2$ at 37°C. The cytotoxicity of extracts was evaluated using the SYBR Green I assay as previously described. HUVEC were seeded in a 96-well plate at 100,000 cells/well and incubated for 24h to adhere. After discarding the old medium, the cells were incubated in the medium containing eight concentrations (0.78-100 µg/mL) of each extract in duplicate. After 48h incubation, cells were visualized using an inverted microscope to check their morphology or the cell viability. The medium was subsequently removed and replaced by lysis buffer without SYBR Green I and the plates were subjected to 3 freeze-thaw cycles. The cell lysis suspension was diluted 1:2 in SYBR Green I lysis buffer. The incorporation of SYBR Green I in cell DNA and the $IC_{50}$ analysis were obtained as previously.

## RESULTS AND DISCUSSION

**Characteristics of Synthetic Molecules**

Tert-butyl 4-(phenylamino) piperidine-1-carboxylate (**4a).** Yield: 7.07 g (85%). m.p: 105. $^1$H RMN ($CDCl_3$, 500 Mhz): 1.3 (m, 2H, $CH_2$); 1.49 (s, 9H, $3CH_3$); 2.0 (m, 2H, $CH_2$); 2.9 (m, 2H, $CH_2$); 3.3 (m, 1H, CH); 3.7 (Broadband, 1H, NH); 4.1 (m, 2H, $CH_2$); 6.5-7.5 (m, $5H_{Ar}$). $^{13}$C RMN (125 MHz, $CDCl_3$) δ: 28.57 ($3\times CH_3$); 32.52 ($2\times CH_2$); 42.30 ($2\times CH_2$); 50.22 (CH); 79.72 (C); 113.42 (2× CH); 117.61 (CH); 129.49 (2×CH); 149.89 (C); 154.92 (C). MS (m/z): calcud for $C_{16}H_{24}N_2O_2$ 276.2 found 277.1 [M+1];

Tert-butyl 4-(3-fluorophenylamino) piperidine-1-carboxylate (**4b)**: Yield: 6.58 g (74%); m.p:114 $^1$H RMN ($CDCl_3$, 500Mhz): 1.3 (m, 2H, $CH_2$); 1.49 (s, 9H, $3CH_3$); 2.0 (m, 2H, $CH_2$); 2.9 (m, 2H, $CH_2$); 3,4 (m, 1H, CH); 3.8 (Broadband, 1H, NH); 4.1 (m, 2H, $CH_2$); 6.5-7.5 (m, $4H_{Ar}$). $^{13}$C (125 MHz, $CDCl_3$) δ: 28.56 ($3\times CH_3$); 32.36 ($2\times CH_2$); 42.73 ($2\times CH_2$); 50.26 (CH); 79.81 (C); 99.95 (d, J= 25.26 Hz, CH); 103.84 (d, J= 21.25 Hz, CH); 109.19 (d, J= 2.2 Hz, CH); 130.58 (d, J= 10.30 Hz, CH); 148.73 (d, J= 10.55 Hz, C); 154.896 (C), 163.34 (C).

Tert-butyl 4-((E)-N-phenylcinnamamido) piperidine-1-carboxylate (**6a**). Yield: 1.3 g (41%). IR $cm^{-1}$: 1686; 1655; 1618. m.p = 153°C. $^1$H RMN (400 MHz, $CDCl_3$): 1.33 (m, 2H, $CH_2$); 1.43 (s, 9H, $3\times CH_3$); 1.89 (m, 2H, $CH_2$); 2.87 (t, J = 12 Hz, 2H, $CH_2$); 4.16 (m, 2H, $CH_2$); 4.91 (m, H, CH); 6.11 (d, J = 16 Hz 1H, CH); 7-7.5 (m, $10H_{Ar}$); 7.66 (d, J = 12 Hz, 1H, CH). $^{13}$C RMN (150

MHz, $CDCl_3$) δ: 28.39 (3 ×$CH_3$); 30.56 (4× $CH_2$); 52.79 (CH); 79.57 (C); 119.38 (CH); 127.81 (2× CH); 128.64 (2× CH); 129.44 (2× CH); 129.49 (2×CH); 130.61 (2× CH); 135.21 (C); 138.36 (C); 141.90 (CH); 154.61 (C); 165.76 (C).

Tert-butyl 4-((E)-3-(2-chlorophenyl)-N-phenylacrylamido) piperidine-1-carboxylate (**6c**). Yield: 2.17 g (60%). m.p = 129°C. $^1$H RMN (600 MHz, $CDCl_3$): 1.33 (m, 2H, $CH_2$); 1.5 (s, 9H, 3× CH3); 1.99 (m, 2H, $CH_2$); 2.87 (m, 2H, $CH_2$); 4.2 (m, 2H, $CH_2$); 4.95 (m, H, CH); 6.11 (d, J= 15.55 Hz, CH); 7-7.5 (m, 9 $H_{Ar}$); 7.99 (d, J = 15.50 Hz, CH). $^{13}$C RMN (150 MHz, $CDCl_3$) δ: 28.49 (3× $CH_3$, $C(CH_3)_3$; 30.61 (2× $CH_2$); 43.42 (2× $CH_2$) ; 53.00 (CH); 79.71 (C); 122.20 (CH); 126.86 (CH); 127.72 (CH); 128.82 (CH); 129.60 (CH); 130.15 (2× CH); 130.34 (CH); 130.67 (2× CH); 134.66 (C); 134.82 (C); 138.025 (CH); 138.30 (C); 154.70 (C) 165.40 (C).

Tert-bnylutyl 4-((E)-3-(2-chlorophenyl)-N-(3-fluorophenyl) acrylamide) piperidine-1-carboxylate (**6d**). Yield: 1.02 g (33%). mp = 129°C. $^1$H RMN (600 MHz, $CDCl_3$): 1.33 (m, 2H, $CH_2$); 1.5 (s, 9H, 3× $CH_3$); 1.99 (m, 2H, $CH_2$); 2.87 (m, 2H, $CH_2$); 4.2 (m, 2H, $CH_2$); 4.95 (m, H, CH); 6.11 (d, J = 15.55 Hz, CH); 7-7.5 (m, 8$H_{Ar}$); 7.99 (d, J = 15,50 Hz, CH).$^{13}$C RMN (150 MHz, $CDCl_3$): 28.39 ($C(CH_3)_3$**;** 30.61 (2× $CH_2$); 43.42 (2× $CH_2$); 53.00 (CH); 79.71 (C); 119.25 (CH); 127.28 (2×CH); 127.98 (2×CH); 128.72 (C); 130.41 (2×CH); 132.01 (2×CH); 135.51 (C); 138.23 (C); 144.28 (CH), 154.55 (C); 161.41 (C); 165.60 (C).

(2E)-N-phenyl-N-(1-((E)-3-phenylacryloyl) piperidin-4-yl) cinnamamide (**7**). Yield: 1.3 g (41%). mp= 167°C. $^1$H RMN (600 MHz, $CDCl_3$): 1.33 (m, 2H, $CH_2$); 1.89 (m, 2H, $CH_2$); 2.87 (m, 2H, $CH_2$); 4.16 (m, 2H, $CH_2$); 4.91 (m, H, CH); 6.11 (d, J = 18 Hz, 2H, 2×CH); 7-7.5 (m, 15$H_{Ar}$); 7.66 (d, J = 12 Hz, 2H, 2×CH). $^{13}$C RMN (150 MHz, $CDCl_3$): 30.56 (2× $CH_2$); 43.42 (2× $CH_2$); 52.79 (CH); 119.38 (2×CH); 127.93 (CH); 127.98 (2× CH); 128.80 (2×CH); 128.92 (2× CH); 128.98 (CH); 129.74 (2×CH); 129.76 (2×CH); 130.61 (CH); 135.21 (C); 138.36 (C); 141.90 (2×CH); 142.28 (CH); 143.05 (CH); 154.61 (C); 165.76 (2×C). ESI (m/z): calcd for $C_{29}H_{28}N_2O_2$ 436.18; found 437.2 [M+1]. IR $cm^{-1}$: 3519; 1651.

(E)-N-phenyl-N-(piperidin-4-yl) cinnamamide (**1a**). Yield: 1.3 g (82%); mp =127°C. IR $cm^{-1}$: 3027; 1651. $^1$H RMN (600 MHz, $CDCl_3$) δppm : 1.70 (m, 2H, $CH_2$); 2.02 (m, 2H, $CH_2$); 2.8 (bande, 1H, NH); 2.98 (m, 2H, $CH_2$); 3.37 (m, 2H, $CH_2$); 4.90 (m, H, CH); 6.05 (d, J = 15 Hz, 1H, CH); 7-7.5 (m, 10$H_{Ar}$); 7.66 (d, J = 15 Hz, 1H, CH).$^{13}$C RMN (150 MHz, $CDCl_3$): 28.303 (2× $CH_2$); 44.27 (2× $CH_2$); 50.16 (CH); 119.07 (CH); 128.00 (2× CH); 128.82 (2× CH); 129.24 (2× CH); 129.49 (2× CH); 130.68 (2× CH); 135.03 (C); 137.54 (C); 142.65 (CH); 166.12 (C). ESI (m/z): calcd for $C_{20}H_{22}N_2O$ 306.19, found 307.2 [M+1].

(E)-3-(2-chlorophenyl)-N-phenyl-(piperidin-4-yl) acrylamide (**1c**). Yield: 1.618 g (96%). IR $cm^{-1}$: 3030; 1665. $^1$H RMN (600 MHz, $CDCl_3$): 1.33 (m, 2H, $CH_2$); 1.89 (m, 2H, $CH_2$); 2.87 (m, 2H, $CH_2$); 4.16 (m, 2H, $CH_2$); 4.91 (m, H, CH); 6.11 (d, J = 16 Hz, 1H, CH); 7-7.5 (m, 9$H_{Ar}$); 7.66 (d, J = 12 Hz, 1H, CH). $^{13}$C RMN (150 MHz, $CDCl_3$) δ: 27.69 (2× $CH_2$); 43.72 (2× $CH_2$); 50.61 (CH); 113.54 (CH); 118.20 (CH); 121.57 (CH); 126.79 (CH); 127.65 (CH); 129.08 (CH); 129.47 (CH); 129.77 (CH); 129.90 (CH); 130.44 (CH); 130.40 (CH); 133.35 (C); 134.76 (C); 138,42 (CH); 146.08 (C); 165.55 (C). ESI (m/z): calcd for $C_{20}H_{21}ClN_2O$ 340.1, found 341.1419 [M+1].

(E)-3-(2-chlorophenyl)-N-(3-fluorophenyl)-N-piperidin-4-yl)-acrylamide (**1d**). Yield: 0.5568 g (71%). mp =127°C. IR $cm^{-1}$: 3552; 1687. $^1$H RMN (500 MHz, $CDCl_3$): 1.33 (m, 2H, $CH_2$); 1.98 (m, 2H, $CH_2$); 2.94 (m, 2H, $CH_2$); 3.46 (m, 2H, $CH_2$); 3.9 (Broadband, 1H, NH); 4.84 (m, H, CH); 5.97 (d, J= 15 Hz, CH); 7-7.5 (m, 8$H_{Ar}$); 7.99 (d, J= 15 Hz, CH). $^{13}$C RMN (125 MHz, $CDCl_3$) δ: 27.79 (2× $CH_2$); 43.64 (2× $CH_2$); 50.78 (CH); 117.82 (d, J = 26,25 Hz, CHAr); 121.16 (CH); 126.83 (CH); 127.03 (CH); 127.65 (CH); 130.00 (CH); 130.12 (CH); 130.34 (CH); 130.82 (d, J = 11.25 Hz, CH); 133.22 (C); 134.52 (C); 134.81 (C); 138.00 (CHAr); 139.00 (CH); 161.41 (d, 311.25 Hz, C); 165.60 (C). ESI (m/z): calcd for $C_{20}H_{20}ClFN_2O$ 358.1, found 359.178 [M+1].

(E)-N-(1-benzylpiperidin-4-yl)-N-phenylcinnamamide (**11a**). Yield: 0.1067 g (55%); mp =139°C. IR $cm^{-1}$: 3423; 1654. $^1$H RMN (600 MHz, $CDCl_3$): 1.50 (m, 2H, $CH_2$); 1.84 (m, 2H, $CH_2$); 2.14 (t, J = 12 Hz, 2H, $CH_2$); 2.91 (m, 2H, $CH_2$); 3.47 (s, 2H, $CH_2$); 4.77 (m, H, CH); 6.05 (d, J = 12 Hz, CH); 7.14-7.47 (m, 15$H_{Ar}$); 7.62 (d, J = 12 Hz, CH).$^{13}$C RMN (150 MHz, $CDCl_3$): 30.62 (2× $CH_2$); 43.72 (2× $CH_2$); 53.14 (CH); 63.14 ($CH_2$); 119.26 (CH); 127.18 (CH); 127.90 (2×CH); 128.32 (2×CH); 128.59 (CH); 128.74 (4×CH); 129.34 (CH); 129.44 (2×CHAr); 129.54 (CHAr); 130.85 (2×CHAr); 135.34 (2×C); 138.50 (C); 141.72 (CH); 165.87 (C). ESI (m/z): calcd for $C_{27}H_{28}N_2O$ 396.22 found 397.22 [M+1].

(E)-N-(1-benzylpiperdin-4-yl)-3-(2-chlorophenyl)-N-phenylacrylamide (**11c**). Yield: 0.0948 g (50%); mp =112°C. IR $cm^{-1}$: 1646. $^1$H RMN (500 MHz, $CDCl_3$): 1.54 (m, 2H, $CH_2$); 1.85 (m, 2H, $CH_2$); 2.19 (m, 2H, $CH_2$); 2.95 (m, 2H, $CH_2$); 3.50 (s, 2H, $CH_2$); 4.80 (m, H, CH); 6.05 (d, J = 15 Hz, CH); 7.14-7.47 (m, 14$H_{Ar}$); 7.98 (d, J = 15 Hz, CH).$^{13}$C RMN (125 MHz, $CDCl_3$): 30.90 (2× $CH_2$); 43.72 (2× $CH_2$); 52.97 (CH); 53.11 ($CH_2$); 63.04 ($CH_2$); 122.42 (CH); 126.84 (2×CH); 127.72 (2×CH); 128.37 (2×CH); 128.66 (CH); 129.50 (2×CH); 130.13 (2×CH); 130.26 (CH), 130.79 (2×CH); 133.76 (2×C); 134,80 (C); 137.77 (CH); 138.43 (C); 165.43 (C). ESI (m/z): calcd for $C_{27}H_{27}ClN_2O$ 430.22 found 431.18 [M+1].

(E)-N-(1-bromobenzyl) piperidin-4-yl)-N-phenylcinnamamide (**12a**). Yield : 0.123 g (53%); mp =134 °C. IR $cm^{-1}$: 1646. $^1$H RMN (600 MHz, $CDCl_3$) : 1.66 (m, 2H, $CH_2$); 1.85 (m, 2H, $CH_2$); 2.33 (m, 2H, $CH_2$); 2.97 (m, 2H, $CH_2$); 3.58 (s, 2H, $CH_2$); 4.80 (t, H, CH); 6.05 (d, J = 18 Hz, CH); 7.14-7.47 (m, 14$H_{Ar}$); 7.64 (d, J = 18 Hz, CH).$^{13}$C RMN (150 MHz, $CDCl_3$) δ: 30.10 (2× $CH_2$); 43.72 (2× $CH_2$); 52.47 (CH); 53.30 ($CH_2$); 62.87 ($CH_2$); 119.40 (CH); 127.43 (C); 127.92 (4×CH); 128.75 (4×CH); 129.52 (CH); 129.58 (2×CH); 129.85 (CH); 130.76 (CH), 132.81 (CH); 135.27 (2×C); 138.48 (C); 141.83 (CH); 165.87 (C). ESI (m/z): calcd for $C_{27}H_{27}BrN_2O$ 474.13 found 477.13 [M+1].

(E)-N-(1-(2-bromobenzyl) piperidin-4-yl)-3-(2-chlorophenyl)-N-phenylacrylamide (**12c**). Yield: 0.118 g (53%). m.p =125°C. IR $cm^{-1}$: 1646. $^1$H RMN (600 MHz, $CDCl_3$): 1.66 (m, 2H, $CH_2$); 1.85 (m, 2H, $CH_2$); 2.33 (m, 2H, $CH_2$); 2.97 (m, 2H, $CH_2$); 3.58 (s, 2H, $CH_2$); 4.80 (t, H, CH); 6.05 (d, J = 18 Hz, CH); 7.14-7.47 (m, 13$H_{Ar}$); 7.64 (d, J = 18 Hz, CH).$^{13}$C RMN (150 MHz, $CDCl_3$) δ: 30.10 (2× $CH_2$); 43.72 (2× $CH_2$); 52.47 (CH); 53.30 ($CH_2$); 62.87 ($CH_2$) ; 119.40 (CH) ; 125.8 (CH); 127.43 (2×C); 127.92 (2×CH); 128.75 (2×CH); 128.45 (CH); 129.52 (CH); 129.50 (CH); 129.58 (CH); 130.76 (CH), 132.81 (2×CH); 133.2 (CH); 135.27 (2×C); 138.48 (C); 141.83 (CH); 165.87 (C). ESI (m/z): calcd for $C_{27}H_{27}BrCl\ N_2O$ 508.0913 found 510.13 [M+1].

(E)-N-(1-(2-chlorobenzyl) piperidin-4-yl)-N-phenylcinnamamide (**13a**). Yield : 0.105 g (50%); mp =121°C. IR $cm^{-1}$: 1653. $^1$H RMN (600 MHz, $CDCl_3$): 1.51 (m, 2H, $CH_2$); 1.84 (m, 2H, $CH_2$); 2.29 (m, 2H, $CH_2$); 2.95 (m, 2H, $CH_2$); 3.59 (s, 2H, $CH_2$,); 4.77 (m, H, CH); 6.05 (d, J = 18 Hz, CH); 7.14-7.47 (m, 14$H_{Ar}$); 7.62 (d, J = 18 Hz, CH). $^{13}$C RMN (150 MHz, $CDCl_3$) δ: 30.73 (2× $CH_2$); 43.50 (2× $CH_2$); 52.91 (CH); 53.28 ($CH_2$); 119.79 (CH), 126.69 (CH); 127.92 (4×CH); 128.62 (CH); 128.88 (2×CH); 129.47 (2×CH); 129.53 (CH); 129.55 (CH); 130.83 (2×CH); 134.35 (C); 135.34 (2×C); 138.76 (C); 141.99 (CH); 165.71 (C). ESI (m/z): calcd for $C_{27}H_{27}ClN_2O$ 430.2 found 431.1887 [M+1].

(E)-N-(1-(perfluorobenzyl) piperidin-4-yl)-N-phenylcinnamamide (**14a**). Yield: 0.135 g (57%); mp =132°C. IR $cm^{-1}$: 1653. $^1$H RMN (600 MHz, $CDCl_3$): 1.48 (m, 2H, $CH_2$); 1.83 (m, 2H, $CH_2$); 2.26 (m, 2H, $CH_2$); 2.90 (m, 2H, $CH_2$); 3.67 (s, 2H, $CH_2$); 4.69 (t, H, CH); 6.03 (d, J=18 Hz, CH); 7.14-7.47 (m, 10$H_{Ar}$); 7.62 (d, J = 18 Hz, CH). $^{13}$C RMN (150, 9 MHz, $CDCl_3$) δ: 30.43 (2× $CH_2$); 48.42 (2× $CH_2$); 51.66 (CH); 52.19 ($CH_2$); 119.23 (C); 119.50 (CH); 127.91 (2×CH) ; 128.66 (CH); 128.75 (2×CH); 129.49 (2×CH); 129.58 (CH); 130.81 (2×CH); 135.23 (C); 138.23 (C); 138.37 (2×C); 136.65 (C); 141.85 (CH); 142.20 (C); 144.73 (C); 146.40 (C); 165.88 (C). ESI (m/z): calcd for $C_{27}H_{23}F_5N_2O$ 486.17 found 487.1813 [M+1].

(E)-3-(2-chlorophenyl)-N-(1-(perfluorobenzyl) piperidin-4-yl)-N-phenylacrylamide (**14c**). Yield: 0.126 g (55%); mp =120°C. IR $cm^{-1}$: 1650. $^1$H RMN (600 MHz, $CDCl_3$): 1.54 (m, 2H, $CH_2$); 1.85 (m, 2H, $CH_2$); 2.33 (m, 2H, $CH_2$); 2.96 (m, 2H, $CH_2$); 3.95 (s, 2H, $CH_2$); 4.69 (m, H, CH); 6.03 (d, J = 15 Hz, CH); 7.14-7.47 (m, 9$H_{Ar}$); 7.97 (d, J = 15 Hz, CH). $^{13}$C RMN (150 MHz, $CDCl_3$): 29.73 (2× $CH_2$); 48.42 (2× $CH_2$); 47.99 (CH); 52.42 ($CH_2$); 122.22 (CH); 126.86 (2×CH); 127.74 (2×CH); 128.81 (CH); 129.61 (CH); 130.15 (CH); 130.33 (CH); 138.19 (C); 130.69 (CH); 133.65 (2×C); 134.81 (2×C); 137.99 (CH); 141.85 (C); 142.20 (C); 144.73 (C); 146.40 (C); 165.48 (C). ESI (m/z): calcd for $C_{27}H_{22}ClF_5N_2O$ 520.1 found 521.1420 [M+1].

**Antimalarial Activity**

The antimalarial activity of extracts/compounds was evaluated against *P. falciparum* 3D7 and *P. falciparum* W2 strains, using the fluorescence-based SYBR Green I assay approach in 96-well microplates as described by Smilkstein and al.[18] with some modifications.

**Tableau 3: The antimalarial activity of compounds derivatives 1.**

| | ***Plasmodium falciparum* 3D7 strain** | ***Plasmodium falciparum* W2 strain** | **HUVEC cells** | **Selectivity Index (3D7)** | **Selectivity Index (W2)** |
|---|---|---|---|---|---|
| Compounds | IC50 ± SD (nM) | $IC_{50}$ ± SD (nM) | CC50 nM ± SD | =CC50/IC50 | =CC50/IC50 |
| **1a** | >100 | >100 | / | / | / |
| **1c** | >100 | >100 | / | / | / |
| **CQ** | 22.38 ± 3.24 | 134.12± 32.29 | 37.56 ± 1.24 | 1.7 | 0.3 |

**Table 4: The antimalarial activity of compounds of reductive amination of 1 with the derivatives benzaldehydes recorded.**

| | ***Plasmodium falciparum* 3D7 strain** | ***Plasmodium falciparum* W2 strain** | **HUVEC cells** | **Selectivity Index (3D7)** | **Selectivity Index (W2)** |
|---|---|---|---|---|---|
| Compounds | $IC_{50}$ ± SD (nM) | $IC_{50}$ ± SD (nM) | $CC_{50}$ nM ± SD | $=CC_{50}/IC_{50}$ | $=CC_{50}/IC_{50}$ |
| **7** | 26.02±4.76 | 41.22±2.38 | >100 | 4.9 | 3.1 |
| **11a** | 11.55±3.5 | 30.31±3.35 | >100 | >21.8 | >8.3 |
| **11c** | 12.2±1.58 | 23.75±1.07 | >100 | >8.19 | >4.21 |
| **12a** | 24.97±3.16 | 45.05±5.23 | >100 | >8.4 | >4.7 |
| **12c** | >100 | >100 | / | / | / |
| **13a** | 54.9±6.5 | 55.39±5.81 | >100 | >4.2 | >4.5 |
| **14a** | 13.18±1.68 | 18.96±5.05 | >100 | >15.6 | >10.8 |
| **14c** | 15.51±1.79 | 38.05±0.82 | >100 | >4.4 | >6.8 |
| **CQ** | 22.38 ± 3.24 | 134.12 ± 32.29 | 37.56 ± 1.24 | 1.7 | 0.3 |

**CQ**: Chloroquine

Compounds **1a** and **1c** showed no activity against both strains (Table 3). After pharmaco-modulation on the piperidine nitrogen, all compounds were active except compound 12c against both strains (Table 4).

Compared to chloroquine (IC50 = 22.38 (3D7) and 134.12 (W2)), compounds **14a** (IC50 = 18.96nM) and **11c** (IC50 = 23.75nM) showed strong activity against W2. The most interesting activities against strain 3D7 are observed with molecules **11a** (IC50 = 11.55 nM), **11c** (IC50 = 12.2 nM) and **14a** (IC50 = 13.18 nM). All the compounds showed cytotoxicity > 100 and good selectivity index against both strains.

Piperidine nitrogen substitution with pentafluorobenzyl provided excellent activity against both strains. Thus, the most interesting activity is observed with the compound 11a against the strain 3D7 and 14a against the strain W2.

Compound **7**, for its part, showed good activity compared to the compounds substituted by benzyls and to the reference molecule (CQ).

## CONCLUSION

In this study, we have prepared a small set of new nitrogen heterocycles displaying scaffold using a flexible chemistry. Ten new derivatives cinnamic acids were prepared in good yield. The antimalarial activity of these compounds has been described. The compounds were tested against P.falciparum 3D7 strains and W2. The best result is observed with the compound **14a** against the 3D7 strains and W2 with a selectivity index greater than chloroquine. These molecules could be improved to be a good malaria drug candidate.

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