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ORIGINAL PAPER

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

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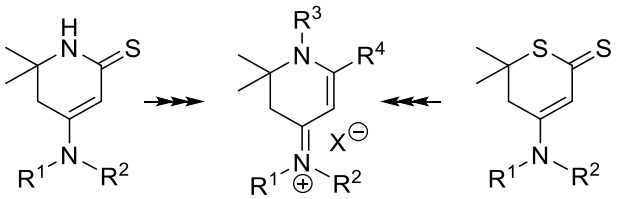
Abstract

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

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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].

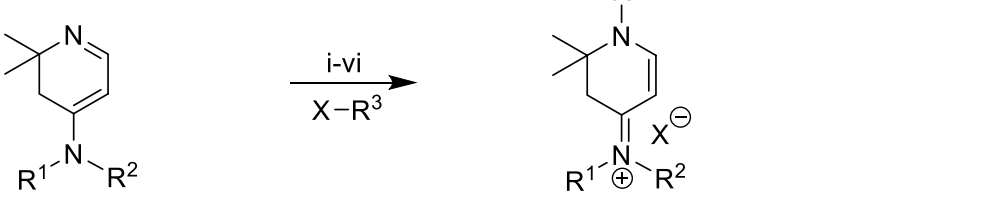
We already reported the antiprotozoal activities of tetrahydropyridin-4-ylidene ammoniumsalts [8]. Since, 1-benzyl substitution significantly enhanced the antiprotozoal activities, we initially focused our efforts on the optimization of these benzyl moieties [9, 10]. To clear up the influence of the substituents attached to the ring nitrogen on the biological activities, we prepared compounds with smaller (methyl-) and larger (phenetyl-, 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-chlorobenzyl-chloride 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-sulfanylidenpiperidin-4-one **8** [11] which reacted with tryptamine to the corresponding 4-amino derivative **9** in a similar procedure as reported [8]. The sulfanylidene group was methylated. Desulfurization was achieved selectively with Raney nickel. The obtained

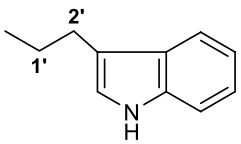
Scheme 1



1a-1e

a: $R^1 + R^2 = -(CH_2)_4-$
b: $R^1 + R^2 = -(CH_2)_5-$
c: $R^1 = R^2 = -CH_3$
d: $R^1 = R^2 = -CH_2-Ph$
e: $R^1 + R^2 = -(CH_2)_6-$

2a-2b: X = I, $R^3 = -CH_3$
3a-3b: X = Br, R^3 = phenethyl-
4a-4b: X = Br, R^3 = 4-Cl-phenethyl-
5a-5b: X = Br, R^3 =



6a-6b: X = Br, R^3 = 4- cyanobenzyl-
7a-7e: X = Cl, R^3 = 4- chlorobenzyl-

Reagents and conditions: (i) CH_3I, $CHCl_3$, 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(1*H*)-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′ was observed, whereas, for the (*Z*) form H-5 showed a through-space coupling to H-1′ (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(1*H*)-one **11**. Reaction of **11** with N^1,N^1-diethylpentane-1,4-diamine gave compound **10g** (Scheme 3).

For the synthesis of compounds with the 7-chloroquinolin-4-amine part of chloroquine, we started from the thiopyrane derivative **12** [12]. The 5,6-dihydropyridin-2(1*H*)-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.

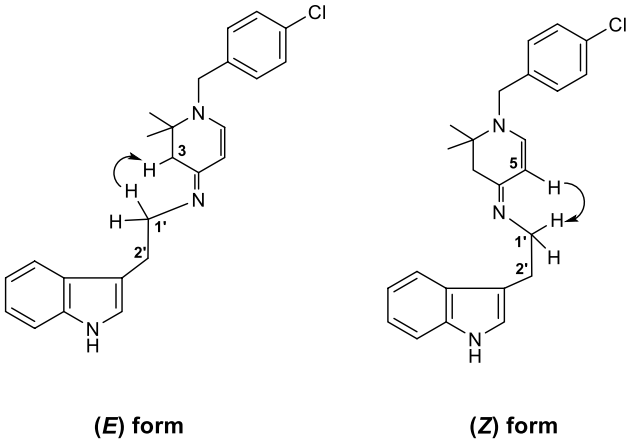
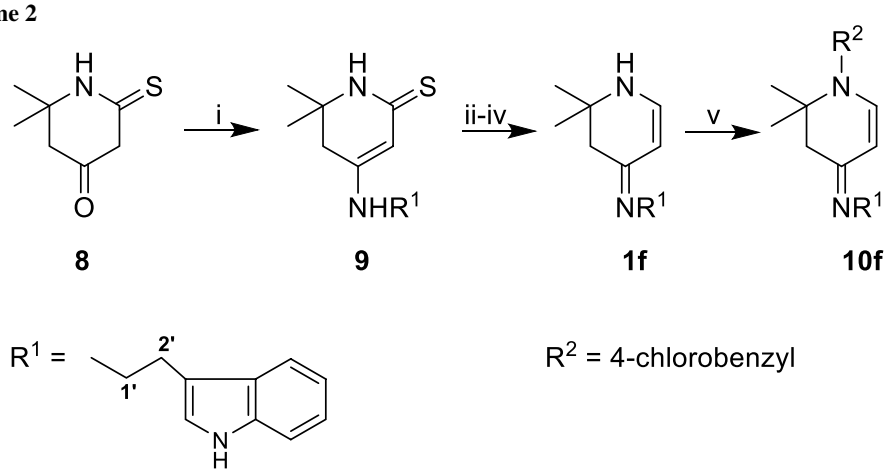


Fig. 1 NOEs observed for the two forms of compound **10f** indicated as arrows

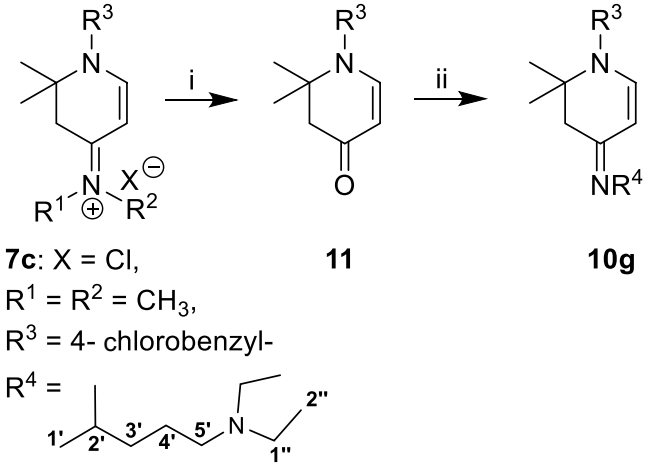
Tetrahydropyridin-4-iminium halides **3**–**7** with lipophilic and bulky groups at the ring nitrogen showed antiplasmodial activity against *Plasmodium falciparum* NF54 in low concentration (IC_{50} = 0.019–0.3 µM), whereas, their 1-methyl analogs **2a** and **2b** were practically ineffective (IC_{50} = 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



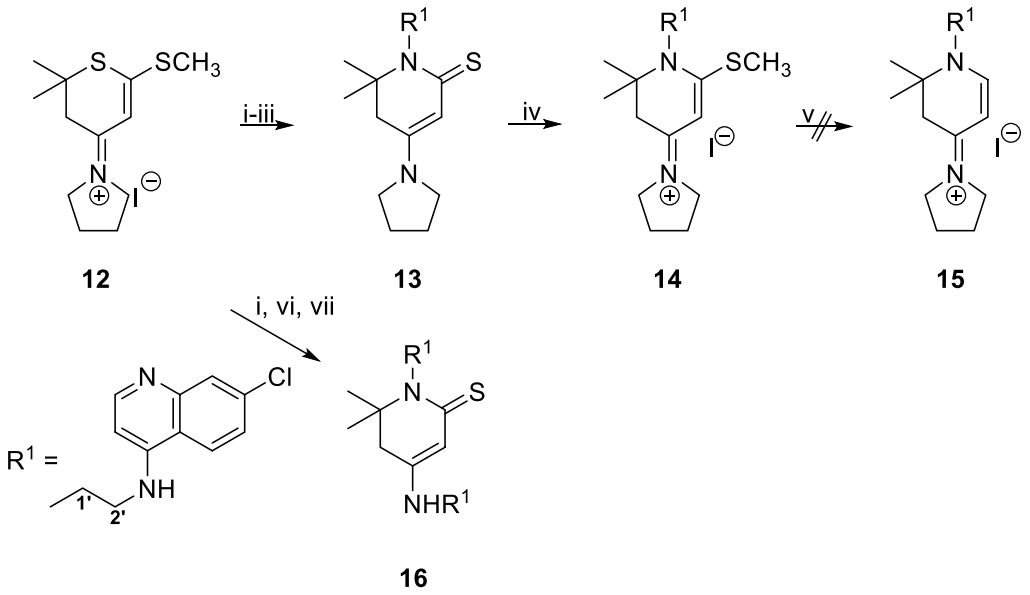
Reagents and conditions: (i) tryptamine, benzene, glacial acetic acid, reflux, overnight; (ii) CH_3I, ethanol, r.t., 16 h; (iii) ethanol, Raney nickel, r.t., 40 min; (iv) suspension in 2 M NaOH, extraction with $CHCl_3$; (v) 4-chlorobenzyl chloride, $CHCl_3$, r.t., 16 h and suspension in 2 M NaOH, extraction with $CHCl_3$.

Scheme 3



Reagents and conditions: (i) benzene, 2 M NaOH, reflux, overnight; (ii) N^1,N^1-diethylpentane-1,4-diamine, toluene, glacial acetic acid, reflux overnight.

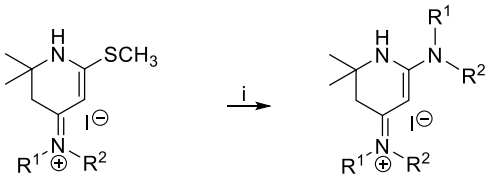
Scheme 4



Reagents and conditions: (i) *N*-(2-aminoethyl)-7-chloroquinolin-4-amine, ethanol, bubbling of compressed air, r.t., 15 d; (ii) suspension in 2 M NaOH, extraction with $CHCl_3$; (iii) DMF, reflux, overnight; (iv) CH_3I, $CHCl_3$, r.t., 16 h; (v) ethanol or methanol, Raney nickel, r.t., 1 h; (vi) suspension in 2 M NaOH, extraction with $CHCl_3$; (vii) DMF, reflux, overnight.

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

Scheme 5



17a,17b **18a,18b**

a: $R^1 + R^2 = -(CH_2)_4-$
b: $R^1 + R^2 = -(CH_2)_5-$

Reagents and conditions: (i) pyrrolidine or piperidine, reflux, 4 h.

Table 1 Antiprotozoal and cytotoxic activities of compounds **2**–**18** (IC_{50} values in µM)

Cpd	*L-6 cells*	*P. falc. NF54*		*T. b. rhod*	
	IC_{50}[a]	IC_{50}[a]	SI_{PN}[b]	IC_{50}[a]	SI_T[c]
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	1.02
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
18[a]	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 (SI_{PN}), expressed as ratio [IC_{50}(L6)/IC_{50}(*P. falciparum* NF54)]

[c]Selectivity index for *T. b. rhodesiense* (SI_T), expressed as ratio [IC_{50}(L6)/IC_{50}(*T. b. rhodesiense*)]

dihydropyridin-2(1*H*)-thiones **13** and **16** showed similar activity (IC_{50} = 0.087–0.12 µM), but the 4-pyrrolidino compound **13** was less cytotoxic and possessed good selectivity (SI_{PN} = 244). Its 2-methylsulfanyl derivative **14** exhibited similar activity (IC_{50} = 0.11 µM) and selectivity (SI_{PN} = 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** (IC_{50} = 0.047 µM) and its 1-unsubstituted 2-piperidino-4-piperidinium analog **18b** (IC_{50} = 0.59 µM) showed good activity but low selectivity (SI_T = 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 (IC_{50} = 0.43 µM) and selectivity (SI_T = 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:

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

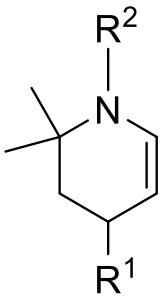
BA_i the biological activity of a series is expressed as the sum of the biological activity contributions a_{jk} of the substituents R_k in each position j, μ is referring to the overall average activity value for the series [13].

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 pIC_{50} values for activities against *Plasmodium falciparum* NF54 led to a model with an R^2 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

Fig. 2 Core molecule for Free-Wilson analysis



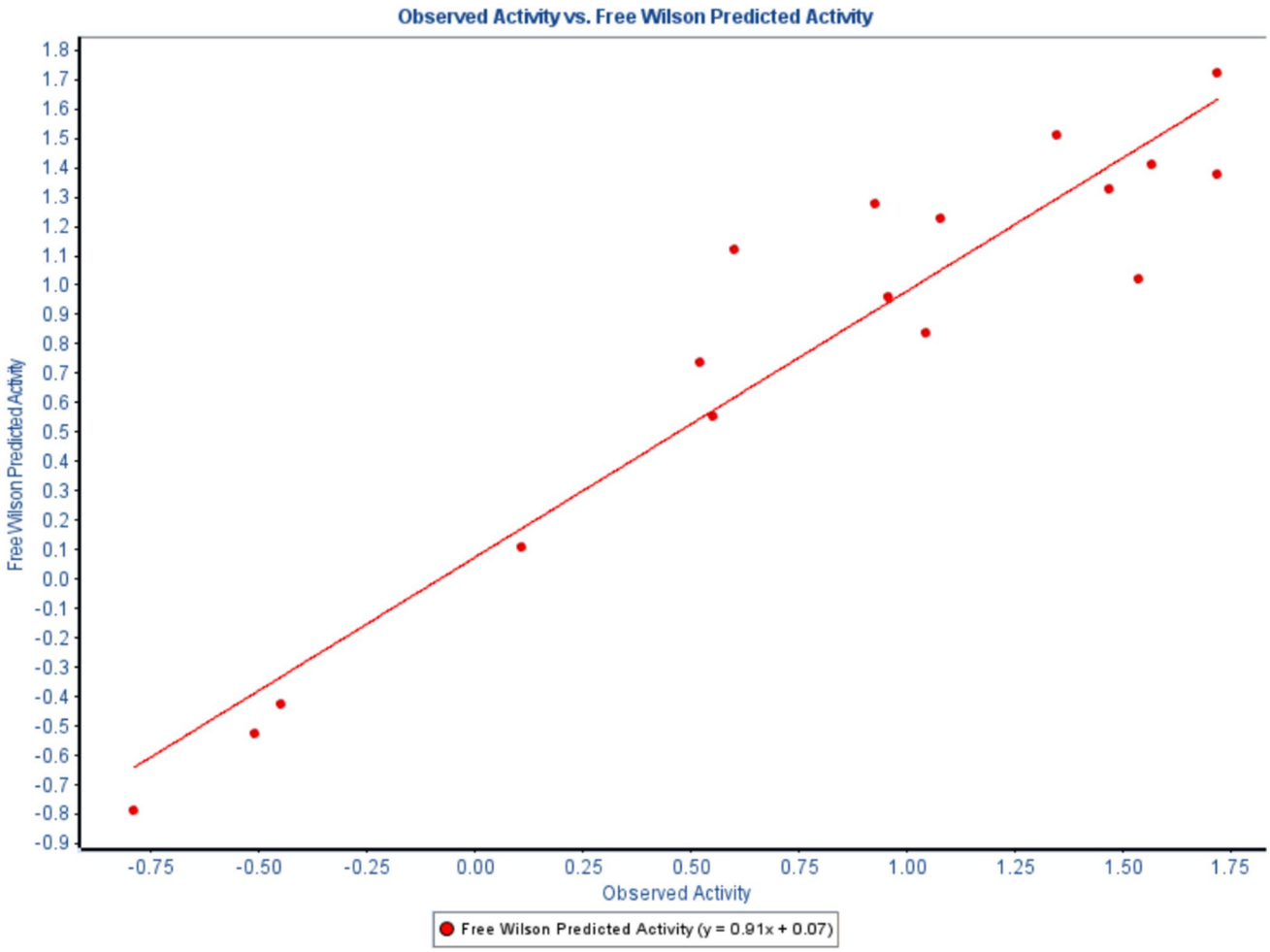


Fig. 3 Predicted Free-Wilson Activity against *Plasmodium falciparum* NF54 vs. observed activity

Table 2 Calculated contributions of the Free-Wilson analysis

Constant μ	− 1.3824
R1 A:[Z] = [N+]1CCCC1	0.85430
R1 B:[Z] = [N+]1CCCCCC1	1.1684
R1 C:[Z] = NCCc1c[nH]c2ccccc12	− 0.44494
R1 D:[Z] = [N+](Cc1ccccc1)Cc2ccccc2	0.40576
R1 E:[Z] = NC[C@@H](C)CCCN(CC)CC	− 1.3403
R1 F:[Z] = [N+]1CCCCC1	0.95545
R2 A:[Z]CCc1c[nH]c2ccccc12	1.8022
R2 B:[Z]CCc1ccccc1	1.2618
R2 C:[Z]CCc1ccc(Cl)cc1	1.7522
R2 D:[Z]Cc1ccc(Cl)cc1	1.9352
R2 E:[Z]Cc1ccc(cc1)C#N	1.5473

Groups not shown in the table had a contribution of zero

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 N^1-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 pyrrolidinium moiety in position 4. It showed activity in low concentration (IC_{50} = 0.029 µM) and possessed excellent selectivity (SI_{PN} = 9207). Noteworthy antitrypanosomal activity was observed for a tetrahydropyridin-4-yliden 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 methylsulfanyl 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 $CDCl_3$ containing 0.03% TMS. Chemical shifts were recorded in parts per million (ppm), for ^{1}H spectra TMS (0.00) was used as internal standard and for ^{13}C spectra the central peak of the $CDCl_3$ peak was used as the internal reference (77.0). Some spectra were acquired in DMSO-d_6. Here the proton signal at 2.49 ppm served as internal reference as well as the central peak of the DMSO-d_6 signal at 39.7 ppm. Abbreviations: aromatic H, ArH; aromatic C, ArC, quaternary aromatic C, ArC_q. Signal multiplicities are abbreviated as follows: *s*, singlet; *d*, doublet; *dd* doubledoublet; *t* triplet; *m*, multiplet; *q*, quartet; *br*, broad. Coupling constants (*J*) are reported in Hertz (Hz). ^{1}H and ^{13}C resonances were assigned using ^{1}H, ^{1}H and ^{1}H,^{13}C correlation spectra. ^{1}H and ^{13}C resonances are numbered as given in the formulae. Assignments marked with an asterisk are interchangeable. HR-MS: Micromass tofspec 3E spectrometer (MALDI), GCT-Premier, Waters (EI, 70 eV). Materials: column chromatography (CC): silica gel 60 (Merck 70–230 mesh, pore-diameter 0.6 nm), aluminium oxide (Alox) basic (Fluka for chromatography, 0.05–0.15 mm, Brockmann activity I, basic); Alox neutral 90 (Merck, 0.063–0.2 mm, activity I, neutral); thin-layer chromatography (TLC): TLC plates (Merck, silica gel 60 F_{254} 0.2 mm, 200 × 200 mm); TLC plates (Merck, Alox 60 F_{254} neutral, 200 × 200 mm); the substances were detected in UV light at 254 nm. If no stationary phase is mentioned (CC and TLC) the separation took place using silica gel. The preparation of the hydroiodides of compounds **1a**–**1e** was reported earlier [8]. The bases were set free by shaking with 2 M NaOH and subsequent extraction with $CHCl_3$. The preparation of compounds **7a** [9] and **7b** [10] was already reported. Compound **8** was prepared according to a reported procedure [11]. Its melting point (139 °C) corresponds well with the reported one (Ref. [11] 138 °C). Synthesis of compound **12** (m.p.: 198 °C) was done at our institute as already described [12] as well as the preparation of **17a** (m.p.: 160 °C [14]) and **17b** (m.p.: 188 °C [11]); the melting points are identical with the reported ones. Compounds **18a** is described, the melting point (192 °C) does not correspond very well with the reported one (204 °C) [15] maybe due to the use of different solvents. The preparation of compound **18b** is also described, but no melting point is given [15]. Therefore, we support full data for compounds **18a** and **18b**.

Preparation of compounds 2–7

The bases **1a**–**1e** were dissolved in chloroform or benzene and alkylation agents were added. The reaction mixture was stirred at r.t. or was refluxed. Occasionally, potassium carbonate was added. The products were precipitated from a solution of the crude product in $CHCl_3$ by addition of ethyl acetate. For analytical purposes the products were recrystallized after treatment with charcoal from chloroform/ethyl acetate or ethanol/acetone or acetone. Subsequently, they were dried at 100 °C at reduced pressure.

***N*-(1,2,2-Trimethyl-1,2,3,4-tetrahydropyridin-4-ylidene)pyrrolidin-1-ium iodide (2a, $C_{12}H_{21}IN_2$)** A mixture of 960 mg of **1a** (5.4 mmol) with 920 mg of CH_3I (6.5 mmol) in 27 cm^3 of $CHCl_3$ was stirred at r.t. overnight and yielded 1.45 g of **2a** (84%) as a beige precipitate. M.p.: 138 °C (ethanol/acetone); ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.28 (*s*, 6H, $2CH_3$), 1.92–1.98 (*m*, 4H, $2CH_2$), 2.87 (*s*, 2H, H-3), 3.14 (*s*, 3H, NCH_3), 3.45–3.48 (*m*, 2H, NCH_2), 3.62–3.66 (*m*, 2H, NCH_2), 5.10 (*d*, *J* = 7.0 Hz, 1H, H-5), 7.59 (*d*, *J* = 6.6 Hz, 1H, H-6) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 22.56 ($2CH_3$), 24.25, 24.53 ($2CH_2$), 37.84 (NCH_3), 39.45 (C-3), 49.52, 49.64 ($2NCH_2$), 56.13 (C-2), 87.47 (C-5), 156.75 (C-6), 161.73 (C-4) ppm; IR (KBr): $\tilde{\nu}$ = 2975, 1617, 1562, 1469, 1448, 1431, 1383, 1369, 1348, 1332, 1159, 1191 cm^{-1}; HRMS (EI^+): *m/z* calcd. $C_{12}H_{20}N_2$ ([M-HI]$^+$) 192.1626, found 192.1643.

***N*-(1,2,2-Trimethyl-1,2,3,4-tetrahydropyridin-4-ylidene)-piperidin-1-ium iodide (2b, $C_{13}H_{23}IN_2$)** A mixture of 1.01 g of **1b** (5.3 mmol) with 894 mg of CH_3I (6.3 mmol) in 25 cm^3 of $CHCl_3$ was stirred at r.t. overnight and yielded 1.55 g of **2b** (87%) as a yellowish precipitate. M.p.: 115 °C (ethanol/acetone); ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.28 (*s*, 6H, $2CH_3$), 1.59–1.66 (*m*, 6H, $3CH_2$), 2.91 (*s*, 2H, H-3), 3.15 (*s*, 3H, NCH_3) 3.64–3.66 (*m*, 4H, $2NCH_2$), 5.39 (*d*, *J* = 7.0 Hz, 1H, H-5), 7.63 (*d*, *J* = 7.0 Hz, 1H, H-6) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 22.46 ($2CH_3$), 23.33, 25.75, 26.89 ($2CH_2$), 37.72 (NCH_3), 37.84 (C-3), 48.97, 49.06 ($2NCH_2$), 56.21 (C-2), 86.74 (C-5), 157.14 (C-6),

162.80 (C-4) ppm; IR (KBr): $\overline{\nu}$ = 2935, 1616, 1564, 1491, 1468, 1429, 1382, 1358, 1271, 1158, 1120, 1013 cm^{-1}; HRMS (EI^+): *m/z* calcd. $C_{13}H_{22}N_2$ ($[M\text{-}HI]^+$) 206.1783, found 206.1781.

***N*-[2,2-Dimethyl-1-(2-phenylethyl)-1,2,3,4-tetrahydropyridin-4-ylidene]pyrrolidin-1-ium bromide (3a, $C_{19}H_{27}BrN_2$)** A mixture of 640 mg of **1a** (3.6 mmol) with 1.77 g of 2-phenylethyl bromide (9.5 mmol) in 10 cm^3 of $CHCl_3$ was stirred at r.t. for 14 d in the presence of 1 g of K_2CO_3 (7.24 mmol) and yielded 270 mg of **3a** (21%) as yellow crystals. M.p.: 204 °C ($CHCl_3$/ethyl acetate); ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.32 (*s*, 6H, $2CH_3$), 1.91–1.96 (*m*, 4H, $2CH_2$), 2.89–2.93 (*m*, 4H, H-3, $ArCH_2$), 3.47 (*t*, *J* = 5.9 Hz, 2H, NCH_2), 3.65–3.69 (*m*, 4H, NCH_2, $ArCH_2CH_2N$), 5.10 (*d*, *J* = 7.0 Hz, 1H, H-5), 7.21–7.31 (*m*, 5H, ArH), 7.53 (*d*, *J* = 7.0 Hz, 1H, H-6) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 23.39 ($2CH_3$), 24.31, 24.57 ($2CH_2$), 36.51 ($ArCH_2$), 40.09 (C-3), 49.57, 49.74 ($2NCH_2$), 51.05 ($ArCH_2CH_2N$), 57.01 (C-2), 88.05 (C-5), 126.73, 128.60, 129.25 (ArC), 137.93 (ArC_q), 156.57 (C-6), 161.82 (C-4) ppm; IR (KBr): $\overline{\nu}$ = 2964, 1612, 1561, 1468, 1448, 1401, 1373, 1360, 1345, 1330, 1230, 1121, 761, 706 cm^{-1}; HRMS (MALDI): *m/z* calcd. $C_{19}H_{27}N_2$ (M^+) 283.2174, found 283.2191.

***N*-[2,2-Dimethyl-1-(2-phenylethyl)-1,2,3,4-tetrahydropyridin-4-ylidene]piperidin-1-ium bromide (3b, $C_{20}H_{29}BrN_2$)** A mixture of 366 mg of **1b** (1.9 mmol) with 595 mg of 2-phenylethyl bromide (3.2 mmol) in 10 cm^3 of dry benzene was refluxed for 2 *d* and yielded 50 mg of **3b** (7%) as red solid. M.p.: 194 °C (acetone); ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.33 (*s*, 6H, $2CH_3$), 1.60–1.68 (*m*, 6H, $3CH_2$), 2.89–2.95 (*m*, 4H, H-3, $ArCH_2$), 3.65–3.70 (*m*, 6H, $ArCH_2CH_2N$, $2NCH_2$), 5.41 (*d*, *J* = 7.0 Hz, 1H, H-5), 7.24–7.35 (*m*, 5H, ArH), 7.52 (*d*, *J* = 7.0 Hz, 1H, H-6) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 23.27 ($2CH_3$), 23.35, 25.85, 26.91 ($3CH_2$), 36.46 ($ArCH_2$), 38.50 (C-3), 49.05, 49.12 ($2NCH_2$), 50.99 ($ArCH_2CH_2N$), 57.05 (C-2), 87.24 (C-5), 126.73, 128.58, 129.19 (ArC), 137.88 (ArC_q), 156.87 (C-6), 162.88 (C-4) ppm; IR (KBr): $\overline{\nu}$ = 2935, 1610, 1550, 1496, 1482, 1467, 1453, 1407, 1375, 1354, 1295, 1263, 1182, 1105, 1016, 761 cm^{-1}; HRMS (EI^+): *m/z* calcd. $C_{20}H_{28}N_2$ ($[M\text{-}HBr]^+$) 296.2253, found 296.2253.

***N*-[1-[2-(4-Chlorophenyl)ethyl]-2,2-dimethyl-1,2,3,4-tetrahydropyridin-4-ylidene]pyrrolidin-1-ium bromide (4a, $C_{19}H_{26}BrClN_2$)** A mixture of 723 mg of **1a** (5.64 mmol) with 2.1 g of 2-(4-chlorophenyl)ethyl bromide (9.58 mmol) in 15 cm^3 of $CHCl_3$ was stirred at r.t. for 14 *d* in the presence of 1 g of K_2CO_3 (7.24 mmol) and yielded a white precipitate. It was dissolved in 2 N NaOH and extracted 5 times with diethyl ether. The aqueous phase was acidified with HBr (48%) and extracted 5 times with chloroform. The combined organic phases were dried (Na_2SO_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): δ = 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, $ArCH_2CH_2N$), 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; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.24 ($2CH_3$), 24.51, 24.96 ($2CH_2$), 36.37 ($ArCH_2$), 41.20 (C-3), 50.07, 50.62 ($2NCH_2$), 51.71 ($ArCH_2CH_2N$), 57.60 (C-2), 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, 1294, 1269, 1234, 1188, 1118, 1097, 759 cm^{-1}; HRMS (EI^+): *m/z* calcd. $C_{19}H_{25}ClN_2$ ($[M\text{-}HBr]^+$) 316.1706, found 316.1699.

***N*-[1-[2-(4-Chlorophenyl)ethyl]-2,2-dimethyl-1,2,3,4-tetrahydropyridin-4-ylidene]piperidin-1-ium bromide (4b, $C_{20}H_{28}BrClN_2$)** A mixture of 528 mg of **1b** (2.75 mmol) with 1.02 g of 2-(4-chlorophenyl)ethyl 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_2CO_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 (DMSO-d_6, 400 MHz): δ = 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*, 6H, $ArCH_2CH_2N$, $2NCH_2$), 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; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 23.24 ($2CH_3$), 23.32, 25.84, 26.91 ($3CH_2$), 35.64 ($ArCH_2$), 38.49 (C-3), 49.05, 49.14 ($2NCH_2$), 50.70 ($ArCH_2CH_2N$), 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. $C_{20}H_{27}ClN_2$ ($[M\text{-}HBr]^+$) 330.1863, found 330.1860.

***N*-[1-[2-(1*H*-Indol-3-yl)ethyl]-2,2-dimethyl-1,2,3,4-tetrahydropyridin-4-ylidene]pyrrolidin-1-ium bromide (5a, $C_{21}H_{28}BrN_3$)** 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_2CO_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 (DMSO-d_6, 400 MHz): δ = 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,

H-6), 7.59 (*d*, *J* = 7.7 Hz, 1H, ArH), 10.91 (*br*, *s*, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 23.57 ($2CH_3$), 24.35, 24.62 ($2CH_2$), 26.63 (C-2′), 40.14 (C-3), 49.49, 49.71 ($2NCH_2$), 50.56 (C-1′), 57.00 (C-2), 87.92 (C-5), 111.70, 118.47, 118.67, 121.32, 123.85 (ArC), 110.07, 127.04, 136.39 (ArC_q), 156.52 (C-6), 161.72 (C-4) ppm; IR (KBr): $\overline{\nu}$ = 3207, 2960, 1613, 1557, 1454, 1395, 1345, 1328, 1274, 1232, 1182, 1120, 1098, 770, 748 cm^{-1}; HRMS (EI$^+$): *m/z* calcd. $C_{21}H_{27}N_3$ ([M-HBr]$^+$) 321.2205, found 321.2212.

***N*-[1-[2-(1*H*-Indol-3-yl)ethyl]-2,2-dimethyl-1,2,3,4-tetrahydropyridin-4-ylidene]piperidin-1-ium bromide (5b, $C_{22}H_{30}BrN_3$)** A mixture of 189 mg of **1b** (0.98 mmol) with 305 mg of 3-(2-bromoethyl)indole (1.36 mmol) in 8 cm^3 of $CHCl_3$ was stirred at r.t. for 18 d in the presence of 500 mg of K_2CO_3 (3.62 mmol) and yielded 60 mg of **5b** (15%) as white precipitate without charcoal treatment. M.p.: 210 °C (acetone); ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.34 (*s*, 6H, $2CH_3$), 1.54–1.70 (*m*, 6H, $3CH_2$), 2.87 (*s*, 2H, H-3), 3.04 (*t*, *J* = 7.1 Hz, 2H, H-2′), 3.64 (*br*, *s*, 4H, $2NCH_2$), 3.71 (*t*, *J* = 7.3 Hz, 2H, H-1′), 5.36 (*d*, *J* = 7.0 Hz, 1H, H-5), 6.99 (*dd*, *J* = 7.3, 7.0 Hz, 1H, ArH), 7.08 (*t*, *J* = 7.3 Hz, 1H, ArH), 7.24 (*s*, 1H, ArH), 7.35 (*d*, *J* = 7.7 Hz, 1H, ArH), 7.46 (*d*, *J* = 7.0 Hz, 1H, H-6), 7.58 (*d*, *J* = 7.7 Hz, 1H, ArH), 10.93 (*br*, *s*, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 23.42 ($2CH_3$, CH_2), 25.81 (CH_2), 26.54 (C-2′), 26.92 (CH_2), 38.51 (C-3), 49.00, 49.05 ($2NCH_2$), 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_q), 156.83 (C-6), 162.75 (C-4) ppm; IR (KBr): $\overline{\nu}$ = 2856, 2360, 1611, 1551, 1471, 1387, 1339, 1269, 1234, 1188, 1103, 1010, 754 cm^{-1}; HRMS (EI$^+$): *m/z* calcd. $C_{22}H_{29}N_3$ ([M-HBr]$^+$) 335.2361, found 335.2372.

***N*-[1-(4-Cyanobenzyl)-2,2-dimethyl-1,2,3,4-tetrahydropyridin-4-ylidene]pyrrolidinium bromide (6a, $C_{19}H_{24}BrN_3$)** A mixture of 732 mg of **1a** (4.11 mmol) with 1.382 g of 4-(bromomethyl)benzonitrile (6.98 mmol) in 20 cm^3 of $CHCl_3$ was stirred at r.t. for 4 d and yielded without second crystallization and without charcoal treatment 1.521 g of **6a** (99%) as yellowish crystals. M.p.: 172 °C ($CHCl_3$/ethyl acetate); ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.21 (*s*, 6H, $2CH_3$), 1.93–2.00 (*m*, 4H, $2CH_2$), 2.95 (*s*, 2H, H-3), 3.55 (*t*, *J* = 6.2 Hz, 2H, NCH_2), 3.67 (*t*, *J* = 6.2 Hz, 2H, NCH_2), 4.85 (*s*, 2H, $ArCH_2$), 5.30 (*d*, *J* = 7.0 Hz, 1H, H-5), 7.54 (*d*, *J* = 8.1 Hz, 2H, ArH), 7.78 (*d*, *J* = 7.0 Hz, 1H, H-6), 7.88 (*d*, *J* = 8.1 Hz, 2H, ArH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 23.50 ($2CH_3$), 24.31, 24.54 ($2CH_2$), 40.30 (C-3), 49.80, 50.00 ($2NCH_2$), 53.10 ($ArCH_2$), 57.46 (C-2), 88.98 (C-5), 110.54 (ArC_q), 118.76 (CN), 128.13, 132.78 (ArC), 143.89 (ArC_q), 157.66 (C-6), 162.60 (C-4) ppm; IR (KBr): $\overline{\nu}$ = 2931, 2225, 1607, 1550, 1479, 1441, 1407, 1336, 1272, 1235, 1187, 1106, 999, 969, 860, 831, 766 cm^{-1}; HRMS (EI$^+$): *m/z* calcd. $C_{19}H_{23}N_3$ ([M-HBr]$^+$) 293.1892, found 293.1886.

***N*-[1-(4-Cyanobenzyl)-2,2-dimethyl-1,2,3,4-tetrahydropyridin-4-ylidene]piperidin-1-ium bromide (6b, $C_{20}H_{26}BrN_3$)** A mixture of 1.171 g of **1b** (6.09 mmol) with 2.05 g of 4-(bromomethyl)benzonitrile (10.4 mmol) in 30 cm^3 of $CHCl_3$ 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 ($CHCl_3$/ethyl acetate); ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.18 (*s*, 6H, $2CH_3$), 1.58–1.73 (*m*, 6H, $3CH_2$), 2.97 (*s*, 2H, H-3), 3.67–3.72 (*m*, 4H, $2NCH_2$), 4.85 (*s*, 2H, $ArCH_2$), 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; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 23.32 (CH_2, $2CH_3$), 25.95, 26.91 ($2CH_2$), 38.62 (C-3), 49.34, 49.40 ($2NCH_2$), 52.99 ($ArCH_2$), 57.56 (C-2), 88.03 (C-5), 110.52 (ArC_q), 118.79 (CN), 128.22, 132.75 (ArC), 143.77 (ArC_q), 157.97 (C-6), 163.65 (C-4) ppm; IR (KBr): $\overline{\nu}$ = 2941, 2860, 2225, 1608, 1558, 1468, 1444, 1403, 1353, 1254, 1238, 1186, 1111, 1018, 951, 859, 736 cm^{-1}; HRMS (EI$^+$): *m/z* calcd. $C_{20}H_{25}N_3$ ([M-HBr]$^+$) 307.2048, found 307.2065.

1-(4-Chlorobenzyl)-*N*,*N*,2,2-tetramethyl-1,2,3,4-tetrahydropyridin-4-iminium chloride (7c, $C_{16}H_{22}Cl_2N_2$) A mixture of 3.735 g of **1c** (24.5 mmol) with 6.72 g of 4-chlorobenzyl chloride (42 mmol) in 30 cm^3 of $CHCl_3$ 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); ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.20 (*s*, 6H, $2CH_3$), 2.95 (*s*, 2H, H-3), 3.21 (*s*, 3H, NCH_3), 3.26 (*s*, 3H, NCH_3), 4.79 (*s*, 2H, $ArCH_2$), 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; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 23.47 ($2CH_3$), 39.13 (C-3), 40.74, 41.07 ($2NCH_3$), 52.79 ($ArCH_2$), 57.46 (C-2), 88.08 (C-5), 128.83, 129.41 (ArC), 132.49, 136.74 (ArC_q), 157.57 (C-6), 165.51 (C-4) ppm; IR (KBr): $\overline{\nu}$ = 3424, 2971, 2360, 1563, 1470, 1401, 1361, 1241, 1179, 1105, 1017, 800, 739 cm^{-1}; HRMS (EI$^+$): *m/z* calcd. $C_{16}H_{21}ClN_2$ ([M-HCl]$^+$) 276.1393, found 276.1393.

***N*,*N*-Dibenzyl-1-(4-chlorobenzyl)-2,2-dimethyl-1,2,3,4-tetrahydropyridin-4-iminium chloride (7d, $C_{28}H_{30}Cl_2N_2$)** A mixture of 109 mg of **1d** (0.35 mmol) with 125 mg of 4-chlorobenzyl chloride (0.77 mmol) in 1.5 cm^3 of $CHCl_3$ 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. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.21 (*s*, 6H, $2CH_3$), 3.12 (*s*, 2H, H-3), 4.79 (*s*, 2H, 4-$ClArCH_2$), 4.88 (*s*, 2H, $ArCH_2$), 4.96 (*s*, 2H, $ArCH_2$), 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; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.32 ($2CH_3$),

39.10 (C-3), 53.16 (4-ClArCH$_2$), 54.38, 54.45 (2ArCH$_2$), 58.21 (C-2), 89.22 (C-5), 126.93, 127.21, 127.96, 128.17, 128.92, 129.03, 129.15, 129.74 (ArC), 132.74, 134.84, 135.40, 135.98 (ArC$_q$), 159.08 (C-6), 166.15 (C-4) ppm; IR (KBr): $\overline{\nu}$ = 3427, 2934, 1544, 1493, 1451, 1404, 1349, 1230, 1181, 1104, 736, 699 cm^{-1}; HRMS (EI$^+$): *m/z* calcd. $C_{28}H_{29}ClN_2$ ([M-HCl]$^+$) 428.2019, found 428.1996.

***N*-[1-(4-Chlorobenzyl)-2,2-dimethyl-1,2,3,4-tetrahydropyridin-4-ylidene]azepin-1-ium chloride (7e, $C_{20}H_{28}Cl_2N_2$)** 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 $CHCl_3$ 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): δ = 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): δ = 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): $\overline{\nu}$ = 3426, 2926, 1557, 1445, 1401, 1237, 1178, 1106, 759 cm^{-1}; HRMS (EI$^+$): *m/z* calcd. $C_{20}H_{27}ClN_2$ ([M-HCl]$^+$) 330.1863, found 330.1852.

4-[2-(1*H*-Indol-3-yl)ethylamino]-6,6-dimethyl-5,6-dihydropyridine-2(1*H*)-thione (9, $C_{17}H_{21}N_3S$) A mixture of 4.55 g of **8** (29 mmol) dissolved in 90 cm^3 of benzene with 4.65 g of tryptamine (29 mmol) dissolved in 20 cm^3 of benzene in the presence of 1.79 g of glacial acetic acid (0.03 mol) was refluxed on a Dean-stark apparatus. After cooling the solution to r.t. a precipitate formed, which was sucked off giving 5.74 g of pure **9** (66%). For analytical purposes a further crystallization was done after treatment with charcoal giving a bright yellow powder. M.p.: 211 °C (propan-2-ol); ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.17 (*s*, 6H, 2CH$_3$), 2.22 (*s*, 2H, H-5), 2.92–2.95 (*m*, 2H, H-2′), 3.28–3.32 (*m*, 2H, H-1′), 5.22 (*s*, 1H, H-3), 6.96–7.08 (*m*, 3H, NH, ArH), 7.18 (*s*, 1H, ArH), 7.34 (*d*, *J* = 8.1 Hz, 1H, ArH), 7.51 (*d*, *J* = 8.1 Hz, 1H, ArH), 8.18 (*br*, *s*, 1H, NH), 10.86 (*br*, *s*, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 23.93 (C-2′), 26.96 (2CH$_3$), 40.03 (C-5), 43.17 (C-1′), 52.38 (C-6), 93.67 (C-3), 111.62, 118.33, 118.52, 121.17, 123.05 (ArC), 127.30, 136.40 (ArC$_q$), 151.93 (C-4), 189.18 (C-2) ppm; IR (KBr): $\overline{\nu}$ = 3373, 3211, 2967, 2919, 1582, 1541, 1507, 1454, 1426, 1383, 1363, 1181, 1142, 1108, 948, 746 cm^{-1}; HRMS (EI$^+$): *m/z* calcd. $C_{17}H_{21}N_3S$ (M$^+$) 299.1456, found 299.1468.

***N*-[2-(1*H*-Indol-3-yl)ethyl]-2,2-dimethyl-1,2,3,4-tetrahydropyridin-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 methyliodide 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_2SO_4), filtered, and the solvent evaporated yielding 517 mg of **1f** (59%) as yellowish resin. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 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): δ = 25.55 (C-2′), 27.40 (2CH$_3$), 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$_q$), 136.29 (ArC$_q$), 149.33 (C-6), 156.56 (C-4) ppm; IR (KBr): $\overline{\nu}$ = 2964, 1538, 1456, 1362, 1283, 1097, 741 cm^{-1}; HRMS (EI$^+$): *m/z* calcd. $C_{17}H_{21}N_3$ (M$^+$) 267.1736, found 267.1735.

1-(4-Chlorobenzyl)-*N*-[2-(1*H*-indol-3-yl)ethyl]-2,2-dimethyl-1,2,3,4-tetrahydropyridin-4-imine (10f, $C_{24}H_{26}ClN_3$) 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_2SO_4), filtered, and the solvent was evaporated giving a red resin. This was purified by CC over basic aluminium oxide with (CH_2Cl_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): δ = 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): δ = 23.87, 23.99 (2CH$_3$), 26.76 (C-2′),

47.87 (C-3), 50.22 (C-1′), 52.04 ($ArCH_2$), 57.13 (C-2), 89.18 (C-5), 111.13 (ArC), 114.43 (ArC_q), 118.86, 118.92, 121.59, 121.64 (ArC), 127.67 (ArC_q), 128.43, 128.90 (ArC), 133.33, 136.34, 137.30 (ArC_q), 146.57 (C-6), 162.03 (C-4) ppm; minor constituent (*E*) form: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.99$ (*s*, 6H, $2CH_3$), 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, $ArCH_2$), 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; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 23.77$, 24.06 ($2CH_3$), 27.35 (C-2′), 39.94 (C-3), 50.48 (C-1′), 52.04 ($ArCH_2$), 56.00 (C-2), 99.82 (C-5), 111.13 (ArC), 114.43 (ArC_q), 118.72, 118.97, 121.76, 121.91 (ArC), 127.55 (ArC_q), 128.47, 128.77 (ArC), 133.08, 136.34, 137.88 (ArC_q), 144.62 (C-6), 163.32 (C-4) ppm; IR (KBr): $\overline{\nu} = 2919$, 1593, 1491, 1457, 1365, 1094, 1013, 741 cm^{-1}; HRMS (EI$^+$): *m/z* calcd. $C_{24}H_{26}ClN_3$ (M^+) 391.1815, found 391.1818.

1-(4-Chlorobenzyl)-2,3-dihydro-2,2-dimethylpyridin-4(1*H*)-one (11, $C_{14}H_{16}ClNO$) To a suspension of 1.12 g of **7c** (2.72 mmol) in 20 cm^3 of benzene, 15 cm^3 of 2 M NaOH were added. The mixture was refluxed overnight and cooled to room temperature. The aqueous phase was diluted with 20 cm^3 of water and the phases were separated. The water phase was extracted three times with benzene. Then the organic layers were combined and washed with water. After drying (Na_2SO_4) and filtration, the solvent was evaporated in vacuo giving 680 mg of **11** (98%) as a yellowish resin. ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 1.11$ (*s*, 6H, $2CH_3$), 2.26 (*s*, 2H, H-3), 4.47 (*s*, 2H, $ArCH_2$), 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; ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 23.80$ ($2CH_3$), 50.40 (C-3), 51.92 ($ArCH_2$), 58.45 (C-2), 96.76 (C-5), 128.69, 129.06 (ArC), 131.95, 138.73 (ArC_q), 154.34 (C-6), 190.42 (C-4) ppm; IR (KBr): $\overline{\nu} = 2972$, 1637, 1588, 1491, 1444, 1409, 1367, 1278, 1247, 1212, 1175, 1100, 1014, 812, 760 cm^{-1}; HRMS (EI$^+$): *m/z* calcd. $C_{14}H_{16}ClNO$ (M^+) 249.0920, found 249.0918.

(*RS*)-()-4-[[1-(4-Chlorobenzyl)-2,2-dimethyl-1,2,3,4-tetrahydropyridin-4-yliden]amino]-*N*,*N*-dimethylpentanamin (10 g, $C_{23}H_{36}ClN_3$) The residue from co-distillation of 613 mg of **11** (2.45 mmol) with benzene was dissolved in 20 cm^3 of toluene. Then 778 mg of N^1,N^1-diethylpentane-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 (CH_2Cl_2:MeOH = 8:1) as eluent. The fractions containing pure products were combined and evaporated, giving 40 mg of **10g** (4.2%). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.00$ (*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, $2CH_3$), 1.45–1.50 (*m*, 4H, H-3′, H-4′), 2.39–2.48 (*m*, 4H, H-3, H-5′), 2.50 (*q*, $J = 7.1$ Hz, 4H, H-1″), 3.52–3.56 (*m*, 1H, H-2′), 4.22 (*br*, *s*, 2H, $ArCH_2$), 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; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 11.65$ (C-2″), 21.89 (C-1′), 23.69 (CH_3), 24.16 (C-4′), 24.23 (CH_3), 36.39 (C-3′), 46.82 (C-1″), 49.00 (C-3), 51.71 ($ArCH_2$), 52.94 (C-5′), 53.23 (C-2′), 56.94 (C-2), 89.68 (C-5), 128.38, 128.77 (ArC), 133.06, 137.84 (ArC_q), 144.96 (C-6), 159.27 (C-4) ppm; IR (KBr): $\overline{\nu} = 2968$, 2931, 2801, 1615, 1597, 1538, 1491, 1466, 1366, 1277, 1248, 1224, 1180, 1093, 1014, 806, 736 cm^{-1}; HRMS (EI$^+$): *m/z* calcd. $C_{23}H_{36}ClN_3$ (M^+) 389.2598, found 389.2604.

1-[2-[(7-Chloroquinolin-4-yl)amino]ethyl]-6,6-dimethyl-4-pyrrolidino-5,6-dihydropyridine-2(1*H*)-thione (13, $C_{22}H_{27}ClN_4S$) 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 cm^3 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 (Na_2SO_4), filtered, and evaporated to get the free base. This was dissolved in 50 cm^3 of dimethyl formamide and refluxed overnight at 170 °C. The solvent was evaporated in vacuo and the residue was crystallized from ethanol. It was sucked off to get 3.35 g of **13** (34%) as beige solid. M.p.: 248 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 1.34$ (*s*, 6H, $2CH_3$), 1.87 (*br*, *s* 4H, $2CH_2$), 2.58 (*s*, 2H, H-5), 3.09–3.42 (*m*, 4H, $2NCH_2$), 3.57 (*br*, *s*, 2H, H-2′), 4.18 (*br*, *s*, 2H, H-1′), 5.43 (*s*, 1H, H-3), 6.80 (*d*, $J = 5.5$ Hz, 1H, ArH), 7.45 (*d*, $J = 8.8$ Hz, 1H, ArH), 7.68 (*br*, *s*, 1H, NH), 7.77 (*br*, *s*, 1H, ArH), 8.18 (*d*, $J = 9.2$ Hz, 1H, ArH), 8.39 (*d*, $J = 5.1$ Hz, 1H, ArH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 24.76$ ($2CH_2$), 25.39 ($2CH_3$), 40.44 (C-5), 42.57 (C-2′), 44.91 (C-1′), 47.32 ($2NCH_2$), 57.86 (C-6), 98.89 (C-3), 99.27 (ArC), 117.44 (ArC_q), 124.12, 124.34 (ArC), 127.70 (ArC), 133.55 (ArC_q), 149.17, 149.24 (C-4, ArC_q), 150.33 (ArC_q), 152.11 (ArC), 189.91 (C-2) ppm; IR (KBr): $\overline{\nu} = 2968$, 1577, 1450, 1407, 1367, 1342, 1300, 1162, 1066, 776 cm^{-1}; HRMS (EI$^+$): *m/z* calcd. $C_{22}H_{27}ClN_4S$ (M^+) 414.1645, found 414.1645.

***N*-[1-[2-[(7-Chloroquinolin-4-yl)amino]ethyl]-2,2-dimethyl-6-methylsulfanyl-1,2,3,4-tetrahydropyridin-4-ylidene]-pyrrolidine-1-ium iodide (14, $C_{23}H_{30}ClIN_4S$)** Compound **13** (3.35 g, (8.07 mmol) was dissolved in 20 cm^3 of $CHCl_3$ and 1.33 mg of CH_3I (9.37 mmol) dissolved in 5 cm^3 of $CHCl_3$ 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; ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 1.39$ (*s*, 6H, $2CH_3$), 1.93–2.00 (*m*, 4H, $2CH_2$), 2.63 (*s*, 3H, SCH_3), 2.91 (*s*, 2H, H-3), 3.55–3.65 (*m*, 6H, H-2′, $2NCH_2$), 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; ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 15.87$ (SCH_3), 23.83 ($2CH_3$), 24.36, 24.68 ($2CH_2$), 39.83 (C-3), 41.21 (C-2′), 45.23 (C-1′), 49.54 ($N(CH_2)_2$), 60.05 (C-2), 87.20 (C-5), 99.01 (ArC), 117.55 (ArC_q), 124.15, 124.64, 127.70 (ArC), 133.81, 149.16, 149.94 (ArC_q), 152.18 (ArC), 158.78 (C-4), 170.78 (C-6) ppm; IR (KBr): $\overline{\nu} = 3441$, 3262, 2977, 1581, 1495, 1445, 1396, 1335, 1307, 1156, 1120, 846, 813 cm^{-1}; HRMS (EI^+): *m/z* calcd. $C_{23}H_{27}ClN_4S$ ([M-HI-H_2]$^+$) 426.1645, found 426.1620.

1-[2-[(7-Chloroquinolin-4-yl)amino]ethyl]-4-[[2-[(7-chloroquinolin-4-yl)amino]ethyl]amino]-6,6-dimethyl-5,6-dihydropyridine-2(1*H*)-thione (16, $C_{29}H_{30}Cl_2N_6S$) The first crystallizate of the synthesis of **13** was suspended in 2 M NaOH. Then the free bases were extracted with chloroform. The solution was dried with sodium sulfate, filtered, and the solvent evaporated yielding 1.626 g of the free bases (2.88 mmol). The residue was dissolved in 20 cm^3 of dimethyl formamide and refluxed overnight. The solvent was evaporated in vacuo and the residue crystallized from ethanol. Yield: 600 mg of **16** (37%) as brownish precipitate. For analytical purposes a part of it was recrystallized from ethanol giving a light brown powder. M.p.: 293 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 1.30$ (*s*, 6H, $2CH_3$), 2.36 (*s*, 2H, H-5), 3.26–3.59 (*m*, 6H, H-1′, 2H-2′), 4.10–4.24 (*m*, 2H, H-1′), 5.61 (*s*, 1H, H-3), 6.52 (*d*, $J = 5.5$ Hz, 1H, ArH), 6.82 (*d*, $J = 5.5$ Hz, 1H, ArH), 7.04 (*br*, *s*, 1H, NH), 7.40 (*t*, $J = 5.1$ Hz, 1H, NH), 7.44–7.46 (*m*, 2H, ArH), 7.65 (*t*, $J = 4.0$ Hz, 1H, NH), 7.77–7.78 (*m*, 2H, ArH), 8.18 (*d*, $J = 9.2$ Hz, 1H, ArH), 8.23 (*d*, $J = 9.2$ Hz, 1H, ArH), 8.38–8.40 (m, 2H, ArH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 25.34$ ($2CH_3$), 40.85 (C-1′, C-2′), 41.56 (C-5), 42.17, 45.20 (C-1′, C-2′), 58.12 (C-6), 96.45 (C-3), 98.83, 99.35 (ArC), 117.50, 117.72 (ArC_q), 124.21, 124.32, 124.45, 127.66 (ArC), 133.56 (ArC_q), 149.28, 150.22 (C-4, $2ArC_q$), 152.11 (ArC), 191.23 (C-2) ppm; IR (KBr): $\overline{\nu} = 3420$, 3253, 2971, 1580, 1538, 1412, 1366, 1161, 1138, 810 cm^{-1}; HRMS (EI^+): no molecule peak was detectable.

***N*-(2,2-Dimethyl-6-pyrrolidino-1,2,3,4-tetrahydropyridin-4-ylidene)pyrrolidin-1-ium iodide (18a, $C_{15}H_{26}IN_3$)** A suspension of 1.96 g of **17a** (5.56 mmol) in 20 g of pyrrolidine (0.28 mol) was refluxed for 4 h on an oil bath. The pyrrolidine was removed by evaporation in vacuo and the residue was dissolved in the minimum amount of hot propan-2-ol. The product precipitated by addition of ethyl acetate, giving 1.69 g of **18a** (81%) as white needles. M.p.: 192 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 1.30$ (*s*, 6H, $2CH_3$), 1.86–1.95 (*m*, 8H, $4CH_2$), 2.62 (*s*, 2H, H-3), 3.29 (*t*, $J = 6.6$ Hz, 2H, NCH_2), 3.40 (*br*, *s*, 4H, $2NCH_2$), 3.51 (*t*, $J = 6.6$ Hz, 2H, NCH_2), 4.58 (*s*, 1H, H-5), 7.01 (*s*, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 24.41$ (CH_2), 24.66 ($2CH_2$), 24.87 (CH_2), 27.21 ($2CH_3$), 38.85 (C-3), 48.19, 48.42 ($4NCH_2$), 51.65 (C-2), 77.08 (C-5), 156.05 (C-6), 157.62 (C-4) ppm; IR (KBr): $\overline{\nu} = 2966$, 1592, 1502, 1444, 1349, 1329, 1230, 1180, 1139, 859, 746 cm^{-1}; HRMS (EI^+): *m/z* calcd. $C_{15}H_{25}N_3$ ([M-HI^+]) 247.2048, found 247.2054.

***N*-(2,2-Dimethyl-6-piperidino-1,2,3,4-tetrahydropyridin-4-ylidene)piperidinium iodide (18b, $C_{17}H_{30}IN_3$)** 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); ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 1.29$ (*s*, 6H, $2CH_3$), 1.54 (*br*, *s*, 8H, $4CH_2$), 1.62–1.65 (*m*, 4H, $2CH_2$), 2.61 (*s*, 2H, 3-H), 3.49–3.54 (*m*, 8H, $4NCH_2$), 5.16 (*s*, 1H, 5-H), 7.32 (*s*, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta = 23.57$, 23.77, 25.55 ($6CH_2$), 26.89 ($2CH_3$), 37.27 (C-3), 47.27, 47.82 ($4NCH_2$), 51.19 (C-2), 77.16 (C-5), 158.05 (C-6), 159.92 (C-4) ppm; IR (KBr): $\overline{\nu} = 3211$, 2939, 2855, 1590, 1546, 1493, 1462, 1449, 1365, 1347, 1288, 1248, 1228, 1180, 1122, 1020, 996, 862, 761 cm^{-1}; HRMS (EI^+): *m/z* calcd. $C_{17}H_{29}N_3$ ([M-HI]$^+$) 275.2361, found 275.2365.

In vitro assays

The in vitro growth inhibition assay of *Plasmodium falciparum* NF54 and the in vitro growth inhibition assay of *Trypanosoma b. rhodesiense,* as well as the assay for the determination of cytotoxicity against L6-cells were performed as described earlier [16].

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