Synthesis of Novel 2-Alkoxy-3-amino-3-arylpropan-1-ols and 5-Alkoxy-4-aryl-1,3-oxazinanes with Antimalarial Activity

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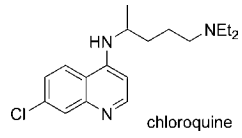
A variety of novel *syn*-2-alkoxy-3-amino-3-arylpropan-1-ols was prepared through $LiAlH_4$-promoted reductive ring-opening of *cis*-3-alkoxy-4-aryl-β-lactams in Et_2O. The latter γ-aminoalcohols were easily converted into *cis*-5-alkoxy-4-aryl-1,3-oxazinanes using formaldehyde in THF. Both series of compounds were evaluated against a chloroquine sensitive strain of *Plasmodium falciparum* (D10), revealing micromolar potency for almost all representatives. Eleven compounds exhibited antimalarial activity with IC_{50} values of ≤ 30 μM, and the majority of these compounds did not show cytotoxicity at the concentrations tested.

Introduction

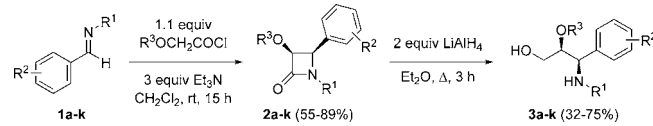
With 300−500 million clinical cases and 2 million deaths each year, malaria remains a major issue in health control, especially in developing countries.[1] Quinoline containing compounds have long been used for the treatment of malaria, and systematic modification has led to a variety of antimalarial drugs with diverse substitutions around the quinoline ring.[2] One of the first drugs to be prepared was the potent and inexpensive chloroquine (CQ), which is a 7-chloroquinoline with an amino substituent at position 4.[3]



chloroquine

The antimalarial activity of chloroquine appears to be linked to the haem metabolism of the causative agent, *Plasmodium falciparum*.[4] However, the spread of chloroquine-resistant *P. falciparum* strains has dashed hopes of global malaria eradication and has complicated the clinical management of malaria in endemic areas. Consequently, many efforts are devoted to the design and synthesis of novel and structurally diverse compounds with potential antimalarial activity. Recently, 1-aminopropan-2-ols were presented as novel antimalarial agents, with activities of the best seven compounds from a library in the 1−10 μM range against both a chloroquine sensitive (3D7) and chloroquine resistant (FCR3) strain of the parasite.[5] From a chemical point of view, the presented methodology was based on the ring-opening of 2-(alkoxymethyl)- and 2-(aminomethyl)epoxides by amines, resulting in the 1-aminopropan-2-ol motif due to ring-opening at the unsubstituted epoxide carbon atom.

Scheme 1. Staudinger Synthesis of *cis*-4-Aryl-β-lactams **2** and Their Reduction toward 3-Aminopropan-1-ols **3**



In the present paper, the synthesis and biological evaluation of a structurally more complex type of aminopropanols is described, i.e., new 2-alkoxy and 2-phenoxy substituted 3-amino-3-arylpropan-1-ols, starting from suitable azetidin-2-ones through reductive ring-opening. We reasoned that the combination of a γ-aminoalcohol moiety and an aryl group in these propanes might result in novel and easily accessible classes of antimalarial agents. Furthermore, cyclization of 3-amino-3-arylpropan-1-ols into 4-aryl-1,3-oxazinanes was performed in order to introduce conformational constraint into the target compounds.

Besides their biological relevance as potential antibiotics, β-lactams have acquired a prominent place in organic chemistry as synthons for further elaboration ("β-lactam synthon method").[6] Since then, the constrained azetidin-2-one ring has been employed successfully in a large variety of different synthetic methodologies toward all kinds of nitrogen-containing target compounds.[7] In spite of the fact that in theory a broad variety of different γ-aminoalcohols can be obtained by reductive ring-opening of β-lactams, mainly by means of complex metal hydrides, this methodology has been applied to a rather limited extend so far.[8]

Results and Discussion

Synthesis. The synthesis of 3-alkoxy and 3-phenoxy substituted 4-aryl-β-lactams **2** was performed by means of the Staudinger reaction between the appropriate imines and ketenes. Thus, treatment of *N*-(arylmethylidene)amines **1**, obtained by condensation of different benzaldehydes in dichloromethane in the presence of $MgSO_4$ and Et_3N utilizing 1 equiv of the appropriate amine,[9] with 1.1 equiv of methoxy-, phenoxy-, or benzyloxyacetyl chloride in dichloromethane in the presence of 3 equiv of triethylamine afforded the corresponding novel 4-arylazetidin-2-ones **2** in good yields at room temperature for 15 h (Scheme 1, also see Supporting Information). The relative

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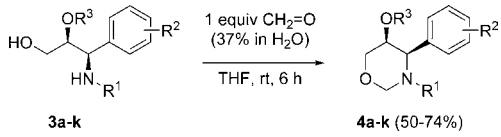
Scheme 2. Conversion of 3-Aminopropan-1-ols **3** into 4-Aryl-1,3-oxazinanes **4**



3a-k **4a-k** (50-74%)

stereochemistry of β-lactams **2** was assigned as *cis* based on the coupling constants between the protons at C3 and C4 in ^{1}H NMR (4.4−4.7 Hz, $CDCl_3$), in accordance with literature data.[10] Subsequently, *cis*-azetidin-2-ones **2** were subjected to a reductive ring-opening by means of 2 mol equiv of lithium aluminum hydride in diethyl ether, affording the corresponding 2-alkoxy or 2-phenoxy substituted *syn*-3-amino-3-arylpropan-1-ols **3** in good yields after reflux for 3 h (Scheme 1, also see Supporting Information).

To obtain molecular diversity within γ-aminoalcohols **3**, a variety of different representatives of this class of compounds was prepared by altering the amino group (R^1 = *i*Pr, *n*Pr, *i*Bu, *t*Bu, *c*Hex, Ph, Bn), the aryl moiety (R^2 = H, 4-Me, 3-OMe, 4-OMe, 4-Cl, 2-Br, 2-F) and the alkoxy or phenoxy substituent (R^3 = Me, Ph, Bn). This small library of novel γ-aminoalcohols **3** was then screened for potential antimalarial activity (see section Biological Evaluation).

With the intention to introduce conformational constraint into the target compounds, 3-aminopropan-1-ols **3** were subsequently converted into new *cis*-5-alkoxy-4-aryl-1,3-oxazinanes **4** by treatment with 1 equiv of formaldehyde (37% in water) in THF at room temperature for 6 h (Scheme 2, also see Supporting Information). There are only a few reports in the literature on the synthesis of oxazinanes,[11] either as biologically relevant targets[12] or as synthons for further elaboration.[13,14] Oxazinanes **4** appear to be highly stable, as these compounds can be stored (neat) for prolonged times without any loss of purity. Furthermore, oxazinanes **4** were shown to be stable under hydrolytic conditions, as these compounds were recovered completely and without loss of purity after stirring for 15 h at room temperature in water or in a water/DMSO (1/1) system.

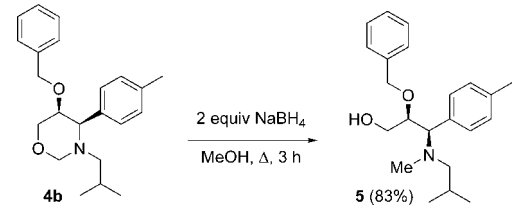
In accordance with literature data, the methylene group between oxygen and nitrogen in oxazinanes **4** appeared as two doublets with characteristic chemical shifts between 4 and 5 ppm (with a $\Delta\delta > 0.5$ ppm) and a coupling constant of 9 Hz (^{1}H NMR, $CDCl_3$).[15] Also, in ^{13}C NMR, this methylene carbon resonated at 79−84 ppm ($CDCl_3$), in accordance with the literature.[15] The *cis*-relationship of the alkoxy group with respect to the aryl moiety is a direct consequence of the stereodefined Staudinger formation of *cis*-β-lactams **2**, followed by transfer of the stereochemical information through the following reaction steps toward 2-alkoxy or 2-phenoxy substituted *syn*-3-amino-3-arylpropan-1-ols **3** and *cis*-1,3-oxazinanes **4**.

This small library of novel oxazinanes **4**, in which different substitution patterns have been incorporated, was then screened for potential antimalarial activity (see section Biological Evaluation).

Further evidence for the presence of a methylene bridge in 1,3-oxazinanes **4** was provided by reductive ring-opening of 5-benzyloxy-3-isobutyl-4-(4-methylphenyl)-1,3-oxazinane **4b** as a selected example by means of 2 equiv of sodium borohydride in methanol under reflux for 3 h, resulting in the corresponding 3-(*N*-methylamino)propan-1-ol **5** in 83% yield (Scheme 3).

Biological Evaluation. Subsequently, 3-aminopropan-1-ols **3a**−**k**, **5**, and 1,3-oxazinanes **4a**−**k** were screened for in vitro antiplasmodial activity. These samples were tested in duplicate

Scheme 3. Reductive Ring-Opening of 5-Benzyloxy-3-isobutyl-4-(4-methylphenyl)-1,3-oxazinane **4b** to 3-(*N*-Methylamino)propan-1-ol **5** by Means of $NaBH_4$



4b **5** (83%)

Table 1. In Vitro Antiplasmodial Activity against *P. falciparum* (CQS) D10 Strain

compd	IC_{50} (μM)	IC_{90} (μM)	compd	IC_{50} (μM)	IC_{90} (μM)
3a	45.89	164.73	**4b**	30.34	ND[a]
3b	15.3	70.76	**4c**	42.57	ND
3c	175.1	ND	**4d**	19.35	137.52
3d	6.36	12.48	**4e**	121.46	ND
3e	ND	ND	**4f**	14.08	38.55
3f	10.46	43.09	**4g**	16.81	118.46
3g	25.13	223.44	**4h**	84.87	ND
3h	85.22	ND	**4i**	129.02	ND
3i	13.73	251.63	**4j**	87.08	ND
3j	16.42	47.78	**4k**	ND	ND
3k	25.24	101.9	**5**	81.97	ND
4a	66.31	ND	CQ ($n = 8$)[b]	0.017	0.067

[a] ND = not determined. [b] n = number of data sets averaged.

on one occasion against a chloroquine sensitive (CQS) strain of *P. falciparum* (D10). Continuous in vitro cultures of asexual erythrocyte stages of *P. falciparum* were maintained using a modified method of Trager and Jensen.[16]

Quantitative assessment of antiplasmodial activity in vitro was determined via the parasite lactate dehydrogenase assay using a modified method described by Makler.[17]

The samples were prepared to a 2 mg/mL stock solution in 10% DMSO and sonicated to enhance solubility. Samples were tested as a suspension if not completely dissolved. Stock solutions were stored at −20 °C. Further dilutions were prepared on the day of the experiment. Chloroquine (CQ) was used as the reference drug in all experiments. A full dose−response was performed for all compounds to determine the concentration inhibiting 50% of parasite growth (IC_{50} value). Test samples were tested at a starting concentration of 100 μg/mL, which was then serially diluted 2-fold in complete medium to give 10 concentrations, with the lowest concentration being 0.2 μg/mL. The same dilution technique was used for all samples. CQ was tested at a starting concentration of 100 ng/mL. The highest concentration of solvent to which the parasites were exposed had no measurable effect on the parasite viability (data not shown). The IC_{50} values were obtained using a nonlinear dose−response curve fitting analysis via Graph Pad Prism v.4.0 software (see Supporting Information). The results of this biological study are presented in Table 1.

Interestingly, these results show micromolar potency for almost all representatives, pointing to the significant biological potential of γ-aminoalcohols **3** and 1,3-oxazinanes **4**. Moreover, 11 compounds exhibited antimalarial activity with IC_{50} values of $\leq$30 μM against *P. falciparum* (CQS) D10 strain, and compounds **3b**, **3d**, **3f**, **3i** and **4f** showed promising biological activity with IC_{50} values $\leq$15 μM. 2-Alkoxy-3-amino-3-arylpropan-1-ols **3** were generally more active than the corresponding oxazinanes **4**, with the most active compound being **3d**. It is noteworthy that these compounds were synthesized in racemic form, and it is conceivable that enantiomerically pure variants could deliver superior activities. Nevertheless, 2-alkoxy-

Table 2. IC_{50} Values of Compounds Tested in Vitro for Antiplasmodial Activity and Cytotoxicity

compd	D10: IC_{50} (μM)	CHO: IC_{50} (μM)	SI[a]
3b	15.3	143.5	9.4
3d	6.36	NT[c]	ND[d]
3f	10.46	NT	ND
3i	13.73	326.38	23.8
3j	16.42	144.58	8.8
4f	14.08	NT	ND
4g	16.81	NT	ND
emetine ($n = 2$)[b]		0.108	ND

[a] Selectivity index (SI) = IC_{50} CHO/IC_{50} D10. [b] n = number of data sets averaged. [c] NT = not toxic at 100 μg/mL. [d] ND = not determined.

3-amino-3-arylpropan-1-ols **3** can be considered as a potential new class of antimalarial agents.

In addition to the above-described antimalarial screenings, cytotoxicity studies were performed on the samples that showed an antimalarial activity of less than 17 μM. Thus, γ-aminoalcohols **3b**, **3d**, **3f**, **3i**, and **3j** and 1,3-oxazinanes **4f** and **4g** were subjected to further testing using the MTT-assay [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide-assay]. The MTT-assay is used as a colorimetric assay for cellular growth and survival and compares well with other available assays.[18] The tetrazolium salt MTT was used to measure all growth and chemosensitivity. The test samples were tested in triplicate on one occasion. The test samples were prepared to a 2 mg/mL stock solution in 10% methanol or 10% DMSO and were tested as a suspension if not properly dissolved. Test compounds were stored at −20 °C until use. Emetine was used as the reference drug in all experiments. The initial concentration of emetine was 100 μg/mL, which was serially diluted in complete medium with 10-fold dilutions to give six concentrations, the lowest being 0.001 μg/mL. The same dilution technique was applied to all the test samples. The highest concentration of solvent to which the cells were exposed had no measurable effect on the cell viability (data not shown). The 50% inhibitory concentration (IC_{50}) values were obtained from full dose−response curves, using a nonlinear dose−response curve fitting analysis via Graph Pad Prism v.4.0 software (see Supporting Information).

The results of this biological study are presented in Table 2. Interestingly, the in vitro cytotoxicity results showed that only compounds **3b** and **3j** have SI's of 9 (Table 2), whereas all other compounds did not show cytotoxicity at the concentrations tested.

In summary, the relevance of 3-alkoxyazetidin-2-ones as synthetic precursors for the biologically important class of 2-alkoxy-3-aminopropan-1-ols has been demonstrated by the preparation of a variety of novel *syn*-2-alkoxy-3-amino-3-arylpropan-1-ols. Cyclization of the latter γ-aminoalcohols by means of formaldehyde afforded a convenient entry into the corresponding new *cis*-5-alkoxy-4-aryl-1,3-oxazinanes. The biological importance of these classes of compounds was demonstrated by evaluation of their in vitro antiplasmodial activity and cytotoxicity, pointing to the promising potential of *syn*-2-alkoxy-3-amino-3-arylpropan-1-ols **3** as a novel type of antimalarial agents.

Experimental Section

^{1}H NMR spectra were recorded at 300 MHz (JEOL ECLIPSE+) with $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 75 MHz (JEOL ECLIPSE+) with $CDCl_3$ as solvent. Mass spectra were obtained with a mass spectrometer Agilent 1100, 70 eV. IR spectra were measured with a Spectrum One FT-IR spectrophotometer. Elemental analyses were performed with a PerkinElmer series II CHNS/O analyzer 2400. Dichloromethane was distilled over calcium hydride, while diethyl ether was dried over sodium benzophenone ketyl. Other solvents were used as received from the supplier. The purity of all new compounds has been assessed by means of gas chromatographic analysis (purity >95%).

Synthesis of *cis*-4-Aryl-β-lactams (2). General procedure: To an ice-cooled solution of *N*-(arylmethylidene)amine **1** (10 mmol) and triethylamine (30 mmol) in dichloromethane (25 mL) was added dropwise a solution of alkoxyacetyl chloride (11 mmol) in CH_2Cl_2 (10 mL). After stirring for 15 h at room temperature, the reaction mixture was poured into water (30 mL) and extracted with CH_2Cl_2 (2 × 25 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent afforded *cis*-3-alkoxy-4-aryl-β-lactam **2**, which was purified by recrystallization from ethanol or column chromatography on silica gel.

***cis*-3-Benzyloxy-1-isopropyl-4-phenylazetidin-2-one (2a).** Recrystallization from absolute EtOH; mp = 101.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 and 1.25 (6H, 2 × d, J = 6.6 Hz), 3.83 (1H, septet, J = 6.6 Hz), 4.10 and 4.25 (2H, 2 × d, J = 11.3 Hz), 4.74 (1H, d, J = 4.4 Hz), 4.78 (1H, d, J = 4.4 Hz), 6.91−6.95, 7.18−7.21 and 7.36−7.44 (10H, 3 × m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.2, 21.4, 44.8, 60.9, 72.2, 82.7, 127.8, 128.2, 128.3, 128.5, 128.7, 135.4, 136.5, 166.6. IR (NaCl, cm^{-1}): $\nu_{C=O}$ = 1739. MS (70 eV): *m*/*z* (%) 296 (M^++1, 100). Anal. calcd for $C_{19}H_{21}NO_2$: C 77.26, H 7.17, N 4.74; found: C 77.40, H 7.42, N 4.61.

Synthesis of *syn*-2-Alkoxy-3-amino-3-arylpropan-1-ols (3). General procedure: To an ice-cooled solution of *cis*-3-alkoxy-4-aryl-β-lactam **2** (10 mmol) in dry diethyl ether (50 mL) was added lithium aluminum hydride (20 mmol) in small portions. After reflux for 3 h, the reaction mixture was cooled to 0 °C and water (10 mL) was added in order to quench the excess of $LiAlH_4$. The resulting suspension was filtered over celite and washed with diethyl ether (40 mL), and the filtrate was poured into water (50 mL) and extracted with Et_2O (3 × 30 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent in vacuo afforded *syn*-2-alkoxy-3-amino-3-arylpropan-1-ol **3**, which was purified by means of column chromatography on silica gel or recrystallization from absolute EtOH.

***syn*-2-Benzyloxy-3-isopropylamino-3-phenylpropan-1-ol (3a).** R_f = 0.14 (hexane/EtOAc 4/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 (6H, d, J = 6.2 Hz), 2.58 (1H, septet, J = 6.2 Hz), 3.46−3.49 (1H, m), 3.79 and 3.99 (2H, 2 × (d × d), J = 12.2, 3.3, 2.2 Hz), 4.05 (1H, d, J = 3.4 Hz), 4.35 and 4.60 (2H, 2 × d, J = 11.8 Hz), 7.15−7.20 and 7.23−7.38 (10H, 2 × m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4, 24.3, 45.0, 63.3, 63.7, 71.6, 81.0, 127.4, 127.6, 127.6, 127.9, 128.3, 128.4, 138.1, 140.6. IR (NaCl, cm^{-1}): $\nu_{NH,OH}$ = 3329. MS (70 eV): *m*/*z* (%) 300 (M^+ + 1, 100). Anal. calcd for $C_{19}H_{25}NO_2$: C 76.22, H 8.42, N 4.68; found: C 76.05, H 8.57, N 4.52.

Synthesis of *cis*-5-Alkoxy-4-aryl-1,3-oxazinanes (4). General procedure: To a solution of *syn*-2-alkoxy-3-amino-3-arylpropan-1-ol **3** (5 mmol) in THF (20 mL) was added formaldehyde (5 mmol, 37% solution in H_2O) at room temperature. The resulting mixture was stirred for 6 h at room temperature, after which the solvent was removed in vacuo. The crude *cis*-5-alkoxy-4-aryl-1,3-oxazinane **4** was purified by column chromatography on silica gel.

***cis*-5-Benzyloxy-3-isopropyl-4-phenyl-1,3-oxazinane (4a).** R_f = 0.19 (hexane/EtOAc 6/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84 and 1.15 (6H, 2 × d, J = 6.6 Hz), 3.05 (1H, septet, J = 6.6 Hz), 3.36−3.39 (1H, m), 3.62 (1H, d × d, J = 12.0, 2.0 Hz), 3.88 (1H, d, J = 3.3 Hz), 4.10 (1H, d × d, J = 12.0, 2.7 Hz), 4.12 (1H, d, J = 8.8 Hz), 4.22 (2H, s), 4.74 (1H, d, J = 8.8 Hz), 6.89−6.93, 7.12−7.17, 7.24−7.37, and 7.50−7.54 (10H, 4 × m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.7, 21.3, 47.6, 65.5, 69.1, 71.9, 74.4, 79.1, 127.2, 127.4, 127.9, 127.95, 128.04, 129.3, 137.9, 139.3. IR (NaCl, cm^{-1}): ν_{max} = 2965, 2868, 1182, 1076, 1067, 1052, 1028, 738, 697. MS (70 eV): *m*/*z* (%) 312 (M^+ + 1, 100). Anal. calcd for $C_{20}H_{25}NO_2$: C 77.14, H 8.09, N 4.50; found: C 76.96, H 8.32, N 4.58.

Synthesis of *syn*-2-Benzyloxy-3-(*N*-isobutyl-*N*-methylamino)-3-(4-methylphenyl)propan-1-ol (5). To an ice-cooled solution of 5-benzyloxy-3-isobutyl-4-(4-methylphenyl)-1,3-oxazinane **4b** (5 mmol) in methanol (20 mL) was added sodium borohydride (10 mmol), after which the resulting suspension was heated under reflux for 3 h. Afterward, the reaction mixture was poured into water (25 mL), extracted with dichloromethane (3 × 20 mL), and dried ($MgSO_4$). Filtration of the drying agent and removal of the solvent yielded the crude *syn*-2-benzyloxy-3-(*N*-isobutyl-*N*-methylamino)-3-(4-methylphenyl)propan-1-ol **5**, which was purified by means of column chromatography on silica gel (hexane/EtOAc 6/1).

$R_f = 0.07$ (hexane/EtOAc 6/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 and 0.90 (6H, 2 × d, $J = 6.4$ Hz), 1.70−1.94 (1H, m), 2.07 and 2.17 (2H, 2 × (d × d), $J = 12.0$, 7.2, 6.9 Hz), 2.27 (3H, s); 2.33 (3H, s), 3.59 (1H, d × d, $J = 11.8$, 4.7 Hz), 3.74 (1H, d, $J =$ 4.9 Hz), 3.83 (1H, d × d, $J = 11.8$, 4.1 Hz), 3.89−3.93 (1H, m), 4.70 (2H, s), 7.11−7.41 (9H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.76, 20.81, 21.1, 25.9, 38.9, 63.5, 64.3, 71.3, 72.4, 79.0, 127.6, 127.8, 128.4, 128.6, 129.9, 132.4, 137.0, 138.6. IR (NaCl, cm^{-1}): $\nu_{OH} = 3403$. MS (70 eV): *m*/*z* (%) 342 ($M^+ + 1$, 100). Anal. calcd for $C_{22}H_{31}NO_2$: C 77.38, H 9.15, N 4.10; found: C 77.59, H 9.33, N 3.96.

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Supporting Information Available: Spectroscopic data of compounds **2b**−**2k**, **3b**−**3g**, and **4b**−**4k**, and full dose−response curves. This material is available free of charge via the Internet at http://pubs.acs.org.

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