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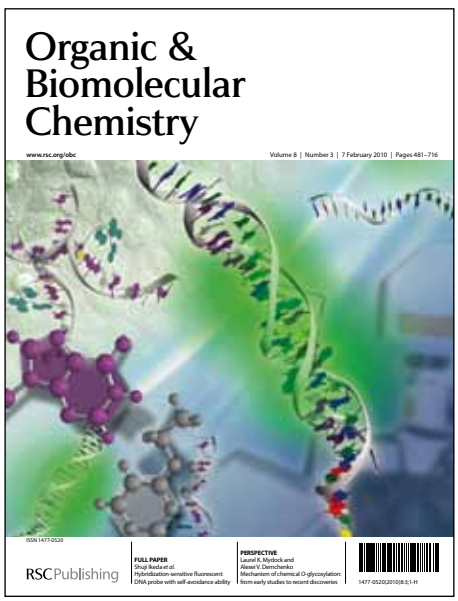

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Enantioselective synthesis of encecaline-derived potent antimalarial agents

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Abstract

The high antiplasmodial activity of racemic benzylamines *rac*-**1** and *rac*-**2** stimulated the synthesis of pure enantiomers. Ellman's chiral sulfinamides (*S*)-**6** and (*R*)-**6** were used as chiral auxiliaries. Condensation of prochiral ketone **5** with enantiomerically pure sulfinamides (*S*)-**6** and (*R*)-**6** and subsequent $NaBH_4$ reduction provided predominantly *unlike* configured diastereomers (*S,R*)-**8** and (*R,S*)-**8** (ratio *unlike*-**8***:like*-**8** = 90 : 10). The same transformation of the phenol **4** led to the diastereomeric sulfinamides (*S,R*)-**12** and (*S,S*)-**12** in the ratio 60 : 40. Acid hydrolysis of the diastereomerically pure sulfinamides followed by monobenzylation yielded the enantiomerically pure benzylamines (*R*)-**1**, (*S*)-**1,** (*R*)-**2** and (*S*)-**2**. The enantiomeric purity of the products was proven by chiral HPLC and the absolute configuration by CD-

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spectroscopy. Generally, benzylamines with (*R*)-configuration show higher antiplasmodial activity than their corresponding (*S*)-configured enantiomers. The phenol (*R*)-**2** represents a very potent lead against *P. falciparum*, with an IC_{50} value of only 0.026 μM against the NF54 strain. The very high eudismic ratio of 34 indicates the enantioselective interaction of phenol (*R*-**2** with a particular target protein of *P. falciparum*.

Key words: Malaria; antiplasmodial activity; enantioselective bioactivity; Ellman's chiral sufinamide; stereoselective synthesis; enantiomerically pure amines; encecaline-derived antimalarial agents

Introduction

Malaria is one of the most significant public health problem in the world. There are about 250 million new cases every year and nearly 1 million people, mostly children less than 5 years old, die due to the inaccessibility of proper treatment. The disease occurs mainly in tropical and subtropical climates and represents a serious problem in South Asia and Africa, where it is responsible for one in every five childhood deaths.[1-3] Malaria is caused by the parasites *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae* and *Plasmodium knowlesi*, among which *P. falciparum* is responsible for the most serious form, Malaria tropica. The rapid development of multiresistant *P. falciparum* strains often renders the therapy difficult.[4] Many of the common antimalarial drugs, i.e. quinine, chloroquine, primaquine, atovaquone, and artemisinine suffer from parasitological resistance developing in many regions

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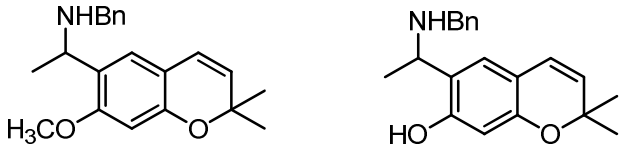
of the world, especially in South Asia and Africa.[5-7] Therefore, there is an urgent need for the development of new antimalarial drugs to ensure the availability of an efficient antimalarial treatment.

Recently, our antiprotozoal activity studies of chromenes derived from encecalol angelate resulted in 7-methoxychromene *rac*-**1** showing high *in vitro* activity against *P. falciparum* (IC_{50} = 0.64 μM).[8] Conversion of the methyl ether *rac*-**1** into the phenol *rac*-**2** increased the antiplasmodial activity dramatically. With an IC_{50}-value of 0.02 μM the phenol *rac*-**2** was found tenfold more potent than the reference compound chloroquine (IC_{50} = 0.263 μM) when tested against the chloroquine-resistant K1 strain.[8] Both methyl ether *rac*-**1** and phenol *rac*-**2** were tested as racemic mixtures. The high antiplasmodial activity of *rac*-**1** and *rac*-**2** encouraged us to study the pharmacological properties of the pure enantiomers.



rac-**1** *rac*-**2**

Figure 1: Chromene based methyl ether *rac*-**1** and phenol *rac*-**2** with high antimalarial activity.

Herein the synthesis and *in vitro* activity against *P. falciparum* of enantiomerically pure methyl ethers (*R*)-**1** and (*S*)-**1** and phenols (*R*)-**2** and (*S*)-**2** are reported.

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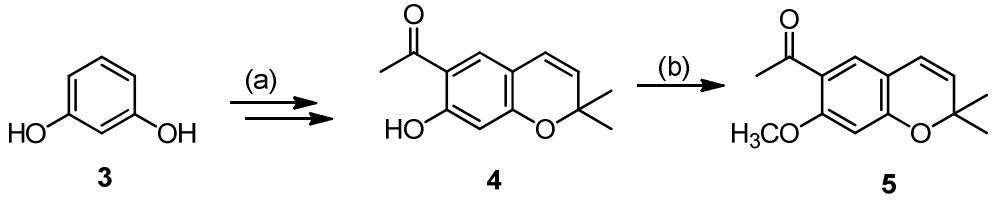
Chemistry

Synthesis

Scheme 1



3 **4** **5**

Synthesis of prochiral ketones **4** and **5** (encecalin).
Reagents and reaction conditions: (a) 3 steps (formation of chromane, acetylation, dehydrogenation).[9] (b) CH_3I, K_2CO_3, DMF, rt.[9]

In order to synthesize the enantiomerically pure methyl ethers **1** and phenols **2** the prochiral ketones **4** and **5** (= natural product encecalin) were synthesized starting with resorcinol (**3**). (Scheme 1) The *o*-hydroxyketone **4** was obtained in a three step synthesis comprising formation of the chromane ring system by reaction of resorcinol (**3**) with 2-methylbut-3-en-2-ol, acetylation and dehydrogenation with DDQ. Methylation of phenol **4** with methyl iodide provided the natural product encecalin **5**.[9]

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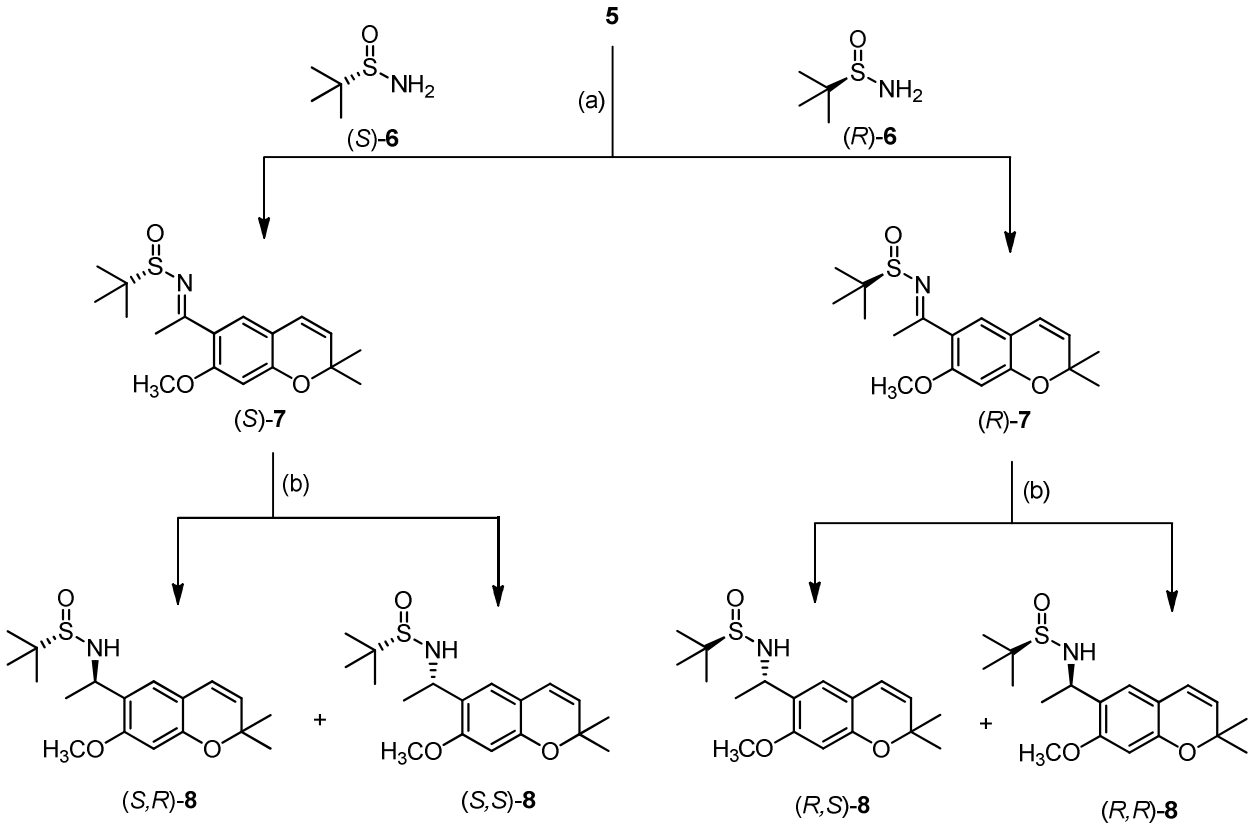
Scheme 2



Synthesis of the four stereoisomers of sulfinamide **8**.
Reagents and reaction conditions: (a) $Ti(OEt)_4$, THF, reflux. (b) $NaBH_4$, THF, 0 ^oC.

For the synthesis of enantiomerically pure benzylamines with methoxy group the chiral auxiliary approach using Ellman's chiral sulfinamides (*S*)-**6** and (*R*)-**6**[10,11] was pursued. (Scheme 2) The prochiral ketone **5** was condensed with (*S*)-configured sulfinamide (*S*)-**6** and $Ti(OEt)_4$ to afford the sulfinylimine (*S*)-**7**. Without purification the sulfinylimine (*S*)-**7** was reduced with $NaBH_4$ to provide the diastereomeric sulfinamides (*S,R*)-**8** and (*S,S*)-**8** in the ratio 90 : 10. Chromatographic separation of the diastereomeric mixture led to the major diastereomer (*S,R*)-**8** in 57 % and the minor diastereomer (*S,S*)-**8** in 5 % yields, respectively. Due to the high diastereoselectivity of 90:10 in the reduction step, only small amounts of the minor diastereomer (*S,S*)-**8** were obtained.

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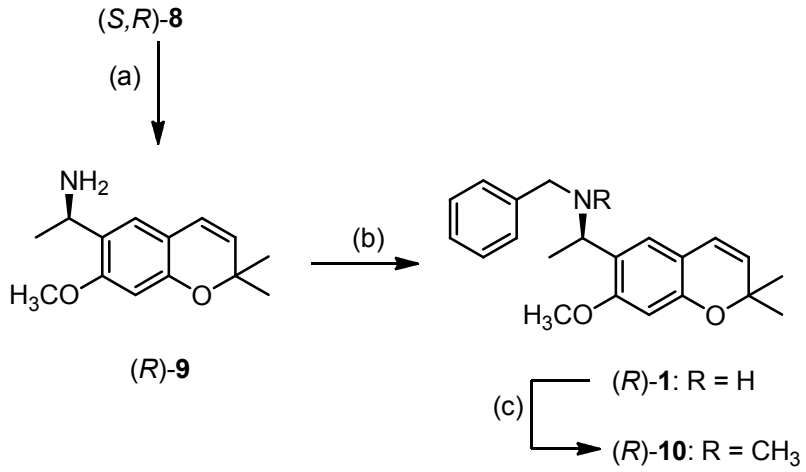
In order to synthesize the enantiomers (*R,S*)-**8** and (*R,R*)-**8** the ketone **5** was condensed with the enantiomeric (*R*)-configured sulfinamide (*R*)-**6** and the resulting sulfinylimine (*R*)-**7** was reduced with $NaBH_4$ to yield the diastereomeric sulfinamides (*R,S*)-**8** and (*R,R*)-**8** in the ratio 90 : 10. Flash chromatographic separation provided the pure diastereomers (*R,S*)-**8** and (*R,R*)-**8** in 55 % and 2.2 % yields, respectively.

Scheme 3



Synthesis of enantiomerically pure amines with methoxy group.
Reagents and reaction condition: (a) HCl, MeOH, THF, rt. (b) PhCHO, $NaBH(OAc)_3$, THF, rt. (c) HCHO, $NaBH(OAc)_3$, THF, rt. The enantiomers (*S*)-**1**, (*S*)-**9** and (*S*)-**10**, were prepared in the same manner starting with (*R,S*)-**8**.

Hydrolysis of the enantiomerically pure major sulfinamide (*S,R*)-**8** with HCl in methanol at room temperature led to the enantiomerically pure primary amine (*R*)-**9**. (Scheme 3) Monobenzylation of the primary amine (*R*)-**9** with one equivalent of benzaldehyde and $NaBH(OAc)_3$ in THF afforded the benzylamine (*R*)-**1**, which was converted into the tertiary amine (*R*)-**10**, upon

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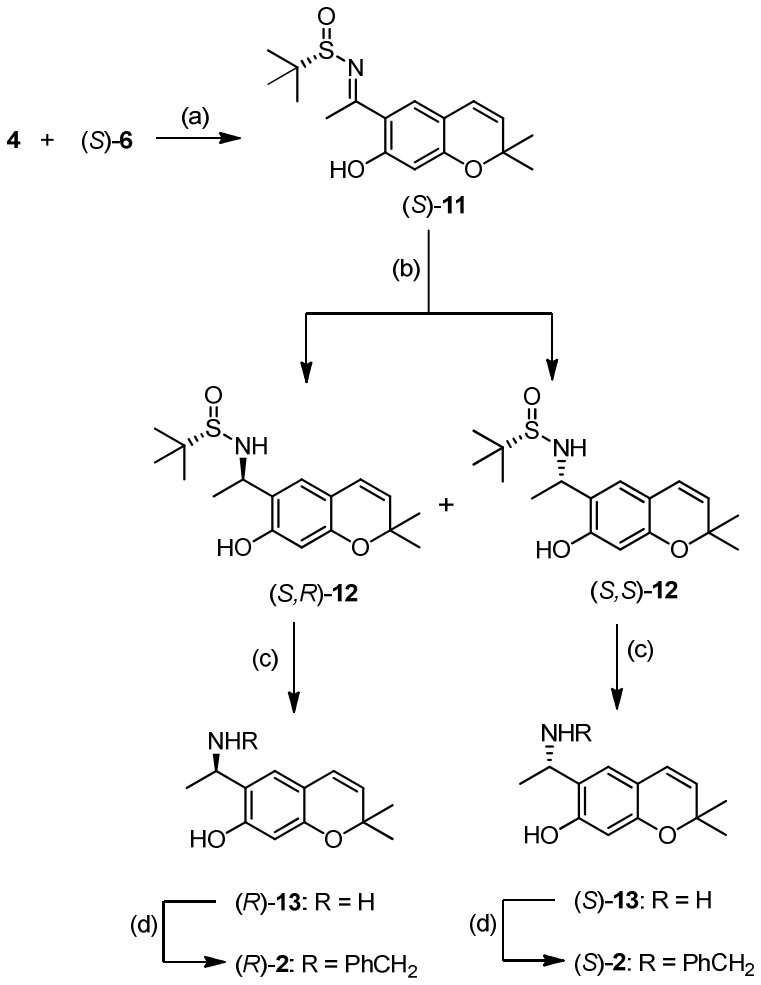
reaction with formaldehyde and $NaBH(OAc)_3$. Analogous reactions performed with the enantiomer (*R,S*)-**8** yielded the enantiomers (*S*)-**1**, (*S*)-**9** and (*S*)-**10**.

Scheme 4



Synthesis of enantiomerically pure phenols **2**.

Reagents and reaction condition: (a) $Ti(OEt)_4$, THF, reflux. (b) $NaBH_4$, THF, 0 ^oC. (c) HCl, Et_2O, 0 ^oC. (d) PhCHO, $NaBH(OAc)_3$, THF, rt.

The enantiomers of the phenol **2** were synthesized starting from the prochiral ketone **4**. (Scheme 4) Condensation of **4** with (*S*)-configured sulfinamide (*S*)-**6** and $Ti(OEt)_4$ led to the sulfinylimine

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(*S*)-**11**, which was reduced with $NaBH_4$ to give the diastereomeric sulfinamides (*S,R*)-**12** and (*S,S*)-**12** in the ratio 60 : 40. Both diastereomers (*S,R*)-**12** and (*S,S*)-**12** were isolated in 28 % and 27 % yields, respectively. An attempt to cleave the sulfinamides (*S,R*)-**12** and (*S,S*)-**12** with methanolic HCl similar to the cleavage of the sulfonamides **8**, resulted in rapid decomposition of the starting material. However, performing the sulfinamide cleavage with HCl in Et_2O at 0 ^oC resulted in the enantiomerically pure primary amines (*R*)-**13** and (*S*)-**13**. Benzylation of primary amines (*R*)-**13** and (*S*)-**13** with one equivalent of benzaldehyde and $NaBH(OAc)_3$ in THF provided the monobenzylamines (*R*)-**2** and (*S*)-**2** with a phenolic hydroxy moiety, respectively.

Enantiomeric purity

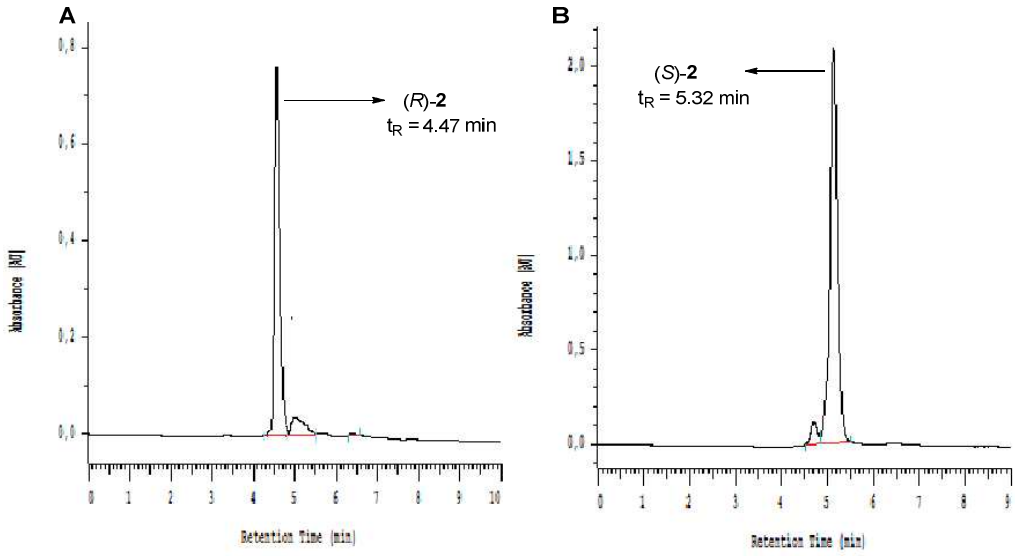

Figure 2: Chiral HPLC chromatograms of pure enantiomers (*R*)-**2** and (*S*)-**2** using Chiralpak AD-H column. Isohexane : methanol = 95 : 5, flow rate: 1 mL/min. injection: 5 µL. **A**: HPLC analysis of (*R*)-**2**, t_R = 4.47 min. **B**: HPLC analysis of (*S*)-**2**, t_R = 5.32 min.

The enantiomeric purity of the synthesized phenols (*R*)-**2** and (*S*)-**2** was determined by chiral HPLC analysis using a Chiralpak AD-H column. (Figure 2) In order to develop a separation

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method, an artificial mixture (1:1) of both enantiomers (*R*)-**2** and (*S*)-**2** was prepared. The enantiomers were baseline separated by an isocratic elution with isohexane : methanol = 95 : 5. According to the HPLC analysis the ratio of enantiomers (*R*)-**2** : (*S*)-**2** is 98.6 : 1.4 (97.2 %ee) for (*R*)-**2** (Figure 2A) and 3.3 : 96.7 (93.4 %ee) for (*S*)-**2** (Figure 2B).

Absolute configuration of benzylamines

The absolute configuration of the synthesized benzylamines (*R*)-**1**, (*S*)-**1,** (*R*)-**2** and (*S*)-**2** was determined by circular dichroism (CD) spectroscopy. For this purpose the CD spectra of the enantiomers (*R*)-**1**, (*S*)-**1**, (*R*)-**2**, and (*S*)-**2** were compared with the CD spectra of the structurally related enantiomerically pure (*R*)- and (*S*)-configured 1-phenylethylamines (*R*)-**14** and (*S*)-**14** whose structure around the center of chirality is identical to that of the chromenylethylamines **1** and **2**.

The CD-spectrum of (*R*)-configured 1-phenylethylamine (*R*)-**14** displays Cotton effects (CEs) attributable to the typical benzene absorption bands ^1L_b, ^1L_a and E_{1u} bands at around 260, 220 and 200 nm with negative, negative and positive signs, respectively, which are in accordance with literature[12] and opposite in the enantiomer (*S*)-**14** (Figure 3, right top panel). Comparison of the CEs observed in the CD spectra of the pure enantiomers of **1** and **2** with those of (*R*)- and (*S*)-**14** allowed assignment of the absolute configuration on the basis of the CEs of the ^1L_b and E_{1u} bands occurring around 300 nm and 230 nm. These bands showed negative and positive signs, respectively, in case of the (*R*)- and the opposite behavior in case of the (*S*)-enantiomer (Figure 2, left panels, spectra of the phenols (*R*)-**2** and (*S*)-**2**). Additionally, CD spectra of the enantiomeric sulfinamides (*S,R*)-**8** and (*R,S*)-**8** as well as of the diastereomeric sulfinamides

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(*S,R*)-**12** and (*S,S*)-**12** were recorded. Here the first stereodescriptor describes the configuration of the sulfonamide substructure and the second one relates to the configuration of the arylethylamine stereocenter. The structure of the corresponding CD spectra is determined by the center of chirality adjacent to the chromophoric system defined by the second stereodescriptor. Therefore, the CD spectra of (S,*R*)-**8** and (*S,R*)-**12** correspond to the CD spectra of (*R*)-configured 1-phenylethylamine (*R*)-**14** and (*R*)-configured chromenylethylamines (*R*)-**1** and (*R*)-**2**. Analogously, the CD-spectra of (*R,S*)-**8** and (*S,S*)-**12** show similar structures as the CD spectra of (*S*)-configured 1-phenylethylamine (*S*)-**14** and (*S*)-configured chromenylethylamines (*S*)-**1** and (*S*)-**2**.

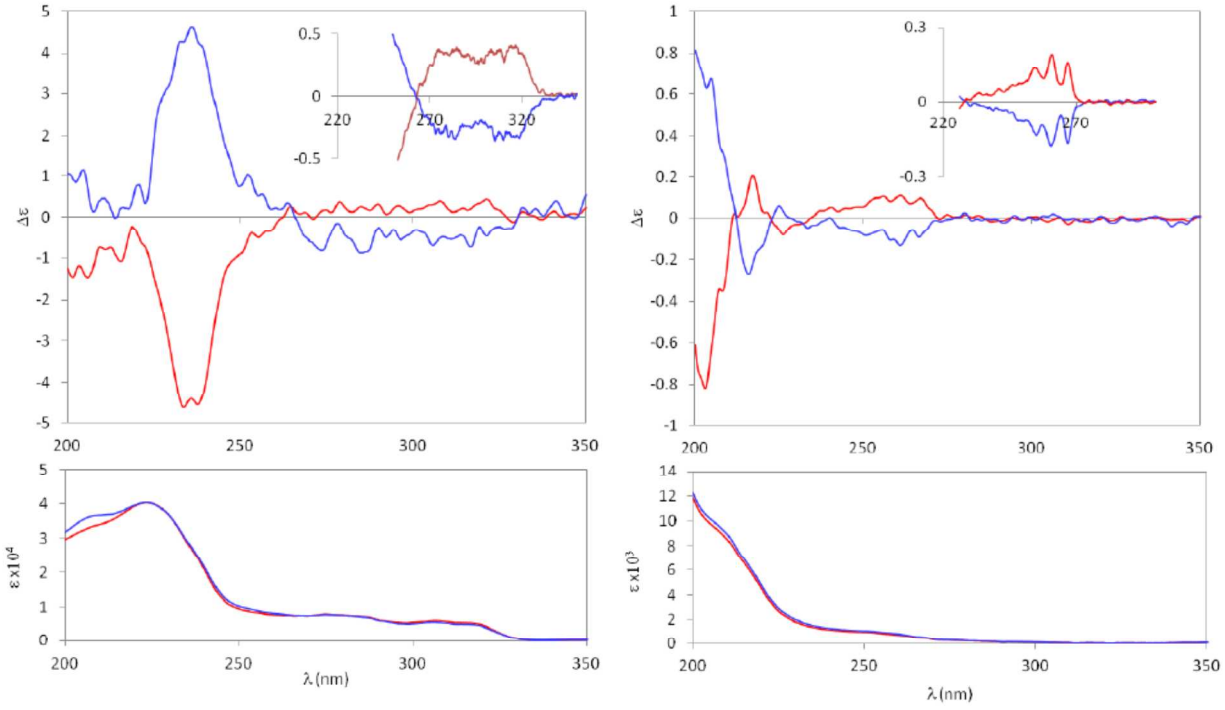

Figure 3: CD and UV absorption spectra of enantiomerically pure phenols (*R*)-**2** and (*S*)-**2** (left panels, blue and red, respectively) compared to the reference compounds (*R*)-**14** and (*S*)-**14** (right panels, blue and red, respectively) (solvent: acetonitrile, concentration: 0.25 mg/mL for **2**, 0.1 mg/mL for **14**; insets in the CD panels: 1 mg/mL for all compounds).

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Antiplasmodial and antitrypanosomal activity of enantiomerically pure chromenes

The antiplasmodial and antitrypanosomal activity of the enantiomerically pure secondary and tertiary amines (*R*)-**1**, (*S*)-**1**, (R)-**2**, (S)-**2**, (*R*)-**10**, and (*S*)-**10** as well as one sulfinamide couple (*S,R*)-**8** and (*R,S*)-**8** was investigated in vitro. Intraerythrocytic stages of *P. falciparum* (*Pfc*) and bloodstream forms of *T. brucei rhodesiense* (*Tbr*) were used in the antiplasmodial and antitrypanosomal assay, respectively. Moreover, the cytotoxicity against L6 rat skeletal myoblasts was recorded, which allowed calculation of selectivity indices for the tested compounds.[13] In Table 1 the antiprotozoal activity data of the enantiomerically pure test compounds are compared with the activity of the corresponding racemic mixtures as well as reference compounds.

The anti-*Pfc* and anti-*Tbr* activity of enantiomerically pure sulfinamides **8** and benzylamines **1**, **2** indicate that the amines are more potent than the sulfinamides. Obviously a basic amino group is required for anti-*Pfc* and anti-*Tbr* activity. The benzylamines (*R*)-**1** and (*S*)-**1** showed high antiplasmodial activity, the (*R*)-enantiomer (*R*)-**1** being three times more active (IC_{50} = 0.28 μM) than (*S*)-**1**. The activity of (*R*)-**1** against the K1 strain of *Pfc* is in the same range as that of the positive control, chloroquine (IC_{50} = 0.26 μM). The *Pfc* selectivity of (*R*)-**1** is also significantly greater than that of (*S*)-**1**, since the cytotoxicity of both enantiomers differs only slightly. Concerning their anti-*Tbr* activity, (*R*)-**1** and (*S*)-**1** show an opposite behavior than observed for the antiplasmodial activity, the (*S*)-enantiomer (*S*)-**1** being more potent than (*R*)-**1**. The enantiomerically pure tertiary amines (*R*)-**10** and (*S*)-**10** are less active compared to non-methylated secondary amines (*R*)-**1** and (*S*)-**1**.

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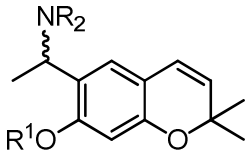
Table 1: Antiprotozoal activity of chromenes and reference compounds against *P. falciparum* and *T. brucei rhodesiense*, as well as cytotoxicity against rat skeletal myoblasts (L6 cells) with selectivity indices (SI) for *Pfc* and *Tbr*.

				IC_{50} (μM)			SI (*Pfc*)	SI (*Tbr*)
compd.	NR_2	R^1	*config.*	*Pfc*	*Tbr*	*cytotoxicity L6 cells*		
rac-**1**[8]	NHBn	CH_3	*rac.*	0.64[a]	2.38	21	33	8.8
(*R*)-**1**	NHBn	CH_3	(*R*)	0.28[a]	2.28	16.7	59	7.3
(*S*)-**1**	NHBn	CH_3	(*S*)	0.75[a]	1.53	16.2	22	10.6
rac-**2**[8]	NHBn	H	*rac.*	0.02[a]	12.4	109	5450	8.8
(*R*)-**2**	NHBn	H	(*R*)	0.026[b]	2.17	18.8	723	8.7
(*S*)-**2**	NHBn	H	(*S*)	0.884[b]	17.2	179	202	10.4
(*S,R*)-**8**	$NHS(=0)^+BnCH_3$		(*S,R*)	2.46[a]	67.0	144	58	2.1
(*R,S*)-**8**	$NHS(=0)^+BnCH_3$		(*R,S*)	15.7[a]	46.3	99.1	6.3	2.1
(*R*)-**10**	$N(CH_3)Bn$	CH_3	(*R*)	1.24[a]	16.0	46.3	37	2.9
(*S*)-**10**	$N(CH_3)Bn$	CH_3	(*S*)	1.28[a]	9.88	45.4	35	4.6
chloroquine				0.26[a] 0.009[b]	-			
melarsoprol				-	0.005			
podophyllotoxin				-	-	0.010		

[a]strain K1 [b]strain NF54

The phenolic congener of the methyl ether (*R*)-**1**, (*R*)-**2,** was found to be the most potent antimalarial compounds within the series. It was found to be much more potent than its (*S*)-configured enantiomer with an eudismic ratio for the antiplasmodial activity of 34. This very high enantioselective activity indicates the stereoselective interaction of (*R*)-**2** with a particular

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target of *P. falciparum*. However, the mode of action of these novel potential antimalarial drugs remains to be elucidated.

The free phenolic group of this novel type of compounds appears to be crucial for high antiplasmodial activity, since the phenol (*R*)-**2** is about tenfold more active than the methyl ether (*R*)-**1**. Additionally the phenolic structural element is also responsible for the high selectivity index, which is increased from 59 for the methyl ether (*R*)-**1** to 723 for the phenol (*R*)-**2**.

In contrast to the antiplasmodial activity the antitrypanosomal activity of the enantiomerically pure methyl ethers and phenols is rather low. This result also points to a specific antiplasmodial rather than an unspecific toxic effect.

Conclusion

Ellman's chiral sulfinamide allowed the stereoselective synthesis of enantiomerically pure encecaline derived amines. The finding that antiplasmodial activity of (*R*)-configured phenol (*R*)-**2** is more than 30-fold higher than the antiplasmodial activity of (*S*)-configured phenol (*S*)-**2** indicates specific and stereoselective interactions of (*R*)-**2** with a clearly defined molecular target, which are responsible for the observed biological activity. Search for the hitherto unknown target and evaluation of the *in vivo* activity of this new and very promising class of antiplasmodial agents is stimulated in particular, since already the racemic mixture of phenol *rac*-**2** was about 10fold more potent against the chloroquine-resistant K1-strain than chloroquine.

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Experimental Section

General, chemistry

Unless otherwise mentioned, THF was dried with sodium/benzophenone and was freshly distilled before use. Thin layer chromatography (tlc): Silica gel 60 F254 plates (Merck). Flash chromatography (fc): Silica gel 60, 40–64 μm (Merck); parentheses include: diameter of the column, length of column, fraction size, eluent, Rf value. Melting point: Melting point apparatus SMP 3 (Stuart Scientific), uncorrected. IR: IR spectrophotometer 480Plus FT-ATR-IR (Jasco). 1H NMR (400 MHz), 13C NMR (100 MHz): Mercury plus 400 spectrometer (Varian); □ in ppm related to tetramethylsilane; coupling constants are given with 0.5 Hz resolution. Where necessary, the assignment of the signals in the 1H NMR and 13C NMR spectra was performed using 1H-1H and 1H-13C COSEY NMR spectra. MS: EI = electron impact, ESI = electro spray ionization: MicroTof (Bruker Daltronics, Bremen), Calibration with sodium formate clusters before measurement. HPLC method for determination of the product purity: Merck Hitachi Equipment; UV detector: L-7400; autosampler: L-7200; pump: L-7100; degasser: L-7614; Method: column: LiChrospher® 60 RP-select B (5 μm), 250-4 mm cartridge; flow rate: 1.00 mL/min; injection volume: 5.0 μL; detection at λ = 210 nm; solvents: A: water with 0.05 % (v/v) trifluoroacetic acid; B: acetonitrile with 0.05 % (v/v) trifluoroacetic acid: gradient elution: (A %): 0-4 min: 90 % , 4-29 min: gradient from 90 % to 0 %, 29-31 min: 0 %, 31-31.5 min: gradient from 0 % to 90 %, 31.5-40 min: 90 %. CD spectra were recorded on a Jasco J-815 spectropolarimeter in CH_3OH, H_2O and CH_3CN at a sample concentration of 0.1mg/mL using a 0.1 cm quartz cuvette. Chiral HPLC: Equipment; Pump: L-6200; injection: Rheodyne 7125i; Diode-Array-Detector: L-7455; data acquisition: HSM software (all except Rheodyne 7125i

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Merck Hitachi); Column: Chiralpak® AD-H (5 µM, 250-4.6 mm); Injection: volume: 5.0 µL; Detection: wavelength: 223 nm; Solvent: isohexane : MeOH = 90 : 10; Flow rate: 1.0 mL/min.

General procedure A: Synthesis of enantiomerically pure sulfinamides 8 and 12

Under N_2 phenol **4**[9] or methyl ether **5**[9] (1 equiv.) was dissolved in dry THF (10 mL). The enantiomerically pure 2-methylpropane-2-sulfinamide (*S*)-**6** or (*R*)-**6** (1.2 equiv.) and $Ti(OEt)_4$ (1.5 equiv.) were added and the reaction mixture was heated to reflux for 12 h. The reaction mixture was cooled to 0 °C. Then $NaBH_4$ (1.6 equiv.) was added and the reaction mixture was stirred at rt for 3 h. Water was added and the reaction mixture was extracted with ethyl acetate (3 x 150 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuum. The formed diastereomers were separated by fc.

(*S*)-N-[(*R*)-1-(7-Methoxy-2,2-dimethyl-2*H*-chromen-6-yl)ethyl]-2-methylpropane-2-sulfinamide ((*S,R*)-8) and (*S*)-N-[(*S*)-1-(7-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)ethyl]-2-methylpropane-2-sulfinamide ((*S,S*)-8)

According to general procedure A methyl ether **5** (250 mg, 1.06 mmol) was reacted with (*S*)-(-)-2-methylpropane-2-sulfinamide ((*S*)-**6**, 143 mg, 1.30 mmol) and $NaBH_4$ (61 mg, 1.62 mmol). The diastereomeric mixture was purified by fc (petroleum ether/EtOAc = 70/30, ø = 2.5 cm, h = 15 cm,).

(*S,R*)-**8** (R_f = 0.27): Colorless oil, yield, 210 mg, (57 %). Purity: 98.2 %, (t_R = 18.7 min). $[\alpha]^{23}_D$ = +38.2 (c = 0.10, $CHCl_3$). Exact mass (ESI): *m/z* = calcd. for $(C_{18}H_{27}NO_3S)H$ 338.1712, found 338.1716. ^1H NMR ($CDCl_3$): δ (ppm) = 1.14 (s, 9H, 3xCH_3), 1.36 (s, 6H, 2xCH_3), 1.37 (d, J = 6.7 Hz, 3H, HNCHC*H*$_3$), 3.61 (d, J = 4.8 Hz, 1H, t-butySON*H*), 3.72 (s, 3H, OCH_3), 4.66 (qd, J

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= 6.7, 4.8 Hz, HNC*H*CH_3), 5.39 (d, J = 9.8 Hz, 1H, 3-CH), 6.18 (d, J = 9.8 Hz, 1H, 4-CH), 6.28 (s, 1H, 8-CH), 6.82 (s, 1H, 5-CH). ^{13}C NMR ($CDCl_3$): δ (ppm) = 21.7 (1C, HNCH*C*H_3), 22.6 (3C, 3xCH_3), 28.2, 28.1 (2C, CH_3), 48.9 (1C, NH*C*HCH$_3$), 55.3 (1C, NHSO*C*$(CH_3)_3$), 55.5 (1C, OCH_3), 76.5 (1C, C-2), 99.8 (1C, C-8), 113.7 (1C, C-4a), 121.8 (1C, C-4), 124.3, 124.5(2C, C-3, C-5), 127.7 (1C, C-6), 153.3, 157.3 (2C, C-7, C-8a).

(*S,S*)-**8** (R_f = 0.25): Colorless oil, yield, 18 mg (5 %), Purity: 96.1 %, (t_R = 19.2 min). Exact mass (ESI): *m/z* = calcd. for ($C_{18}H_{27}NO_3S$)H 338.1712, found 338.1714. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.13 (s, 9H, 3xCH_3), 1.37 (s, 6H, 2xCH_3), 1.38 (d, J = 6.7 Hz, 3H, HNCHC*H*$_3$), 3.62 (d, J = 4.8 Hz, 1H, t-butySON*H*), 3.71 (s, 3H, OCH_3), 4.67 (qd, J = 6.7, 4.8 Hz, HNC*H*CH_3), 5.38 (d, J = 9.8 Hz, 1H, 3-CH), 6.17 (d, J = 9.8 Hz, 1H, 4-CH), 6.29 (s, 1H, 8-CH), 6.80 (s, 1H, 5-CH).

(*R*)-N-[(*S*)-1-(7-Methoxy-2,2-dimethyl-2*H*-chromen-6-yl)ethyl]-2-methylpropane-2-sulfinamide (*R,S*)-8 and (*R*)-N-[(*R*)-1-(7-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)ethyl]-2-methylpropane-2-sulfinamide (*R,R*)-8

According to general procedure A methyl ether **5** (250 mg, 1.06 mmol) was reacted with (*R*)-(+)-2-methylpropane-2-sulfinamide ((*R*)-**6**, 143 mg, 1.30 mmol) and $NaBH_4$ (61 mg, 1.62 mmol). The diastereomeric mixture was purified by fc (petroleum ether/EtOAc = 70/30, ø = 2.5 cm, h = 15 cm,).

(*R,S*)-**8** (R_f = 0.28): Colorless oil, yield, 200 mg, (55 %). Purity: 96.5 %, (t_R = 17.6 min). $[\alpha]^{23}_D$ = -38.5 (c = 0.10, $CHCl_3$). Exact mass (ESI): *m/z* = calcd. for ($C_{18}H_{27}NO_3S$)H 338.1712, found 338.1718. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.14 (s, 9H, 3xCH_3), 1.36 (s, 6H, 2xCH_3), 1.37 (d, J = 6.7 Hz, 3H, HNCHC*H*$_3$), 3.59 (d, J = 4.8 Hz, 1H, t-butySON*H*), 3.72 (s, 3H, OCH_3), 4.69 (qd, J = 6.7, 4.8 Hz, HNC*H*CH_3), 5.39 (d, J = 9.8 Hz, 1H, 3-CH), 6.18 (d, J = 9.8 Hz, 1H, 4-CH), 6.28

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(s, 1H, 8-CH), 6.81 (s, 1H, 5-CH). ^{13}C NMR ($CDCl_3$): δ (ppm) = 21.7 (1C, HNCH*C*H_3), 22.6 (3C, 3xCH_3), 28.0, 28.1 (2C, CH_3), 48.7 (1C, NH*C*HCH$_3$), 55.3 (1C, NHSO*C*$(CH_3)_3$), 55.5 (1C, OCH_3), 76.5 (1C, C-2), 99.8 (1C, C-8), 113.7 (1C, C-4a), 121.8 (1C, C-4), 124.3, 124.5(2C, C-3, C-5), 127.7 (1C, C-6), 153.3, 157.3 (2C, C-7, C-8a).

(*R,R*)-**8** (R_f = 0.26): Colorless oil, yield, 8 mg (2.2 %). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.13 (s, 9H, 3xCH_3), 1.37 (s, 6H, 2xCH_3), 1.37 (d, J = 6.7 Hz, 3H, HNCHC*H*$_3$), 3.59 (d, J = 4.8 Hz, 1H, t-butySON*H*), 3.72 (s, 3H, OCH_3), 4.57 (qd, J = 6.7, 4.8 Hz, HNC*H*CH_3), 5.36 (d, J = 9.8 Hz, 1H, 3-CH), 6.17 (d, J = 9.8 Hz, 1H, 4-CH), 6.26 (s, 1H, 8-CH), 6.78 (s, 1H, 5-CH).

(*R*)-N-Benzyl-1-(7-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)ethanamine ((*R*)-1)

Under N_2 sulfinamide (*S,R*)-**8** (200 mg, 0.59 mmol) was dissolved in Et_2O (5 mL), 2.0 M MeOH:HCl (5 mL) was added and the reaction mixture was stirred for 3 h. The reaction mixture was concentrated in vacuum and the residue ((*R*)-**9**) was dissolved in dry THF (5 mL). Benzaldehyde (63 mg, 0.59 mmol) and $NaBH(OAc)_3$ (186 mg, 0.89 mmol) were added and the reaction mixture was stirred at rt for 5 h. Water was added and the mixture was extracted with EtOAc (3 x 100 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuum and the residue was purified by fc (dichloromethane/MeOH = 95/5, ø = 2.5 cm, h = 15 cm, R_f = 0.26). Colorless oil, yield, 70 mg, (37 %). Purity: 97 % (t_R = 19.2 min). $[\alpha]^{23}_D$ = +40.6 (c = 0.10, $CHCl_3$). Exact mass (ESI): *m/z* = calcd. for $(C_{21}H_{25}NO_2)$H 324.1885, found 324.11892. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.27 (d, J = 6.7 Hz, 3H, HNCHC*H*$_3$), 1.35 (s, 6H, 2xCH_3), 1.94 (bs, 1H, NH), 3.53 (d, J = 13.0 Hz, 1H, PhC*H*$_2$NH), 3.58 (d, J = 13.0 Hz, 1H, PhC*H*$_2$NH), 3.69 (s, 3H, OCH_3), 3.97 (q, J = 6.7 Hz, HNC*H*CH_3), 5.38 (d, J = 9.8 Hz, 1H, 3-CH), 6.21 (d, J = 9.8 Hz, 1H, 4-CH), 6.29 (s, 1H, 8-CH), 6.89 (s, 1H, 5-CH), 7.29 – 7.10 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ

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(ppm) = 22.3 (1C, HNCH*C*H_3), 28.1 (2C, CH_3), 51.6 (1C, HN*C*HCH$_3$, 51.8 (1C, HN*C*H_2Ph), 55.4 (1C, OCH_3), 76.4 (1C, C-2), 99.8 (1C, C-8), 113.8 (1C, C-4a), 122.1 (1C, C-4), 125.0, 125.2 (2C, C-3, C-5), 126.7 (1C, C-6), 127.5 (1C, Ph), 128.2 (2C, o-Ph), 128.3 (2C, m-Ph), 140.8 (1C, Ph), 152.7, 157.8 (2C, C-7, C-8a).

(*S*)-N-Benzyl-1-(7-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)ethanamine ((*S*)-1)

Under N_2 sulfinamide (*R,S*)-**8** (200 mg, 0.59 mmol) was dissolved in Et_2O (5 mL), 2.0 M MeOH:HCl (5 mL) was added and the reaction mixture was stirred for 3 h. The reaction mixture was concentrated in vacuum and the residue ((*S*)-**9**) was dissolved in dry THF (5 mL). Benzaldehyde (63 mg, 0.59 mmol) and $NaBH(OAc)_3$ (186 mg, 0.89 mmol) were added and the reaction mixture was stirred at rt for 5 h. Water was added to reaction mixture and extracted with EtOAc (3x100 mL). The organic layer was dried (Na_2SO_4), and concentrated in vacuum and the residue was purified by fc (dichloromethane/MeOH = 95/5, ø = 2.5 cm, h = 15 cm, R_f = 0.27). Colorless oil, yield, 65 mg, (34 %). Purity: 97 % (t_R = 19.5 min). $[\alpha]^{23}_D$ = -40.9 (c = 0.10, $CHCl_3$). Exact mass (ESI): *m/z* = calcd. for ($C_{21}H_{25}NO_2$)H 324.1885, found 324.1891. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.27 (d, J = 6.7 Hz, 3H, NHCHC*H*$_3$), 1.36 (s, 6H, 2xCH_3), 1.77 (bs, 1H, NH), 3.53 (d, J = 13.0 Hz, 1H, PhC*H*$_2$NH), 3.59 (d, J = 13.0 Hz, 1H, PhC*H*$_2$NH), 3.70 (s, 3H, OCH_3), 3.98 (q, J = 6.7 Hz, HNC*H*CH_3), 5.39 (d, J = 9.8 Hz, 1H, 3-CH), 6.21 (d, J = 9.8 Hz, 1H, 4-CH), 6.29 (s, 1H, 8-CH), 6.90 (s, 1H, 5-CH), 7.18 – 7.26 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ (ppm) = 22.3 (1C, HNCH*C*H_3), 28.1 (2C, CH_3), 51.6 (1C, HN*C*HCH$_3$), 51.8 (1C, HN*C*H_2Ph), 55.3 (1C, OCH_3), 76.4 (1C, C-2), 99.5 (1C, C-8), 113.7 (1C, C-4a), 122.0 (1C, C-4), 125.0, 125.1 (2C, C-3, C-5), 126.7 (1C, C-6), 127.5 (1C, Ph), 128.1 (2C, o-Ph), 128.3 (2C, m-Ph), 140.9 (1C, Ph) 152.6, 157.9 (2C, C-7, C-8a).

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(*R*)-N-Benzyl-1-(7-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)-N-methylethanamine ((*R*)-10)

Benzylamine (*R*)-**1** (50 mg, 0.15 mmol), was dissolved in THF (5 mL), formaline (5.0 mg, 0.17 mmol) and $NaBH(OAc)_3$ (48 mg, 0.23 mmol) were added and the reaction mixture was stirred for 2 h at rt. Water was added and reaction mixture was extracted with EtOAc (3x25 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuum and the residue was purified by fc (dichloromethane/MeOH = 90/10, ø = 2.5 cm, h = 15 cm, R_f = 0.24). Pale yellow oil, yield 35 mg, (69 %). Purity: 96 %, (t_R = 18.7 min.). $[\alpha]^{27}_D$ = +42.1 (c = 0.10, $CHCl_3$). Exact mass (ESI): *m/z* = calcd. for $(C_{22}H_{27}NO_2)H$ 338.2042, found 338.2047. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.34 (d, J = 6.7 Hz, 3H, NCHC*H*$_3$), 1.43 (s, 6H, 2xCH_3), 2.12 (s, 3H, $PhCH_2NCH_3$), 3.26 (d, J = 13.0 Hz, 1H, $PhCH_2NCH_3$), 3.61 (d, J = 13.0 Hz, 1H, $PhCH_2NCH_3$), 3.77 (s, 3H, OCH_3), 4.01 (q, J = 6.8 Hz, $NCHCH_3$), 5.46 (d, J = 9.8 Hz, 1H, 3-CH), 6.31 (d, J = 9.8 Hz, 1H, 4-CH), 6.36 (s, 1H, 8-CH), 7.11 (s, 1H, 5-CH), 7.22 – 7.37 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ (ppm) = 19.8 (1C, $NCHCH_3$), 28.3, 28.4 (2C, CH_3), 38.7 (1C, $PhCH_2NCH_3$) 55.4 (1C, $NCHCH_3$), 55.7 (1C, $PhCH_2NCH_3$), 59.5 (1C, OCH_3), 76.5 (1C, C-2), 99.7 (1C, C-8), 113.9 (1C, C-4a), 122.5 (1C, C-4), 124.8, 125.8 (2C, C-3, C-5), 126.3 (1C, Ph), 126.8 (1C, C-6), 128.3 (2C, o-Ph), 129.1 (2C, m-Ph), 140.6 (1C, Ph) 152.8, 158.1 (2C, C-7, C-8a).

(*S*)-N-Benzyl-1-(7-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)-N-methylethanamine ((*S*)-10)

Sulfinamide (*S*)-**1** (50 mg, 0.15 mmol), was dissolved in THF (5 mL), formaline (5.0 mg, 0.17 mmol) and $NaBH(OAc)_3$ (48 mg, 0.23 mmol) were added and the reaction mixture was stirred for 2 h at rt. Water was added and reaction mixture was extracted with EtOAc (3x25 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuum and the residue was purified by fc

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(dichloromethane/MeOH = 90/10, ø = 2.5 cm, h = 15 cm, R_f = 0.24). Pale yellow oil, yield 28 mg, (55 %). Purity: 95.2%, (t_R = 18.7 min.). $\alpha]^{27}_D$ = - 41.9 (c = 0.10, $CHCl_3$). Exact mass (ESI): *m/z* = calcd. for $(C_{22}H_{27}NO_2)H$ 338.2042, found 338.2043. ^{1}H NMR and ^{13}C NMR data are identical with the data of its enantiomer (*R*)-**10**.

(*S*)-N-[(*R*)-1-(7-Hydroxy-2,2-dimethyl-2*H*-chromen-6-yl)ethyl]-2-methylpropane-2-sulfinamide ((*S,R*)-12) and (*S*)-N-[(S)-1-(7-hydroxy-2,2-dimethyl-2*H*-chromen-6-yl)ethyl]-2-methylpropane-2-sulfinamide ((*S,S*)-12)

According to general procedure A phenol **4** (300 mg, 1.38 mmol) was reacted with *S*-(-)-2-methylpropane-2-sulfinamide ((*S*)-**6**, 140 mg, 1.66 mmol) and $Ti(OEt)_4$ (472 mg, 2.07 mmol). The diastereomers were separated by fc (petroleum ether/EtOAc = 80/20, ø = 1.5 cm, h = 10 cm).

(*S,R*)-**12** (R_f = 0.32): Colorless oil, yield 125 mg (28 %). Purity: 95.1 %, (t_R = 14.2 min.). $[\alpha]^{23}_D$ = +24.6 (c = 0.10, $CHCl_3$). Exact mass (ESI): *m/z* = calcd. for $(C_{17}H_{25}NO_3S)H$ 324.1555, found 324.1547. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.24 (s, 9H, 3xCH_3), 1.38 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.55 (d, J = 6.8 Hz, 3H, HNCHC*H*$_3$), 3.62 (s, OH), 4.55 (q, J = 6.8 Hz, HNC*H*CH_3), 5.44 (d, J = 9.8 Hz, 1H, 3-CH), 6.22 (d, J = 9.8 Hz, 1H, 4-CH), 6.37 (s, 1H, 8-CH), 6.74 (s, 1H, 5-CH), 8.36 (bs, 1H, SON*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 20.7 (1C, NCH*C*H_3), 22.8 (3C, 3xCH_3), 28.2, 28.3 (2C, CH_3), 51.7 (1C, HN*C*HCH_3), 55.8 (1C, NHSO*C*$(CH_3)_3$), 76.4 (1C, C-2), 105.6 (1C, C-8), 113.9 (1C, C-4a), 120.9 (1C, C-4), 122.1, 124.9 (2C, C-3, C-5), 128.0 (1C, C-6), 155.2, 156.7 (2C, C-7, C-8a).

(*S,S*)-**12** (R_f = 0.30): Colorless oil, yield 120 mg (27 %). Purity: 94.2 %, (t_R = 13.6 min.). $[\alpha]^{23}_D$ = -23.5 (c = 0.10, $CHCl_3$). Exact mass (ESI): *m/z* = calcd. for $(C_{17}H_{25}NO_3S)H$ 324.1555, found

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324.1547. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.24 (s, 9H, 3xCH_3), 1.40 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.56 (d, J = 6.7 Hz, 3H, HNCHC*H*$_3$), 3.66 (s, OH), 4.58 (q, J = 6.7 Hz, HNC*H*CH_3), 5.46 (d, J = 9.8 Hz, 1H, 3-CH), 6.22 (d, J = 9.8 Hz, 1H, 4-CH), 6.32 (s, 1H, 8-CH), 6.72 (s, 1H, 5-CH), 7.88 (s, 1H, SON*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) = 20.7 (1C, NCH*C*H$_3$), 22.8 (3C, 3xCH_3), 28.2, 28.3 (2C, CH_3), 51.5 (1C, NH*C*HCH$_3$), 55.8 (1C, NHSO*C*$(CH_3)_3$), 76.4 (1C, C-2), 105.6 (1C, C-8), 113.9 (1C, C-4a), 120.9 (1C, C-4), 122.1, 124.9 (2C, C-3, C-5), 128.0 (1C, C-6), 154.1, 156.2 (2C, C-7, C-8a).

(*R*)-6-[1-(Benzylamino)ethyl]-2,2-dimethyl-2*H*-chromen-7-ol ((*R*)-2)

Sulfinamide (*S,R*)-**12** (150 mg, 0.46 mmol) was dissolved in dry Et_2O (5 mL), 2M Et_2O:HCl solution (5 mL) was added and the mixture was stirred for 2 h. The mixture was concentrated in vacuum and the residue ((*R*)-**13**) was dissolved in dry THF (5 mL). Benzaldehyde (54 mg, 0.51 mmol) and $NaBH(OAc)_3$ (146 mg, 0.69 mmol) were added and reaction mixture was stirred at rt for 3 h. Water was added and the reaction mixture was extracted with EtOAc (3x100 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuum and the residue was purified by fc (petroleum ether/EtOAc = 70/30, ø = 1.5 cm, h = 15 cm, R_f = 0.26). Colorless oil, yield 45 mg (32 %). Purity: 95.2 %, (t_R = 18.2 min.). $[\alpha]^{23}_D$ = + 4.5 (c = 0.10, $CHCl_3$). Exact mass (ESI): *m/z* = calcd. for ($C_{20}H_{23}NO_2$)H 310.4021, found 310.4029. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.34 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.37 (d, J = 6.7 Hz, 3H, HNCHC*H*$_3$), 3.59 (d, J = 12.9 Hz, 1H, HNC*H*$_2$Ph), 3.77 (d, J = 12.9 Hz, 1H, HNC*H*$_2$Ph), 3.84 (q, J = 6.7 Hz, NHC*H*CH_3), 5.36 (d, J = 9.8 Hz, 1H, 3-CH), 6.15 (d, J = 9.8 Hz, 1H, 4-CH), 6.26 (s, 1H, 8-CH), 6.49 (s, 1H, 5-CH), 7.29 – 7.16 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ (ppm) = 22.6 (1C, HNCH*C*H$_3$), 28.4, 28.3 (2C, CH_3), 51.5 (1C, HN*C*HCH$_3$), 57.9 (1C, HN*C*H$_2$Ph), 76.4 (1C, C-2), 105.1 (1C, C-8), 113.6 (1C, C-4a),

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118.5 (1C, Ph), 122.1 (1C, C-4), 126.1, 127.6 (2C, C-3, C-5), 127.8 (1C, C-6), 128.7 (2C, o-Ph), 128.9 (2C, m-Ph), 138.4 (1C, Ph), 153.8, 158.5 (2C, C-7, C-8a).

(*S*)-6-[1-(Benzylamino)ethyl]-2,2-dimethyl-2*H*-chromen-7-ol ((*S*)-2)

Sulfinamide (*S,S*)-**12** (150 mg, 0.46 mmol) was dissolved in dry Et_2O (5 mL), 2M Et_2O:HCl solution (5 mL) was added and the mixture was stirred for 2 h at rt. The mixture was concentrated in vacuum and residue ((*S*)-**13**) was dissolved in dry THF (5 mL). Benzaldehyde (54 mg, 0.51 mmol) and $NaBH(OAc)_3$ (146 mg, 0.69 mmol) were added and mixture was stirred at rt for 3 h. Water was added and the mixture was extracted with EtOAc (3x100 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuum and the residue was purified by fc (petroleum ether/EtOAc = 70/30, ø = 1.5 cm, h = 15 cm, R_f = 0.27). Colorless oil, yield 30 mg (21 %). Purity: 96.2 %, (t_R = 18.5 min.). $[\alpha]^{23}_D$ = - 5.2 (c = 0.10, $CHCl_3$). Exact mass (ESI): *m/z* = calcd. for $(C_{20}H_{23}NO_2)H$ 310.4021, found 310.4029. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.34 (s, 6H, CH_3), 1.48 (d, J = 6.7 Hz, 3H, HNCHC*H*$_3$), 3.59 (d, J = 13.0 Hz, 1H, HNC*H*$_2$Ph), 3.78 (d, J = 13.0 Hz, 1H, HNC*H*$_2$Ph), 3.83 (q, J = 6.7 Hz, HNC*H*CH_3), 5.36 (d, J = 9.8 Hz, 1H, 3-CH), 6.16 (d, J = 9.8 Hz, 1H, 4-CH), 6.26 (s, 1H, 8-CH), 6.49 (s, 1H, 5-CH), 7.29 – 7.16 (m, 5H, Ph).

Investigation of the antiprotozoal activity

In vitro assays for activity against *Trypanosoma brucei rhodesiense* (bloodstream trypomastigote stage, STIB 900 strain) and *Plasmodium falciparum* (erythrocytic stage, K1 or NF54 (compounds (*R*)-**2** and (*S*)-**2**) strain) as well as cytotoxicity determinations against L6 rat skeletal myoblasts were carried out at the Swiss Tropical and Public Health Institute according to established standard protocols described earlier.[13] Compounds used as positive controls were of

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commercial origin, with the exception of melarsoprol, which was a gift from WHO. Their purity (generally >95%) was specified by the manufacturers.

Acknowledgement

This work was done within the framework of the NRW International Graduate School of Chemistry, Münster, which is funded by the Government of the state Nordrhein-Westfalen and Westfälische Wilhelms-University Münster. The financial support is deeply acknowledged. The biological part of this study is an activity of the Research Network Natural Products against Neglected Diseases (ResNet NPND, http://www.uni-muenster.de/ResNetNPND)

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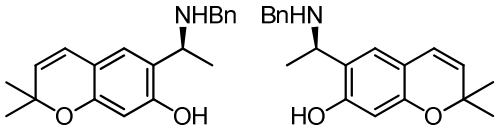
Graphical Abstract

(*S*)-**2**
antimalarial activity
IC_{50} = 0.884 μM



(*R*)-**2**
antimalarial activity
IC_{50} = 0.025 μM

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