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Bioorganic & Medicinal Chemistry 15 (2007) 4016–4037
Bioorganic & Medicinal Chemistry

Antimicrobial and cytotoxic activity of agelasine and agelasimine analogs

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Received 22 January 2007; revised 23 March 2007; accepted 30 March 2007
Available online 2 April 2007

Abstract—Agelasine and agelasimine derivatives with substantially less complicated terpenoid side chains compared to the naturally occurring compounds have been synthesized and their ability to inhibit growth of microorganisms and cancer cells has been studied. Compounds with excellent activity against cancer cell lines (MIC ca. 1 μM for the most potent compounds), including a drug resistant renal cell line, have been identified. Most compounds studied also exhibited broad spectrum antimicrobial activity including activity against *Mycobacterium tuberculosis*.

1. Introduction

Agelasines[1] and agelasimines[2] are isolated from marine sponges (*Agelas* sp.) and these natural products are associated with various bioactivities including antimicrobial and cytotoxic effects. More than ten agelasines are currently known, and agelasine A,[3] B,[4] C,[5] D,[6] E,[7] and (±) agelasine F[8] have been synthesized. The structures of some agelasines are shown in Figure 1. Agelasimines are also purine derivatives carrying a diterpenoid side chain. However, these compounds are neutral 3,7-dialkylated purines. Only agelasimine A and B (Fig. 1) have been found in nature and both have been prepared synthetically.[9]

Activity against *Mycobacterium tuberculosis* has been reported for agelasine F.[10] We have found only modest antimycobacterial activity for agelasine E, but several agelasine analogs exhibited profound inhibitory activity against *M. tuberculosis*.[7] We have also shown that agelasine D and close analogs display a broad spectrum of antibacterial activities including effect on *M. tuberculosis*, Gram-positive and Gram-negative bacteria (both aerobes and anaerobes), and that the same compounds also display profound cytotoxic activity against several cancer cells including a multi-drug resistant renal cell line.[6b] In order to obtain structure–activity relationship (SAR) knowledge on agelasines, and analogs as antimicrobials and cytotoxic compounds, with the ultimate goal to develop analogs with better selectivity against bacteria or cancer cells, we have synthesized several analogs of agelasines and agelasimines and evaluated their ability to inhibit bacterial growth and their cytotoxicity against certain cancer cell lines.

2. Synthesis

We have utilized the same strategy for the preparation of the agelasine analogs **3** and **5**, as for our previously reported agelasines,[6,7] and the synthetic route is outlined in Scheme 1. 9-Alkyl-6-chloropurines **1** were converted to the N^6-alkoxypurines **2** and subsequently reacted with allylic halides. Ammonia was present in the eluent, when compounds **3** were purified chromatographically. Thus,

Keywords: Antimicrobial agent; Anti-cancer agent; Adenine derivative; Natural product.
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doi:10.1016/j.bmc.2007.03.086

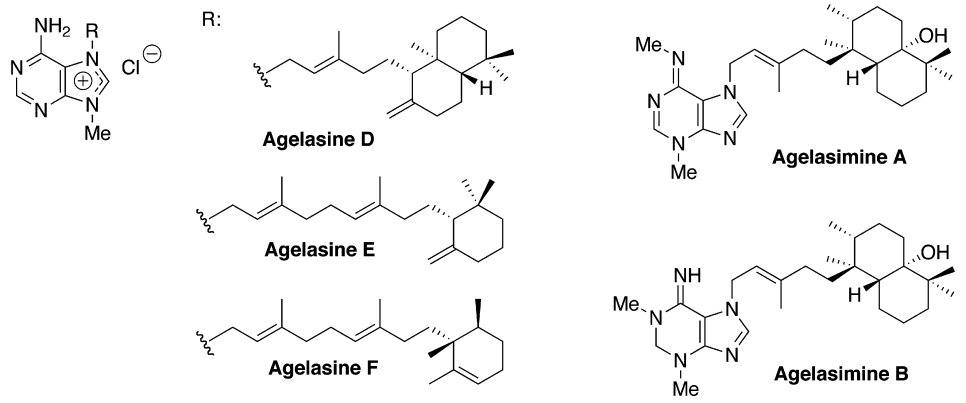
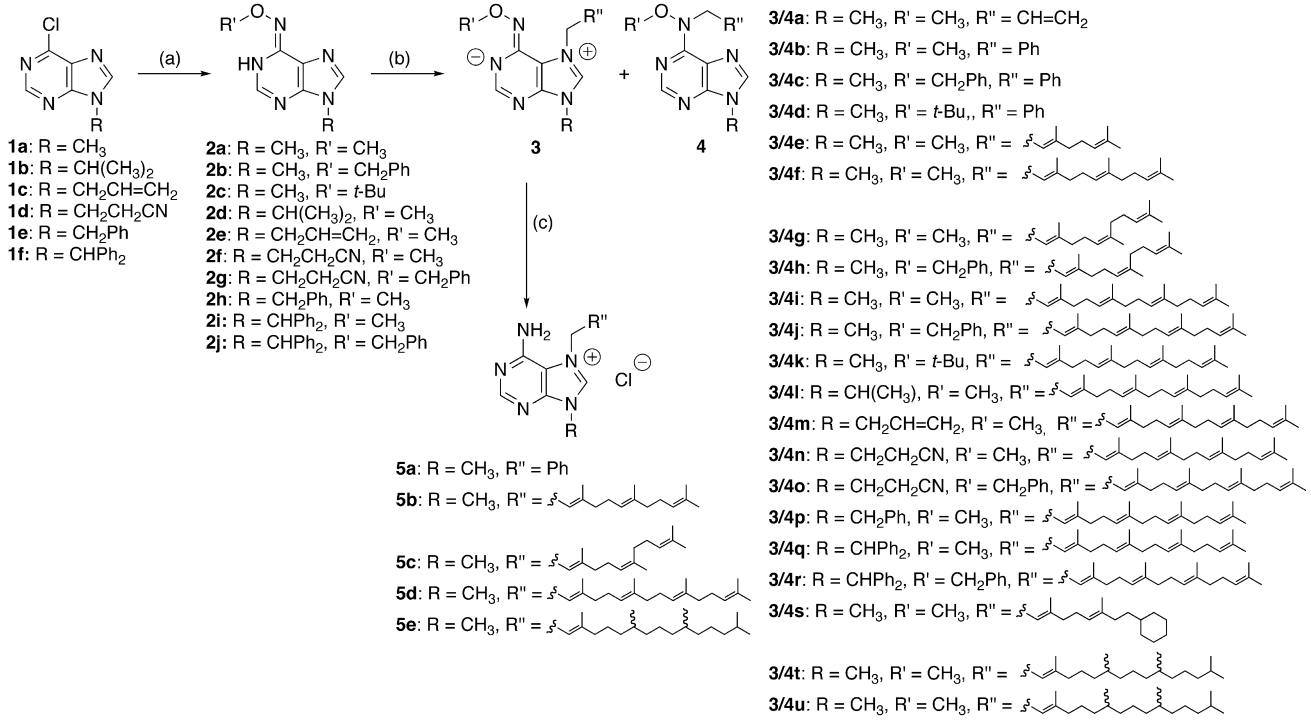


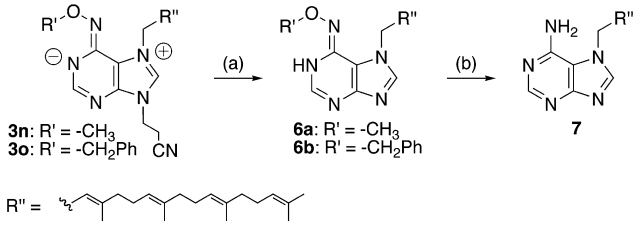
Figure 1. Structures of some agelasines and agelasimines.



Scheme 1. Reagents and conditions: (a) R′ONH$_2$·HCl, Et$_3$N, *n*-BuOH, Δ; (b) R″CH$_2$Br, DMA, 50 °C; (c) Zn, AcOH, MeOH, H$_2$O, 60 °C.

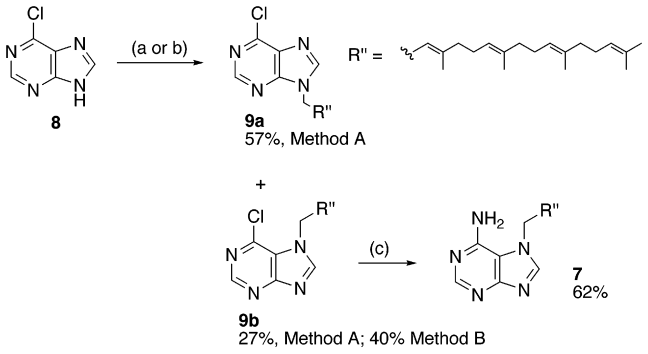
compounds **3** were generally isolated as betaines. The desired compounds **3** were formed together with various amounts of N^6-alkylated compounds **4**. The regiochemistry was improved when N^6 was sterically shielded (*i.e.*, compounds **2b**, **2c**, **2g** or **2j**). Reductive removal of the N^6-alkoxy groups gave the agelasine analogs **5**. In order to gain increased knowledge on SAR of antimicrobial and cytotoxic agelasine analogs, compounds with various substituents at N^6, *N*-7, and *N*-9 were prepared.

We wanted to compare biological activities of the agelasine analogs **3** and **5** with activities found for related structures without a permanently charged imidazole ring. Compounds **6** and **7** were prepared as shown in Scheme 2. Compounds **3n** and **3o** were treated with K_2CO_3 in methanol in order to remove the *N*-9 substituent, and reductive cleavage of the benzyloxy group in



Scheme 2. Reagents and condition: (a) K_2CO_3, MeOH; (b) Zn, AcOH, MeOH, H$_2$O, 75 °C.

compound **6b** gave 7-geranylgeranyladenine **7**. An alternative route to compound **7** is shown in Scheme 3. 6-Chloro-7-geranylgeranylpurine **9b** was formed, together with the isomer **9a**, when 6-chloropurine **8** was reacted with geranylgeranyl bromide in the presence of base.



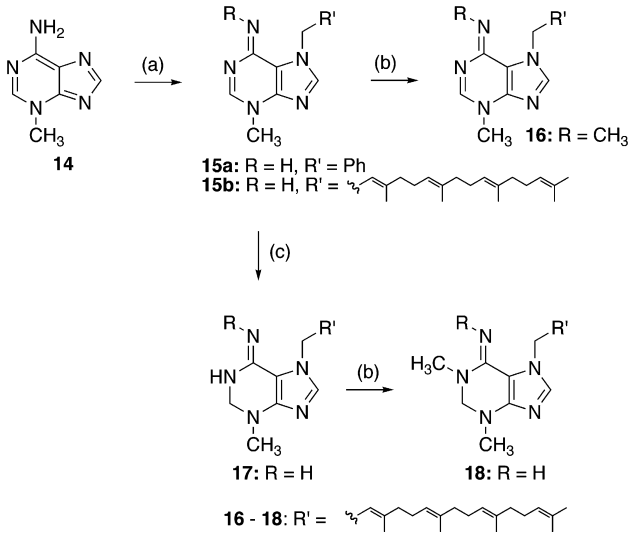
Scheme 3. Reagents and condition: (a) $R''CH_2Br$, K_2CO_3, DMF; (b) $R''CH_2Br$, methylaquacobaloxime, K_2CO_3, DMA; (c) NH_3, *t*-BuOH, 100 °C.

Selective *N*-7 alkylation was achieved when 6-chloropurine **8** was reacted with geranylgeranyl bromide in the presence of methylaquacobaloxime,[11] and compound **9b** was isolated in 40% yield when DMA was used as solvent. Chloropurine **9b** was easily converted to the adenine derivative **7** when reacted with ammonia. *t*-BuOH was used as solvent to avoid nucleophilic substitution from solvent attack, in the purine 6-position.

In order to evaluate the importance of an intact purine ring for antibiotic activity of agelasine analogs, we also prepared the simple imidazolium and benzimidazolium bromides **11** from *N*-methylimidazole **10a** or *N*-ethylbenzimidazole **10b** (Scheme 4).

When the N^6 alkoxy substituent in compounds **2** is present, the second *N*-alkyl substituent is directed to *N*-7 (see Scheme 1 above). *N*-Alkylation of 9-methyladenine **12** with benzyl bromide or geranylgeranyl bromide gave the 1,9-dialylated purines **13**, which can be regarded as regioisomers of agelasines (Scheme 5).

Since analogs of agelasines carrying a simple terpenoid side chain (i.e., geranylgeranyl) are shown to exhibit antimycobacterial activity,[7] we also wanted to synthesize geranylgeranyl analogs of agelasimines and evaluate their potential as antibiotics (Scheme 6). 3-Methyladenine **14** was alkylated at *N*-7 to give compounds **15**. The agelasimine A analog **16** was prepared by N^6-methylation of **15b**. Sodium borohydride mediated reduction of **15b** followed by *N*-1 methylation of the dihydropurine **17** gave the agelasimine B analog **18**.

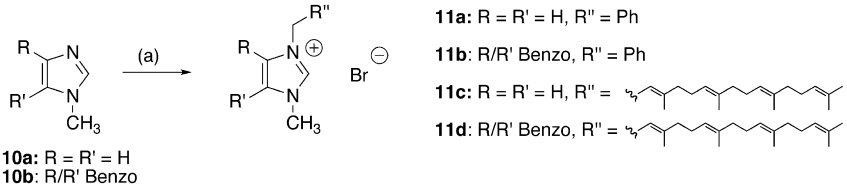


Scheme 6. Reagents and condition: (a) $R'CH_2Br$, DMA, 50 °C; (b) CH_3I, DMA; (c) $NaBH_4$, MeOH, H_2O.

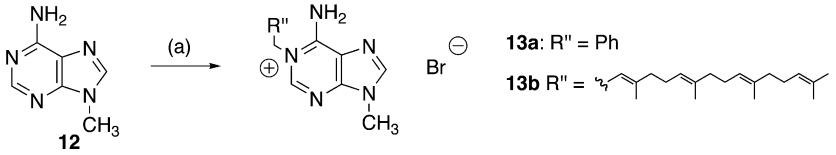
3. Antimicrobial and cytotoxic activity

Antibacterial activities as well as cytotoxicity toward cancer cell lines were examined for the agelasine analogs **3**, **5**–**7**, **9b**, **11**, and **13**, and the agelasimine analogs **15**–**18**. The results are summarized in Tables 1–6. Compounds **4** were only isolated in minor amounts and we have previously demonstrated that related structures were only weak inhibitors of *M. tuberculosis*. Hence bioactivity of compounds **4** was not determined in the present study.

Biological activities found for agelasines **3** and **5** are shown in Table 1. A comparison of compounds **3** carrying *N*-7 substituents of various lengths reveals that the

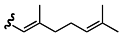
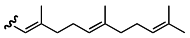
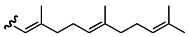
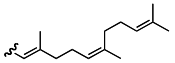
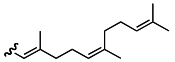
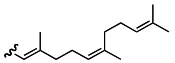
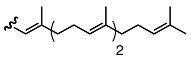
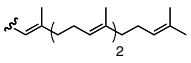
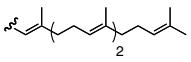
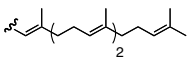
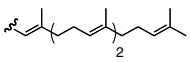
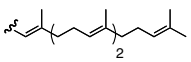
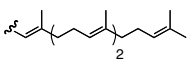
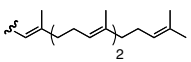
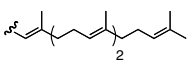


Scheme 4. Reagents and condition: (a) $R''CH_2Br$, DMA, 50 °C.



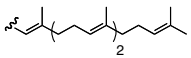
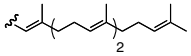
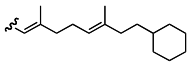
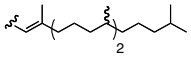
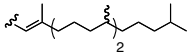
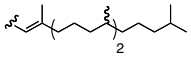
Scheme 5. Reagents and condition: (a) $R''CH_2Br$, DMA, 50 °C.

Table 1. Antibacterial activity of compounds **3** and **5** against *Mycobacterium tuberculosis*, *Staphylococcus aureus*, *Escherichia coli*, *Bacteroides fragilis*, and *Bacteroides thetaiotaomicron*, and cytotoxic activity against the cell lines U-937 GTB (lymphoma), RPMI 8226/s (myeloma), CEM/s (leukemia), and ACHN (renal)

Compound	R	R′	R″	% Inhib. *M. tuberculosis* 6.25 μg/mL	MIC *M. tuberculosis*[a] (μg/mL)	MIC *S. aureus*[b] (μg/mL)	MIC *E. coli*[c] (μg/mL)	MIC *B. fragilis*[d] (μg/mL)	MIC *B. thetaiotaomicron*[e] (μg/mL)	IC_{50} (μM) U-937 GTB[f]	IC_{50} (μM) RPMI 8226/s[g]	IC_{50} (μM) CEM/s[h]	IC_{50} (μM) ACHN[i]
3a	$-CH_3$	$-CH_3$	$-CH{=}CH_2$	27[j]	n.d.[k]	>32[l]	>32[m]	n.d.	n.d.	>80	>80	>80	>80
3b	$-CH_3$	$-CH_3$	–Ph	4	n.d.	>32[l]	>32[m]	n.d.	n.d.	>80	>80	>80	>80
3c	$-CH_3$	$-CH_2Ph$	–Ph	0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
3d	$-CH_3$	$-Bu^t$	–Ph	53	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
5a	$-CH_3$	—	–Ph	0	n.d.	>32[l]	>32[m]	>32	>32	>80	>80	>80	>80
3e	$-CH_3$	$-CH_3$		27[j]	n.d.	>32[l]	>32[m]	n.d.	n.d.	17.5	18.4	27.4	>80
3f	$-CH_3$	$-CH_3$		99	3.13	8[l]	16[m]	16	16	1.32	1.24	1.16	40.4
5b	$-CH_3$	—		13	n.d.	32[l]	>32[m]	n.d.	n.d.	>80	>80	>80	>80
3g[n]	$-CH_3$	$-CH_3$		98	3.13	6[l]	16[m]	32	16	1.40	0.736	1.23	28.7
3h[n]	$-CH_3$	$-CH_2Ph$		99	3.13	8	12	4	4-8	7.55	6.76	10.0	25.2
5c	$-CH_3$	—		8	n.d.	32[l]	>32[m]	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
3i	$-CH_3$	$-CH_3$		100[j]	3.13[j]	4[l]	16[m]	8	8	1.42	1.11	1.91	7.38
3j	$-CH_3$	$-CH_2Ph$		99	3.13	6[l]	>32[m]	8	16	6.79	8.24	14.0	20.9
3k	$-CH_3$	$-Bu^t$		100	3.13	24	>32	n.d.	n.d.	4.87	2.09	3.86	8.40
5d	$-CH_3$	—		38[j]	n.d.	32	>32	n.d.	n.d.	3.17	2.79	3.06	20.3
3l	$-CH(CH_3)_2$	$-CH_3$		100	1.56	n.d.	n.d.	n.d.	n.d.	1.10	0.886	2.05	2.45
3m	$-CH_2CH{=}CH_2$	$-CH_3$		100	3.13	32	>32	n.d.	n.d.	1.39	1.25	2.94	4.61
3n	$-CH_2CH_2CN$	$-CH_3$		100	>6.25	4	32	n.d.	n.d.	3.33	3.96	5.36	11.4
3o	$-CH_2CH_2CN$	$-CH_2Ph$		86	n.d.	>32	>32	n.d.	n.d.	24.2	9.46	19.1	38.9
3p	$-CH_2Ph$	$-CH_3$		99	1.56	32	>32	n.d.	n.d.	1.07	1.04	2.24	3.40

(*continued on next page*)

Table 1 (*continued*)

Compound	R	R′	R″	% Inhib. *M. tuberculosis* 6.25 μg/mL	MIC *M. tuberculosis*[a] (μg/mL)	MIC *S. aureus*[b] (μg/mL)	MIC *E. coli*[c] (μg/mL)	MIC *B. fragilis*[d] (μg/mL)	MIC *B. thetaiotaomicron*[e] (μg/mL)	IC_{50} (μM) U-937 GTB[f]	IC_{50} (μM) RPMI 8226/s[g]	IC_{50} (μM) CEM/s[h]	IC_{50} (μM) ACHN[i]
3q	$-CHPh_2$	$-CH_3$		99	3.13	8	>32	n.d.	n.d.	1.97	2.60	3.54	4.75
3r	$-CHPh_2$	$-CH_2Ph$		78	n.d.	8	>32	n.d.	n.d.	4.24	59.0	9.11	17.2
3s	$-CH_3$	$-CH_3$		99[j]	1.56[j]	6	16	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
3t	$-CH_3$	$-CH_3$		56	n.d.	32	>32	n.d.	n.d.	5.40	3.75	7.92	16.9
3u	$-CH_3$	$-CH_2Ph$		72	n.d.	>32	>32	n.d.	n.d.	10.8	7.07	6.30	20.5
5e	$-CH_3$	—		99	6.25	4	>32	n.d.	n.d.	3.18	2.41	5.82	11.3

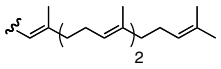
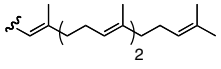
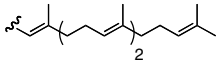
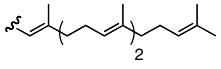
[a] MIC rifampicin 0.25 μg/mL.
[b] MIC gentamycin 0.1 μg/mL.
[c] MIC gentamycin 0.5 μg/mL.
[d] MIC metronidazole 0.5 μg/mL.
[e] MIC metronidazole 1.0 μg/mL.
[f] IC_{50} doxorubicin 0.11 μM, IC_{50} cisplatin 2.56 μM, IC_{50} palitaxel 0.0059 μM.
[g] IC_{50} doxorubicin 0.13 μM, IC_{50} cisplatin 14.8 μM, IC_{50} palitaxel 0.007 μM.
[h] IC_{50} doxorubicin 0.18 μM, IC_{50} cisplatin 2.48 μM, IC_{50} palitaxel 0.007 μM.
[i] IC_{50} doxorubicin 14.2 μM, IC_{50} cisplatin 17.8 μM, IC_{50} palitaxel 31.5 μM.
[j] Data from Ref. 7.
[k] Not determined.
[l] MIC gentamycin 0.03 μg/mL.
[m] MIC gentamycin 0.13 μg/mL.
[n] *E*/*Z* ratio (R′; double bond closest to N) 75:25.

Table 2. Antibacterial activity of compound **3i** against *Streptococcus pyogenes*, *Enterococcus faecalis*, and *Pseudomonas aeruginosa*

Compound	MIC (μg/mL) *S. pyogenes*[a]	MIC (μg/mL) *E. faecalis*[b]	MIC (μg/mL) *P. aeruginosa*[c]
3i	4.0	8.0	>32

[a] MIC gentamycin 1–2 μg/mL.
[b] MIC gentamycin >4 μg/mL.
[c] MIC gentamycin 0.13 μg/mL.

Table 3. Antibacterial activity of compounds **6–9** against *Mycobacterium tuberculosis*, *Staphylococcus aureus* and *Escherichia coli*, and cytotoxic activity against the cell lines U-937 GTB (lymphoma), RPMI 8226/s (myeloma), CEM/s (leukemia), and ACHN (renal)

Compound	R′	R″	% Inhib. *M. tuberculosis* 6.25 μg/mL	MIC *M. tuberculosis*[a] (μg/mL)	MIC *S. aureus*[b] (μg/mL)	MIC *E. coli*[c] (μg/mL)	IC_{50} (μM) U-937 GTB[d]	IC_{50} (μM) RPMI 8226/s[e]	IC_{50} (μM) CEM/s[f]	IC_{50} (μM) ACHN[g]
6a	$-CH_3$		74	n.d.[h]	>32	>32	3.31	3.00	5.69	18.1
6b	$-CH_2Ph$		40	n.d.	>32	>32	11.2	10.9	20.4	27.4
7	—		99	1.56	>32	>32	3.60	2.78	2.88	7.24
9b	—		33	n.d.	>32	>32	5.07	5.20	6.79	6.75

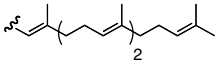
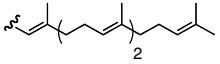
[a] MIC rifampicin 0.25 μg/mL.
[b] MIC gentamycin 0.1 μg/mL.
[c] MIC gentamycin 0.5 μg/mL.
[d] IC_{50} doxorubicin 0.11 μM, IC_{50} cisplatin 2.56 μM, IC_{50} palitaxel 0.0059 μM.
[e] IC_{50} doxorubicin 0.13 μM, IC_{50} cisplatin 14.8 μM, IC_{50} palitaxel 0.007 μM.
[f] IC_{50} doxorubicin 0.18 μM, IC_{50} cisplatin 2.48 μM, IC_{50} palitaxel 0.007 μM.
[g] IC_{50} doxorubicin 14.2 μM, IC_{50} cisplatin 17.8 μM, IC_{50} palitaxel 31.5 μM.
[h] Not determined.

chain length of the 7-substituent is (extremely) important for both antibacterial and cytotoxic activities. 7-Allyl (**3a**), 7-benzyl (**3b–d**), and 7-geranyl derivatives (**3e**) were more or less inactive against the bacteria and cancer cell lines examined. (2*E*,6*E*)-Farnesyl (**3f**) and the isomeric (2*E*,6*Z*)-farnesyl derivatives (**3g–h**), on the other hand, exhibited profound inhibitory activity against *M. tuberculosis* and *Staphylococcus aureus*. These compounds were also active against *Escherichia coli* and even against *Bacteroides fragilis* and *Bacteroides thetaiotaomicron* (anaerobe). The geometry of the terpenoid side chain appears to have no significant influence on antibacterial activity. Compounds **3f–h** also displayed inhibitory activity against the cancer cell lines examined. When the *N*-7 terpenoid side chain was extended even further to geranylgeranyl, cytotoxicity toward the cancer cells increased whereas, the antibacterial activities remained essentially unchanged (geranylgeranyl derivative **3i** compared with (*E*,*E*)-farnesyl derivative **3f** and (*E*,*Z*)-farnesyl derivative **3g**). Compound **3i** exhibited profound activity against the cancer cell lines and this agelasine analog was also a potent inhibitor of ACHN (renal adenocarcinoma cells) growth. Renal cell carcinomas (RCC) are quite resistant to chemotherapy;[12] hence it was especially intriguing to find that compound **3i** was more effective against the primary multidrug-resistant (MDR) cell line ACHN[13] than any of the anticancer drugs used as positive controls. Antibacterial activities against other bacteria for compound **3i** were also determined (Table 2). Geranylgeranylpurine **3i** was also active against *Streptococcus pyogenes* and *Enterococcus facealis*, but not against *Pseudomonas aeruginosa*, in the concentration range examined. Reduced inhibitory activity, especially against bacteria, was found for the phytyl derivatives **3t–u** compared to the geranylgeranylpurines **3i–j**, indicating that unsaturations in the side chain are important for the bioactivities studied.

The identity of the N^6-substituent in compounds **3** also influences bioactivity. Comparison of the farnesyl derivatives **3g–h**, the geranylgeranyl compounds **3i–k**, and the phytylpurines **3t–u** revealed that cytotoxicity toward cancer cells generally decreases when a larger alkoxy substituent, benzyloxy or *tert*-butyloxy, is introduced at N^6, whereas the antimycobacterial activity is virtually unchanged and there are only minor variations in activities against other bacteria.

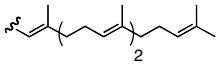
When the N^6-alkoxy groups were reductively removed (Scheme 1), compounds **5** were formed. These adeninium salts are structurally more closely related to naturally occurring agelasines than compounds **3**. However, with the exception of the phytyl derivative **5e**, substantially reduced activity toward both bacteria and cancer cells was observed for compounds **5** compared to analogous compounds **3**.

Table 4. Antibacterial activity of compounds **11** against *Mycobacterium tuberculosis*, *Staphylococcus aureus*, and *Escherichia coli*, and cytotoxic activity against the cell lines U-937 GTB (lymphoma), RPMI 8226/s (myeloma), CEM/s (leukemia), and ACHN (renal)

Compound	R	R′	R″	% Inhib. *M. tuberculosis* 6.25 μg/mL	MIC *M. tuberculosis*[a] (μg/mL)	MIC *S. aureus*[b] (μg/mL)	MIC *E. coli*[c] (μg/mL)	IC_{50} (μM) U-937 GTB[d]	IC_{50} (μM) RPMI 8226/s[e]	IC_{50} (μM) CEM/s[f]	IC_{50} (μM) ACHN[g]
11a	H	H	Ph	19	n.d.[h]	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
11b			Ph	19	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
11c	H	H		58	n.d.	8	>32	2.64	2.60	8.64	>80
11d				98	>6.25	8	16	1.33	0.99	3.42	11.3

[a] MIC rifampicin 0.25 μg/mL.
[b] MIC gentamycin 0.1 μg/mL.
[c] MIC gentamycin 0.5 μg/mL.
[d] IC_{50} doxorubicin 0.11 μM, IC_{50} cisplatin 2.56 μM, IC_{50} palitaxel 0.0059 μM.
[e] IC_{50} doxorubicin 0.13 μM, IC_{50} cisplatin 14.8 μM, IC_{50} palitaxel 0.007 μM.
[f] IC_{50} doxorubicin 0.18 μM, IC_{50} cisplatin 2.48 μM, IC_{50} palitaxel 0.007 μM.
[g] IC_{50} doxorubicin 14.2 μM, IC_{50} cisplatin 17.8 μM, IC_{50} palitaxel 31.5 μM.
[h] Not determined.

Table 5. Antibacterial activity of compounds **13** against *Mycobacterium tuberculosis*, *Staphylococcus aureus*, and *Escherichia coli*, and cytotoxic activity against the cell lines U-937 GTB (lymphoma), RPMI 8226/s (myeloma), CEM/s (leukemia), and ACHN (renal)

Compound	R″	% Inhib. *M. tuberculosis* 6.25 μg/mL	MIC *M. tuberculosis*[a] (μg/mL)	MIC *S. aureus*[b] (μg/mL)	MIC *E. coli*[c] (μg/mL)	IC_{50} (μM) U-937 GTB[d]	IC_{50} (μM) RPMI 8226/s[e]	IC_{50} (μM) CEM/s[f]	IC_{50} (μM) ACHN[g]
13a	–Ph	0	n.d.[h]	>32	>32	n.d.	n.d.	n.d.	n.d.
13b		72	n.d.	8	>32	39.4	18.6	20.8	>80

[a] MIC rifampicin 0.25 μg/mL.
[b] MIC gentamycin 0.1 μg/mL.
[c] MIC gentamycin 0.5 μg/mL.
[d] IC_{50} doxorubicin 0.11 μM, IC_{50} cisplatin 2.56 μM, IC_{50} palitaxel 0.0059 μM.
[e] IC_{50} doxorubicin 0.13 μM, IC_{50} cisplatin 14.8 μM, IC_{50} palitaxel 0.007 μM.
[f] IC_{50} doxorubicin 0.18 μM, IC_{50} cisplatin 2.48 μM, IC_{50} palitaxel 0.007 μM.
[g] IC_{50} doxorubicin 14.2 μM, IC_{50} cisplatin 17.8 μM, IC_{50} palitaxel 31.5 μM.
[h] Not determined.

Table 6. Antibacterial activity of compounds **15–18** against *Mycobacterium tuberculosis*, *Staphylococcus aureus*, and *Escherichia coli*, and cytotoxic activity against the cell lines U-937 GTB (lymphoma), RPMI 8226/s (myeloma), CEM/s (leukemia), and ACHN (renal)

Compound	R	R′	% Inhib. *M. tuberculosis* 6.25 μg/mL	MIC *M. tuberculosis*[a] (μg/mL)	MIC *S. aureus*[b] (μg/mL)	MIC *E. coli*[c] (μg/mL)	IC_{50} (μM) U-937 GTB[d]	IC_{50} (μM) RPMI 8226/s[e]	IC_{50} (μM) CEM/s[f]	IC_{50} (μM) ACHN[g]
15a	–H	–Ph	0	n.d.[h]	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
15b	–H		84	n.d.	4	8	6.40	6.78	7.77	12.32
16	$–CH_3$		94	3.13	3	16	>80	>80	>80	>80
17	–H		99	n.d.	8	16	>80	18.2	21.7	>80
18	–H		99	3.13	16	>32	3.36	2.51	3.15	5.16

[a] MIC rifampicin 0.25 μg/mL.
[b] MIC gentamycin 0.1 μg/mL.
[c] MIC gentamycin 0.5 μg/mL.
[d] IC_{50} doxorubicin 0.11 μM, IC_{50} cisplatin 2.56 μM, IC_{50} palitaxel 0.0059 μM.
[e] IC_{50} doxorubicin 0.13 μM, IC_{50} cisplatin 14.8 μM, IC_{50} palitaxel 0.007 μM.
[f] IC_{50} doxorubicin 0.18 μM, IC_{50} cisplatin 2.48 μM, IC_{50} palitaxel 0.007 μM.
[g] IC_{50} doxorubicin 14.2 μM, IC_{50} cisplatin 17.8 μM, IC_{50} palitaxel 31.5 μM.
[h] Not determined.

We also examined if variations in the purine 9-substituent would affect biological activities. The geranylgeranyl derivative **3i**, carrying a methyl group in the purine 9-position, just as naturally occurring agelasines, was compared with compounds **3l–3n**, **3p**, and **3q**. With respect to antimycobacterial activity, a variety of *N*-9 substituents were well tolerated and the 9-isopropyl and 9-benzyl derivatives, **3l** and **3p**, are among the most active antimycobacterials examined (MICs 1.56 μg/mL). A negative influence on other antibacterial activity, especially against *E. coli*, may be observed when the *N*-9 substituent is increased. Cytotoxicity against cancer cells is also generally high for the compounds in this series. The isopropyl (**3l**), allyl (**3m**), benzyl (**3p**), and diphenylmethylpurine **3q** are all excellent inhibitors of ACHN cell growth (IC_{50} < 5 μM). As mentioned above, this renal cell line is regarded as drug resistant. The 9-cyanoethyl derivatives **3n** and **3o** were not among the most active antimycobacterials. However, the cyanoethyl group is easily removed, at least under basic conditions (see Scheme 2 above). If this 9-substituent also is cleaved to some extent during the antimycobacterial testing, the less active compounds **6a** and **6b** (Table 3) are formed.

Naturally occurring agelasines are 7,9-dialkylated purinium salts just as are the analogs **3** and **5**. We were curious to see if the mono-alkylated neutral purines **6**, **7**, and **9b** also exhibited similar biological activities as the cationic species. The antibacterial and cytotoxic activities found for these compounds are shown in Table 3. Some antimycobacterial activity was observed at 6.25 μg/mL for compounds **6** and **9b**, and 7-geranylgeranyladenine **7** is actually among the most active inhibitors of *M. tuberculosis* growth described in this study (MIC 1.56 μg/mL). It is interesting to note that for the purinium salts **3** and **5**, the free NH_2-group found in compounds **5** generally resulted in low antimycobacterial activity, whereas the primary amine **7** is substantially more active than the N^6 alkoxy derivatives **6**. It is possible that a cationic charge is required for antimycobacterial activity and that compound **7**, but not the less basic compounds **6**, is protonated in the cell culture. However, none of the compounds **6**, **7** or **9b** were active against *S. aureus* or *E. coli* at 32 μg/mL. Compounds **6**, **7**, and **9b** exhibited significant inhibitory activity against the cancer cell lines examined, but none of these mono *N*-alkylated purines could compete with the most active geranylgeranyl purinium salts **3** (see Table 1).

Compounds **11** were designed to reveal if simple imidazolium or benzimidazolium salts might exhibit the same biological profile as the purinium salts **3** and **5**. Table 4 displays antibacterial and anticancer activities found for compounds **11**. The *N*-benzyl-*N*-methyl (benz)imidazolium bromides **11a** and **11b** were only very weak antimycobacterials, just as the benzyl derivatives **3b–d** and **5a**, and **11a** and **11b** were not screened against other bacteria or against cancer cells. The geranylgeranyl derivatives **11c** and **11d** displayed moderate antibacterial activity and fairly good activity against most of the cancer cells. The benzimidazole **11d** was generally the most potent of these compounds.

Compounds **13a** and **13b** (Table 5) are isomers of the purinium salts **5a** and **5d** (Table 1). It was not unexpected that also the benzyl derivative **13a**, just like all other *N*-benzyl derivatives studied herein, was inactive against the bacteria examined. The geranylgeranyl derivative **13b** was found to be slightly more active against *M. tuberculosis* and *S. aureus* than the isomer **5d**, and far less active against all cancer cells examined.

Since we have demonstrated that analogs of agelasines carrying much less complicated terpenoid side chains may still be highly potent inhibitors of bacterial growth and growth of cancer cells, we found it interesting to examine if the same simplification of agelasimine structure also would lead to compounds with potent biological activity. Hence we prepared analogs of agelasimines (compounds **15**–**18**) and examined their ability to act as antibacterials and inhibitors of cancer cells (Table 6). All geranylgeranyl derivatives were profound inhibitors of *M. tuberculosis* and *S. aureus*, and except for compound **18**, the geranylgeranyl derivatives were also active against *E. coli* in the concentration range examined. Compounds **15b** and **18** were also strong inhibitors of cancer cells, whereas compounds **16** and **17** appear to be much less cytotoxic.

It has been reported that agelasine B displays activity against certain yeasts (*Candida neoformans* and to a lesser extent *Candida albicans*).[1g] To investigate if the agelasine and agelasimine analogs described herein possess antimycotic activity, the control strain ATCC 6258 of the clinically important yeast *Candida krusei* was included in the study (Table 7). Although *C. albicans* is considered to be the most pathogenic species, *C. krusei* is increasingly associated with infections of both immunocompromised and non-immunocompromised hosts.[14] *C. krusei* can show intrinsic and acquired resistance to azole antifungals (fluconazole and itraconazole); The widespread use of fluconazole has probably led to an increase in *C. krusei* infections and patients receiving fluconazole prophylaxis are at risk of developing infections caused by fluconazole-resistant *C. krusei*.[15] Except for compounds **5d** and **7**, both carrying free primary amino group in the purine 7-positions, the compounds examined displayed profound inhibitory activity against *C. krusei*, often in the same range as the reference drug amphotericine B. Again the length of the terpenoid side chain appears to be important for activity; the farnesyl derivative **3f** displays a somewhat higher MIC value than the geranylgeranyl derivatives **3i**–**k**. The detailed structure of the heterocycle seems to be less important since both agelasine derivatives **3i**–**k**, imidazole and benzimidazole analogs **11c**–**d**, and the agelasimine derivative **15b** are found to be strong inhibitors of fungal growth.

Table 7. Antifungal activity of selected compounds[a] against *Candida krusei*

Compound	MIC *C. krusei*[b] (μg/mL)
3f	8.0
3i	2.0
3j	1.0
3k	2.0
5d	>16
7	>16
11c	4.0
11d	2.0
15b	2.0
18	16

[a] Structures of compounds **3** and **5**, see Scheme 1; compound **7**, see Scheme 2; compounds **11**, see Scheme 4 and compounds **15** and **18**, see Scheme 6.

[b] MIC amphotericin B 1.0 μg/mL.

The mode of action for the agelasines and agelasimines as antibacterials or cytotoxic compounds has not been shown. However, our hypothesis is that these amphiphilic compounds, carrying a hydrophilic 'head' (purine) and a hydrophobic 'tail' (terpenoid chain), may very well interact with cell membranes. We could detect no changes in the morphology of *C. krusei* cells after treatment with the compounds studied (antifungal results, see Table 7). The morphology of yeast cells taken from wells containing 50% of the MIC of each test substance was investigated. Examination by phase contrast microscopy revealed no differences between these cells and those grown in the absence of agelasine analogs. This may indicate that agelasines exert their effect(s) in a way, which does not affect the gross cell morphology, but a mechanism of action involving interactions with cell membranes cannot be excluded. Several classes of amphiphilic molecules, especially naturally occurring peptides and analogs,[16] but also for instance cationic stereoids,[17] interact with cell membranes. It is claimed that antibiotics that interrupt cell membranes may escape most drug resistance mechanisms compared with classical antibiotics that must penetrate the target cell.[16b] Compounds that discriminate sufficiently between prokaryote and eukaryotes are highly interesting as antibacterials. It is known that the lipid composition in bacteria and eukaryote cells differs significantly. For instance, bacterial membranes are negatively charged, whereas the outer leaflets of mammalian cells are neutral at physiological pH, and bacterial membranes do not contain sterols. These facts may account for the selectivity observed for some of the agelasine and agelasimine analogs described herein. Increased knowledge of interaction between the compounds studied and cell membranes may eventually lead to development of agelasines or agelasimine analogs with increased selectivity. Of the molecules described herein, 7-geranylgeranyladenine **7** is among the most interesting, with a MIC = 1.56 μg/mL against *M. tuberculosis*. Further modifications of the structure of **7** may indeed lead to an improved antimycobacterial compound with less cytotoxicity. It is also interesting to note that compound **7** is inactive against *S. aureus* and *E. coli* in the concentration range examined (MIC > 32 μg/mL for both bacteria). For treatment of mycobacterial infections, organism-specific agents are recommended.[18]

4. Conclusions

We have demonstrated that agelasine and agelasimine derivatives with substantially less complicated terpenoid

side chains compared to the naturally occurring compounds may still exhibit very interesting biological activities. These analogs are much easier to synthesize compared to the natural products and they are therefore more interesting as potential drugs. Several agelasine analogs with excellent activity against cancer cell lines, including a drug resistant renal cell line, have been identified. Furthermore, determination of the mechanism by which these compounds act as antibiotics and further functionalization of the agelasine analogs may also result in compounds with more specific antimicrobial activity. The seemingly unavoidable development of resistance against any antibacterial compound used clinically calls for the development of new agents with novel mechanisms and chemical structures.[18] It is especially intriguing to find compounds with activity against *M. tuberculosis*, since there have been launched no new drugs to treat tuberculosis for approximately 40 years, even though the disease claims ca. 2 million lives every year, and infections with multidrug resistant strains are an increasing problem.[19]

5. Experimental

Melting points are uncorrected. The ^{1}H NMR spectra were recorded at 500 MHz with a Bruker Avance DRX 500 instrument, 300 at 300 MHz with a Bruker Avance DPX 300, or at 200 MHz with a Bruker Avance DPX 200 instrument. The decoupled ^{13}C NMR spectra were recorded at 125, 75 or 50 MHz using the instruments mentioned above. All spectra were obtained at ambient temperature. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane. Mass 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.). Electrospray MS spectra were recorded with a Bruker Apex 47e FT-ICR mass spectrometer. Elemental analyses were performed by Ilse Beetz Mikroanalytisches Laboratorium, Kronach, Germany. As is typical of the class, some of the agelasine and agelasimine analogs prepared in this work analyze poorly by this microanalytical method;[6,7] however, NMR analysis demonstrated that these compounds were greater than 97% pure. DMA, DMF, and *n*-butanol were distilled from BaO and stored over molecular sieves (3 Å). Dry diethyl ether was obtained by distillation from Na/benzophenone. Triethylamine, acetonitrile, and pyridine were distilled from CaH_2 and stored over molecular sieves (3 Å). Methanol was saturated with NH_3 by bobbling NH_3 (g) in the methanol at ambient temperature for ca. 5 min. Silica gel for flash chromatography was purchased from Merck, Darmstadt, Germany (Merck No. 09385). *O*-*tert*-Butylhydroxylamine hydrochloride was synthesized according to the literature[20] from *N*-(*tert*-butoxy)phthalimide.[21] Compounds available by literature methods: (2*E*,6*E*,10*E*)-1-bromo-3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraene,[7] methylaquacobaloxime,[11] **1a**,[7] **1b**,[22] **1c**,[23] **1d**,[24] **1e**,[25] **1f**,[26] **2a**,[7] **2b**,[6b], **2c**,[6b] **2g**,[24] **2j**,[24] **3a**,[7] **3b**,[6b] **3c**,[6b] **3d**,[6b] **3e**,[7] **3i**,[7] **3s**,[7] **5d**,[7] **12**.[27] Antimicrobial activities against *M. tuberculosis* H_{37}Rv (ATCC 27294),[7,28] *S. pyogenes* (ATCC 19615),[6b,29] *E. faecalis* (ATCC 700802),[6b,29] *P. aeruginosa* (ATCC 27853),[6b,29] *B. fragilis* (DSM 2151),[6b] *B. thetaiotaomicron* (DSM 2255),[6b] and *C. krusei* (ATCC 6258),[30] and activity against cancer cell lines (U-937 GTB, RPMI 8226/s, CEM/s, and ACHN)[6b] were determined as reported before.

5.1. (2*E*,6*E*)-1-Bromo-3,7,11-trimethyl-2,6,10-dodecatriene

trans,*trans*-Farnesol (667 mg, 3.00 mmol) was dissolved in dry diethyl ether (15 mL) under N_2 before phosphorus tribromide (0.35 mL, 3.6 mmol) was added. The mixture was stirred for 3 h at 0 °C, diluted with diethyl ether (25 mL), washed with satd aq $NaHCO_3$ (2× 10 mL) and satd aq NaCl (10 mL), dried ($MgSO_4$), and evaporated in vacuo; yield 630 mg (74%), yellow oil. The crude allylic bromide was used directly in the next step. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.64 (s, 6H, 2× CH_3), 1.72 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 1.90–2.20 (m, 8H, 4× CH_2), 4.06 (d, J = 8.4 Hz, 2H, CH_2Br), 5.13 (m, 2H, 2× CH=), 5.53 (t, J = 8.4 and 1.3 Hz, 1H, CH=).

5.2. (2*E*,6*Z*)-1-Bromo-3,7,11-trimethyl-2-dodecatriene

cis-Nerolidol (7.0 mmol, 1.56 g) was dissolved in dry diethyl ether (25 mL) and pyridine (7.0 mmol, 0.57 mL) at −35°C under N_2, before phosphorus tribromide (9.8 mmol, 0.93 mL) was added dropwise, and the solution was stirred for 1 h. The mixture was diluted with diethyl ether (80 mL) and aq HCl (10%, 30 mL). The phases were separated and the organic phase was washed with aq HCl (10%, 30 mL) and satd aq $NaHCO_3$ (30 mL), dried with $MgSO_4$, filtered, and evaporated in vacuo; yield 1.762 g (88%), pale yellow oil (2*E*/2*Z* ratio 3:1). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.65 (s, 3H, CH_3), 1.65 (s, 6H, 2× CH_3), 1.81 (s, 3H, CH_3), 1.95–2.15 (m, 8H, 4× CH_2), 4.06 (d, J = 8.5 Hz, 2H, CH_2Br), 5.14 (m, 2H, 2× CH=), 5.69 (m, 1H, CH=).

5.3. (*E*)-1-Bromo-3,7,11,15-tetramethyl-2-hexadecene

An isomeric mixture of phytol (about 65:35 mixture of *E* and *Z* isomers) was purified by flash chromatography on silica gel eluting with hexane/EtOAc/EtOH (50:3:1). Fractions containing more than 90% pure (*E*)-isomers were combined and purified once more using the same flash chromatography system. Pure fractions were collected to give (*E*)-3,7,11,15-tetramethyl-2-hexadecen-1-ol, (*E*/*Z* ratio 99:1; GC). From 1.6 g isomeric mixture, 0.57 g pure *E* isomers were obtained. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.81–0.85 (m, 12H, CH_3), 1.04–1.50 (m, 13H), 1.64 (s, 3H, CH_3), 1.95 (t, J = 7.7 Hz, 1H, CH_2), 4.12 (d, J = 6.7 Hz, 2 H, CH_2OH), 5.40 (t, J = 6.7 Hz, 1H, CH=). The isomeric mixture of (*E*)-phytol was dissolved in diethyl ether (4 mL) and stirred at 0 °C under N_2. Phosphorus tribromide (0.063 mL, 0.68 mmol) in hexane (1 mL) was added, and the resulting mixture was stirred for 20 min. The colorless precipitate was removed by filtration and washed with hexane (25 mL). The organic phase was washed with aq HCl (2 M, 5 mL), satd aq $NaHCO_3$ (5 mL) and satd aq NaCl (2× 10 mL), dried over $MgSO_4$, filtered, and evaporated in

vacuo to give the crude allylic bromide; yield 463 mg (95%), which was used directly in the next step. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.87–0.92 (m, 12H, CH_3), 1.0–1.7 (m, 19H), 1.75 (s, 3H, CH_3), 2.09 (t, J = 7.6 Hz, 2H, CH_2), 4.07 (d, J = 8.4 Hz, 2H, CH_2Br), 5.57 (m, J = 8.4 and 1.3 Hz, 1H, CH=).

5.4. *N*-Methoxy-9-isopropyl-9*H*-purin-6-amine (2d)

A mixture of 6-chloro-9-isopropyl-9*H*-purine **1b** (200 mg, 1.00 mmol), triethylamine (1.5 mL, 10.8 mmol), and *O*-methylhydroxylamine hydrochloride (400 mg, 5.00 mmol) in dry *n*-butanol (10 mL) was stirred at reflux for 17 h and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with EtOH/EtOAc/CH_2Cl_2 (1:5:4); yield 119 mg (57%), mp 178–180 °C. The compound exists as a mixture of imino and amino tautomers in DMSO, NMR resonances for the imino form are given below. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.46 (d, J = 6.8 Hz, 6H, *i*-Pr), 3.74 (s, 3H, OCH_3), 4.61 (m, 1H, *i*-Pr), 7.71 (s, 1H, H-2), 8.01 (s, 1H, H-8), 11.0 (br s, NH); ^{13}C NMR (DMSO-δ_6, 125 MHz) δ 22.32 (CH_3 in *i*-Pr), 46.51 (CH in *i*-Pr), 61.41 (OCH_3), 118.97 (C-5), 138.61 (C-5), 143.61 (C-4 and C-6), 146.59 (C-2); MS EI *m*/*z* (rel.%) 207 (62, M^+), 177 (31), 165 (14), 162 (25), 150 (12), 135 (100), 120 (31), 108 (59); HRMS $C_9H_{13}N_5O$ requires 207.1120, found 207.1119.

5.5. 9-Allyl-*N*-methoxy-9*H*-purin-6-amine (2e)

The product was prepared from 9-allyl-6-chloro-9*H*-purine **1c** (427 mg, 2.17 mmol) as described for compound **2d** above; yield 245 mg (55%), mp 183–185 °C. The compound exists as a mixture of imino and amino tautomers in DMSO, NMR resonances for the imino form are given below. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.74 (s, 3H, CH_3), 4.67 (br d, J = 5.4 Hz, 2H, NCH_2), 4.98 (dd, J = 17.1 and 1.3 Hz, 1H in =CH_2), 5.16 (dd, J = 10.3 and 1.3 Hz, 1H in =CH_2), 5.96–6.07 (m, 1H, =CH), 7.55 (br s, 1H, H-2), 7.80 (s, 1H, H-8), 11.18 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 45.00 (CH_2), 60.88 (CH_3), 117.36 (=CH_2), 117.96 (C-5), 133.58 (=CH), 138.23 (C-8), 141.06 (C-4/C-6), 141.16 (C-4/C-6), 144.05 (C-2); MS EI *m*/*z* (rel.%) 205 (79, M^+), 190 (6), 175 (54), 174 (100), 160 (45), 159 (15), 148 (21), 147 (24); HRMS $C_9H_{11}N_5O$ requires 205.0964, found 205.0957.

5.6. 6-Methoxyamino-9*H*-purine-9-propanenitrile (2f)

The product was prepared from 6-chloro-9*H*-purine-9-propanenitrile **1d** (620 mg, 3.00 mmol) as described for compound **2d** above and purified by flash chromatography on silica gel eluting with EtOH/EtOAc (1:4) followed by recrystallization from EtOAc; yield 340 mg (51%), mp 184–185 °C, colorless crystals. The compound exists as a mixture of imino and amino tautomers in DMSO, NMR resonances for the imino form is given below. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.11 (m, 2H, CH_2), 3.79 (s, 3H, CH_3O), 4.34 (m, 2H, CH_2), 7.62 (br s, 1H) 7.91 (br s, 1H), 11.2 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 19.38 (CH_2), 38.69 (CH_2), 61.78 (CH_3O), 119.0 (CN and C-5), 139.08 (C-8) 141.77 (C-4/C-6), 141.80 (C-4/C-6), 145.11 (C-2); MS EI *m*/*z* (rel.%) 218 (27, M^+), 188 (56), 173 (31), 135 (100), 108 (39); Anal. Calcd for $C_9H_{10}N_6O$: C, 49.54; H, 4.62; N, 38.51. Found: C, 49.54; H, 4.67; N, 38.44%.

5.7. 9-Benzyl-*N*-methoxy-9*H*-purin-6-amine (2h)

The product was prepared from 9-benzyl-6-chloro-9*H*-purine **1e** (600 mg, 2.50 mmol) as described for compound **2d** above; yield 370 mg (64%), mp 216–219 °C, colorless crystals. The compound exists as a mixture of imino and amino tautomers in DMSO, NMR resonances for the imino form are given below. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.74 (s, 3H, CH_3), 5.26 (s, 2H, CH_2), 7.24–7.34 (m, 5H, Ph), 7.57 (s, 1H, H-2), 7.95 (s, 1H, H-8), 11.20 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 46.00 (CH_2), 60.89 (CH_3), 118.12 (C-5), 127.36 (CH in Ph), 127.72 (CH in Ph), 128.67 (CH in Ph), 137.12 (C in Ph), 138.41 (C-8), 141.03 (C-4/C-6), 141.23 (C-4/C-6), 144.22 (C-2); MS EI *m*/*z* (rel.%) 255 (18, M^+), 224 (42), 210 (7), 91 (100); HRMS $C_{13}H_{13}N_5O$ requires 255.1120, found 255.1116.

5.8. 9-(Diphenylmethyl)-*N*-methoxy-9*H*-purin-6-amine (2i)

The product was prepared from 6-chloro-9-(diphenylmethyl)-9*H*-purine **1f** (642 mg, 2.00 mmol) as described for compound **2d** above and purified by flash chromatography on silica gel eluting with EtOAc; yield 83 mg (43%), mp 232–234 °C, colorless crystals. The compound exists as a mixture of imino and amino tautomers in DMSO, NMR resonances for the imino form is given below. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.75 (s, 3H, CH_3O), 6.94 (s, 1H, $CHPh_2$), 7.19 (m, 4H, Ph), 7.36 (m, 6H, Ph), 7.55 (s, 1H, H-2), 7.62 (s, 1H, H-8), 11.23 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 60.86 ($CHPh_2$), 60.91 (CH_3O), 118.33 (C-5), 127.97 (4× CH, Ph), 128.06 (2× CH, Ph), 128.77 (4× CH, Ph) 137.28 (C-8), 138.84 (2× C, Ph), 140.94 (C-6), 141.35 (C-4), 144.29 (C-2); MS EI *m*/*z* (rel.%) 331 (21, M^+), 301 (15), 167 (100), 165 (28), 152 (15); HRMS $C_{19}H_{17}N_5O$ requires 331.1433, found 331.1430.

5.9. (2′*E*,6′*E*)-6-Methoxyamino-9-methyl-7-(3,7,11-trimethyl-2,6,10-dodecatrienyl)-7*H*-purinium (3f) and (2′*E*,6′*E*)-*N*-methoxy-9-methyl-*N*-(3,7,11-trimethyl-2,6,10-dodecatrienyl)-9*H*-purin-6-amine (4f)

(2*E*,6*E*)-1-Bromo-3,7,11-trimethyl-2-dodecene (630 mg, 2.10 mmol) was added to a solution of purine **2a** (179 mg, 1.00 mmol) in dry DMA (2 mL) and the resulting mixture was stirred at 50 °C under N_2 overnight. The solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel eluting with EtOAc followed by EtOH/EtOAc (1:15) and CH_2Cl_2/MeOH (satd NH_3) (10:1).

Compound **3f**: Yield 205 mg (53%), yellow wax. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.60 (s, 6H, CH_3), 1.70 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 1.97–2.20 (m, 8H), 3.78 (s, 3H, CH_3), 3.83 (s, 3H, CH_3), 5.06 (m, 4H, CH_2N

and 2× CH═), 5.45 (t, J = 6.8 Hz, 1H, CH═), 7.81 (s, 1H, H-2), 8.17 (s, 1H, H-8); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.48 (CH_3), 17.23 (CH_3), 18.08 (CH_3), 26.08 (CH_3), 26.44 (CH_2), 27.07 (CH_2), 31.51 (NCH_3), 39.86 (CH_2), 40.12 (CH_2), 48.11 (NCH_2), 61.92 (OCH_3), 109.98 (C-5), 116.40 (CH═), 123.59 (CH═), 124.44 (CH═), 129.91 (C-8), 131.92 (C═), 136.33 (C═), 145.36 (C-4), 146.05 (C═), 147.56 (C-6), 157.05 (C-2); HRMS (ESI) $C_{22}H_{33}N_5O$ requires 384.2757, found 384.2773.

Compound **4f**: Yield 112 mg (29%), colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.57 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 1.90–2.11 (m, 8H, CH_2), 3.84 (s, 3H, NCH_3), 3.95 (s, 3H, OCH_3), 4.76 (d, J = 6.8 Hz, 2H, NCH_2), 5.07 (m, 2H, CH═), 5.46 (t, J = 6.8 Hz, 1H, CH═), 7.82 (s, 1H, H-8), 8.49 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.36 (CH_3), 16.92 (CH_3), 18.04 (CH_3), 26.06 (CH_3), 26.27 (CH_2), 26.69 (CH_2), 27.08 (CH_2), 30.16 (NCH_3), 40.03 (CH_2), 40.05 (CH_2), 48.65 (NCH_2), 62.92 (OCH_3), 118.84 (CH═), 119.55 (C-5), 124.26 (CH═), 124.72 (CH═), 131.62 (C═), 135.57 (C═), 140.87 (C═), 141.35 (C-8), 152.06 (C-4), 152.64 (C-2), 156.28 (C-6); MS EI m/z (rel.%) 386 (6, M^+), 352 (16), 247 (17), 246 (100), 216 (20), 215 (20), 179 (30), 162 (5), 150 (10), 149 (12); HRMS (EI): $C_{22}H_{33}N_5O$ requires 383.2685, found 383.2686. Anal. Calcd for $C_{22}H_{33}N_5O$: C, 68.90; H, 8.67. Found: C, 68.14; H, 8.40%.

5.10. (2′*E*,6′Z)-6-Methoxyamino-9-methyl-7-(3,7,11-trimethyl-2,6,10-dodecatrienyl)-7*H*-purinium (3g) and (2′*E*,6′Z)-*N*-methoxy-9-methyl-*N*-(3,7,11-trimethyl-2,6,10-dodecatrienyl)-9*H*-purin-6-amine (4g)

(2*E*,6*Z*)-1-Bromo-3,7,11-trimethyl-2-dodecene (570 mg, 2.00 mmol) was added to a solution of purine **2a** (179 mg, 1.00 mmol) in dry DMA (2 mL) and the resulting mixture was stirred at 50 °C under N_2 overnight. The solvent was removed in vacuo and the products were separated by flash chromatography on silica gel eluting with EtOAc followed by EtOAc/EtOH/MeOH (satd NH_3) (200:10:5) and CH_2Cl_2/MeOH/MeOH (satd NH_3) (160:10:5). Compound **3g** was purified further by flash chromatography eluting with CH_2Cl_2/MeOH/MeOH (satd NH_3) (150:10:5) and compound **4g** was purified by flash chromatography eluting with EtOH/EtOAc (1:25).

Compound **3g**: Yield 218 mg (57%), yellow wax. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.59 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 1.9–2.2 (m, 8H, 4× CH_2), 3.76 (s, 3H, NCH_3), 3.83 (s, 3H, OCH_3), 5.05 (m, 4H, CH_2N and 2× CH═), 5.43 (t, J = 7.5 Hz, 1H, CH═), 7.80 (s, 1H, H-2), 7.95 (s, 1H, H-8); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.15 (CH_3), 18.04 (CH_3), 23.83 (CH_3), 26.10 (CH_3), 26.23 (CH_2), 26.91 (CH_2), 31.43 (NCH_3), 32.39 (CH_2), 40.11 (CH_2), 48.09 (CH_2N), 61.87 (OCH_3), 109.88 (C-5), 116.50 (CH═), 124.42 (CH═) 124.45 (CH═), 129.37 (C-8), 132.13 (C═), 136.47 (C═), 145.58 (C-4), 145.70 (C═), 148.21 (C-6), 157.48 (C-2); HRMS (ESI) $C_{22}H_{33}N_5O$+H requires 384.2757, found 384.2771.

Compound **4g**: Yield 111 mg (29%), colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.56 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 1.9–2.2 (m, 8H, 4× CH_2), 3.82 (s, 3H, NCH_3), 3.93 (s, 3H, OCH_3), 4.73 (d, J = 6.8 Hz, 2H, CH_2N), 5.05 (m, 2H, 2× CH═), 5.43 (t, J = 6.8 Hz, 1H, CH═), 7.80 (s, 1H, H-2), 8.47 (s, 1H, H-8); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.86 (CH_3), 18.01 (CH_3), 23.69 (CH_3), 26.07 (CH_3), 26.06 (CH_2), 26.49 (CH_2), 26.94 (CH_2), 30.13 (NCH_3), 32.32 (CH_2), 40.31 (CH_2), 48.67 (CH_2N), 62.92 (OCH_3), 118.92 (CH═), 119.63 (C-5), 124.68 (CH═), 125.07 (CH═), 131.86 (C═), 135.67 (C═), 140.75 (C═), 141.31 (C-2), 152.09 (C-4), 152.69 (C-8), 156.40 (C-6); MS EI m/z (rel.%) 383 (3, M^+), 353 (10), 352 (19), 246 (98), 216 (100), 179 (38), 162 (21), 150 (26), 149 (33); HRMS (ESI) $C_{22}H_{33}N_5O$ requires 383.2685, found 383.2671.

5.11. (2′*E*,6′Z)-6-Benzyloxyamino-9-methyl-7-(3,7,11-trimethyl-2,6,10-dodecatrienyl)-7*H*-purinium (3h) and (2′*E*,6′Z)-*N*-benzyloxy-9-methyl-*N*-(3,7,11-trimethyl-2,6,10-dodecatrienyl)-9*H*-purin-6-amine (4h)

The products were prepared from purine **2b** (393 mg, 1.63 mmol) and (2*E*,6*Z*)-1-bromo-3,7,11-trimethyl-2,6,10-dodecatriene (695 mg, 2.44 mmol; 2*E*/2*Z*-ratio 75:25) as described for compounds **3f** and **4f** above. The products were separated by flash chromatography on silica gel eluting with EtOAc/hexane (4:1) followed by CH_2Cl_2/MeOH (satd NH_3) (12:1). Compound **3f** was further purified by flash chromatography eluting with CH_2Cl_2/MeOH (satd NH_3) (12:1), and compound **4f** by flash chromatography eluting with EtOAc/hexane (4:1).

Compound **3h**: Yield 427 mg (59%), yellow wax, 2*E*/2*Z*-ratio 75:25. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.60 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 1.95–2.22 (m, 8H, CH_2), 3.80 (s, 3H, CH_3), 4.98 (s, 2H, CH_2O), 4.99 (m, 2H, NCH_2), 5.08 (m, 2H, CH═), 5.44 (t, J = 7.0 Hz, 1H, CH═), 7.16 (m, 2H, Ph), 7.28 (m, 3H, Ph), 7.81 (s, 1H, H-2), 9.31 (s, 1H, H-8); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.27 (CH_3), 18.07 (CH_3), 23.84 (CH_3), 26.14 (CH_3), 26.30 (CH_2), 26.95 (CH_2), 31.66 (NCH_3), 32.40 (CH_2), 40.16 (CH_2), 48.00 (CH_2N), 76.22 (OCH_2), 110.23 (C-5), 116.76 (CH═), 124.53 (2× CH═), 127.59 (CH in Ph), 128.25 (2× CH in Ph), 128.80 (2× CH in Ph), 132.05 (C═), 134.28 (C-8), 136.24 (C═), 138.59 (C in Ph), 143.03 (C-6), 143.74 (C-4), 145.61 (C═), 153.60 (C-2); MS EI m/z (rel.%) 459 (10, M^+), 322 (40), 284 (21), 255 (48), 238 (28), 216 (85), 174 (42), 149 (27), 134 (14), 107 (24), 91 (100); HRMS (EI) $C_{28}H_{37}N_5O$ requires 459.2998, found 459.3018.

Compound **4h**: Yield 113 mg (15%), colorless oil, 2*E*/2*Z*-ratio 75:25. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.58 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 1.95–2.15 (m, 8H, CH_2), 3.84 (s, 3H, NCH_3), 4.67 (d, J = 7.0 Hz, 2H, NCH_2), 5.10 (m, 2H, CH═), 5.17 (s, 2H, CH_2O), 5.45 (t, J = 7 Hz, 1H, CH═), 7.32–7.43 (m, 3H, Ph), 7.55–7.60 (m, 2H, Ph), 7.83 (s, 1H, H-8), 8.52 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$,

75 MHz) δ 16.92 (CH_3), 18.01 (CH_3), 23.72 (CH_3), 26.10 (CH_3), 26.54 (CH_2), 26.97 (CH_2), 30.16 (NCH_3), 32.34 (CH_2), 40.37 (CH_2), 49.87 (NCH_2), 77.65 (CH_2O), 118.98 (CH=), 119.97 (C-5), 124.72 (CH=), 125.11 (CH=), 128.11 (2× CH, Ph), 130.11 (2× CH, Ph), 130.19 (CH, Ph), 131.89 (C=), 135.70 (C=), 136.45 (C=), 140.58 (C=), 141.29 (C-8), 152.17 (C-4), 152.70 (C-2), 157.00 (C-6); MS EI *m/z* (rel.%) 459 (16, M^+), 352 (14), 323 (27), 322 (100), 255 (39), 238 (15), 223 (19), 216 (31), 164 (21), 91 (45); HRMS (EI): $C_{28}H_{37}N_5O$ requires 459.2998, found 459.3019.

5.12. (2′*E*,6*E*,10′*E*)-6-Benzyloxyamino-9-methyl-7-(3,7,11,15-tetramethyl-2,6,10,14- hexadecatetraenyl)-7*H*-purinium (3j) and (2′*E*,6′,10′*E*)-*N*-benzyloxy-9-methyl-*N*-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenyl)-9*H*-purin-6-amine (4j)

The products were prepared from purine **2b** (153 mg, 0.60 mmol) and (2*E*,6*E*,10*E*)-1-bromo-3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraene (338 mg, 1.09 mmol) as described for compounds **3f** and **4f** above, and purified by flash chromatography on silica gel eluting with EtOAc/hexane (1:1) followed by EtOAc/MeOH (satd NH_3) (20:1) and CH_2Cl_2/MeOH (satd NH_3) (15:1).

Compound **3j**: Yield 222 mg (70%), yellow wax. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.60 (s, 9H, CH_3), 1.68 (s, 3H, CH_3), 1.95–2.20 (m, 12H, CH_2), 3.61 (s, 3H, CH_3), 4.94 (d, J = 7.3 Hz, 2H, NCH_2), 5.04 (s, 2H, CH_2O), 5.09 (m, 3H, CH=), 5.37 (t, J = 7.2 Hz, 1H, CH=), 7.28 (m, 3H, Ph), 7.43 (d, J = 7.2 Hz, 2H, Ph), 7.81 (s, 1H), 7.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.42 (CH_3), 16.52 (CH_3), 17.13 (CH_3), 18.08 (CH_3), 26.09 (CH_3), 26.51 (CH_2), 27.04 (CH_2), 27.14 (CH_2), 31.22 (NCH_3), 39.84 (CH_2), 40.11 (CH_2), 40.16 (CH_2), 47.92 (NCH_2), 75.95 (CH_2O), 109.94 (C-5), 116.51 (CH=), 123.64 (CH=), 124.32 (CH=), 124.70 (CH=), 127.52 (CH, Ph), 128.31 (2× CH, Ph), 128.91 (2× CH, Ph), 129.10 (C-8), 131.71 (C=), 135.60 (C=), 136.35 (C=), 140.13 (C=), 145.60 (C-4), 145.78 (C=), 148.46 (C-6), 157.70 (C-2); HRMS (ESI) $C_{33}H_{45}N_5O$ requires 528.3696, found 528.3715.

Compound **4j**: Yield 45 mg (14%), colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.57 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 1.90–2.12 (m, 12H, CH_2), 3.85 (s, 3H, NCH_3), 4.67 (d, J = 7.0 Hz, 2H, NCH_2), 5.10 (m, 3H, 3× CH=), 5.45 (t, J = 7.0 Hz, 1H, CH=), 7.35–7.42 (m, 3H, Ph), 7.58 (m, 2H, Ph), 7.83 (s, 1H, H-8), 8.52 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.38 (2× CH_3), 16.98 (CH_3), 18.07 (CH_3), 26.08 (CH_3), 26.77 (CH_2), 27.02 (CH_2), 27.07 (CH_2), 27.16 (CH_2), 30.14 (NCH_3), 40.06 (CH_2), 40.11 (CH_2), 49.84 (NCH_2), 77.65 (CH_2O), 118.91 (CH=), 119.96 (C-5), 124.33 (CH=), 124.62 (CH=), 124.80 (CH=), 128.74 (3× CH, Ph), 130.11 (2× CH, Ph), 131.61 (C=), 135.27 (C=), 135.81 (C=), 136.46 (C, Ph), 140.66 (C=), 141.29 (C-8), 152.17 (C-4), 152.69 (C-2), 156.99 (C-6); MS CI *m/z* (rel.%) 527 (2, M^+), 458 (3), 322 (36), 284 (11), 255 (11), 216 (100), 162 (14), 150 (17), 91 (11); Anal. Calcd for $C_{33}H_{45}N_5O$: C, 75.10; H, 8.59; N, 13.27. Found: C, 75.01; H, 8.60; N, 13.22%.

5.13. (2′*E*,6*E*,10′*E*)-6-*tert*-Butoxyamino-9-methyl-7-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenyl)-7*H*-purinium (3k)

The product was prepared from purine **2c** (73 mg, 0.33 mmol) and (2*E*,6*E*,10*E*)-1-bromo-3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraene (140 mg, 0.40 mmol) as described for compound **3f** above, and purified by flash chromatography on silica gel eluting with CH_2Cl_2/MeOH (satd NH_3) (10:1); yield 113 mg (69%), colorless wax. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26 (s, 9H, *t*-Bu), 1.56 (s, 9H, CH_3), 1.64 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 1.95–2.08 (m, 12H, CH_2), 3.84 (s, 3H, NCH_3), 5.09 (m, 5H, NCH_2 and 3× CH=), 5.52 (t, J = 6.8 Hz, 1H, CH=), 7.80 (s, 1H, H-2), 8.56 (s, 1H, H-8); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.96, 16.03, 16.92, 17.63, 25.64, 26.04, 26.59, 26.69, 27.66 (3× CH_3, *t*-Bu), 31.18 (NCH_3), 39.42, 39.66, 39.68, 47.61 (NCH_2), 77.10 (C, *t*-Bu), 110.67 (C-5), 116.23 (CH=), 123.20 (CH=), 123.91 (CH=), 124.26 (CH=), 130.33 (C-8), 131.24 (C=), 135.1 (C=), 135.88 (C=), 144.20 (C-6), 144.40 (C-4), 145.48 (C=), 155.87 (C-2); HRMS (ESI) $C_{30}H_{47}N_5O$ requires 494.3853, found 494.3849.

5.14. (2′*E*,6*E*,10′*E*)-6-Methoxyamino-9-isopropyl-7-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenyl)-7*H*-purinium (3l)

The product was prepared from purine **2d** (119 mg, 0.60 mmol) and (2*E*,6*E*,10*E*)-1-bromo-3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraene (274 mg, 0.80 mmol) as described for compound **3f** above, and purified by flash chromatography on silica gel eluting with CH_2Cl_2/MeOH (satd NH_3) (17:1). Compound **4l** was also formed but not isolated in pure form.

Compound **3l**: Yield 138 mg (48%), yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.48–1.58 (m, 15H), 1.69–1.73 (m, 7H, *i*-Pr), 1.95–2.04 (m, 12H), 3.73 (s, 3H, OCH_3), 5.01–5.07 (m, 4H), 5.39 (m, 1H), 7.75 (s, 1H, H-8), 8.07 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.37 (2× C), 17.28 (2× C), 18.03, 22.50 (CH_3, *i*-Pr), 26.05, 26.78, 27.01, 39.88, 40.08 (2× C), 48.01 (NCH_2), 61.79 (OCH_3), 110.41 (C-5), 123.30 (2× CH=), 125.15 (2× CH=), 131.61, 135.40 (2× C), 136.30, 145.30 (C-4), 149.03, 157.56 (C-2); HRMS (ESI) $C_{29}H_{45}N_5O$+H requires 480.3696, found 480.3690.

5.15. (2′*E*,6*E*,10′*E*)-9-Allyl-6-methoxyamino-7-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenyl)-7*H*-purinium (3m)

The product was prepared from purine **2e** (200 mg, 0.98 mmol) and (2*E*,6*E*,10*E*)-1-bromo-3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraene (465 mg, 1.40 mmol) as described for compound **3f** above, and purified by flash chromatography on silica gel eluting with CH_2Cl_2/MeOH (satd NH_3) (17:1). Compound **4m** was also formed but not isolated in pure form.

Compound **3m**: Yield 224 mg (48%), yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.52–1.63 (m, 15H), 1.78 (s, 3H, CH_3), 1.98–2.12 (m, 12H), 3.77 (s, 3H, OCH_3), 4.67 (m, 2H, $=CH_2$), 5.01–5.04 (m, 4H, 4× CH=), 5.30 (m, 1H, CH=), 5.93 (m, 1H, CH=), 7.73 (s, 1H, H-8), 7.75 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.87, 16.71, 17.52, 25.55, 26.21, 26.55, 26.99, 39.36, 39.60 (2× C), 46.75 (NCH_2), 61.31 (OCH_3), 109.45 (C-5), 123.82 (2× CH=), 127.79 ($=CH_2$), 130.02 (C-8), 131.13 (C=), 134.99 (2× C=), 136.35 (C=), 145.32 (C-6), 148.21 (C-4), 157.31 (C-2); MS ESI *m*/*z* (rel.%) 478 (16, M+1), 434 (17), 206 (100).

5.16. (2′*E*,6*E*,10′*E*)-9-Cyanoethyl-6-methoxyamino-7-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenyl)-7*H*-purinium (3n) and (2′*E*,6′,10′*E*)-9-cyanoethyl-*N*-methoxy-*N*-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenyl)-9*H*-purin-6-amine (4n)

The products were prepared from purine **2f** (153 mg, 0.70 mmol) and (2*E*,6*E*,10*E*)-1-bromo-3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraene (430 mg, 1.20 mmol) as described for compounds **3f** and **4f** above, and purified by flash chromatography on silica gel eluting with CH_2Cl_2/MeOH (satd NH_3) (12:1). Compound **4n** was purified further by flash chromatography eluting with EtOAc.

Compound **3n**: Yield 140 mg (41%), colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.60 (s, 6H, CH_3), 1.62 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.83 (s, 3H, CH_3), 1.90–2.12 (m, 8H, CH_2), 2.12–2.16 (m, 4H, CH_2), 3.08 (t, J = 6.4 Hz, 2H, CH_2CN), 3.83 (s, 3H, OCH_3), 4.47 (t, J = 6.4 Hz, 2H, NCH_2), 5.10 (m, 5H), 5.49 (t, J = 6.9 Hz, 1H), 7.78 (s, 1H, H-2), 8.42 (s, 1H, H-8); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.41 (CH_3), 16.50 (CH_3), 17.31 (CH_3), 18.08 (CH_3), 18.87 (*C*H_2CN), 26.09 (CH_3), 26.53 (CH_2), 27.06 (CH_2), 27.15 (CH_2), 39.92 (CH_2), 40.11 (CH_2), 40.14 (CH_2), 41.31 (CH_2), 48.55 (CH_2), 62.00 (CH_3O), 110.30 (C-5), 115.68 (CH=), 116.73 (CN), 123.53 (CH=), 124.37 (CH=), 124.71 (CH=), 129.62 (C-8), 131.70 (C=), 135.57 (C=), 136.46 (C=), 145.13 (C-4), 147.12 (C=), 147.59 (C-6), 157.25 (C-2); HRMS (ESI) $C_{29}H_{42}N_6O+H^+$ requires 491.3492, found 491.3513.

Compound **4n**: Yield 86 mg (25%), pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.58 (s, 6H, CH_3), 1.60 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 1.90–2.20 (m, 12H, CH_2), 3.03 (t, J = 6.5 Hz, 2H, CH_2CN), 3.95 (s, 3H, OCH_3), 4.50 (t, J = 6.5 Hz, 2H, NCH_2), 4.75 (d, J = 6.8 Hz, 2H, NCH_2), 5.09 (m, 3H, CH=), 5.45 (t, J = 6.8 Hz, 1H, CH=), 7.93 (s, 1H), 8.45 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.39 (2× CH_3), 16.96 (CH_3), 18.07 (CH_3), 19.24 (CH_2CN), 26.08 (CH_3), 26.74 (CH_2), 27.01 (CH_2), 27.15 (CH_2), 40.06 (2× CH_2), 40.10 (CH_2), 40.21 (NCH_2), 48.44 (NCH_2), 63.02 (OCH_3), 117.02 (CN), 118.57 (CH=), 119.72 (C-5), 124.25 (CH=), 124.59 (CH=), 124.78 (CH=), 131.63 (C=), 135.30 (C=), 135.66 (C=), 140.17 (C-8), 141.18 (C=), 151.33 (C-4), 152.84 (C-2), 156.19 (C-6); MS EI *m*/*z* (rel.%) 490 (2, M^+), 459 (7), 285 (93), 255 (100), 218 (35), 189 (18), 135 (14); HRMS (EI) $C_{29}H_{42}N_6O$ requires 490.3420, found 490.3409.

5.17. (2′*E*,6*E*,10′*E*)-6-Benzyloxyamino-9-cyanoethyl-6-methoxyamino-7-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenyl)-7*H*-purinium (3o) and (2′*E*,6′,10′*E*)-*N*-benzyloxy-9-cyanoethyl-*N*-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenyl)-9*H*-purin-6-amine (4o)

The products were prepared from purine **2g** (630 mg, 1.80 mmol) and (2*E*,6*E*,10*E*)-1-bromo-3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraene (430 mg, 1.20 mmol) as described for compounds **3f** and **4f** above, and purified by flash chromatography on silica gel eluting with CH_2Cl_2/MeOH (satd NH_3) (16:1). Compound **4o** was purified further by flash chromatography eluting with EtOAc/hexane (1:1).

Compound **3o**: Yield 410 mg (61%), yellow wax. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.63 (s, 9H, CH_3), 1.70 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 1.97–2.13 (m, 12H, CH_2), 2.88 (t, J = 6.2 Hz, 2H, CH_2CN), 4.24 (t, J = 6.2 Hz, 2H, NCH_2), 4.99 (d, J = 7.4 Hz, 2H, NCH_2), 5.04 (s, 2H, CH_2O), 5.13 (m, 3H, CH=), 5.46 (t, J = 7.4 Hz, 1H, CH=), 7.20–7.34 (m, 3H, Ph), 7.40–7.44 (m, 2H, Ph), 7.77 (s, 1H, H-2), 8.41 (s, 1H, H-8); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.98 (CH_3), 16.07 (CH_3), 16.76 (CH_3), 17.64 (CH_3), 18.21 (CH_2), 25.65 (CH_3), 26.12 (CH_2), 26.63 (CH_2), 26.70 (CH_2), 39.45 (CH_2), 39.67 (CH_2), 39.70 (CH_2), 40.54 (NCH_2), 47.78 (NCH_2), 75.68 (CH_2O), 109.58 (C-5), 115.44 (CH=), 116.32 (CN), 123.14 (CH=), 123.94 (CH=), 124.27 (CH=), 127.36 (CH, Ph), 128.01 (2× CH, Ph), 128.60 (2× CH, Ph), 129.27 (C-8), 131.26 (C=), 135.12 (C=), 135.95 (C=), 139.31 (C, Ph), 144.63 (C-4), 146.20 (C=), 147.84 (C-6), 157.13 (C-2); HRMS (ESI) $C_{35}H_{46}N_6O$ requires 567.3805, found 567.3824.

Compound **4o**: Yield 12 mg (18%), colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.53 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 1.70 (s, 3H, CH_3), 1.90–2.05 (m, 12H, CH_2), 3.00 (t, J = 6.5 Hz, 2H), 4.46 (t, J = 6.5 Hz, 2H), 4.63 (d, J = 6.9 Hz, 2H, NCH_2), 5.05 (m, 3H, CH=), 5.06 (s, 2H, CH_2O), 5.41 (t, J = 6.5 Hz, 1H, CH=), 7.31–7.38 (m, 3H, Ph), 7.56 (m, 2H, Ph), 7.91 (s, 1H), 8.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.39 (2× CH_3), 17.00 (CH_3), 18.08 (CH_3), 19.27 (*C*H_2CN), 26.09 (CH_3), 26.77 (CH_2), 27.02 (CH_2), 27.16 (CH_2), 40.06 (CH_2), 40.11 (2× CH_2), 40.19 (CH_2), 49.53 (NCH_2), 77.72 (CH_2O), 117.10 (CN), 118.66 (CH=), 120.11 (C-5), 124.29 (CH=), 124.61 (CH=), 124.79 (CH=), 128.30 (2× CH, Ph), 128.88 (CH, Ph), 130.15 (2× CH, Ph), 131.64 (C=), 135.30 (C=), 135.65 (C=), 136.20 (C, Ph), 140.14 (C-8), 140.95 (C=), 151.42 (C-4), 152.88 (C-2), 156.94 (C-6); MS EI *m*/*z* (rel.%) 566 (4, M^+), 391 (9), 361 (28), 323 (12), 294 (15), 255 (100), 201 (19), 91 (23); Anal. Calcd for $C_{35}H_{46}N_6O$: C, 74.17; H, 8.18; N, 14.83. Found: C, 74.10; H, 8.10; N, 14.93%.

5.18. (2′*E*,6*E*,10′*E*)-9-Benzyl-6-methoxyamino-7-(3,7,11,15-tetramethyl-2,6,10,14- hexadecatetraenyl)-7*H*-purinium (3p)

The product was prepared from purine **2h** (128 mg, 0.50 mmol) and (2*E*,6*E*,10*E*)-1-bromo-3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraene (237 mg, 0.70 mmol) as described for compound **3f** above, and purified by flash chromatography on silica gel eluting with CH_2Cl_2/MeOH (satd NH_3) (17:1). Compound **4p** was also formed but not isolated in pure form.

Compound **3p**: Yield 115 mg (44%), yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.47–1.67 (m, 15H), 1.83–1.96 (m, 12H), 3.71 (s, 3H, CH_3), 4.95–5.00 (m, 4H), 5.22 [s, 2H, N(9)CH_2], 5.28–5.32 (m, 1H, CH=), 7.31–7.35 (m, 5H, Ph), 7.73 (1H, H-8), 8.05 (1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.81, 15.83, 16.67 (2× C), 25.48, 26.00, 26.41, 26.53, 39.27, 39.50, 47.61, 61.22 (CH_3), 109.33 (C-5), 123.01 (2× C), 124.13 (2× C), 128.23 (CH, Ph), 128.72 (CH, Ph), 129.07 (CH, Ph), 131.03, 133.76, 134.90, 135.65, 144.92 (C-8), 147.73 (C-4), 156.90 (C-2); HRMS (ESI) $C_{33}H_{45}N_5O$+H^+ requires 528.3696, found 528.3666.

5.19. (2′*E*,6*E*,10′*E*)-9-(Diphenylmethyl)-6-methoxyamino-7-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenyl)-7*H*-purinium (3q) and (2′*E*,6′,10′*E*)-9-(diphenylmethyl)-*N*-methoxy-*N*-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenyl)-9*H*-purin-6-amine (4q)

The products were prepared from purine **2i** (196 mg, 0.90 mmol) and (2*E*,6*E*,10*E*)-1-bromo-3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraene (441 mg, 1.25 mmol) as described for compounds **3f** and **4f** above, and the products were separated by flash chromatography on silica gel eluting with CH_2Cl_2/MeOH (satd NH_3) (12:1). Compound **4q** was purified further by flash chromatography eluting with EtOAc.

Compound **3q**: Yield 221 mg (50%), yellow wax. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.53 (s, 3H, CH_3), 1.55 (s, 6H, CH_3), 1.63 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.89–2.05 (m, 12H, CH_2), 3.80 (s, 3H, CH_3O), 5.02 (m, 3H, CH=), 5.07 (d, J = 7.1 Hz, 2H, NCH_2), 5.33 (t, J = 7.1 Hz, 1H, CH=), 7.03 (s, 1H, C*H*Ph_2), 7.05–7.10 (m, 4H, Ph), 7.30–7.36 (m, 6H, Ph), 7.50 (s, 1H, H-8), 7.78 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.94 (CH_3), 15.95 (CH_3), 16.83 (CH_3), 17.60 (CH_3), 25.61 (CH_3), 26.33 (CH_3), 26.51 (CH_2), 26.66 (CH_2), 39.39 (CH_2), 39.58 (CH_2), 39.63 (CH_2), 47.83 (NCH_2), 61.51 (CH_3O), 62.16 (*C*HPh_2), 110.14 (C-5), 115.80 (CH=), 122.94 (CH=), 123.90 (CH=), 124.24 (CH=), 127.78 (C-8), 127.96 (4× CH, Ph), 129.01 (2× CH, Ph), 129.21 (4× CH, Ph), 131.21 (C=), 135.01 (C=), 135.93 (C=), 136.54 (2× C, Ph), 145.62 (C-4), 145.87 (C=), 147.73 (C-6), 157.32 (C-2); HRMS (ESI) $C_{39}H_{49}N_5O$+H^+ requires 604.4009, found 604.4019.

Compound **4q**: Yield 148 mg (34%), colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.55 (s, 9H, CH_3), 1.67 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 1.90–2.15 (m, 12H, CH_2), 3.93 (s, 3H, OCH_3), 4.72 (d, J = 6.8 Hz, 2H, NCH_2), 5.07 (m, 3H, CH=), 5.44 (dt, J = 6.5 and 1.0 Hz, 1H, CH=), 7.11–7.17 (m, 4H, Ph), 7.15 (s, 1H, *C*HPh_2), 7.28–7.37 (m, 6H, Ph), 7.65 (s, 1H, H-8), 8.44 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.99 (CH_3), 16.00 (CH_3), 16.55 (CH_3), 17.67 (CH_3), 25.68 (CH_2), 26.38 (CH_2), 26.62 (CH_2), 26.75 (CH_2), 39.67 (CH_2), 39.69 (CH_2), 39.70 (CH_2), 48.22 (NCH_2), 61.26 (*C*HPh_2), 62.68 (CH_3O), 118.42 (CH=), 119.39 (C-5), 123.92 (CH=), 124.20 (CH=), 124.39 (CH=), 128.11 (4× CH, Ph), 128.39 (2× CH, Ph), 128.94 (4× CH, Ph), 131.22 (C=), 134.90 (C=), 135.23 (C=), 138.44 (2× C, Ph), 139.95 (C-8), 140.56 (C=), 151.41 (C-4), 152.42 (C-2), 156.23 (C-6); MS EI *m*/*z* (rel.%) 603 (2, M^+), 572 (5), 398 (68), 368 (34), 167 (100), 165 (19); Anal. Calcd for $C_{39}H_{49}N_5O$: C, 77.57; H, 8.18; N, 11.60. Found: C, 77.46; H, 8.23; N, 11.36%.

5.20. (2′*E*,6*E*,10′*E*)-6-Benzyloxyamino-9-(diphenylmethyl)-7-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenyl)-7*H*-purinium (3r) and (2′*E*,6′,10′*E*)-*N*-benzyloxy-9-(diphenylmethyl)-*N*-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenyl)-9*H*-purin-6-amine (4r)

The products were prepared from purine **2j** (338 mg, 0.83 mmol) and (2*E*,6*E*,10*E*)-1-bromo-3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraene (353 mg, 1.00 mmol) as described for compounds **3f** and **4f** above, and purified by flash chromatography on silica gel eluting with EtOAc/hexane (1:4) followed by EtOAc/EtOH (10:1). The isolated bromide of **3r** was dissolved methanol saturated with NH_3 (5 mL) and purified by flash chromatography eluting with CH_2Cl_2/MeOH (satd NH_3) (10:1).

Compound **3r**: Yield 340 mg (60%), yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.58 (s, 3H, CH_3), 1.60 (s, 9H, 3× CH_3), 1.71 (s, 3H, CH_3), 1.90–2.16 (m, 12H, 6× CH_2), 4.98 (d, J = 7.2 Hz, 2H, CH_2N), 5.07–5.12 (m, 5H, CH_2O and 3× CH=), 5.29 (t, J = 7.2 Hz, 1H, CH=), 7.05 (s, 1H, C*H*Ph_2), 7.08–7.11 (m, 4H, Ph), 7.16–7.31 (m, 3H, Ph), 7.36.7.46 (m, 9H, Ph and H-8), 7.84 (s, 1H, H-2); ^{13}C ($CDCl_3$, 75 MHz) δ 15.96 (2× CH_3), 16.77 (CH_3), 17.71 (CH_3), 25.72 (CH_3), 26.44 (CH_2), 26.63 (CH_2), 26.77 (CH_2), 39.42 (CH_2), 39.70 (CH_2), 39.74 (CH_2), 47.80 (CH_2N), 62.01 (*C*HPh_2), 75.49 (CH_2O), 110.23 (C-5), 115.87 (CH=), 123.00 (CH=), 123.93 (CH=), 124.26 (CH=), 126.85 (CH in Ph), 127.26 (C-8), 127.83 (2× CH in Ph), 127.96 (4× CH in Ph), 128.21 (2× CH in Ph), 129.01 (2× CH in Ph), 129.22 (4× CH in Ph), 131.25 (C=), 135.01 (C=), 135.91 (C=), 136.60 (2× C in Ph), 140.00 (C in Ph), 145.67 (C-4), 145.73 (C=), 149.00 (C-6), 157.68 (C-2); HRMS (ESI) $C_{45}H_{53}N_5O$+H^+ requires 680.4322, found 680.4305. Anal. Calcd for $C_{45}H_{53}N_5O$: C, 79.49; H, 7.86; N, 10.30. Found: C, 78.90; H, 7.93; N, 10.79%.

Compound **4r**: Yield 66 mg (12%), colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.63 (s, 9H, 3× CH_3), 1.72 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 1.93–2.20 (m, 12H, 6× CH_2), 4.70 (d, J = 6.9 Hz, 2H, CH_2N), 5.16 (m, 3H, 3× CH=), 5.23 (s, 2H, CH_2 in Bn), 5.51 (t, J = 6.9 Hz, 1H, CH=), 7.19–7.24 (m, 5H), 7.35–50 (m, 9H), 7.59–7.68 (m, 2H) 7.75 (s, 1H), 8.52 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.96 (2× CH_3), 16.56 (CH_3),

17.64 (CH_3), 25.65 (CH_3), 26.36 (CH_2), 26.58 (CH_2), 26.72 (CH_2), 39.67 (3× CH_2), 49.04 (CH_2N), 61.19 ($CHPh_2$), 77.33 (CH_2O), 118.41 (CH=), 119.79 (C-5), 123.91 (CH=), 124.18 (CH=), 124.36 (CH=), 128.11 (4× CH in Ph), 128.30 (2× CH in Ph), 128.33 (3× CH in Ph), 128.89 (4× CH in Ph), 129.72 (2× CH in Ph), 131.16 (C in Ph), 134.83 (C=), 135.17 (C=), 135.89 (C=), 138.47 (2× C in Ph), 139.94 (C-8), 140.32 (C=), 151.49 (C-4), 152.30 (C-2), 156.74 (C-6); HRMS (ESI) $C_{45}H_{53}N_5O$+H requires 680.4322, found 680.4336.

5.21. (*E*)-6-Methoxyamino-9-methyl-7-(3,7,11,15-tetramethyl-2-hexadecenyl)-7*H*-purinium (3t) and (*E*)-*N*-methoxy-9-methyl-*N*-(3,7,11,15-tetramethyl-2-hexadecenyl)-9*H*-purin-6-amine (4t)

Purine **2a** (197 mg, 1.10 mmol) was dissolved in dry DMA and stirred at 50 °C under N_2. A solution of (*E*)-1-bromo-3,7,11,15-tetramethyl-2-hexadecene (610 mg, 1.70 mmol) in diethyl ether (1 mL) was added and the flask was flushed with N_2 to remove the diethyl ether. The resulting mixture was stirred at 50 °C overnight, the solvent was removed in vacuo, and the products were purified by flash chromatography on silica gel eluting with CH_2Cl_2/MeOH (satd NH_3) (15:1). Compound **4t** was purified further by flash chromatography eluting with EtOAc/hexane (1:1).

Compound **3t**: Yield 271 mg (54%), colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.84–0.86 (m, 6H, 2× CH_3), 0.87 (d, J = 6.6 Hz, 6H, 2× CH_3), 1.08–1.50 (m, 18H), 1.53 [sept, J = 6.6 Hz, 1H, C*H*(CH_3)$_2$], 1.80 (s, 3H, CH_3), 2.10 (t, J= 7.7 Hz, 2H, CH_2), 3.78 (s, 3H, NCH_3), 3.85 (s, 3H, OCH_3), 5.08 (d, J = 7.4 Hz, 2H, NCH_2), 5.44 (t, J = 7.4 Hz, 1H, CH=), 7.82 (s, 1H, H-2), 7.84 (s, 1H, H-8); ^{13}C NMR ($CDCl_3$, 125 MHz, double set of signals due to diastereomers are marked 'd') δ 17.17 (CH_3), 20.01 (d, CH_3), 20.06 (d, CH_3), 23.01 (CH_3), 23.10 (CH_3), 24.87 (CH_2), 25.18 (CH_2), 25.53 (CH_2), 28.36 (CH), 31.45 (CH), 31.51 (NCH_3), 33.07 (CH), 33.17 (CH), 37.16 (d, CH_2), 37.25 (d, CH_2), 37.68 (d, CH_2), 37.71 (d, CH_2), 39.75 (CH_2), 40.29 (CH_2), 48.12 (NCH_2), 61.91 (OCH_3), 109.92 (C-5), 116.09 (CH=), 128.93 (C-4), 145.68 (C=), 146.55 (C-8), 148.40 (C-6), 157.66 (C-2); HRMS (ESI) $C_{27}H_{47}N_5O$ requires 458.3853, found 458.3839; Anal. Calcd for $C_{27}H_{47}N_5O$: C, 70.85; H, 10.35; N, 15.30. Found: C, 70.00; H, 10.36; N, 15.20%.

Compound **4t**: Yield 193 mg (38%), colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.76–0.79 (m, 6H, 2× CH_3), 0.82 (d, J = 6.6 Hz, 6H, 2× CH_3), 0.95–1.41 (m, 18H, 9× CH_2), 1.48 [sept, J = 6.6 Hz, 1H, C*H*(CH_3)$_2$], 1.73 (s, 3H, CH_3), 2.00 (m, 2H, CH_2), 3.80 (s, 3H, NCH_3), 3.90 (s, 3H, OCH_3), 4.71 (d, J = 6.8 Hz, 2H, NCH_2), 5.39 (dt, J = 6.8 and 1.1 Hz, 1H, CH=), 7.78 (s, 1H, H-8), 8.44 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 125 MHz, double set of signals due to diastereomers are marked 'd') δ 16.83, 20.10 (d), 20.14 (d), 23.03, 23.85, 25.20 (CH_2), 25.50 (CH), 25.52 (CH_2), 28.35 [*C*H(CH_3)$_2$], 30.14 (NCH_3), 33.06, 33.18, 37.08 (d, CH_2), 37.18 (d, CH_2), 37.68 (d, CH_2), 37.74 (d, CH_2), 39.75 (CH_2), 40.39 (CH_2), 48.69 (NCH_2), 62.90 (OCH_3), 118.62 (CH=), 119.66 (C-5), 141.25 (C=), 141.31 (C-8), 152.11 (C-4), 152.73 (C-2), 156.44 (C-6); MS EI *m*/*z* (rel.%) 457 (4, M^+), 428 (7), 427 (40), 426 (100), 246 (8), 216 (9), 179 (38), 174 (8), 149 (13); Anal. Calcd for $C_{27}H_{47}N_5O$: C, 70.85; H, 10.35; N, 15.30. Found: C, 70.80; H, 10.36; N, 15.20%.

5.22. (*E*)-6-Benzyloxyamino-9-methyl-7-(3,7,11,15-tetramethyl-2-hexadecenyl)-7*H*-purinium (3u) and (*E*)-*N*-benzyloxy-9-methyl-*N*-(3,7,11,15-tetramethyl-2-hexadecenyl)-9*H*-purin-6-amine (4u)

The products were prepared from purine **2b** (117 mg, 0.46 mmol) and (*E*)-1-bromo-3,7,11,15-tetramethyl-2-hexadecene (215 mg, 0.60 mmol) as described for compounds **3t** and **4t** above, and purified by flash chromatography on silica gel eluting with CH_2Cl_2/MeOH (satd NH_3) (15:1). Compound **4u** was purified further by flash chromatography eluting with EtOAc/hexane (1:2).

Compound **3u**: Yield 122 mg (55%), yellow wax. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.84–0.88 (m, 12H, CH_3), 1.00–1.60 (m, 18H, CH_2 and CH), 1.72 (s, 3H, CH_3), 2.00 (t, J = 7.8 Hz, 2H, CH_2), 3.63 (s, 3H, NCH_3), 4.95 (d, J = 7.5 Hz, 2H, NCH_2), 5.04 (s, 2H, CH_2O), 5.37 (t, J = 7.5 Hz, 1H, CH=), 7.17–7.28 (m, 3H, Ph), 7.36–7.42 (m, 2H, Ph), 7.81 (s, 1H, H-2), 7.99 (s, 1H, H-8); ^{13}C NMR ($CDCl_3$, 125 MHz, double set of signals due to diastereomers are marked 'd') δ 16.63, 19.58 (d), 19.62 (d), 22.57, 22.66, 24.44, 24.74, 25.10, 27.91, 30.80 (NCH_3), 32.64, 32.73, 36.80 (d), 37.24 (d), 37.34 (d), 37.38 (d), 39.31, 39.83, 47.48 (NCH_2), 75.52 (CH_2O), 109.43 (C-5), 115.92 (CH=), 127.09 (CH, Ph), 127.86 (2× CH, Ph), 128.48 (2× CH, Ph), 129.04 (C-8), 139.60 (C=), 145.06 (C-4), 145.58 (C, Ph), 147.92 (C-6), 157.10 (C-2); Anal. Calcd for $C_{33}H_{51}N_5O$: C, 74.25; H, 9.36; N, 13.12. Found: C, 74.00; H, 9.56; N, 12.99%.

Compound **4u**: Yield 31 mg (13%), colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.76–0.84 (m, 12H, CH_3), 0.95–1.40 (m, 17H, CH_2 and CH), 1.49 [sept, J = 6.6 Hz, 1H, C*H*(CH_3)$_2$], 1.67 (s, 3H, CH_3), 1.91 (t, J = 7.7 Hz, CH_2), 3.81 (s, 3H, NCH_3), 4.63 (d, J = 6.9 Hz, 2H, NCH_2), 5.13 (s, 2H, CH_2O), 5.39 (m, 1H, CH=), 7.30-7.38 (m, 3H, Ph), 7.53-7.57 (m, 2H, Ph), 7.79 (s, 1H, H-8), 8.48 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 125 MHz, double set of signals due to diastereomers are marked 'd') δ 16.40, 19.58 (d), 19.70 (d), 22.59, 22.68, 24.42 (CH_2), 24.75 (CH_2), 25.09 (CH_2), 27.93, 29.71 (NCH_3), 32.65, 32.72, 36.75 (d, CH_2), 37.25 (d, CH_2), 37.30 (d, CH_2), 37.35 (d, CH_2), 39.33 (CH_2), 40.01 (CH_2), 49.44 (NCH_2), 77.20 (CH_2O), 118.27 (CH=), 119.54 (C-5), 128.31 (3× CH, Ph), 129.67 (2× CH, Ph), 136.04 (C, Ph), 140.59 (C=), 140.85 (C-8), 151.73 (C-4), 152.27 (C-2), 156.58 (C-6); MS EI *m*/*z* (rel.%) 533 (26, M^+), 516 (38), 426 (85), 255 (78), 216 (100), 202 (42), 174 (63), 150 (40), 149 (47), 91 (23); Anal. Calcd for $C_{33}H_{51}N_5O$: C, 74.25; H, 9.63; N, 13.12. Found: C, 74.29; H, 9.64; N, 13.12%.

5.23. 6-Amino-7-benzyl-9-methyl-7*H*-purinium chloride (5a)

Betaine **3c** (107 mg, 0.31 mmol) and zinc (182 mg, 2.79 mmol) were dissolved in methanol (5 mL) and water (1 mL). Concd acetic acid (0.2 mL) was added and the resulting mixture was stirred at 60 °C overnight. The mixture was filtered, the solid washed with methanol (25 mL), and satd aq NaCl (3 mL) was added to the combined filtrates. The resulting mixture was stirred at ambient temperature for 1.5 h and evaporated in vacuo. Satd aq NaCl (5 mL) and water (15 mL) were added to the residue and the mixture was extracted with EtOH/$CHCl_3$ (1:2; 4× 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo, and the product was purified by flash chromatography on a short silica gel column eluting with CH_2Cl_2/MeOH/MeOH (satd NH_3) (6:1:1); yield 74 mg (87%), mp 249–250 °C, colorless crystals. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.90 (s, 3H, CH_3), 6.03 (s, 2H, CH_2), 7.33–7.52 (m, 5H, Ph), 7.97 (br s, 2H, NH_2), 8.43 (s, 1H, H-2), 9.97 (s, 1H, H-8); ^{13}C NMR: (DMSO-d_6, 75 MHz) δ 32.48 (CH_3), 52.20 (CH_2), 109.70 (C-5), 128.71 (2× CH, Ph), 129.56 (CH, Ph), 129.80 (2× CH, Ph), 134.89 (C, Ph), 143.26 (C-8), 150.00 (C-4), 152.93 (C-6), 156.41 (C-2); MS CI *m*/*z* (rel.%) 240 (20, M^+), 178 (8), 164 (8), 151 (10), 150 (100), 149 (78), 122 (10), 105 (7); HRMS (ESI) $C_{13}H_{14}N_5^+$ requires 240.1243, found 240.1232.

5.24. (2′*E*,6′*E*)-6-Amino-9-methyl-7-(3,7,11-trimethyl-2,6,10-dodecatrienyl)-7*H*-purinium chloride (5b)

The product was prepared from betaine **3f** (115 mg, 0.30 mmol) essentially as described for the synthesis of compound **5a** above, and the product was purified by flash chromatography on silica gel eluting with MeOH/CH_2Cl_2 (1:5), yield 94 mg (80%), colorless wax. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.54 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 1.88–2.22 (m, 8H, CH_2), 3.89 (s, 3H, NCH_3), 5.05 (m, 2H, CH=), 5.23 (d, J = 7.0 Hz, 2H, NCH_2), 5.44 (t, J = 7.0 Hz, 1H, CH), 8.00 (br s, 2H, NH_2), 8.43 (s, 1H), 9.74 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 16.70 (CH_3), 17.57 (CH_3), 18.42 (CH_3), 26.35 (CH_3), 26.45 (CH_2), 27.03 (CH_2), 32.24 (NCH_3), 39.84 (CH_2), 40.02 (CH_2), 47.84 (NCH_2), 110.07 (C-5), 116.15 (CH=), 124.28 (CH=), 124.90 (CH=), 131.55 (C=), 135.78 (C=), 141.74 (C-8), 146.17 (C=), 149.82 (C-4), 153.22 (C-6), 156.28 (C-2); HRMS (ESI) $C_{21}H_{32}N_5^+$ requires 354.2652, found 354.2635.

5.25. (2′*E*,6′*Z*)-6-Amino-9-methyl-7-(3,7,11-trimethyl-2,6,10-dodecatrienyl)-7*H*-purinium chloride (5c)

The product was prepared from betaine **3h** (194 mg, 0.42 mmol) essentially as described for the synthesis of compound **5a** above, and the product was purified by flash chromatography on silica gel eluting with MeOH/CH_2Cl_2 (1:4), yield 122 mg (74%), colorless wax. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.57 (3H, CH_3), 1.62 (6H, 2× CH_3), 1.79 (3H, CH_3), 1.91–2.23 (m, 8H, 4× CH_2), 3.90 (s, 3H, NCH_3), 5.08 (m, 2H, 2× CH), 5.25 (d, J = 6.9 Hz, 2H, CH_2N), 5.45 (t, J = 6.9 Hz, 1H, CH=), 8.00 (br s, 2H, NH_2), 8.45 (s, 1H, H-2), 9.79 (br s, 1H, H-8); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 17.50 (CH_3), 18.33 (CH_3), 23.97 (CH_3), 26.28 (CH_2), 26.37 (CH_3), 26.87 (CH_2), 32.26 (CH_2), 32.34 (NCH_3), 40.15 (CH_2), 47.83 (CH_2N), 110.02 (C-5), 116.35 (CH=), 124.90 (CH=), 125.22 (CH=), 131.81 (C=), 135.80 (C=), 141.81 (C-8), 145.99 (C=), 149.83 (C-4), 153.22 (C-6), 156.27 (C-2); HRMS (ESI) $C_{21}H_{32}N_5^+$ requires 354.2652, found 354.2651.

5.26. (*E*)-6-Methoxyamino-9-methyl-7-(3,7,11,15-tetramethyl-2-hexadecenyl)-7*H*-purinium (5e)

The product was prepared from betaine **3t** (225 mg, 0.56 mmol) essentially as described for the synthesis of compound **5a** above, except that the reaction temperature was 70 °C, and the product was purified by flash chromatography on silica gel eluting with MeOH/CH_2Cl_2 (1:7), yield 175 mg (69%), mp 172–174 °C, colorless crystals. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.79–1.03 (m, 12 H, CH_3), 1.06–1.23 (m, 21H), 1.77 (s, 3H, CH_3), 2.04 (t, J = 7.2 Hz, CH_2), 3.88 (s, 3H, CH_3), 5.24 (d, J = 7.0 Hz, NCH_2), 5.43 (t, J = 7.0 Hz, CH=), 7.99 (br s, 2H, NH_2), 8.43 (s, 1H), 9.76 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz, double set of signals due to diastereomers are marked 'd') δ 16.55, 19.43 (d), 19.49 (d), 22.42, 22.51, 23.76 (CH_2), 24.10 (CH_2), 24.36 (CH_2), 27.33, 31.34 (NCH_3), 31.98, 32.01, 36.11 (d), 36.58 (d), 36.68 (d), 36.69 (d), 38.73 (CH_2), 39.21 (CH_2), 46.97 (NCH_2), 109.15 (C-5), 115.18 (CH=), 140.94 (C-8), 145.47 (C=), 148.93 (C-4), 152.33 (C-6), 155.36 (C-2); HRMS (ESI) $C_{26}H_{46}N_5^+$ requires 428.3747, found 428.3758.

5.27. (2′*E*,6*E*,10′*E*)-6-Methoxyamino-7-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenyl)-7*H*-purine (6a)

A mixture of betaine **3n** (160 mg, 0.33 mmol) and K_2CO_3 (320 mg, 2.30 mmol) in MeOH (15 mL) was stirred vigorously for 2 h at ambient temperature. The mixture was filtered, the solid was washed with MeOH (10 mL), and the combined filtrates were evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with MeOH/CH_2Cl_2 (1:11); yield 135 mg (95%), mp 111–112 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.60 (s, 9H, CH_3), 1.68 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 1.95–2.20 (m, 12H, CH_2), 3.86 (s, 3H, OCH_3), 4.89 (d, J = 7.2 Hz, 2H, NCH_2), 5.10 (m, 3H), 5.43 (dt, J = 7.2 and 1.0 Hz, 1H, CH=), 7.59 (s, 1H, H-8), 7.68 (s, 1H, H-2), 9.29 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.39 (CH_3), 16.44 (CH_3), 17.02 (CH_3), 18.07 (CH_3), 26.08 (CH_3), 26.62 (CH_2), 26.98 (CH_2), 27.15 (CH_2), 39.89 (CH_2), 40.05 (CH_2), 40.11 (CH_2), 45.65 (NCH_2), 62.13 (OCH_3), 110.70 (C-5), 118.57 (CH=), 123.80 (CH=), 124.52 (CH=), 124.77 (CH=), 131.65 (C=), 135.38 (C=), 136.15 (C=), 139.80 (C-8), 140.72 (C-6), 142.17 (C-2), 142.71 (C=), 150.43 (C-4); MS EI *m*/*z* (rel.%) 437 (28, M^+), 407 (18), 368 (15), 338 (10), 203 (33), 166 (100), 165 (66), 136 (62), 135 (68); HRMS (EI) $C_{26}H_{39}N_5O$ requires 437.3154, found 437.3140; Anal. Calcd for $C_{26}H_{39}N_5O$: C, 71.36.; H, 8.98. Found: C, 71.31; H, 8.98.

5.28. (2′*E*,6*E*,10′*E*)-6-Benzyloxyamino-7-(3,7,11,15-tetramethyl-2,6,10,14- hexadecatetraenyl)-7*H*-purine (6b)

The product was prepared from betaine **3o** (350 mg, 0.62 mmol) essentially as described for the synthesis of compound **5a** above, except that the reaction mixture was stirred overnight, and the product was purified by flash chromatography on silica gel eluting with EtOH/CH_2Cl_2 (1:19), yield 302 mg (95%), colorless wax. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.54 (s, 9H, CH_3), 1.62 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.91–2.10 (m, 12H, CH_2), 4.76 (d, J = 7.0 Hz, 2H, NCH_2), 4.99 (s, 2H, CH_2O), 5.05 (m, 3H, CH=), 5.28 (t, J = 7.0 Hz, 1H, CH=), 7.21–7.36 (m, 6H, Ph and H-8), 7.80 (s, 1H, H-2), 10.11 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.93 (CH_3), 15.98 (CH_3), 16.53 (CH_3), 17.60 (CH_3), 25.61 (CH_3), 26.20 (CH_2), 26.53 (CH_2), 26.68 (CH_2), 39.39 (CH_2), 39.59, 39.63 (CH_2), 45.12 (NCH_2), 76.03 (CH_2O), 110.08 (C-5), 118.40 (CH=), 123.40 (CH=), 124.06 (CH=), 124.31 (CH=), 127.90 (CH, Ph), 128.28 (2× CH, Ph), 128.58 (2× CH, Ph), 131.15 (C=), 134.90 (C=), 135.59 (C=), 137.69 (C, Ph), 139.27 (C-8), 140.54 (C-6), 141.76 (C=), 142.59 (C-2), 150.09 (C-4); MS EI *m*/*z* (rel.%) 513 (38, M^+), 445 (14), 407 (30), 242 (90), 203 (47), 136 (88), 135 (53), 91 (65), 69 (100); Anal. Calcd for $C_{32}H_{43}N_5O$: C, 74.82; H, 8.44; N, 13.63. Found: C, 74.88; H, 8.45; N, 13.54%.

5.29. (2′*E*,6*E*,10′*E*)-6-Amino-7-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenyl)-7*H*-purine (7)

Method A: Compound **6b** (250 mg, 0.47 mmol) and zinc (330 mg, 2.79 mmol) were dissolved in methanol (20 mL) and water (2 mL). Concd acetic acid (0.5 mL) was added and the resulting mixture was stirred at 75 °C overnight. The mixture was filtered, the filtrate was evaporated in vacuo, and the product was purified by flash chromatography on silica gel eluting with CH_2Cl_2/EtOH (7:1); yield 95 mg (50%), mp 117.0–117.5 °C, colorless crystals. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.56 (s, 9H, CH_3), 1.64 (s, 3H, CH_3), 1.81 (s, 3H, CH_3), 1.87–2.08 (m, 8H, CH_2), 2.13 (m, 4H), 4.88 (d, 2H, J = 6.0 Hz, NCH_2), 5.05 (m, 3H, CH=), 5.30 (br s, 2H, NH_2), 5.41 (dt, J = 6.0 and 0.75 Hz, 1H, CH=), 7.92 (s, 1H, H-8), 8.45 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.98 (CH_3), 16.05 (CH_3), 16.85 (CH_3), 17.65 (CH_3), 25.66 (CH_3), 26.01 (CH_2), 26.51 (CH_2), 26.72 (CH_2), 39.32 (CH_2), 39.64 (CH_2), 39.68 (CH_2), 45.69 (NCH_2), 112.10 (C-5), 119.20 (CH=), 122.79 (CH=), 123.79 (CH=), 124.29 (CH=), 131.28 (C=), 135.13 (C=), 136.37 (C=), 143.19 (C=), 145.04 (C-8), 150.81 (C-6), 153.17 (C-4), 161.19 (C-2); MS EI *m*/*z* (rel.%) 407 (51, M^+), 338 (20), 284 (10), 271 (16), 203 (77), 136 (100), 135 (86), 93 (31); Anal. Calcd for $C_{25}H_{37}N_5$: C, 73.67; H, 9.15; N, 17.18. Found: C, 73.62; H, 9.14; N, 17.03%.

Method B: Compound **9b** (180 mg, 0.42 mmol) and *t*-BuOH (40 mL) saturated with NH_3 (g) were stirred at 100 °C in a sealed container for 48 h. The mixture was evaporated in vacuo and the residue purified by flash chromatography on silica gel eluting with CH_2Cl_2/EtOH (7:1); yield 106 mg (62%), colorless crystals. Data see above.

5.30. (2′*E*,6*E*,10′*E*)-6-Chloro-9-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenyl)-9*H*-purine (9a) and (2′*E*,6*E*,10′*E*)-6-chloro-7-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenyl)-7*H*-purine (9b)

Method A: A mixture of 6-chloropurine **8** (53 mg, 0.34 mmol), (2*E*,6*E*,10*E*)-1-bromo-3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraene (242 mg, 0.68 mmol, crude, purity 92%), and potassium carbonate (140 mg, 1.02 mmol) in dry DMF (2 mL) was stirred under N_2 for 20 h, before the mixture was filtered and evaporated in vacuo. The products were separated by flash chromatography on silica gel eluting with EtOAc/hexane (2:3).

Compound **9a**: Yield 82 mg (57%), colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.54 (s, 6H, CH_3), 1.62 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 1.90–2.11 (m, 12H, CH_2), 2.07 (s, 3H, CH_3), 4.82 (d, J = 7.0 Hz, 2H, NCH_2), 5.05 (m, 3H, CH=), 5.40 (t, J = 6.9 Hz, 1H, CH=), 8.06 (s, 1H, H-8), 8.69 (s, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.40, 16.45, 17.03, 18.08, 26.09, 26.45, 26.93, 27.13, 39.83, 40.04, 40.10, 42.17, 116.96 (CH=), 123.57 (CH=), 124.40 (CH=), 124.73 (CH=), 131.65 (C=), 132.04 (C-5), 135.43 (C=), 136.34 (C=), 144.35 (C=), 145.11 (C-8), 151.25 (C-4), 152.09 (C-6), 152.24 (C-2); MS EI *m*/*z* (rel.%) 428/426 (12/33, M^+), 392 (24), 391 (84), 222 (25), 157 (32), 155 (100), 136 (6), 135 (19), 93 (20); HRMS (EI) $C_{25}H_{35}ClN_4$ requires 426.2550, found 426.2536.

Compound **9b**: Yield 37 mg (27%), mp 50–53 °C, colorless solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.55 (s, 9H, CH_3), 1.63 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 1.90–2.10 (m, 12H, CH_2), 5.04 (m, 5H, CH_2 and CH=), 5.42 (t, J = 7.3 Hz, 1H, CH=), 8.20 (s, 1H, H-8), 8.83 (s, 1H, H-2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.40, 16.47, 17.19, 18.07, 26.09, 26.45, 26.92, 27.13, 39.81, 40.02, 40.10, 45.64, 117.41 (CH=), 122.93 (C-5), 123.49 (CH=), 124.39 (CH=), 124.74 (CH=), 131.66 (C=), 135.44 (C=), 136.48 (C=), 143.50 (C-4), 144.42 (C=), 148.71 (C-8), 152.71 (C-2), 162.52 (C-6); MS EI *m*/*z* (rel.%) 428/426 (5/14, M^+), 222 (13), 157 (31), 155 (98), 135 (43), 121 (24), 107 (27), 93 (57); HRMS (EI) $C_{25}H_{35}ClN_4$ requires 426.2550, found 426.2569; Anal. Calcd for $C_{25}H_{35}ClN_4$: C, 70.32; H, 8.26. Found: C, 70.61; H, 8.01%.

Method B: A mixture of 6-chloropurine **8** (182 mg, 1.18 mmol) and methylaquacobaloxime (419 mg, 1.30 mmol) in dry DMA (20 mL) was stirred at ambient temperature under N_2 for 5 min before K_2CO_3 (195 mg, 1.30 mmol) was added. The resulting mixture was stirred for 20 min in the dark before (2*E*,6*E*,10*E*)-1-bromo-3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraene (500 mg, 1.42 mmol) in DMA (2 mL) was added. The reaction mixture was stirred in the dark for 43 h and evaporated in vacuo. The residue was dissolved in $CHCl_3$ (200 mL) and washed with 2 M NaOH

(100 mL), brine (100 mL), and 1 M HCl (100 mL), dried ($MgSO_4$), and evaporated in vacuo. The product was isolated by flash chromatography on silica gel eluting with EtOAc/hexane (2:1); yield 203 mg (40%) of compound **9b**, data see above. Compound **9a** was not formed.

5.31. 1-Benzyl-3-methylimidazolium bromide (11a)

A mixture of 1-methylimidazole **10a** (164 mg, 2.00 mmol) and benzyl bromide (0.48 mL, 4.00 mmol) in dry DMA (5 mL) was stirred at 50 °C under N_2 overnight and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with MeOH/CH_2Cl_2 (1:6); yield 465 mg (92%), colorless wax. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.08 (s, 3H, CH_3), 5.45 (s, 2H, CH_2), 7.40–7.46 (m, 5H, Ph), 7.74 (s, 1H), 7.93 (s, 1H), 9.32 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 36.77 (NCH_3), 52.64 (CH_2), 123.19 (CH, Ar), 124.84 (CH, Ar), 129.19 (2× CH, Ph), 129.58 (CH, Ph), 129.83 (2× CH, Ph), 135.79 (C, Ph), 137.52 (C-2); HRMS (ESI) $C_{11}H_{13}N_2^+$ requires 173.1073, found 173.1081.

5.32. 1-Benzyl-3-methylbenzimidazolium bromide (11b)

The product was prepared from 1-methylbenzimidazole **10b** (132 mg, 1.00 mmol) and benzyl bromide (0.24 mL, 2.00 mmol) as described for the synthesis of compound **11a** above. The product was purified by flash chromatography on silica gel eluting with MeOH/CH_2Cl_2 (1:8); yield 291 mg (96%), colorless wax. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.09 (s, 3H, CH_3), 5.80 (s, 2H, CH_2), 7.27–7.41 (3H, Ar), 7.51–7.54 (2H, Ar), 7.64–7.70 (m, 2H, Ar), 7.94–8.05 (m, 2H, Ar), 9.92 (s, 1H, H-2); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 34.28 (NCH_3), 50.59 (CH_2), 114.55 (Ar), 114.63 (CH, Ar), 127.42 (CH, Ar), 127.48 (CH, Ar), 129.14 (2× CH, Ph), 129.56 (CH, Ph), 129.91 (2× CH, Ph), 131.55 (C, Ar), 132.91 (C, Ar), 134.94 (C, Ph), 143.81 (C-2); MS (ESI) *m*/*z* 223 (100, M^+-Br^-).

5.33. (2′*E*,6*E*,10′*E*)-3-Methyl-1-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenyl)imidazolium bromide (11c)

The product was prepared from 1-methylimidazole **10a** (53 mg, 0.65 mmol) and (2*E*,6*E*,10*E*)-1-bromo-3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraene (410 mg, 1.16 mmol) as described for the synthesis of compound **11a** above. The product was purified by flash chromatography on silica gel eluting with MeOH/CH_2Cl_2 (1:9); yield 219 mg (78%), pale yellow wax. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.57 (s, 9H, CH_3), 1.65 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 1.90 (m, 12H, CH_2), 4.11 (s, 3H, CH_3), 4.92 (d, J = 7.5 Hz, 2H, NCH_2), 5.05 (m, 3H, CH=), 5.38 (t, J = 7.5 Hz, 1H, CH=), 7.25 (m, 1H), 7.54 (m, 1H), 10.34 (br s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.91 (CH_3), 16.00 (CH_3), 16.82 (CH_3), 17.58 (CH_3), 25.59 (CH_3), 25.97 (CH_2), 26.50 (CH_2), 26.63 (CH_2), 36.71 (NCH_3), 39.35 (CH_2), 39.59 (2× CH_2), 47.32 (NCH_2), 115.06 (CH=), 121.03 (C-5), 122.98 (CH=), 123.47 (C-4), 123.89 (CH=), 124.22 (CH=), 131.17 (C=), 134.98 (C=), 135.92 (C=), 137.22 (C-2), 146.47 (C=); MS (ESI) *m*/*z* 355 (M^+-Br).

5.34. (2′*E*,6*E*,10′*E*)-3-Methyl-1-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenyl)benzimidazolium bromide (11d)

The product was prepared from 1-methylbenzimidazole **10b** (86 mg, 0.65 mmol) and (2*E*,6*E*,10*E*)-1-bromo-3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraene (410 mg, 1.16 mmol) as described for the synthesis of compound **11a** above. The product was purified by flash chromatography on silica gel eluting with MeOH/CH_2Cl_2 (1:10); yield 283 mg (90%), colorless wax. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.55 (s, 6H, CH_3), 1.58 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.90–2.12 (m, 12H, CH_2), 1.94 (s, 3H, CH_3), 4.31 (s, 3H, NCH_3), 5.07 (m, 3H, CH=), 5.21 (d, J = 7.0 Hz, 2H, NCH_2), 5.41 (t, J = 7.0 Hz, 1H, CH=), 7.62–7.68 (m, 3H, Ar), 7.74 (m, 1H, Ar), 11.38 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.90 (CH_3), 15.99 (CH_3), 17.05 (CH_3), 17.59 (CH_3), 25.60 (CH_3), 25.90 (CH_2), 26.49 (CH_2), 26.64 (CH_2), 33.70 (NCH_3), 39.33 (CH_2), 39.55 (CH_2), 39.61 (CH_2), 45.87 (NCH_2), 112.80 (CH, Ar), 113.24 (CH, Ar), 115.20 (CH=), 122.99 (CH=), 123.95 (CH=), 124.23 (CH=), 127.01 (CH, Ar), 127.12 (CH, Ar), 130.92 (C=), 131.18 (C=), 132.21 (C-3a), 134.92 (C=), 135.81 (C=), 142.91 (C-2), 145.19 (C-7a); HRMS (ESI) $C_{28}H_{41}N_2$ requires 405.3264, found 405.3268.

5.35. 6-Amino-1-benzyl-9-methyl-1*H*-purinium bromide (13a)

A mixture of 9-methyladenine **12** (149 mg, 1.00 mmol) and benzyl bromide (0.18 mL, 1.5 mmol) in DMA (5 mL) was stirred overnight at 50 °C. The mixture was evaporated in vacuo and the residue purified by flash chromatography on silica gel using CH_2Cl_2/MeOH (6:1); yield 79 mg (25%), mp 250–254 °C, colorless solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.84 (s, 3H, CH_3), 5.63 (s, 2H, CH_2), 7.27–7.42 (m, 5H, Ph), 8.50 (s, 1H), 8.91 (s, 1H), 9.51 (br s, 2H, NH_2). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 30.19 (CH_3), 51.73 (CH_2), 118.77 (C-5), 127.00 (2× CH in Ph), 128.25 (CH in Ph), 128.82 (2× CH in Ph), 133.90 (C in Ph), 145.17 (C-8), 147.15 (C-4), 147.59 (C-2), 150.06 (C-6); HRMS (ESI): $C_{13}H_{14}N_5^+$ requires 240.1243, found 240.1240.

5.36. (2′*E*,6*E*,10′*E*)-6-Amino-9-methyl-1-(3,7,11,15-tetramethyl-2,6,10,14- hexadecatetraenyl)-1*H*-purinium bromide (13b)

A mixture of 9-methyladenine **12** (134 mg, 0.90 mmol) and (2*E*,6*E*,10*E*)-1-bromo-3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraene (576 mg, 1.63 mmol) in DMA (8 mL) was stirred under N_2 at 50 °C overnight. The mixture was evaporated in vacuo and the residue purified by flash chromatography on silica gel eluting with MeOH/CH_2Cl_2 (1:7); yield 147 mg (33%), colorless wax. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.58 (s, 6H, CH_3), 1.60 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 1.89 (s, 3H, CH_3), 1.95–2.22 (m, 12H, CH_2), 3.90 (s, 3H,

NCH_3), 5.09 (m, 3H, CH=), 5.28 (d, J = 7.4 Hz, 2H, NCH_2), 5.57 (t, J = 5.7 Hz, 1H, CH=), 8.30 (s, 1H, H-8), 9.45 (s, 1H, H-2), 10.64 (br s, 1H, NH), 10.76 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.96 (CH_3), 16.09 (CH_3), 17.29 (CH_3), 17.63 (CH_3), 25.63 (CH_3), 26.04 (CH_2), 26.53 (CH_2), 26.70 (CH_2), 30.66 (NCH_3), 39.58 (2× CH_2), 39.66 (CH_2), 50.11 (NCH_2), 114.04 (CH=), 118.17 (C=), 123.06 (CH=), 124.00 (CH=), 124.26 (CH=), 131.23 (C=), 134.99 (C=), 136.15 (C=), 144.96 (C-2), 147.11 (C-4 and C-8), 148.05 (C=), 150.03 (C-6); HRMS (ESI) $C_{26}H_{40}N_5$ requires 422.3278, found 422.3266.

5.37. 3-Methyl-3*H*-adenine (14)

A mixture of adenine (4.00 g, 29.6 mmol), methyl-*p*-toluenesulfonate (13 mL), and DMA (25 mL) was stirred at 100 °C for 2 h. The mixture was evaporated in vacuo and the resulting syrup was subjected to flash chromatography on silica gel eluting with CH_2Cl_2 followed by CH_2Cl_2/MeOH (6:1). The fractions containing a compound with $R_f < 0.20$ (TLC: SiO_2, eluent CH_2Cl_2/MeOH 6:1) were combined and evaporated in vacuo. The residue was recrystallized twice from EtOH to give approximately 3.7 g of the tosylate salt of 3-methyladenine. The salt was recrystallized from aq NH_3 to give the desired product; yield 1.08 g (24%), mp 282–290 °C (dec) (lit.[31] 310–313 °C) colorless solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.91 (s, 3H, CH_3), 7.79 (s, 1H), 7.85 (br s, 2H, NH_2), 8.31 (s, 1H); MS CI m/z (rel.%) 149 (100, M^+), 121 (29), 94 (19).

5.38. 7-Benzyl-3-methyl-3*H*-purine-6(7*H*)-imine (15a)

A mixture of 3-methyladenine **14** (75 mg, 0.50 mmol) and benzyl bromide (0.71 mL, 0.60 mmol) in DMA (3 mL) was stirred at 50 °C under N_2 for 4 h, and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with MeOH (satd NH_3)/CH_2Cl_2 (1:7); yield 72 mg (60%), mp 159–161 °C, colorless crystals. ^{1}H NMR (CD_3OD, 300 MHz) δ 3.70 (s, 3H, CH_3), 5.69 (s, 2H, CH_2), 7.26–7.56 (m, 5H, Ph), 7.81 (s, 1H, H-2), 8.00 (s, 1H, H-8); ^{13}C NMR (CD_3OD, 75 MHz) δ 33.89 (CH_3), 49.85 (CH_2), 112.70 (C-5), 127.83 (2× CH, Ph), 128.23 (CH, Ph), 128.91 (2× CH, Ph), 137.14 (C, Ph), 141.67 (C-8), 145.27 (C-5), 146.77 (C-2), 156.76 (C-6); MS EI m/z (rel.%) 239 (93, M^+), 238 (100), 224 (10), 162 (47), 91 (31); Anal. Calcd for $C_{13}H_{13}N_5$: C, 65.25; H, 5.48; N, 29.27. Found C, 65.12; H, 5.83; N, 29.03%.

5.39. (2′*E*,6*E*,10′*E*)-3-Methyl-7-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenyl)-3*H*-purine-6(7*H*)-imine (15b)

The compound was prepared from 3-methyladenine **14** (100 mg, 0.67 mmol) and (2*E*,6*E*,10*E*)-1-bromo-3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraene (330 mg, 0.93 mmol) as described for the synthesis of compound **15a** above. The product was purified by flash chromatography on silica gel eluting with MeOH/EtOAc (1:4) followed by MeOH (satd NH_3)/CH_2Cl_2 (1:7); yield 153 mg (54%), yellow wax. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.59 (s, 9H, CH_3), 1.67 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 1.92–2.21 (m, 12H, CH_2), 3.72 (s, 3H, NCH_3), 5.09 (m, 3H, CH=), 5.19 (d, J = 7.2 Hz, NCH_2), 5.49 (t, J = 7.2 Hz, 1H, CH=), 7.62 (s, 1H, H-8), 7.74 (s, 1H, H-2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.41 (CH_3), 16.46 (CH_3), 17.08 (CH_3), 18.08 (CH_3), 26.10 (CH_3), 26.56 (CH_2), 26.97 (CH_2), 27.14 (CH_2), 34.92 (NCH_3), 39.88 (CH_2), 40.07 (CH_2), 40.11 (CH_2), 45.48 (NCH_2), 113.22 (C-5), 117.93 (CH=), 123.82 (CH=), 124.50 (CH=), 124.75 (CH=), 131.68 (C=), 135.40 (C=), 136.19 (C=), 139.87 (C-8), 143.80 (C=), 145.43 (C-4), 145.66 (C-2), 156.28 (C-6); MS EI m/z (rel.%) 421 (7, M^+), 352 (13), 285 (5), 284 (27), 217 (22), 216 (100), 150 (19); Anal. Calcd for $C_{26}H_{39}N_5$: C, 74.07; H, 9.32; N, 16.61. Found: C, 73.85; H, 9.20; N, 16.20%.

5.40. (2′*E*,6*E*,10′*E*)-3,N^6-Dimethyl-7-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenyl)-3*H*-purine-6(7*H*)-imine (16)

A mixture of compound **15b** (93 mg, 0.20 mmol) and iodomethane (0.125 mL, 2.00 mmol) in DMA (2 mL) was stirred in a sealed flask at ambient temperature for 5 h. The mixture was evaporated in vacuo and the residue was dissolved in 10% aq NaOH (5 mL) and extracted with CH_2Cl_2 (5× 5 mL). The combined organic extracts were evaporated and the product was isolated by flash chromatography on silica gel eluting with MeOH/CH_2Cl_2 (1:12); yield 33 mg (38%), pale yellow wax. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.59 (s, 9H, CH_3), 1.67 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 1.95–2.12 (m, 12H, CH_2), 3.25 (s, 3H, NCH_3), 3.77 (s, 3H, NCH_3), 5.08 (m, 3H, CH=), 5.29 (d, J = 7.0 Hz, 2H, NCH_2), 5.42 (t, J = 7.0 Hz, 1H, CH=) 7.62 (s, 1H, H-2), 7.88 (br s, 1H, H-8); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.94 (CH_3), 16.00 (CH_3), 16.65 (CH_3), 17.61 (CH_3), 25.62 (CH_3), 26.09 (CH_2), 26.52 (CH_2), 26.69 (CH_2), 32.82 (NCH_3), 34.64 (NCH_3), 39.44 (CH_2), 39.61 (CH_2), 39.65 (CH_2), 45.58 (CH_2N), 113.21 (C-5), 117.30 (CH=), 123.39 (CH=), 124.04 (CH=), 124.29 (CH=), 131.19 (C=), 134.94 (C=), 135.72 (C=), 138.58 (br s, C-8), 143.74 (br s, C-4), 144.63 (C=), 145.61 (C-2), 150.89 (C-6); HRMS (ESI) $C_{27}H_{41}N_5$+H requires 436.3434, found 436.3427.

5.41. (2′*E*,6*E*,10′*E*)-2,3-Dihydro-3-methyl-7-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenyl)-3*H*-purine-6(7*H*)-imine (17)

Compound **15b** (256 mg, 0.61 mmol) was dissolved in 70% aq MeOH (10 mL), $NaBH_4$ (92 mg, 2.4 mmol) was added in small portions, and the resulting mixture was stirred at ambient temperature for 2.5 h. The mixture was evaporated in vacuo and the residue transferred to a separatory funnel using CH_2Cl_2 (50 mL) and satd aq K_2CO_3 (30 mL). The layers were separated and the aq phase was extracted with CH_2Cl_2 (5× 25 mL). The organic phases were combined, dried (K_2CO_3), and evaporated in vacuo. The product was purified by flash chromatography on silica gel eluting with MeOH/CH_2Cl_2 (1:6); yield 143 mg (56%), pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.60 (s, 9H, CH_3), 1.71 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 1.92–2.15 (m, 12H), 2.88

(s, 3H, NCH_3), 4.30 (s, 2H, CH_2), 4.60 (br s, 1H, NH), 4.73 (d, $J = 6.5$ Hz, 2H, NCH_2), 5.09 (m, 3H, CH=), 5.37 (t, $J = 6.5$ Hz, 1H, CH=), 7.28 (s, 1H, H-8), one NH could not be observed; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.97 (CH_3), 16.01 (CH_3), 16.63 (CH_3), 17.64 (CH_3), 25.65 (CH_3), 26.13 (CH_2), 26.55 (CH_2), 26.72 (CH_2), 34.22 (NCH_3), 39.34 (CH_2), 39.64 (CH_2), 39.68 (CH_2), 44.94 (NCH_2), 65.95 (C-2), 105.10, 118.84 (CH=), 123.16 (CH=), 124.93 (CH=), 124.33 (CH=), 131.23 (C=), 134.99 (C=), 135.93 (C=), 138.06 (C-8), 142.30 (C=), 152.90 (C-6), 157.05 (C-4); MS EI *m/z* (rel.%) 423 (2, M^+), 354 (8), 352 (7), 284 (17), 218 (27), 216 (100), 150 (30), 149 (12); HRMS (EI) $C_{26}H_{41}N_5$ requires 423.3361, found 423.3344.

5.42. (2′*E*,6*E*,10′*E*)-2,3-Dihydro-1,3,-dimethyl-7-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenyl)-3*H*-purine-6(7*H*)-imine (18)

A mixture of compound **17** (156 mg, 0.37 mmol) and iodomethane (0.090 mL, 1.47 mmol) in DMA (1.5 mL) was stirred in a sealed flask at ambient temperature for 2.5 h. The mixture was evaporated in vacuo and the residue purified by flash chromatography on silica gel eluting with $MeOH/CH_2Cl_2$ (1:12); yield 83 mg (51%), pale yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.55 (s, 9H, CH_3), 1.64 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 1.90–2.12 (m, 12H, CH_2), 2.83 [s, 3H, N(3)CH_3], 2.92 [s, 3H, N(1)CH_3], 4.08 (s, 2H, CH_2), 4.85 (d, $J = 6.8$ Hz, 2H, NCH_2), 5.05 (m, 3H, CH=), 5.26 (t, $J = 5.8$ Hz, 1H, CH=), 7.18 (s, 1H, H-8), NH could not be observed; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.96 (CH_3), 15.99 (CH_3), 16.55 (CH_3), 17.64 (CH_3), 25.66 (CH_3), 26.19 (CH_2), 26.53 (CH_2), 26.68 (CH_2), 33.40 [N(1)CH_3], 35.24 [N(3)CH_3], 39.40 (CH_2), 39.62 (CH_2), 39.66 (CH_2), 44.82 (NCH_2), 71.21 (C-2), 107.27 (C-5), 118.36 (CH=), 123.42 (CH=), 124.08 (CH=), 124.31 (CH=), 131.21 (C=), 134.90 (C=), 135.60 (C=), 137.36 (C-8), 141.80 (C=), 154.35 (C-4), 155.57 (C-6); MS EI *m/z* (rel.%) 437 (5, M^+), 394 (15), 368 (7), 300 (10), 232 (100), 230 (13), 164 (9), 122 (34), 81 (21); HRMS (EI) $C_{27}H_{43}N_5$ requires 437.3518, found 437.3499.

5.43. Determination of antibacterial activity against *E. coli* (ATCC 25922) and *S. aureus* (ATCC 25923)

The reference strains tested were *E. coli* (ATCC 25922) and *S. aureus* (ATCC 25923). The strains were maintained as thick suspensions in sterile deionized water at −80 °C. Prior to experiment strains were grown for 24 h at 35 °C on Tryptone-soya agar (Oxoid, Basingstoke, Hampshire, UK). Reagent grade gentamycin sulfate and streptomycin sulfate (Sigma–Aldrich, St. Louis, MO, USA) and agelasine or agelasimine analogs were prepared as stock solutions of 5120 μg/mL according to the recommendations of the National Committee for Clinical Laboratory Standards:[32] sterile deionized water (the reference antibiotics) or dimethylsulfoxide (agelasine or agelasimine analogs) was used as the solvent, and sterile deionized water was used as the diluent. Stock solutions of agelasine or agelasimine analogs were stored in polyethylene vials at −80 °C until the day of use. Antibiotic solutions were prepared fresh for each experimental run. After the samples were thawed, serial twofold dilutions were prepared in Mueller–Hinton broth (Oxoid). Working concentrations ranging from 1.25 to 320 μg/mL were made to obtain final antibiotic concentrations of 0.125–32 μg/mL after dilution in broth. A direct suspension of colonies was prepared in 10 mL physiological saline. The turbidity of the suspension was adjusted spectrophotometrically to match a 0.5 McFarland standard. This suspension was further diluted 1:10 with Mueller–Hinton broth to obtain the inoculum having a concentration of about 10^7 CFU/mL. Susceptibility testing was performed using the broth microdilution technique.[32] Dilutions (100 μL) were added in triplicate to the wells of a microtiter plate. To each well was added 5 μL of the inoculum. Broth alone, inoculated broth, and broth amended with antimicrobial without inoculate were used as controls. After inoculation, plates were lidded and incubated aerobically at 35 °C for 20 h. The MIC value was read as the lowest concentration of antimicrobial agent that completely inhibits growth of the organism. Tests were repeated at least once with fresh samples and a fresh inoculum. The MIC values for gentamycin sulfate and streptomycin sulfate were for both strains within the range previously reported,[32,33] providing a quality control for the analysis. Compounds **3a–b**, **3e–g**, **3i–j**, **3t**, **5a–c**, and **9b** were examined against *E. coli* (ATCC 25922) and *S. aureus* (ATCC 25923) as described before.[29]

5.44. Determination of cytotoxic activities

A Fluorometric Microculture Cytotoxity Assay (FMCA) was used to determine cytotoxicity of the agelasine analogs **3**, **5–7**, **9b**, **11**, and **13**, and the agelasimine analogs **15–18**.[34] The procedure was conducted as outlined in our previous publication.[6b]

Acknowledgments

The Norwegian Research Council is greatly acknowledged for a scholarship to A.V. (KOSK program, Grant 149339/431) as well as for partial financing of the Bruker Avance instrument used in this study. The work has also been supported by the Swedish Research for Environment, Agricultural Science and Spatial Planning. Antimycobacterial data were provided by the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) through a research and development contract with the U.S. National Institute of Allergy and Infectious Diseases; we are grateful for all help provided by Dr. C. Kwong and his co-workers. M. C. Olsen at University Hospital of North Norway is acknowledged for technical assistance with some of the antibacterial susceptibility assays.

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