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Original article

Synthesis and antiprotozoal activities of simplified analogs of naphthylisoquinoline alkaloids

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Dedicated to Prof. Peter Riederer on the occasion of his 65th birthday

Abstract

The naphthylisoquinoline alkaloids (NIQs) represent a class of natural products with manifold activities against various tropical diseases. They are isolated from rare and difficult-to-cultivate tropical plants. In order to find novel, more easily accessible analogs and to study structure–activity relationships, a variety of simplified analogs were produced, which bear the functional groups typical of the NIQs, but avoid the synthetically difficult elements of chirality, stereogenic centers and rotationally hindered axes. Their syntheses and activities against *Plasmodium falciparum*, *Trypanosoma cruzi*, and *Leishmania donovani* are described and compared with those of the natural NIQs. Remarkably, quite good activities were found for naphthalene-devoid halogenated isoquinolinic analogs.

1. Introduction

Infectious diseases, like malaria, leishmaniasis, and African sleeping sickness, constitute a major threat to the so-called Third World countries, causing ca. 1.3 million death cases per year just to mention malaria [1]. With drug resistance becoming a rapidly increasing problem and given the lack of suitable vaccines, the development of efficient, non-toxic, and inexpensive new drugs is an urgent task [2–4]. The naphthylisoquinoline alkaloids (NIQs) represent a novel class of natural products that feature manifold promising bioactivities against these diseases. Among them are the antimalarial compounds dioncophylline C (**1**) and dioncopeltine A (**2**) [5], and ancistrotanzanine B (**3**), which is active against *Leishmania donovani*, the pathogen causing leishmaniasis [6,7]. These acetogenic isoquinoline alkaloids [8] with their characteristic structures involving axial chirality and stereogenic centers, occur exclusively in two families of tropical plants, *viz*. the Dioncophyllaceae and the Ancistrocladaceae [9,10]. Since many of the highly active NIQs are only found in traces in their natural source and because the plants are difficult to cultivate [11], there is need to either synthesize the authentic natural products, or to find structural analogs that are easy to prepare but still bear the functionalities required for bioactivity.

Although elegant pathways have been developed for the stereoselective total synthesis of NIQs [12–15], there is urgent demand for the design and synthesis of even more active and less toxic analogs with simpler structures that permit production of the compounds on a larger scale, if required in kilogram quantities. As a first example towards this goal, we have recently prepared a series of aminomethyl-substituted phenylnaphthalenes like **4** (see Fig. 1), which are active against *Trypanosoma cruzi*, but still bear two stereogenic elements, *viz*. a biaryl axis and a stereogenic center [16,17]. In this paper, we report on a group of new NIQ-related biaryls of type **5**, whose isoquinoline portion is significantly simplified by the fact that the two methyl groups at C-1 and C-3 are now both located at C-3, thus avoiding the existence of any of the two stereogenic centers present in the natural alkaloids **1**–**3**. To the underlying novel 3,3-dimethylisoquinoline building block, *para*-substituted aryl substituents with only one oxygen functionality are coupled instead of naphthyl

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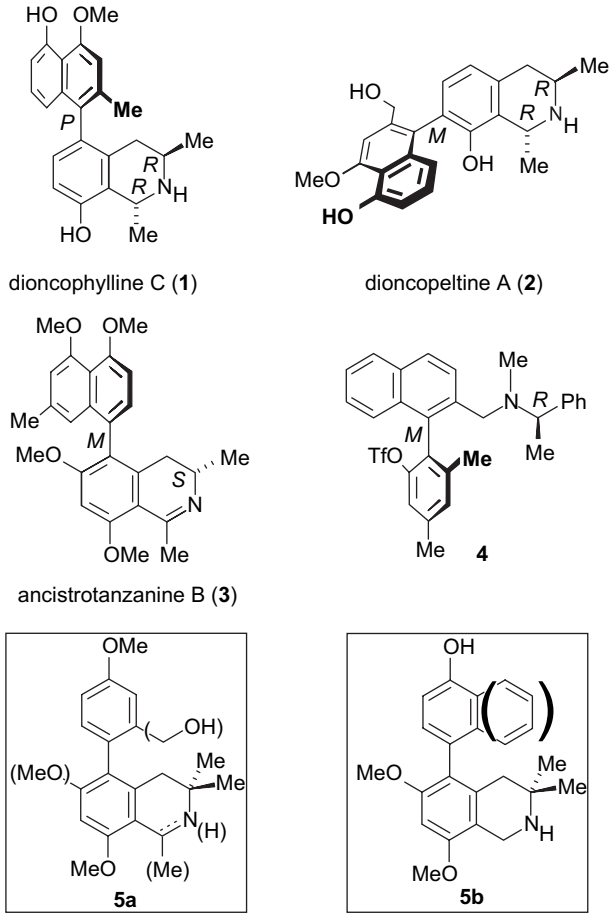


Fig. 1. The bioactive naphthylisoquinoline alkaloids dioncophylline C (**1**), dioncopeltine A (**2**), and ancistroealaine A (**3**), the related simplified biaryl **4**, and the general structures of the new biaryl analogs **5**.

groups with three substituents as found in natural NIQs [18]. Furthermore, by using symmetrical and non-bulky, freely rotating phenyl substituents, even NIQ analogs devoid of axial chirality are produced.

2. Results and discussion

2.1. Chemistry

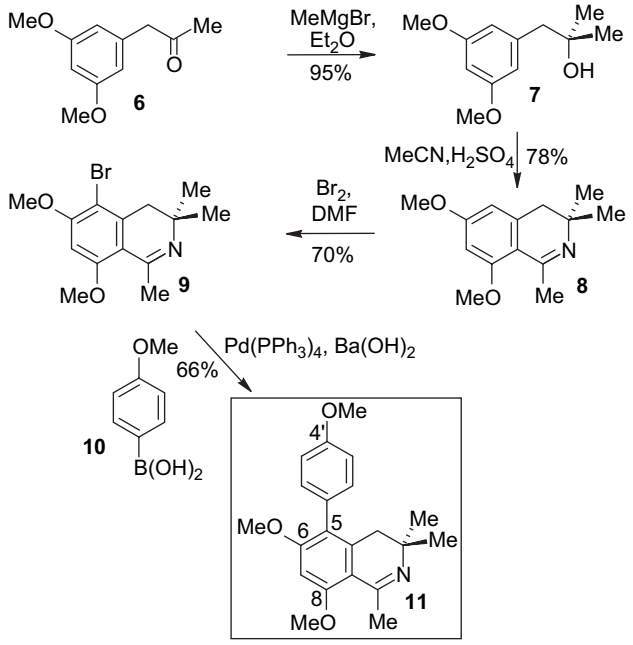
*2.1.1. A simplified structural analog **11** related to ancistrotanzanine B (**3**)*

In view of the structures of natural NIQ alkaloids with the highest activity as yet against *L. donovani*, ancistrotanzanine B (**3**) [6] and its atropisomer, ancistroealaine A [7], a most promising synthetic analog might be the 5-phenyl dihydroisoquinoline **11**. Although — like the natural precedent — bearing methoxy groups in the 6- and 8-positions, and also at 4′, i.e., *para* to the biaryl axis, it would be simplified in having a 'slim' and symmetric phenyl group at C-5 instead of the bicyclic naphthyl substituent in **3**, which, in addition, would avoid the phenomenon of axial chirality and the necessity to synthesize it atropo-selectively (although this has been successfully achieved for **3**, see [19]). Moreover, due to the additional methyl group at C-3, compound **11** is also devoid of stereogenic centers and thus achiral, making it a rewarding, simple-to-prepare synthetic target molecule. Since **11** (like the natural precedent **3**) is a 3,4-dihydroisoquinoline and thus sp^2-configured at C-1, there was, in this case, no necessity to omit the methyl group at this C-atom.

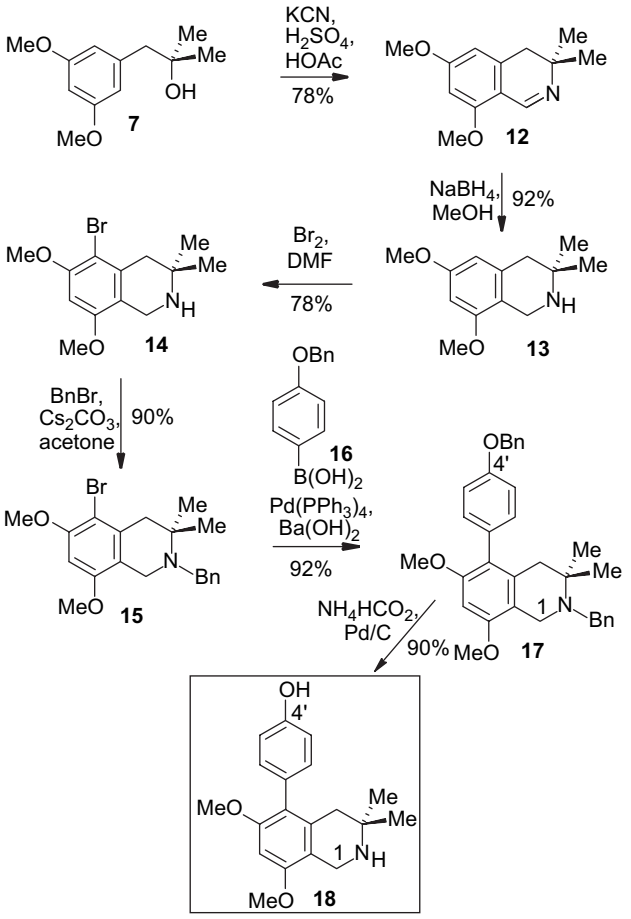
The simple and short synthesis of **11** is shown in Scheme 1. Starting from the known [20] ketone **6**, Grignard reaction with methyl magnesium bromide led to the tertiary alcohol **7**, which was submitted to a Ritter reaction with acetonitrile with in situ cyclization, directly providing the novel achiral isoquinoline building block **8**. Regioselective 5-bromination to **9** and Suzuki cross coupling with the known boronic acid **10** gave the desired ancistrotanzanine B analog **11** in good yields.

*2.1.2. The phenyl tetrahydroisoquinoline **18***

Another possible target molecule, **18**, this time related to the antimalarial alkaloid dioncophylline C (**1**), was again intended to bear a phenyl instead of a naphthyl ring, but this time with a free OH function in the 4′-position and a tetrahydroisoquinoline moiety with a free NH function, as found in **1**. Its synthesis, as shown in Scheme 2, required the preparation of a new, again achiral, tetrahydroisoquinoline **13**, which, due to the sp^3 character of C-1, was planned to have no methyl group at this C-atom. This building block was again synthesized by a Ritter reaction of the tertiary alcohol **7**, now with sodium cyanide as the nitrile reagent, again with in situ cyclization to give the 1-unsubstituted dihydroisoquinoline **12**, which was reduced to provide **13**. Bromination to give **14** and subsequent N-benzylation delivered **15**, which underwent a Suzuki cross coupling with the boronic acid **16** to give **17**, whose deprotection completed the synthesis of the achiral 4′-hydroxyphenyl tetrahydroisoquinoline **18**.



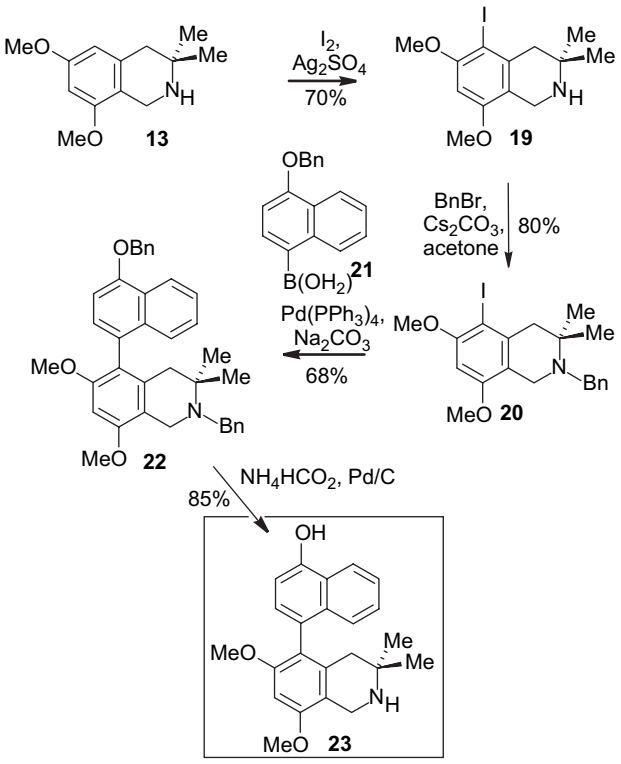
Scheme 1. Synthesis of the ancistrotanzanine A analog **11**.



Scheme 2. Synthesis of the phenyl tetrahydroisoquinoline **18** as a simplified analog of dioncophylline C (**1**).

2.1.3. The naphthyl tetrahydroisoquinoline *23*

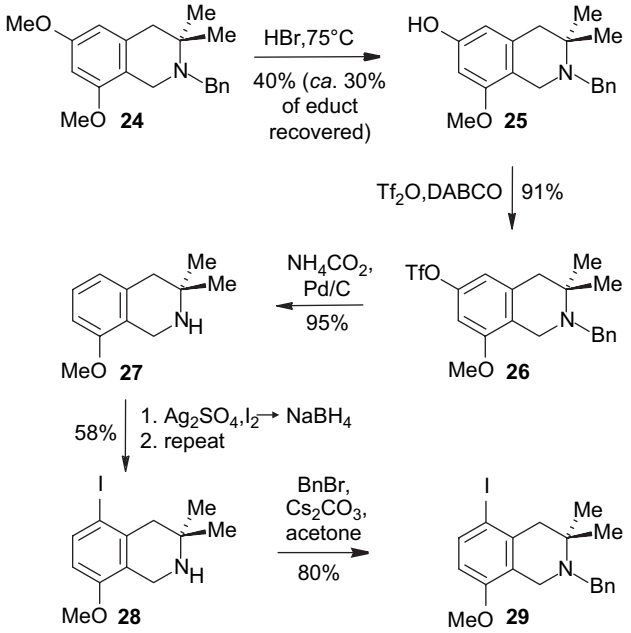
For an investigation of the influence of the naphthyl ring in the natural products, e.g. in **1**, vs. a phenyl ring as in **18**, the slightly less simplified analog **23** was synthesized (Scheme 3). Due to the higher steric hindrance of the naphthylboronic acid **21** as compared to the phenyl analog **16**, the brominated tetrahydroisoquinoline **15** initially failed to undergo the required Suzuki cross coupling. For this reason, the tetrahydroisoquinoline **13** was activated by iodination, leading to **19**, which, after N-protection to **20**, did permit the desired coupling with the naphthylboronic acid **21** to give the biaryl **22**. Hydrogenolytic N- and O-deprotection provided the naphthyl tetrahydroisoquinoline **23**. Different from the other simplified analogs prepared above, **11** and **18**, compound **23** is axially chiral. As already for its precursor **22**, its chirality is evident from the diastereotopic character of the two methyl groups at C-3 (two singlets at 1.17 and 1.24 ppm) and of the protons at C-4 (two doublets at 2.15 and 2.51 ppm, $J = 16.7$ Hz), while the protons at C-1, being more distant from the chiral axis, appear as a (slightly broadened) singlet. For the model analogs **11** and **18** and all other compounds prepared above, by contrast, the respective resonances had been isochronous. For reasons of economy, **23** was prepared and tested in a racemic form.



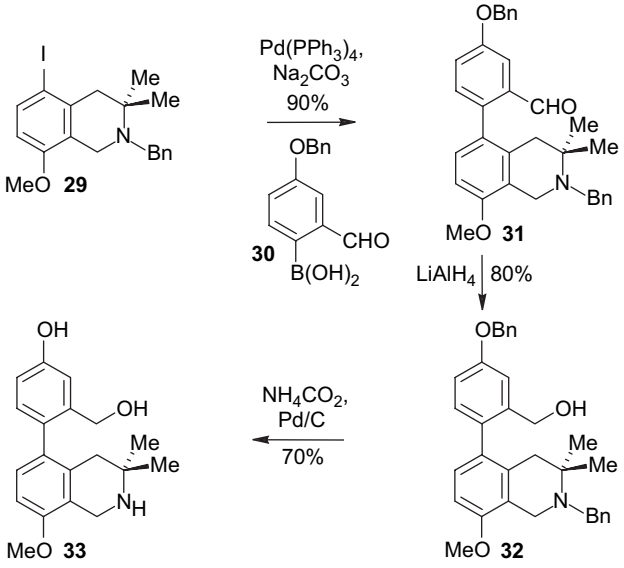
Scheme 3. Synthesis of the naphthylisoquinoline **23**.

2.1.4. Synthesis of *33* as a simplified analog of dioncopeltine A (*2*)

One of the most active antiplasmodial NIQ alkaloids, both *in vitro* and *in vivo*, is dioncopeltine A (**2**) [5]. Its most characteristic structural feature is the presence of a hydroxymethyl group on the naphthalene portion. Reductive deoxygenation of the benzylic OH group is known to decrease the antimalarial activity substantially [21], making the introduction of a CH_2OH group into the phenyl portion of a respective model analog rewarding. Furthermore, due to results from recent QSAR studies [22] and following the structures of the highly antimalarial Dioncophyllaceae alkaloids **2** and **3**, the 6-OMe group was omitted, leading to **33** as a promising structure with an expected high antimalarial activity. The synthesis of the required *N*-protected and halogen-activated new building block **29** is shown in Scheme 4. Removal of the 6-methoxy group of **24** was achieved by regioselective O-demethylation at C-6 to give the phenol **25**, followed by O-triflation to give **26** and hydrogenolytic elimination of the OTf group, unfortunately with simultaneous N-debenzylation, leading to the tetrahydroisoquinoline **27**, which had already been synthesized earlier [23], but via a different route (yields not specified). Its iodination under various conditions proved difficult, accompanied by an undesired oxidation to the respective dihydroisoquinoline. The reaction mixture was therefore cautiously reduced and submitted to a renewed iodination–reduction sequence, finally giving **28** in an acceptable yield. A renewed introduction of the *N*-benzyl group completed the synthesis of the 6-deoxygenated and thus Dioncophyllaceae-like [9] isoquinoline **29**.



Scheme 4. Synthesis of the achiral 6-deoxygenated tetrahydroisoquinoline building block **29**.



Scheme 5. Final steps to the dioncopeltine A analog **24**.

This valuable new building block **29** was coupled to the commercially available boronic acid aldehyde **30**, to give the 5-(2′-formylphenyl)-tetrahydroisoquinoline **31** (see Scheme 5). Reduction of its aldehyde function to give **32** introduced the desired hydroxymethyl group. Cautious hydrogenolysis of both, the *O*- and *N*-benzyl groups, but with conservation of the CH_2OH function, generated the dioncopeltine A analog **33** as a relatively unstable compound. It appears chiral on the NMR time scale, as seen from the diastereotopic nature of the methyl groups at C-3 and the protons at C-4 and C-1 as already for **23** and, in addition, from the splitting of the two benzylic protons in the CH_2OH side chain (4.16 and 4.23 ppm, $J = 17$ Hz). Still, as expected from previous experience [24,25], it should certainly be configurationally unstable at the biaryl axis, thus not necessitating to develop an atropo-selective synthesis as previously achieved for dioncopeltine A [26].

2.2. Biology

With the target compounds, **11**, **18**, **23**, and **33** synthetically available, these four NIQ analogs and also 14 of their isoquinolinic precursors were tested for their bioactivities.

Among the compounds assayed against *T. cruzi*, the phenylisoquinoline **11** displayed a quite good activity, just somewhat more than an order of magnitude less than the standard, benznidazole, with a therapeutical index of ca. 12.

Surprisingly, the biaryl compounds did not show the best antimalarial activities. Thus, compound **33** only showed a very weak antiplasmodial activity, despite bearing the assumed key functionalities of dioncopeltine A, but, at least, proved to be not cytotoxic. The most active candidates were, by contrast, the halogenated isoquinoline precursors, some of them with virtually no cytotoxicity, resulting in excellent therapeutic indices, four examples being the bromo- or iodo-tetrahydroisoquinolines **14**, **15** and **28** and the dihydro analog **9**, with indices of 150 and more.

Remarkably, the naphthylisoquinoline **23** displayed better activities than the phenylisoquinoline **18**, by one order of magnitude in the case of *T. cruzi*. Moreover, **23** was also active in the antimalarial testing, while **18** was not active at all. This suggests a larger influence of the aromatic portion than anticipated.

A likewise remarkable substance is the noncytotoxic and quite active tetrahydroisoquinoline **25**, whose *N*-benzyl protection group on the isoquinoline nitrogen might mimic an aryl substituent similar to those otherwise linked *via* a biaryl axis at C-5 or C-7 in **1**–**3**. In this respect, its molecular framework is reminiscent of the recently discovered *N*,*C*- instead of *C*,*C*-coupled natural NIQs from Ancistrocladaceae plants [27–30].

A similar influence of the *N*-benzyl group is observed with the results of the antileishmanial testing, where the best activities were obtained with the naphthalene-free compounds **15** and **20**, with IC_{50} values of 4.2 and 2.4 μg/ml, respectively, i.e., only ca. a factor of 10 weaker than the standard, miltefosin.

Although not yet reaching the excellent antiprotozoal activities of natural NIQs, the simplified compounds prepared here and their activities provide further valuable data for our ongoing QSAR studies [22,31].

3. Conclusions

New, simplified synthetic di- and tetrahydroisoquinoline building blocks have been designed and prepared, mimicking the difficult-to-access, authentic tetrahydroisoquinoline portions of the anti-infectious naphthylisoquinoline alkaloids. The replacement of a 1,3- by a 3,3-dimethyl substitution

pattern makes these compounds achiral and thus easy to prepare. The attachment of symmetric phenyl instead of naphthyl substituents at C-5 furthermore avoids the − stereochemically intriguing, but difficult-to-control − phenomenon of axial chirality. Several representatives of this class of compounds possess promising activities against *T. cruzi*, *L. donovani*, and *Plasmodium falciparum*. Surprisingly, the best antiplasmodial activities were found for the simple, non-coupled, i.e., naphthalene- or phenyl-devoid tetrahydroisoquinolines. The results give further valuable information on structure–activity relationships, involving new, more efficient QSAR methods [31], which will hopefully lead to the directed prediction of simplified, even more active and less toxic substances for further development.

4. Experimental

4.1. Instrumentation and chemicals

Melting points were determined with a Kofler melting point apparatus and are uncorrected. IR spectra were scanned from KBr pellets or neat using a *Jasco* FT-410 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance 400 (400 MHz) instrument using the deuterated solvent as an internal reference; *J* values are given in Hertz. Elemental analyses were performed at the Institute of Inorganic Chemistry of the University of Würzburg. Mass spectra were measured on a Finnigan MAT 2000 mass spectrometer at 70 eV. All reactions with moisture and/or air sensitive materials were carried out with flame-dried glassware using the Schlenk tube technique under inert argon atmosphere. The ketone **6** [33] and the boronic acids **10**, **16**, and **21** were synthesized according to literature procedures [34,35]. The commercially available boronic acid **30** was purchased from Frontier Scientific, Inc.

4.2. Chemistry

4.2.1. 1,1-Dimethyl(3′,5′-dimethoxyphenyl)ethanol (7)

To a solution of **6** (6.00 g, 30.9 mmol) in diethyl ether (100 ml), a 1.5 M solution of methyl magnesium bromide in diethyl ether (21 ml, 31.5 mmol) was added dropwise at 0 °C. After refluxing for 1 h, the solution was acidified with 2 N HCl (40 ml) with ice cooling. Washing of the organic layer with water (50 ml), drying over $MgSO_4$ and removal of the solvent yielded **7** (6.17 g, 29.4 mmol, 95%) as a yellow oil. IR (neat, cm^{-1}) ν 3416, 2967, 2837, 1595, 1462, 1430, 1340, 1205, 1150, 1064. ^{1}H NMR ($CDCl_3$) δ 6.34 (m, 3H, Ar–H), 3.79 (s, 6H, O–CH_3), 2.71 (s, 2H, C–CH_2), 1.25 (s, 6H, C–CH_3). ^{13}C NMR ($CDCl_3$) δ 161.0, 140.4, 109.0, 98.83, 71.03, 55.69, 50.39, 29.68. EI-MS (70 eV) *m/z* (%): 210 (10) [M^+], 195 (14), 192 (21), 177 (28), 152 (100), 91 (26), 77 (20), 59 (53), 51 (11), 43 (23). Anal. calcd for $C_{12}H_{18}O_3$ (210.28): C, 68.25; H, 8.46; found: C, 68.55; H, 8.62.

4.2.2. General procedure for the Ritter reaction of 7 leading to dihydroisoquinolines

This reaction was carried out following a literature protocol [36]. To a solution of the alcohol **7** in glacial acetic acid (1.5 mol/l), the nitrile (1.00 eq) was added. Concd. sulfuric acid (1.4 ml/mmol) was added dropwise to the mixture with ice cooling. *Caution!* during the reaction HCN gas is formed; it was quenched in bottles filled with aqueous sodium hypochloride (NaOCl, 2 M) solution. The reaction mixture was allowed to warm to room temperature. The brownish solution was transferred to a separation funnel equipped with ice and washed three times with diethyl ether. The aqueous layer was treated with a saturated sodium carbonate solution and extracted three times with diethyl ether. Drying with $MgSO_4$ and removal of the solvent afforded the respective dihydroisoquinoline.

*4.2.2.1. 1,3,3-Trimethyl 6,8-dimethoxy-3,4-dihydroisoquinoline (**8**).* Brownish oil. Yield: 65%. IR (neat, cm^{-1}) ν 2965, 1604, 1574, 1464, 1340, 1301, 1205, 1150, 1100. ^{1}H NMR ($CDCl_3$) δ 6.37 (d, $J = 2.3$ Hz, 1H, Ar–H), 6.33 (d, $J = 2.3$ Hz, 1H, Ar–H), 3.88 (s, 3H, O–CH_3), 3.87 (s, 3H, O–CH_3), 2.71 (s, 2H, C–CH_2), 2.68 (s, 3H, C–CH_3), 1.35 (s, 6H, C–CH_3). ^{13}C NMR ($CDCl_3$) δ 161.8, 160.8, 158.3, 141.1, 112.3, 105.1, 97.05, 55.28, 55.26, 52.59, 40.43, 28.01, 27.45. EI-MS (70 eV) *m/z* (%): 234 (15) [$M^+ + 1$], 233 (100) [M^+], 219 (9), 218 (71), 204 (6), 203 (25), 192 (7), 191 (55), 190 (10), 177 (12), 176 (28), 161 (8), 91 (9), 77 (10), 40 (19). Anal. calcd for $C_{14}H_{19}NO_2$ (233.31): C, 72.07; H, 8.21; N, 6.00; found: C, 72.10; H, 8.38; N, 5.99.

*4.2.2.2. 3,3-Dimethyl 6,8-dimethoxy-3,4-dihydroisoquinoline (**12**).* Brownish oil. Yield: 78%. IR (neat, cm^{-1}) ν 2965, 1604, 1574, 1464, 1340, 1301, 1205, 1150, 1100. ^{1}H NMR ($CDCl_3$) δ 8.54 (s, 1H, C–H), 6.35 (d, $J = 2.3$ Hz, 1H, Ar–H), 6.26 (d, $J = 2.3$ Hz, 1H, Ar–H), 3.86 (s, 3H, O–CH_3), 3.85 (s, 3H, O–CH_3), 2.66 (s, 2H, C–CH_2), 1.27 (s, 6H, C–CH_3). ^{13}C NMR ($CDCl_3$) δ 206.7, 201.9, 152.6, 139.3, 105.1, 96.22, 55.43, 55.36, 53.69, 38.87, 30.77, 27.56. EI-MS (70 eV) *m/z* (%): 219 (85) [M^+], 204 (100), 189 (23), 163 (35), 77 (13), 51 (8). MS (EI) exact mass calcd for $C_{13}H_{17}NO_2$: 219.2859; found: 219.1254.

4.2.3. 3,3-Dimethyl 6,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (13)

The dihydroisoquinoline **12** (2.00 g, 9.13 mmol) was dissolved in methanol (20 ml) and treated with sodium borohydride (346 mg, 9.13 mmol). The solvent was removed *in vacuo*. The residue was taken up in dichloromethane and filtered through a plug of celite. Removal of the solvent delivered **13** (1.85 g, 8.34 mmol, 92%) as colorless crystals (diethyl ether); mp 81 °C. IR (KBr, cm^{-1}) ν 3253, 2957, 2924, 2852, 1592, 1293, 1222, 1201, 1147, 1103, 1081, 1051, 953, 802, 734. ^{1}H NMR ($CDCl_3$) δ 6.28 (d, $J = 2.3$ Hz, 1H, Ar–H), 6.19 (d, $J = 2.3$ Hz, 1H, Ar–H), 3.90 (s, 2H, N–CH_2), 3.79 (s, 3H, O–CH_3), 3.78 (s, 3H, O–CH_3), 2.58 (s, 2H, C–CH_2), 1.18 (s, 6H, C–CH_3). ^{13}C NMR ($CDCl_3$) δ 157.7, 155.8, 136.3, 115.8, 104.7, 95.76, 55.16, 55.06, 48.23, 41.89, 39.57, 27.51. EI-MS

(70 eV) *m/z* (%): 221 (29) [M^+], 220 (17), 206 (47), 164 (100), 91 (10). Anal. calcd for $C_{13}H_{19}NO_2$ (221.30): C, 70.56; H, 8.65; N, 6.33; found: C, 69.99; H, 8.38; N, 5.99.

4.2.4. General procedure for the bromination of isoquinolines

To a solution of the isoquinoline (0.25 M) in dichloromethane (20 ml), a catalytic amount of DMF and a solution of bromine (1.05 eq) in dichloromethane (0.25 M) were added dropwise at 0 °C. After stirring for 1 h, the solution was washed twice with 50 ml of a saturated aqueous solution of sodium carbonate. The residue was purified by column chromatography on deactivated silica gel.

*4.2.4.1. 5-Bromo-1,3,3-trimethyl 6,8-dimethoxy-3,4-dihydroisoquinoline (**9**).* Yellow solid (diethyl ether). Yield: 70%; mp 143 °C. IR (KBr, cm^{-1}) ν 2960, 2924, 2867, 1612, 1585, 1561, 1470, 1437, 1338, 1306, 1259, 1219, 1174, 1089, 1066, 1026, 970, 946, 898, 821. ^{1}H NMR ($CDCl_3$) δ 6.42 (s, 1H, Ar−H), 3.95 (s, 3H, O−CH_3), 3.88 (s, 3H, O−CH_3), 2.72 (s, 2H, C−CH_2), 2.40 (s, 3H, C−CH_3), 1.17 (s, 6H, C−CH_3). ^{13}C NMR ($CDCl_3$) δ 160.6, 158.1, 157.9, 140.3, 113.9, 104.8, 94.83, 56.21, 55.68, 52.88, 39.64, 27.76, 27.63. EI-MS (70 eV) *m/z* (%): 314 ($M^+ + 3$, 16), 313 (99) [$M^+ + 2$], 312 (39) [$M^+ + 1$], 311 (100) [M^+], 298 (55), 296 (60), 283 (12), 281 (11), 271 (39), 269 (41), 256 (20), 254 (24), 217 (27), 202 (14), 176 (13), 161 (11), 109 (12), 86 (22), 84 (40), 77 (12), 57 (11), 42 (15). Anal. calcd for $C_{14}H_{18}BrNO_2$ (312.21): C, 53.86; H, 5.81; N, 4.49; found: C, 53.71; H, 5.90; N, 3.92.

*4.2.4.2. 5-Bromo-3,3-dimethyl 6,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**14**).* Colorless crystals (diethyl ether). Yield: 78%; mp 157 °C. IR (KBr, cm^{-1}) ν 3299, 3004, 2960, 2938, 2839, 1599, 1571, 1478, 1464, 1450, 1435, 1350, 1330, 1313, 1278, 1208, 1150, 1091, 1071, 1016, 828, 798, 749, 700. ^{1}H NMR ($CDCl_3$) δ 6.37 (s, 1H, Ar−H), 3.94 (s, 2H, N−CH_2), 3.82 (s, 3H, O−CH_3), 3.88 (s, 3H, O−CH_3), 2.64 (s, 2H, C−CH_2), 1.25 (s, 6H, C−CH_3). ^{13}C NMR ($CDCl_3$) δ 155.8, 155.1, 135.2, 116.2, 105.1, 93.94, 56.44, 55.41, 49.61, 41.64, 39.12, 27.11. EI-MS (70 eV) *m/z* (%): 301 (24) [$M^+ + 2$], 300 (16) [$M^+ + 1$], 299 (37) [M^+], 286, 284 (100), 244 (79), 242 (79), 204 (18), 202 (15), 162 (19), 103 (15), 77 (14), 42 (12). Anal. calcd for $C_{13}H_{18}BrNO_2$ (300.20): C, 52.01; H, 6.04; N, 4.67; found: C, 52.05; H, 6.05; N, 4.77.

4.2.5. Iodination of tetrahydroisoquinolines

*4.2.5.1. 5-Iodo-3,3-dimethyl 6,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**19**).* Following a procedure for the iodination of related tetrahydroisoquinolines [37], silver sulfate (8.45 g, 27.1 mmol) was added to a solution of **13** (2.00 g, 9.04 mmol), and then added dropwise a solution of iodine (2.41 g, 9.50 mmol) in ethanol (20 ml). After stirring for 30 min, the inorganic salts were removed by filtration, and the residue was chromatographed on deactivated silica gel (dichloromethane/petroleum ether, 5:1) resulting in colorless crystals (diethyl ether) of **19** (2.20 g, 6.33 mmol, 70%); mp 118 °C. IR (neat, cm^{-1}) ν 3418, 2976, 1605, 1458, 1434, 1360, 1311, 1204, 1158, 1102, 1072, 1044, 992, 856, 731. ^{1}H NMR ($CDCl_3$) δ 6.35 (s, 1H, Ar−H), 3.91 (s, 2H, N−CH_2), 3.88 (s, 3H, O−CH_3), 3.84 (s, 3H, O−CH_3), 2.56 (s, 2H, C−CH_2), 1.24 (s, 6H, C−CH_3). ^{13}C NMR ($CDCl_3$) δ 157.3, 157.1, 138.3, 117.5, 93.36, 83.16, 56.95, 55.39, 50.07, 47.24, 39.53, 27.28. EI-MS (70 eV) *m/z* (%): 347 (1) [M^+], 219 (100), 204 (98), 189 (17), 163 (27), 71 (8). Anal. calcd for $C_{13}H_{18}INO_2$ (347.20): C, 44.97; H, 5.23; N, 4.03; found: C, 45.29; H, 5.23; N, 3.80.

*4.2.5.2. 5-Iodo-3,3-dimethyl-8-methoxy-1,2,3,4-tetrahydroisoquinoline (**28**).* According to Section 4.2.5.1, the isoquinoline **27** (47 mg, 0.25 mmol) was iodinated with silver sulfate (307 mg, 0.98 mmol) and iodine (75 mg, 9.50 mmol). The reaction mixture contained the desired product **28** along with the corresponding dihydroisoquinoline and its iodide. The solvent was removed under reduced pressure, the mixture was taken up with methanol and treated with sodium borohydride (0.5 eq) giving a mixture of the iodide **28** and starting material. Repetition of the iodination−reduction sequence and chromatography on deactivated silica gel (dichloromethane/petroleum ether/methanol, 100:20:1) yielded **28** as bright yellow crystals (diethyl ether) (45 mg, 0.14 mmol, 58%); mp 114 °C. IR (KBr) ν 3300, 3094, 2953, 2930, 2831, 1647, 1578, 1457, 1432, 1380, 1364, 1289, 1251, 1088, 1074, 1029, 822, 803. ^{1}H NMR ($CDCl_3$) δ 7.64 (d, $J = 8.6$ Hz, 1H, Ar−H), 6.48 (d, $J = 8.6$ Hz, 1H, Ar−H), 3.93 (s, 2H, N−CH_2), 3.79 (s, 3H, O−CH_3), 2.50 (s, 2H, C−CH_2), 1.21 (s, 6H, C−CH_3). ^{13}C NMR ($CDCl_3$) δ 156.0, 137.4, 136.8, 126.0, 109.5, 91.90, 55.30, 49.52, 47.03, 40.02, 27.43. EI-MS (70 eV) *m/z* (%): 318 (3) [$M^+ + 1$], 317 (25) [M^+], 303 (13), 302 (100), 300 (11), 286 (11), 285 (4), 261 (6), 260 (50), 230 (10), 174 (9), 151 (11), 103 (13), 80 (13). MS (EI) exact mass calcd for $C_{12}H_{16}NOI$: 317.0276; found: 317.0270.

4.2.6. General procedure for the N-benzylation of tetrahydroisoquinolines

The reactions were performed as described for similar substances in the literature [37]. A suspension of the isoquinoline, benzyl bromide (1.05 eq), and cesium carbonate (2.10 eq) in acetone was stirred overnight. The suspension was filtered from inorganic salts and the residue purified by column chromatography on deactivated silica gel (petroleum ether/dichloromethane/methanol, 100:10:1) giving the *N*-benzylated tetrahydroisoquinolines.

*4.2.6.1. N-Benzyl-3,3-dimethyl 6,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**24**).* Yield: 92%; mp 109 °C (petroleum ether). IR (neat, cm^{-1}) ν 2963, 2835, 1604, 1496, 1453, 1426, 1377, 1360, 1328, 1278, 1208, 1149, 1109, 1055, 826, 699. ^{1}H NMR ($CDCl_3$) δ 7.41 (d, $J = 7.1$ Hz, 2H, Ar−H), 7.31 (t, $J = 7.6$ Hz, 2H, Ar−H), 7.23 (t, $J = 7.3$ Hz, 1H, Ar−H), 6.24 (d, $J = 2.1$ Hz, 1H, Ar−H), 6.22 (d, $J = 2.1$ Hz, 1H, Ar−H), 3.76 (s, 3H, O−CH_3), 3.73 (s, 2H, N−CH_2), 3.69 (s,

3H, O–CH_3), 3.50 (s, 2H, N–CH_2), 2.74 (s, 2H, C–CH_2), 1.21 (s, 6H, C–CH_3). ^{13}C NMR ($CDCl_3$) δ 159.2, 157.3, 136.5, 129.0, 128.6, 127.0, 104.4, 96.11, 55.68, 55.46, 54.23, 53.02, 46.37, 44.09, 24.03. EI-MS (70 eV) *m/z* (%): 311 (20) [M^+], 310 (15), 297 (20), 296 (100), 205 (7), 204 (24), 165 (9), 164 (76), 146 (8), 91 (74). Anal. calcd for $C_{20}H_{25}NO_2$ (311.43): C, 77.14; H, 8.09; N, 4.50; found: C, 76.65; H, 8.06; N, 4.40.

*4.2.6.2. N-Benzyl-5-bromo-3,3-dimethyl 6,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**15**).* Yield: 90%; mp 198 °C (petroleum ether). IR (KBr, cm^{-1}) ν 2960, 2927, 1596, 1576, 1488, 1449, 1430, 1373, 1342, 1322, 1207, 1164, 1107, 1080, 982, 803, 762, 723, 697. ^{1}H NMR (C_3D_6O) δ 7.42 (d, $J = 7.6$ Hz, 2H, Ar–H), 7.31 (t, $J = 7.6$ Hz, 2H, Ar–H), 7.22 (t, $J = 7.6$ Hz, 1H, Ar–H), 6.61 (s, 1H, Ar–H), 3.88 (s, 3H, O–CH_3), 3.76 (s, 5H, O–CH_3 and N–CH_2), 3.47 (s, 2H, N–CH_2), 2.74 (s, 2H, C–CH_2), 1.25 (s, 6H, C–CH_3). ^{13}C NMR (C_3D_6O) δ 156.7, 155.8, 136.0, 129.2, 129.0, 127.4, 104.4, 94.99, 56.57, 55.70, 53.31, 54.02, 46.35, 44.87, 23.67. EI-MS (70 eV) *m/z* (%): 391 (3) [M^+], 390 (3), 389 (4), 377 (5), 376 (30), 374 (31), 284 (5), 282 (5), 244 (13), 242 (12), 146 (6), 91 (100), 77 (7), 65 (11), 57 (13), 43 (10). Anal. calcd for $C_{20}H_{24}BrNO_2$ (390.32): C, 61.54; H, 6.20; N, 3.59; found: C, 62.06; H, 6.14; N, 3.60.

*4.2.6.3. N-Benzyl-5-iodo-3,3-dimethyl 6,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**20**).* Yield: 80%; mp 174 °C (petroleum ether). IR (neat, cm^{-1}) ν 3026, 3006, 2962, 2930, 2886, 2836, 2758, 1583, 1483, 1455, 1431, 1340, 1206, 1159, 1080, 1057, 1027, 979, 853, 808, 755, 738. ^{1}H NMR ($CDCl_3$) δ 7.40 (m, 2H, Ar–H), 7.31 (t, $J = 7.2$ Hz, 2H, Ar–H), 7.23 (t, $J = 7.2$ Hz, 1H, Ar–H), 6.30 (s, 1H, Ar-H), 3.87 (s, 3H, O–CH_3), 3.73 (br s, 5H, O–CH_3 and N–CH_2), 3.51 (s, 2H, N–CH_2), 2.71 (s, 2H, C–CH_2), 1.24 (s, 6H, C–CH_3). ^{13}C NMR ($CDCl_3$) δ 157.1, 157.0, 140.7, 138.6, 129.6, 128.5, 128.2, 126.6, 93.07, 82.13, 56.59, 55.23, 53.41, 49.32, 45.82, 23.73. EI-MS (70 eV) *m/z* (%): 437 (14) [M^+], 423 (19), 422 (100), 330 (4), 294 (4), 290 (32), 254 (10), 204 (6), 203 (6), 133 (5), 103 (6), 91 (84), 77 (6). Anal. calcd for $C_{20}H_{24}INO_2$ (437.32): C, 54.93; H, 5.53; N, 3.20; found: C, 55.08; H, 5.56; N, 3.09.

*4.2.6.4. N-Benzyl-5-iodo-3,3-dimethyl-8-methoxy-1,2,3,4-tetrahydroisoquinoline (**29**).* Yield: 90%; mp 149 °C (petroleum ether). IR (KBr, cm^{-1}) ν 2959, 2935, 2875, 1647, 1576, 1472, 1455, 1436, 1370, 1295, 1261, 1231, 1207, 1093, 1054, 1026, 797, 735, 702, 605. ^{1}H NMR ($CDCl_3$) δ 7.64 (d, $J = 8.6$ Hz, 1H, Ar–H), 7.41 (d, $J = 7.3$ Hz, 2H, Ar–H), 7.33 (t, $J = 7.3$ Hz, 2H, Ar–H), 7.26 (t, $J = 7.1$ Hz, 1H, Ar–H), 6.43 (d, $J = 8.6$ Hz, 1H, Ar–H), 3.75 (s, 2H, N–CH_2), 3.69 (s, 3H, O–CH_3), 3.57 (s, 2H, N–CH_2), 2.68 (s, 2H, C–CH_2), 1.26 (s, 6H, C–CH_3). ^{13}C NMR ($CDCl_3$) δ 156.1, 149.3, 136.5, 129.5, 129.4, 128.3, 126.7, 113.1, 109.3, 90.77, 55.19, 53.37, 48.93, 46.11, 29.68, 23.67. EI-MS (70 eV) *m/z* (%): 407 (11) [M^+], 393 (20), 392 (100), 265 (5), 260 (16), 224 (8), 173 (7), 146 (13), 103 (7), 91 (100), 65 (8). MS (EI) exact mass calcd for $C_{19}H_{22}NOI$: 407.0745; found: 407.0739.

4.2.7. General procedure for the Suzuki coupling of isoquinolines

The coupling reactions were carried out as described for similar reactions in the literature [37]. In the case of the bromide **9**, dimethoxyethane/water, 3:1 was used as the solvent, and barium hydroxide as the base; the mixture was kept under argon overnight at 80 °C. For the iodides **20** and **29**, the reactions were performed in toluene:water, 1:1 and heated for 12 h to 90 °C. Tetrakis(triphenylphosphane)-palladium(0) was used in a catalytical amount of 0.1 eq.

*4.2.7.1. 5-(4′-Methoxyphenyl)-1,3,3-trimethyl 6,8-dimethoxy-3,4-dihydroisoquinoline (**11**).* Yield: 66%; mp 128 °C (diethyl ether). IR (KBr, cm^{-1}) ν 2957, 2926, 2857, 2840, 1609, 1582, 1516, 1482, 1460, 1435, 1367, 1338, 1309, 1287, 1246, 1207, 1166, 1103, 1089, 1025, 838, 806. ^{1}H NMR (C_3D_6O) δ 7.06 (d, $J = 8.9$ Hz, 2H, Ar–H), 6.95 (d, $J = 8.9$ Hz, 2H, Ar–H), 6.69 (s, 1H, Ar–H), 3.97 (s, 3H, O–CH_3), 3.83 (s, 3H, O–CH_3), 2.78 (s, 3H, O–CH_3), 2.34 (s, 3H, C–CH_3), 2.25 (s, 2H, C–CH_2), 0.96 (s, 6H, C–CH_3). ^{13}C NMR (C_3D_6O) δ 160.4, 160.2, 159.4, 158.8, 139.4, 132.4, 129.4, 123.0, 114.1, 112.5, 94.95, 55.89, 55.78, 55.34, 53.26, 38.29, 28.27, 27.76. EI-MS (70 eV) *m/z* (%): 326 (16) [$M^+ + 1$], 325 (100) [M^+], 311 (9), 310 (41), 283 (27), 268 (14), 238 (5), 155 (6), 42 (7). Anal. calcd for $C_{21}H_{23}NO_3$ (339.44): C, 74.31; H, 7.42; N, 4.13; found: C, 74.43; H, 7.11; N, 3.93.

*4.2.7.2. N-Benzyl-5-(4-benzoxyphenyl)-3,3-dimethyl-6,8-dimethoxy-1,2,3,4-tetrahydroiso-quinoline (**17**).* Yield: 92%; mp 194 °C (diethyl ether). IR (KBr, cm^{-1}) ν 2924, 2835, 1599, 1517, 1491, 1454, 1376, 1324, 1239, 1197, 1141, 1068, 1026, 825, 810, 722, 734, 698. ^{1}H NMR ($CDCl_3$) δ 7.20–7.52 (m, 10H, Ar–H), 7.14 (d, $J = 8.8$ Hz, 2H, Ar–H), 7.05 (d, $J = 8.8$ Hz, 2H, Ar–H), 6.39 (s, 1H, Ar–H), 5.11 (s, 2H, O–CH_2), 3.78 (s, 3H, O–CH_3), 3.72 (s 3H, O–CH_3), 3.72 (s, 2H, N–CH_2), 3.57 (s, 2H, N–CH_2), 2.43 (s, 2H, C–CH_2), 1.21 (s, 6H, C–CH_3). ^{13}C NMR ($CDCl_3$) δ 157.5, 155.9, 155.7, 155.1, 137.2, 134.9, 131.6, 129.6, 128.8, 128.6, 128.6, 128.1, 127.9, 127.6, 126.5, 122.0, 114.4, 92.81, 70.00, 56.06, 55.11, 53.88, 52.40, 46.26, 42.35, 29.69, 23.45. EI-MS (70 eV) *m/z* (%): 493 (12) [M^+], 492 (12), 479 (34), 478 (100), 387 (13), 346 (13), 255 (77), 91 (74), 57 (15). Anal. calcd for $C_{33}H_{35}NO_3$ (493.65): C, 80.29; H, 7.15; N, 2.84; found: C, 79.93; H, 7.22; N, 2.50.

*4.2.7.3. N-Benzyl-5-(4′-benzoxynaphthyl)-3,3-dimethyl-6,8-dimethoxy-1,2,3,4-tetrahydroiso-quinoline (**22**).* Yield: 68%; mp 204 °C (diethyl ether). IR (KBr, cm^{-1}) ν 2955, 2836, 1588, 1508, 1452, 1433, 1371, 1318, 1279, 1233, 1200, 1110, 1096, 1071, 1020, 811, 767, 696. ^{1}H NMR ($CDCl_3$) δ 8.36 (d, $J = 8.3$ Hz, 1H, Ar–H), 7.67 (d, $J = 7.3$ Hz, 2H, Ar–H), 7.33–7.50 (m, 10H, Ar–H), 7.24 (t, $J = 7.7$ Hz, 1H, Ar–H), 7.17 (d, $J = 7.7$ Hz, 1H, Ar–H), 7.12 (d, $J = 7.9$ Hz, 1H, Ar–H), 6.65 (s, 1H, Ar–H), 5.37 (s, 2H, O–CH_2), 3.89

(s, 3H, O–CH_3), 3.58 (s, 3H, O–CH_3), 3.40–3.88 (m, 4H, N–CH_2), 2.41 (d, $J = 16.7$ Hz, 1H, C–CH_2), 1.20 (d, $J = 16.7$ Hz, 1H, C–CH_2), 1.05 (s, 3H, C–CH_3), 0.97 (s, 3H, C–CH_3). ^{13}C NMR ($CDCl_3$) δ 157.7, 156.9, 154.4, 141.9, 138.5, 136.3, 134.6, 129.3, 129.1, 128.9, 128.6, 128.6, 128.5, 127.3, 126.7, 126.2, 125.6, 122.9, 120.5, 115.9, 106.0, 93.71, 70.67, 55.92, 55.44, 54.53, 52.62, 47.16, 42.86, 24.70, 22.04. EI-MS (70 eV) *m/z* (%): 543 (10) [M^+], 542 (11), 529 (29), 528 (71), 478 (15), 468 (23), 467 (40), 452 (17), 451 (30), 438 (12), 437 (18), 377 (21), 376 (62), 361 (18), 360 (29), 347 (22), 346 (13), 306 (10), 305 (38), 105 (13), 91 (9), 91 (100). Anal. calcd for $C_{37}H_{37}NO_3$ (543.71): C, 81.74; H, 6.86; N, 2.58; found: C, 81.43; H, 7.02; N, 2.51.

*4.2.7.4. 5-[(2′-Carboxy-4′-benzoxy)phenyl])-N-benzyl-3,3-dimethyl-8-methoxy-3,4-dihydroisoquinoline (**31**).* Yellow oil. Yield: 90%. IR (KBr, cm^{-1}) ν 2958, 2927, 2852, 1690, 1646, 1601, 1481, 1383, 1272, 1223, 1166, 1081, 1028, 818, 739, 698. ^{1}H NMR (C_3D_6O) δ 9.70 (s, 1H, C(O)–H), 7.20–7.57 (m, 13H, Ar–H), 7.03 (d, $J = 8.2$ Hz, 1H, Ar–H), 6.84 (d, $J = 8.3$ Hz, 1H, Ar–H), 5.26 (s, 2H, O–CH_2), 3.67–3.83 (m, 5H, O–CH_3 and N–CH_2), 3.62 (d, $J = 17.6$ Hz, 1H, N–CH_2), 3.55 (d, $J = 17.6$ Hz, 1H, N–CH_2), 2.50 (d, $J = 16.3$ Hz, 1H, C–CH_2), 2.32 (d, $J = 16.3$ Hz, 1H, C–CH_2), 1.13 (s, 3H, C–CH_3), 1.08 (s, 3H, C–CH_3). ^{13}C NMR (C_3D_6O) δ 191.7, 159.0, 156.2, 141.5, 138.7, 137.7, 135.9, 134.7, 133.4, 129.6, 129.5, 129.1, 128.9, 128.7, 128.6, 128.3, 127.2, 124.0, 121.9, 111.3, 107.2, 70.54, 55.26, 54.28, 52.45, 47.19, 43.30, 23.90, 22.48. EI-MS (70 eV) *m/z* (%): 491 (6) [M^+], 490 (4), 478 (6), 477 (29), 476 (94), 385 (6), 344 (5), 327 (8), 253 (21), 225 (11), 146 (16), 91 (100). Anal. calcd for $C_{33}H_{33}NO_3$ (491.64): C, 80.62; H, 6.77; N, 2.85; found: C, 81.41; H, 7.02; N, 2.51.

*4.2.8. N-Benzyl-3,3-dimethyl 6-hydroxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (**25**)*

A suspension of the *N*-benzylated isoquinoline (500 mg, 1.61 mmol) **24** in 48% HBr (20 ml) was heated for 45 min to 75 °C until the conversion was approximately 50% according to tlc, because further heating was shown to give double O-demethylation and subsequent decomposition, and thus loss of material. The reaction mixture was quenched by addition of an aqueous sodium carbonate solution. The crude product was extracted with dichloromethane and separated from the starting material by column chromatography on deactivated silica gel (eluent: petroleum ether/dichloromethane/methanol, 100:25:1) (192 mg, 0.64 mmol, 40% **25** and 150 mg, 0.48 mmol, 30% starting material **24**); mp 217 °C. IR (KBr, cm^{-1}) ν 3399, 2962, 2839, 1604, 1457, 1381, 1315, 1261, 1148, 1023, 805, 758, 698. ^{1}H NMR (C_3D_6O) δ 7.39 (d, $J = 7.5$ Hz, 2H, Ar–H), 7.29 (t, $J = 7.2$ Hz, 2H, Ar–H), 7.21 (t, $J = 7.3$ Hz, 1H, Ar–H), 6.22 (d, $J = 2.0$ Hz, 1H, Ar–H), 6.18 (d, $J = 2.0$ Hz, 1H, Ar–H), 3.73 (s, 2H, N–CH_2), 3.64 (s, 3H, O–CH_3), 3.40 (s, 2H, N–CH_2), 2.65 (s, 2H, C–CH_2), 1.18 (s, 6H, C–CH_3). ^{13}C NMR (C_3D_6O) δ 157.7, 157.2, 142.1, 136.9, 129.1, 128.9, 127.3, 114.7, 107.4, 96.81, 55.23, 54.57, 52.75, 46.95, 44.57, 23.60. EI-MS (70 eV) *m/z* (%): 298 (4) [$M^+ + 1$], 297 (21) [M^+], 296 (18), 283 (21), 282 (100), 191 (6), 190 (24), 150 (17), 148 (41), 146 (10), 91 (99). Anal. calcd for $C_{19}H_{23}NO_2$ (297.40): C, 76.64; H, 7.80; N, 4.71; found: C, 76.07; H, 8.01; N, 4.38.

*4.2.9. N-Benzyl-3,3-dimethyl-6-trifluormethansulfonyloxy-8-methoxy-1,2,3,4-tetrahydroiso-quinoline (**26**)*

To a suspension of the tetrahydroisoquinoline **25** (400 mg, 1.35 mmol) in absolute dichloromethane, DABCO (332 mg, 2.96 mmol) and trifluoromethanesulfonyl anhydride (0.25 ml, 418 mg, 1.48 mmol) were added at 0 °C. The reaction mixture was allowed to warm to room temperature. The solvent was removed under reduced pressure, the residue dissolved in dichloromethane and washed twice with a saturated aqueous sodium carbonate solution. Flash chromatography on deactivated silica gel (petroleum ether/dichloromethane/methanol, 100:10:1) resulted in **26** as white crystals (petroleum ether) (547 mg, 1.27 mmol, 95%); mp 145 °C. IR (KBr, cm^{-1}) ν 2923, 2853, 1588, 1514, 1465, 1383, 1351, 1250, 1099, 1068, 1024, 810. ^{1}H NMR (C_3D_6O) δ 7.40 (d, $J = 7.4$ Hz, 2H, Ar–H), 7.31 (t, $J = 7.5$ Hz, 2H, Ar–H), 7.23 (t, $J = 7.2$ Hz, 1H, Ar–H), 6.81 (d, $J = 2.3$ Hz, 1H, Ar–H), 6.77 (d, $J = 2.3$ Hz, 1H, Ar–H), 3.79 (s, 3H, O–CH_3), 3.77 (s, 2H, N–CH_2), 3.50 (s, 2H, N–CH_2), 2.82 (s, 2H, C–CH_2), 1.22 (s, 6H, C–CH_3). ^{13}C NMR (C_3D_6O) δ 157.8, 149.2, 141.5, 138.4, 129.1, 129.0, 127.4, 124.6, 119.6 (q, $^3J_{C-F} = 320$ Hz), 113.6, 101.9, 56.13, 54.29, 52.61, 46.70, 44.15, 23.36. EI-MS (70 eV) *m/z* (%): 429 (7) [M^+], 416 (4), 415 (12), 414 (62), 296 (4), 282 (6), 281 (10), 205 (4), 190 (5), 180 (6), 146 (15), 121 (6), 97 (6), 91 (100), 83 (6), 71 (12), 57 (16), 55 (10), 43 (13), 41 (10). MS (EI) exact mass calcd for $C_{20}H_{22}F_3NO_4S$: 429.1220; found: 429.1214.

4.2.10. General procedure for the removal of benzyl and triflate protection groups

A solution of the protected compound, ammonium formate (4 eq) and 10% Pd/C in methanol (0.1 M) was refluxed for 30 min. The solvent was removed *in vacuo*, the residue dissolved in dichloromethane and washed with water. The product was gained by column chromatography on deactivated silica gel.

*4.2.10.1. 5-(4′-Hydroxyphenyl)-3,3-dimethyl-6,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**18**).* Yield: 90%; mp 235 °C (dichloromethane). IR (KBr, cm^{-1}) ν 3383, 2246, 2961, 2839, 1608, 1518, 1465, 1405, 1328, 1270, 1198, 1138, 1092, 1023, 836. ^{1}H NMR ($CDCl_3$) δ 6.95 (d, $J = 8.1$ Hz, 2H, Ar–H), 6.84 (d, $J = 8.1$ Hz, 2H, Ar–H), 6.42 (s, 1H, Ar–H), 4.11 (s, 2H, N–CH_2), 3.86 (s, 3H, O–CH_3), 3.69 (s, 3H, O–CH_3), 2.42 (s, 2H, C–CH_2), 1.26 (s, 6H, C–CH_3). ^{13}C NMR ($CDCl_3$) δ 158.9, 157.5, 157.4, 133.9, 132.5, 128.5, 124.4, 116.1, 115.9, 94.86, 56.39, 56.09, 52.91, 39.30, 39.27, 25.39. EI-MS (70 eV) *m/z* (%): 314 (7) [$M^+ + 1$], 313 (36) [M^+], 311 (37), 299 (15), 298 (72), 257 (20), 256 (100), 255 (24), 241 (32), 239 (36), 225 (36), 149

(10). Anal. calcd for $C_{19}H_{23}NO_3$ (313.40): C, 72.82; H, 7.40; N, 4.47; found: C, 72.46; H, 7.22; N, 4.39.

*4.2.10.2. 5-(4′-Hydroxynaphthyl)-3,3-dimethyl-6,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**23**).* Yield: 85%; mp 168 °C (dichloromethane). IR (KBr, cm^{-1}) ν 3436, 2926, 2855, 1738, 1587, 1460, 1382, 1350, 1321, 1261, 1203, 1104, 1084, 1024, 810, 767. ^1H NMR ($CDCl_3$) δ 8.25 (d, $J = 8.4$ Hz, 1H, Ar–H), 7.36 (m, 1H, Ar–H), 7.26 (m, 1H, Ar–H), 7.19 (d, $J = 8.3$ Hz, 1H, Ar–H), 6.99 (d, $J = 7.5$ Hz, 1H, Ar–H), 6.88 (d, $J = 7.5$ Hz, 1H, Ar–H), 6.73 (s, 1H, Ar–H), 4.21 (s, 2H, N–CH_2), 3.98 (s, 3H, O–CH_3), 3.64 (s, 3H, O–CH_3), 2.51 (d, $J = 16.7$ Hz, 1H, C–CH_2), 2.15 (d, $J = 16.7$ Hz, 1H, C–CH_2), 1.24 (s, 3H, C–CH_3), 1.17 (s, 3H, C–CH_3). ^{13}C NMR ($CDCl_3$) δ 160.4, 158.3, 154.7, 135.3, 134.2, 129.8, 127.6, 127.1, 126.3, 126.3, 125.8, 124.1, 122.6, 109.5, 109.2, 95.36, 56.73, 56.64, 54.17, 39.36, 38.63, 25.67, 24.60. EI-MS (70 eV) *m/z* (%): 363 (1) [M^+], 280 (4), 265 (7), 264 (13), 167 (4), 151 (4), 149 (7), 137 (4), 125 (4), 123 (5), 113 (25), 112 (64), 97 (19), 85 (7), 84 (16), 83 (32), 71 (88), 70 (36), 67 (16), 57 (100), 55 (45), 43 (42), 41 (29). Anal. calcd for $C_{23}H_{25}NO_3$ (363.46): C, 76.01; H, 6.93; N, 3.85; found: C, 76.52; H, 6.84; N, 3.79.

*4.2.10.3. 3,3-Dimethyl-8-methoxy-1,2,3,4-tetrahydroisoquinoline (**27**).* Yield: 95%; mp 55 °C (diethyl ether). IR (KBr, cm^{-1}) ν 3303, 2923, 2853, 1586, 1468, 1434, 1380, 1353, 1253, 1084, 1071, 1021, 852, 824, 776. ^1H NMR (C_3D_6O) δ 7.07 (t, $J = 7.7$ Hz, 1H, Ar–H), 6.72 (d, $J = 7.9$ Hz, 1H, Ar–H), 6.63 (d, $J = 7.7$ Hz, 1H, Ar–H), 3.85 (s, 2H, N–CH_2), 3.80 (s, 3H, O–CH_3), 2.55 (s, 2H, C–CH_2), 1.10 (s, 6H, C–CH_3). ^{13}C NMR (C_3D_6O) δ 156.7, 136.9, 127.0, 124.5, 122.3, 107.6, 55.33, 48.40, 42.09, 40.54, 27.69.

*4.2.11. 5-[(2′-Hydroxymethyl-4′-benzoxy)phenyl]-N-benzyl-3,3-dimethyl-8-methoxy-3,4-dihydroisoquinoline (**32**)*

To a solution of **31** (20 mg) in absolute diethyl ether at 0 °C, 8 mg of lithium aluminium hydride was added slowly. After 5 min an aqueous solution of sodium carbonate was added. Extraction with dichloromethane and chromatography on deactivated silica gel (eluent: petroleum ether/dichloromethane/methanol, 30:10:1) resulted in **32** (16 mg, 16.2 μmol, 80%); mp 157 °C (diethyl ether). IR (KBr, cm^{-1}) ν 3416, 2958, 2927, 2851, 1602, 1477, 1464, 1374, 1293, 1262, 1230, 1159, 1100, 1078, 1026, 813, 737, 696. ^1H NMR (C_3D_6O) δ 7.54 (d, $J = 7.3$ Hz, 2H, Ar–H), 7.42 (m, 4H, Ar–H), 7.27–7.38 (m, 4H, Ar–H), 7.22 (t, $J = 7.3$ Hz, 1H, Ar–H), 6.95 (m, 2H, Ar–H), 6.89 (d, $J = 8.3$ Hz, 1H, Ar–H), 6.76 (d, $J = 8.3$ Hz, 1H, Ar–H), 4.35 (d, $J = 13.8$ Hz, 1H, CH_2–OH), 4.26 (d, $J = 13.8$ Hz, 1H, CH_2–OH), 3.85 (d, $J = 17.4$ Hz, 1H, N–CH_2), 3.74 (s, 3H, O–CH_3), 3.63 (m, 2H, N–CH_2), 3.49 (d, $J = 17.4$ Hz, 1H, N–CH_2), 2.45 (d, $J = 16.5$ Hz, 1H, C–CH_2), 2.25 (d, $J = 16.5$ Hz, 1H, C–CH_2), 1.13 (s, 3H, C–CH_3), 1.08 (s, 3H, C–CH_3). ^{13}C NMR (C_3D_6O) δ 158.8, 155.5, 142.3, 141.5, 138.2, 134.3, 132.5, 132.1, 131.1, 128.9, 128.8, 128.6, 128.2, 128.2, 128.1, 127.0, 123.5, 113.4, 113.0, 107.0, 70.06, 62.07, 55.00, 54.20, 52.29, 47.14, 42.65, 24.77, 21.47. EI-MS (70 eV) *m/z* (%): 493 (3) [M^+], 492 (3), 480 (6), 479 (32), 478 (100), 476 (5), 387 (6), 315 (6), 255 (11), 91 (47). EI-MS exact mass calcd for $C_{32}H_{32}NO_3$: 478.2377; found: 478.2376.

*4.2.12. 5-[(2′-Hydroxymethyl-4′-hydroxy)phenyl)]-3,3-dimethyl-8-methoxy-3,4-dihydroiso-quinoline (**33**)*

To a solution of **32** (12 mg) in abs. methanol (4 ml) under nitrogen, a small amount of 10% Pd/C was added. Hydrogen was flushed into the Schlenk tube. After 20 min, the solution was filtered over Celite and the pure **33** was gained after chromatography (eluent: dichloromethane/methanol, 3:1) (6 mg, 21 μmol, 70%). IR (KBr, cm^{-1}) ν 3400, 2926, 2853, 1655, 1633, 1600, 1406, 1370, 1288, 1259, 1156, 1104, 1084, 1018, 831, 704, 669. ^1H NMR (CD_3OD) δ 7.02 (d, $J = 2.5$ Hz, 1H, Ar–H), 6.94 (d, $J = 8.4$ Hz, 1H, Ar–H), 6.83 (d, $J = 8.2$ Hz, 1H, Ar–H), 6.80 (d, $J = 8.3$ Hz, 1 H, Ar–H), 6.70 (dd, $J = 8.2$ Hz, $J = 2.6$ Hz, 1H, Ar–H), 4.23 (d, $J = 13.4$ Hz, 1H, CH_2–OH), 4.16 (d, $J = 13.4$ Hz, 1H, CH_2–OH), 3.83 (s, 3H, O–CH_3), 3.72 (d, $J = 17.1$ Hz, 1H, N–CH_2), 3.64 (d, $J = 17.1$ Hz, 1H, N–CH_2), 2.38 (d, $J = 16.9$ Hz, 1H, C–CH_2), 2.18 (d, $J = 16.9$ Hz, 1H, C–CH_2), 1.03 (s, 3H, C–CH_3), 0.98 (s, 3H, C–CH_3). ^{13}C NMR (CD_3OD) δ 157.9, 156.3, 141.9, 134.6, 133.7, 131.9, 131.6, 129.7, 122.9, 114.9, 114.8, 107.9, 62.81, 55.76, 53.41, 50.67, 42.30, 23.37, 20.78. EI-MS (70 eV) *m/z* (%): 313 (23) [M^+], 312 (100), 311 (20), 296 (8), 278 (11), 237 (22), 226 (11), 225 (23), 207 (12), 195 (10), 165 (8), 147 (8), 137 (10), 121 (7), 119 (10), 111 (26), 110 (8), 109 (23), 97 (42), 95 (34), 91 (8), 85 (32), 83 (44), 81 (33), 71 (49), 69 (53), 67 (23), 57 (83), 55 (60), 43 (67), 41 (38). Anal. calcd for $C_{19}H_{23}NO_3$ (313.40): C, 72.82; H, 7.40; N, 4.47; found: C, 73.03; H, 7.50; N, 4.51.

4.3. Biological tests (Table 1)

4.3.1. P. falciparum

Antiplasmodial activity was determined using the K1 strain of *P. falciparum* (resistant to chloroquine and pyrimethamine). A modification of the [^3H] hypoxanthine incorporation assay [38] was used [39]. Briefly, infected human red blood cells were exposed to serial drug dilutions in microtiter plates for 48 h at 37 °C in a gas mixture with reduced oxygen and elevated CO_2. [^3H] hypoxanthine was added to each well and after further incubation for 24 h the wells were harvested on glass fiber filters and counted in a liquid scintillation counter. From the sigmoidal inhibition curve the IC_{50} value was calculated.

4.3.2. T. cruzi

Rat skeletal myoblasts (L 6 cells) were seeded in 96-well microtiter plates at 2000 cells/well/100 μl in RPMI 1640 medium with 10% FBS and 2 mM L-glutamine. After 24 h 5000 trypomastigotes of *T. cruzi* [Tulahuen strain C2C4 containing the galactosidase (Lac Z) gene] were added in 100 μl per well with 2× of a serial drug dilution. The plates were

Table 1
In vitro activities against *T. cruzi*, *L. donovani*, *P. falciparum* and L 6 cells

Compound	*T. cruzi* IC_{50} (μg/ml)	Therapeutic index	*L. donovani* IC_{50} (μg/ml)	Therapeutic index	*P. falciparum* K1 IC_{50} (μg/ml)	Therapeutic index	Cytotoxicity (L 6 cells) IC_{50} (μg/ml)
8	44.78		18.2		4.059	22.17	>90
9	19.80		18.9		0.377	152.5	57.5
11	3.60	12.06	>30		>5		43.4
12	59.10		18.3		>5		>90
13	>90		>30		3.458	26.03	>90
14	40.70		>10		0.628	>143.3	>90
15	5.80	14.62	4.2	20.19	0.424	200	84.8
18	45.20		12.75		>5		28.2
19	37.70		>10		0.463	71.6	33.2
20	3.70	17.84	2.4	27.50	1.023	64.5	66
23	5.50	1.53	5.2	1.62	0.349	24.1	8.4
24	20.10		>10		1.396	64.5	>90
25	22.70		30		0.521	152.8	79.6
26	12.05		n.a.		4.670	>19.2	>90
27	33.00		n.a.		>5		>90
28	10.00		n.a.		0.341	246	83.9
29	5.20	5.77	n.a.		3.866	7.8	30.0
33	>30		>30		3.554	25.32	>90
Standard drugs	0.25 (Benznidazole)	>360	0.23 (Miltefosin)		0.055 (Chloroquine)	1090	0.006 (Podophyllotoxin)

IC_{50} values are means of at least two independent assays run in duplicate. n.a.: These compounds were not active in the axenic amastigote assay [32] and therefore no assay was performed in infected mouse macrophages.

incubated at 37 °C in 5% CO_2 for 4 d. For measurement of the IC_{50} the substrate CPRG/Nonidet was added to the wells. The color reaction that developed during the following 2–4 h was read photometrically at 540 nm. IC_{50} values were calculated from the sigmoidal inhibition curve. Cytotoxicity was assessed in the same assay using non-infected L 6 cells and the same serial drug dilution. The MIC was determined microscopically after 4 d.

4.3.3. L. donovani

Mouse peritoneal macrophages (4×10^4 in 100 μl RPMI 1640 medium with 10% heat-inactivated FBS) were seeded into Lab-tek 16-chamber slides. After 24 h 1.2×10^5 *L. donovani* amastigotes in 100 μl were added. The amastigotes were taken from an axenic amastigote culture grown at pH 5.4. Four hours later the medium containing free amastigote forms was removed and replaced by fresh medium. The next day the medium was replaced by fresh medium containing different compound dilutions. After 96 h of incubation the medium was removed and the slides were fixed with methanol for 10 min followed by a staining with a 10% Giemsa solution. Infected and non-infected macrophages were counted for the control cultures and the ones exposed to the serial drug dilutions. The infection rates were determined. The results were expressed as % reduction in parasite burden compared to control wells, and the IC_{50} calculated by linear regression analysis.

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