



Original article

Synthesis of 2-(aminomethyl)aziridines and their microwave-assisted ring opening to 1,2,3-triaminopropanes as novel antimalarial pharmacophores

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ABSTRACT

A variety of 2-(aminomethyl)aziridines was prepared and converted into the corresponding 1,2,3-triaminopropanes through a novel, microwave-assisted and regioselective ring opening by diethylamine in acetonitrile. Antiplasmodial assays revealed antimalarial activity for 2-[(1,2,4-triazol-1-yl)methyl]aziridines and 2-(*N,N*-diethylaminomethyl)aziridines, as well as for the corresponding 1-(diethylamino)propanes obtained through ring opening, pointing to the relevance of both the 2-(aminomethyl)aziridine and the 1,2,3-triaminopropane unit as novel antimalarial pharmacophores.

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1. Introduction

With 247 million clinical cases and nearly one million deaths in 2008, mostly among African children, malaria remains a major issue in health control [1]. Quinoline-containing compounds, such as the potent and inexpensive chloroquine (CQ) [2–4], have a long tradition in the treatment of malaria, and systematic modification has led to a variety of antimalarial drugs with diverse substitutions around the quinoline ring [5,6]. However, the spread of chloroquine-resistant *Plasmodium 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, the β -amino alcohol moiety has been introduced as a promising antimalarial pharmacophore, and the synthesis of a number of novel aminopropanols with significant antimalarial activity has revealed the medicinal importance of this class of

glycerol analogues [7–9]. Their aza-derivatives, i.e. 1,2,3-triaminopropanes, however, have not been the subject of antimalarial screening up to now.

In this paper, the preparation and biological evaluation of novel 2-(aminomethyl)aziridines and 1,2,3-triaminopropanes is described as potential new lead compounds within the framework of malaria management and treatment.

The aziridine moiety represents one of the most valuable three-membered ring systems in organic chemistry [10–17], and the regiocontrolled ring opening of C-substituted aziridines constitutes a powerful approach toward the preparation of a large variety of nitrogen-containing target compounds. In contrast to their activated counterparts, non-activated aziridines have been evaluated to a limited extent up to now, both from a synthetic and a pharmacological point of view. Due to the presence of an electron-donating substituent at nitrogen, the latter aziridines have to be activated toward aziridinium ion intermediates prior to ring opening [18–31]. Within the present work, the scarcely studied subclass of non-activated 1-alkyl-2-(aminomethyl)aziridines [32–39] was employed as a source of substrates for the development of a novel entry toward the biologically relevant 1,2,3-triaminopropane unit through a highly regioselective and microwave-assisted ring opening by diethylamine in acetonitrile.

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2. Results and discussion

2.1. Synthesis

Given the recently disclosed antimalarial properties of amino-propanols [7–9], and taking structure–activity relationship studies with regard to chloroquine into account [40], the elaboration of a 1,2,3-triaminopropane unit substituted with an aryl group, an *N,N*-diethylamino moiety and an azaheteroaromatic nucleus was envisaged as a potential novel antimalarial pharmacophore. From a retrosynthetic point of view, 2-(aminomethyl)aziridines can be regarded as suitable precursors for the preparation of 1,2,3-triaminopropanes through ring opening by amines. Thus, the synthesis of properly substituted aziridines, bearing an azaheteroaromatic group in their side chain, was proposed, which then could serve as eligible substrates for the preparation of the desired targets through aziridine ring opening by a nucleophilic amine.

At first, a variety of 2-(aminomethyl)aziridines **2** was prepared via coupling of different nitrogen nucleophiles with 2-(bromomethyl)aziridines **1** [41–43], employing the electrophilicity of the latter as a convenient handle for their connection to other moieties [33]. In order to introduce structural diversity within the amino side chain, aziridines **1** were connected to different classes of aromatic azaheterocycles such as adenine [44], thymine and 1,2,4-triazole en route to the corresponding 2-(aminomethyl)aziridines **2a–h** (Scheme 1, Table 1). In addition, also diethylamine was used for the preparation of 2-(*N,N*-diethylaminomethyl)aziridines **2i–k** in order to evaluate the difference between the presence of an aromatic azaheterocyclic moiety and a simple acyclic amino group in 1,2,3-triaminopropanes with regard to their biological activity.

The synthesis of 2-[(6-aminopurin-9-yl)methyl]aziridines **2a–c** was accomplished upon treatment of 2-(bromomethyl)aziridines **1** with 1 equiv of adenine in DMF at 80 °C for 5 h in the presence of 5 equiv of K₂CO₃ (Table 1, entries 1–3). Next to the desired *N*9-substituted adenines **2a–c**, isomeric *N*7-alkylation products were observed as well in minor amounts (*N*9/*N*7 ~3/1), which is in accordance with literature data on the *N*-alkylation of adenine [45]. The premixed adenine derivatives **2a–c** were isolated in pure form through crystallization. In recent years, the synthesis of functionalized adenines has gained much interest due to the pronounced biological activities, such as antitumor and antiviral, associated to this class of compounds [46–48]. Besides purines, also pyrimidines are known to be of importance as lead compounds in medicinal chemistry [48–50]. In that respect, thymine was used as a nucleophile toward the preparation of 2-[(2,4-dioxo-5-methylpyrimidin-1-yl)methyl]aziridines **2d,e** upon treatment of 2-(bromomethyl)aziridines **1** with one equiv of thymine and one equiv of NaH in DMF at 80 °C for 3 h (Table 1, entries 4–5). The former aziridines **2d,e** were obtained in good crude yields, and were purified by crystallization from CH₂Cl₂/Et₂O (4/1) in order to obtain analytically

Table 1
Synthesis of 2-(aminomethyl)aziridines **2a–k**.

Entry	Ar	R ¹ R ² NH	Reaction conditions ^a	Product (yield ^b)
1	Ph	Adenine	A	2a (31%)
2	4-ClC ₆ H ₄	Adenine	A	2b (51%)
3	4-MeOC ₆ H ₄	Adenine	A	2c (32%)
4	4-ClC ₆ H ₄	Thymine	B	2d (34%)
5	4-MeOC ₆ H ₄	Thymine	B	2e (26%)
6	Ph	1,2,4-triazole	C	2f (90%)
7	4-ClC ₆ H ₄	1,2,4-triazole	C	2g (63%)
8	4-MeOC ₆ H ₄	1,2,4-triazole	C	2h (54%)
9	Ph	Et ₂ NH	D	2i (90%)
10	4-ClC ₆ H ₄	Et ₂ NH	D	2j (63%)
11	4-MeOC ₆ H ₄	Et ₂ NH	D	2k (64%)

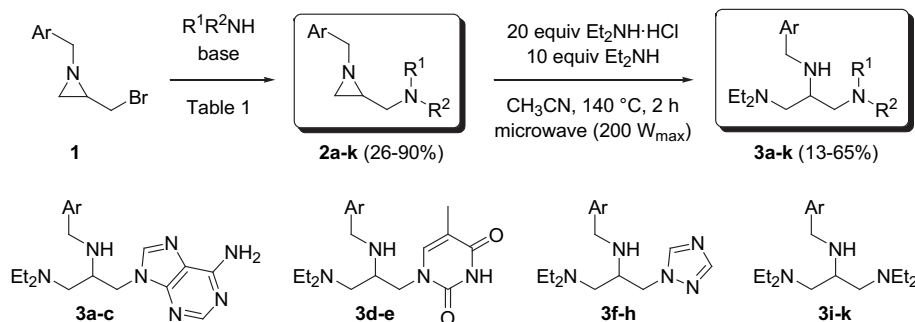
^a Reaction conditions: **A** = 1 equiv adenine, 5 equiv K₂CO₃, DMF, 80 °C, 5 h; **B** = 1 equiv thymine, 1 equiv NaH, DMF, 80 °C, 3 h; **C** = 5 equiv 1,2,4-triazole, 4 equiv K₂CO₃, CH₃CN, Δ, 2.5 d; **D** = 16 equiv Et₂NH, MeOH, Δ, 1 d.

^b Yield after purification by crystallization or column chromatography.

pure samples (the yields in Table 1 are yields obtained after purification).

Next to DNA bases, the 1,2,4-triazole moiety was introduced as an aziridine side chain through reaction of aziridines **1** with 5 equiv of 1,2,4-triazole [51] in CH₃CN under reflux for 2.5 d in the presence of 4 equiv of K₂CO₃, affording the corresponding triazoles **2f–h** in good yields (Table 1, entries 6–8) [33]. These long reaction times appeared to be necessary in order to drive the reaction to completion. Finally, a number of 2-(*N,N*-diethylaminomethyl)aziridines **2i–k** were prepared in good yields using an excess (16 equiv) of diethylamine in methanol under reflux for one day (Table 1, entries 9–11).

Subsequently, 2-(aminomethyl)aziridines **2a–k** were converted into novel 1,2,3-triaminopropanes **3a–k** bearing a diethylamino group through elaboration of the constrained aziridine moiety. The interest in this type of compounds stems from the known antimalarial activity of aminopropanols on the one hand and the relevance of a diethylamino unit in potent antimalarial agents (e.g. chloroquine) on the other hand. With the intention to introduce a diethylamino group, the ring opening of aziridines **2** by diethylamine was envisaged. Given the necessary activation of non-activated aziridines prior to ring opening, the use of diethylamine hydrochloride was contemplated. In this way, protonation of the aziridine ring provides a highly electrophilic aziridinium intermediate which is prone to nucleophilic ring opening. In order to drive the reaction to completion, and to avoid competition between chloride- and diethylamine-induced ring opening, a large excess of Et₂NH·HCl (20 equiv) and an additional amount of diethylamine (10 equiv) was used. Nonetheless, only partial conversion (<80%) of aziridines **2** was achieved after heating under reflux for 7 days in acetonitrile under the given reaction conditions. Fortunately, the poor reactivity of 2-(aminomethyl)aziridines **2** with regard to the



Scheme 1. Synthesis of 2-(aminomethyl)aziridines **2** and their microwave-assisted conversion into 1,2,3-triaminopropanes **3**.

$\text{Et}_2\text{NH}\cdot\text{HCl}/\text{Et}_2\text{NH}$ system under conventional heating was easily overcome through the application of microwave irradiation. Heating of the latter aziridines **2** at 140°C ($200\text{ W}_{\text{max}}$) in CH_3CN resulted in full and selective conversion to the desired triaminopropanes **3** after 2 h (Scheme 1), which were purified by crystallization or column chromatography (Al_2O_3) in order to obtain analytically pure samples (13–65% yield).

For aziridines **2a–h**, bearing an aromatic azaheterocyclic side chain, the ring opening of intermediate aziridinium ions **4a–h** proceeded with excellent regioselectivity through attack at the unhindered aziridinium carbon atom (Scheme 2). In the case of 2-(*N,N*-diethylaminomethyl)aziridines **2i–k**, however, a mixture of regioisomers ($\sim 3/2$ **3i–k/6i–k**) was obtained, with the major isomers **3i–k** being formed through ring opening of the initially formed aziridinium salts **4i–k** at the less hindered position (Scheme 2, pathway a). Due to the presence of a nucleophilic nitrogen atom in the diethylaminomethyl group, rearrangement of aziridinium salts **4i–k** to the corresponding 1,1-diethylaziridinium intermediates **5** occurred as well. Then, ring opening by diethylamine at the unhindered aziridinium carbon atom took place, giving rise to the formation of 1-(arylmethyl)amino-2,3-bis(diethylamino)propanes **6** (Scheme 2, pathway b). Only the major isomers **3i–k** were isolated in pure form through column chromatography on aluminium oxide.

The observed regioselectivity was confirmed through detailed spectroscopic analysis of triaminopropanes **3**. In addition, the formation of symmetric compounds **3i–k** further corroborates the regiochemical ring opening of aziridinium salts **4** by diethylamine at the unsubstituted carbon atom.

3. Results and discussion

3.1. Biological evaluation

Both classes of compounds, i.e. 2-(aminomethyl)aziridines **2** and 1,2,3-triaminopropanes **3**, were screened for *in vitro* antiplasmodial activity. All samples were tested in triplicate on one occasion against a chloroquine sensitive (CQS) strain of *P. falciparum* (D10). Additionally, those samples showing promising antimalarial activity were tested in triplicate on one occasion against a chloroquine-resistant (CQR) strain of *P. falciparum* (Dd2)

and screened for *in vitro* cytotoxicity against a mammalian cell-line, Chinese Hamster Ovarian (CHO), in triplicate on one occasion.

The test samples were prepared to a 2 mg/mL stock solution in 10% DMSO and sonicated to enhance solubility. The samples were tested as a suspension and stock solutions were stored at -20°C . Further dilutions were prepared on the day of the experiment.

3.1.1. Antiplasmodial assay

Continuous *in vitro* cultures of asexual erythrocyte stages of *P. falciparum* were maintained using a modified method of Trager and Jensen [52]. Quantitative assessment of antiplasmodial activity *in vitro* was determined via the parasite lactate dehydrogenase assay using a modified method described by Makler [53]. Chloroquine diphosphate (Sigma) (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 organism growth (IC_{50} -value).

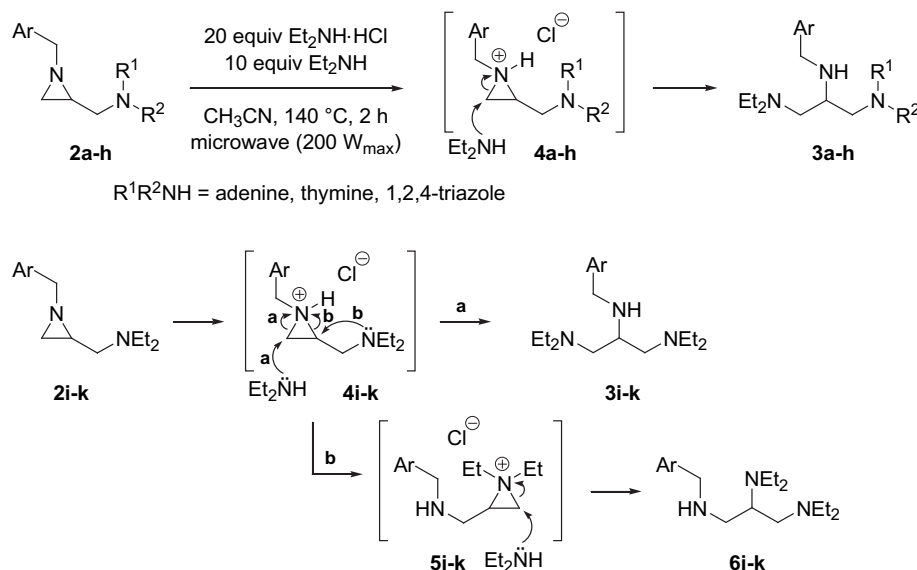
3.1.2. Cytotoxicity assay

The MTT-assay [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide-assay] is used as a colorimetric assay for cellular growth and survival, and compares well with other available assays [54,55]. The tetrazolium salt MTT was used to measure all growth and chemosensitivity. Emetine dihydrochloride (Sigma) was used as the reference drug in all experiments.

The results of the biological evaluation are summarized in Table 2 for 2-(aminomethyl)aziridines **2** and in Table 3 for 1,2,3-triaminopropanes **3**.




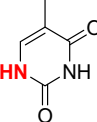
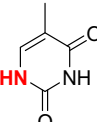



Although the aziridine moiety was initially not considered as a template for biological screening, both 2-[(1,2,4-triazol-1-yl)methyl]aziridine **2h** and 2-(*N,N*-diethylaminomethyl)aziridines **2i–k** exhibited antiplasmodial activity against the CQS D10 strain of *P. falciparum*, with IC_{50} -values between 15.3 and $4.2\text{ }\mu\text{M}$ (Table 2). Moreover, aziridines **2h** and **2i–k** also showed antimalarial activity against the CQR Dd2 strain of *P. falciparum* (IC_{50} -values between 48.3 and $18.0\text{ }\mu\text{M}$), and low (**2i–k**) or no (**2h**) cytotoxicity (Table 2).

With regard to the screening of 1,2,3-triaminopropanes **3**, all representatives showed weak to potent antiplasmodial activities against the chloroquine sensitive (CQS) strain of *P. falciparum*, with IC_{50} -values ranging from 214.1 to $2.0\text{ }\mu\text{M}$ (Table 3), with some degree of cross resistance being displayed by **3h**. In particular,



Scheme 2. Regioselectivity in the ring opening of 2-(aminomethyl)aziridines **2** using $\text{Et}_2\text{NH}\cdot\text{HCl}/\text{Et}_2\text{NH}$.

Table 2
IC₅₀-values of 2-(aminomethyl)aziridines **2** tested for *in vitro* antiplasmodial activity and cytotoxicity.

Compound	Ar	R ¹ R ² NH	D10: IC ₅₀ (μM)	Dd2: IC ₅₀ (μM)	CHO: IC ₅₀ (μM)	RI ^a	SI ^b
2a	Ph		>350	ND	ND	ND	ND
2b	4-ClC ₆ H ₄		>300	ND	ND	ND	ND
2c	4-MeOC ₆ H ₄		266.76	ND	ND	ND	ND
2d	4-ClC ₆ H ₄		137.92	ND	ND	ND	ND
2e	4-MeOC ₆ H ₄		172.16	ND	ND	ND	ND
2f	Ph		80.74	ND	ND	ND	ND
2g	4-ClC ₆ H ₄		125.97	ND	ND	ND	ND
2h	4-MeOC ₆ H ₄		4.18 (<i>n</i> = 2)	23.17	>400	5.6	ND
2i	Ph	Et ₂ NH	15.25	48.32	401.67	3.2	26.3
2j	4-ClC ₆ H ₄	Et ₂ NH	6.49	23.74	247.33	3.7	38.1
2k	4-MeOC ₆ H ₄	Et ₂ NH	8.54 (<i>n</i> = 2)	18.04	193.15	2.1	22.6
CQ			0.040 (<i>n</i> = 3)	0.298		7.5	
emetine					0.145		

ND = not determined. *n* = number of data sets averaged.

^a RI (Resistance Index) = IC₅₀ Dd2/IC₅₀ D10.

^b SI (Selectivity Index) = IC₅₀ CHO/IC₅₀ D10.

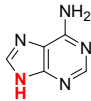


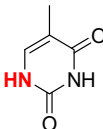
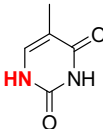



triazoles **3g,h** and 1,3-bis(diethylamino)propanes **3j,k** exhibited superior antimalarial activities with IC₅₀-values between 8.4 and 2.0 μM. Furthermore, triazoles **3f–h** and 1,3-bis(diethylamino)propanes **3i–k** were tested against the chloroquine-resistant (CQR) strain of *P. falciparum*, again showing antiplasmodial activities. Interestingly, the *in vitro* cytotoxicity results showed that only compounds **3j** and **3k** have SI's of 9 and 24, respectively (Table 3), whereas all other compounds did not show cytotoxicity at the concentrations tested.

It should be stressed that a number of 2-(aminomethyl)aziridines (e.g. **2h,j,k**) and 1,2,3-triaminopropanes (e.g. **3g,h,j,k**), with

IC₅₀-values less than 10 μM, exhibited better antiplasmodial activities as compared to the previously reported class of amino-propanols [8], pointing to the promising potential of aziridines **2** and aminopropanes **3** within the context of the development of novel antimalarial agents. It is noteworthy that these compounds were synthesized in racemic form, and it is conceivable that enantiomerically pure variants could deliver superior activities.

With regard to structure–activity relationships, substituted propanes bearing a 1,2,4-triazole group at the 1-position, a 4-chloro- or 4-methoxybenzylamino substituent at the 2-position and an *N,N*-diethylamino moiety at the 3-position appear to be of

Table 3IC₅₀-values of 1,2,3-triaminopropanes **3** tested for *in vitro* antiplasmodial activity and cytotoxicity.

Compound	Ar	R ¹ R ² NH	D10: IC ₅₀ (μM)	Dd2: IC ₅₀ (μM)	CHO: IC ₅₀ (μM)	RI ^a	SI ^b
3a	Ph		214.11	ND	ND	ND	ND
3b	4-ClC ₆ H ₄		78.21	ND	ND	ND	ND
3c	4-MeOC ₆ H ₄		81.91	ND	ND	ND	ND
3d	4-ClC ₆ H ₄		71.68	ND	ND	ND	ND
3e	4-MeOC ₆ H ₄		127.80	ND	ND	ND	ND
3f	Ph		42.90	98.75	>300	2.3	ND
3g	4-ClC ₆ H ₄		6.52	13.11	>300	2.0	ND
3h	4-MeOC ₆ H ₄		1.98	80.90	158.62	41.1	ND
3i	Ph	Et ₂ NH	23.67	30.16	>300	1.3	ND
3j	4-ClC ₆ H ₄	Et ₂ NH	8.41	19.82	76.37	2.4	9.1
3k	4-MeOC ₆ H ₄	Et ₂ NH	6.66	13.53	170.00	2.0	24.2
CQ			0.030 (<i>n</i> = 6)	0.215 (<i>n</i> = 4)		7.27	
Emetine					0.127 (<i>n</i> = 2)		

ND = not determined. *n* = number of data sets averaged.^a RI (Resistance Index) = IC₅₀ Dd2/IC₅₀ D10.^b SI (Selectivity Index) = IC₅₀ CHO/IC₅₀ D10.

particular interest in terms of their antimalarial activity. In addition, 1,3-bis(diethylamino)propanes bearing a 4-chloro- or 4-methoxybenzylamino substituent at the 2-position are also of importance in that respect.

In conclusion, a novel synthetic protocol was established for the straightforward conversion of a variety of 2-(aminomethyl)aziridines into 1,2,3-triaminopropanes through microwave-assisted regioselective ring opening by diethylamine using a combination of Et₂NH·HCl and Et₂NH in acetonitrile. Furthermore, both 2-(aminomethyl)aziridines and 1,2,3-triaminopropanes were shown to be of biological relevance as potential antimalarial agents, in particular 2-[(1,2,4-triazol-1-yl)methyl]aziridines and 2-(*N,N*-diethylamino-methyl)aziridines as well as the corresponding 1-(diethylamino)

propanes obtained through ring opening by diethylamine. Both the 2-(aminomethyl)aziridine and the 1,2,3-triaminopropane unit can thus be considered as novel antimalarial pharmacophores.

4. Experimental section

¹H NMR spectra were recorded at 300 MHz (JEOL ECLIPSE+) with CDCl₃ as solvent and tetramethylsilane as internal standard. ¹³C NMR spectra were recorded at 75 MHz (JEOL ECLIPSE+) with CDCl₃ as solvent and tetramethylsilane as internal standard. 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. Melting points of crystalline compounds were measured with a Büchi 540 apparatus. The purity of all new compounds was assessed by means of NMR analysis (purity > 95%).

4.1. Microwave reactions

All microwave reactions were performed in a CEM Focused MicrowaveTM Synthesis System, Model Discover, with a selectable power output from 0 to 300 Watt. The reactions were performed in 10 mL thick walled Pyrex reaction vessels closed with a 'snap-on' septa cap and equipped with a small stirring bar. The temperature control uses a non-contact infrared sensor to measure the temperature on the bottom of the vessel and is used in a feedback loop with the on-board computer to regulate the temperature from 25 to 250 °C by adjusting the power output (1 Watt increments). The pressure control, IntelliVentTM Pressure Control System, uses an indirect measurement of the pressure by sensing changes in the external deflection of the septa on the top of the sealed pressure vessel. Stirring is performed by a rotating magnetic plate located below the floor of the microwave cavity. Cooling of the vessel (after the reaction) is performed by a stream of clean air onto the vessel which decreases the temperature of a 2 mL solution from 150 °C to 40 °C in less than 120 s. A ramp time of maximum 5 min is used during which the temperature increases from room temperature to the desired one. This temperature is maintained during the course of the reaction for the indicated time.

4.1.1. Synthesis of 2-(6-aminopurin-9-yl)methyl-1-(arylmethyl)aziridines (**2a–c**)

General procedure: To a solution of 1-arylmethyl-2-(bromomethyl)aziridine **1** [41–43] (5 mmol) and adenine (5 mmol, 1 equiv) in dimethylformamide (50 mL) was added potassium carbonate (25 mmol, 5 equiv). After stirring for 5 h at 80 °C, the solvent was removed under reduced pressure. The residue was poured into water (25 mL), extracted with CHCl₃ (3 × 25 mL) and washed with brine (3 × 25 mL). The combined organic layers were dried over anhydrous magnesium sulfate. Filtration of the drying agent and removal of the solvent in vacuo afforded the crude products **2a–c**, which were purified by recrystallization.

4.1.2. 2-(6-Aminopurin-9-yl)methyl-1-(phenylmethyl)aziridine (**2a**)

Recrystallization from CH₂Cl₂/Et₂O (4/1); yield 31%; mp = 145.2 °C ¹H NMR (300 MHz, CDCl₃): δ 1.64 (1H, d, *J* = 6.6 Hz), 1.89 (1H, d, *J* = 3.3 Hz), 2.07–2.13 (1H, m), 3.06 and 3.63 (2H, 2 × d, *J* = 12.6 Hz), 3.77 (1H, d × d, *J* = 14.3, 8.3 Hz), 4.50 (1H, d × d, *J* = 14.3, 3.9 Hz), 5.87 (2H, br s), 7.09–7.21 (4H, m), 7.64 and 8.34 (2H, 2 × s). ¹³C NMR (75 MHz, CDCl₃): δ 33.2, 37.7, 46.8, 64.4, 119.5, 127.4, 128.2, 128.4, 138.2, 140.7, 149.8, 152.9, 155.6. IR (ATR, cm^{−1}): ν_{NH} = 3289 and 3103. MS (70 eV): *m/z* (%) 281 (M⁺ + 1, 100). Anal. calcd. for C₁₅H₁₆N₆: C 64.27, H 5.75, N 29.90; found: C 64.06, H 5.74, N 29.73.

4.1.3. 2-(6-Aminopurin-9-yl)methyl-1-[(4-chlorophenyl)methyl]aziridine (**2b**)

Recrystallization from CH₂Cl₂; yield 51%; mp = 167.6 °C ¹H NMR (300 MHz, CDCl₃): δ 1.64 (1H, d, *J* = 6.1 Hz), 1.91 (1H, d, *J* = 3.3 Hz), 2.06–2.14 (1H, m), 2.91 and 3.62 (2H, 2 × d, *J* = 12.9 Hz), 3.72 (1H, d × d, *J* = 14.3, 8.3 Hz), 4.50 (1H, d × d, *J* = 14.3, 3.9 Hz), 5.72 (2H, br s), 6.97–7.00 and 7.08–7.11 (4H, 2 × m), 7.64 and 8.34 (2H, 2 × s). ¹³C NMR (75 MHz, CDCl₃): δ 33.4, 37.7, 46.7, 63.6, 119.4, 128.4, 129.4, 133.1, 136.6, 140.5, 149.6, 152.8, 155.5. IR (ATR, cm^{−1}): ν_{NH} = 3311 and 3119. MS (70 eV): *m/z* (%) 315/7 (M⁺ + 1, 100). Anal. calcd. for C₁₅H₁₅ClN₆: C 57.24, H 4.80, N 26.70; found: C 57.04, H 4.97, N 26.85.

4.1.4. 2-(6-Aminopurin-9-yl)methyl-1-[(4-methoxyphenyl)methyl]aziridine (**2c**)

Recrystallization from CH₂Cl₂/Et₂O (4/1); yield 32%; mp = 181.1 °C ¹H NMR (300 MHz, CDCl₃): δ 1.63 (1H, d, *J* = 6.6 Hz), 1.87 (1H, d, *J* = 3.3 Hz), 2.04–2.11 (1H, m), 2.93 and 3.60 (2H, 2 × d, *J* = 12.6 Hz), 3.72 (1H, d × d, *J* = 14.3, 8.6 Hz), 3.78 (3H, s), 4.49 (1H, d × d, *J* = 14.3, 3.8 Hz), 5.52 (2H, br s), 6.65–6.70 (2H, m), 6.97–7.01 (2H, m), 7.65 and 8.34 (2H, 2 × s). ¹³C NMR (75 MHz, CDCl₃): δ 33.1, 37.5, 46.9, 55.3, 63.8, 113.7, 119.4, 129.4, 130.4, 140.7, 149.7, 152.8, 155.6, 158.8. IR (ATR, cm^{−1}): ν_{NH} = 3310 and 3121. MS (70 eV): *m/z* (%): 311 (M⁺ + 1, 100). Anal. calcd. for C₁₆H₁₈N₆O: C 61.92, H 5.85, N 27.08; found: C 61.45, H 5.97, N 26.91.

4.1.5. Synthesis of 1-arylmethyl-2-[(2,4-dioxo-5-methylpyrimidin-1-yl)methyl]aziridines (**2d–e**)

General procedure: To a solution of 1-arylmethyl-2-(bromomethyl)aziridine **1** [41–43] (5 mmol) and thymine (5 mmol, 1 equiv) in dimethylformamide (25 mL) was added sodium hydride (60% in mineral oil; 5 mmol, 1 equiv). After stirring for 3 h at 80 °C, the solvent was removed under reduced pressure. The residue was poured into water (10 mL), extracted with chloroform (3 × 15 mL) and washed with brine (3 × 15 mL). The combined organic layers were dried over anhydrous magnesium sulfate. Filtration of the drying agent and removal of the solvent in vacuo afforded the crude products **2d–e**, which were purified by recrystallization from dichloromethane/ether (4/1).

4.1.6. 1-(4-Chlorophenyl)methyl-2-[(2,4-dioxo-5-methylpyrimidin-1-yl)methyl]aziridine (**2d**)

Recrystallization from CH₂Cl₂/Et₂O (4/1); yield 34%; mp = 149.4 °C ¹H NMR (300 MHz, CDCl₃): δ 1.64 (1H, d, *J* = 6.1 Hz), 1.74 (3H, d, *J* = 1.1 Hz), 1.86 (1H, d, *J* = 3.9 Hz), 2.00–2.07 (1H, m), 2.79 (1H, d, *J* = 12.1 Hz), 2.86 (1H, d × d, *J* = 14.2, 8.8 Hz), 3.87 (1H, d, *J* = 12.1 Hz), 4.35 (1H, d × d, *J* = 14.2, 3.1 Hz), 6.81 (1H, d, *J* = 1.1 Hz), 7.16–7.21 and 7.23–7.27 (4H, 2 × m), 9.42 (1H, br s). ¹³C NMR (75 MHz, CDCl₃): δ 12.2, 32.4, 37.5, 51.1, 63.5, 110.0, 128.6, 130.0, 133.5, 136.9, 140.7, 151.0, 164.2. IR (ATR, cm^{−1}): ν_{CO} = 1698 and 1660, ν_{NH} = 3192. MS (70 eV): *m/z* (%): 306/8 (M⁺ + 1, 100). Anal. calcd. for C₁₅H₁₆ClN₃O₂: C 58.92, H 5.27, N 13.74; found: C 59.31, H 5.46, N 13.46.

4.1.7. 2-(2,4-Dioxo-5-methylpyrimidin-1-yl)methyl-1-[(4-methoxyphenyl)methyl]aziridine (**2e**)

Recrystallization from CH₂Cl₂/Et₂O (4/1); yield 26%; mp = 167.7 °C ¹H NMR (300 MHz, CDCl₃): δ 1.64 (1H, d, *J* = 6.6 Hz), 1.67 (3H, s), 1.84 (1H, d, *J* = 3.3 Hz), 1.99–2.05 (1H, m), 2.60 (1H, d, *J* = 12.1 Hz), 2.71 (1H, d × d, *J* = 14.3, 9.4 Hz), 3.79 (3H, s), 3.90 (1H, d, *J* = 12.1 Hz), 4.41 (1H, d × d, *J* = 14.3, 2.7 Hz), 6.73 (1H, s), 6.77–6.79 (2H, m), 7.11–7.14 (2H, m), 8.92 (1H, br s). ¹³C NMR (75 MHz, CDCl₃): δ 12.2, 32.4, 37.8, 51.3, 55.2, 63.8, 109.7, 113.8, 129.9, 130.5, 140.7, 150.9, 159.0, 164.3. IR (ATR, cm^{−1}): ν_{CO} = 1696 and 1660, ν_{NH} = 3189. MS (70 eV): *m/z* (%): 302 (M⁺ + 1, 100). Anal. calcd. for C₁₆H₁₉N₃O₃: C 63.77, H 6.36, N 13.94; found: C 63.46, H 5.99, N 13.46.

4.1.8. Synthesis of 1-arylmethyl-2-[(1,2,4-triazol-1-yl)methyl]aziridines (**2f–h**) [33]

General procedure: To a solution of 1-arylmethyl-2-(bromomethyl)aziridine **1** [41–43] (7.78 mmol) and 1,2,4-triazole (38.9 mmol, 5 equiv) in acetonitrile (100 mL) was added potassium carbonate (31.12 mmol, 4 equiv), after which the resulting suspension was heated under reflux for 2 days. Afterwards, the solvent was removed under reduced pressure. The residue was poured into 75 mL of a 1 M sodium hydroxide solution and extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried over anhydrous potassium carbonate. Filtration of the drying agent and removal of the solvent in vacuo afforded the

crude products **2f–h**, which were purified by column chromatography on silica gel (CHCl₃/MeOH 97/3).

4.1.9. 1-(4-Methoxyphenyl)methyl-2-[(1,2,4-triazol-1-yl)methyl]aziridine (**2h**)

R_f = 0.17 (CHCl₃/MeOH 97/3); yield 54%. ¹H NMR (300 MHz, CDCl₃): δ 1.60 (1H, d, J = 6.6 Hz), 1.81 (1H, d, J = 3.3 Hz), 1.99–2.06 (1H, m), 3.19 and 3.44 (2H, 2 \times d, J = 12.6 Hz), 3.78 (3H, s), 3.91 (1H, d \times d, J = 14.2, 7.7 Hz), 4.30 (1H, d \times d, J = 14.2, 4.2 Hz), 6.79–6.83 (2H, m), 7.09–7.13 (2H, m), 7.86 and 7.96 (2H, 2 \times s). ¹³C NMR (75 MHz, CDCl₃): δ 32.6, 37.5, 52.6, 55.2, 63.5, 113.9, 129.3, 130.4, 143.1, 151.6, 158.9. IR (ATR, cm⁻¹): ν_{\max} = 2836, 1612, 1511, 1273, 1244, 1176, 1139, 1031, 817, 751, 733, 679. MS (70 eV): m/z (%): 245 (M⁺ + 1, 100). Anal. calcd for C₁₃H₁₆N₄O: C 63.91, H 6.60, N 22.93; found: C 63.78, H 6.67, N 22.78.

4.1.10. Synthesis of 1-arylmethyl-2-(diethylaminomethyl)aziridines (**2i–k**)

General procedure: A solution of 1-arylmethyl-2-(bromomethyl)aziridine **1** [41–43] (6.67 mmol) and diethylamine (106.72 mmol, 16 equiv) in methanol (100 mL) was heated under reflux for 3 days. Afterwards, the reaction mixture was neutralized by means of a saturated sodium bicarbonate solution. The resulting suspension was poured into water (70 mL) and extracted with CH₂Cl₂ (3 \times 50 mL). The combined organic layers were dried over anhydrous potassium carbonate. Filtration of the drying agent and removal of the solvent under reduced pressure afforded the crude products **2i–k**, which were purified by column chromatography on silica gel.

4.1.11. 2-(*N,N*-Diethylamino)methyl-1-(phenylmethyl)aziridine (**2i**)

R_f = 0.14 (CHCl₃/MeOH 95/5); yield 90%. ¹H NMR (300 MHz, CDCl₃): δ 0.97 (6H, t, J = 7.2 Hz), 1.40 (1H, d, J = 6.6 Hz), 1.60 (1H, d, J = 3.3 Hz), 1.63–1.70 (1H, m), 2.38–2.62 (6H, m), 3.34 and 3.46 (2H, 2 \times d, J = 13.2 Hz), 7.20–7.39 (5H, m). ¹³C NMR (75 MHz, CDCl₃): δ 11.6, 32.7, 38.0, 47.0, 56.2, 64.7, 127.1, 128.4, 139.1. IR (ATR, cm⁻¹): ν_{\max} = 2968, 2799, 2360, 2341, 1454, 1348, 1202, 1069, 1028, 757, 731, 697. MS (70 eV): m/z (%): 219 (M⁺ + 1, 100). Anal. calcd. for C₁₄H₂₂N₂: C 77.01, H 10.16, N 12.83; found: C 76.79, H 10.03, N 12.77.

4.1.12. 1-(4-Chlorophenyl)methyl-2-[(*N,N*-diethylamino)methyl]aziridine (**2j**)

R_f = 0.22 (CHCl₃/MeOH 95/5); yield 63%. ¹H NMR (300 MHz, CDCl₃): δ 0.99 (6H, t, J = 7.2 Hz), 1.42 (1H, d, J = 6.6 Hz), 1.63 (1H, d, J = 3.9 Hz), 1.66–1.71 (1H, m), 2.47–2.64 (6H, m), 3.33 and 3.46 (2H, 2 \times d, J = 13.5 Hz), 7.30 (5H, s). ¹³C NMR (75 MHz, CDCl₃): δ 11.41, 32.61, 37.99, 46.89, 56.02, 63.79, 128.44, 129.58, 132.80, 137.55. IR (ATR, cm⁻¹): ν_{\max} = 2970, 1491, 1346, 1202, 1087, 1071, 1015, 806, 732. MS (70 eV): m/z (%): 253/5 (M⁺ + 1, 100). Anal. calcd. for C₁₄H₂₁ClN₂: C 66.52, H 8.37, N 11.08; found: C 66.67, H 8.62, N 10.99.

4.1.13. 2-(*N,N*-Diethylamino)methyl-1-[(4-methoxyphenyl)methyl]aziridine (**2k**)

R_f = 0.07 (CHCl₃/MeOH 95/5); yield 64%. ¹H NMR (300 MHz, CDCl₃): δ 0.99 (6H, t, J = 7.2 Hz), 1.43 (1H, d, J = 6.1 Hz), 1.60 (1H, d, J = 3.3 Hz), 1.65–1.70 (1H, m), 2.43–2.64 (6H, m), 3.33 and 3.41 (2H, 2 \times d, J = 13.2 Hz), 3.80 (3H, s), 6.84–6.88 (2H, m), 7.25–7.28 (2H, m). ¹³C NMR (75 MHz, CDCl₃): δ 11.5, 32.5, 37.7, 46.9, 55.3, 56.1, 64.1, 113.8, 129.4, 131.2, 158.8. IR (ATR, cm⁻¹): ν_{\max} = 2970, 2933, 1612, 1512, 1463, 1300, 1244, 1174, 1035, 819, 730. MS (70 eV): m/z (%): 249 (M⁺ + 1, 100). Anal. calcd. for C₁₅H₂₄N₂O: C 72.54, H 9.74, N 11.28; found: C 72.43, H 9.84, N 11.16.

4.1.14. Synthesis of 1-(6-aminopurin-9-yl)-2-(arylmethyl)amino-3-diethylaminopropanes (**3a–c**)

General procedure: In a 10 mL thick walled Pyrex reaction vessel, 2-(6-aminopurin-9-yl)methyl-1-(arylmethyl)aziridine

2a–c (0.89 mmol), diethylamine (17.8 mmol) and diethylamine hydrochloride (8.9 mmol) were dissolved in acetonitrile (6 mL). The mixture was heated to 140 °C for 2 h under microwave irradiation (200 W_{max}). Afterwards, the reaction mixture was neutralized by means of a saturated sodium bicarbonate solution, poured into water (15 mL), extracted with diethyl ether (3 \times 10 mL) and washed with brine (3 \times 10 mL). The combined organic layers were dried over anhydrous potassium carbonate. Filtration of the drying agent and removal of the solvent in vacuo afforded the crude products **3a–c**, which were purified by recrystallization from CH₂Cl₂/Et₂O (4/1).

4.1.15. 1-(6-Aminopurin-9-yl)-3-diethylamino-2-(phenylmethyl)aminopropane (**3a**)

Recrystallization from CH₂Cl₂/Et₂O (4/1); yield 34%; mp = 114.7 °C ¹H NMR (300 MHz, CDCl₃): 0.90 (3H, t, J = 7.2 Hz), 1.86 (1H, br s), 2.18–2.51 (6H, m), 3.04–3.09 (1H, m), 3.71 and 3.79 (2H, 2 \times d, J = 13.2 Hz), 4.19 (1H, d \times d, J = 13.9, 5.0 Hz), 4.24 (1H, d \times d, J = 13.9, 4.7 Hz), 5.59 (2H, br s), 7.23–7.33 (5H, m), 7.96 and 8.37 (2H, 2 \times s). ¹³C NMR (75 MHz, CDCl₃): δ 11.7, 45.7, 46.9, 52.1, 54.7, 55.4, 119.6, 127.0, 128.1, 128.4, 140.2, 142.0, 150.3, 152.9, 155.3. IR (ATR, cm⁻¹): ν_{NH} = 3286, 3228, 3130. MS (70 eV): m/z (%): 354 (M⁺ + 1, 100). Anal. calcd. for C₁₉H₂₇N₇: C 64.56, H 7.70, N 27.74; found: C 64.83, H 7.85, N 27.49.

4.1.16. 1-(6-Aminopurin-9-yl)-2-[(4-chlorophenyl)methyl]amino-3-diethylaminopropane (**3b**)

Recrystallization from CH₂Cl₂/Et₂O (4/1); yield 18%; mp = 135.5 °C ¹H NMR (300 MHz, CDCl₃): 0.92 (6H, t, J = 7.2 Hz), 1.80 (1H, br s), 2.21–2.52 (6H, m), 3.01–3.09 (1H, m), 3.68 and 3.75 (2H, 2 \times d, J = 13.5 Hz), 4.17 (1H, d \times d, J = 14.1, 5.3 Hz), 4.23 (1H, d \times d, J = 14.1, 4.7 Hz), 5.61 (2H, br s), 7.15–7.18 and 7.23–7.25 (4H, 2 \times m), 7.93 and 8.37 (2H, 2 \times s). ¹³C NMR (75 MHz, CDCl₃): δ 11.7, 45.9, 47.0, 51.4, 54.6, 55.4, 119.4, 128.5, 129.4, 132.7, 138.6, 141.8, 150.6, 152.9, 155.4. IR (ATR, cm⁻¹): ν_{NH} = 3284 and 3132. MS (70 eV): m/z (%): 388/90 (M⁺ + 1, 100). Anal. calcd. for C₁₉H₂₆ClN₇: C 58.83, H 6.67, N 25.28; found: C 58.72, H 7.14, N 24.96.

4.1.17. 1-(6-Aminopurin-9-yl)-3-diethylamino-2-[(4-methoxyphenyl)methyl]aminopropane (**3c**)

Recrystallization from CH₂Cl₂/Et₂O (4/1); yield 13%; mp = 106.8 °C ¹H NMR (300 MHz, CDCl₃): 0.91 (3H, t, J = 7.2 Hz), 2.20–2.52 (6H, m), 3.03–3.11 (1H, m), 3.65 and 3.73 (2H, 2 \times d, J = 13.2 Hz), 3.79 (3H, s); 4.19 (1H, d \times d, J = 14.5, 5.2 Hz), 4.23 (1H, d \times d, J = 14.5, 4.4 Hz), 5.85 (2H, br s), 6.81–6.85 (2H, m), 7.14–7.18 (2H, m), 7.97 and 8.37 (2H, 2 \times s). ¹³C NMR (75 MHz, CDCl₃): δ 11.7, 45.8, 46.9, 51.5, 54.5, 55.3, 55.4, 113.8, 129.3, 132.2, 141.9, 150.6, 152.9, 155.4, 158.7. IR (ATR, cm⁻¹): ν_{NH} = 3322 and 3159. MS (70 eV): m/z (%): 384 (M⁺ + 1, 100). Anal. calcd. for C₂₀H₂₉N₇O: C 62.64, H 7.62, N 25.57; found: C 62.38; H 7.74; N 25.41.

4.1.18. Synthesis of 2-(arylmethyl)amino-3-diethylamino-1-(2,4-dioxo-5-methylpyrimidin-1-yl)propanes (**3d–e**)

The procedure for the synthesis of compounds **3a–c** was applied for the preparation of 2-(arylmethyl)amino-3-diethylamino-1-(2,4-dioxo-5-methylpyrimidin-1-yl)propanes **3d–e**. The crude products **3d–e** were purified by column chromatography on aluminum oxide or by recrystallization.

4.1.19. 2-[(4-Chlorophenyl)methyl]amino-3-diethylamino-1-(2,4-dioxo-5-methylpyrimidin-1-yl)-propane **3d**

Recrystallization from CH₂Cl₂/Et₂O (4/1); yield 18%; mp = 42.1 °C ¹H NMR (300 MHz, CDCl₃): 0.95 (3H, t, J = 6.9 Hz), 1.90 (3H, s), 2.30–2.54 (6H, m), 2.89–2.94 (1H, m), 3.63–3.77 (4H, m), 7.10 (1H, s), 7.19–7.29 (4H, m), 8.86 (1H, br s). ¹³C NMR (75 MHz, CDCl₃): δ 11.8,

12.2, 47.0, 50.9, 51.5, 54.2, 55.3, 109.6, 128.6, 129.4, 132.8, 138.8, 142.2, 151.2, 164.2. IR (ATR, cm^{-1}): ν_{CO} = 1706 and 1660, ν_{NH} = 3248. MS (70 eV): m/z (%): 379/81 ($\text{M}^+ + 1$, 100). Anal. calcd. for $\text{C}_{19}\text{H}_{27}\text{ClN}_4\text{O}_2$: C 60.23, H 7.18, N 14.79; found: C 60.55, H 7.42, N 14.57.

4.1.20. 3-Diethylamino-1-(2,4-dioxo-5-methylpyrimidin-1-yl)-2-[(4-methoxyphenyl)methyl]aminopropane **3e**

R_f = 0.08 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$); yield 65%. ^1H NMR (300 MHz, CDCl_3): 0.94 (3H, t, J = 7.2 Hz), 1.90 (3H, s), 2.32–2.53 (6H, m), 2.90–2.98 (1H, m), 3.65–3.74 (4H, m), 3.77 (3H, s), 7.13 (1H, s), 6.82–6.85 (2H, m), 7.13 (1H, s), 7.17–7.20 (2H, m). ^{13}C NMR (75 MHz, CDCl_3): δ 11.7, 12.3, 46.9, 50.9, 51.5, 53.8, 55.2, 55.3, 109.5, 113.8, 129.4, 132.3, 142.2, 151.7, 158.6, 165.0. IR (ATR, cm^{-1}): ν_{CO} = 1674, ν_{NH} = 3172 and 3029. MS (70 eV): m/z (%): 375 ($\text{M}^+ + 1$, 100). Anal. calcd. for $\text{C}_{20}\text{H}_{30}\text{N}_4\text{O}_3$: C 64.15, H 8.07, N 14.96; found: C 63.97, H 8.21, N 14.82.

4.1.21. Synthesis of 2-(arylmethyl)amino-3-diethylamino-1-(1,2,4-triazol-1-yl)propanes (**3f–h**)

The procedure for the synthesis of compounds **3a–c** was applied for the preparation of 2-(arylmethyl)amino-3-diethylamino-1-(1,2,4-triazol-1-yl)propanes **3f–h**. The crude products **3f–h** were purified by column chromatography on aluminum oxide ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 99/1).

4.1.22. 3-Diethylamino-2-(phenylmethyl)amino-1-(1,2,4-triazol-1-yl)propane **3f**

R_f = 0.54 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 99/1); yield 40%. ^1H NMR (300 MHz, CDCl_3): 0.91 (6H, t, J = 6.9 Hz), 2.27 (1H, d \times d, J = 14.2, 6.3 Hz), 2.30 (1H, d \times d, J = 14.2, 8.3 Hz), 2.34–2.48 (4H, m), 3.00–3.08 (1H, m), 3.64 and 3.69 (2H, 2 \times d, J = 13.5 Hz), 4.12 (1H, d \times d, J = 14.0, 5.2 Hz), 4.21 (1H, d \times d, J = 14.0, 4.7 Hz), 7.20–7.36 (5H, m), 7.93 and 8.13 (2H, 2 \times s). ^{13}C NMR (75 MHz, CDCl_3): δ 11.7, 46.9, 51.9, 52.0, 54.6, 55.2, 127.0, 128.1, 140.1, 144.1, 151.6. IR (ATR, cm^{-1}): ν_{NH} = 3300. MS (70 eV): m/z (%): 288 ($\text{M}^+ + 1$, 100). Anal. calcd. for $\text{C}_{16}\text{H}_{25}\text{N}_5$: C 66.86, H 8.77, N 24.37; found: C 66.94, H 8.95, N 24.42.

4.1.23. 2-[(4-Chlorophenyl)methyl]amino-3-diethylamino-1-(1,2,4-triazol-1-yl)propane **3g**

R_f = 0.12 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 99/1); yield 31%. ^1H NMR (300 MHz, CDCl_3): 0.93 (6H, t, J = 7.2 Hz), 2.27 (1H, d \times d, J = 12.8, 6.3 Hz), 2.31 (1H, d \times d, J = 12.8, 8.3 Hz), 2.33–2.53 (4H, m), 3.00–3.08 (1H, m), 3.60 and 3.64 (2H, 2 \times d, J = 13.5 Hz), 4.13 (1H, d \times d, J = 13.9, 5.8 Hz), 4.23 (1H, d \times d, J = 13.9, 4.4 Hz), 7.16–7.23 and 7.26–7.29 (4H, 2 \times m), 7.94 and 8.14 (2H, 2 \times s). ^{13}C NMR (75 MHz, CDCl_3): δ 11.7, 47.0, 51.3, 52.0, 54.6, 55.2, 128.51, 129.4, 132.7, 138.6, 144.1, 151.7. IR (ATR, cm^{-1}): ν_{NH} = 3290. MS (70 eV): m/z (%): 322/4 ($\text{M}^+ + 1$, 100). Anal. calcd. for $\text{C}_{16}\text{H}_{24}\text{ClN}_5$: C 59.71, H 7.52, N 21.76; found: C 59.83, H 7.68, N 21.74.

4.1.24. 3-Diethylamino-2-[(4-methoxyphenyl)methyl]amino-1-(1,2,4-triazol-1-yl)propane **3h**

R_f = 0.20 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 99/1); yield 19%. ^1H NMR (300 MHz, CDCl_3): 0.93 (6H, t, J = 7.2 Hz), 2.29–2.32 (2H, m), 2.35–2.50 (4H, m), 3.04–3.06 (1H, m), 3.59 and 3.64 (2H, 2 \times d, J = 12.7 Hz), 3.80 (3H, s), 4.11–4.26 (2H, m), 6.84–6.87 (2H, m), 7.16–7.19 (2H, m), 7.95 and 8.16 (2H, 2 \times s). ^{13}C NMR (75 MHz, CDCl_3): δ 11.6, 46.9, 51.5, 52.0, 54.5, 55.2, 55.3, 113.9, 129.3, 132.1, 144.2, 151.7, 158.7. IR (ATR, cm^{-1}): ν_{NH} = 3311. MS (70 eV): m/z (%): 318 ($\text{M}^+ + 1$, 100). Anal. calcd. for $\text{C}_{17}\text{H}_{27}\text{N}_5\text{O}$: C 64.32, H 8.57, N 22.06; found: C 64.45, H 8.73, N 12.89.

4.1.25. Synthesis of 2-(arylmethyl)amino-1,3-bis(diethylamino)propanes (**3i–k**)

The procedure for the synthesis of compounds **3a–c** was applied for the preparation of 2-(arylmethyl)amino-1,3-bis

(diethylamino)propanes **3i–k**. The crude products **3i–k** were purified by column chromatography on aluminum oxide ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 99/1).

4.1.26. 1,3-Bis(diethylamino)-2-(phenylmethyl)aminopropane **3i**

R_f = 0.10 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 99/1); yield 31%. ^1H NMR (300 MHz, CDCl_3): 0.98 (12H, t, J = 7.2 Hz), 2.39–2.53 (12H, m), 2.66–2.74 (1H, m), 3.87 (2H, s), 7.28–7.34 (5H, m). ^{13}C NMR (75 MHz, CDCl_3): δ 12.0, 47.6, 52.0, 52.7, 57.1, 126.9, 128.4, 128.5, 140.8. IR (ATR, cm^{-1}): ν_{NH} = 3295. MS (70 eV): m/z (%): 292 ($\text{M}^+ + 1$, 100). Anal. calcd. for $\text{C}_{18}\text{H}_{33}\text{N}_3$: C 74.14, H 11.41, N 14.42; found: C 74.03, H 11.36, N 14.30.

4.1.27. 2-[(4-Chlorophenyl)methyl]amino-1,3-bis(diethylamino)propane **3j**

R_f = 0.16 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 99/1); yield 25%. ^1H NMR (300 MHz, CDCl_3): 0.98 (12H, t, J = 7.2 Hz), 2.37–2.55 (12H, m), 2.59–2.71 (1H, m), 3.83 (2H, s), 7.18–7.29 (4H, m). ^{13}C NMR (75 MHz, CDCl_3): δ 11.9, 47.5, 51.3, 52.7, 57.1, 128.4, 129.5, 132.4, 139.5. IR (ATR, cm^{-1}): ν_{NH} = 3288. MS (70 eV): m/z (%): 326/8 ($\text{M}^+ + 1$, 100). Anal. calcd. for $\text{C}_{18}\text{H}_{32}\text{ClN}_3$: C 66.33, H 9.90, N 12.89; found: C 66.57, H 10.13, N 12.77.

4.1.28. 1,3-Bis(diethylamino)-2-[(4-methoxyphenyl)methyl]amino-propane **3k**

R_f = 0.19 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 99/1); yield 13%. ^1H NMR (300 MHz, CDCl_3): 1.00 (12H, t, J = 7.2 Hz), 2.41–2.58 (12H, m), 2.64–2.81 (1H, m), 3.80 (3H, s), 3.90 (2H, s), 6.86–6.89 (2H, m), 7.25–7.31 (2H, m). ^{13}C NMR (75 MHz, CDCl_3): δ 11.6, 47.3, 50.5, 52.2, 55.3, 56.3, 113.9, 129.7, 130.3, 158.8. IR (ATR, cm^{-1}): ν_{NH} = 3298. MS (70 eV): m/z (%): 322 ($\text{M}^+ + 1$, 100). Anal. calcd. for $\text{C}_{19}\text{H}_{35}\text{N}_3\text{O}$: C 70.98, H 10.97, N 13.07; found: C 71.18, H 11.07, N 13.00.

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References

- [1] WHO, Fact Sheet Malaria No.94 (January 2009).
- [2] P.M.S. Chauhan, S.K. Srivastava, *Curr. Med. Chem.* 8 (2001) 1535–1542.
- [3] C.W. Jefford, *Curr. Med. Chem.* 8 (2001) 1803–1826.
- [4] T.R. Sweeney, *Med. Res. Rev.* 1 (1981) 281–301.
- [5] A. Kumar, S.B. Katiyar, A. Agarwal, P.M.S. Chauhan, *Curr. Med. Chem.* 10 (2003) 1137–1150.
- [6] L.J. Bruce-Chwatt, R.H. Black, C.J. Canfield, D.F. Clyde, W. Peters, W.H. Wernsdorfer (Eds.), *Chemotherapy of Malaria*, second ed. WHO, Geneva, 1986.
- [7] A. Robin, F. Brown, N. Bahamontes-Rosa, B. Wu, E. Beitz, J.F.J. Kun, S.L. Flitsch, *J. Med. Chem.* 50 (2007) 4243–4249.
- [8] M. D'hooghe, S. Dekeukeleire, K. Mollet, C. Lategan, P.J. Smith, K. Chibale, N. De Kimpe, *J. Med. Chem.* 52 (2009) 4058–4062.
- [9] S. Pérez-Silanes, L. Berrade, R.N. García-Sánchez, A. Mendoza, S. Galiano, B.M. Pérez-Solórzano, J.J. Nogal-Ruiz, A.R. Martínez-Fernández, I. Aldana, A. Monge, *Molecules* 14 (2009) 4120–4135.
- [10] B. Zwanenburg, P. ten Holte, *Top. Curr. Chem.* 216 (2001) 93–124.
- [11] J.B. Sweeney, *Chem. Soc. Rev.* 31 (2002) 247–258.
- [12] X.E. Hu, *Tetrahedron* 60 (2004) 2701–2743.
- [13] D. Tanner, *Angew. Chem. Int. Ed. Engl.* 33 (1994) 599–619.
- [14] W.M. McCoull, F.A. Davis, *Synthesis* (2000) 1347–1365.
- [15] I.D.G. Watson, L. Yu, A.K. Yudin, *Acc. Chem. Res.* 39 (2006) 194–206.
- [16] A. Padwa, S.S. Murphree, *Arkivoc* iii (2006) 6–33.
- [17] G.S. Singh, M. D'hooghe, N. De Kimpe, *Chem. Rev.* 107 (2007) 2080–2135.
- [18] T.N. Wade, *J. Org. Chem.* 45 (1980) 5328–5333.
- [19] D. Gnecco, L. Orea, F.A. Galindo, R.G. Enríquez, R.A. Toscano, W.F. Reynolds, *Molecules* 5 (2000) 998–1003.
- [20] P. O'Brien, T.D. Towers, *J. Org. Chem.* 67 (2002) 304–307.
- [21] T.B. Sim, S.H. Kang, K.S. Lee, W.K. Lee, H. Yun, Y. Dong, H.-J. Ha, *J. Org. Chem.* 68 (2003) 104–108.

- [22] M. D'hooghe, V. Van Speybroeck, M. Waroquier, N. De Kimpe, *Chem. Commun.* (2006) 1554–1556.
- [23] M. D'hooghe, K. Vervisch, A. Van Nieuwenhove, N. De Kimpe, *Tetrahedron Lett.* 48 (2007) 1771–1774.
- [24] M. D'hooghe, V. Van Speybroeck, A. Van Nieuwenhove, M. Waroquier, N. De Kimpe, *J. Org. Chem.* 72 (2007) 4733–4740.
- [25] Y. Kim, H.-J. Ha, S.Y. Yoon, W.K. Lee, *Chem. Commun.* (2008) 4363–4365.
- [26] M. D'hooghe, W. Aelterman, N. De Kimpe, *Org. Biomol. Chem.* 7 (2009) 135–141.
- [27] S.Y. Yun, S. Catak, W.K. Lee, M. D'hooghe, N. De Kimpe, V. Van Speybroeck, M. Waroquier, Y. Kim, H.-J. Ha, *Chem. Commun.* (2009) 2508–2510.
- [28] H.A. Song, M. Dadwal, Y. Lee, E. Mick, H.S. Chong, *Angew. Chem. Int. Ed.* 48 (2009) 1328–1330.
- [29] T.X. Metro, B. Duthion, D.G. Pardo, J. Cossy, *Chem. Soc. Rev.* (2010) 89–102.
- [30] S. Catak, M. D'hooghe, N. De Kimpe, M. Waroquier, V. Van Speybroeck, *J. Org. Chem.* 75 (2010) 885–896.
- [31] H.S. Chong, H.A. Song, M. Dadwal, X. Sun, I. Sin, Y.W. Chen, *J. Org. Chem.* 75 (2010) 219–221.
- [32] M. D'hooghe, N. De Kimpe, *Arkivoc* x (2007) 365–373.
- [33] M. D'hooghe, N. De Kimpe, *Arkivoc* ix (2008) 6–19.
- [34] M. D'hooghe, N. De Kimpe, *Chem. Commun.* (2007) 1275–1277.
- [35] M. Karikomi, N. De Kimpe, *Tetrahedron Lett.* 41 (2000) 10295–10298.
- [36] J.L. Pierre, P. Baret, *Comptes Rendus* 272 (1971) 2069–2072.
- [37] V.R. Gaertner, *J. Heterocycl. Chem.* 8 (1971) 177–178.
- [38] V.R. Gaertner, *J. Org. Chem.* 35 (1970) 3952–3959.
- [39] G. Szeimies, *Chem. Ber.* 106 (1973) 3695–3724.
- [40] P.M. O'Neill, P.G. Bray, S.R. Hawley, S.A. Ward, B.K. Park, *Pharmacol. Ther.* 77 (1998) 29–58.
- [41] N. De Kimpe, R. Jolie, D. De Smaele, J. Chem. Soc. Chem. Commun. (1994) 1221–1222.
- [42] M. D'hooghe, A. Waterinckx, N. De Kimpe, *J. Org. Chem.* 70 (2005) 227–232.
- [43] M. D'hooghe, M. Rottiers, R. Jolie, N. De Kimpe, *Synlett* (2005) 931–934.
- [44] L. Harmse, R. van Zyl, N. Gray, P. Schultz, S. Leclerc, L. Meijer, C. Doerig, I. Havlik, *Biochem. Pharmacol.* 62 (2001) 341–348.
- [45] G. Abu Sheikha, P. La Colla, A.G. Loi, *Nucleosides, Nucleotides Nucleic Acids* 21 (2002) 619–653.
- [46] M. Legraverend, D.S. Grierson, *Bioorg. Med. Chem.* 14 (2006) 3987–4006.
- [47] M. Legraverend, *Tetrahedron* 64 (2008) 8585–8603.
- [48] V. Ralevic, G. Burnstock, *Pharmacol. Rev.* 50 (1998) 413–492.
- [49] B. Tarnchompoo, C. Sirichaiwat, W. Phupong, C. Intaraudom, W. Sirawaraporn, S. Kamchonwongpaisan, J. Vanichtanankul, Y. Thebtaranonth, Y.J. Yuthavong, *J. Med. Chem.* 45 (2002) 1244–1252.
- [50] C. Sirichaiwat, C. Intaraudom, S. Kamchonwongpaisan, J. Vanichtanankul, Y. Thebtaranonth, Y. Yuthavong, *J. Med. Chem.* 47 (2004) 345–354.
- [51] Y. Chen, M. Lopez-Sanchez, D.N. Savoy, D.D. Billadeau, G.S. Dow, A.P. Kozikowski, *J. Med. Chem.* 51 (2008) 3437–3448.
- [52] W. Trager, J.B. Jensen, *Science* 193 (1976) 673–675.
- [53] M.T. Makler, J.M. Ries, J.A. Williams, J.E. Bancroft, R.C. Piper, B.L. Gibbins, D. Hinrichs, *J. Am. J. Trop. Med. Hyg.* 48 (1993) 739–741. Test samples were tested at a starting concentration of 100 µg/mL, which was then serially diluted two-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 to had no measurable effect on the parasite viability. The IC₅₀-values were obtained using a non-linear dose-response curve fitting analysis via Graph Pad Prism v.4.0 software.
- [54] T. Mosmann, *J. Immunol. Methods* 65 (1983) 55–63. The initial concentration of emetine was 100 µg/mL, which was serially diluted in complete medium with ten-fold dilutions to give 6 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 to had no measurable effect on the cell viability (data not shown). The IC₅₀-values were obtained from full dose-response curves, using a non-linear dose-response curve fitting analysis via GraphPad Prism v.4 software.
- [55] L.V. Rubinstein, R.H. Shoemaker, K.D. Paull, R.M. Simon, S. Tosini, P. Skehan, D.A. Scudiero, A. Monks, M.R. Boyd, J. Natl. Cancer Inst. 82 (1990) 1113–1118.