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Original article

QSAR guided synthesis of simplified antiplasmodial analogs of naphthylisoquinoline alkaloids

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Dedicated to Prof. Karlheinz Drauz on the occasion of his 60th birthday.

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ABSTRACT

Naphthylisoquinoline alkaloids have attracted considerable interest because of their intriguing structure, their unique biosynthetic origin, and their biological activities against several pathogens causing tropical diseases. Their promising pharmacologic properties make them suitable lead structures for new agents, in particular against malaria. Since these natural products are not easy to isolate in sufficient quantities or to synthesize stereoselectively, quantitative structure–activity relationship studies were accomplished to find new antiplasmodial analogs that are structurally related to the naturally occurring naphthylisoquinoline alkaloids, but more easily accessible, more active against *Plasmodium falciparum*, and, last but not least, less toxic. We report on the synthesis of several simplified compounds by a Suzuki coupling between the naphthalene and the isoquinoline moieties and on their activities against different pathogens causing infectious diseases. Some structures were found to exhibit excellent – and selective – activities against *P. falciparum* in vitro.

1. Introduction

In spite of all recent efforts to find new potential drugs, infectious diseases are still the number one reason for mortality worldwide [1]. During the past years many vector-borne diseases like leishmaniasis, dengue fever, and malaria emerged in new areas or re-emerged in areas affected previously [1]. With a number of over 300 million infected people and about one million of lethal cases per year malaria is still the most fatal tropical disease [2]. The increasing resistance of *P. falciparum* against traditional antimalarial drugs like chloroquine or the antifolates makes the development of new, highly efficient, and easily available agents an urgent task.

Promising new lead structures for the design potent novel substances originate from tropical Dioncophyllaceae and Ancistrocladaceae plants, which are the only known producers of the naphthylisoquinoline alkaloids [3,4]. These secondary metabolites differ from all other isoquinoline alkaloids by their acetogenic origin [5,6], and they feature manifold pharmacological properties [7–10]. Some of these biaryl alkaloids exhibit excellent activities against pathogens causing different tropical infectious diseases. The *N,C*-coupled representatives of the naphthylisoquinoline alkaloids, like, e.g. ancistrocladinium A (**1**), as recently isolated by our group [11], and their synthetic derivatives have proven to be highly active against the pathogens causing leishmaniasis, trypanosomiasis or malaria (see Fig. 1) [12–15]. Some C,C-linked naphthylisoquinolines, among them e.g. dioncophylline C (**2**, 0.01 μM) and dioncopeltine A (**3**, 0.02 μM), show interesting in vitro and even in vivo activities against *P. falciparum* [7,16,17]. These and other promising bioactivities make the naphthylisoquinoline alkaloids suitable pharmaceutical lead structures for the synthesis of new potent agents [18,19].

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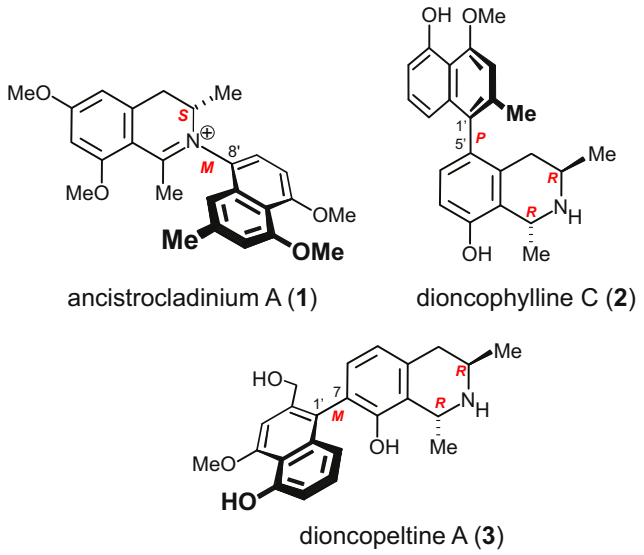


Fig. 1. Ancistrocladinium A (**1**), dioncophylline C (**2**), and dioncopeltine A (**3**), naphthylisoquinoline alkaloids with remarkable biological activities.

Naphthylisoquinoline alkaloid-producing plants are rare and difficult to cultivate [20] and the stereoselective synthesis of the active compounds is quite complex. Although elegant pathways to obtain this class of compounds have already been developed [21–38] the synthesis of structurally simplified derivatives with further improved antiplasmodial activities and a better accessibility was worthwhile. Therefore, extensive (Q)SAR studies based on the data of over 40 naphthylisoquinoline alkaloids were accomplished [39,40].

We have recently published the synthesis of simplified derivatives that show significant antiprotozoal activities, especially against the pathogens of malaria and trypanosomiasis [41]. In this paper we report on the synthesis of structurally modified naphthyl- and phenylisoquinolines with systematically altered functional groups that can provide exact information about the pharmacologically essential structural parameters and an improved activity against *P. falciparum* in comparison to derivatives of anti-infective naphthylisoquinolines alkaloids previously synthesized [41]. The target molecules of type **I** (see Fig. 2), which are derived from dioncophylline C (**2**), were chosen with respect to (Q)SAR studies. These investigations suggested that the structures should, on the one hand, have no oxygen substituent at C-6 of the isoquinoline subunit, since that should reduce the antiplasmodial activity [42], and, on the other hand, possess no methyl substituent at C-1 resulting in a better accessibility of the nitrogen to improve hydrogen bonding, and, thus, permit stronger interactions with the biological targets.

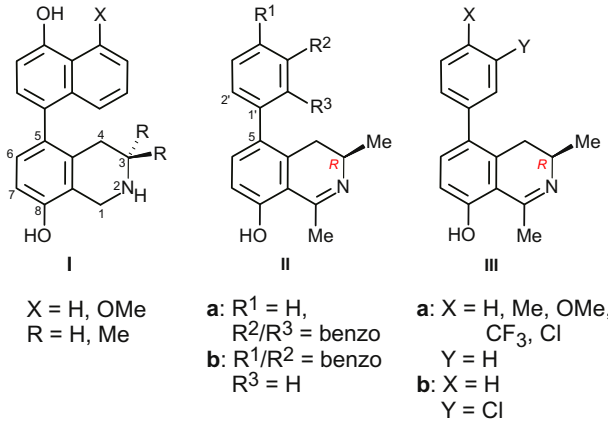


Fig. 2. Simplified achiral target compounds with systematically altered functional groups (type **I**) and some chiral derivatives (type **II**, **III**) of dioncophylline C (**2**).

For reasons of simplicity, the target structures of type **I** possess no stereogenic centers. The biaryl axis, a characteristic feature of the naphthylisoquinoline alkaloids, should be configurationally semistable [41], because of the lack of a substituent at C-6 of the isoquinoline moiety (in nature mostly OH or OMe) and the missing methyl group at C-2′ of the naphthalene part, which is present in all natural naphthylisoquinolines [3,16]. The conformational flexibility of the biaryl axis should favor flexible interactions between the target molecules and a potential protozoan target and, in addition, avoid the need for a directed, atropo-enantioselective synthesis.

Furthermore, a couple of chiral analogs (type **II**, **III**) were synthesized, with an *R*-configuration at C-3 and a free hydroxy group at C-8. Like the structures of type **I**, these compounds are also derived from dioncophylline C (**2**), but possess a dihydroisoquinoline subunit. The respective building block was coupled with several naphthyl- and arylboronic acids, thus permitting to investigate the influence of the northern part on the biological activity.

2. Results and discussion

2.1. Chemistry

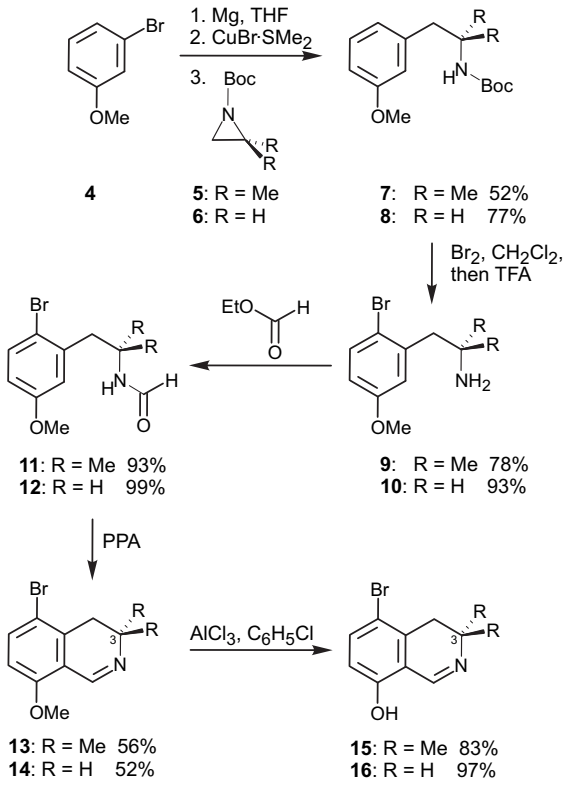
2.1.1. A general route to the achiral isoquinoline building blocks *15* and *16*

The isoquinoline building blocks were synthesized via a route first described by Hoye et al. and recently improved in our group [43,44]. The key step in this synthesis is the reaction of the cuprate of 3-bromoanisole (**4**) with *N*-activated aziridines, here **5** and **6**, which are available from 2-aminoethanol and 2-amino-2-methylpropan-1-ol by functionalization of the nitrogen and aziridine formation with tosyl chloride under basic conditions [45]. Although 3,3-dimethylisoquinolines can be prepared by Ritter reaction [41], this approach should not be applicable to the isoquinoline building block **16** bearing two hydrogen atoms at C-3. These strained heterocycles were then opened (regioselectively in the case of **5**) by the cuprate derived from 3-bromoanisol (**4**). The resulting carbamates **7** and **8** were regioselectively brominated at C-4, followed by removal of the *N*-Boc group in a one-pot reaction. N-formylation of the resulting amines **9** and **10** with ethyl formate, and Bischler–Napieralski cyclization gave both isoquinolines **13** and **14** in good overall yields. The introduced bromo substituent did not only deliver the halogen atom for the later coupling with the naphthalene building blocks, but also served as a directing group for the regioselective cyclization into the C-2 position. Final deprotection of **13** and **14** using aluminum trichloride at elevated temperature gave the achiral 8-hydroxyisoquinolines **15** and **16** (see Scheme 1).

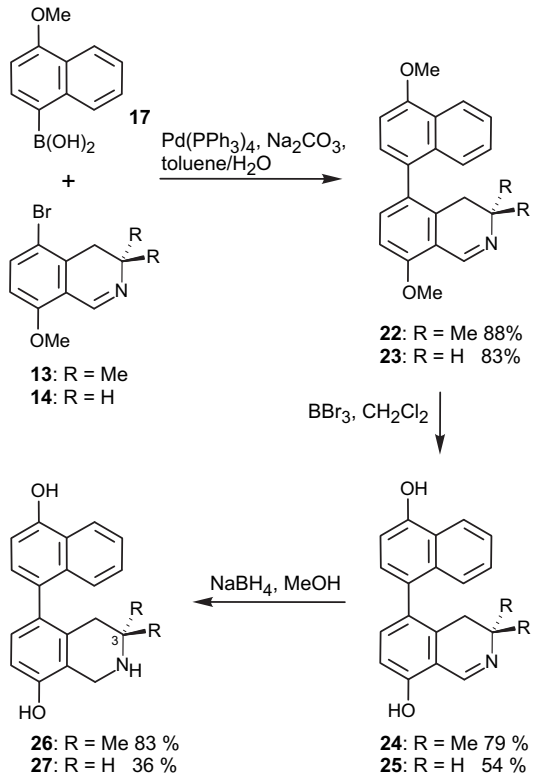
2.1.2. Synthesis of the boronic acid *17* and the boronic acid ester *21*

The naphthylboronic acid **17** was obtained from 1-methoxynaphthalene by *para*-selective bromination [46], and conversion to the desired product with *n*BuLi and $B(OMe)_3$ [47].

The naphthylboronic acid ester **21**, as required for the investigation of the influence of a second oxygen substituent on the biological activity, was obtained from commercially available 1,8-naphthosultone. Following a protocol by Erdmann [48], the diol **18** was obtained in satisfying yield. Mono-*O*-isopropylation and acylation of the remaining phenolic group under standard conditions gave naphthalene **19**, which was regioselectively brominated to afford **20** in quantitative yield after ester saponification (see Scheme 2). O-Methylation yielded the respective ether, which was



Scheme 1. Synthetic route to 5-bromo-8-hydroxyisoquinolines **15** and **16**.

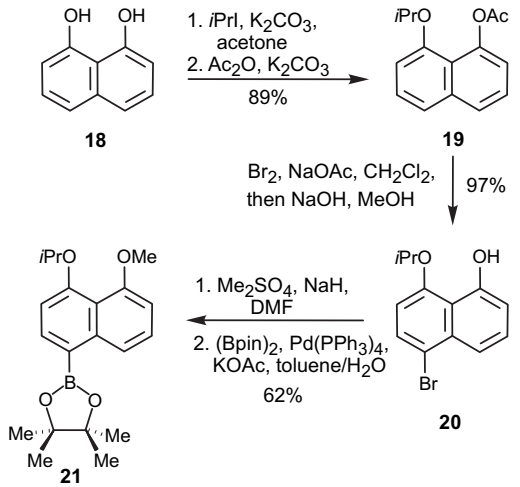


Scheme 3. Synthesis of the naphthyltetrahydroisoquinolines **26** and **27**.

converted into the boronic acid ester **21** by Miyaura borylation [49]. The reaction sequence from 1,8-naphthosultone to **21** in six steps was attained in an excellent overall yield of 40%.

*2.1.3. Synthesis of naphthyltetrahydroisoquinolines of type **I***

The biaryl coupling of the 8-methoxyisoquinoline **13** and the boronic acid **17** was attained with $Pd(PPh_3)_4$ and Na_2CO_3 in a toluene/water-mixture. Deprotection of the biaryl **22** with boron tribromide and reduction with sodium borohydride gave the naphthyldihydroisoquinoline **26**. Starting from isoquinoline **14** the same reaction sequence was successfully applied to the synthesis of the 3-unsubstituted analog **27** (see Scheme 3).



Scheme 2. Synthesis of the naphthylboronic acid ester **21** from 1,8-naphthosultone (**18**).

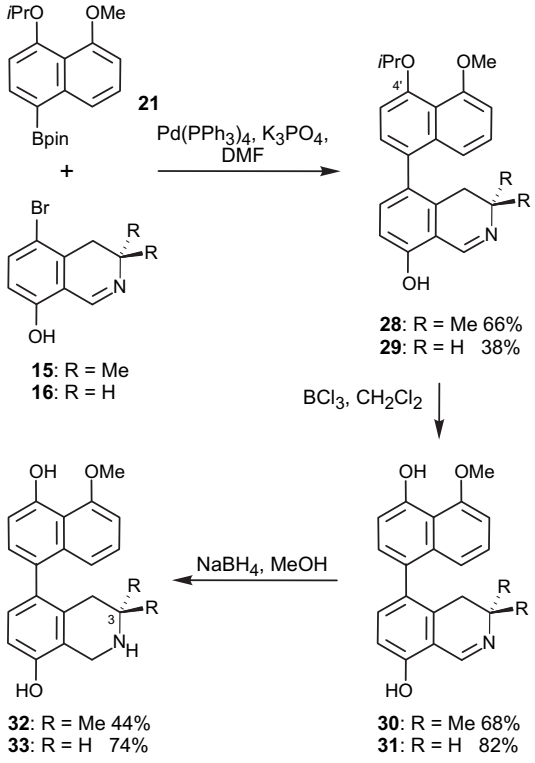
By using a slightly different route, the target compounds **32** and **33** were obtained: to circumvent regioselectivity problems in the required selective deprotection step of the oxygen function at C-4′ in the naphthalene subunit, the isoquinoline portions were used in a free, hydroxylated form (**15** and **16**) as the coupling partners in the Suzuki reaction with the pinacol ester **21** (see Scheme 4). In this case the reaction in DMF with potassium phosphate gave better results than the conditions used before. Cleavage of the isopropyl ether with boron trichloride and reduction of the naphthyldihydroisoquinolines gave the desired target compounds **32** and **33**.

*2.1.4. Synthesis of aryl- and naphthyldihydroisoquinolines of type **II** and **III***

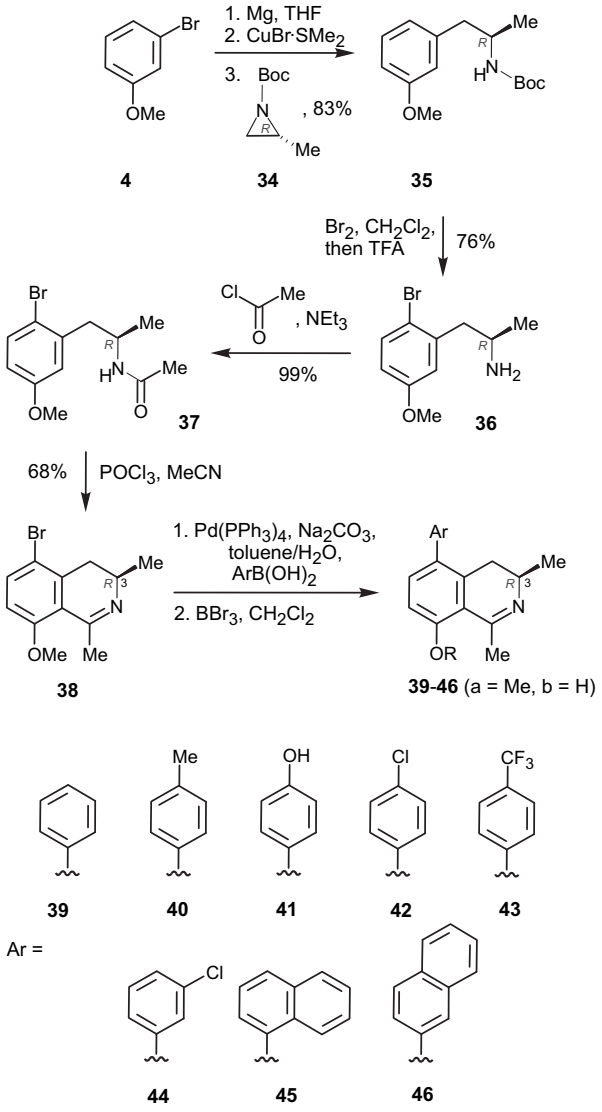
The isoquinoline building block **38** bearing an *R*-configuration at C-3, as in the lead structure dioncophylline C (**2**), was also synthesized via the aziridine route mentioned before, here only requiring seven steps. Ring opening of the aziridine **34** with the cuprate of **4** gave the carbamate **35**, which was regioselectively brominated, followed by cleavage of the *N*-Boc group (see Scheme 5). Acylation and Bischler–Napieralski reaction yielded the desired isoquinoline **38**. This building block was submitted to a Suzuki–Miyaura coupling with several commercially available aryl- and naphthylboronic acids mostly possessing diverse electron-donating or -withdrawing substituents. In the last step of the synthesis the biaryl compounds were *O*-deprotected with boron tribromide, to give the corresponding structures **39b**–**46b** with a free hydroxy function at C-8.

2.2. Biology and QSAR studies

The target structures and their synthetic precursors were tested at the Swiss Tropical and Public Health Institute in Basel, and within



Scheme 4. Synthesis of the naphthyltetrahydroisoquinolines **32** and **33**.



Scheme 5. Synthesis of target structures of types **II** and **III**.

the Z1 project of the SFB 630 network in Würzburg for their bioactivities against *Leishmania donovani*, *Leishmania major*, *Trypanosoma brucei brucei*, *T. brucei rhodesiensis*, *Trypanosoma cruzi*, and *P. falciparum*.

The most potent compounds with respect to their activity against *P. falciparum* were the naphthyldihydroisoquinolines **28** ($IC_{50} = 0.138$ μM) and **29** ($IC_{50} = 0.119$ μM), the naphthyltetrahydroisoquinolines **32** ($IC_{50} = 0.223$ μM) and **33** ($IC_{50} = 0.264$ μM), and − surprisingly − the naphthalene-devoid dihydroisoquinoline **15** ($IC_{50} = 0.708$ μM) (see Table 1). Their activities were in the range of the value of chloroquine ($IC_{50} = 0.259$ μM), the reference drug against *P. falciparum*, but inferior relating cytotoxicity. The activity values of the *C*,*C*-coupled molecules were found to be higher than those of other structurally simplified naphthylisoquinolines we reported recently, by one order of magnitude [41], and, in particular, the selectivity indices of these five structures − i.e., the ratio of the cytotoxicities divided by the IC_{50} values of the anti-infective activities − were very high (between >141 and >725). Due to their simultaneous lack of activity against other protozoan pathogens causing infectious diseases(*T. brucei rhodesiense*, *T. cruzi*, *L. major*, and *L. donovani*) or L6 cells, all the molecules showed promising selectivities against the pathogen that causes malaria, a good precondition for potential anti-infective agents. It is noteworthy that all compounds exhibiting good antiplasmodial activities possess a free phenolic hydroxy function at C-8 of the isoquinoline moiety. Similar molecules with a methyl ether group at C-8 had previously shown a reduced antiplasmodial activity [41]. Apparently the antimalarial potency of the biaryl structures of type **I** profits from the presence of a two-fold oxygenated naphthalene portion. Both target structures **26** and **27** with only one *O*-function in the naphthalene subunit and also the corresponding precursors were not active against *P. falciparum* in the single-concentration tests and so no IC_{50} values were determined. A free hydroxy group at C-4′ of the northern portion, however, decreases the antiplasmodial activity.

The positive influence of a free hydroxy group at C-8 of the isoquinoline portion was also seen for the antiplasmodial activity of the aryl- and naphthylisoquinolines **39b**–**46b** (see Table 2). All of the precursors with an *O*-methylated hydroxy function (**39a**–**46a**) at this position show a drastically reduced activity against *P. falciparum*. Here, as seen for the molecules of type **I** (see above), a free hydroxy group at C-4′ of the northern portion has also a negative influence on the antimalarial activity. Furthermore, no unambiguous effect of the electron-donating or -withdrawing substituents of the aryl part was found.

A 3D-QSAR analysis using GRID/PLS [50] was carried out in order to quantify the influence of the structural changes. The resulting QSAR model showed sufficient predictivity with an R^2_{Test} of 0.69 ($RMSEP_{Test}$: 0.32). The computation of the statistical figures as well as the details of the analysis can be found in Methods section. The analysis immediately revealed the paramount influence of the substitution pattern at the 8-position of the isoquinoline ring. Moreover, it can be seen that the presence of an sp^3-hybridized nitrogen in the isoquinoline ring is advantageous. The same is true for a lipophilic substituent on the 4′-position (i.e.,

Table 1
In vitro activities of compounds of the type **I** series against *P. falciparum*, *T. cruzi*, *T. brucei rhodesiense*, *T. brucei brucei*, *L. major*, *L. donovani*, and L6 cells

Compound	IC_{50} (μM)							
	T. cruzi	*T. brucei rhodesiense*	*T. brucei brucei*	*L. donovani*	*L. major*	*P. falciparum*	Cytotoxicity (L6 cells)	Selectivity index
15	ina[h]	ina	>100	ina	>100	0.708	>100	>141
16	ina	ina	ina	ina	ina	1.239	>100	
22	ina	ina	30.40	1.954	37.25	2.399	43.79	
23	10.90	ina	26.30	ina	46.30	1.701	34.34	
25	ina	ina	ina	ina	ina	3.490	94.18	
28	ina	ina	ina	ina	ina	0.138	>100	>725
29	ina	ina	ina	ina	ina	0.119	27.00	227
30	ina	ina	34.14	ina	>100	1.701	>100	
31	ina	ina	ina	ina	ina	1.988	98.20	
32	ina	2.919	ina	ina	ina	0.223	37.51	168
33	ina	2.483	ina	ina	ina	0.264	40.23	152
Standard drugs	1.979[a]	0.007[b]	0.003[c]	0.351[d]	2.51[e]	0.259[f]	0.017[g]	

[a] Benznidazole.
[b] Melarsoprol.
[c] Pentamidin.
[d] Miltefosine.
[e] Amphotericine B.
[f] Chloroquine.
[g] Podophyllotoxin.
[h] ina = inactive in the medium-throughput assay and therefore not screened for IC_{50} value.

the free phenolic group is disadvantageous). In Fig. 3 these findings are shown as the back-projection (PLS regression coefficients times standard deviation of the respective grid point) of the O probe (H-bond acceptor). Apart from the aforementioned effect, no pronounced influence of the variations of the molecules in the northern ring was found.

Fig. 4 shows the residual plot for the computed model based on the predicted ensemble averages. Few less active molecules are predicted with large deviations while the more active molecules are predicted quite precisely. Those molecules that are flagged show residuals larger than 0.5 pIC_{50} units. The naphthalene-devoid isoquinoline **38** is predicted to be more active since the detrimental influence of the methylation in position 8 is underestimated by the model. Phenylisoquinolines **41a** and **41b** are predicted incorrectly since the O-methylation of position 8 has no influence on the biological data here while the model does not account for this special case (both molecules show the disadvantageous free phenolic group in the northern part of the molecule).

The values of the most promising candidates **40b**, **42b**, **43b**, and **44b** were – like those of the compounds of type **I** – still in the range of that of chloroquine (IC_{50} = 0.259 μM), and the activities (IC_{50} values between 0.437 μM and 0.532 μM) and therapeutic indices (152 to >229) were comparable to those of simplified naphthylisoquinolines synthesized previously [41]. Furthermore, the compounds were not active against any other pathogen or L6 cells and, thus, had a good selectivity for *P. falciparum*.

Table 2
In vitro activities of types **II** and **III** compounds against *P. falciparum*, *T. cruzi*, *T. brucei rhodesiense*, *T. brucei brucei*, *L. major*, *L. donovani*, and L6 cells.

Compound	IC50 (μM)							
	T. cruzi	*T. brucei rhodesiense*	*T. brucei brucei*	*L. donovani*	*L. major*	*P. falciparum*	Cytotoxicity (L6 cells)	Selectivity index
38	>100	>100	ina[h]	>100	ina	>18.87	>100	
39a	46.67	6.484	14.84	74.87	>100	1.877	58.84	
39b	57.12	4.737	13.42	>100	>100	0.820	52.22	
40a	19.29	5.83	20.20	35.54	>83	2.491	>100	
40b	39.34	7.123	32.00	52.00	>86	0.437	>100	>229
41a	25.52	4.773	ina	21.36	ina	10.83	>100	
41b	>100	53.49	ina	>100	ina	9.91	>100	
42a	15.04	7.805	ina	15.94	ina	6.437	56.70	
42b	ina	ina	>40	ina	>100	0.532	>100	>188
43a	>100	7.379	10.40	18.30	>100	2.997	>100	
43b	19.19	14.81	15.92	35.07	>100	0.460	96.76	210
44a	13.98	1.179	ina	13.00	ina	7.957	38.36	
44b	13.87	7.631	27.07	24.72	52.35	0.856	50.76	
45a	15.88	3.963	ina	14.39	ina	6.911	34.87	
45b	15.79	11.05	2.74	27.11	13.4	0.763	57.07	
46a	20.85	4.436	10.10	21.21	28.10	1.181	71.98	
46b	16.73	1.011	25.40	38.21	34.70	0.476	72.54	152
Standard drugs	1.979[a]	0.007[b]	0.003[c]	0.351[d]	2.51[e]	0.259[f]	0.017[g]	

[a] Benznidazole.
[b] Melarsoprol.
[c] Pentamidin.
[d] Miltefosine.
[e] Amphotericine B.
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[g] Podophyllotoxin.
[h] ina = inactive in the medium-throughput assay and therefore not screened for IC_{50} value.

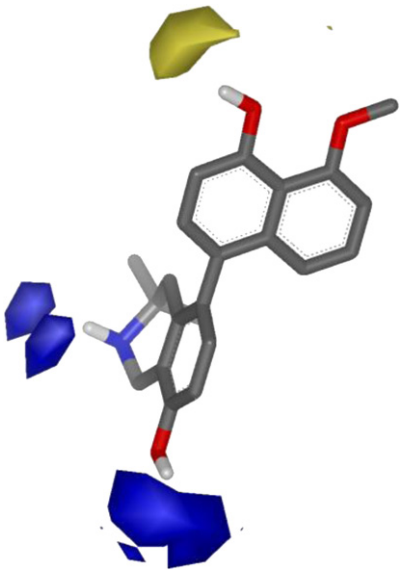

Fig. 3. Compound **32** with back-projection of the O probe (H-bond acceptor). Repulsive forces are displayed in yellow and attractive forces are shown in blue. Attractive areas clearly indicate that H-bond donors are advantageous at the nitrogen and at the 8-position of the isoquinoline scaffold while an H-bond donor in the C-4′ position of the northern part are disadvantageous. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

Due to their excellent in vitro activities and their promising selectivity indices five compounds of type **I**, namely **15**, **28**, **29**, **32**, **33**, and in addition, four structures of type **II, 40b**, **42b**, **43b**, **44b** appear potent enough for in vivo studies. Of these, compound **44b** was already tested in vivo in *Plasmodium berghei*-infected mice, showing a reduction of the parasitemia by 44% (4 day intraperitoneal application of 50 mg/kg/day). This first preliminary in vivo result seems quite promising since the majority of the suggested structures have even better in vitro activities than **44b**, so that higher activities may be expected.

3. Conclusion

A general route to simplified analogs of naphthylisoquinoline alkaloids with remarkable in vitro antiplasmodial activities was elaborated. New chiral and achiral isoquinoline building blocks were synthesized, by ring opening of protected aziridines as the key step. Suzuki–Miyaura coupling of the isoquinolines with the boronic acids or boronic esters of the aryl building blocks gave new biaryl structures, some of which showed excellent activity against *P. falciparum*. Furthermore, these compounds have good selectivity indices and a high selectivity for the pathogen that causes malaria, due to their significantly lower toxicity and activity against pathogens causing other infectious diseases. Remarkably all of the most active compounds have in common a phenolic OH function at C-8 of the isoquinoline moiety and, in the case of the type **I** series, benefit from a two-fold oxygenated naphthalene moiety in the northern subunit. Moreover, for all compounds the presence of an sp^3-hybridized nitrogen in the isoquinoline ring was beneficial, whereas a free phenolic group at C-4′ appeared to be disadvantageous. Apart from this, no pronounced influence of the variations of the molecules in the northern ring was found. The most promising compounds were almost as active as their natural precedents, but much more easily available, since most of them have no stereocenters and lack the phenomenon of axial chirality. Furthermore, the obtained biological data complement the existing SAR dataset and will thus contribute to the design of new (Q)SAR-derived target structures, as a more rational alternative to the mostly difficult total synthesis or isolation of the natural products. Studies on the in vivo antimalarial activities of the most active compounds and on the synthesis of further improved structures are currently in progress.

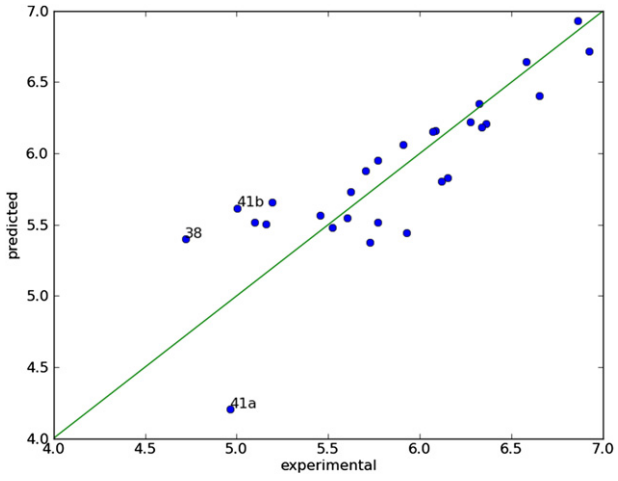

Fig. 4. Residual plot for the predictions (pIC_{50} values). It can be seen that the predictions for the more active molecules are precise while few less active molecules are flagged as unusual objects (residual > 0.5 pIC_{50}). For the discussion, see text.

4. Experimental

4.1. Instrumentations and chemicals

Melting points were measured with a Kofler melting point apparatus and are uncorrected. IR spectra were recorded with a Jasco FT/IR-410 spectrometer and are reported in wave numbers (cm^{-1}). NMR spectra were taken either with a Bruker AC 250, a Bruker AV 400 or a Bruker DMX 600 at ambient temperature. The chemical shifts δ are given on the ppm scale while taking the signals of the deuterated solvents as internal reference for ^1H and ^{13}C NMR spectroscopy; the coupling constants J are given in Hertz (Hz). Elemental analyses were performed on an Elementar vario MICRO cube elemental analyzer at the Institute of Inorganic Chemistry of the University of Würzburg. Mass spectra were taken on a Finnigan MAT 8200 mass spectrometer at 70 eV for EI and on a Bruker Daltonics micrOTOF-focus for ESI. All reactions with air and/or moisture sensitive material were carried out in flame dried glassware using the Schlenk tube technique under an inert nitrogen atmosphere. Preparative HPLC was performed on a SymmetryPrep-C18-column (*Waters*; 19 × 300 mm) using the following gradient: H_2O + 0.05% TFA (A), MeCN + 0.05% TFA (B); 10 mL/min; 0 min 25% B; 20 min 45% B; 20.5 min 100% B; 24 min 100% B; 24.5 min 25% B; 28 min 25% B.

4.2. Chemistry

4.2.1. *tert*-Butyl-1-(3-methoxyphenyl)-2-methylpropan-2-ylcarbamate (**7**)

A Grignard reagent, freshly prepared from 3-bromoanisol (**4**) (11.8 g, 63.1 mmol) and magnesium (11.1 g, 456 mmol) in THF (45 mL) was cooled to −30 °C. $CuBr \cdot SMe_2$ (720 mg, 3.50 mmol) was added in four portions and the mixture was stirred at this temperature for 30 min. After cooling to −78 °C a solution of **5** (6.00 g, 35.0 mmol) in THF (40 mL) was added over a period of 30 min and the mixture was allowed to warm up to room temperature over night. The insoluble components were filtered off and washed with H_2O, Et_2O and CH_2Cl_2. The organic solvents were

evaporated and the remaining aqueous phase extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, concentrated in vacuo and the residue purified by flash chromatography (petroleum ether/ethyl acetate 25:1) giving **7** (5.07 g, 18.1 mmol, 52%) as a colorless oil; IR (neat, cm^{-1}) ν 3416, 2948, 2932, 1716, 1602, 1584, 1500, 1263, 1168, 1076. ^1H NMR ($CDCl_3$) δ 7.19 (dd, $J = 7.9$ Hz, $J = 7.9$ Hz, 1H, Ar-H), 6.70–6.80 (m, 3H, Ar-H), 4.30 (s, 1H, NH), 3.79 (s, 3H, O–CH_3), 2.95 (s, 2H, C–CH_2), 1.47 (s, 9H, C–$(CH_3)_3$), 1.27 (s, 6H, C–CH_3). ^{13}C NMR ($CDCl_3$) δ 159.3, 154.6, 139.7, 128.7, 123.1, 116.4, 111.6, 78.8, 55.1, 52.8, 45.1, 27.6, 28.5. EI-MS (70 eV) *m/z* (%): 206 (2), 178 (2), 158 (33), 121 (16), 102 (54), 57 (100). MS (ESI) exact mass calcd for $C_{16}H_{25}NO_3$: 302.17266 $[M + H]^+$; found: 302.17266 $[M + H]^+$.

4.2.2. *tert*-Butyl 3-methoxyphenethylcarbamate (**8**)

The compound was prepared as described for **7**, using aziridine **6**. Purification by flash chromatography on deactivated silica gel (petroleum ether/ethyl acetate 25:1) gave **8** as a colorless oil (2.74 g, 10.9 mmol, 78%). IR (KBr, cm^{-1}) ν 3384, 2976, 2934, 1696, 1603, 1585, 1518, 1491, 1455, 1366, 1259, 1168, 1042. ^1H NMR ($CDCl_3$) δ 7.22 (dd, $J = 7.8$ Hz, $J = 7.8$ Hz, Ar-H) 6.76–6.79 (m, 2H, Ar-H), 6.74 (m, 1H, Ar-H), 4.56 (br s, 1H, NH), 3.80 (s, 3H, O–CH_3), 3.37 (m, 2H, N–CH_2), 2.77 (t, $J = 7.0$ Hz, 2H, C–CH_2), 1.44 (s, 9H, C–CH_3). ^{13}C NMR ($CDCl_3$) δ 160.0156.1, 140.8, 129.8, 121.3, 114.7, 112.0, 55.4, 41.9, 36.4, 28.6. EI-MS (70 eV) *m/z* (%):251 (13) $[M]^+$, 195 (53), 134 (100), 122 (24), 91 (10), 57 (88). Anal. calcd for $C_{14}H_{21}NO_3$ (251.32): C, 66.91; H, 8.42; N, 5.57; found: C, 66.40; H, 8.29; N, 6.17.

4.2.3. 1-(2-Bromo-5-methoxyphenyl)-2-methylpropan-2-amine (**9**)

To a solution of **7** (1.32 g, 4.74 mmol) in CH_2Cl_2 (25 mL) a solution of Br_2 (833 mg, 5.21 mmol) in CH_2Cl_2 (5 mL) was added dropwise within 30 min at 0 °C. After complete addition the mixture was stirred for 3 h at ambient temperature. TFA (0.5 mL) was added and after stirring over night the solvent was removed under reduced pressure. The residue was taken up in H_2O, acidified with diluted HCl and was washed with ethyl acetate twice. The aqueous layer was basified with NaOH pellets and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$. Evaporation of the solvent gave **9** as yellowish oil (952 mg, 3.69 mmol, 78%). IR (KBr, cm^{-1}) ν 3356, 2962, 1595, 1437, 1239, 1280, 1166, 1015. ^1H NMR ($CDCl_3$) δ 7.44 (d, $J = 8.9$ Hz, 1H, Ar-H), 6.83 (d, $J = 3.1$ Hz, 1H, Ar-H), 6.66 (dd, $J = 8.9$ Hz, $J = 3.1$ Hz, 1H, Ar-H), 3.77 (s, 3H, O–CH_3), 2.86 (s, 2H, CH_2), 1.18 (s, 6H, C–CH_3), 1.34 (br s, 2H, NH_2). ^{13}C NMR ($CDCl_3$) δ 158.5, 139.2, 133.6, 118.0, 116.7, 113.7, 55.5, 51.5, 49.4, 30.6. EI-MS (70 eV) *m/z* (%): 244 (2), 201 (2), 77 (6), 63 (3), 58 (100), 42 (8). MS (ESI) exact mass calcd for $C_{11}H_{16}BrNO$: 258.04862; found: 258.04880.

4.2.4. 2-(2-Bromo-5-methoxyphenyl)ethanamine (**10**)

Following the procedure described for **9**, **10** was obtained as a colorless oil (1.10 g, 4.78 mmol, 93%). IR (KBr, cm^{-1}) ν 3365, 2936, 2836, 1594, 1573, 1474, 1308, 1279, 1242, 1164, 1015. ^1H NMR ($CDCl_3$) δ 7.41 (d, $J = 8.7$ Hz, 1H, Ar-H) 6.78 (d, $J = 3.0$ Hz, 1H, Ar-H), 6.64 (dd, $J = 8.7$ Hz, $J = 3.0$ Hz, 1H, Ar-H), 3.77 (s, 3H, O–CH_3), 2.96 (t, $J = 7.1$ Hz, 2H, N–CH_2), 2.84 (t, $J = 7.1$ Hz, 2H, C–CH_2), 1.40 (br s, 2H, NH_2). ^{13}C NMR ($CDCl_3$) δ 158.9, 140.0, 133.3, 116.6, 115.1, 113.4, 55.4, 42.0, 40.4. MS (ESI) exact mass calcd for $C_9H_{12}BrNO$: 230.01750 $[M + H]^+$; found: 230.01758 $[M + H]^+$. Anal. calcd for $C_9H_{12}BrNO$ (230.10): C, 46.98; H, 5.26; N, 6.09; found: C, 46.40; H, 4.93; N, 6.50.

4.2.5. N-(1-(2-Bromo-5-methoxyphenyl)-2-methylpropan-2-yl) formamide (**11**)

Amine **9** (1.88 g, 7.28 mmol) was refluxed in ethyl formate (50 mL) for 48 h. After complete consumption of the starting material the solvent was removed in vacuo and the residue was crystallized from CH_2Cl_2/petroleum ether to give **11** as colorless cubes (1.94 g, 6.76 mmol, 93%). Mp 84–85 °C (CH_2Cl_2/petroleum ether). IR (KBr, cm^{-1}) ν 3313, 3038, 2986, 2969, 2938, 2871, 2830, 1681, 1656, 1592, 1577, 1524, 1472, 1388, 1309, 1293, 1253, 1237, 1170, 1106, 861, 800, 604. ^1H NMR ($CDCl_3$) *Z*-isomer: δ 8.09 (d, $J = 1.9$ Hz, 1H, CHO) 7.42 (d, $J = 8.7$ Hz, 1H, Ar-H), 6.79 (d, $J = 3.0$ Hz, 1H, Ar-H), 6.66 (dd, $J = 8.7$ Hz, $J = 3.0$ Hz, 1H, Ar-H), 5.40 (br s, 1H, NH), 3.75 (s, 3H, O–CH_3), 3.22 (s, 2H, CH_2), 1.41 (s, 6H, CH_3). *E*-isomer: δ 8.00 (d, $J = 12.1$ Hz, 1H, CHO) 7.44 (d, $J = 8.7$ Hz, 1H, Ar-H), 6.73 (d, $J = 3.0$ Hz, 1H, Ar-H), 6.68 (dd, $J = 8.7$ Hz, $J = 3.0$ Hz, 1H, Ar-H), 6.05 (br d, $J = 12.1$ Hz, 1H, NH), 3.76 (s, 3H, O–CH_3), 2.97 (s, 2H, CH_2), 1.39 (s, 6H, CH_3). ^{13}C NMR ($CDCl_3$) *Z*-isomer: δ 160.8, 158.5, 136.8, 133.4, 117.9, 116.4, 114.1, 55.4, 54.0, 43.7, 27.4. *E*-isomer: δ 162.8, 158.5, 138.3, 133.8, 117.9, 116.4, 114.6, 55.4, 55.3, 48.3, 28.5. EI-MS (70 eV) *m/z* (%):206 (2), 188 (100), 145 (17), 127 (16), 115 (43), 86 (12), 44 (15). MS (ESI) exact mass calcd for $C_{12}H_{16}BrNO_2$: 308.02566 $[M + Na]^+$; found: 308.02567 $[M + Na]^+$.

4.2.6. N-(2-Bromo-5-methoxyphenethyl)formamide (**12**)

The compound was synthesized as described for **11**. Compound **12** was obtained as colorless needles (1.11 g, 4.30 mmol, 99%). Mp 66–67 °C (CH_2Cl_2/petroleum ether). IR (KBr, cm^{-1}) ν 3288, 3047, 2918, 1653, 1572, 1543, 1473, 1387, 1258, 1235, 1166, 1061, 1014. ^1H NMR ($CDCl_3$) *Z*-isomer: δ 8.17 (s, 1H, CHO), 7.43 (d, $J = 8.7$ Hz, 1H, Ar-H), 6.79 (d, $J = 3.0$ Hz, 1H, Ar-H), 6.68 (dd, $J = 8.7$ Hz, $J = 3.0$ Hz, 1H, Ar-H), 5.61 (br s, 1H, NH), 3.78 (s, 3H, O–CH_3), 3.59 (dt, $J = 7.0$ Hz, $J = 6.4$ Hz, 2H, N–CH_2), 2.96 (t, $J = 7.0$ Hz, 2H, C–CH_2). *E*-isomer: δ 7.96 (br d, $J = 11.5$ Hz, 1H, CHO), 7.44 (d, $J = 8.7$ Hz, 1H, Ar-H), 6.74 (d, $J = 3.0$ Hz, 1H, Ar-H), 6.69 (dd, $J = 8.7$ Hz, $J = 3.0$ Hz, 1H, Ar-H), 5.61 (br s, 1H, NH), 3.78 (s, 3H, O–CH_3), 3.50 (dt, $J = 6.8$ Hz, $J = 6.5$ Hz, 2H, N–CH_2), 2.92 (t, $J = 6.8$ Hz, 2H, C–CH_2). ^{13}C NMR ($CDCl_3$) *Z*-isomer: δ 161.2, 159.1, 138.8, 133.5, 116.6, 114.8, 114.1, 55.5, 37.8, 35.9. *E*-isomer: δ 164.4, 159.1, 137.8, 133.7, 117.0, 114.7, 114.1, 55.5, 41.3, 38.3. EI-MS (70 eV) *m/z* (%): 259/257 (12/13) $[M]^+$, 214/212 (100/100), 201/199 (10/12), 178 (64), 89 (11), 77 (11), 58 (41). Anal. calcd for $C_{10}H_{12}BrNO_2$ (258.11): C, 46.53; H, 4.69; N, 5.43; found: C, 45.57; H, 4.38; N, 5.28.

4.2.7. 5-Bromo-8-methoxy-3,3-dimethyl-3,4-dihydroisoquinoline (**13**)

The formamide **11** (53.5 mg, 187 μmol) was heated to 140 °C in polyphosphoric acid (1 g) for 4 h. After cooling to room temperature the mixture was basified with aqueous 2 N NaOH and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography on deactivated silica (7.5% NH_3, petroleum ether/ethyl acetate 4:1) gave **13** as yellow solid (28.3 mg, 106 μmol, 56%). Mp 58–59 °C (CH_2Cl_2). IR (KBr, cm^{-1}) ν 2965, 2838, 1617, 1572, 1469, 1440, 1362, 1273, 1173, 1083, 800. ^1H NMR ($CDCl_3$) δ 8.54 (s, 1H, CH), 7.50 (d, $J = 8.9$ Hz, 1H, Ar-H), 6.71 (d, $J = 8.9$ Hz, 1H, Ar-H), 3.86 (s, 3H, O–CH_3), 2.72 (s, 2H, CH_2), 1.25 (s, 6H, CH_3). ^{13}C NMR ($CDCl_3$) δ 156.5, 152.1, 137.0, 135.5, 118.4, 115.1, 111.2, 56.0, 54.4, 37.9, 28.4. EI-MS (70 eV) *m/z* (%): 269/267 (98/100) $[M]^+$, 254/252 (56/56), 239/237 (14/14), 211 (12), 173 (45), 132 (46), 89 (9), 41 (10). MS (ESI) exact mass calcd for $C_{12}H_{15}BrNO$: 268.03315 $[M + H]^+$; found: 268.03315 $[M + H]^+$.

4.2.8. 5-Bromo-8-methoxy-3,4-dihydroisoquinoline (**14**)

Following the procedure described for **13**, the isoquinoline **14** was obtained after chromatography on deactivated silica (7.5% NH_3, petroleum ether/ethyl acetate 6:1) as pale brown solid (8.57 mg, 35.7 μmol, 52%). Mp 58–60 °C (CH_2Cl_2). IR (KBr, cm^{-1}) ν 3005, 22940, 2848, 1616, 1584, 1572, 1469, 1276, 1186, 1140, 1091, 805. ^1H NMR ($CDCl_3$) δ 8.64 (d, $J = 2.0$ Hz, 1H, C–H), 7.48 (d, $J = 8.9$ Hz, 1H, Ar-H), 6.71 (d, $J = 8.9$ Hz, 1H, Ar-H), 3.85 (s, 3H, O–CH_3), 3.72 (td, $J = 8.0$ Hz, $J = 2.0$ Hz, 2H, N–CH_2), 2.72 (t, $J = 8.0$ Hz, 2H, C–CH_2). ^{13}C

NMR ($CDCl_3$) δ 156.5, 155.1, 137.8, 135.4, 119.3, 114.2, 111.2, 56.0, 46.8, 25.2. EI-MS (70 eV) *m/z* (%):241/239 (97/100) $[M]^+$, 226/224 (40/45), 145 (12), 132 (19), 89 (18), 63 (11). Anal. calcd for $C_{10}H_{10}BrNO$ (240.10): C, 50.02; H, 4.20; N, 5.83; found: C, 50.27; H, 4.32; N, 5.76.

*4.2.9. 5-Bromo-3,3-dimethyl-3,4-dihydroisoquinolin-8-ol (**15**)*

A solution of **13** (133 mg, 494 μmol) in chlorobenzene (7 mL) was treated with $AlCl_3$ (198 mg, 1.48 mmol) and heated to 130 °C for 90 min. After cooling to room temperature saturated $NaHCO_3$ solution was added and the mixture extracted with ethyl acetate. After drying over $MgSO_4$ the ethyl acetate was removed under reduced pressure whereupon the product crystallized from the remaining chlorobenzene at −20 °C as orange-colored cubes (104 mg, 409 μmol, 83%). Mp 214–216 °C (C_6H_5Cl). IR (KBr, cm^{-1}) ν 3433, 3165, 3093, 2975, 2958, 2925, 1613, 1587, 1472, 1439, 1360, 1295, 1274, 1162, 1130. ^1H NMR (MeOD) δ 8.44 (s, 1H, CH), 6.58 (d, $J = 9.1$ Hz, 1H, Ar-H), 6.40 (d, $J = 9.1$ Hz, 1H, Ar-H), 2.80 (s, 2H, CH_2), 1.30 (s, 6H, CH_3). ^{13}C NMR (MeOD) δ 165.4, 157.2, 141.4, 137.2, 129.6, 120.7, 111.5, 56.2, 40.1, 27.3. EI-MS (70 eV) *m/z* (%): 255/253 (99/100) $[M]^+$, 240/238 (52/55), 227/225 (11/11), 212 (12), 173 (18), 159 (48), 132 (14), 89 (11). Anal. calcd for $C_{11}H_{12}BrNO$ (254.12): C, 51.99; H, 4.76; N, 5.51; found: C, 52.49; H, 4.79; N, 5.44.

*4.2.10. 5-Bromo-3,4-dihydroisoquinolin-8-ol (**16**)*

According to the procedure described above, **16** (25.5 mg, 113 μmol, 53%) was obtained as orange-colored crystals (25.5 mg, 113 μmol, 53%). Evaporating the mother liquor to dryness gave additional product as a yellow oil (21.0 mg, 92.9 μmol, 44%) with only small impurities. Yield: 97%. Mp 181–183 °C (C_6H_5Cl). IR (KBr, cm^{-1}) ν 3434, 2954, 2914, 2855, 1626, 1577, 1451, 1349, 1329, 1299, 1176, 1055, 1011, 805. ^1H NMR (MeOD) δ 8.58 (s, 1H, CH), 7.42 (d, $J = 9.1$ Hz, 1H, Ar-H), 6.62 (d, $J = 9.1$ Hz, 1H, Ar-H), 3.69 (td, $J = 7.8$ Hz, $J = 1.3$ Hz, 2H, N–CH_2), 2.83 (t, $J = 7.8$ Hz, 2H, C–CH_2). ^{13}C NMR (MeOD) δ = 158.8, 140.3, 137.9, 127.7, 120.1, 117.5, 110.6, 44.8, 26.5. EI-MS (70 eV) *m/z* (%): 227/225 (99/100) $[M]^+$, 200/198 (9/11), 145 (23), 118 (14), 112 (11), 91 (22), 59 (15), 44 (14). MS (ESI) exact mass calcd for C_9H_8BrNO: 225.98629 $[M + H]^+$; found: 225.98634 $[M + H]^+$. Anal. calcd for C_9H_8BrNO (226.07): C, 47.82; H, 3.57; N, 6.20; found: C, 46.45; H, 3.64; N, 5.80.

4.2.11. 8-Isopropoxynaphthalen-1-ol

A mixture of **18** (940 mg, 5.87 mmol) and K_2CO_3 (891 mg, 6.45 mmol) in acetone (30 mL) was treated with 2-iodopropane (1.50 g, 8.82 mmol). After stirring at ambient temperature for 16 h and heating up to 56 °C for 4 h, the mixture was diluted with water (20 mL) and extracted with Et_2O. The organic layer was washed with water and sat. K_2CO_3 solution, dried over $MgSO_4$, and concentrated in vacuo to give the desired product as brownish oil (1.10 g, 5.42 mmol, 92%). ^1H NMR ($CDCl_3$) δ 9.77 (s, 1H, OH), 7.40 (dd, $J = 8.2$ Hz, $J = 0.9$ Hz, 1H, Ar-H), 7.29–7.37 (m, 3H, Ar-H), 6.85 (dd, $J = 7.2$ Hz, $J = 1.7$ Hz, 1H, Ar-H), 6.80 (d, $J = 7.6$ Hz, 1H, Ar-H), 4.86 (sept, $J = 6.1$ Hz, 1H, CH), 1.51 (d, $J = 6.1$ Hz, 6H, CH_3). ^{13}C NMR ($CDCl_3$) δ 154.9, 154.2, 137.0, 127.6, 125.7, 121.6, 118.9, 116.0, 110.2, 106.5, 72.7, 22.0. EI-MS (70 eV) *m/z* (%): 202 (20) $[M]^+$, 160 (100), 131 (7), 114 (20), 77 (6), 51 (9). MS (ESI) exact mass calcd for $C_{13}H_{14}O_2$: 225.08860 $[M + Na]^+$; found: 225.08858 $[M + Na]^+$.

*4.2.12. 8-Isopropoxynaphthalen-1-yl acetate (**19**)*

To a solution of 8-isopropoxynaphthalen-1-ol in Ac_2O (20 mL) K_2CO_3 (1.06 g, 7.64 mmol) was added and the mixture was heated to 60 °C for 6 h. The cold mixture was poured onto ice water and stirred for 2 h. The precipitate was filtered off, the aqueous phase extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated in vacuo. The residue was combined with the precipitate and purified by flash chromatography (petroleum ether/ethyl acetate 20:1) to give **19** as yellowish solid (1.45 g, 5.92 mmol, 93%). Mp 56–58 °C (CH_2Cl_2). IR (KBr, cm^{-1}) ν 3057, 2981, 2932, 1758, 1576, 1381, 1366, 1268, 1212, 1117, 1053, 1027. ^1H NMR ($CDCl_3$) δ 7.68 (dd, $J = 8.1$ Hz, $J = 1.2$ Hz, 1H, Ar-H), 7.32–7.43 (m, 3H, Ar-H), 7.02 (dd, $J = 7.3$ Hz, $J = 1.2$ Hz, 1H, Ar-H), 6.87 (dd, $J = 7.3$ Hz, $J = 0.9$ Hz, 1H, Ar-H), 4.74 (sept, $J = 6.1$ Hz, 1H, CH), 2.38 (s, 3H, CH_3), 1.42 (d, $J = 6.1$ Hz, 6H, CH_3). ^{13}C NMR ($CDCl_3$) δ 170.1, 153.7, 146.9, 137.4, 126.8, 126.6, 126.0, 120.7, 120.4, 119.5, 108.3, 70.4, 22.2, 21.8. EI-MS (70 eV) *m/z* (%): 244 (12) $[M]^+$, 202 (10), 160 (100), 131 (5), 114 (5), 77 (2). MS (ESI) exact mass calcd for $C_{15}H_{16}O$: 267.09917 $[M + Na]^+$; found: 267.09916 $[M + Na]^+$.

*4.2.13. 5-Bromo-8-isopropoxy-naphthalen-1-ol (**20**)*

A solution of Br_2 (945 mg, 5.91 mmol) in CH_2Cl_2 (10 mL) was added to a mixture of **19** (61.6 mg, 252 μmol) and NaOAc (103 mg, 1.26 mmol) in CH_2Cl_2 (10 mL) at −20 °C over a period of 30 min. After warming up to ambient temperature and stirring for 4 h, the reaction was quenched with aqueous $Na_2S_2O_3$ solution. The organic phase was washed with water, dried over $MgSO_4$ and concentrated to dryness. The residue was dissolved in MeOH (10 mL) and treated with 2 N NaOH (2 mL) at 80 °C for 4 h. After cooling to room temperature the mixture was acidified with diluted HCl and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, concentrated and subjected to column chromatography (petroleum ether/ethyl acetate 25:1) to afford the product as an orange-colored solid (68.8 mg, 245 mol, 97%) mp 74–75 °C (CH_2Cl_2/petroleum ether). IR (KBr, cm^{-1}) ν 3337, 2984, 2937, 1622, 1601, 1388, 1376, 1240, 1110, 1051, 804. ^1H NMR ($CDCl_3$) δ 9.87 (s, 1H, OH), 7.68 (dd, $J = 8.5$ Hz, $J = 1.1$ Hz, 1H, Ar-H), 7.61 (d, $J = 8.4$ Hz, 1H, Ar-H), 7.46 (dd, $J = 8.5$ Hz, $J = 7.63$ Hz, 1H, Ar-H), 6.93 (dd, $J = 7.6$ Hz, $J = 1.1$ Hz, 1H, Ar-H), 6.67 (d, $J = 8.4$ Hz, 1H, Ar-H), 4.84 (sept, $J = 6.1$ Hz, 1H, CH), 1.51 (d, $J = 6.1$ Hz, 6H, CH_3). ^{13}C NMR ($CDCl_3$) δ 155.1, 154.0, 134.6, 129.4, 129.0, 118.4, 116.8, 114.8, 111.4, 106.9, 73.3, 21.9. EI-MS (70 eV) *m/z* (%): 282/280 (21/20) $[M]^+$, 240/238 (96/100), 194 (10), 159 (8), 102 (23), 59 (74), 43 (35). Anal. calcd for $C_{13}H_{13}BrO_2$ (281.15): C, 55.54; H, 4.66; found: C, 55.01; H, 4.64.

4.2.14. 1-Bromo-5-isopropoxy-4-methoxynaphthalene

A solution of **20** (1.37 g, 4.86 mmol) in DMF was treated with NaH (175 mg, 7.28 mmol) and stirred at ambient temperature until gas evolution had ceased. Dimethylsulfate (918 mg, 7.28 mmol) was added and the mixture was stirred for 2 h. The reaction was quenched by careful addition of water and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, concentrated to dryness and the residue crystallized from CH_2Cl_2/petroleum ether to afford the desired compound as an orange-colored solid (1.42 g, 4.82 mmol, 99%). Mp 63–65 °C (CH_2Cl_2/petroleum ether). IR (KBr, cm^{-1}) ν 3107, 2983, 2929, 1586, 1374, 1276, 1092, 813, 753. ^1H NMR ($CDCl_3$) δ 7.83 (dd, $J = 8.5$ Hz, $J = 0.9$ Hz, 1H, Ar-H), 7.65 (d, $J = 8.3$ Hz, 1H, Ar-H), 7.46 (dd, $J = 8.5$ Hz, $J = 7.3$ Hz, 1H, Ar-H), 6.90 (d, $J = 7.3$ Hz, 1H, Ar-H), 6.79 (d, $J = 8.3$ Hz, 1H, Ar-H), 4.53 (sept, $J = 6.1$ Hz, 1H, CH), 3.95 (s, 3H, O–CH_3), 1.40 (d, $J = 6.1$ Hz, 6H, CH_3). ^{13}C NMR ($CDCl_3$) δ 157.3, 155.0, 135.1, 130.3, 127.5, 120.7, 120.2, 114.3, 112.9, 107.4, 73.2, 56.5, 22.0. EI-MS (70 eV) *m/z* (%): 294 $[M]^+$ (33), 252 (100), 237 (57), 209 (29), 173 (5), 102 (24), 75 (10), 43 (8). Anal. calcd for $C_{14}H_{15}BrO_2$ (295.17): C, 56.97; H, 5.12; found: C, 57.09; H, 5.08.

*4.2.15. 2-(4-Isopropoxy-5-methoxynaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**21**)*

1-Bromo-5-isopropoxy-4-methoxynaphthalene (113 mg, 382 μmol), KOAc (375 mg, 3.82 mmol), bispinacolatodiborane (292 mg, 1.15 mmol) and Pd(dppf)Cl_2 (31.2 mg, 38.2 μmol) were solved in a toluene/water-mixture (7 mL, 5:2), degassed and afterwards heated to 90 °C for 6 h. After cooling to room temperature water (10 mL) was added and the aqueous layer extracted

with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, concentrated and the residue purified by flash chromatography (petroleum ether/ethyl acetate 35:1) to afford the desired product as a yellowish solid (82.0 mg, 240 μmol, 63%). Mp 86–88 °C (ethyl acetate). IR (KBr, cm^{-1}) ν 2979, 2930, 2827, 1612, 1584, 1324, 1285, 1268, 1146, 1117. ^{1}H NMR ($CDCl_3$) δ 8.39 (dd, J = 8.5 Hz, J = 0.9 Hz, 1H, Ar-H), 7.98 (d, J = 7.8 Hz, 1H, Ar-H), 7.39 (dd, J = 8.5 Hz, J = 8.0 Hz, 1H, Ar-H), 6.89 (d, J = 8.0 Hz, 1H, Ar-H), 6.85 (d, J = 7.8 Hz, 1H, Ar-H), 4.65 (sept, J = 6.1 Hz, 6H, CH), 1.40 (s, 12H, CH_3), 3.92 (s, 3H, O–CH_3), 1.42 (d, J = 6.1 Hz, 6H, CH_3). ^{13}C NMR ($CDCl_3$) δ 158.0, 157.4, 141.4, 137.0, 126.5, 121.4, 119.1, 110.4, 107.0, 83.4, 72.0, 56.6, 24.9, 22.0. EI-MS (70 eV) m/z (%):342 (36) $[M]^+$, 300 (100), 227 (18), 200 (19), 157 (10), 127 (6). Anal. calcd for $C_{20}H_{27}BO_4$ (342.24): C, 70.19; H, 7.95; found: C, 69.61; H, 7.81.

4.2.16. 8-Methoxy-5-(4′-methoxynaphthalen-1′-yl)-3,3-dimethyl-3,4-dihydroisoquinoline (**22**)

$Pd(PPh_3)_4$ (15.1 mg, 13.1 μmol) was added to a degassed mixture of **13** (35.0 mg, 131 μmol), 4-methoxynaphthylboronic acid (**17**) (36.9 mg, 183 μmol) and 2 M Na_2CO_3 solution (1 mL) in toluene (5 mL). After heating up to 80 °C over night, water (10 mL) was added to the reaction mixture and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, concentrated and purified via column chromatography on deactivated silica gel (7.5% NH_3, petroleum ether/ethyl acetate 6:1) to give **28** as a brown oil (39.4 mg, 115 μmol, 88%), that was crystallized from CH_2Cl_2/petroleum ether as a colorless solid. Mp 130–132 °C (CH_2Cl_2/petroleum ether). IR (KBr, cm^{-1}) ν 2931, 1735, 1638, 1584, 1460, 1390, 1277, 1083. ^{1}H NMR ($CDCl_3$) δ 8.74 (s, 1H, CH), 8.35 (d, 1H, J = 8.3 Hz, Ar-H), 7.50–7.46 (m, 1H, Ar-H), 7.43–7.38 (m, 2H, Ar-H), 7.28 (d, J = 8.6 Hz, 1H, Ar-H), 6.89 (d, J = 7.3 Hz, 1H, Ar-H), 6.87 (d, J = 7.6 Hz, 1H, Ar-H), 4.06 (s, 3H, O–CH_3), 3.94 (s, 3H, O–CH_3), 2.32 (d, J = 16.6 Hz, 1H, CH_2), 2.24 (d, J = 16.6 Hz, 1H, CH_2), 1.12 (s, 3H, CH_3), 1.07 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 156.4, 155.0, 152.9, 136.7, 134.5, 133.3, 131.8, 129.8, 127.1, 126.5, 125.7, 125.5, 125.2, 122.2, 116.0, 108.7, 103.3, 55.6, 55.5, 53.9, 35.7, 28.2, 27.3. EI-MS (70 eV) m/z (%):345 (100) $[M]^+$, 330 (23), 298 (17), 257 (6), 165 (7). Anal. calcd for $C_{23}H_{23}NO_2$ (345.43): C, 79.97; H, 6.71; N, 4.05; found: C, 79.21; H, 6.60; N, 3.98.

4.2.17. 8-Methoxy-5-(4′-methoxynaphthalen-1′-yl)-3,4-dihydroisoquinoline (**23**)

The naphthylisoquinoline **23** was obtained by reaction of **14** (29.7 mg, 124 μmol) and 4-methxonaphthylboronic acid (**17**) (35.0 mg, 172 μmol) as described for **22**. The rude product was purified by column chromatography on deactivated silica (7.5% NH_3, petroleum ether/ethyl acetate 4:1). After crystallisation from ethyl acetate/petroleum ether **29** was obtained as a colorless solid (32.6 mg, 103 μmol, 83%). Mp 196–198 °C (ethyl acetate/petroleum ether). IR (KBr, cm^{-1}) ν 2938, 2839, 1618, 1584, 1463, 1389, 1372, 1270, 1241, 1083, 808, 768. ^{1}H NMR ($CDCl_3$) δ 8.86 (s, 1H, CH), 8.34 (d, J = 8.3 Hz, 1H, 5′-H), 7.46–7.50 (m, 1H, Ar-H), 7.41 (m, 2H, Ar-H), 2.32 (m, 2H, C–CH_2), 7.32 (d, J = 8.5 Hz, 1H, Ar-H), 7.22 (d, J = 7.8 Hz, 1H, Ar-H), 6.91 (d, J = 8.5 Hz, 1H, Ar-H), 6.86 (d, J = 7.8 Hz, 1H, Ar-H), 4.05 (s, 3H, O–CH_3), 3.95 (s, 3H, O–CH_3), 3.56 (m, 2H, N–CH_2). ^{13}C NMR ($CDCl_3$) δ 156.5, 156.1, 155.1, 137.5, 134.6, 133.1, 131.0, 129.7, 127.1, 126.6, 125.5, 125.5, 125.1, 122.3, 108.9, 103.2, 55.6, 55.5, 46.8, 23.3. EI-MS (70 eV) m/z (%): 317 (100) $[M]^+$, 302 (17), 286 (17), 202 (6), 151 (9), 101 (7). Anal. calcd for $C_{21}H_{19}NO_2$ (317.38): C, 79.47; H, 6.03; N, 4.41; found: C, 78.90; H, 5.98; N, 4.41.

4.2.18. 5-(4′-Isopropoxy-5′-methoxynaphthalen-1′-yl)-3,3-dimethyl-3,4-dihydroisoquinolin-8-ol (**28**)

To a degassed mixture of **15** (37.9 mg, 111 μmol), boronic acid ester **21** (49.4 mg, 144 μmol), and K_3PO_4 (118 mg, 555 μmol) in DMF (5 mL) $Pd(PPh_3)_4$ (12.8 mg, 11.1 μmol) was added. After heating up to 90 °C for 5 h, the reaction mixture was diluted with water (10 mL) and the aqueous phase extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, concentrated and purified via column chromatography on deactivated silica gel (7.5% NH_3, CH_2Cl_2/MeOH 12:1) to give **28** as a yellow oil (21.8 mg, 56.0 μmol, 66%). IR (KBr, cm^{-1}) ν 3426, 2972, 2929, 1603, 1406, 1381, 1269, 1117. ^{1}H NMR (MeOD) δ 8.76 (s, 1H, CH), 7.28 (dd, J = 8.2 Hz, J = 8.0 Hz, 1H, Ar-H), 7.27 (d, J = 8.9 Hz, 1H, Ar-H), 7.16 (d, J = 7.9 Hz, 1H, Ar-H), 7.01 (d, J = 7.9 Hz, 1H, Ar-H), 6.99 (dd, J = 8.5 Hz, J = 0.7 Hz, 1H, Ar-H), 6.94 (d, J = 7.6 Hz, 1H, Ar-H), 6.81 (d, J = 8.7 Hz, 1H, Ar-H), 4.62 (sept, J = 6.1 Hz, 1H, CH), 3.94 (s, 3H, O–CH_3), 2.50 (d, J = 16.8 Hz, 1H, CH_2), 2.36 (d, J = 16.8 Hz, 1H, CH_2), 1.42 (d, J = 6.1 Hz, 6H, CH_3), 1.23 (s, 3H, CH_3), 1.18 (s, 3H, CH_3). ^{13}C NMR (MeOD) δ 165.8, 158.8, 158.3, 155.9, 141.6, 137.5, 136.7, 131.3, 130.6, 129.1, 127.7, 120.7, 119.8, 118.3, 114.0, 113.2, 108.1, 74.2, 56.9, 55.2, 37.7, 27.0, 26.4, 22.4, 22.4. EI-MS (70 eV) m/z (%):389 (100) $[M]^+$, 347 (54), 332 (41), 290 (24), 258 (49), 189 (11). MS (ESI) exact mass calcd for $C_{25}H_{27}NO_3$: 390.20637 $[M + H]^+$; found: 390.20698 $[M + H]^+$.

4.2.19. 5-(4′-Isopropoxy-5′-methoxynaphthalen-1′-yl)-3,4-dihydroisoquinolin-8-ol (**29**)

Treating **16** (36.7 mg, 162 μmol) and **21** (66.7 mg, 195 μmol) as described in Section 4.2.18 gave after column chromatography on deactivated silica gel (7.5% NH_3, CH_2Cl_2/MeOH 15:1) the desired product as a yellow oil (22.6 mg, 62.4 μmol, 38%). IR (KBr, cm^{-1}) ν 3431, 2963, 2923, 2855, 1612, 1582, 1459, 1406, 1380, 1266, 1096, 1051, 807. ^{1}H NMR (MeOD) δ 8.73 (s, 1H, CH), 7.27 (dd, J = 8.4 Hz, J = 8.0 Hz, 1H, Ar-H), 7.2 (d, J = 8.1 Hz, 2H, Ar-H), 7.01 (dd, J = 8.4 Hz, J = 0.7 Hz, 1H, Ar-H), 7.00 (d, J = 8.0 Hz, 1H, Ar-H), 6.92 (d, J = 7.6 Hz, 1H, Ar-H), 6.76 (d, J = 8.7 Hz, 1H, Ar-H), 4.60 (sept, J = 6.1 Hz, 1H, CH), 3.93 (s, 3H, O–CH_3), 3.44–3.52 (m, 2H, N–CH_2), 2.24–2.41 (m, 2H, C–CH_2), 1.40 (d, J = 6.1 Hz, 6H, CH_3). ^{13}C NMR (MeOD) δ 159.3, 158.7, 155.6, 139.4, 137.5, 137.3, 132.1, 129.3, 129.0, 127.6, 120.8, 119.8, 118.1, 116.0, 113.5, 108.1, 74.3, 56.9, 24.6, 24.6, 22.4. EI-MS (70 eV) m/z (%): 361 (65) $[M]^+$, 319 (100), 304 (36), 286 (10), 231 (5), 202 (7), 189 (8). MS (ESI) exact mass calcd for $C_{23}H_{23}NO_3$: 362.17507 $[M + H]^+$; found: 362.17489 $[M + H]^+$.

4.2.20. 5-(4′-Hydroxynaphthalen-1′-yl)-3,3-dimethyl-3,4-dihydroisoquinolin-8-ol (**24**)

A solution of **22** (11.1 mg, 32.1 μmol) in CH_2Cl_2 (5 mL) was treated with BBr_3 (0.1 mL, 1 M solution in *n*-hexane) at −20 °C. The reaction mixture was allowed to warm up to room temperature over night before a second portion of BBr_3 (0.1 mL, 1 M solution in hexanes) was added. After 3 h of vigorous stirring MeOH (5 mL) was added, the mixture concentrated to dryness and purified by column chromatography on deactivated silica (7.5% NH_3, CH_2Cl_2/MeOH 20:1) to give **24** as a yellow oil (8.00 mg, 25.2 μmol, 79%). IR (KBr, cm^{-1}) ν 3414, 3180, 2967, 2925, 1602, 1580, 1468, 1444, 1369, 1293, 1266, 1177, 1157. ^{1}H NMR (MeOD) δ 8.72 (s, 1H, CH), 8.27 (d, J = 8.3 Hz, 1H, Ar-H), 7.41–7.43 (m, 1H, Ar-H), 7.37–7.38 (m, 2H, Ar-H), 7.27 (d, J = 8.6 Hz, 1H, Ar-H), 7.07 (d, J = 7.6 Hz, 1H, Ar-H), 6.87 (d, J = 7.6 Hz, 1H, Ar-H), 6.79 (d, J = 8.6 Hz, 1H, Ar-H), 2.49 (d, J = 16.8 Hz, 1H, CH_2), 2.37 (d, J = 16.8 Hz, 1H, CH_2), 1.21 (s, 3H, CH_3), 1.16 (s, 3H, CH_3). ^{13}C NMR (MeOD) δ 165.8, 158.3, 154.5, 141.9, 136.9, 134.7, 130.3, 129.0, 128.8, 127.4, 126.5, 126.4, 125.6, 123.8, 118.2, 114.0, 108.3, 55.3, 37.8, 26.9, 26.4. EI-MS (70 eV) m/z (%):317 (100) $[M]^+$, 302 (22), 260 (59), 231 (26), 202 (12), 150 (6), 101 (10), 58 (17). MS (ESI) exact mass calcd for $C_{21}H_{19}NO_2$: 318.14886 $[M + H]^+$; found: 318.14893 $[M + H]^+$.

4.2.21. 5-(4′-Hydroxynaphthalen-1′-yl)-3,4-dihydroisoquinolin-8-ol (**25**)

BBr_3 (0.25 mL, 1 M solution in *n*-hexane) was added to a solution of **23** (27.4 mg, 86.2 μmol) in CH_2Cl_2 (6 mL) at 0 °C. After stirring at 0 °C for 5 h the mixtures was warmed to room temperature and stirred for additional 24 h. Then MeOH (5 mL) was added and the

solvent removed under reduced pressure. The residue was submitted to column chromatography on deactivated silica (7.5% NH_3, CH_2Cl_2/MeOH 15:1 to 10:1). The obtained product still contained small impurities, which were removed by preparative HPLC to afford **25** as a yellow oil (13.5 mg, 46.5 μmol, 54%). IR (KBr, cm^{-1}) ν 3421, 2950, 2919, 1677, 1587, 1509, 1448, 1351, 1305, 1197, 1137, 1053, 836, 800, 770, 723. ^{1}H NMR (MeOD) δ 9.23 (s, 1H, CH), 8.30 (d, J = 8.0 Hz, 1H, Ar-H), 7.59 (d, J = 8.6 Hz, 1H, Ar-H), 7.41–7.46 (m, 2H, Ar-H), 7.35 (d, J = 7.8 Hz, 1H, Ar-H), 7.15 (d, J = 7.7 Hz, 1H, Ar-H), 7.04 (d, J = 8.6 Hz, 1H, Ar-H), 6.89 (d, J = 7.7 Hz, 1H, Ar-H), 3.71–3.80 (m, 2H, N–CH_2), 2.75–2.80 (m, 1H, C–CH_2), 2.66–2.75 (m, 1H, C–CH_2). ^{13}C NMR (MeOD) δ 163.6, 162.5, 155.0, 144.5, 138.2, 134.3, 132.4, 128.9, 127.8, 127.7, 126.5, 125.8, 124.0, 116.1, 113.5, 108.3, 42.3, 24.1. EI-MS (70 eV) m/z (%): 289 (100) $[M]^+$, 272 (21), 261 (11), 231 (12), 202 (15), 135 (11). MS (ESI) exact mass calcd for $C_{19}H_{15}NO_2$: 290.11756 $[M + H]^+$; found: 290.11756 $[M + H]^+$.

4.2.22. 5-(4′-Hydroxy-5′-methoxynaphthalen-1′-yl)-3,3-dimethyl-3,4-dihydroisoquinolin-8-ol (**30**)

A solution of **28** (31.0 mg, 79.7 μmol) in CH_2Cl_2 (10 mL) was treated with BCl_3 (0.4 mL, 1 M solution in *n*-hexane) at 0 °C. After being stirred at this temperature for 2 h, MeOH (2 mL) was added and the mixture concentrated to dryness. The residue was submitted to column chromatography on deactivated silica (7.5% NH_3, CH_2Cl_2/MeOH 15:1 to 10:1) to afford the desired product along with small impurities which were removed by preparative HPLC to give pure **30** as a yellow oil (18.7 mg, 53.9 μmol, 68%). IR (KBr, cm^{-1}) ν 3411, 2979, 2925, 1673, 1637, 1588, 1459, 1410, 1307, 1271, 1181, 1133, 1086, 1039. ^{1}H NMR (MeOD) δ 9.10 (s, 1H, CH), 7.54 (d, J = 8.6 Hz, 1H, Ar-H), 7.32 (dd, J = 8.5 Hz, J = 8.0 Hz, 1H, Ar-H), 7.17 (d, J = 7.8 Hz, 1H, Ar-H), 7.04 (d, J = 8.6 Hz, 1H, Ar-H), 6.99 (d, J = 7.8 Hz, 1H, Ar-H), 6.95 (d, J = 8.5 Hz, 1H, Ar-H), 6.88 (d, J = 8.0 Hz, 1H, Ar-H), 4.11 (s, 3H, O–CH_3), 2.74 (d, J = 17.1 Hz, 1H, CH_2), 2.58 (d, J = 17.1 Hz, 1H, CH_2), 1.36 (s, 3H, CH_3), 1.31 (s, 3H, CH_3). ^{13}C NMR (MeOD) δ 162.8, 161.6, 158.2, 156.3, 144.7, 137.7, 136.3, 133.2, 130.4, 127.9, 127.3, 120.0, 116.4, 112.5, 110.9, 105.8, 57.0, 56.3, 37.6, 26.0, 25.6. EI-MS (70 eV) m/z (%): 347 (88) $[M]^+$, 332 (33), 315 (14), 290 (24), 258 (43), 120 (17), 44 (100). MS (ESI) exact mass calcd for $C_{22}H_{21}NO_3$: 348.15942 $[M + H]^+$; found: 348.15961 $[M + H]^+$.

4.2.23. 5-(4′-Hydroxy-5′-methoxynaphthalen-1′-yl)-3,4-dihydroisoquinolin-8-ol (**31**)

To a solution of **29** (8.92 mg, 24.7 μmol) in CH_2Cl_2 (7 mL) BCl_3 (0.1 mL, 1 M solution in *n*-hexane) was added at −20 °C. After 2 h of vigorous stirring the reaction was quenched by addition of MeOH (2 mL) and the solvent removed in vacuo. Gel chromatography on Sephadex LH-20 (100% MeOH) followed by final purification by preparative HPLC gave the desired product as a yellow oil (6.45 mg, 20.2 μmol, 82%). IR (KBr, cm^{-1}) ν 3395, 2958, 2922, 2851, 1677, 1459, 1410, 1263, 1193, 1132. ^{1}H NMR (MeOD) δ 9.21 (s, 1H, CH), 7.55 (d, J = 8.6 Hz, 1H, Ar-H), 7.32 (dd, J = 8.3 Hz, J = 8.0 Hz, 1H, Ar-H), 7.20 (d, J = 7.8 Hz, 1H, Ar-H), 7.03 (d, J = 8.7 Hz, 1H, Ar-H), 6.99 (d, J = 6.4 Hz, 1H, Ar-H), 6.97 (d, J = 8.7 Hz, 1H, Ar-H), 6.88 (d, J = 7.8 Hz, 1H, Ar-H), 4.11 (s, 3H, O–CH_3), 3.69–3.82 (m, 2H, N–CH_2), 2.61–2.80 (m, 2H, C–CH_2). ^{13}C NMR (MeOD) δ 163.6, 162.6, 158.2, 156.3, 144.4, 138.2, 136.3, 132.5, 130.4, 127.9, 127.5, 119.9, 116.3, 116.2, 113.6, 110.8, 105.8, 56.9, 42.2, 24.0. EI-MS (70 eV) m/z (%):319 (100) $[M]^+$, 304 (28), 275 (14), 247 (7), 189 (9). MS (ESI) exact mass calcd for $C_{20}H_{17}NO_3$: 320.12812 $[M + H]^+$; found: 320.12864 $[M + H]^+$.

4.3. General procedure for the reduction of naphthyldihydroisoquinolines

A solution of the corresponding naphthyldihydroisoquinoline in an appropriate amount of MeOH was cooled to 0 °C and treated with $NaBH_4$ (3 equiv.). After being stirred at this temperature for 2 h water was added and the mixture concentrated to dryness. The residue was taken up in CH_2Cl_2/MeOH (20:1), the insoluble parts were filtered off and the filtrate concentrated and purified by preparative HPLC.

4.3.1. 5-(4′-Hydroxynaphthalen-1′-yl)-3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-8-ol (**26**)

Colorless oil (7.70 mg, 24.1 μmol, 83%). IR (KBr, cm^{-1}) ν 3434, 2925, 2852, 1680, 1433, 1385, 1324, 1207, 1139. ^{1}H NMR (MeOD) δ 8.27 (dd, J = 8.4 Hz, J = 0.5 Hz, 1H, Ar-H), 7.41–7.44 (m, 1H, Ar-H), 7.34–7.37 (m, 1H, Ar-H), 7.26 (d, J = 8.4 Hz, 1H, Ar-H), 7.08 (d, J = 8.1 Hz, 1H, Ar-H), 7.07 (d, J = 7.6 Hz, 1H, Ar-H), 6.87 (d, J = 7.6 Hz, 1H, Ar-H), 6.86 (d, J = 8.1 Hz, 1H, Ar-H), 4.33 (s, 2H, CH_2), 2.53 (d, J = 17.5 Hz, 1H, CH_2), 2.39 (d, J = 17.5 Hz, 1H, CH_2), 1.28 (s, 3H, CH_3), 1.27 (s, 3H, CH_3). ^{13}C NMR (MeOD) δ 154.7, 154.4, 134.7, 133.1, 132.4, 132.2, 130.0, 128.6, 127.4, 126.4, 126.2, 125.6, 123.8, 114.9, 113.4, 108.4, 54.3, 39.3, 37.9, 24.6, 24.3. EI-MS (70 eV) m/z (%): 319 (75) $[M]^+$, 304 (100), 262 (59), 247 (26), 152 (18). MS (ESI) exact mass calcd for $C_{21}H_{21}NO_2$: 320.16451 $[M + H]^+$; found: 320.16450 $[M + H]^+$.

4.3.2. 5-(4′-Hydroxy-5′-methoxynaphthalen-1′-yl)-3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-8-ol (**32**)

Colorless oil (4.46 mg, 12.8 μmol, 44%). IR (KBr, cm^{-1}) ν 3413, 2981, 2923, 2851, 1677, 1611, 1409, 1268, 1203, 1137. ^{1}H NMR (MeOD) δ 7.26 (dd, J = 7.9 Hz, J = 8.4 Hz, 1H, Ar-H), 7.13 (d, J = 7.8 Hz, 1H, Ar-H), 7.05 (d, J = 8.2 Hz, 1H, Ar-H), 6.96 (d, J = 7.5 Hz, 1H, Ar-H), 6.90 (dd, J = 8.6 Hz, J = 0.7 Hz, 1H, Ar-H), 6.85 (d, J = 7.8 Hz, 2H, Ar-H), 4.32 (s, 2H, CH_2), 4.11 (s, 3H, O–CH_3), 2.50 (d, J = 17.5 Hz, 2H, CH_2), 2.36 (d, J = 17.5 Hz, 1H, CH_2), 1.28 (s, 3H, CH_3), 1.27 (s, 3H, CH_3). ^{13}C NMR (MeOD) δ 158.1, 155.6, 154.8, 136.6, 132.3, 133.2, 132.2, 130.1, 129.8, 127.4, 120.3, 116.2, 115.0, 113.5, 110.8, 105.5, 56.9, 54.3, 39.2, 37.8, 24.7, 24.3. EI-MS (70 eV) m/z (%): 349 (91) $[M]^+$, 334 (100), 318 (17), 292 (79), 277 (24), 260 (33), 167 (24), 159 (15). MS (ESI) exact mass calcd for $C_{22}H_{23}NO_3$: 350.17507 $[M + H]^+$; found: 350.17546 $[M + H]^+$.

4.3.3. 5-(4′-Hydroxynaphthalen-1′-yl)-1,2,3,4-tetrahydroisoquinolin-8-ol (**27**)

Colorless oil (5.33 mg, 18.3 μmol, 36%). IR (KBr, cm^{-1}) ν 3422, 2927, 2851, 1679, 1588, 1430, 1343, 1206, 1138, 840, 803, 769, 724. ^{1}H NMR (MeOD) δ 8.26 (d, J = 8.2 Hz, 1H, Ar-H), 7.42 (ddd, J = 8.2 Hz, J = 8.0 Hz, J = 1.3 Hz, 1H, Ar-H), 7.36 (ddd, J = 8.1 Hz, J = 8.0 Hz, J = 1.3 Hz, 1H, Ar-H), 7.32 (d, J = 8.1 Hz, 1H, Ar-H), 7.09 (d, J = 7.6 Hz, 1H, Ar-H), 7.07 (d, J = 8.2 Hz, 1H, Ar-H), 6.87 (d, J = 7.6 Hz, 1H, Ar-H), 6.84 (d, J = 8.2 Hz, 1H, Ar-H), 4.36 (d, J = 16.3 Hz, 1H, CH_2), 4.30 (d, J = 16.3 Hz, 1H, CH_2), 3.27–3.33 (m, 2H, CH_2), 2.61–2.66 (m, 1H, CH_2), 2.51–2.56 (m, 1H, CH_2). ^{13}C NMR (MeOD) δ 154.8, 154.4, 134.7, 133.0, 132.8, 132.2, 130.0, 128.5, 127.4, 126.4, 126.3, 125.5, 123.7, 116.3, 113.4, 108.4, 42.5, 42.3, 24.9. EI-MS (70 eV) m/z (%): 291 (100) $[M]^+$, 262 (27), 247 (11), 231 (8), 215 (9), 145 (10), 126 (20). MS (ESI) exact mass calcd for $C_{19}H_{17}NO_2$: 292.13321 $[M + H]^+$; found: 292.13321 $[M + H]^+$.

4.3.4. 5-(4′-Hydroxy-5′-methoxynaphthalen-1′-yl)-1,2,3,4-tetrahydroisoquinolin-8-ol (**33**)

Colorless solid (9.21 mg, 28.7 μmol, 74%). Mp >200 °C decomp. IR (KBr, cm^{-1}) ν 3382, 3222, 3030, 2932, 1685, 1611, 1589, 1460, 1425, 1410, 1266, 1200, 1153, 840, 766, 726. ^{1}H NMR (MeOD) δ 7.26 (dd, J = 8.7 Hz, J = 7.5 Hz, 1H, Ar-H), 7.14 (d, J = 7.8 Hz, 1H, Ar-H), 7.03 (d, J = 8.2 Hz, 1H, Ar-H), 6.95 (d, J = 8.7 Hz, 1H, Ar-H), 6.95 (d, J = 7.5 Hz, 1H, Ar-H), 6.85 (d, J = 7.8 Hz, 1H, Ar-H), 6.84 (d, J = 8.2 Hz, 1H, Ar-H), 4.35 (d, J = 16.3 Hz, 1H, CH_2), 4.30 (d, J = 16.3 Hz, 1H, CH_2), 4.10 (s, 3H, O–CH_3), 3.27–3.31 (m, 2H, CH_2), 2.58–2.66 (m, 1H, CH_2), 2.46–2.54 (m, 1H, CH_2). ^{13}C NMR (MeOD) δ 158.0, 155.6, 154.9, 136.6, 132.9, 132.9, 131.9, 130.1, 129.9, 127.3, 120.4, 116.4, 116.3,

113.5, 110.8, 105.5, 56.9, 42.5, 42.2, 24.8. EI-MS (70 eV) *m/z* (%): 321 (100) $[M]^+$, 304 (23), 292 (23), 277 (17), 260 (18), 160 (10), 101 (7). MS (ESI) exact mass calcd for $C_{20}H_{19}NO_3$: 322.14377 $[M + H]^+$; found: 322.14320 $[M + H]^+$.

*4.3.5. (R)-3-(N-tert-Butoxycarbonyl-propyl-2′-amino)-anisole (**35**)*

A Grignard reagent, freshly prepared from 3-bromoanisole (**4**) (9.95 g, 53.2 mmol) and magnesium (9.10 g, 374 mmol) in THF (45 mL) was cooled to −30 °C. $CuBr \cdot SMe_2$ (620 mg, 3.02 mmol) was added in four portions and the mixture was stirred at this temperature for 30 min. After cooling to −78 °C a solution of **34** (4.56 g, 29.0 mmol) in THF (30 mL) was added over a period of 30 min and the mixture was allowed to warm up to room temperature over night. The insoluble components were filtered off and washed with H_2O, Et_2O and CH_2Cl_2. The organic solvents were evaporated and the remaining aqueous phase extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, concentrated in vacuo and the residue was ingested in *n*-hexane/2-propanol (100:1) and the desired product was obtained as beige crystals. The mother liquor was concentrated and remains of the desired product were purified by flash chromatography (petroleum ether/ethyl acetate 9:1) (6.36 g, 24.0 mmol, 83%); mp 70–72 (*n*-hexane/2-propanol). $[\alpha]_D^{25}$ = −93.4° (*c* = 0.11 mol/l, MeOH). IR (KBr, cm^{-1}) *ν* 3384, 3008, 2981, 2968, 2936, 2873, 2841, 1682, 1602, 1514, 1446, 1391, 1366, 1259, 1168, 1057, 1036, 882, 841, 791, 754, 739, 699, 553, 466, 410. ^1H NMR ($CDCl_3$) *δ* 7.20 (t, ^3J = 7.7 Hz, 1H, Ar-H), 6.77 (d, ^3J = 8.1 Hz, 1H, Ar-H), 6.76 (d, ^3J = 8.1 Hz, 1H, Ar-H), 6.72 (dd, ^4J = 2.0 Hz, ^4J = 1.6 Hz, 1H, Ar-H), 4.37 (s, 1H, NH), 3.92 (m, 1H, CH), 3.80 (s, 3H, O−CH_3), 2.82 (dd, ^2J = 13.3 Hz, ^3J = 5.5 Hz, 1H, CH_2), 2.62 (dd, ^2J = 13.3 Hz, ^3J = 7.4 Hz, 1H, CH_2), 1.43 (s, 9H, $C(CH_3)_3$), 1.08 (d, ^3J = 6.7 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) *δ* 159.6, 155.2, 139.8, 129.2, 121.9, 115.0, 111.8, 79.1, 55.1, 47.3, 43.0, 28.4, 20.2. EI-MS (70 eV) *m/z* (%): 265 $[M]^+$ (1), 144 (11), 57 (65), 44 (100). Anal. calcd for $C_{15}H_{23}NO_3$ (265.35): C, 67.90; H, 8.74; N, 5.28; found: C, 67.77; H, 8.78; N, 5.52.

*4.3.6. (R)-4-Bromo-3-(2′-acetamidoprop-1′-yl)-anisole (**37**)*

A solution of **36** (400 mg, 1.64 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C. Successively NEt_3 (199 mg, 1.96 mmol) and dest. acetylchloride (142 mg, 1.80 mmol) was added. The reaction mixture was allowed to warm up to room temperature and stirred for 1 h. After addition of water (10 mL) the mixture was extracted with CH_2Cl_2 and the organic layer dried over Na_2SO_4. Purification by column chromatography (CH_2Cl_2/MeOH 30:1) gave the desired product as yellow solid (370 mg, 1.29 mmol, 79%); mp. 138–139 °C (CH_2Cl_2/MeOH). $[\alpha]_D^{25}$ = −5.35° (*c* = 0.10 mol/l, MeOH). IR (KBr, cm^{-1}) *ν* 3429, 3071, 2966, 2837, 1638, 1542, 1458, 1378, 1243, 1167, 1127, 1081, 1019, 970, 858, 810, 701, 601, 463, 412. ^1H NMR ($CDCl_3$) *δ* 7.38 (d, ^3J = 8.8 Hz, 1H, Ar-H), 6.78 (d, ^4J = 3.1 Hz, 1H, Ar-H), 6.62 (dd, ^3J = 8.8 Hz, ^4J = 3.1 Hz, 1H, Ar-H), 5.71 (s, 1H, NH), 4.29 (m, 1H, CH), 3.74 (s, 3H, O−CH_3), 2.91 (dd, ^2J = 13.2 Hz, ^3J = 7.6 Hz, 1H, CH_2) 2.82 (dd, ^2J = 13.2 Hz, ^3J = 7.6 Hz, 1H, CH_2), 1.89 (s, 3H, $COCH_3$), 1.17 (d, 3H, ^3J = 6.7 Hz, CH_3). ^{13}C NMR ($CDCl_3$) *δ* 171.3, 160.9, 140.8, 135.2, 118.5, 117.3, 116.0, 57.4, 48.2, 44.0, 25.4, 22.5. EI-MS (70 eV) *m/z* (%): 206 (4), 86 (16), 44 (100). Anal. calcd for $C_{12}H_{16}BrNO_2$ (286.16): C, 50.37; H, 5.64; N, 4.89; found: C, 50.16; H, 5.50; N, 4.71.

*4.3.7. (R)-5-Bromo-8-methoxy-1,3-dimethyl-3,4-dihydroisoquinoline (**38**)*

$POCl_3$ (2.51 g, 5.79 mmol) was added to a solution of **37** (100 mg, 349 μmol) in abs. MeCN (10 mL) and the reaction mixture refluxed for 1.5 h. First water and then 20% NaOH-solution was added. Afterwards the solvent was removed under reduced pressure and the residue extracted with CH_2Cl_2. The crude product was purified by column chromatography on deactivated silica (7.5% NH_3, CH_2Cl_2) and the desired compound was obtained as yellow solid (64 mg, 239 μmol, 68%); mp 75–76 °C (CH_2Cl_2). $[\alpha]_D^{25}$ = −76.1° (*c* = 0.13 mol/l, MeOH). IR (KBr, cm^{-1}) *ν* 2973, 2927, 2843, 1612, 1577, 1564, 1454, 1424, 1364, 1345, 1313, 1281, 1250, 1203, 1114, 1088, 1060, 1019, 951, 871, 797, 688, 647, 634, 612. ^1H NMR ($CDCl_3$) *δ* 7.49 (d, ^3J = 8.8 Hz, 1H, Ar-H), 6.76 (d, ^3J = 8.8 Hz, 1H, Ar-H), 3.85 (s, 3H, O−CH_3), 3.31 (m, 1H, CH), 2.91 (dd, ^2J = 16.4 Hz, ^3J = 4.6 Hz, 1H, CH_2), 2.44 (s, 3H, $CNCH_3$), 2.22 (dd, ^2J = 16.4 Hz, ^3J = 13.1 Hz, 1H, CH_2), 1.40 (d, ^3J = 6.7 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) *δ* 165.7, 158.8, 141.7, 136.8, 123.1, 116.0, 113.7, 57.6, 52.9, 36.1, 28.7, 23.3. EI-MS (70 eV) *m/z* (%): 269 (69), 268 $[M]^+$ (55), 267 (100), 266 (47), 254 (68), 252 (61), 239 (20), 237 (19), 224 (23), 173 (26), 132 (17), 115 (29), 103 (20), 102 (22), 44 (16). MS (ESI) exact mass calcd for $C_{12}H_{15}BrNO$: 268.03315 $[M + H]^+$; found: 268.03314 $[M + H]^+$.

*4.4. General procedure of the Suzuki–Miyaura coupling between **38** and the boronic acids*

$Pd(PPh_3)_4$ (10 mol%) was added to a degassed mixture of **38** (100 mg), boronic acid (2 equiv.) and 2 M Na_2CO_3 solution (5 mL) in toluene (40 mL). After heating up to 80 °C over night, water (15 mL) was added to the reaction mixture and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, concentrated and purified via column chromatography on deactivated silica gel (7.5% NH_3, petroleum ether/ethyl acetate 5:1) giving the biaryl compounds.

*4.4.1. (R)-8-Methoxy-1,3-dimethyl-5-phenyl-3,4-dihydroisoquinoline (**39a**)*

Yellowish oil (60 mg, 0.23 mmol, 77%); $[\alpha]_D^{25}$ = −112° (0.1 mol/l). IR (KBr, cm^{-1}) *ν* 3732, 3628, 3032, 2926, 2852, 1616, 1583, 1474, 1440, 1406, 1368, 1268, 1199, 1153, 1105, 1088, 1064, 1025, 814, 770, 738, 702, 668, 649, 638, 623, 614, 605. ^1H NMR ($CDCl_3$) *δ* 7.41–7.25 (m, 6H, Ar-H), 6.91 (d, ^3J = 8.5 Hz, 1H, Ar-H), 3.89 (s, 3H, O−CH_3), 3.16 (m, 1H, CH), 2.56 (dd, ^2J = 16.0 Hz, ^3J = 4.2 Hz, 1H, CH_2), 2.51 (s, 3H, $CNCH_3$), 2.25 (dd, ^2J = 13.3 Hz, ^3J = 2.6 Hz, 1H, CH_2), 1.30 (d, ^3J = 6.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) *δ* 157.0, 140.5, 138.5, 133.1, 132.9, 129.6, 128.4, 127.2, 119.9, 110.1, 55.7, 52.0, 32.9, 27.7, 22.1. EI-MS (70 eV) *m/z* (%): 266 (20), 265 $[M]^+$ (100), 264 (47), 250 (40), 236 (9), 235 (9), 222 (9), 178 (12), 165 (11), 57 (9). MS (ESI) exact mass calcd for $C_{18}H_{20}NO$: 266.15394 $[M + H]^+$; found: 266.15394 $[M + H]^+$.

*4.4.2. (R)-8-Methoxy-1,3-dimethyl-5-p-tolyl-3,4-dihydroisoquinoline (**40a**)*

Yellow oil (98 mg, 0.35 mmol, 78%); $[\alpha]_D^{25}$ = −59.5° (*c* = 0.02 mol/l, CH_2Cl_2). IR (KBr, cm^{-1}) *ν* 2962, 2926, 1616, 1581, 1477, 1439, 1373, 1346, 1270, 1250, 1198, 1153, 1104, 1087, 1063, 1021, 954, 875, 808, 724, 689, 632, 620. ^1H NMR ($CDCl_3$) *δ* 7.29 (d, ^3J = 8.6 Hz, 1H, Ar-H), 7.21 (d, ^3J = 7.9 Hz, 2H, Ar-H), 7.15 (d, ^3J = 8.1 Hz, 2H, Ar-H), 6.88 (d, ^3J = 8.6, 1H, Ar-H), 3.13 (m, 1H, CH), 2.57 (dd, ^2J = 16.0 Hz, ^3J = 4.24 Hz, 1H, CH_2), 2.50 (d, ^5J = 1.69 Hz, 3H, $CNCH_3$), 2.23 (dd, ^2J = 13.1 Hz, ^3J = 2.7 Hz, 1H, CH_2), 1.29 (d, ^3J = 6.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) *δ* 164.9, 157.0, 138.4, 137.5, 136.9, 133.0, 129.5, 129.1, 119.8, 115.6, 110.1, 55.7, 51.9, 32.9, 27.6, 22.0, 21.4. EI-MS (70 eV) *m/z* (%): 280 (22), 279 $[M]^+$ (100), 278 (47), 265 (10), 264 (47), 250 (10), 249 (10), 236 (10), 222 (8), 178 (10). MS (ESI) exact mass calcd for $C_{19}H_{22}NO$: 280.16959 $[M + H]^+$; found: 280.16959 $[M + H]^+$.

*4.4.3. (R)-8-Methoxy-5-(4′-methoxyphenyl)-1,3-dimethyl-3,4-dihydroisoquinoline (**41a**)*

Yellowish oil (29.3 mg, 99.0 μmol, 87%); $[\alpha]_D^{25}$ = −163° (*c* = 1.00 mol/l, CH_2Cl_2). IR (KBr, cm^{-1}) *ν* 2925, 2852, 1615, 1478, 1030. ^1H NMR ($CDCl_3$) *δ* 7.30 (d, ^3J = 8.6 Hz, 1H, Ar-H), 7.20 (d, ^3J = 8.8 Hz, 2H, Ar-H), 6.95 (d, ^3J = 8.8 Hz, 2H, Ar-H), 6.90 (d, ^3J = 8.6 Hz, 1H, Ar-H), 3.90 (s, 3H, O−CH_3), 3.85 (s, 3H, O−CH_3), 3.16 (m, 1H, CH), 2.58 (dd, ^2J = 16.0 Hz, ^3J = 4.2 Hz, 1H, CH_2), 2.52 (d,

^5J = 1.9 Hz, 3H, $CNCH_3$), 2.24 (dd, ^2J = 16.0 Hz, ^3J = 13.3 Hz, 1H, CH_2), 1.31 (d, ^3J = 6.7 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 173.4, 164.5, 158.7, 156.6, 138.3, 132.4, 132.7, 130.4, 119.7, 113.6, 109.8, 55.5, 55.3, 51.8, 32.7, 27.4, 21.9. EI-MS (70 eV) *m*/*z* (%): 296 (26), 295 $[M]^+$ (100), 294 (58), 293 (73), 282 (15), 281 (16), 280 (46), 279 (14), 237 (21), 165 (20), 152 (13), 97 (14), 83 (16), 69 (18). MS (ESI) exact mass calcd for $C_{22}H_{22}NO$: 296.16451 $[M + H]^+$; found: 296.16454 $[M + H]^+$.

4.4.4. (*R*)-5-(4′-Chlorophenyl)-8-methoxy-1,3-dimethyl-3,4-dihydroisoquinoline (**42a**)

White solid (29.0 mg, 96.7 μmol, 83%); mp 114 °C (CH_2Cl_2/MeOH). $[\alpha]_D^{25}$ = −123° (*c* = 1.00 mol/l, CH_2Cl_2). IR (KBr, cm^{-1}) ν 2925, 2852, 1620, 1475. ^{1}H NMR ($CDCl_3$) δ 7.39 (d, ^3J = 8.6 Hz, 2H, Ar-H), 7.29 (d, ^3J = 8.6 Hz, 1H, Ar-H), 7.21 (d, ^3J = 8.6 Hz, 2H, Ar-H), 6.92 (d, ^3J = 8.6 Hz, 1H, Ar-H), 3.91 (s, 3H, O—CH_3), 3.19 (m, 1H, CH), 2.53 (d, ^5J = 1.9 Hz, 3H, $CNCH_3$), 2.52 (dd, ^2J = 15.8 Hz, ^3J = 4.2 Hz, 1H, CH_2), 2.23 (dd, ^2J = 15.8 Hz, ^3J = 13.1 Hz, 1H, CH_2), 1.32 (d, ^3J = 6.7 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 157.7, 139.3, 138.8, 133.7, 133.3, 132.2, 131.4, 129.1, 110.6, 56.2, 52.3, 33.3, 28.1, 22.5. EI-MS (70 eV) *m*/*z* (%): 301 (35), 300 (38), 299 $[M]^+$ (100), 298 (49), 286 (18), 285 (13), 284 (52), 270 (14), 269 (14), 256 (13), 178 (18), 165 (13). MS (ESI) exact mass calcd for $C_{17}H_{18}NO$: 300.11497 $[M + H]^+$; found: 300.11408 $[M + H]^+$.

4.4.5. (*R*)-8-Methoxy-1,3-dimethyl-5-(4′-(trifluoromethyl)phenyl)-3,4-dihydroisoquinoline (**43a**)

White solid (105 mg, 0.31 mmol, 84%); mp 123 °C (CH_2Cl_2/MeOH). $[\alpha]_D^{25}$ = −127° (*c* = 0.01 mol/l, CH_2Cl_2). IR (KBr, cm^{-1}) ν 2952, 2896, 2845, 1735, 1616, 1585, 1565, 1523, 1478, 1442, 1420, 1399, 1368, 1323, 1286, 1270, 1196, 1170, 1153, 1113, 1095, 1068, 1043, 1017, 964, 942, 924, 905, 876, 857, 812, 766, 748, 710, 683, 664, 621. ^{1}H NMR ($CDCl_3$) δ 7.66 (d, ^3J = 8.0 Hz, 2H, Ar-H), 7.38 (d, ^3J = 7.9, 2H, Ar-H), 7.28 (d, ^3J = 8.6 Hz, 1H, Ar-H), 6.92 (d, ^3J = 8.6 Hz, 1H, Ar-H), 3.90 (s, 3H, O—CH_3), 3.13 (m, 1H, CH), 2.49 (d, ^5J = 2.0 Hz, 3H, $CNCH_3$), 2.49 (dd, ^2J = 15.9 Hz, ^3J = 4.2, 1H, CH_2), 2.22 (dd, ^2J = 13.2 Hz, ^3J = 2.7 Hz, 1H, CH_2), 1.29 (d, ^3J = 6.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 157.4, 144.2, 138.5, 132.6, 131.6, 129.9, 129.5, 129.2, 125.4, 120.1, 110.2, 55.7, 51.9, 32.8, 27.7, 22.2. EI-MS (70 eV) *m*/*z* (%): 334 (23), 333 $[M]^+$ (100), 332 (41), 331 (12), 320 (33), 319 (14), 318 (70), 304 (14), 303 (11), 290 (15), 275 (10). MS (ESI) exact mass calcd for $C_{19}H_{19}F_3NO$: 334.14133 $[M + H]^+$; found: 334.14118 $[M + H]^+$.

4.4.6. (*R*)-5-(3-Chlorophenyl)-8-methoxy-1,3-dimethyl-3,4-dihydroisoquinoline (**44a**)

Yellowish oil (53 mg, 0.18 mmol, 64%); $[\alpha]_D^{25}$ = 104° (*c* = 0.1 mol/l). IR (KBr, cm^{-1}) ν 2927, 1614, 1453, 1398, 1323, 1267, 1234, 1197, 1133, 1109, 1075, 973, 838, 803, 764, 697. ^{1}H NMR ($CDCl_3$) δ 7.38—7.29 (m, 3H, Ar-H), 7.25 (m, 1H, Ar-H), 7.12 (m, 1H, Ar-H), 6.91 (d, ^3J = 8.6 Hz, 1H, Ar-H), 3.89 (s, 3H, O—CH_3), 3.17 (m, 1H, CH), 2.57 (s, 3H, $CNCH_3$), 2.56 (m, 1H, CH_2), 2.27 (dd, ^2J = 15.5 Hz, ^3J = 12.5 Hz, 1H, CH_2), ^{13}C NMR ($CDCl_3$) δ 142.2, 138.3, 134.4, 133.2, 131.8, 129.7, 129.6, 129.6, 129.5, 127.8, 127.5, 127.4, 119.7, 110.2, 109.0, 55.8, 51.6, 32.7, 27.4, 21.7. EI-MS (70 eV) *m*/*z* (%): 302 (7), 301 (35), 300 (36), 299 $[M]^+$ (100), 298 (50), 286 (18), 285 (11), 284 (47), 270 (12), 269 (12), 256 (12), 243 (6). MS (ESI) exact mass calcd for $C_{18}H_{19}NO$: 300.11497 $[M + H]^+$; found: 300.11497 $[M + H]^+$.

4.4.7. (*R*)-8-Methoxy-1,3-dimethyl-5-(naphthalen-1-yl)-3,4-dihydroisoquinoline (**45a**)

Yellowish oil (28.7 mg, 91.0 μmol, 78%); $[\alpha]_D^{25}$ = −129° (*c* = 1.00 mol/l, CH_2Cl_2). IR (KBr, cm^{-1}) ν 2925, 2853, 1618, 1277, 1022, 938. ^{1}H NMR ($CDCl_3$) δ 7.93—7.88 (m, 2H, Ar-H), 7.55—7.46 (m, 3H, Ar-H), 7.43—7.28 (m, 3H, Ar-H), 6.89 (d, ^3J = 8.5 Hz, 1H, Ar-H), 3.96 (s, 3H, O—CH_3), 3.28—3.15 (m, 1H, CH), 2.58 (d, ^5J = 1.9 Hz, 3H, $CNCH_3$), 2.26—2.15 (m, 1H, CH_2), 2.07—1.93 (m, 1H, CH_2), 1.20 (d, ^3J = 6.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 164.0, 156.9, 139.7, 138.4, 133.7, 133.4, 132.4, 131.2, 128.4, 127.8, 127.6, 127.0, 126.2, 125.9, 125.4, 119.4, 55.5, 51.6, 32.3, 27.7, 21.8. EI-MS (70 eV) *m*/*z* (%): 317 (39), 316 (31), 315 $[M]^+$ (78), 314 (58), 313 (100), 304 (36), 303 (46), 302 (30), 300 (41), 288 (36), 286 (29), 257 (30), 215 (32), 202 (32), 189 (18) 57 (31). MS (ESI) exact mass calcd for $C_{19}H_{22}NO$: 316.16959 $[M + H]^+$; found: 316.16961 $[M + H]^+$.

4.4.8. (*R*)-8-Methoxy-1,3-dimethyl-5-(naphthalen-2-yl)-3,4-dihydroisoquinoline (**46a**)

Bright yellow solid (25.8 mg, 82.0 μmol, 72%); mp 119 °C (ethyl acetate). $[\alpha]_D^{25}$ = −129° (*c* = 1.00 mol/l, CH_2Cl_2). IR (KBr, cm^{-1}) ν 2924, 2852, 1620, 1028, 938, 865. ^{1}H NMR ($CDCl_3$) δ 7.90—7.85 (m, 3H, Ar-H), 7.74 (s, 1H, Ar-H), 7.52 (m, 2H, Ar-H), 7.43 (m, 2H, Ar-H), 6.96 (d, ^3J = 8.6 Hz, 1H, Ar-H), 3.93 (s, 3H, O—CH_3), 3.18 (m, 1H, CH), 2.62 (dd, ^2J = 16.0 Hz, ^3J = 4.2 Hz, 1H, CH_2), 2.55 (d, ^5J = 1.9 Hz, 3H, CH_3), 2.31 (dd, ^2J = 16.0 Hz, ^3J = 13.3 Hz, 1H, CH_2), 1.30 (d, ^3J = 6.7 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 164.3, 156.8, 138.5, 137.8, 133.2, 132.8, 132.7, 132.2, 128.0, 127.9, 127.7, 126.3, 126.0, 119.7, 109.8, 55.5, 51.7, 32.7, 27.5, 21.9. EI-MS (70 eV) *m*/*z* (%): 315 $[M]^+$ (4), 314 (27), 313 (100), 270 (7), 257 (22), 239 (7), 229 (13), 228 (17), 226 (8), 156 (4), 113 (4). MS (ESI) exact mass calcd for $C_{22}H_{22}NO$: 316.16959 $[M + H]^+$; found: 316.16972 $[M + H]^+$.

4.5. General procedure of O-demethylation of **39a**—**46a** using BBr_3

BBr_3 (0.25 mL, 1 M solution in *n*-hexane, 5 equiv.) was added to a solution of the isoquinoline in CH_2Cl_2 (6 mL) at 0 °C. After stirring at 0 °C for 5 h the mixtures were warmed to room temperature and stirred for additional 24 h. Then MeOH (5 mL) was added and the solvent removed under reduced pressure. The residue was submitted to column chromatography on deactivated silica (7.5% NH_3, CH_2Cl_2/MeOH 15:1 to 12:1).

4.5.1. (*R*)-1,3-Dimethyl-5-phenyl-3,4-dihydroisoquinolin-8-ol (**39b**)

Yellowish oil (27 mg, 0.11 mmol, 73%); $[\alpha]_D^{25}$ = 99.8° (*c* = 0.02 mol/l, CH_2Cl_2). IR (KBr, cm^{-1}) ν 2974, 2927, 2363, 2160, 2001, 1716, 1610, 1528, 1472, 1451, 1426, 1364, 1340, 1303, 1279, 1229, 1206, 1180, 1161, 1076, 1046, 1023, 877, 829, 773, 756, 735, 703, 674, 622, 611. ^{1}H NMR ($CDCl_3$) δ 7.39—7.18 (m, 6H, Ar-H), 6.78 (d, ^3J = 8.8 Hz, 1H, Ar-H), 3.54—3.48 (m, 1H, CH), 2.83 (d, ^4J = 1.4 Hz, 3H, $CNCH_3$), 2.75 (dd, ^2J = 16.0 Hz, ^3J = 4.5 Hz, 1H, CH_2), 2.48 (dd, ^2J = 16.0 Hz, ^3J = 11.4 Hz, 1H, CH_2), 1.33 (d, ^3J = 6.7, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 171.5, 168.2, 140.9, 137.3, 135.1, 129.7, 128.4, 127.1, 126.7, 120.6, 115.7, 49.5, 33.2, 25.3, 19.9. EI-MS (70 eV) *m*/*z* (%): 251 $[M]^+$ (4), 91 (16), 83 (10), 70 (12), 69 (15), 67 (10), 57 (17), 44 (90), 43 (20), 41 (31). MS (ESI) exact mass calcd for $C_{17}H_{18}NO$: 252.13829 $[M + H]^+$; found: 252.13829 $[M + H]^+$.

4.5.2. (*R*)-1,3-Dimethyl-5-p-tolyl-3,4-dihydroisoquinolin-8-ol (**40b**)

Yellowish oil (10 mg, 37.7 μmol, 72%); $[\alpha]_D^{25}$ = 43.2° (*c* = 0.02 mol/l, CH_2Cl_2). IR (KBr, cm^{-1}) ν 2923, 2363, 1611, 1440, 1301, 1203, 1019, 816, 698, 643, 632, 612. ^{1}H NMR ($CDCl_3$) δ 7.18—7.10 (m, 5H, Ar-H), 6.77 (d, ^3J = 8.8 Hz, 1H, Ar-H), 3.47 (m, 1H, CH), 2.80 (s, 3H, CH_3), 2.74 (dd, ^2J = 16.1 Hz, ^3J = 4.6 Hz, 1H, CH_2), 2.45 (dd, ^2J = 16.0 Hz, ^3J = 11.6 Hz, 1H, CH_2), 2.37 (s, 3H, CH_3), 1.31 (d, ^3J = 4.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ = 171.3, 168.1, 138.0, 137.4, 136.4, 135.1, 129.6, 129.1, 127.2, 120.7, 115.6, 49.6, 33.2, 25.4, 21.3, 20.0. EI-MS (70 eV) *m*/*z* (%): 266 (21), 265 $[M]^+$ (100), 264 (37), 250 (21), 237 (21), 236 (10), 178 (10), 165 (8). MS (ESI) exact mass calcd for $C_{18}H_{20}NO$: 266.15394 $[M + H]^+$; found: 266.15394 $[M + H]^+$.

4.5.3. (R)-5-(4-Hydroxyphenyl)-1,3-dimethyl-3,4-dihydroisoquinolin-8-ol (**41b**)

Yellowish oil (15.4 mg, 57.6 μmol, 67%); $[\alpha]_D^{25} = 101°$ ($c = 1.00$ mol/l, CH_2Cl_2/MeOH). IR (KBr, cm^{-1}) ν 3430, 2925, 2853, 2360, 1632, 1026. ^1H NMR (MeOD) δ 7.52 (d, $^3J = 8.6$ Hz, 1H, Ar-H), 7.10 (d, $^3J = 8.6$ Hz, 2H, Ar-H), 6.99 (d, $^3J = 8.6$ Hz, 1H, Ar-H), 6.85 (d, $^3J = 8.6$ Hz, 2H, Ar-H), 3.84 (m, 1H, CH), 2.99 (dd, 1H, $^2J = 16.7$ Hz, $^3J = 5.1$ Hz, 1H, CH_2), 2.90 (d, $^5J = 1.5$ Hz, 3H, $CNCH_3$), 2.80 (dd, $^2J = 16.7$ Hz, $^3J = 11.6$ Hz, 1H, CH_2), 1.38 (d, $^3J = 6.7$ Hz, 3H, CH_3). ^{13}C NMR (MeOD) $\delta = 178.9, 162.0, 158.4, 141.6, 137.2, 134.1, 131.7, 131.4, 117.4, 116.5, 114.5, 55.0, 33.2, 25.1, 18.2$. EI-MS (70 eV) m/z (%): 268 (22), 267 $[M]^+$ (100), 266 (41), 254 (19), 252 (18), 239 (23), 238 (12), 165 (10), 81 (10). MS (ESI) exact mass calcd for $C_{17}H_{18}NO_2$: 268.13321 $[M + H]^+$; found: 268.13266 $[M + H]^+$.

4.5.4. (R)-5-(4-Chlorophenyl)-1,3-dimethyl-3,4-dihydroisoquinolin-8-ol (**42b**)

Bright yellow solid (10.2 mg, 35.7 μmol, 99%); mp 115 °C (CH_2Cl_2/MeOH). $[\alpha]_D^{25} = 22°$ ($c = 1.00$ mol/l, CH_2Cl_2/MeOH 4:1). IR (KBr, cm^{-1}) ν 3418, 2925, 2854, 1385, 1027. ^1H NMR (CD_3COCD_3) δ 7.54 (d, $^3J = 8.6$ Hz, 1H, Ar-H), 7.45 (d, $^3J = 8.6$ Hz, 2H, Ar-H), 7.29 (d, $^3J = 8.6$ Hz, 2H, Ar-H), 7.04 (d, $^3J = 8.6$ Hz, 1H, Ar-H), 3.30 (m, 1H, CH), 2.62 (s, 3H, $CNCH_3$), 2.63 (dd, $^2J = 12.7$ Hz, $^3J = 4.3$ Hz, 1H, CH_2), 2.33 (dd, $^2J = 12.6$ Hz, $^3J = 3.2$ Hz, 1H, CH_2), 1.27 (d, $^3J = 6.7$ Hz, 3H, CH_3). ^{13}C NMR (MeOD) $\delta = 178.7, 162.4, 141.1, 139.0, 137.4, 134.8, 132.6, 114.5, 132.1, 129.8, 117.5, 50.2, 33.0, 30.8, 18.0$. EI-MS (70 eV) m/z (%): 287 (27), 286 (29), 285 $[M]^+$ (79), 283 (100), 272 (43), 269 (18), 257 (20), 178 (20), 97 (22), 83 (23), 69 (30), 57 (43). MS (ESI) exact mass calcd for $C_{17}H_{17}ClNO$: 286.09932 $[M + H]^+$; found: 286.09949 $[M + H]^+$.

4.5.5. (R)-1,3-Dimethyl-5-(4-(trifluoromethyl)phenyl)-3,4-dihydroisoquinolin-8-ol (**43b**)

Yellow oil (92 mg, 28.8 mmol, 93%); $[\alpha]_D^{25} = 29.2°$ ($c = 0.01$ mol/l, CH_2Cl_2). IR (KBr, cm^{-1}) ν 2964, 1720, 1612, 1520, 1434, 1324, 1279, 1163, 1124, 1070, 1017, 829, 618, 607. ^1H NMR (CD_3COCD_3) δ 7.75 (d, $^3J = 8.1$ Hz, 2H, Ar-H), 7.53 (d, $^3J = 7.9$ Hz, 2H, Ar-H), 7.22 (d, $^3J = 8.7$ Hz, 1H, Ar-H), 6.93 (d, $^3J = 8.6$ Hz, 1H, Ar-H), 3.28 (m, 1H, CH), 2.62 (dd, $^2J = 13.3$ Hz, $^3J = 4.4$ Hz, 1H, CH_2), 2.60 (s, 3H, $CNCH_3$), 2.35 (dd, $^2J = 14.0$ Hz, $^3J = 9.8$ Hz, 1H, CH_2), 1.26 (d, $^3J = 5.4$ Hz, 3H, CH_3). ^{13}C NMR (CD_3COCD_3) δ 166.9, 146.6, 146.0, 137.8, 135.1, 131.1, 130.5, 130.2, 129.4, 128.8, 128.4, 126.0, 118.8, 117.5, 51.6, 33.5, 26.8, 21.5. EI-MS (70 eV) m/z (%): 319 $[M]^+$ (27), 318 (11), 291 (7), 175 (5), 149 (10), 70 (11), 63 (15), 43 (100). MS (ESI) exact mass calcd for $C_{18}H_{17}F_3NO$: 320.12568 $[M + H]^+$; found: 320.12569 $[M + H]^+$.

4.5.6. (R)-5-(3-Chlorophenyl)-1,3-dimethyl-3,4-dihydroisoquinolin-8-ol (**44b**)

Yellowish oil (19.0 mg, 66.5 μmol, 69%); $[\alpha]_D^{25} = 133°$ ($c = 0.01$ mol/l, CH_2Cl_2). IR (KBr, cm^{-1}) ν 3651, 3639, 2982, 1969, 1591, 1562, 1524, 1422, 1361, 1339, 1298, 1204, 1157, 1076, 1043, 1004, 879, 825, 785, 763, 729, 700, 645, 626, 606. ^1H NMR ($CDCl_3$) δ 7.28–7.21 (m, 3H, Ar-H), 7.14–7.08 (m, 2H, Ar-H), 6.76 (d, $^3J = 8.8$ Hz, 1H, Ar-H), 3.50 (m, 1H, CH), 2.81 (s, 3H, $CNCH_3$), 2.71 (dd, $^2J = 16.0$ Hz, $^3J = 4.6$ Hz, 1H, CH_2), 2.45 (dd, $^2J = 16.0$ Hz, $^3J = 11.4$ Hz, 1H, CH_2), 1.32 (d, $^3J = 6.7$ Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 142.7, 137.4, 135.1, 134.2, 130.3, 129.7, 129.6, 128.4, 127.9, 126.9, 125.5, 121.3, 115.3, 49.3, 33.1, 25.3, 19.8. EI-MS (70 eV) m/z (%): 287 (34), 286 (32), 285 $[M]^+$ (100), 270 (19), 257 (29), 256 (14), 179 (11), 178 (22), 176 (10), 165 (17), 152 (13). MS (ESI) exact mass calcd for $C_{17}H_{17}ClNO$: 286.09932 $[M + H]^+$; found: 286.09987 $[M + H]^+$.

4.5.7. (R)-1,3-Dimethyl-5-(naphthalen-1-yl)-3,4-dihydroisoquinolin-8-ol (**45b**)

Yellow solid (23.8 mg, 79.0 μmol, 99%); mp 202 °C (CH_2Cl_2/MeOH) $[\alpha]_D^{25} = 13°$ ($c = 1.00$ mol/l, CH_2Cl_2/MeOH). IR (KBr, cm^{-1}) ν 3424, 2924, 2852, 1633, 1026, 857, 698. ^1H NMR (MeOD) δ 7.89–7.90 (m, 2H, Ar-H), 7.56–7.27 (m, 6H, Ar-H), 7.10 (d, $^3J = 8.6$ Hz, 1H, Ar-H), 3.85 (m, 1H, CH), 2.96 (s, 3H, $CNCH_3$), 2.66 (dd, $^2J = 16.7$ Hz, $^3J = 5.3$ Hz, 1H, CH_2), 2.44 (dd, $^2J = 16.7$ Hz, $^3J = 10.9$ Hz, 1H, CH_2), 1.28 (d, $^3J = 6.7$ Hz, 3H, CH_3). ^{13}C NMR (MeOD) $\delta = 178.6, 162.6, 142.0, 138.6, 138.6, 138.0, 135.3, 133.4, 132.2, 129.7, 128.9, 127.8, 127.3, 126.6, 126.4, 117.5, 114.4, 50.0, 32.9, 25.2, 17.9$. EI-MS (70 eV) m/z (%): 302 (5), 301 $[M]^+$ (2), 289 (27), 288 (100), 259 (6), 231 (8), 215 (6), 202 (6), 136 (6). MS (ESI) exact mass calcd for $C_{21}H_{20}NO$: 302.15394 $[M + H]^+$; found: 302.15409 $[M + H]^+$.

4.5.8. (R)-1,3-Dimethyl-5-(naphthalen-2-yl)-3,4-dihydroisoquinolin-8-ol (**46b**)

Yellowish solid (20.3 mg, 67.5 μmol, 99%); mp 235 °C (CH_2Cl_2/MeOH). $[\alpha]_D^{25} = 41°$ ($c = 1.00$ mol/l, CH_2Cl_2/MeOH). IR (KBr, cm^{-1}) ν 3430, 2924, 2851, 2359, 1633, 1028. ^1H NMR (MeOD) δ 7.93–7.80 (m, 3H, Ar-H), 7.73 (s, 1H, Ar-H), 7.61 (d, $^3J = 8.7$ Hz, 1H, Ar-H), 7.53–7.43 (m, 2H, Ar-H), 7.37 (dd, $^3J = 8.3$ Hz, $^4J = 1.5$ Hz, 1H, Ar-H), 7.04 (d, $^3J = 8.5$ Hz, 1H, Ar-H), 3.82 (m, 1H, CH), 2.97 (dd, $^2J = 16.8$ Hz, $^3J = 5.2$ Hz, 1H, CH_2), 2.90 (s, 3H, $CNCH_3$), 2.84 (dd, $^2J = 16.8$ Hz, $^3J = 11.6$ Hz, 1H, CH_2), 1.32 (d, $^3J = 6.7$ Hz, 3H, CH_3). ^{13}C NMR (MeOD) $\delta = 178.8, 162.3, 141.4, 137.4, 137.7, 134.7, 134.1, 133.9, 129.4, 129.3, 129.1, 128.8, 128.3, 127.7, 127.5, 117.5, 114.5, 50.1, 33.1, 25.1, 18.0$. EI-MS (70 eV) m/z (%): 303 (40), 302 (91), 301 $[M]^+$ (100), 300 (32), 287 (10), 286 (13), 274 (14), 273 (19), 228 (11), 215 (13), 202 (11). MS (ESI) exact mass calcd for $C_{21}H_{20}NO$: 302.15394 $[M + H]^+$; found: 302.15336 $[M + H]^+$.

4.6. Biological tests

In vitro assays (in Basel) with *T. brucei rhodesiense* STIB900, *P. falciparum* K1, *T. cruzi* Tulahuen Lac Z C4 strain, *L. donovani* axenic amastigotes, and rat skeletal myoblast (L6) cells were carried out as previously reported [51]. IC_{50} values are means of two independent assays. Individual measurement differed less than 50%. In vitro assays (in Würzburg) with *L. major* promastigotes, *T. brucei brucei*, and J774.1 macrophages were assessed as described earlier [9,12].

In the in vivo studies each treatment group includes three mice. Infected and not treated mice die between day 6 and 8 post infection. The chloroquine-treated group (4×10 mg/kg i.p.) showed an activity of 99.6% and a mean survival time of 20 days. Compound **44b** did not show toxicity at the tested dose.

4.7. Methods

4.7.1. Data set

Compound **29** was sketched in MOE (Version 2009.10, Chemical Computing Group) and afterwards the geometry was optimized using the default MOE force field (MMFF94×) with default parameters. This compound was used as a template for all other compounds, which were obtained by modifying the template accordingly. The basic amino function in **32** and **33** was used in its protonated form since this would resemble the protonation state under physiological conditions. The modified parts of each molecule were subjected to a renewed geometry optimization while the common substructure with **29** was kept fixed. Since all compounds show a substantial maximum common substructure, this procedure was found to work well. It resulted in a data set that was implicitly superimposed since it was based on the same template.

4.7.2. GRID/PLS

The aforementioned data set was input into GRID (Version 22a, Molecular Discovery) using a grid spacing of 1 Å and a grid size that extended the superimposed molecules by 4 Å in each dimension. Molecular-interaction fields (MIF) for the following probes were computed: N1, O, C3, and DRY. The energy cut-off was set to 0 kcal/

mol (i.e. GRID directive EMAX = 0). The MIFs for each probe were scaled blockwise to assure that each MIF showed equal variance. The scaled MIFs were arranged to obtain one matrix of the dimension 28 × 26,928. This matrix was thinned by only using those columns that showed the top 1% variance. The thinned matrix was related to bioactivity using partial least squares regression (PLS), where the optimal number of PLS factors was determined by leave-one-out cross-validation. Test set predictivity was assessed using leave-multiple out cross-validation in an outer loop [52], i.e., in the outer loop three test set objects were set aside. The remaining 25 molecules were used to form the GRID/PLS model. After all model parameters were estimated, the test set objects were predicted, which assured that the test set prediction was independent of the model selection. 100 partitions into test and training data set were computed to obtain a reliable estimate of test set predictivity. The ensemble average based on the 100 cross-validation runs was computed for the left out objects. All statistical figures of merit as well as the residual plot are based on these ensemble averages for the test objects [53]. Back-projection of the MIFs onto the molecules was done in the standard fashion by multiplying the PLS regression coefficients by the standard deviation of the respective column of the MIF. Displayed are the results of the O probe at a cut-off level of ±0.011.

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