Modifications and hybrids of 1,2,3,4-tetrahydropyridinium salts and their antiprotozoal potencies

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Received: 25 March 2021 / Accepted: 6 September 2021 / Published online: 16 October 2021
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Abstract
The antiprotozoal activity of 1-benzyltetrahydropyridin-4-yliden iminium salts is reported. This paper describes the preparation of a series of analogs from dihydropyridines or dihydrothiopyrans as educts. The new compounds were investigated for their activity against Plasmodium falciparum NF54, a causative organism of Malaria tropica and Trypanosoma brucei rhodesiense, the causative organism of Human African Trypanosomiasis (sleeping sickness). Several structure–activity relationships were detected. Both the substituents in ring positions 1 and 4 of the tetrahydropyridinium moiety had a strong impact on the antiprotozoal activities as well as on the cytotoxicity of compounds against L-6 cells (rat skeletal myoblasts). All new compounds were characterized using FT-IR spectroscopy, HRMS, and NMR spectroscopy.

Graphic abstract

Keywords Heterocycles · Antiprotozoal activity · Drug research · Hybrids

Introduction

In 2019, an estimated 229 million cases of malaria, leading to estimated 409 000 deaths, occurred worldwide. Children aged under 5 years are the most vulnerable group affected by malaria. In 2019, they accounted for 67% of all malaria deaths worldwide. Plasmodium falciparum is the most prevalent malaria parasite [1]. There is currently a restricted arsenal of drugs [2] and the extension of Plasmodium falciparum resistance to existing antimalarial drugs is worrying. Faced with this problem, the search for new and effective compounds is necessary [3].

Human African Trypanosomiasis (HAT), also known as sleeping sickness is one of 20 neglected tropical diseases listed by the World Health Organization, which lead to death if left untreated [4]. This disease is caused by Trypanosoma brucei gambiense, which causes the chronic form of the
disease in western and central Africa, and by *T. brucei rhodesiense* (Tbr), which causes the acute form of the disease in eastern and southern Africa [5]. Currently, melarsoprol, an old arsenical drug, is the only drug available for the late-stage Tbr infection treatment [6]. Unfortunately, it causes a deadly encephalopathy in more than 5% of the patients [7].

We already reported the antiprotozoal activities of tetrahydropyridin-4-ylidene ammoniumsalts [8]. Since, 1-benzyl substitution significantly enhanced the antiprotozoal activities, we initially focused our efforts on the optimization of these benzyl moieties [9, 10]. To clear up the influence of the substituents attached to the ring nitrogen on the biological activities, we prepared compounds with smaller (methyl-) and larger (phenethyl-, indolylethyl-) residues at this position. Since, 4-chlorobenzyl derivatives showed enhanced activities [9, 10], we prepared some derivatives with other exocyclic amino residues. In addition to that, we prepared some hybrid molecules bearing partial structures of chloroquine, the diethylaminopentyl- and the 7-chloroquinolin-4-yl residue on different positions. This paper reports the synthesis of a series of new tetrahydropyridin-4-ylidene ammonium salts and their activities against *Plasmodium falciparum* NF54 and *Trypanosoma brucei gambiense*.

### Results and discussion

Starting from 2,3-dihydropyridin-4-amines 1a, 1b [10], we prepared 1-methyl derivatives 2a, 2b using methyl iodide. Compounds 3a, 3b and 4a, 4b were prepared by N-alkylation with 2-phenylethyl bromide or 2-(4-chlorophenyl)ethyl bromide, respectively. Compounds 5a–5b, 6a–6b, and 7a–7e were yielded in a similar manner by reaction of the bases 1a–1e [10] with 3-(2-bromoethyl)indole, 4-(bromomethyl)benzonitrile, and 4-chlorobenzylchloride or -bromide as alkylating agents. Reactions were carried out with or without potassium carbonate as catalyst (Scheme 1). The connectivity was approved for example in 5b by a long-range coupling of H-1’ to C-6 and to C-2 and from H-6 to C-1’ in HMBC NMR spectra.

The preparation of the base 1f started from the 6-sulfanylidenepiperidin-4-one 8 [11] which reacted with tryptamine to the corresponding 4-amino derivative 9 in a similar procedure as reported [8]. The sulfamidene group was methylated. Desulfurization was achieved selectively with Raney nickel. The obtained

![Scheme 1](image-url)

Reagents and conditions: (i) CH$_3$I, CHCl$_3$, r.t., 16 h; (ii) 2-phenylethyl bromide, refluxing benzene, 2 d or 2-phenylethyl bromide, CHCl$_3$, potassium carbonate, r.t., 14 d; (iii) 2-(4-chlorophenyl)ethyl bromide, CHCl$_3$, potassium carbonate, r.t., 14-16 d; (iv) 3-(2-bromoethyl)indole, CHCl$_3$, potassium carbonate, r.t., 14-18 d; (v) 4-(bromomethyl)benzonitrile, CHCl$_3$, r.t., 4-5 d; (vi) 4-chlorobenzyl chloride or bromide, CHCl$_3$, r.t., 16 h to 2 d.
dihydropyridin-4(1H)-imine 1f was alkylated with 4-chlorobenzyl chloride giving 10f (Scheme 2).

The $^1$H NMR spectrum of compound 10f showed two sets of signals belonging to the corresponding (E) and (Z) forms. NOE-experiments established the main component as (Z) form. For the (E) form a through-space coupling from H-3 to H-1$^\prime$ was observed, whereas, for the (Z) form H-5 showed a through-space coupling to H-1$^\prime$ (Fig. 1).

For the preparation of compounds with a partial structure of chloroquine, we used differing pathways: the chlorobenzyl derivative 10g exhibits the aminoalkyl side-chain of chloroquine in ring position 4. It was synthesized from its $N,N$-dimethyliminium analog 7c. Hydrolysis of the iminium salt yielded the respective dihydropyridin-4(1H)-one 11. Reaction of 11 with $N^1,N^1$-diethylpentane-1,4-diamine gave compound 10g (Scheme 3).

For the preparation of compounds with a partial structure of chloroquine, we started from the thio-pyrane derivative 12 [12]. The 5,6-dihydropyridin-2(1H)-thiones 13 and 16 were obtained by a aminolysis/Dimroth rearrangement sequence. Subsequent reaction of 13 with iodomethane yielded the methylsulfanyl derivative 14. Surprisingly, we were not able to remove the methylthio group via the usual reduction process with Raney nickel. Not a trace of 15 was found in the reaction mixture (Scheme 4).

$N$-(6-Amino-1,2,3,4-tetrahydropyridin-4-ylidene)ammonium iodides 18a and 18b were prepared via reaction of their 6-methylsulfanyl analogs 17a and 17b [11] with the corresponding amines (Scheme 5).

All compounds were investigated for their antiplasmodial and antitrypanosomal activities against *Plasmodium falciparum* NF54 and *Trypanosoma brucei rhodesiense*, respectively. In addition, the cytotoxicity was determined using L-6 cells. The results are presented in Table 1.

Tetrahydropyridin-4-iminium halides 3–7 with lipophilic and bulky groups at the ring nitrogen showed antiplasmodial activity against *Plasmodium falciparum* NF54 in low concentration (IC$_{50}$ = 0.019–0.3 µM), whereas, their 1-methyl analogs 2a and 2b were practically ineffective (IC$_{50}$ = 2.80–3.22 µM). Due to their usually low cytotoxicity most of them showed very promising selectivity (SI$_{PN}$ = 268–9207). The most promising compound of this series had a 4-cyanobenzyl group in ring position 1 and a pyrrolidinium moiety. It shows high

**Scheme 2**

\[
\begin{align*}
\text{8} & \xrightarrow{(i)} \text{9} \xrightarrow{(ii)-(iv)} \text{1f} \\
\text{R}^1 &= 1' \quad 2' \\
\text{R}^2 &= 4\text{-chlorobenzyl}
\end{align*}
\]

Reagents and conditions: (i) tryptamine, benzene, glacial acetic acid, reflux, overnight; (ii) CH$_3$I, ethanol, r.t., 16 h; (iii) ethanol, Raney nickel, r.t., 40 min; (iv) suspension in 2 M NaOH, extraction with CHCl$_3$; (v) 4-chlorobenzyl chloride, CHCl$_3$, r.t., 16 h and suspension in 2 M NaOH, extraction with CHCl$_3$. 

\[\text{Fig. 1 NOEs observed for the two forms of compound 10f indicated as arrows}\]
antiplasmodial activity (IC$_{50}$ = 0.029 μM) and excellent selectivity (SI$_{PN}$ = 9207). Only the 1-(4-chlorobenzyl) derivatives 7d and 7e exhibited high cyctotoxicity and as a consequence low selectivity (SI$_{PN}$ = 6.55–77.9). The effect of an additional amino substituent in 1-unsubstituted analogs is varying. Compound 18a was active in low concentration and possessed good selectivity, whereas, 18b was weakly active and quite cytotoxic. The
dihydropyridin-2(1H)-thiones 13 and 16 showed similar activity (IC₅₀ = 0.087–0.12 µM), but the 4-pyrrolidino compound 13 was less cytotoxic and possessed good selectivity (SIₚₙ = 244). Its 2-methylsulfanyl derivative 14 exhibited similar activity (IC₅₀ = 0.11 µM) and selectivity (SIₚₙ = 540) (Figs. 2, 3).

The antitrypanosomal activity of most tetrahydropyridin-4-iminium halides 2–7 and 18 was very low. Only the N-benzyl-1-(4-chlorobenzyl) derivative 7d (IC₅₀ = 0.047 µM) and its 1-unsubstituted 2-piperidino-4-piperidinium analog 18b (IC₅₀ = 0.59 µM) showed good activity but low selectivity (SIT = 7.86–15.3). The influence of an additional amino substituent in 1-unsubstituted analogs is unclear. The most promising antitrypanosomal compound was the 2-methylsulfanyl derivative 14 which showed quite good activity (IC₅₀ = 0.43 µM) and selectivity (SIT = 138).

Free-Wilson analysis

Free-Wilson analysis is a QSAR method to assign a contribution to the overall activity to each occurring substitution group in an SAR dataset using the following equation:

$$\text{Log BA}_i = \sum a_{jk} + X_{jk} + \mu.$$ 

BAᵢ is the biological activity of a series is expressed as the sum of the biological activity contributions aᵢⱼₖ of the substituents Rᵢ in each position j, µ is referring to the overall average activity value for the series [13].

A Free-Wilson least squares model was calculated in Biovia’s Pipeline Pilot with the script “Create Free-Wilson least squares model”. The Free-Wilson predicted activity was based on a 17-compound subset (2a–10g) of the tested molecules that shared.

The Free-Wilson analysis based on the pIC₅₀ values for activities against Plasmodium falciparum NF54 led to a model with an R² of 0.906. For the individual groups, the contributions which were calculated are presented in Table 2.

The different contributions of substitutions to the total activity against Plasmodium falciparum NF54 in the R₁ position show that the tetrahydropyridin-4-iminium halides

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**Table 1** Antiprotozoal and cytotoxic activities of compounds 2–18 (IC₅₀ values in µM)

| Cpd   | L-5 cells | P. falc. NF54 | T. b. rhod |
|-------|-----------|--------------|-----------|
|       | IC₅₀      | IC₅₀        | IC₅₀      | IC₅₀      | IC₅₀      | IC₅₀      | IC₅₀      | IC₅₀      |
|       | a         | b           | P. falc. NF54 | a         | b           | T. b. rhod |
| 2a    | > 312     | 3.22        | 96.9       | 180       | 1.73       |
| 2b    | > 299     | 2.80        | 107        | 127       | 2.35       |
| 3a    | 155       | 0.30        | 517        | 7.21      | 21.5       |
| 3b    | 142       | 0.09        | 1578       | 1.97      | 72.1       |
| 4a    | 109       | 0.083       | 1313       | 5.63      | 19.4       |
| 4b    | 62.2      | 0.034       | 1829       | 5.15      | 12.1       |
| 5a    | 117       | 0.118       | 992        | 1.55      | 75.5       |
| 5b    | 9.63      | 0.019       | 507        | 1.04      | 9.26       |
| 6a    | > 267     | 0.029       | 9207       | 156       | 1.71       |
| 6b    | > 258     | 0.25        | 1032       | 105       | 2.46       |
| 7a    | 20.1      | 0.027       | 744        | 19.7      | 102       |
| 7b    | 116       | 0.045       | 2578       | 4.42      | 26.2       |
| 7c    | 74.9      | 0.28        | 268        | 143       | 0.52       |
| 7d    | 0.72      | 0.11        | 6.55       | 0.047     | 15.3       |
| 7e    | 1.48      | 0.019       | 77.9       | 1.79      | 0.83       |
| 10f   | 7.5       | 0.78        | 9.62       | 1.94      | 3.87       |
| 10 g  | 167       | 6.13        | 27.2       | 100       | 1.67       |
| 11    | 150       | > 40.0      | 3.75       | 112       | 1.34       |
| 13    | 21.2      | 0.087       | 244        | 4.36      | 4.86       |
| 14    | 59.4      | 0.11        | 540        | 0.43      | 138       |
| 16    | 2.68      | 0.12        | 22.3       | 5.02      | 0.53       |
| 18b   | 186       | 0.26        | 715        | 23.5      | 7.91       |
| 18b   | 4.64      | 1.12        | 4.14       | 0.59      | 7.86       |
| Mel   | 7.78      |             |            | 0.0039    | 1995       |
| CQ    | 116.9     | 0.007       | 16.700     |           |
| P     | 0.012     |             |            |           |

Mel melarsoprol, CQ chloroquine diphosphate, P podophyllotoxin

a Values represent the average of four determinations (two determinations of two independent experiments) indicated in µM

b Selectivity index for P. falciparum NF54 (SIₚₙ), expressed as ratio [IC₅₀(L₆)/IC₅₀(P. falciparum NF54)]

c Selectivity index for T. b. rhodesiense (SIₜ), expressed as ratio [IC₅₀(L₆)/IC₅₀(T. b. rhodesiense)]
show an increase in activity with a larger ring size with R1 B (compound 7e) yielding a higher activity contribution than R1 F and R1 A. Negative contributions are found for the R1 indol substitution (R1 C) and the N1-diethylpentane group (R1 E).

The substitutions in the R2 position all showed a positive contribution, the strongest being observed in the chlorophenyl groups (R2 C/D) with the chlorobenzyl group yielding the best contribution (1.9352).

**Conclusion**

A number of tetrahydropyridin-4-yliden iminiumsalts and a few related compounds have been prepared in several steps from dihydropyridines or dihydrothiopyrans as starting compounds. The new compounds were tested for antiplasmodial activity against *Plasmodium falciparum* NF54 as well as for antitrypanosomal activity against *Trypanosoma brucei rhodesiense*. Furthermore, their cytotoxicity against L6-cells was determined. Some tetrahydropyridin-4-yliden iminium salts with large and lipophilic substituents at the tetrahydropyridine nitrogen atom showed high antiplasmodial activity.
and selectivity. The most promising compound of this series has a 4-cyanobenzyl substituent in ring position 1 and a pyrroloidinium moiety in position 4. It showed activity in low concentration (IC50 = 0.029 µM) and possessed excellent selectivity (SI50 = 9207). Noteworthy antitrypanosomal activity was observed for a tetrahydropyridin-4-yldien iminium salt with in total 3 benzyl substituents on the nitrogen atoms. However, due to its high cytotoxicity the selectivity index was quite low. Far better selectivity was observed for an analog with an additional methylsulfonyl group in ring position 2. The effect of an amino substituent in the same ring position was non-uniform. Further modifications at this ring position are in progress.

**Experimental**

Melting points were obtained on a digital melting point apparatus Electrothermal IA 9200. IR spectra: Bruker Alpha Platinum ATR FT-IR spectrometer (KBr discs). NMR spectra: Varian Inova 400 (300 K) 5 mm tubes, spectra were acquired in CDCl3 containing 0.03% TMS. Chemical shifts were recorded in parts per million (ppm), for 1H spectra were recorded in parts per million (ppm), for 13C spectra were dried at 100 °C at reduced pressure.

N-(1,2,2-Trimethyl-1,2,3,4-tetrahydropyridin-4-ylidene)pyrroloidin-1-ium iodide (2a, C12H21IN2) A mixture of 960 mg of 1a (5.4 mmol) with 920 mg of CH3I (6.5 mmol) in 27 cm3 of CHCl3 was stirred at r.t. overnight and yielded 1.45 g of 2a (84%) as a beige precipitate. M.p.: 138 °C (ethanol/acetone); 1H NMR (DMSO-d6, 400 MHz): δ = 1.28 (s, 6H, 2CH3), 1.92–1.98 (m, 4H, 2CH2), 2.87 (s, 2H, H-3), 3.14 (s, 3H, NCH3), 3.45–3.48 (m, 2H, NCH2), 3.62–3.66 (m, 2H, NCH2), 5.10 (d, J = 6.6 Hz, 1H, H-5), 7.59 (d, J = 6.6 Hz, 1H, H-6) ppm; 13C NMR (DMSO-d6, 100 MHz): δ = 22.56 (2CH2), 24.25, 24.53 (2CH2), 37.84 (NCH3), 39.45 (C-3), 49.52, 49.64 (2NCH2), 56.13 (C-2), 87.47 (C-5), 121.16 (C-6), 161.73 (C-4) ppm; IR (KBr): ν = 2975, 1617, 1511, 1458, 1381, 1369, 1348, 1332, 1159, 1191 cm−1; HRMS (EI+): m/z calcd. C12H20N2 ([M-HI]+) 192.1626, found 192.1643.

N-(1,2,2-Trimethyl-1,2,3,4-tetrahydropyridin-4-ylidene)piperidin-1-ium iodide (2b, C13H23IN2) A mixture of 1.01 g of 1b (5.3 mmol) with 894 mg of CH3I (6.3 mmol) in 28 cm3 of CHCl3 was stirred at r.t. overnight and yielded 1.55 g of 2b (87%) as a yellowish precipitate. M.p.: 188 °C (ethanol/acetone); 1H NMR (DMSO-d6, 400 MHz): δ = 1.12 (s, 6H, 2CH3), 1.59–1.66 (m, 2H, 2CH2), 2.87 (s, 2H, H-3), 3.57 (m, 2H, NCH2), 3.64–3.66 (m, 2H, NCH2), 5.10 (d, J = 6.6 Hz, 1H, H-5), 7.59 (d, J = 6.6 Hz, 1H, H-6) ppm; 13C NMR (DMSO-d6, 100 MHz): δ = 22.56 (2CH2), 24.25, 24.53 (2CH2), 37.84 (NCH3), 39.45 (C-3), 49.52, 49.64 (2NCH2), 56.13 (C-2), 87.47 (C-5), 156.75 (C-6). M.p.: 115 °C (ethanol/acetone); HRMS (EI+): m/z calcd. C13H22N2 ([M-HI]+) 192.1626, found 192.1643.
organic phases were dried (Na$_2$SO$_4$), filtered, and evaporated in vacuo. The residue was recrystallized from ethanol/acetone giving 50 mg of 4a (2%) of white crystals. M.p.: 191 °C (ethanol/acetone); $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 1.49$ (s, 6H, 2CH$_3$), 2.11 (br, s, 4H, 2CH$_2$), 3.00 (t, $J = 7.3$ Hz, 2H, ArCH$_2$), 3.15 (s, 2H, H-3), 3.51–3.55 (m, 2H, NCH$_2$), 3.67 (t, $J = 7.1$ Hz, 2H, ArCH$_2$CH$_2$N), 3.88–3.94 (m, 2H, NCH$_2$), 5.09 (d, $J = 7.0$ Hz, 1H, H-5), 7.20 (d, $J = 8.4$ Hz, 2H, ArH), 7.32 (d, $J = 8.1$ Hz, 2H, ArH), 7.35 (d, $J = 7.0$ Hz, 1H, H-6) ppm; $^1$C NMR (CDCl$_3$, 100 MHz): $\delta = 23.24$ (2CH$_3$), 24.51, 24.96 (2CH$_2$), 36.37 (ArCH$_2$N), 41.20 (C-3), 50.07, 50.62 (2NCH$_2$), 51.71 (ArCH$_2$CH$_2$N), 57.60 (2-C), 88.88 (C-5), 128.98, 130.51 (ArC), 132.86, 135.41 (ArC$_q$), 156.70 (C-6), 162.02 (C-4) ppm; IR (KBr): $\overline{\nu} = 2947, 1610, 1555, 1493, 1450, 1403, 1375, 1345, 1330, 1269, 1234, 1188, 1118, 1097, 759$ cm$^{-1}$; HRMS (EI$^+$): m/z calcd. C$_{19}$H$_{27}$BrCN$_2$ ([M-HBr]$^+$) 316.1706, found 316.1699.

$N$-[2-(2-Chlorophenylethyl)-2,2-dimethyl-1,2,3,4-tetrahydroxyquinolin-4-ylidene]pyrrolidin-1-ium bromide (4b, C$_{20}$H$_{26}$BrN$_2$) A mixture of 528 mg of 1b (2.75 mmol) with 1.02 g of 2-(4-chlorophenethyl) bromide (4.7 mmol) in 12 cm$^3$ of CHCl$_3$ was stirred at r.t. for 16 d in the presence of 1 g of K$_2$CO$_3$ (7.24 mmol) and yielded 414 mg of 4b (37%) as beige precipitate without charcoal treatment. M.p.: 198 °C (acetone); $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 1.34$ (s, 6H, 2CH$_3$), 1.62–1.68 (m, 6H, 3CH$_2$), 2.93–2.96 (m, 4H, H-3, ArCH$_2$), 3.67–3.71 (m, 2H, ArCH$_2$CH$_2$N), 5.43 (d, $J = 7.3$ Hz, 1H, H-5), 7.38 (s, 4H, ArH), 7.59 (d, $J = 7.3$ Hz, 1H, H-6) ppm; $^1$C NMR (CDCl$_3$, 400 MHz): $\delta = 23.24$ (2CH$_3$), 23.32, 23.84, 26.91 (3CH$_2$), 35.64 (ArCH$_2$), 38.49 (C-3), 49.05, 49.14 (2NCH$_2$), 50.70 (ArCH$_2$CH$_2$N), 57.05 (C-2), 87.29 (C-5), 128.46, 131.16 (ArC), 131.34, 136.94 (ArC$_q$), 156.89 (C-6), 162.93 (C-4) ppm; IR (KBr): $\overline{\nu} = 2934, 1608, 1549, 1495, 1467, 1451, 1437, 1413, 1401, 1375, 1356, 1338, 1295, 1265, 1226, 1181, 1104, 1008, 857, 757$ cm$^{-1}$; HRMS (EI$^+$): m/z calcd. C$_{20}$H$_{27}$ClN$_2$ ([M-HCl]$^+$) 330.1863, found 330.1860.

$N$-[1-[2-[1H-Indol-3-yl]ethyl]-2,2-dimethyl-1,2,3,4-tetrahydroxyquinolin-4-ylidene]pyrrolidin-1-ium bromide (5a, C$_{31}$H$_{32}$BrN$_2$) A mixture of 578 mg of 1a (3.22 mmol) with 1 g of 3-(2-bromoethyl)indole (4.46 mmol) in 10 cm$^3$ of CHCl$_3$ was stirred at r.t. for 14 d in the presence of 1 g of K$_2$CO$_3$ (7.24 mmol) and yielded 330 mg of 5a (23%) as yellowish precipitate without charcoal treatment. M.p.: 205 °C (ethanol); $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 1.35$ (s, 6H, 2CH$_3$), 1.91–1.97 (m, 4H, 2CH$_2$), 2.87 (s, 2H, H-3), 3.03 (t, $J = 7.3$ Hz, 2H, H-2'), 3.46 (br, t, $J = 5.5$ Hz, 2H, NCH$_2$), 3.63 (br, t, $J = 5.5$ Hz, 2H, NCH$_2$), 3.70 (t, $J = 7.3$ Hz, 2H, H-1'), 5.08 (d, $J = 7.0$ Hz, 1H, H-5), 6.99 (dd, $J = 7.7$, 7.0 Hz, 1H, ArH), 7.08 (dd, $J = 7.7$, 7.3 Hz, 1H, ArH), 7.23 (s, 1H, ArH), 7.35 (d, $J = 8.1$ Hz, 1H, ArH), 7.42 (d, $J = 7.0$ Hz, 1H, ArH).
N-[1-(4-Cyanobenzyl)-2,2-dimethyl-1,2,3,4-tetrahydropyridin-4-ylidene]piperidin-1-ium bromide (6b, C20H25BrN3) A mixture of 1.171 g of 1b (6.09 mmol) with 2.05 g of 4-(bromomethyl)benzonitrile (10.4 mmol) in 30 cm3 of CHCl3 was stirred at r.t. for 5 days and yielded without second crystallization 1.75 g of 6b (74%) as yellowish crystals. M.p.: 133 °C (CHCl3/ethyl acetate); 1H NMR (DMSO-d6, 400 MHz): δ = 1.18 (s, 6H, 2CH3), 1.58–1.73 (m, 6H, 3CH2), 2.97 (2H, 2H-3), 3.67–3.72 (m, 4H, 2NCH2), 4.85 (s, 2H, ArCH2), 5.58 (d, J = 7.0 Hz, 1H, H-5), 7.55 (d, J = 7.0 Hz, 2H, ArH), 7.78 (d, J = 6.2 Hz, 1H, H-6), 7.87 (d, J = 7.0 Hz, 2H ArH) ppm; 13C NMR (DMSO-d6, 100 MHz): δ = 32.32 (CH2, 2CH3), 25.95, 26.91 (2CH3), 38.62 (C-3), 49.34, 49.40 (2NCH2), 52.99 (ArCH3), 57.56 (C-2), 88.03 (C-5), 110.52 (ArC), 118.79 (CN), 128.22, 132.75 (ArC), 134.77 (ArC), 159.77 (C-6), 163.65 (C-4) ppm; IR (KBr): ν = 2941, 2860, 2225, 1608, 1558, 1468, 1444, 1403, 1353, 1254, 1238, 1186, 1111, 1018, 951, 859, 736 cm−1; HRMS (EI+): m/z calcd. C20H15N3 ([M-HBr]+) 307.0248, found 307.2065.

1-(4-Chlorobenzyl)-N,N,2-tetramethyl-1,2,3,4-tetrahydroquinidin-4-ium chloride (7c, C16H22Cl2N2) A mixture of 3.735 g of 1c (24.5 mmol) with 6.72 g of 4-chlorobenzyl chloride (0.77 mmol) in 1.5 cm3 of CHCl3 was stirred at r.t. overnight and yielded without second crystallization and without charcoal treatment 6.41 g of 7c (83%) as yellow precipitate. M.p.: 218 °C (chloroform/ethyl acetate); 1H NMR (DMSO-d6, 400 MHz): δ = 1.20 (s, 6H, 2CH3), 2.95 (s, 2H, H-3), 3.21 (s, 3H, NCH3), 3.26 (s, 3H, NCH3), 4.79 (s, 2H, ArCH2), 5.37 (d, J = 7.0 Hz, 1H, H-5), 7.38 (d, J = 8.8 Hz, 2H, ArH), 7.45 (d, J = 8.4 Hz, 2H, ArH), 7.88 (d, J = 7.0 Hz, 1H, H-6) ppm; 13C NMR (DMSO-d6, 100 MHz): δ = 23.42 (2CH2, CH2), 25.81 (CH2), 26.54 (C-2'), 26.92 (CH2), 38.51 (C-3), 49.00, 49.05 (2NCH2), 50.50 (C-1'), 57.02 (C-2), 87.11 (C-5), 111.67, 118.42, 118.61, 121.25, 123.80 (ArC), 110.07, 127.04, 136.35 (ArC), 156.83 (C-6), 162.75 (C-4) ppm; IR (KBr): ν = 2856, 2360, 1611, 1515, 1471, 1387, 1339, 1269, 1234, 1188, 1103, 1010, 754 cm−1; HRMS (EI+): m/z calcd. C16H22ClN3 ([M-HCl]+) 307.0248, found 307.2065.

N-[1-(4-Cyanobenzyl)-2,2-dimethyl-1,2,3,4-tetrahydroquinidin-4-ylidene]piperidin-1-ium chloride (7d, C28H30Cl2N2) A mixture of 109 mg of 1d (0.35 mmol) with 125 mg of 4-chlorobenzyl chloride (0.77 mmol) in 1.5 cm3 of CHCl3 was stirred at r.t. for 2 d and yielded without second crystallization and without charcoal treatment 60 mg of 7d (37%) as yellowish resin. 1H NMR (CDCl3, 400 MHz): δ = 1.21 (s, 6H, 2CH3), 3.12 (s, 2H, H-3), 4.79 (s, 2H, 4-ClArCH2), 4.88 (s, 2H, ArCH2), 4.96 (s, 2H, ArCH2), 5.52 (d, J = 7.0 Hz, 1H, H-5), 7.27–7.47 (m, 14H, ArH), 7.92 (d, J = 7.0 Hz, 1H, H-6) ppm; 13C NMR (CDCl3, 100 MHz): δ = 23.32 (2CH3), 24.31, 24.54, 40.30 (C-3), 49.80, 50.00 (2NCH2), 53.10 (ArCH2), 57.46 (C-2), 88.98 (C-5), 110.54 (ArCq), 118.76 (CN), 128.13, 132.78 (ArCq), 143.89 (ArCq), 157.66 (C-6), 162.60 (C-4) ppm; IR (KBr): ν = 2931, 2225, 1607, 1550, 1479, 1441, 1407, 1336, 1272, 1235, 1187, 1106, 999, 969, 860, 831, 766 cm−1; HRMS (EI+): m/z calcd. C19H23N3 ([M-HBr]+) 293.1892, found 293.1886.
N-[1-(4-Chlorobenzyl)-2,2-dimethyl-1,2,3,4-tetrahydropropyridin-4-ylidene]azepin-1-ium chloride (7e, C$_{28}$H$_{29}$ClN$_2$) A mixture of 200 mg of 1e (0.96 mmol) with 310 mg of 4-chlorobenzyl chloride (1.93 mmol) in 1.5 cm$^3$ of CH$_2$Cl$_2$ was stirred at r.t. for 2 d and yielded without charcoal treatment and without second crystallization 320 mg of 7e (91%) as gray but pure precipitate. For analytical purposes it was also recrystallized from CHCl$_3$/ethyl acetate giving beige platelets. M.p.: 132–140 °C (chloroform/ethyl acetate); $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ = 1.21 (s, 6H, 2CH$_3$), 1.51 (br, s, 4H, 2CH$_2$), 1.67–1.74 (m, 4H, 2CH$_2$), 2.98 (s, 2H, H-3), 3.71–3.75 (br, s, 4H, 2NCH$_2$), 4.79 (s, 2H, ArCH$_2$), 5.43 (d, J = 7.0 Hz, 1H, H-5), 7.40 (d, J = 8.4 Hz, 2H, ArH), 7.45 (d, J = 8.4 Hz, 2H, ArH), 7.88 (d, J = 7.0 Hz, 1H, H-6) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ = 23.21 (2CH$_3$), 25.34, 25.42, 25.65, 27.92 (4CH$_2$), 38.54 (C-3), 51.35, 51.67 (2NCH$_2$), 52.81 (ArCH$_2$), 57.61 (C-2), 87.72 (C-5), 128.80, 129.51 (ArC), 132.49, 136.63 (ArC$_q$), 157.70 (C-6), 164.82 (C-4) ppm; IR (KBr): $\tilde{\nu}$ = 3426, 2926, 1557, 1445, 1401, 1237, 1178, 1106, 759 cm$^{-1}$; HRMS (EI$^+$): $m/z$ calcld. C$_{28}$H$_{29}$ClN$_2$ ([M+H$^+$]) 428.2019, found 428.1996.

N-[2-(1H-Indol-3-yl)ethyl]-2,2-dimethyl-1,2,3,4-tetrahydropropyridin-4-imine (1f, C$_{17}$H$_{21}$N$_3$) A solution of 1g of 9 (3.34 mmol) in 20 cm$^3$ of ethanol was treated with 0.61 g (4.3 mmol) of methyllodide overnight. The solvent was evaporated and the residue further used. 6 g of powdered nickel/aluminium alloy (containing 50% Ni, 51 mmol) was transferred into a big beaker. Water was added and 12 g of solid NaOH (0.3 mol) was added cautiously. After the reaction ceased, the beaker was put into a water bath at 70 °C for 30 min. Subsequently, the liquid was decanted, and the solid nickel was washed at first 15 times with water and then twice with ethanol. The obtained solid was given into a solution of 1.458 g of the residue (3.3 mmol) in 20 cm$^3$ of ethanol resulting in a total volume of 40 cm$^3$. The suspension was stirred for 30 min at r.t. The catalyst was sucked off and washed with ethanol. The filtrate was evaporated in vacuo and the residue dissolved in chloroform. The mixture was filtered and the solvent evaporated. The residue was suspended in 2 M NaOH and extracted 4 times with CHCl$_3$. Combined organic layers were shaken with 2 M NaOH and water, dried (Na$_2$SO$_4$), filtered, and the solvent evaporated yielding 517 mg of 1f (59%) as yellowish resin. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ = 1.18 (s, 6H, 2CH$_3$), 2.10 (s, 2H, H-3), 3.08 (t, J = 7.3 Hz, 2H, H-2$'$), 3.50 (t, J = 7.3 Hz, 2H, H-1$'$), 4.02 (br, s, 1H, NH), 4.90 (d, J = 5.9 Hz, 1H, H-5), 7.01 (s, 1H, ArH), 7.09–7.20 (m, 3H, H-6, ArH), 7.36 (d, J = 8.1 Hz, 1H, ArH), 7.61 (d, J = 8.1 Hz, 1H, ArH), 8.90 (br, s, 1H, NH) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ = 25.55 (C-2$'$), 27.40 (2CH$_2$), 42.29 (C-3), 46.38 (C-1$'$), 52.67 (C-2), 87.41 (C-5), 111.24 (ArC), 113.36 (ArC$_q$), 118.67 (ArC), 119.12 (ArC), 121.84 (ArC), 127.43 (ArC$_q$), 143.39 (C-6), 156.56 (C-4) ppm; IR (KBr): $\tilde{\nu}$ = 2964, 1538, 1456, 1362, 1283, 1097, 741 cm$^{-1}$; HRMS (EI$^+$): $m/z$ calcld. C$_{17}$H$_{21}$N$_3$ (M$^+$) 267.1736, found 267.1735.

1-(4-Chlorobenzyl)-N-[2-(1H-Indol-3-yl)ethyl]-2,2-dimethyl-1,2,3,4-tetrahydropropyridin-4-imine (10f, C$_{28}$H$_{29}$ClN$_3$) A mixture of 517 mg of 1f (1.934 mmol) with 374 mg of 4-chlorobenzyl chloride (2.32 mmol) in 3 cm$^3$ of chloroform was stirred at r.t. overnight. After evaporation of the solvent a residue was obtained, which was suspended in 2 M NaOH and extracted 4 times with CHCl$_3$. Combined organic layers were shaken with 2 M NaOH and water, dried (Na$_2$SO$_4$), filtered, and the solvent was evaporated giving a red resin. This was purified by CC over basic aluminium oxide with (CH$_2$Cl$_2$:MeOH = 9:1) as eluent yielding 61 mg of 10f (8%) as an orange resin. Main component (Z) form: $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ = 1.13 (s, 6H, 2CH$_3$), 2.54 (s, 2H, H-3), 3.13 (br, t, J = 7.9 Hz, 2H, H-2$'$), 3.64 (br, t, J = 8.1 Hz, 2H, H-1$'$), 4.20 (s, 2H, ArCH$_2$), 5.03 (d, J = 7.7 Hz, 1H, H-5), 6.41 (d, J = 7.7 Hz, 1H, H-6), 7.01–7.65 (m, 9H, ArH), 8.72 (br, s, 1H, NH) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ = 23.87, 23.99 (2CH$_3$), 26.76 (C-2$'$).
47.87 (C-3), 50.22 (C′-1), 52.04 (ArCH2), 57.13 (C-2), 89.18 (C-5), 111.13 (ArC), 114.43 (ArCH2), 118.86, 118.92, 121.59, 121.64 (ArC), 127.67 (ArCH2), 128.43, 128.90 (ArC), 133.33, 136.34, 137.30 (ArC), 146.57 (C-6), 162.03 (C-4) ppm; minor constituent (E) form: 1H NMR (CDCl3, 400 MHz): δ = 0.99 (s, 6H, 2CH3), 2.29 (s, 2H, H-3), 3.13 (br, t, J = 7.9 Hz, 2H, H-2′), 3.64 (br, t, J = 8.1 Hz, 2H, H-1′), 4.09 (s, 2H, ArCH2), 5.22 (d, J = 8.1 Hz, 1H, H-5), 6.28 (d, J = 7.7 Hz, 1H, H-6), 7.01–7.65 (m, 9H, ArH), 8.76 (br, s, 1H, NH) ppm; 13C NMR (CDCl3, 100 MHz): δ = 23.77, 24.06 (2CH2), 27.35 (C-2′′), 39.94 (C-3), 50.48 (C′-1), 52.04 (ArCH2), 56.00 (C-2), 99.82 (C-5), 111.13 (ArC), 114.43 (ArCH2), 118.72, 118.97, 121.76, 121.91 (ArC), 127.55 (ArC), 128.47, 127.77 (ArC), 133.08, 136.34, 137.88 (ArCq), 144.62 (C-6), 163.32 (C-4) ppm; IR (KBr): ν = 2919, 1593, 1491, 1457, 1365, 1094, 1013, 741 cm−1; HRMS (EI+): m/z calcd. C24H26ClN3 (M+) 391.1818, found 389.2598.

1-[2-[7-Chloroquinolin-4-ylamino][ethyl]-6,6-dimethyl-4-pyrrolidino-5,6-dihydropyridine-2(1H)-thione (13, C22H27ClN4S) Aminolysis of 8.87 g of 12 (24 mmol) with 5.32 g of N-(2-aminoethyl)-7-chloroquinolin-4-amine (24 mmol) took place in 45 cm3 of ethanol via stirring at r.t.. During the reaction, compressed air was passed through the reaction mixture. After 15 d the solvent was evaporated in vacuo and the residue crystallized from chloroform/ethyl acetate. The precipitate was dissolved in hot ethanol, treated with charcoal, and filtered and part of the solvent was evaporated. Crystallization took place overnight and the solid was sucked off and used for the synthesis of thione 16. The mother liquor was evaporated and the residue crystallized from acetone via stirring overnight at room temperature. It was sucked off and dried to get the desired compound 13.

The solid was stirred with 2 M NaOH, extracted 3 times with chloroform and washed twice with water. Then it was dried (Na2SO4) and filtration, the solvent was evaporated in vacuo giving 680 mg of 11 (98%) as a yellowish resin. 1H NMR (DMSO-d6, 400 MHz): δ = 1.11 (s, 6H, 2CH3), 2.26 (s, 2H, H-3), 4.47 (s, 2H, ArCH2), 4.76 (d, J = 7.7 Hz, 1H, H-5), 7.26 (d, J = 7.3 Hz, 1H, H-6), 7.36 (d, J = 8.4 Hz, 2H, ArH), 7.42 (d, J = 8.4 Hz, 2H, ArH) ppm; 13C NMR (DMSO-d6, 100 MHz): δ = 23.80 (2CH3), 50.40 (C-3), 51.92 (ArCH2), 58.45 (C-2), 96.76 (C-5), 128.69, 129.06 (ArC), 131.95, 138.73 (ArCq), 154.34 (C-6), 190.42 (C-4) ppm; IR (KBr): ν = 2972, 1637, 1588, 1491, 1444, 1409, 1367, 1278, 1247, 1212, 1175, 1100, 1014, 812, 760 cm−1; HRMS (EI+): m/z calcd. C14H16ClNO (M+) 249.0920, found 249.0918.

(RS)-[4]·[4-Chlorobenzyl]-2,2-dimethyl-1,2,3,4-tetrahydropyridin-4-ylidene][amino]-N,N-dimethylpentanamin (10 g, C22H26ClN3) The residue from co-distillation of 613 mg of 11 (2.45 mmol) with benzene was dissolved in 20 cm3 of toluene. Then 778 mg of N4,N4-dimethylpentane-1,4-diamine (4.9 mmol) and 273 mg of glacial acetic acid (4.55 mmol) were added and the mixture was refluxed overnight using a Dean-stark apparatus, filled with 0.4 nm activated molecular sieves. The solvent was evaporated in vacuo and the residue was subjected to CC over basic aluminium oxide using (CH2Cl2:MeOH = 8:1) as eluent. The fractions containing pure products were combined and evaporated, giving 40 mg of 10g (4.2%). 1H NMR (CDCl3, 400 MHz): δ = 1.00 (t, J = 7.1 Hz, 6H, H-2′′), 1.10 (d, J = 6.2 Hz, 3H, H-1′′), 1.15, 1.16 (2 s, 6H, 2CH3), 1.45–1.50 (m, 4H, H-3′, H-4′), 2.39–2.48 (m, 4H, H-3′, H-5′), 2.50 (g, J = 7.1 Hz, 4H, H-1′, H-3′), 3.52–3.56 (m, 1H, H-2′′), 4.22 (br, s, 2H, ArCH2), 5.11 (d, J = 8.1 Hz, 1H, H-5), 6.36 (d, J = 8.1 Hz, 1H, H-6), 7.23 (d, J = 8.4 Hz, 2H, ArH), 7.32 (d, J = 8.4 Hz, 2H, ArH) ppm; 13C NMR (CDCl3, 100 MHz): δ = 11.65 (C-2′′), 21.89 (C-1′), 23.69 (CH3), 24.16 (C-4′), 24.23 (CH3), 36.39 (C-3′), 46.82 (C-1′′), 49.00 (C-3′), 51.71 (ArCH2), 52.94 (C-5′), 53.23 (C-2′), 56.94 (C-2′′), 89.68 (ArC), 128.38, 128.77 (ArC), 133.06, 137.84 (ArCq), 144.96 (C-6), 159.27 (C-4′) ppm; IR (KBr): ν = 2968, 2931, 2801, 1615, 1517, 1538, 1491, 1466, 1366, 1277, 1248, 1224, 1180, 1093, 1014, 806, 736 cm−1; HRMS (EI+): m/z calcd. C23H26ClN3 (M+) 389.2598, found 389.2604.
N-[1-2-[7-Chloroquinolin-4-yl]amino]ethyl]-2,2-dimethyl-6-methylsulfanyl-1,2,3,4-tetrahydropyridin-4-ylidene]-pyrroldine-1-ium iodide (14, C<sub>21</sub>H<sub>30</sub>Cl<sub>n</sub>S) Compound 13 (3.35 g, 8.07 mmol) was dissolved in 20 cm<sup>3</sup> of CHCl<sub>3</sub> and 1.33 mg of CH<sub>3</sub>I (9.37 mmol) dissolved in 5 cm<sup>3</sup> of CHCl<sub>3</sub> was added dropwise to the solution. After stirring overnight, the formed solid was sucked off giving 4.02 g (89%) of 14 as a gray solid. For analytical purposes, a part of it was dissolved in ethanol, treated with charcoal, filtered, the solvent evaporated, and the residue recrystallized from ethanol/acetone giving a light gray solid. M.p.: 163 °C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz): δ = 1.39 (s, 6H, CH<sub>3</sub>), 1.93–2.00 (m, 4H, 2CH<sub>2</sub>), 2.63 (s, 3H, SCH<sub>3</sub>), 2.91 (s, 2H, H-3), 3.55–3.65 (m, 6H, H-2, 2NCH<sub>2</sub>), 3.84 (t, J = 7.0 Hz, 2H, H-1′), 5.17 (s, 1H, 5-H), 6.60 (d, J = 5.5 Hz, 1H, ArH), 7.50 (d, J = 8.8 Hz, 1H, ArH), 7.54 (br, s, 1H, NH), 8.22 (d, J = 8.8 Hz, 1H, ArH), 7.80 (s, 1H, ArH), 8.45 (d, J = 5.5 Hz, 1H, ArH) ppm; <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 100 MHz): δ = 15.87 (SCH<sub>3</sub>), 23.83 (2CH<sub>3</sub>), 23.46, 24.68 (2CH<sub>2</sub>), 39.83 (C-3), 41.21 (C-2′), 45.23 (C-1′), 49.54 (NCH<sub>2</sub>), 60.05 (C-2), 87.20 (C-5), 99.01 (ArC), 115.77 (ArC), 124.15, 124.64, 127.70 (ArC), 133.81, 149.16, 149.94 (ArC), 152.18 (ArC), 158.78 (C-4), 170.78 (C-6) ppm; IR (KBr): ν = 3441, 3262, 2977, 1581, 1495, 1445, 1396, 1335, 1307, 1156, 1120, 846, 813 cm<sup>−1</sup>; HRMS (EI<sup>+</sup>): m/z calcld. C<sub>21</sub>H<sub>30</sub>Cl<sub>n</sub>S [(M+HI<sup>+</sup>)]<sup>+</sup> 427.2048, found 427.2054.

N-[2,2-Dimethyl-6-pyrroldino-1,2,3,4-tetrahydropyridin-4-ylidene]pyrroldinium iodide (18b, C<sub>17</sub>H<sub>30</sub>IN<sub>3</sub>) A suspension of 2.1 g of 17b (5.73 mmol) in 21 g of piperidine (0.247 mol) was refluxed for 4 h. Piperidine was removed by evaporation in vacuo and the residue dissolved in propan-2-ol. The product precipitated by addition of ethyl acetate, giving 2.07 g of 18b (90%). For analytical purposes, the product was dissolved in ethanol, treated with charcoal, and filtered. The solvent was evaporated and the residue recrystallized giving yellowish prisms. M.p.: 182 °C (acetone); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz): δ = 1.29 (s, 6H, 2CH<sub>3</sub>), 1.54 (br, s, 8H, 4CH<sub>2</sub>), 1.62–1.65 (m, 4H, 2CH<sub>2</sub>), 2.61 (s, 2H, H-3′), 3.49–3.54 (m, 2H, 4CH<sub>2</sub>), 5.16 (s, 1H, 5-H), 7.32 (s, 1H, NH) ppm; <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 100 MHz): δ = 23.57, 23.77, 25.55 (6CH<sub>3</sub>), 26.89 (2CH<sub>3</sub>), 37.27 (C-3), 47.27, 47.82 (4CH<sub>2</sub>), 51.19 (C-2), 77.16 (C-5), 158.05 (C-6), 159.92 (C-4) ppm; IR (KBr): ν = 3211, 2939, 2855, 1590, 1546, 1493, 1462, 1449, 1365, 1347, 1288, 1248, 1228, 1180, 1122, 1020, 996, 862, 761 cm<sup>−1</sup>; HRMS (EI<sup>+</sup>): m/z calcld. C<sub>17</sub>H<sub>30</sub>IN<sub>3</sub> [(M+HI<sup>+</sup>)]<sup>+</sup> 275.2361, found 275.2365.

In vitro assays

The in vitro growth inhibition assay of <i>Plasmodium falciparum</i> NF54 and the in vitro growth inhibition assay of <i>Trypanosoma b. rhodesiense</i>, as well as the assay for the determination of cytotoxicity against L6-cells were performed as described earlier [16].
Funding  Open access funding provided by University of Graz.

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