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Synthesis and antimycobacterial activity of agelasine E and analogs

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Agelasine E, previously isolated from the marine sponge *Agelas nakamurai*, has been synthesized for the first time, together with analogs with various terpenoid side chains. Treatment of N^6-methoxy-9-methyl-9*H*-purin-6-amine with allylic bromides gave the desired 7,9-dialkylpurinium salts together with minor amounts of the N^6-alkylated isomer. The N^6-methoxy group was finally removed reductively. ^{1}H–^{15}N HMBC and ^{1}H–^{15}N HSQC NMR spectroscopy gave additional information on tautomerism and charge delocalization in the purine derivatives studied. The heterocyclic products were screened for activity against *Mycobacterium tuberculosis* and agelasine analogs carrying a relatively long terpenoid substituent in the purine 7-position and a methoxy group at *N*-6 were potent inhibitors of bacterial growth. Since agelasine analogs with the geranylgeranyl chain at *N*-7 exhibited antimicrobial activity, several strategies for synthesis of geometrically pure (2*E*,6*E*,10*E*)-geranylgeranyl bromide from geranyllinalool were evaluated.

Introduction

Agelasines are 7,9-dialkylpurinium salts isolated from marine sponges (*Agelas* sp.). At the present time a total of eleven 9-methyladeninium salts, agelasine A–I, epiagelasine C and agelin B, are known.[1–7] All compounds carry a diterpenoid side chain in the adenine 7-position. Until recently, only (−)-agelasine A,[8] (−)-agelasine B,[9] and (±)-agelasine F[10] had been synthesized and we have just completed the synthesis of (+)-agelasine D[11] from (+)-manool.

Agelasines are associated with bioactivities such as antimicrobial and cytotoxic effects, as well as contractive responses of smooth muscles and inhibition of Na/K-ATPases. Furthermore, *in vitro* activity against *Mycobacterium tuberculosis* is reported for agelasine F (Fig. 1).[12] Tuberculosis (TB) is caused by *M. tuberculosis* and TB is the major cause of death from a single infectious agent among adults in developing countries and there has been an unfortunate revival of TB in the industrialized world. Human immunodeficiency virus (HIV) infections have further increased TB morbidity and mortality. Multidrug-resistant tuberculosis (MDR-TB), defined as resistance to the two most important drugs isoniazid (INH) and rifampicin (RMP), is a growing problem among HIV-infected patients. It has been estimated that *ca.* 30 million people will die from tuberculosis in about 10 years.[13] There is an urgent need for new antimycobacterial agents, but no new chemotherapeutic agents directed specifically against TB have been introduced for the last 30 years.

We recently published the first synthesis of (+)-trixagol (Fig. 1) as well as the enantiomer which corresponds to the terpenoid side chain of (−)-agelasine E.[14] We herein report the first synthesis of (−)-agelasine E from *ent*-trixagol and a study of antimycobacterial activity of agelasine E and agelasine analogs.

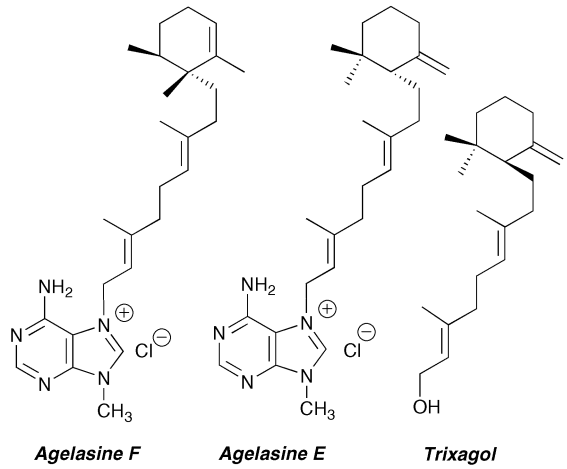
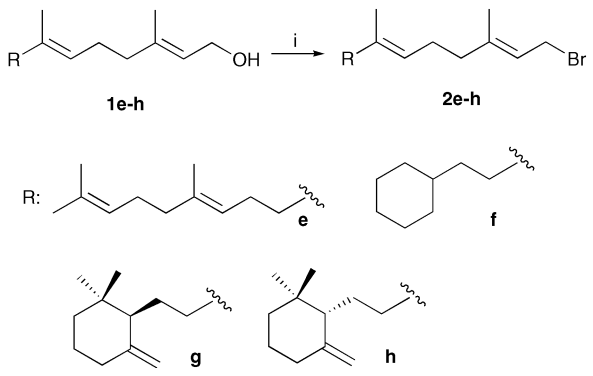


Fig. 1 Structure of (−)-agelasine F, (−)-agelasine E and (+)-trixagol.



Scheme 1 *Reagents and conditions:* i) PBr_3, Et_2O, 0 °C.

Results and discussion

The non-commercially available allylic halides required for the introduction the *N*-7 substituent in agelasine E and agelasine analogs were generated by reaction of the corresponding allylic alcohols with PBr_3 (Scheme 1).

Geranylgeraniol **1e** is much more expensive than the isomer geranyllinalool. Hence, we investigated the alternative synthesis of the primary allylic bromides **2d** (R = Me) and **2e** from tertiary allylic alcohols **3**. The same set of reaction conditions as used in the bromination of primary alchohols **1** gave *E*/*Z*-mixtures of the product (ratio *ca.* 7 : 3) (Scheme 2, Table 1). Various other procedures for halogenation of the alchohols **3** or corresponding acetates **4** employing boron trichloride,[15] boron tribromide or zinc iodide and TMS–bromide[16] were employed and the results are summarized in Table 1. In the reactions with ZnI_2–TMSBr minor amounts of the cyclization product **6** were also formed. Improved selectivity was obtained with BCl_3, but the allylic

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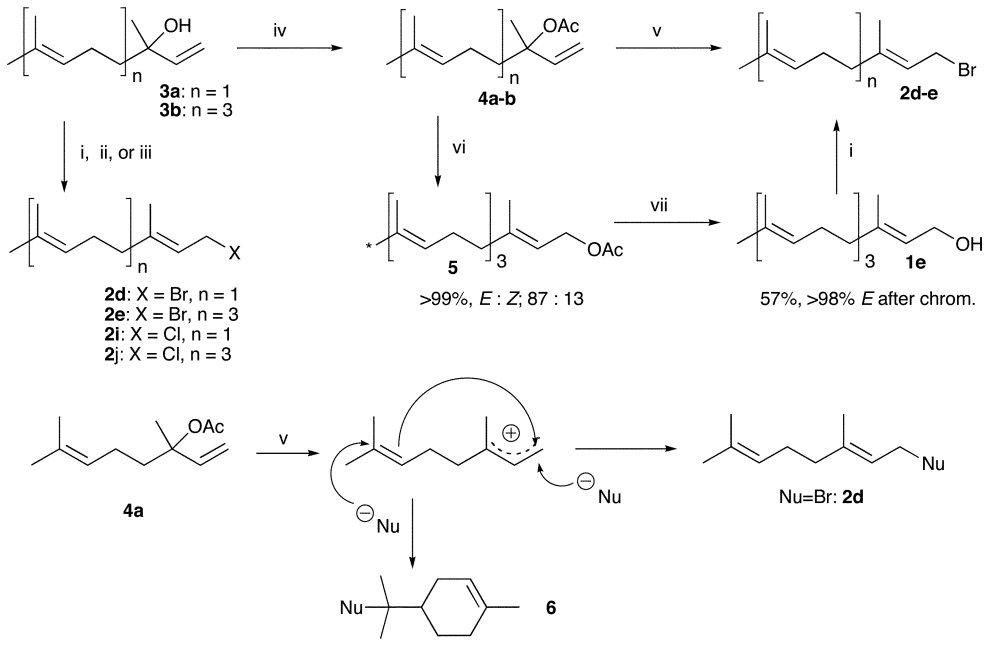


Scheme 2 *Reagents and conditions:* i) PBr_3, Et_2O; ii) BBr_3, hexane; iii) BCl_3, hexane; iv) Ac_2O, DMAP, CH_2Cl_2; v) ZnI_2, TMS–Br, Et_2O, −78 °C; vi) $PdCl_2(MeCN)_2$, THF; vii) K_2CO_3, MeOH.

Table 1 Conversion of tertiary allylic alcohols **3** or acetates **4** to primary allylic halides

Starting material	Reagents	Solvent	Temp./°C	Time	Conversion (%)[a]	*E* : *Z* comp. **2**	Yield **6** (%)[a]
3a	PBr_3	Et_2O	0	3 h	96	70 : 30	—[b]
3b	PBr_3	Et_2O	0	3 h	99	72 : 28	—[b]
3a	PBr_3, pyridine	Et_2O	−35	1 h	86	71 : 29	—[b]
3b	PBr_3, pyridine	Et_2O	−35	1 h	86	70 : 30	—[b]
3a	BCl_3	Hexane	20	10 min	80	83 : 17	—[b]
3b	BCl_3	Hexane	20	40 min	95	85 : 15	—[b]
3a	BBr_3	Hexane	20	10 min	100	55 : 45	—[b]
4a	ZnI_2, TMSBr	CH_2Cl_2	RT	4 h	—[c]	n.d.	n.d.
4a	ZnI_2, TMSBr	Et_2O	−15	35 min	100	86 : 14	13
4b	ZnI_2, TMSBr	Et_2O	−15	20 min	100	74 : 26	4–10[d]

[a] From ^{1}H NMR of crude compound. [b] Not detected by ^{1}H NMR. [c] No known products could be detected. [d] Sensitive to the rate of TMSBr addition.

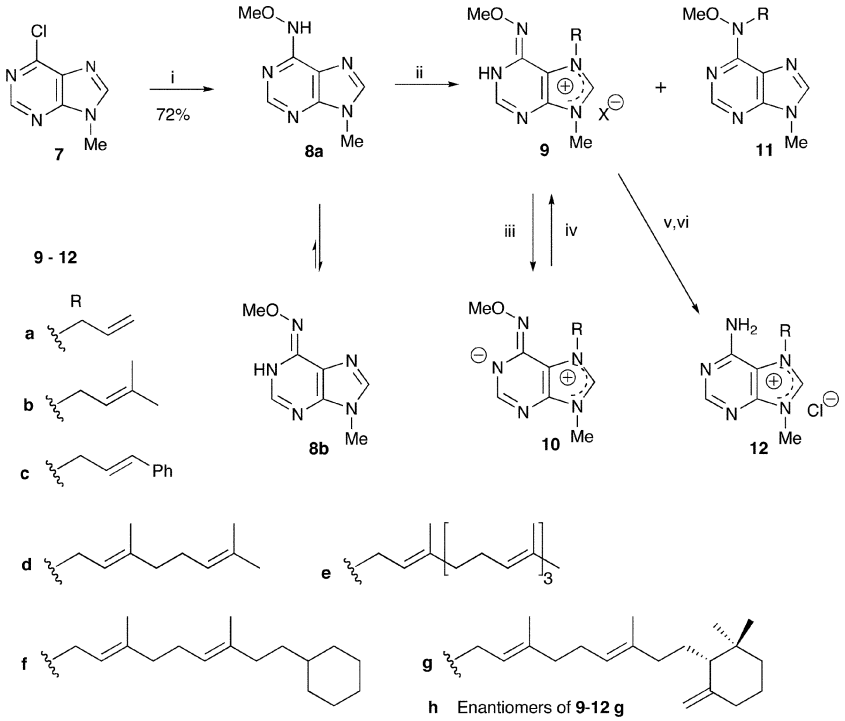
chlorides formed were not reactive enough for introduction of the *N*-7 substituent in the target agelasine analogs.

Palladium(II)-catalyzed rearrangement of tertiary allylic acetates are reported to give primary acetates with high *E*-selectivities[17] and when the geranyllinalyl acetate **4b** was treated with $PdCl_2(MeCN)_2$ geranylgeranyl acetate **5** with 87% *E*-selectivity was formed. Pure (*E*)-geranylgeraniol **1e** was obtained after ester hydrolysis and chromatographic purification of the alcohol.

Synthesis of agelasines requires regioselective alkylation of an adenine derivative to give a 7,9-dialkylated purinium salt. However, alkylation of 9-substituted adenine gives mainly 1,9-dialkyl derivatives and when 7-alkyladenines are reacted with alkyl halides, the second *N*-substituent is preferably introduced at *N*-3.[18] In contrast, treatment of *N*-methoxy-9-methyl-9*H*-purin-6-amine[19] with alkylating agents gives the desired alkylating pattern.[18] In our hands, synthesis of the N^6-methoxyamine **8** from the 6-chloropurine **7** (Scheme 3) was more successful than the rearrangement of 1-methoxyadenine reported previously.[19] When the adenine derivative **8** was alkylated with allylic bromides **2** the desired purinium salt **9** or betaine form **10** were formed, together with the isomer **11** (Table 2). When *E*/*Z* mixtures of bromides **2** were used, the same *E*/*Z* ratios were found in the products and separation of stereoisomers was tedious. Attempts to alkylate compound **8** with the allylic chloride **2j** were met with little success. When the alkylating agent was activated by the addition of sodium iodide conversion was substantially improved, but purification of the products was more complicated.

If the allylic substituent that was introduced was relatively short (**9a–c**) the salts could be separated by selective crystallization from EtOAc, although the more lipophilic salts **9d–h** had to be separated from their isomers **11d–h** by flash chromatography. After elution with a basic eluent the betaines **10** were isolated and could be converted to the purinium chlorides **9** by treatment with Amberlite–Cl. Finally, the methoxy directing group in compounds **9** were removed reductively to give the agelasine analogs **12a–f**, agelasine E **12g** and *ent*-agelasine E **12h**.

Detailed information regarding the structures of compound **8** and the simple agelasine analogs **9a**, **10a** and **12a** could be found from ^{1}H, ^{13}C and ^{15}N NMR spectroscopy. The 6-methoxyaminopurine **8** existed as an 8 : 2 mixture of two tautomers in DMSO-d_6 solution. The minor isomer was the amino tautomer **8a** (Scheme 3) as judged by ^{1}H and ^{13}C NMR, as well as HMBC and HMQC. The chemical shifts for the nitrogens in the major compound could be assigned from ^{1}H–^{15}N HMBC[20] and it was determined that the NH was situated in the purine 1-position and, hence, that the major tautomer had the structure **8b**. These findings were in accordance with previous tautomeric studies on compound **8** by ^{1}H NMR and UV.[21] The imines in Fig. 2 are presented in their most probable double bond configuration.[21] For compounds **9a**, **10a**, **12a** and **13** only one tautomer could be detected and these are shown in Fig. 2 together with their ^{15}N NMR shifts. Similar to other



Scheme 3 *Reagents and conditions:* i) $MeONH_2{\cdot}HCl$, Et_3N, *n*-BuOH, Δ; ii) R–Br **2**, DMA, 50 °C; iii) EtOAc, MeOH, NH_3(aq.), SiO_2; iv) Amberlite–Cl, MeOH, H_2O; v) Zn, AcOH, MeOH, H_2O; vi) NaCl(aq.).

Table 2 Yields of compounds **9**, **11** and **12**

Yield **9** (%)	Yield **11** (%)	Yield **12** (%)
63, **9a**	28, **11a**	52, **12a**
40, **9b**	23, **11b**	74, **12b**
54, **9c**	37, **11c**	82, **12c**
51, **9d**	28, **11d**	71, **12d**
49, **9e**	35, **11e**	72, **12e**
50, **9f**	24, **11f**	69, **12f**
48, **9g**	32, **11g**	52, **12g**
44, **9h**	26, **11h**	89, **12h**

purine derivatives described previously,[22] in the neutral purine **8b** the *N*-7 has an azine like shift and the alkylated *N*-9 a pyrrole like shift, but in the purinium cation **9a** the *N*-7 shift is moved towards the shift for *N*-9 while only small changes are observed for the other nitrogen resonances. The nearly identical shifts for the imidazolium nitrogens indicate an almost even distribution of the positive charge. The nitrogen shifts found for compound **9a** are also quite close to the chemical shifts reported for the nitrogen in compound **14**.[23] The negative charge in the betaine **10a** could, in theory, be stabilized over *N*-6, *N*-1 and *N*-3 but the spectroscopic data obtained indicated a high degree of negative charge at *N*-1. The purine resonances in the NMR spectra of **9b–h**, **10b–h** and **12b–h** are very close to those described for the simple allyl derivatives shown in Fig. 2, a strong indication that the same tautomers dominate regardless of the identity of the *N*-7 substituent.

Adenine derivatives **8–13** were screened for antibacterial activity against *Mycobacterium tuberculosis* $H_{37}Rv$ at 6.25 μg mL^{-1}.[24] For compounds displaying at least 90% inhibition of bacterial growth in the initial screening, minimum inhibitory concentrations (MICs) against *M. tuberculosis* were determined. MIC is defined as the minimum concentration of compound required to give 90% inhibition of bacterial growth. The results are summarized in Table 3.

Much to our surprise, and in contrast with what has been reported for agelasine F,[12] we found only modest antimycobacterial activity for agelasine E and agelasine analogs with free NH_2 in the purine 6-position (compounds **12**). However, many

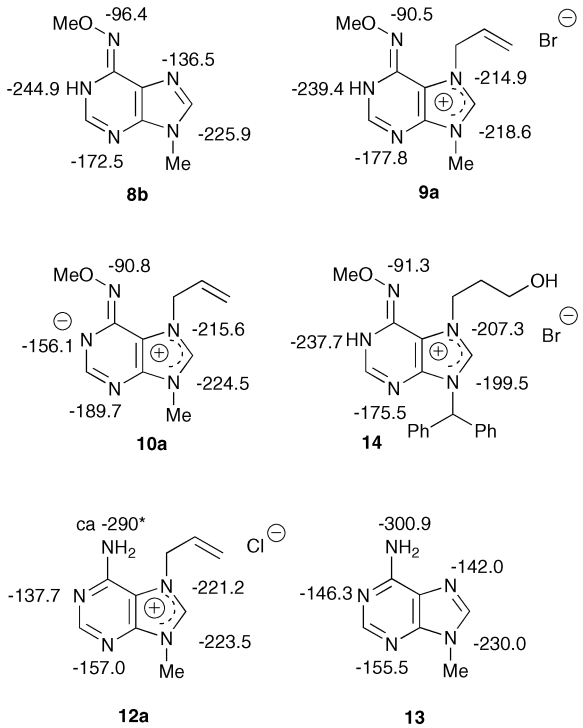


Fig. 2 ^{15}N NMR shifts (rel. to $MeNO_2$), deduced from ^1H–^{15}N HMBC, for the neutral purines **8** and **13** the betaine **10a** and the purinium cations **9a** and **12a**. The shifts for compound **14** are taken from ref. 23 and converted to the $MeNO_2$ scale. *Not observed in ^1H–^{15}N HMBC, weak correlation found in ^1H–^{15}N HSQC.

of the agelasine analogs still carrying the MeO-directing group at *N*-6 were highly potent inhibitors. A relatively long *N*-7 side chain was required for significant activity. *M. tuberculosis* has an extremely thick and waxy cell wall, which is an effective barrier for many chemicals. Hence, effective drugs should have a reasonable lipophilicity in order to penetrate this wall. This may explain why the more polar compounds **12** were less efficient than the synthetic intermediates **9** or **10** and also why compounds **9e–h**

Table 3 Antimycobacterial activity against *Mycobacterium tuberculosis* for adenine derivatives **8–9** and **11–13**, as well as the positive control rifampicin. Structures are shown in Scheme 2 and Scheme 3

Compound No.	Inhibition at 6.25 μg mL^{-1} (%)	MIC/μg mL^{-1}
8	8	n.d.
9a	27	n.d.
9b	11	n.d.
9c	35	n.d.
9d	27	n.d.
9e	100	3.13
9f	99	1.56
9g	100	3.13
9h	99	3.13
11a	0	n.d.
11b	17	n.d.
11c	30	n.d.
11d	41	n.d.
11e	86	n.d.
11g	92	6.25
11h	63	n.d.
12a	2	n.d.
12c	0	n.d.
12d	2	n.d.
12e	38	n.d.
12f	21	n.d.
12g	30	n.d.
12h	38	n.d.
13	94[a]	6.25
Rifampicin	>90	0.25

[a] At 12.5 μg mL^{-1}.

and **10e–h** were more potent antimycobacterials when compared to compounds **9a–d** or **10a–d**. The reason for the large difference in activity previously found for agelasine F,[12] and for agelasine E **12g**, *ent*-agelasine E **12h** and the related cyclohexyl analog **12f** in this study, is however not clear to us.

Even for some of the N^6-alkylated isomers **11**, formed as by-products in the alkylating step (Scheme 3), significant activities were found when the terpenoid side chain was relatively large (compounds **10e**, **10g** and **10h**). Furthermore, while the methoxyadenine **8** was essentially inactive, the simple 9-methyladenine **13** actually exhibited a MIC against *M. tuberculosis* at 6.25 mg mL^{-1}. Reasonable antimycobacterial activity has also been reported for some simple 9-benzyladenines.[25]

Experimental

General

The ^{1}H NMR spectra were acquired on a Bruker Avance AV 600 spectrometer, a Bruker Avance DRX 500 spectrometer, a Bruker Avance DPX 300 spectrometer or a Bruker Avance DPX 200 spectrometer at 600, 500, 300 or 200 MHz respectively. The ^{1}H decoupled ^{13}C NMR spectra were recorded at 150, 125, 75 or 50 MHz using the above mentioned spectrometers. Assignments of ^{1}H and ^{13}C resonances are inferred from 1D ^{1}H NMR, 1D ^{13}C NMR, APT, DEPT and/or from 2D NMR (gs-COSY, gs-HMQC, gs-HMBC, NOESY) spectral data. ^{15}N NMR data were acquired at 50 MHz on the Bruker Avance DRX 500 with a 5 mm TXI (^{1}H/^{13}C,^{15}N–^{2}H) Triple Resonance Inverse probe, equipped with *Z*-gradient coil, by applying 2D NMR experiments based on gradient pulse selection and inverse detection methods: gs-[^{1}H,^{15}N] HSQC, optimized for $1J$ ^{15}N/^{1}H-couplings of 80 Hz (Bruker pulse program: invietgpsi, ^{15}N-pulses *via* F2-channel, relaxation delay: 1.5 s, acquisition time: 0.17 s) and gs-[^{1}H,^{15}N] HMBC, optimized for $2J/3J$ ^{15}N/^{1}H-couplings of 10 Hz (Bruker pulse program: inv4gplplrndqf, ^{15}N-pulses *via* F2-channel, relaxation delay: 1.5 s, acquisition time: 0.17 s, delay for evolution of long range couplings: 0.1 s). ^{15}N chemical shifts are reported relative to external Me^{15}NO$_2$ at 0 ppm (MeNO$_2$ dissolved in the respective deuterated solvent in ratio 9 : 1). MS spectra under electron impact conditions were recorded with a VG Prospec instrument at 70 eV ionizing voltage and are presented as m/z (% rel. int.). CH_4 was employed as the ionization gas for chemical ionization (CI). Electrospray MS spectra were recorded with a Bruker Apex 47e FT-ICR mass spectrometer. Analysis on GC were performed on a HP 6890 GC equipped with a DB5 micropor 0.53 i.d. capillary column. Elemental analyses were performed by Ilse Beetz Mikroanalytisches Laboratorium, Kronach, Germany. Melting points are uncorrected. Silica gel for flash chromatography was purchased from Merck, Darmstadt, Germany (Merck No. 9385). Analytical thin layer chromatography was performed with E. Merck silica gel 60F254 0.25 mm plates (Merck No. 1.05554). Amberlite–Cl was treated with sat. aq. NaCl over night and washed with water and MeOH–water (2 : 1) prior to use. DMA was distilled from BaO, diethyl ether from Na–benzophenone and dichloromethane from CaH_2. Dry hexane was obtained from distilled hexane stored over molecular sieves (3 Å). Allyl bromide **3a**, prenyl bromide **3b**, cinnamyl bromide **3c**, geranyl bromide **3d** and linalyl actetate **4a** were commercially available. The following compounds were prepared by literature methods: (2*E*,6*E*)-9-Cyclohexyl-3,7-dimethyl-2,6-nonadien-1-ol **1f**,[14] (*R*)-(−)-(2*E*,6*E*)-9-(2,2-dimethyl-6-methylenecyclohexyl)-3,7-dimethyl-2,6-nonadien-1-ol (*ent*-trixagol) **1g**,[14] (*S*)-(+)-(2*E*,6*E*)-9-(2,2-dimethyl-6-methylenecyclohexyl)-3,7-dimethyl-2,6-nonadien-1-ol (trixagol) **1h**,[14] 6-chloro-9-methyl-9*H*-purine **7**[26] and 9-methyladenine **13**.[27]

(2*E*,6*E*,10*E*)-Geranylgeraniol (1e). A mixture of geranylgeranyl acetate **5** (0.88 g, 2.66 mmol) in a 3% solution of K_2CO_3 in methanol (30 mL) was stirred at ambient temperature over night. The mixture was evaporated *in vacuo* and the residue was transferred to a separation funnel using water (50 mL) and diethyl ether (50 mL). The organic layer was separated and the aqueous phase was extracted with diethyl ether (2 × 40 mL) and hexane (2 × 40 mL). The combined organic layers were washed with sat. aq. NaCl (20 mL), dried ($MgSO_4$) and evaporated, to give 0.67 g of residue containing both the (2*E*)- and (2*Z*)-isomer. The *E*-isomer was isolated by flash chromatography on silica gel using hexane : EtOAc : EtOH (220 : 20 : 4) (R_f 0.13); yield 0.44 g (57%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.58 (s, 9H, CH_3), 1.66 (s, 6H, CH_3), 1.9–2.2 (m, 12H, CH_2), 4.12 (d, J = 6.9 Hz, 2H, CH_2), 5.09 (m, 3H, CH) and 5.40 (t, J = 6.9 Hz, 1H, CH).

(2*E*,6*E*,10*E*)-Geranylgeranyl bromide (2e). Phosphorus tribromide (0.016 mL, 0.17 mmol) was added dropwise to a stirred solution of geranylgeraniol (100 mg, 0.34 mmol) in dry diethyl ether (2 mL) at 0 °C under N_2. The resulting mixture was stirred in the dark at 0 °C for 3 h, diluted with diethyl ether and washed with sat. aq. $NaHCO_3$ (2 × 10 mL). The aqueous phase was extracted with diethyl ether and the combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give crude compound **2e** (100 mg, 82%) which was used directly in the synthesis of compound **9e**. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.67 (s, 6H, CH_3), 1.72 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 2.05 (m, 12 H, CH_2), 4.06 (d, J = 8.4 Hz, 2H, CH_2Br), 5.14 (m, 3H, CH=C), 5.57 (t, J = 8.4 Hz, 1H, CH=C). Alternatively the same procedure could be employed on geranyllinalol **3b**; for yield see Table 1.

(2*E*,6*E*)-9-Cyclohexyl-3,7-dimethyl-2,6-nonadien-1-yl bromide (2f). (2*E*,6*E*)-9-Cyclohexyl-3,7-dimethyl-1-tetrahydro-2-pyranyloxy)-2,6-nonadien-1-ol (100 mg, 0.399 mmol) was reacted with phosphorous tribromide (0.019 mL, 0.20 mmol) as described for the synthesis of compound **2e** above; yield 114 mg (91%) pale yellow liquid, which was used directly without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.85 (m, 2H), 1.16 (m, 6H), 1.56 (s, 3H, CH_3, H-7′), 1.65 (m, 5H), 1.71 (s, 3H, CH_3, H-3′), 1.94 (dd, J = 7.8 Hz, 2H, H-8), 2.07 (m, 4H, H-4 and H-5), 4.01 (d, J = 8.4 Hz, 2H, H-1), 5.05 (m, 1H,

H-6), 5.51 (m, 1H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.97 (CH_3), 16.02 (CH_3), 26.1 (C-4 or C-5), 26.4 (CH_2), 26.7 (C-11 or C-12), 29.7 (CH_2Br), 33.4 (CH_2), 35.8 (CH_2), 36.9 (C-8), 37.4 (C-10), 39.5 (C-4 or C-5), 120.5 (C-2), 122.9 (C-6), 136.4 (C-7), 143.7 (C-3); MS (EI) *m/z* (rel. %) 233 (M^+–Br, 8), 109 (63), 97 (22), 95 (79), 93 (38), 83 (62), 81 (96), 69 (36), 68 (27), 67 (54), 55 (100), 41 (65).

(*R*)-(+)-(2*E*,6*E*)-9-(2,2-Dimethyl-6-methylenecyclohexyl)-3,7-dimethyl-2,6-nonadien-1-yl bromide (2g). *ent*-Trixagol (120 mg, 0.41 mmol) was reacted with phosphorous tribromide (0.019 mL, 0.20 mmol) as described for the synthesis of compound **2e** above; yield 139 mg (96%) pale yellow liquid, which was used directly without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.81 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 1.38–1.52 (m, 7H), 1.57 (s, 3H, CH_3), 1.65–1.69 (m, 1H), 1.71 (s, 3H, CH_3), 1.91–1.98 (m, 2H), 2.04–2.10 (m, 5H), 4.01 (d, J = 8.4 Hz, 2H, CH_2Br), 4.51 (d, J = 2.0 Hz, 1H, =CH), 4.80 (br s, 1H, =CH), 5.04 (br t, J = 4.6 Hz, 1H, =CH), 5.51 (br t, J = 8.4 Hz, 1H, =CH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.0 (CH_3), 16.1 (CH_3), 23.7 (CH_2), 24.8 (CH_2), 26.1 (CH_2), 28.4 (CH_3), 29.7 (CH_2Br), 32.6 (CH_2), 34.9 (CH_3), 36.4 (CH_2), 38.2 (CH_2), 39.6 (CH_2), 53.6 (CH), 108.8 (=CH_2), 120.6 (=CH), 123.1 (=CH), 136.3 (=C), 143.6 (=C), 149.4 (=C).

(*S*)-(−)-(2*E*,6*E*)-9-(2,2-Dimethyl-6-methylenecyclohexyl)-3,7-dimethyl-2,6-nonadien-1-yl bromide (2h). Trixagol (124 mg, 0.43 mmol) was reacted with phosphorous tribromide (0.02 ml, 0.2 mmol) as described for the synthesis of compound **2e** above; yield 124 mg (82%) pale yellow liquid, which was used directly without further purification. For spectral data, see **2g**.

Geranyllinalyl acetate (4b). Geranyllinalool (1.77 g, 6.1 mmol) and DMAP (1.49 g, 12.2 mmol) were dissolved in dry dichloromethane (12 mL) under N_2. and stirred at 0 °C. Acetic anhydride (1.15 mL, 12.2 mmol) was added and the reactiom mixture was stirred at 0 °C for 1 h and then at ambient temperature for 21 h. The mixture was diluted with CH_2Cl_2 (150 mL) and extracted with sat. aq. $CuSO_4$ (4 × 50 ml), sat. aq. $NaHCO_3$ (2 × 50 ml) and sat. aq. NaCl (50 mL), dried with $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel using EtOAc : hexane 1 : 9 as eluent; yield 1.64 g (81%) colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.52 (s, 3 H, CH_3), 1,57 (s, 9 H, CH_3), 1.65 (s, 3 H, CH_3), 1.98 (s, 3 H, CH_3CO), 1.9–2.2 (m, 12 H, CH_2), 5.04–5.07 (m, 5H, CH=C), 5.95 (dd, J = 10.9 and 17.5 Hz, 1H, CH=C).

(*E*)-Geranyl chloride (2i). Linalool (5.0 mmol, 0.77 g) was dissolved in dry hexane (20 mL) and stirred under N_2 at 10 °C. Boron trichloride (6.3 mmol, 6.3 mL, 1 M in hexane) was added dropwise over 10 min. The resulting mixture was stirred at ambient temperature for 10 min, before water (13 mL) was added and the mixture stirred for additional 10 min. The phases were separated and the organic layer was washed with aq. NaCl (10 mL, 20% sol.) The aqueous layers were extracted with hexane (10 mL) and the combined hexane layers were dried ($MgSO_4$) and evaporated to give crude allylic bromide; yield 720 mg (*E*/*Z*; 83 : 17, cont. 20% starting material), colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.62 (3H, CH_3), 1.70 (3H, CH_3), 1.74 (3H, CH_3), 2.0–2.2 (m, 4H, CH_2), 4.12 (d, J = 7.9 Hz, 2H, CH_2), 5.46 (t, J = 7.9 Hz, 1H, CH).

(2*E*,6*E*,10*E*)-Geranylgeranyl chloride (2j). Geranyllinalool (581 mg, 2.00 mmol) was dissolved in dry hexane (20 mL) and stirred under N_2 at 10 °C. Boron trichloride (2.8 mL of an 1 M hexane solution, 2.80 mmol) was added dropwise over 10 min. The resulting mixture was stirred at ambient temperature for 40 min, before water (10 mL) was added and the mixture stirred for additional 5 min. The phases were separated and the organic layer was washed with aq. NaCl (2 × 10 mL, 20% sol.). The aqueous layers were extracted with hexane (10 mL) and the combined hexane layers were dried ($MgSO_4$) and evaporated to give crude allylic bromide; yield 606 mg (98%, *E*/*Z*; 85 : 15, cont. 5% starting material) clear oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.5–1.8 (m, 15H, 5 × CH_3), 1.9–2.2 (m, 12H, 6 × CH_2), 4.14 (d, J = 7.7 Hz, 2H, H-1), 5.16 (m, 3H, H-6, H-10 and H-14), 5.47 (t, J = 7.7 Hz, 1H, H-2).

General procedure for converting tertiary allylic acetates 4 to allylic bromides 2

Allylic acetate **4** (0.90 mmol) and zinc iodide (0.135 mmol) were dissolved in dry diethyl ether (6 mL) under N_2 at −15 °C. A solution of bromotrimethylsilane (1.35 mmol) in diethyl ether (3 mL) was added dropwise over 15 min and the mixture was allowed to stir for 20 min at −15 °C. The reaction mixture was diluted with diethyl ether (60 mL) and washed with sat. aq. $NaHCO_3$ (20 mL). The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* at ambient temperature to give crude allylic bromides (for yields, see Table 1).

(2*E*,6*E*,10*E*)-Geranylgeranyl acetate (5). Geranyllinalyl acetate **4b** (1.62 g, 4.87 mmol) was dissolved dry THF. $PdCl_2(CH_3CN)_2$ (0.063 g, 0.24 mmol) was added and the mixture was stirred under N_2 for 40 h. Additional $PdCl_2(CH_3CN)_2$ (2 × 0.24 mmol) was added after 18 h and 28 h. The mixture was evaporated *in vacuo* and the residue was purified by flash chromatography on silica gel using hexane : EtOAc (20 : 1) as eluent; yield 1.29 g (80%), pale yellow oil. Analysis on GC showed an *E*/*Z* ratio of 87 : 13. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.63 (s, 9H, CH_3), 1.68 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 1.9–2.2 (m, 14H, 6 × CH_2 and OCH_3), 4.56 (d, J = 7.1 Hz, 2H, CH_2), 5.10 (m, 3H, CH), 5.32 (t, J = 7.1 Hz, CH).

***N*-Methoxy-9-methyl-9*H*-purin-6-amine (8).** A mixture of 6-chloro-9-methyl-9*H*-purine **7** (842 mg, 5.00 mmol), *O*-methylhydroxylamine hydrochloride (2.09 g, 25.0 mmol), triethylamine (7.6 mL, 55 mmol) and *n*-butanol (40 mL) was heated at reflux under a N_2 atmosphere for 17 h and evaporated *in vacuo*. Methanol (45 mL) was added and the mixture was stirred at 50 °C until all solid material was dissolved, before cooling to −45 °C for 5 min. The resulting mixture was filtered and the product was washed with cold (−45 °C) MeOH (20 mL) and cold (−45 °C) Et_2O (40 mL); yield 643 mg (72%), mp 239–241 °C (lit.[19] 239 °C), pale yellow solid. Both tautomers **8a** and **8b** were present in a *ca.* 2 : 8 ratio in DMSO-d_6 according to NMR. Comp. **8a**: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.73 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 8.18 (s, 1H, H-8), 8.29 (s, 1H, H-2), 10.87 (br s, 1H, NH); Comp. **8b**: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.62 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 7.56 (d, J = 3.6 Hz, 1H, H-2), 7.77 (s, 1 H, H-8), 11.17 (br s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6, **8a** and **8b**) δ 29.4 (CH_3), 29.5 (CH_3), 60.9 (CH_3), 63.5 (CH_3), 117.4, 117.9, 138.9, 141.1, 141.6, 142.7, 143.9; MS (EI) *m/z* (rel. %) 179 (M^+, 60), 164 (8), 150 (7), 149 (100), 148 (18), 122 (38), 107 (35), 94 (11), 80 (9).

General procedure for the synthesis of the 7-alkyl-9-methyl purinium halides (9) and the 6-alkylamino purines (11)

A mixture of *N*-methoxy-9-methyl-9*H*-purin-6-amine **8** (90 mg, 0.5 mmol) and allylic bromide **2** (1–5 eq.) in DMA (4 mL) was stirred at 50 °C under a N_2 atmosphere for 21 h. Work up for **9a–c** and **11a–c**: EtOAc (10 mL) was added and the mixture was stored in the refrigerator for precipitation of compound **9** which was isolated by centrifugation and, if necessary, purified by crystallization. The supernatant was evaporated and compound **11** was isolated by flash chromatography on silica gel. Work up for **9d–h** and **11d–h**: The reaction mixture was evaporated *in vacuo* and the products were separated by flash chromatography on silica gel eluting with CH_2Cl_2, EtOAc : EtOH : NH_3(aq.) (160 : 5 : 2), EtOAc : EtOH : NH_3(aq.) (40 : 10 : 1), and CH_2Cl_2 : MeOH : NH_3(aq.) (35 : 5 : 1) to give compound **11** and the betaine **10**. Compound **10** was dissolved in MeOH (10 mL) and water (5 mL) and eluted through a column with Amberlite–Cl

(*ca*. 1.5 mL). The amberlite was washed with MeOH–water (2 : 1), *ca.* 25 mL, and the combined eluents were evaporated *in vacuo* to give the purinium chloride **9**.

7-(Allyl)-6-(methoxyamino)-9-methyl-7*H*-purinium bromide (9a). 5 Eq. of allyl bromide **2a** were used; yield 95 mg (63%), mp 251–252 °C (dec.) colorless crystals. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.81 (s, 3H, CH_3), 3.83 (s, 3H, CH_3), 5.01 (d, J = 5.6 Hz, 2H, H-1′), 5.33 (d, J = 17.3 Hz, H-3′), 5.37 (d, J = 10.3 Hz, H-3′), 6.05 (m, 1H, H-2′), 7.85 (d, J = 3.6 Hz, H-2), 9.39 (s, 1H, H-8), 12.15 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 50 MHz) 31.7(CH_3N), 51.2 (CH_2N), 61.9 (CH_3O), 109.9 (C-5), 120.3 (=CH_2), 131.3 (=CH), 136.6 (C-6), 138.0 (C-8), 141.2 (C-4), 148.7 (C-2); MS (electrospray) m/z (rel. %) 220 (M^+, 100), 189 (12), 188 (16), 179 (16), 174 (33), 162 (5); HRMS: found 220.1201, calcd for $C_{10}H_{14}N_5OBr^+$ 220.1192. Anal.: found: C, 39.82; H, 4.59; N, 23.42%. $C_{10}H_{14}N_5OBr$ requires C, 40.01; H, 4.70; N, 23.33%.

***N*-(Allyl)-*N*-methoxy-9-methyl-9*H*-purin-6-amine (11a).** 5 Eq. of allyl bromide **2a** were used and the product was purified by flash chromatography eluting with EtOAc : EtOH : NH_3(aq.) (160 : 5 : 2); yield 31 mg (28%), colorless oil. ^{1}H NMR (CD_3OD, 500 MHz) δ 3.84 (s, 3H, CH_3N), 3.86 (s, 3H, CH_3O), 4.76 (d, J = 5.9 Hz, 2H, CH_2N), 5.18 (dd, J = 1.3 and 10.3 Hz, 1H, H-3′), 5.30 (dd, J = 1.3 and 17.1 Hz, 1H, H-3′), 5.97 (m, 1H, H-2′), 8.16 (s, 1H, H-2/H-8), 8.36 (s, 1H, H-2/H-8); ^{13}C NMR (CD_3OD, 50 MHz) δ 30.3 (CH_3N), 53.4 (CH_2N), 62.5 (CH_3O), 118.9 (=CH_2), 119.5 (C-5), 133.6 (=CH), 144.0 (C-8), 152.7 (C-4), 152.8 (C-2), 156.4 (C-6); MS (EI) m/z (rel. %) 219 (M^+, 21), 189 (17), 188 (100), 174 (18), 134 (11), 133 (28), 107 (10); HRMS: found 219.1126, calcd for $C_{10}H_{13}N_5O$ 219.1120. Anal.: found: C, 54.90; H, 5.84; N, 32.31%. $C_{10}H_{13}N_5O$ requires C, 54.78; H, 5.98; N, 31.94%.

6-(Methoxyamino)-9-methyl-7-(3-methyl-2-butenyl)-7*H*-purinium bromide (9b)[9b]. 3.4 Eq. of prenyl bromide **2b** were used and the product was purified by crystallisation from isopropanol; yield 66 mg (40%), mp 202–203 °C (dec.) colorless crystals. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.76 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 3.79 (s, 3H, CH_3N), 3.83 (s, 3H, CH_3O), 4.96 (d, J = 7.0 Hz, 2H, CH_2N), 5.41 (m, 1H, H-2′), 7.84 (d, J = 3.0 Hz, 1H, H-2), 9.41 (s, 1H, H-8), 12.12 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 18.2 (CH_3,), 25.5 (CH_3), 31.7 (CH_3N), 47.3 (CH_2N), 61.8 (CH_3O), 109.7 (C-5), 116.8 (=CH), 136.8 (C-4/C-6), 137.6 (C-8), 140.4 (C-3′), 141.4 (C-4/C-6), 148.5 (C-2); MS (electrospray) m/z (rel. %) 248 (M^+, 12), 227 (9), 193 (8), 180 (100), 179 (16), 149 (13); HRMS: found 248.1493, calcd for $C_{12}H_{18}N_5O^+$ 248.1505. Anal.: found: C, 44.02; H, 5.36%. $C_{12}H_{18}N_5OBr$ requires C, 43.91; H, 5.53%.

***N*-Methoxy-9-methyl-*N*-(3-methyl-2-butenyl)-9*H*-purin-6-amine (11b).** 3.4 Eq. of prenyl bromide **2b** were used and the product was purified by flash chromatography eluting with CH_2Cl_2–MeOH (30 : 1); yield 28 mg (23%), mp 121–123 °C (dec.) colorless crystals. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.70 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 3.81 (s, 3H, CH_3N), 3.91 (s, 3H, CH_3O), 4.71 (d, J = 6.8 Hz, 2H, CH_2N), 5.39 (m, 1H, H-2′), 7.80 (s, 1H, H-2/H-8), 8.47 (s, 1H, H-2/H-8); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.1 (CH_3), 25.8 (CH_3), 29.8 (CH_3N), 48.2 (CH_2N), 62.4 (CH_3O), 118.6 (=CH), 119.2 (C-1′), 137.1 (C-3′), 141.0 (C-8), 151.7 (C-4), 152.2 (C-2), 155.8 (C-6); MS (EI) m/z (rel. %) 247 (M^+, 25), 216 (100), 179 (49), 149 (38), 134 (32), 133 (21), 122 (22), 107 (15), 69 (21), 41 (31); HRMS: found 247.143447, calcd for $C_{12}H_{17}N_5O$ 247.143310. Anal.: found: C, 57.43; H, 6.93; N, 27.89%. $C_{12}H_{17}N_5O$ requires C, 58.28; H, 6.93; N, 28.32%.

(*E*)-6-(Methoxyamino)-9-methyl-7-(3-phenyl-2-propenyl)-7*H*-purinium bromide (9c). 1.0 Eq. of cinnamyl bromide **2c** were used; yield 91 mg (54%), mp 225–227 °C (dec.) colorless crystals. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.81 (s, 3H, CH_3N), 3.86 (s, 3H, CH_3O), 5.17 (d, J = 6.5 Hz, 2H, CH_2N), 6.47 (dd, J = 15.9 and 6.5 Hz, 1H, H-2′), 6.80 (d, J = 15.9 Hz, 1H, H-3′), 7.30 (m, 1H, H-7′), 7.36 (m, 2H, Ph), 7.47 (d, J = 7.4 Hz, 2H, Ph), 7.86 (d, J = 3.8 Hz, 1H, H-2), 9.45 (s, 1H, H-8), 12.16 (d, J = 3.4 Hz, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 31.7 (CH_3N), 51.0 (CH_2N), 62.0 (CH_3O), 109.9 (C-5), 122.0 (=CH), 126.7 (CH in Ph), 128.5 (=CH), 128.8 (CH and Ph), 135.3 (CH in Ph), 135.5 (C in Ph), 136.7 (C-6), 137.9 (C-8), 141.2 (C-4), 148.6 (C-2); MS (electrospray) m/z (rel. %): 296 (M^+, 100), 264 (4), 192 (4); HRMS: found 296.1495, calcd for $C_{16}H_{18}N_5O^+$ 296.1505. Anal.: found: C, 50.99; H, 4.77; N, 18.27%. $C_{16}H_{18}N_5OBr$ requires C, 51.08; H, 4.82; N, 18.61%.

(*E*)-*N*-Methoxy-9-methyl-*N*-(3-phenyl-2-propenyl)-9*H*-purin-6-amine (11c). 1.0 Eq. of cinnamyl bromide **2c** were used and the product was purified by flash chromatography eluting with EtOAc : EtOH : NH_3(aq.) (160 : 5 : 2); yield 55 mg (37%), mp 75–78 °C (dec.) colorless crystals. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.82 (s, 3H, CH_3N), 3.96 (s, 3H, CH_3O), 4.90 (dd, J = 6.3 and 0.9 Hz, 2H, CH_2N), 6.38 (m, 1H, CH=), 6.66 (d, J 15.9 Hz, 1H, CH=), 7.18 (m, 1H, Ph), 7.25 (m, 2H, Ph), 7.33 (m, 2H, Ph), 7.82 (s, 1H, H-8), 8.49 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.8 (CH_3N), 52.5 (CH_2N), 62.6 (CH_3O), 119.2 (C-5), 123.8 (=CH), 126.4 (CH in Ph), 127.6 (CH in Ph), 128.4 (CH in Ph), 133.6 (=CH), 136.7 (C in Ph), 141.1 (C-8), 151.8 (C-4), 152.3 (C-2), 155.8 (C-6); MS (EI) m/z (rel. %) 295 (M^+, 31), 264 (94), 174 (14), 133 (13), 118 (12), 117 (100), 116 (12), 115 (69), 91 (21); HRMS: found 295.1421, calcd for $C_{15}H_{17}N_5O$ 295.1433.

(*E*)-6-(Methoxyamino)-9-methyl-7-(3,7-dimethyl-2,6-octadienyl)-7*H*-purinium chloride (9d). 0.67 mmole purine **8** and 2 eq. of geranyl bromide **2d** were used; yield 120 mg (51%). Data for the betaine **10d**: mp 173–176 °C (dec.) colorless crystals. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.53 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.78 (s, 3H, CH_3, H-10′), 2.01 (m, 2H, H-4′), 2.07 (m, 2H, H-5′), 3.56 (s, 3H, CH_3O), 3.64 (s, 3H, CH_3N), 5.01 (d, J = 7.2 Hz, 2H, H-1′), 5.05 (m, 1H, H-6′), 5.49 (m, 1H, H-2′), 7.53 (s, 1H, H-2), 8.83 (s, 1H, H-8); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 16.5 (CH_3), 17.6 (CH_3), 25.5 (CH_3), 25.7 (CH_2), 30.6 (CH_3N), 38.9 (C-4′), 46.5 (CH_2, C-1′), 60.2 (CH_3O), 107.7 (C-5), 118.3 (C-2′), 123.7 (C-6′), 131.2 (C-7′), 132.7 (C-8), 141.8 (C-3′), 144.9 (C-4), 148.3 (C-6), 155.9 (C-2); anal.: found: C, 64.95; H, 7.98%. $C_{17}H_{25}N_5O$ requires C, 64.73; H, 7.99%. Data for the purinium chloride **9d**: mp 189–191 °C colorless crystals. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.53 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 2.05 (m, 4H, CH_2), 3.84 (s, 3H, OCH_3), 3.97 (s, 3H, NCH_3), 5.00 (m, 1H, CH), 5.02 (d, J = 5.6 Hz, 2H, CH_2), 5.43 (m, 1H, CH), 7.99 (s, 1H, H-2), 10.09 (s, 1H, H-8), 11.98 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.1, 17.7, 25.6, 26.0, 32.1, 39.6, 48.2, 62.3, 110.5, 115.8, 123.3, 132.1, 136.1, 137.3, 141.4, 145.7, 149.5; MS (electrospray) m/z (rel. %) 316 (M^+, 8), 181 (9), 180 (100), 149 (16); HRMS: found 316.2124, calcd for $C_{17}H_{26}N_5O^+$ 316.2131.

(*E*)-*N*-(3,7-Dimethyl-2,6-octadienyl)-*N*-methoxy-9-methyl-9*H*-purin-6-amine (11d). 0.43 mmole purine **8** and 1.5 eq. of geranyl bromide **2d** were used, yield 38 mg (28%), pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.43 (bs, 3H, CH_3), 1.53 (bs, 3H, CH_3), 1.69 (bs, 3H, CH_3), 1.92 (m, 2H), 2.00 (m, 2H), 3.74 (s, 3H, CH_3N), 3.85 (s, 3H, CH_3O), 4.66 (d, J = 6.9 Hz, 2H, CH_2N), 4.95 (m, 1H, H-6′), 5.35 (m, 1H, H-2′), 7.73 (s, 1H, H-8), 8.39 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.3 (CH_3), 17.5 (CH_3), 25.4 (CH_3), 26.1 (CH_2), 29.6 (CH_3N), 39.4 (CH_2), 48.1 (CH_2N), 62.3 (CH_3O), 118.3 (C-2′), 119.1 (C-5), 123.8 (C-6′), 131.3 (C-7′), 140.2 (C-3′), 140.8 (C-8), 151.5 (C-4), 152.1 (C-2), 155.8 (C-6); MS (EI) m/z (rel. %) 315 (M^+, 3), 247 (14), 246 (100), 216 (18), 215 (19), 179 (32), 174 (11), 150 (12), 133 (12), 69 (24), 41 (19); HRMS: found 315.2059, calcd for $C_{17}H_{25}N_5O$ 315.2059.

(2′*E*,6′*E*,10′*E*)-6-(Methoxyamino)-9-methyl-7-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenyl)-7*H*-purinium chloride (9e). 0.24 mmole purine **8** and 1.2 eq. of the allylic bromide **2e** were used; yield 62 mg (57%) of betaine, 57 mg (49%) of chloride. Data for the betaine **10e**: mp 168–173 °C, pale yellow solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.52 (s, 6H, 2 × CH_3), 1.54 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.74 (s, 3H, CH_3, H-20′), 1.91 (m, 4H), 1.98 (m, 4H), 2.06 (m, 4H, H-4′, H-5′), 3.68 (s, 3H, CH_3N), 3.76 (s, 3H, CH_3O), 5.01 (m, 5H, H-1′, H-6′, H-10′ and H-14′), 5.37 (m, 1H, H-2′), 7.70 (s, 1H, H-2), 7.82 (s, 1H, H-8); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.9 (CH_3), 16.0 (CH_3), 16.7 (CH_3, C-20′), 17.6 (CH_3), 25.6 (CH_3), 26.0 (CH_2), 26.5 (CH_2), 26.6 (CH_2), 30.9 (CH_3N), 39.4 (CH_2), 39.57 (CH_2), 39.61 (CH_2), 47.5 (NCH_2), 61.3 (CH_3O), 109.2 (C-5), 116.0 (C-2′), 123.1 (=CH), 123.8 (=CH), 124.2 (=CH), 128.9 (C-8), 131.2 (=C), 135.0 (=C), 135.8 (=C), 145.0 (=C), 145.3 (=C), 148.0 (C-6), 157.0 (C-2). Data for the purinium chloride **9e**: colorless solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.56 (s, 6H, 2 × CH_3), 1.57 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 1.91–196 (m, 4H), 2.00–2.05 (m, 4H), 2.10 (m, 4H), 3.79 (s, 3H, CH_3N), 3.81 (s, 3H, CH_3O), 5.05 (m, 5H, H-1′, H-6′, H-10′ and H-14′), 5.42 (br t, *J* 7.2 Hz, 1H, H-2′), 7.81 (s, 1H, H-2), 8.35 (s, 1H, H-8); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.0 (CH_3), 16.1 (CH_3), 16.9 (CH_3), 17.6 (CH_3), 25.7 (CH_3), 26.0 (CH_2), 26.6 (CH_2), 26.7 (CH_2), 31.2 (CH_3N), 39.5 (CH_2), 39.67 (CH_2), 39.70 (CH_2), 47.8 (NCH_2), 61.6 (CH_3O), 109.8 (C-5), 115.9 (=CH, C-2′), 123.2 (=CH), 123.9 (=CH), 124.3 (=CH), 130.6 (C-8), 131.3 (=C), 135.1 (=C), 135.9 (=C), 144.4 (C-4), 145.5 (C-6), 155.6 (C-2); MS (electrospray) *m*/*z* (rel. %) 452 (M^+, 100), 180 (11); HRMS: found 452.3399, calcd for $C_{27}H_{42}N_5O^+$ 452.3383.

(2′*E*,6′*E*,10′*E*)-*N*-(3,7,11,15-Tetramethyl-2,6,10,14-hexadecatetraenyl)-*N*-methoxy-9-methyl-9*H*-purin-6-amine (11e). 0.24 mmole purine **8** and 1.2 eq. of the allylic bromide **2e** were used; yield 41 mg (29%), colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.54 (bs, 6H, 2 × CH_3), 1.56 (bs, 3H, CH_3), 1.64 (bs, 3H, CH_3), 1.75 (bs, 3H, CH_3), 1.92 (m, 4H), 2.03 (m, 8H), 3.80 (s, 3H, CH_3N), 3.90 (s, 3H, CH_3O), 4.71 (d, J = 6.8 Hz, 2H, CH_2N), 5.05 (t, J = 6.5 Hz, 3H), 5.41 (m, 1H, H-2′), 7.79 (s, 1H, H-8), 8.45 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.0 (CH_3), 16.5 (CH_3), 17.6 (CH_3), 25.7 (CH_3), 26.3 (CH_2), 26.6 (CH_2), 26.7 (CH_2), 29.7 (CH_3N), 39.6 (CH_2), 39.7 (CH_2), 48.2 (CH_2N), 62.5 (CH_3O), 118.4 (CH, C-2′), 119.2 (C-5), 123.9 (CH), 124.2 (CH), 124.3 (CH), 131.2 (C), 134.9 (C), 135.2 (C), 140.5 (C-3′), 140.9 (C-8), 151.7 (C-4), 152.3 (C-2), 156.0 (C-6), 2 sign. were hidden; MS (EI) *m*/*z* (rel. %) 451 (M^+, 2), 247 (14), 246 (100), 216 (79), 215 (19), 179 (31), 162 (16), 150 (20), 149 (19), 69 (29), 41 (13); HRMS: found 451.3329, calcd for $C_{27}H_{41}N_5O$ 451.3311.

(2′*E*,6′*E*)-6-(Methoxyamino)-9-methyl-7-(9-cyclohexyl-3,7-dimethyl-2,6-nonadien-1-yl)-7*H*-purinium chloride (9f). 0.27 mmole purine **7** and *ca.* 1.2 eq. of crude (2′*E*,6′*E*)-9-cyclohexyl-3,7-dimethyl-2,6-nonadien-1-yl bromide **2f** were used; 52 mg (50%) of chloride. Data for the betaine **10f**: mp 175–178 °C (dec.) colorless crystals. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.82 (m, 2H), 1.14 (m, 6H), 1.53 (s, 3H, CH_3), 1.62 (m, 5H), 1.75 (s, 3H, CH_3), 1.90 (m, 2H), 2.07 (br s, 4H), 3.70 (s, 3H, CH_3N), 3.78 (s, 3H), 5.01 (m, 1H, H-6′), 5.01 (d, J = 7.3 Hz, 2H, CH_2N), 5.38 (t, J = 7.3 Hz, 1H, H-2′), 7.73 (s, 1H, H-2), 7.78 (s, 1H, H-8); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.0 (CH_3), 16.7 (CH_3), 26.6 (CH_2), 26.3 (CH_2), 26.6 (CH_2), 31.0 (CH_3N), 33.2 (CH_2), 35.7 (CH_2), 37.0 (CH_2), 37.3 (CH), 39.4 (CH_2), 47.6 (CH_2N), 61.4 (CH_3O), 109.3 (C-5), 115.9 (C-2′), 122.6 (C-6′), 128.7 (C-8), 136.6 (C-7′), 145.1 (C-4), 145.5 (C-3′), 148.0 (C-6), 157.1 (C-2). Data for the purinium chloride **9f**: wax. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.81–0.87 (m, 2H), 1.06–1.24 (m, 6H), 1.50 (s, 3H, CH_3), 1.60–1.70 (m, 5H), 1.81 (s, 3H, CH_3), 1.92–1.97 (m, 2H), 2.12 (br s, 4H), 3.80 (s, 3H, CH_3N), 3.84 (s, 3H, CH_3O), 5.04 (m, 1H, H-6′), 5.08 (d, J = 7.5 Hz, 2H, CH_2N), 5.43 (t, J = 7.3 Hz, 1H, H-2′), 7.83 (s, 1H, H-2), 8.39 (s, 1H, H-8); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.1 (CH_3), 16.9 (CH_3), 26.0 (CH_2), 26.4 (CH_2), 26.7 (CH_2), 31.4 (CH_3N), 33.3 (2 × CH_2), 35.8 (CH_2), 37.0 (CH_2), 37.4 (CH), 39.5 (CH_2), 47.9 (CH_2N), 61.8 (CH_3O), 110.0 (C-5), 115.6 (=CH, C-2′), 122.7 (=CH, C-6′), 130.8 (C-8), 136.7 (=C), 144.2 (C-4), 146.2 (=C), 155.0 (C-2), C-6 was hidden; MS (electrospray) *m*/*z* (rel. %) 412 (100, M^+), 182 (14); HRMS: found 412.3089, calcd for $C_{24}H_{38}N_5O^+$ 412.3070.

(2′*E*,6′*E*)-*N*-(9-Cyclohexyl-3,7-dimethyl-2,6-nonadien-1-yl)-*N*-methoxy-9-methyl-9*H*-purin-6-amine (11f). 0.27 mmole purine **8** and *ca.* 1.2 eq. of crude (2′*E*,6′*E*)-9-cyclohexyl-3,7-dimethyl-2,6-nonadien-1-yl bromide **2f** were used; yield 23 mg (24%), colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.82 (m, 2H), 1.15 (m, 6H), 1.52 (s, 3H, CH_3), 1.63 (m, 5H), 1.75 (br s, 3H, CH_3), 1.88 (m, 2H), 1.99 (m, 2H), 2.04 (m, 2H), 3.80 (s, 3H, CH_3N), 3.90 (s, 3H, CH_3O), 4.71 (d, J = 6.8 Hz, 2H), 5.03 (m, 1H), 5.42 (m, 1H), 7.79 (s, 1H, H-8), 8.45 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.9 (CH_3), 16.5 (CH_3), 26.3 (CH_2), 26.4 (CH_2), 26.7 (CH_2), 29.8 (CH_3N), 33.3 (CH_2), 35.8 (CH_2), 36.9 (CH_2), 37.3 (CH), 39.7 (CH_2), 48.2 (CH_2), 62.5 (CH_3O), 118.4 (CH), 119.2 (C-5), 123.4 (C-6′), 135.9 (C-7′), 140.5 (C-3′), 140.9 (C-8), 151.7 (C-4), 152.3 (C-2), 155.9 (C-6); MS (EI) *m*/*z* (rel. %) 411 (M^+, 3), 380 (27), 247 (13), 246 (100), 216 (35), 215 (16), 179 (34), 150 (11), 149 (14); HRMS: found 411.2993, calcd for $C_{24}H_{37}N_5O^+$ 411.2998.

(*R*)-(2′*E*,6′*E*)-6-(Methoxyamino)-9-methyl-7-[2,2-dimethyl-6-methylenecyclohexyl)-3,7-dimethyl-2,6-nonadien-1-yl]-7*H*-purinium chloride (9g). 0.32 mmole purine **8** and *ca.* 1.2 eq. of crude (*R*)-(−)-(2*E*,6*E*)-9-(2,2-dimethyl-6-methylenecyclohexyl)-3,7-dimethyl-2,6-nonadien-1-yl bromide **2g** were used; yield 75 mg (48%) of chloride. Data for the betaine **10g**: colorless wax. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.76 (s, 3H, CH_3), 0.84 (s, 3H, CH_3), 1.42–1.48 (m, 7H), 1.53 (s, 3H, CH_3), 1.59–1.60 (m, 1H), 1.72 (s, 3H, CH_3), 1.73–2.06 (m, 7H), 3.68 (s, 3H, CH_3N), 3.76 (s, 3H, CH_3O), 4.45 (d, J = 2.4 Hz, 1H, =CH), 4.68 (br s, 1H, =CH), 4.98–5.01 (m, 3H, =CH and NCH_2), 5.37 (m, 1H, =CH), 7.71 (s, 1H, H-2), 7.76 (s, 1H, H-8). Data for the purinium chloride **9g**: colorless wax. $[\alpha]_D^{20}$ −4.6 (*c* 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.81 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 1.41–1.52 (m, 7H), 1.53 (s, 3H, CH_3), 1.58–1.63 (m, 1H), 1.67 (s, 3H, CH_3), 1.81–2.14 (m, 7H), 3.80 (s, 3H, CH_3N), 3.86 (s, 3H, CH_3O), 4.50 (d, J = 2.4 Hz, 1H, =CH), 4.73 (br s, 1H, =CH), 5.05–5.10 (m, 3H, =CH and NCH_2), 5.44 (m, 1H, =CH), 7.84 (s, 1H, H-2), 8.45 (s, 1H, H-8); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.1 (XH_3),16.9 (XH_3), 23.6 (CH_2), 24.7 (CH_2), 26.0 (CH_3), 26.2 (CH_2), 28.4 (CH_3), 34.2 (CH_2), 34.8 (CH_3N), 36.2 (CH_2), 38.3 (CH_2), 39.5 (CH_2), 47.8 (CH_2N), 53.6 (CH), 61.7 (CH_3O), 108.8 (=CH_2), 109.9 (C-5), 115.8 (=CH), 123.0 (=CH), 132.0 (C-8), 136.5 (=C), 143.7 (=C /C-4), 143.9 (=C/C-4), 145.8 (C-6), 149.3 (=C), 154.4 (C-2); MS (ESI) *m*/*z* (rel. %) 452 (M^+, 100), 440 (7), 408 (8), 180 (7); HRMS: found 452.3385, calcd for $C_{27}H_{42}N_5O$ 452.3383.

(*R*)-(2′*E*,6′*E*)-*N*-[2,2-Dimethyl-6-methylenecyclohexyl)-3,7-dimethyl-2,6-nonadien-1-yl]-*N*-methoxy-9-methyl-9*H*-purin-6-amine (11g). 0.32 mmole purine **8** and *ca.* 1.2 eq. of crude (*R*)-(2*E*,6*E*)-9-(2,2-dimethyl-6-methylenecyclohexyl)-3,7-dimethyl-2,6-nonadien-1-yl bromide **2g** were used; 46 mg (32%), colorless oil. $[\alpha]_D^{20}$ −4.8 (*c* 0.92, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.77 (s, 3H, CH_3), 0.85 (s, 3H, CH_3), 1.44–1.49 (m, 7H), 1.52 (s, 3H, CH_3), 1.60–1.65 (m, 1H), 1.75 (s, 3H, CH_3), 1.95–2.06 (m, 7H), 3.79 (s, 3H, CH_3N), 3.90 (s, 3H, CH_3O), 4.47 (d, J = 2.3 Hz, 1H, =CH), 4.70–4.72 (m, 3H, =CH and NCH_2), 5.02 (m, 1H, =CH), 5.41 (m, 1H, =CH), 7.77 (s, 1H, H-8), 8.44 (s, 1H, H-2); MS (EI) *m*/*z* (rel. %) 451 (M^+1), 436 (3), 421 (5), 420 (8), 298 (5), 246 (35), 216 (100), 162 (26), 150 (31), 149 (37); HRMS: found 451.3319, calcd for $C_{27}H_{41}N_5O$ 451.3311.

(*S*)-(2′*E*,6′*E*)-6-(Methoxyamino)-9-methyl-7-[2,2-dimethyl-6-methylenecyclohexyl)-3,7-dimethyl-2,6-nonadien-1-yl]-7*H*-purinium chloride (9h). .32 mmole purine **8** and *ca.* 1.2 eq. of crude (*S*)-(2*E*,6*E*)-9-(2,2-dimethyl-6-methylenecyclohexyl)-3,

7-dimethyl-2,6-nonadien-1-yl bromide **2h** were used; 62 mg (44%), colorless wax. $[\alpha]_D^{20}$ +4.3 (*c* 1.2, $CHCl_3$); for spectral data, see **9g**.

(*S*)-(2′*E*,6′*E*)-*N*-[2,2-Dimethyl-6-methylenecyclohexyl)-3,7-dimethyl-2,6-nonadien-1-yl]-*N*-methoxy-9-methyl-9*H*-purin-6-amine (11h). 0.32 mmole purine **8** and *ca.* 1.2 eq. of crude (*S*)-(2*E*,6*E*)-9-(2,2-dimethyl-6-methylenecyclohexyl)-3,7-dimethyl-2,6-nonadien-1-yl bromide **2h** were used; 37 mg (26%), colorless oil. $[\alpha]_D^{20}$ +4.9 (*c* 0.66, $CHCl_3$); for spectral data, see **11g**.

General procedure for the synthesis of compounds 12

A mixture of compound **9** (0.9 mmol) and Zn powder (9.0 mmol) in MeOH (25 mL), water (5 mL) and conc. acetic acid (0.62 mL) was stirred under a N_2 atmosphere at 60 °C for 15 h. After cooling to ambient temperature, the mixture was filtered and the solid washed with 25 mL MeOH. The filtrate was mixed with MeOH (20 mL), sat. aq. NaCl (2.5 mL) and water (20 mL) and the mixture was stirred for 1 h before evaporation. The residue was dissolved in sat. aq. NaCl (5 mL) and water (5 mL), extracted with CH_2Cl_2 (5 × 25 mL), dried ($MgSO_4$) and evaporated. The product was purified by flash chromatography on silica gel eluting with CH_2Cl_2 followed by CH_2Cl_2 : MeOH (80 : 1), CH_2Cl_2 : MeOH (30 : 1), and CH_2Cl_2 : MeOH (4 : 1).

7-(Allyl)-6-amino-9-methyl-7*H*-purinium chloride (12a). Yield 122 mg (52%), mp 227–230 °C (dec.) colorless crystals. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.88 (s, 3H, CH_3), 5.24 (d, J = 17.2 Hz, H-3′), 5.31 (d, J = 10.4 Hz, H-3′), 5.36 (br s, 2H, H-1′), 6.07 (m, 1H, H-2′), 7.92 (br s, 2H, NH_2), 8.41 (s, 1H, H-2), 9.89 (s, 1H, H-8); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 31.6 (CH_3), 50.5 (NCH_2), 108.9 (C-5), 119.4 (=CH_2), 131.8 (CH=), 142.0 (C-8), 149.0 (C-4), 152.0 (C-6), 155.9 (C-2); MS (ESI) *m*/*z* (rel. %) 190 (M^+, 74), 181 (100), 163 (60), 156 (57), 149 (11); HRMS: found 190.1083, calcd for $C_9H_{12}N_5^+$ 190.1087.

6-Amino-9-methyl-7-(3-methyl-2-butenyl)-7*H*-purinium chloride (12b). The compound was prepared by reduction of compound **9c** (56 mg, 0.17 mmol); yield 32 mg (74%), mp 161–165 °C (lit.[9] 164–169 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.88 (s, 3H, CH_3), 5.27 (d, J = 6.4 Hz, 2H, NCH_2), 5.43 (br t, J = 6.4 Hz, 1H, =CH), 7.00 (br s, 2H, NH_2), 8.48 (s, 1H, H-2), 9.76 (s, 1H, H-8).

(*E*)-6-Amino-9-methyl-7-(3-phenyl-2-propenyl)-7*H*-purinium chloride (12c). The compound was prepared by reduction of compound **9c** (76 mg, 0.20 mmol); yield 50 mg (82%), mp 181–185 °C (dec.). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.90 (s, 3H, CH_3), 5.50 (d, J = 5.8 Hz, 2H, NCH_2), 6.48–6.54 (m, 1H, =CH), 6.76 (d, J = 16.0 Hz, 1H, =CH), 7.28 (m, 1H, Ph), 7.35 (m, 2H, Ph), 7.44 (d, J = 7.4 Hz, 2H, Ph), 8.02 (br s, 2H, NH_2), 8.45 (s, 1H, H-2), 9.97 (s, 1H, H-8); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 31.4 (CH_3), 50.3 (NCH_2), 109.0 (C-5), 122.6 (=CH), 126.7 (CH in Ph), 128.4 (CH in Ph), 128.7 (CH in Ph), 134.2 (=CH), 135.6 (C in Ph), 142.0 (C-8), 149.0 (C-4), 152.0 (C-6), 155.5 (C-2); MS (ESI) *m*/*z* (rel. %) 266 (M^+, 100), 214 (7), 182 (7), 158 (12), 159 (13), 141 (6), 117 (60); HRMS: found 266.1387, calcd for $C_{15}H_{15}N_5^+$ 266.1400.

(*E*)-6-Amino-9-methyl-7-(3,7-dimethyl-2,6-octadienyl)-)-7*H*-purinium chloride (12d). The compound was prepared by reduction of compound **9d** (59 mg, 0.168 mmol); yield 40 mg (71%), mp 144–146 °C colorless crystals (lit.[9] 145–150 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.53 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 2.07 (m, 4H, CH_2), 4.17 (s, 3H, OCH_3), 4.99 (m, 1H, CH), 5.57 (m, 3H, CH_2 and CH), 6.69 (br s, 2H, NH_2), 8.44 (s, 1H, H-2), 9.92 (s, 1H, H-8); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.7 (CH_3), 18.1 (CH_3), 26.0 (CH_3), 26.4 (CH_2), 32.5 (CH_3), 39.8 (CH_2), 49.1 (NCH_2), 110.2 (C-5), 116.5 (=CH), 123.6 (=CH), 132.7 (=C), 142.0 (C-8), 146.9 (=C), 149.9 (C-4), 152.8 (C-6), 156.4 (C-2); MS (ESI) *m*/*z* (rel. %) 286 (M^+, 100), 151 (6), 150 (50); HRMS: found 286.2032, calcd for $C_{16}H_{24}N_5^+$ 286.2026.

(2′*E*,6′*E*,10′*E*)-6-Amino-9-methyl-7-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenyl)-7*H*-purinium chloride (12e). The compound was prepared by reduction of compound **9e** (34 mg, 0.070 mmol); yield 23 mg (72%) pale yellow waxy solid, mp 155–158 (lit.[9] 158–162 °C). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.52 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 1.87–1.94 (m, 4H), 1.95–2.02 (m, 4H), 2.04 (br s, 4H), 4.06 (s, 3H, NCH_3), 5.00 (m, 1H, =CH), 5.04 (m, 2H, =CH), 5.45 (br t, J = 6.5 Hz, 1H, =CH), 5.55 (d, J 6.5 = Hz, 2H, NCH_2), 6.88 (br s, 2H, NH_2), 8.42 (s, 1H, H-2), 10.12 (s, 1H, H-8); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.0 (CH_3), 16.1 (CH_3), 17.4 CH_3), 17.7 CH_3), 25.7 CH_3), 26.1 (CH_2), 26.6 (CH_2), 26.7 (CH_2), 32.1 (NCH_3), 39.5 (CH_2), 39.6 (CH_2), 39.7 (CH_2), 48.7 (NCH_2), 109.8 (C-8), 116.0 (=CH), 123.1 (=CH), 124.0 (=CH), 124.3 (=CH), 131.2 (=C), 135.1 (=C), 136.0 (=C), 141.6 (C-8), 146.3 (=C), 149.5 (C-4), 152.2 (C-6), 155.9 (C-2); MS (ESI) *m*/*z* (rel.%): 422 (100, M^+), 294 (5), 224 (8), 150 (8).

(2′*E*,6′*E*)-6-Amino-9-methyl-7-(9-cyclohexyl-3,7-dimethyl-2,6-nonadien-1-yl)-7*H*-purinium chloride (12f). The compound was prepared by reduction of compound **9f** (31 mg, 0.069 mmol); yield 20 mg (69%), colorless waxy material. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.77–0.84 (m, 2H), 1.05–1.22 (m, 6H), 1.50 (s, 3H, CH_3), 1.58–1.64 (m, 5H), 1.80 (s, 3H, CH_3), 1.86 (m, 2H), 2.03 (br s, 4H), 4.06 (NCH_3), 4.97 (m, 1H, =CH), 5.45 (br t, J = 6.2 Hz, 1H, =CH), 5.57 (d, J = 6.2 Hz, 2H, NCH_2), 6.95 (br s, 2H, NH_2), 8.42 (s, 1H, H-2), 10.19 (s, 1H, H-8); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.0 (CH_3), 17.4 (CH_3), 26.1 (CH_2), 26.3 (2 × CH_2), 26.7 (CH_2), 32.2 (NCH_3), 33.3 (2 × CH_2), 35.8 (CH_2), 36.9 (CH_2), 37.4 (CH), 39.5 (CH_2), 48.7 (NCH_2), 109.8 (C-5), 116.0 (=CH), 122.6 (=CH), 136.6 (=C), 141.6 (C-8), 146.4 (=C), 149.5 (C-4), 152.3 (C-6), 155.9 (C-2); MS (ESI) *m*/*z* (rel.%): 382 (100, M^+), 205 (1), 150 (6), 141 (2); HRMS: found 382.2961, calcd. for $C_{23}H_{36}N_5^+$ 382.2965.

(*R*)-(2′*E*,6′*E*)-6-Amino-9-methyl-7-[2,2-dimethyl-6-methylenecyclohexyl)-3,7-dimethyl-2,6-nonadien-1-yl]-7*H*-purinium chloride (12g), agelasine E. The compound was prepared by reduction of compound **9g** (40 mg, 0.082 mmol); yield 24 mg (52%), mp 176–178 °C colorless crystals (lit.[2] 180–182 °C); $[\alpha]_D$ −2.1 (*c* 0.36, $CHCl_3$); (lit.[2] $[\alpha]_D^{20}$ −17.1 (*c* 1.88, CH_3OH)). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.78 (s, 3H, CH_3), 0.87 (s, 3H, CH_3), 1.36–1.49 (m, 7H), 1.52 (s, 3H, CH_3), 1.61–1.64 (m, 1H), 1.81 (s, 3H, CH_3), 1.94–2.15 (m, 7H), 4.06 (s, 3H, NCH_3), 4.48 (d, J = 2.4 Hz, 1H, =CH), 4.71 (br s, 1H, =CH), 4.98 (m, 1H, =CH), 5.49 (d, J = 6.3 Hz, 1H, =CH), 5.56 (d, J = 6.3 Hz, 1H, NCH_2), 6.79 (br s, 2H, NH_2), 8.43 (s, 1H, H-2), 10.2 (s, 1H, H-8); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.1 (CH_3), 17.3 (CH_3), 23.7 (CH_2), 24.7 (CH_2), 26.1 (CH_2), 28.4 (CH_3), 32.1 (CH_3), 32.3 (CH_2), 32.4 (NCH_3), 36.2 (CH_2), 38.2 (CH_2), 39.5 (CH_2), 48.7 (CH_2), 53.6 (CH), 108.9 (=CH_2), 109.9 (C-5), 116.1 (=CH), 122.8 (=CH), 136.7 (=C), 142.0 (C-8), 146.6 (=C), 149.3 (=C/C-4), 149.5 (=C/C-4), 152.2 (C-6), 156.0 (C-2), MS (ESI) *m*/*z* (rel. %) 422 (M^+, 100).

(*S*)-(2′*E*,6′*E*)-6-Amino-9-methyl-7-[2,2-dimethyl-6-methylenecyclohexyl)-3,7-dimethyl-2,6-nonadien-1-yl]-7*H*-purinium chloride (12h). The compound was prepared by reduction of compound **9h** (45 mg, 0.092 mmol); yield 34 mg (89%), mp 176–179 °C, colorless crystals $[\alpha]_D^{20}$ +2.2 (*c* 0.68, $CHCl_3$). For spectral data, see **12g**.

Activity against *Mycobacterium tuberculosis*

The primary screening against *Mycobacterium tuberculosis* $H_{37}Rv$ (ATCC 27294) was conducted at 6.25 μg mL^{-1} in BACTEC 12B medium using the Microplate Alamar Blue Assay (MABA) as described.[24] Compounds exhibiting fluorescence were tested in the BACTEC 460-radiometric system[24] and

compounds demonstrating at least 90% inhibition in the primary screen were retested at lower concentrations against *M. tuberculosis* $H_{37}Rv$ to determine the actual minimum inhibitory concentration (MIC) in the MABA. MIC for rifampicin was 0.25 μg mL^{-1}.

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