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Synthesis of 9-substituted tetrahydrodiazepinopurines—asmarine A analogues

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Abstract—Asmarines are marine alkaloids, with a unique tetrahydro[1,4]diazepino-[1,2,3-*g*,*h*]purine (THDAP) structure and interesting biological properties. Three synthetic approaches were employed for the preparation of the THDAP system. Several N-9, of the purine, protecting groups were investigated. ^{15}N-Chemical shifts measured from ^{15}NH HMBC experiments for several compounds, that demonstrate the influence of various structural features on the ^{15}N-resonances are reported.

1. Introduction

The selective cytotoxicity to tumor cells of the marine sponge metabolites asmarines A and B[1] triggered a synthetic project aimed at the preparation of asmarine analogues. The asmarines (e.g. asmarine A, **1**) are composed of a diterpene half, chelodane,[2] and an adenine half, constructing the N(10)hydroxy-9-substituted tetrahydro[1,4]diazepino-[1,2,3-*g*,*h*]purine (THDAP).

This report describes the synthesis of the basic, non-protected THDAP system of asmarines A and B (**2**), two 9-alkylated analogues (**3**–**4**) and the 9-oxo-derivative (**5**) (Fig. 1).†

^{15}N NMR is a powerful tool for structure determination.[3–5] The suitability of ^{15}N NMR spectroscopy is attributed to the wide range of chemical shifts (ca. 900 ppm, and over 300 ppm for natural compounds) and its great sensitivity to structural and environmental changes. A major disadvantage of this spectroscopy is the extremely low sensitivity of ^{15}N at the natural abundance level. However, despite the inherently low sensitivity, ^{15}N still has useful potential as a structural probe even at natural abundance, since inverse-detection makes it possible to acquire one bond and long-range ^{1}H–^{15}N correlations, circumventing the low sensitivity, and therefrom obtain the ^{15}N chemical shifts. Herewith we report the N-atom chemical shifts of the synthesized compounds and show the relationship between the structures and the N-resonances.

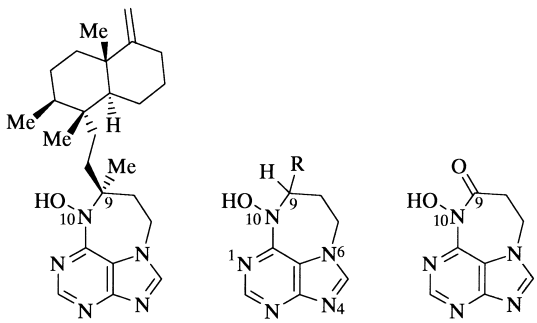

Figure 1. Asmarine A (**1**) and synthetic analogues.

2. Results and discussion

2.1. Synthesis of the THDAP system

Recently, we reported the synthesis of the diprotected N(4),N(10)O-dibenzyl-THDAP ring system (**8**)[6] in two steps starting from N^6-benzyloxy-9-benzyladenine (**6**)[7] (Scheme 1). Synthesis of the third, diazepino, ring to afford compound **8**, was achieved by an internal S_N2 reaction between the BnON= nitrogen atom and the primary halide obtained by treatment of the CH_2OH group of **7** with $SOCl_2$.

Keywords: asmarine; diazepinopurine; purine; ^{15}NH HMBC; ^{15}N resonances; Mitsunobu reaction.

Abbreviations: MPM, (4-methoxyphenyl)methyl; DMPM, (3,4-dimethoxyphenyl)methyl; TMPM, (3,4,5-trimethoxyphenyl)methyl; DPM, diphenylmethyl; MPPM, (4-methoxyphenyl)phenylmethyl; THP, tetrahydo-2H-pyran-2-yl; SEM, [2-(trimethylsilyl)ethoxy]methyl.

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† The present atoms numbers for compounds **2**–**5** are according to the IUPAC nomenclature and differ from our previous numbering which was based on the purine numbers.

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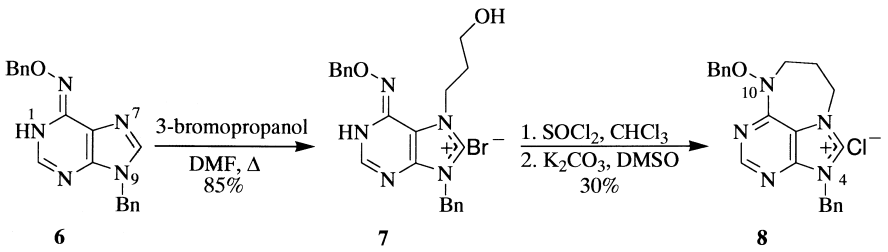


Scheme 1. Synthesis of N(4),N(10)O-dibenzyl-THDAP (**8**).

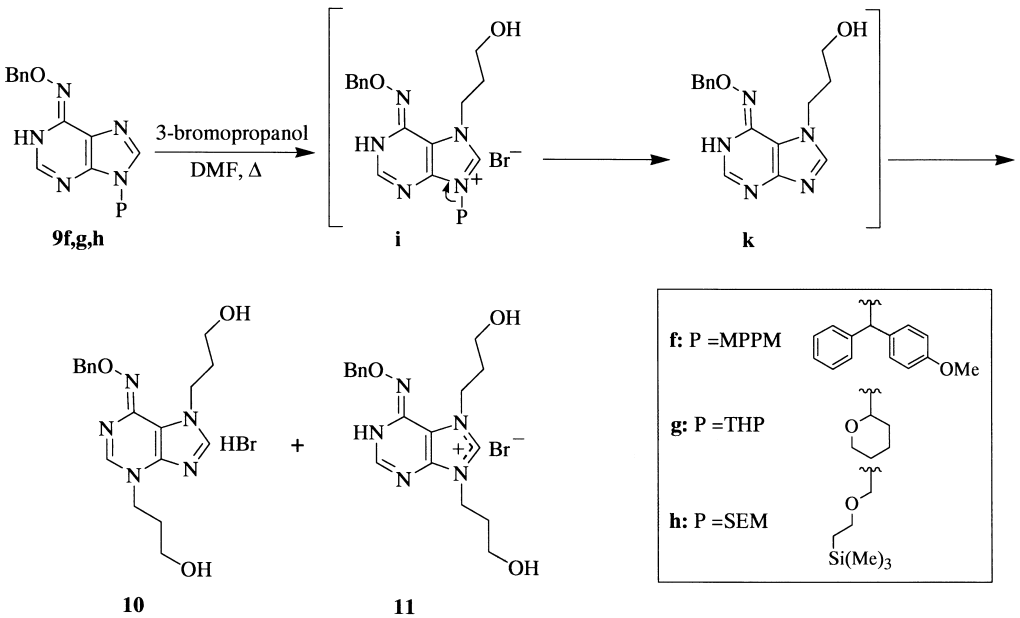
Removing both the *N*-benzyl and *O*-benzyl protecting groups of **8** was, however, not straightforward. Pd-catalyzed hydrogenolysis of **8** occasionally removed the *O*-benzyl group leaving the free amine, rather than the hydroxylamine group, and did not affect the *N*-benzyl group. Therefore other deprotection conditions, as well as more suitable protecting groups, were sought.

The suitability of a variety of nitrogen protecting groups, for the protection of the N-9 atom of the purine system, was investigated. Among the groups checked were: (**a**) benzyl, (**b**) MPM, (**c**) DMPM, (**d**) TMPM, (**e**) DPM, (**f**) MPPM, (**g**) THP and (**h**) SEM.[8] Three of the latter groups, **f** to **h**, separated readily upon alkylation of N-7 as a result of the generation of the imidazolium ion (**i**), namely, each of the MPPM, THP and SEM groups donates a pair of electrons to the imidazolium ion (**i**) (Scheme 2), detaches from the heterocycle and, by itself, gives a stable cation which is the driving force for the cleavage.[9] The latter described cleavage of the N-9 protecting group leaves the purine system free (intermediate **k**) for a second alkylation at N-3 or N-9 to afford compounds **10** and **11**, respectively, as the main products (Scheme 2). Hence, protecting groups **f**–**h** are not suitable.

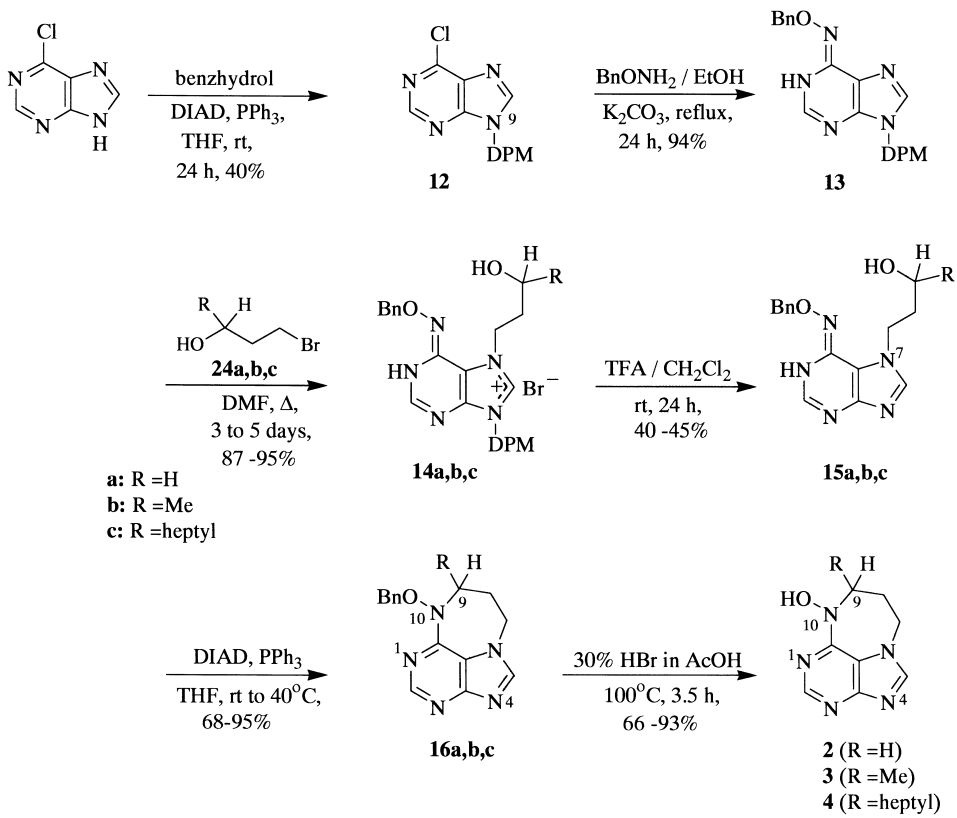
Among the other tested N-9 protecting groups (**a**–**e**), the DPM group (**e**) was found to give the best results (Scheme 3); groups **b**–**d**, on the other hand, were too difficult to be removed selectively. The DPM group of compound **13** (prepared from 6-chloropurine in two steps) was not cleaved during reaction with 3-bromopropanol to afford compound **14a**, in 95% yield, avoiding a second alkylation. Yet the DPM group could easily be selectively removed under stronger acidic conditions, TFA in CH_2Cl_2, to give compound **15a** in 45% yield. Closure of the diazepine ring was achieved by a Mitsunobu reaction (DIAD, Ph_3P)[10] to afford compound **16a**. Deprotection of the *O*-benzyl group was accomplished by warming compound **16a** in a solution of 30% HBr in AcOH at 100°C for 3.5 h affording compound **2**, the heterocyclic fragment of asmarine A, which was recently also prepared by a different route.[11]

Compounds **3** and **4** were prepared in the same way as compound **2**, namely, reacting compound **13** with suitable bromo secondary alcohols (Scheme 3; bromo alcohol **24c** was prepared by the reaction of heptylmagnesium bromide with 3-bromopropanal).

Determination of the structures of compounds **2** to **4** was achieved by suitable ^{1}H NMR, ^{13}C NMR and MS spectroscopy and confirmed by ^{13}CH and ^{15}NH HMBC experiments. The $^2J_{CH}$ and $^3J_{CH}$ correlations proved, unequivocally, both the THDAP ring system and the location of the attached alkyl substituent at C-9. The various CH– correlations for compound **3**, for



Scheme 2. Suggested mechanism for removing protecting groups **f**–**h**.



Scheme 3. Synthesis of the 10-hydroxy-9-substituted THDAP (**2** to **4**).

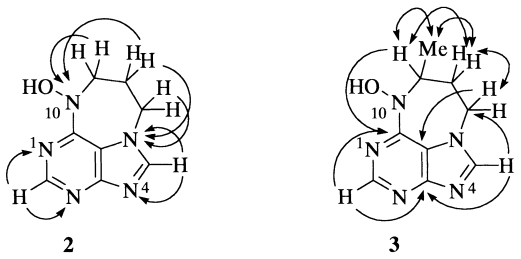


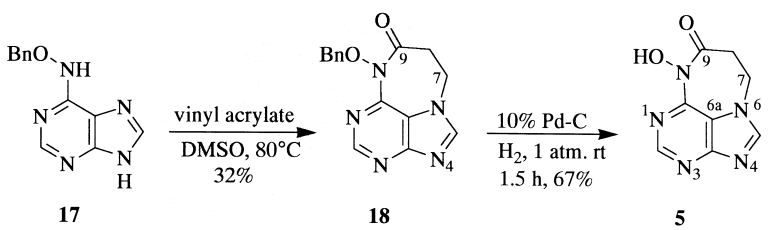
Figure 2. Long-range $^{1}H-^{15}N$ heteronuclear shift correlations measured for compound **2**, and selective long-tange $^{1}H-^{13}C$ heteronuclear shift correlations measured for compound **3**.

example Figure 2, demonstrate clearly the confirmation of the suggested structure. Further support comes from the ^{15}N- chemical shifts and long-range NH correlations (Fig. 2) vide infra.

A second approach to the THDAP ring system based on an amidation and a Michael reaction[12] could also be applied to compound **17** (Scheme 4), affording the expected 9-oxo derivative **18**. In contrast to the failure to deprotect the *O*-benzyl group in the case of compounds **16a–c**, compound **18**, under same hydrogenolysis conditions (10% Pd–C, H_2, 1 atm), afforded the required free hydroxylamine of the purine hydroxamate **5** in 67% yield. Compound **18** serves as a starting material for the desired C-9 substituted THDAP's.

As described above for compounds **2** to **4**, the structure of **5** was also established by HMBC experiments. The CH correlation between H_2-7 and the purine carbons (C-5 and C-6a), confirmed the structure of the THDAP system. Further support for the structure came from the ^{15}NH HMBC correlations, which also enabled the measurement of the ^{15}N chemical shifts (Table 1).

In addition to the synthesis of compounds **2** to **4**, we also prepared the THDAP system **21**, with the unsubstituted NH-10 group (Scheme 5). This synthesis started from compound **19**, possessing a N-3 protecting group known to direct the second alkylation to N-7,[13] thus affording compound **20** which, after the acidic deprotection of the TMPM group, afforded compound **21**. The latter tricyclic



Scheme 4. Synthesis of the 9-oxo derivative (**5**).

Table 1. ^{15}N chemical shifts deduced from long-range $^{1}H-^{15}N$ heteronuclear shift correlations (40 MHz, d_6-DMSO, 25°C)

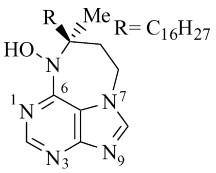
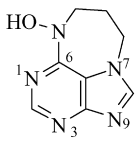
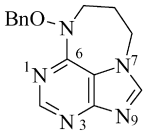
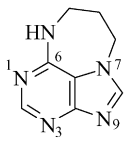
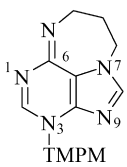
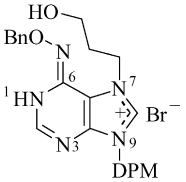
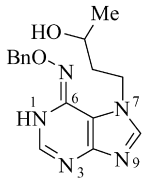
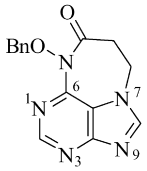
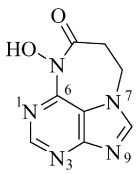
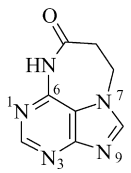
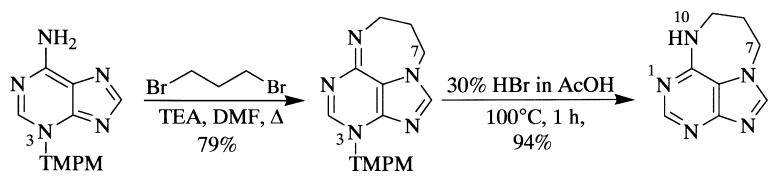
Compound number	Structure	N-1	N-3	N-7	N-9	N^6
1[a]		247.0	233.3	153.9	245.9	166.5
2[a]		245.7	235.3	156.0	245.4	149.3
16a		250.8	237.9	155.6	245.4	168.7
21		238.0	235.7	155.4	245.0	92.6
20		234.0	161.3	167.3	231.9	119.2
13		136.9	207.9	247.4	173.9	285.3
14a		141.8	204.0	172.2	180.0	288.2
15b		134.4	226.7	164.5	250.0	280.0
18		n.o.[b]	263.5	155.9	244.5	203.9
5		n.o.[b]	262.6	155.7	244.2	188.3

Table 1 (*continued*)

Compound number	Structure	N-1	N-3	N-7	N-9	N^6
22		248.0	260.5	154.7	245.4	150.7[c]

Chemical shifts in ppm upfield from liquid NH_3. The N-atoms numbers for all the compounds in this Table are according to the purine numbers.
[a] The experiment was performed at 50°C in order to separate the line of H-2 from that of H-8.
[b] Not observable.
[c] The correlation was determined by a ^{15}N-HSQC experiment.



19 **20** **21**

Scheme 5. Synthesis of the 10-hydro-THDAP (**21**).

system is the heterocyclic system of the recently isolated asmarine H.[14] The structure of **21** was confirmed by the various NMR techniques discussed, including ^{15}N chemical shifts.

2.2. ^{15}N NMR as a tool for structure determination

The ^{15}N NMR spectra, as shown above for representative compounds[‡] (Table 1, Fig. 2) demonstrate well the feasibility of acquiring structural information from these ^{15}N-resonance measurements. It is used, for example, to establish whether N^6 is a free NH, as in compound **21** and **22**, or a NOR group as in compounds **1**, **2**, **5**, **16a**, **18**, to find the major tautomeric form of the N(1)–C(6)–N^6 moiety (e.g. in compounds **13**, **14a**, **15b** vs **21** and **22**) or determine if a particular N-atom is in the sp^2 or sp^3 hybridization.

The ^{15}N resonances of the herewith described compounds range from ca. 90–290 ppm, agreeing well with known ^{15}N resonances[3] and, furthermore, adding resonance values for previously unreported functionalities such as BnO–N= and combinations of functional groups, for example values for the THDAP-system, purine hydroxamate and purine hydroxyl amine systems. Comparison of the ^{15}N resonances of the purine part of the natural compound asmarine A (**1**) with those of adenine,[§,5] show remarkable changes for N-7 and N-9 (see Table 1). Whereas the most upfield N-resonance for the adenine ring system is 156.9 for N-9, it is 153.9 for N-7 of **1**; $\delta_{N\text{-}7}$ for adenine is 239.2 and $\delta_{N\text{-}9}$ for **1** is 245.9 ppm. The latter N-7/N-9 chemical shift exchange agrees with their sp^2/sp^3 exchange. The hybridization effect can clearly be seen for substituted imidazoales where one N-atom resonates at ca. 250 (sp^2) and the other (sp^3) around 160 ppm.[3] In addition, the N-1 atom of **1** is downfield shifted, compared with adenine, by 19 ppm due to the N^6 substituents and, of course, N^6 itself is 88 ppm downfield shifted, in **1**, due to the hydroxylamine group and the α to N^6 substituents. In the case of compound **21**, lacking the N–OH group, N^6 resonates at 92.6 ppm. Further changes of N^6 are seen with the alteration of its own and the neighbor substituents, e.g. compounds **2** and **16a**. In addition, comparison of N-7 and -9, of compound **14a**, with the values for **13** and **15b** suggest that the positive charge in **14a** is evenly spread over both N-7 and -9 as both shift ca. 6–8 ppm downfield from the uncharged sp^3 N-atoms. In addition, removing the DPM group from **14a** results in a 70 ppm downfield shift of N-9 (to δ 250.0 for **15b**) and a 7.7 ppm upfield shift of N-7 due to cancellation of the positive charge. Hence, change of hybridization has a much stronger effect than the positive charge.

Another example for the sp^2/sp^3 hybridization change is seen for the N-1 and N^6 atoms in compounds **13** and **21**. Namely, N-1 in compound **13** is in the sp^3 hybridization and N^6 in the sp^2 hybridization ($\delta_{N\text{-}1}$ 136.9 and δ_{N^6} 285.3 ppm) while, in **21**, N-1 is sp^2 and N^6 is sp^3 hybridized ($\delta_{N\text{-}1}$ 238.0 and δ_{N^6} 92.6 ppm).

Additional interesting ^{15}N values are those measured for the amido- and hydroxamate-purine systems, compounds **5**, **18** and **22**.[15] While the amide and hydroxamate functionalities have a minimal effect on N-7 and 9, in comparison with compound **2**, the N-3 atom is shifted ca. 25 ppm downfield. Of course, N^6 changes notably with its substituent. Noteworthy is the ^{13}C-resonance of the carbonyl group of the latter compounds (168.1, 168.2 and 172.2 ppm, respectively) showing a 4 ppm difference between the hydroxamates and the amide resonances.

The above-described synthetic routes with suitable substrates

[‡] In the following discussion, the atoms numbers of all compounds are according to the purine numbers.
[§] The ^{15}N chemical shifts of adenine reported originally in respect to CH_3NO_2 as the reference standard,[5] are in this case converted to the liquid NH_3 scale: i.e. ^{15}N (d_6-DMSO) δ 233.8 (N-1), 228.0 (N-3), 239.2 (N-7), 156.9 (N-9), 78.3 (N^6).

(e.g. compounds **4** and **5**) as well as further alterations of compounds, such as **18**, by substitution of the carbonyl group leads to asmarine analogues which are ready for SAR studies.

3. Experimental

3.1. General methods

Starting materials and reagents were purchased from commercial suppliers and were used without further purification. Petroleum ether refers to the fractions with bp 64–68°C. THF was freshly distilled from sodium and benzophenone before use. DMSO was distilled from CaH_2 under vacuum. Vacuum liquid chromatography (VLC) was performed using silica gel 60 H (Merck), prewashed with methanol. Melting points were determined on a Electrothermal IA9000 melting points apparatus and are uncorrected. IR spectra were obtained with a Bruker FTIR Vector 22 spectrometer and are reported in cm^{-1}. MS spectra were recorded on a Fisons, Autospec Q instrument. NMR Spectra were recorded on a Bruker ARX-500 and Bruker Avance-400 spectrometers using standard Bruker pulse sequences. The $^{1}H-^{15}N$ HMBC experiments were optimized for delays of 55, 70 and 90 ms. the ^{15}N chemical shifts are reported with respect to liquid NH_3 as the reference standard. 3-Bromopropanol (**24a**) is commercially available. 4-Bromo-2-butanol (**24b**) was prepared according to a literature procedure.[16]

3.1.1. 9-Diphenylmethyl-6-chloropurine (12). To a stirred mixture of triphenyl-phosphine (5 g, 20 mmol), benzhydrol (3 g, 16 mmol) and 6-chloropurine (2 g, 13 mmol) in dry THF (70 mL) at 0°C under an argon atmosphere, was added diisopropyl azodicarboxylate (3.7 g, 18 mmol). The mixture was stirred for 5 min while a yellow precipitate formed. The mixture was allowed to warm up to room temperature and was then stirred overnight. The solvent was evaporated under vacuum, and the residue vacuum chromatographed. Elution with petroleum ether–ethyl acetate, 5:1, afforded the protected purine contaminated with diisopropyl hydrazodicarboxylate. The mixture was triturated with ethanol and filtered, affording compound **12** (1.5 g, 40%) as a white solid. Recrystallization with ethanol gave colorless crystals, mp 161–162°C; ν_{max} (KBr) 3114, 1584, 1557, 1203 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.73 (1H, s, H-2), 7.95 (1H, s, H-8), 7.13–7.40 (11H, m, two Ph rings and PhC*H*Ph); δ_C (125 MHz, $CDCl_3$) 146.9, 146.6, 146.0, 139.4, 132.2, 123.9, 126.5, 123.6, 122.8, 57.0; MS (CI) *m/z* (relative intensity): 321 (77, MH^+), 167 (100, $C_{13}H_{11}^+$); HRMS (CI): MH^+, found 321.0907, requires $C_{18}H_{14}N_4Cl$ 321.0908.

3.1.2. N^6-Benzyloxy-9-diphenylmethyladenine (13). A mixture of **12** (2.27 g, 7 mmol), *O*-benzyl hydroxylamine (2 g, 16 mmol), and potassium carbonate (0.8 g, 6 mmol) in ethanol (30 mL) was heated under reflux for 18 h. The cooled mixture was then filtered and the precipitate washed twice with cold water (2 mL) providing compound **13** (2.73 g, 94%) as a white solid. Recrystallization from methanol gave colorless crystals, mp 212°C; ν_{max} (KBr) 3028, 2856, 1663, 1594, 1535 cm^{-1}; δ_H (400 MHz, d_6-DMSO) 11.29 (1H, s, N*H*), 7.57 (1H, s, H-8), 7.53 (1H, s, H-2), 7.36–7.14 (15H, m, three Ph rings), 6.92 (1H, s, PhC*H*Ph), 5.00 (2H, s, PhCH_2); δ_C (125 MHz, d_6-DMSO) 144.8, 141.8, 141.6, 139.2, 137.7, 129.2, 128.4, 128.0, 127.8, 118.8, 75.0, 61.3; MS (CI) *m/z* (relative intensity): 408 (8, MH^+), 302 (100, $MH^+-C_7H_7O$), 107 (90, $C_7H_7O^+$); HRMS (CI): MH^+, found 408.1824, requires $C_{25}H_{22}N_5O$ 408.1849.

3.1.3. N^6-Benzyloxy-7-(3-hydroxypropyl)-9-diphenylmethyladeninium bromide (14a). A mixture of compound **13** (600 mg, 1.47 mmol) and 3-bromopropanol (1.00 g, 7.2 mmol) in DMF (10 mL) was kept at 70°C, under an argon atmosphere, for 3 days. The solvent was then evaporated and the residue chromatographed under vacuum. Elution with ethyl acetate–methanol, 10:1, afforded compound **14a** (770 mg, 95%) as a colorless oil; ν_{max} (KBr) 3018, 1675, 1618, 1558 cm^{-1}; δ_H (400 MHz, d_6-DMSO) 12.20 (1H, br s, N*H*), 9.08 (1H, s, H-8), 7.79 (1H, s, H-2), 7.25–7.42 (15H, m, three Ph rings), 7.17 (1H, s, PhC*H*Ph), 5.07 (2H, s, PhCH_2), 4.62 (1H, br t, O*H*), 4.38 (2H, m, H-11), 3.41 (2H, m, H-13), 1.88 (2H, m, H-12); δ_C (100 MHz, d_6-DMSO) 149.4, 141.3, 137.5, 137.2, 136.0, 135.4, 129.4, 129.3, 128.4, 128.2, 128.0, 127.8, 111.3, 76.4, 64.4, 57.7, 48.4, 32.0; MS (FAB) *m/z* (relative intensity): 466 (44, M^+), 167 (100, $C_{13}H_{11}^+$); HRMS (FAB) *m/z* (relative intensity): M^+, found 466.2236, requires $C_{28}H_{28}N_5O_2$ 466.2243.

3.1.4. N^6-Benzyloxy-7-(3-hydroxybutyl)-9-diphenylmethyladeninium bromide (14b). Compound **14b** was prepared from **13** under the same procedure as described for the preparation of **14a**. A mixture of compound **13** (1.18 g, 2.9 mmol) and 4-bromobutan-2-ol (1.0 g, 6.5 mmol), in DMF (10 mL), was kept at 70°C for 3 days under an argon atmosphere, afforded after VLC eluting with ethyl acetate–methanol, 6:1, compound **14b** (1.34 g, 83%) as a colorless oil; ν_{max} ($CHCl_3$) 3019, 1671, 1594, 1208 cm^{-1}; δ_H (400 MHz, d_6-DMSO) 12.19 (1H, br s, N*H*), 9.20 (1H, s, H-8), 7.80 (1H, s, H-2), 7.40–7.18 (15H, m, three Ph rings), 7.08 (1H, s, PhC*H*Ph), 5.08 (2H, s, PhCH_2), 4.64 (1H, br s, O*H*), 4.36 (2H, m, H-11), 3.63 (1H, m, H-13), 1.76 (2H, m, H-12), 1.01 (3H, d, J=6.0 Hz, H-14); δ_C (100 MHz, d_6-DMSO) 149.1, 141.4, 138.1, 137.5, 137.1, 136.8, 129.4, 129.0, 128.7, 128.6, 128.2, 111.5, 76.0, 64.3, 63.3, 49.0, 48.4, 24.1; MS (FAB) *m/z* (relative intensity): 480 (100, M^+), 374 (10, $M^+-C_6H_6O$), 314 (21, $M^+-C_{13}H_{11}$); HRMS (FAB) *m/z* (relative intensity): M^+, found 480.2411, requires $C_{29}H_{30}N_5O_2$ 480.2400.

3.1.5. N^6-Benzyloxy-7-(3-hydroxydecanyl)-9-diphenylmethyladeninium bromide (14c). Compound **14c** was prepared from **13** under the same procedure described for the preparation of **14a**. A mixture of compound **13** (710 mg, 1.74 mmol) and **24c** (1.3 g, 5.48 mmol), in DMF (10 mL), was kept at 70°C for 5 days under an argon atmosphere, afforded after VLC eluting with ethyl acetate–methanol, 20:1, compound **14c** (980 mg, 87%) as a colorless oil; ν_{max} ($CHCl_3$) 3382, 3019, 1671, 1594, 1208 cm^{-1}; δ_H (400 MHz, d_6-DMSO) 12.17 (1H, br s, N*H*), 9.09 (1H, s, H-8), 7.79 (1H, s, H-2), 7.25–7.42 (15H, m, three Ph rings), 7.15 (1H, s, PhC*H*Ph), 5.07 (2H, s, PhCH_2), 4.52 (1H, d, J=5.2 Hz, O*H*), 4.44 (2H, m, H-11), 3.55 (1H, m, H-13),

1.88 (2H, m, H-12), 1.26–1.42 (12H, m, $-CH_2-$), 0.88 (3H, t, J=6.0 Hz, CH_2CH_3); δ_C (100 MHz, d_6-DMSO) 148.5, 141.2, 137.1, 136.5, 136.1, 135.2, 135.1, 129.6, 129.5, 128.6, 128.3, 128.2, 111.8, 76.0, 68.9, 64.4, 49.1, 37.7, 36.5, 31.8, 29.5, 29.2, 25.5, 22.6, 14.1; MS (FAB) *m/z* (relative intensity): 564 (70, M^+), 398 (7, $M^+-C_{13}H_{11}$), 166 (100, $C_{13}H_{11}^+$); HRMS (FAB) *m/z* (relative intensity): M^+, found 564.3341, requires $C_{35}H_{42}N_5O_2$ 564.3339.

3.1.6. N^6-Benzyloxy-7-(3-hydroxypropyl)adenine (15a). TFA (10 mL) was added slowly to a solution of **14a** (726 mg, 0.82 mmol) in CH_2Cl_2 (10 mL) at 0°C. The solution was stirred for 24 h and then evaporated under vacuum. The residue was taken into ethyl acetate and washed with 0.5 M aq. $NaHCO_3$, brine and dried over sodium sulfate. The solvent was then evaporated and the residue chromatographed under vacuum. Elution with ethyl acetate–methanol, 20:1, afforded compound **15a** (180 mg, 45%) as a colorless oil; ν_{max} ($CHCl_3$) 3398, 3018, 1655, 1597, 1208 cm^{-1}; δ_H (400 MHz, d_6-DMSO) 11.20 (1H, br, N*H*), 8.26 (1H, s, H-2), 7.68 (1H, s, H-8), 7.31–7.45 (5H, m, Ph*H*), 5.01 (2H, s, PhCH_2), 4.26 (2H, m, H-11), 3.35 (2H, t, H-13), 1.84 (2H, m, H-12); δ_C (100 MHz, d_6-DMSO) 147.5, 145.2, 140.4, 139.1, 138.4, 128.8, 128.5, 128.1, 110.0, 75.7, 57.7, 45.5, 33.6; MS (CI) *m/z* (relative intensity): 300 (10, MH^+), 194 (27, $MH^+-C_7H_7O$), 107 (75, $C_7H_7O^+$); HRMS (CI): MH^+, found 300.1462, requires $C_{15}H_{18}N_5O_2$ 300.1460.

3.1.7. N^6-Benzyloxy-7-(3-hydroxybutyl)adenine (15b). Compound **15b** was prepared from **14b** under the same procedure described for the preparation of **15a**; TFA (3 mL) was added to a solution of compound **14b** (535 mg, 0.95 mmol) in CH_2Cl_2 (7 mL). The solution was stirred for 24 h at ambient temperature, affording after VLC eluting with ethyl acetate–methanol, 20:1, compound **15b** (120 mg, 40%) as a colorless oil; ν_{max} ($CHCl_3$) 3014, 1655, 1598, 1208 cm^{-1}; δ_H (400 MHz, d_6-DMSO) 11.23 (1H, br s, N*H*), 7.84 (1H, s, H-2), 7.54–7.24 (6H, m, 1H-8 and 5H-Ph), 5.00 (2H, s, PhCH_2), 4.70 (1H, d, J=4 Hz, O*H*), 4.19 (2H, m, H-11), 3.56 (1H, m, H-13), 1.71 (2H, m, H-12), 0.98 (3H, d, J=6.0 Hz, H-14); δ_C (100 MHz, d_6-DMSO) 150.7, 143.4, 141.4, 140.1, 138.7, 128.5, 127.9, 109.6, 75.3, 63.4, 44.5, 40.6, 23.9; MS (CI) *m/z* (relative intensity): 314 (63, MH^+), 208 (51, $MH^+-C_7H_7O$), 107 (88, $C_7H_7O^+$), 91 (100, $C_7H_7^+$); HRMS (CI): MH^+, found 314.1609, requires $C_{16}H_{20}N_5O_2$ 314.1617.

3.1.8. N^6-Benzyloxy-7-(3-hydroxydecanyl)adenine (15c). Compound **15c** was prepared from **14c** under the same procedure described for the preparation of **15a**; TFA (6 mL) was added to a solution of compound **14c** (532 mg, 0.82 mmol) in CH_2Cl_2 (14 mL). The solution was stirred for 24 h affording after VLC eluting with ethyl acetate–methanol, 20:1, compound **15c** (130 mg, 40%) as a colorless oil; ν_{max} ($CHCl_3$) 3398, 3018, 1655, 1597, 1208 cm^{-1}; δ_H (400 MHz, CDCl3) 10.96 (1H, br s, N*H*), 8.11 (1H, s, H-2), 7.43 (2H, m, Ph*H*), 7.34 (3H, m, Ph*H*), 7.04 (1H, s, H-8), 5.06 (2H, s, PhCH_2), 4.45 (1H, m, H-11), 4.05 (1H, m, H-11), 3.37 (1H, m, H-13), 1.69–1.82 (2H, m, H-12), 1.48–1.24 (12H, m, $-CH_2-$), 0.86 (3H, t, J=6.0 Hz, CH_2CH_3); δ_C (125 MHz, $CDCl_3$) 150.6, 143.3, 141.2, 140.7, 137.1, 129.1, 128.5, 128.3, 110.0, 76.3, 66.7, 43.6, 39.7, 37.1, 31.7, 29.6, 29.2, 22.7, 22.6, 14.0; MS (CI) *m/z* (relative intensity): 398 (38, MH^+), 292 (10, $MH^+-C_7H_7O$), 107 (100, $C_7H_7O^+$), 91 (75, $C_7H_7^+$); HRMS (CI): MH^+, found 398.2545, requires $C_{22}H_{32}N_5O_2$ 398.2556.

3.1.9. 7,8,9,10-Tetrahydro-10-benzyloxy-[1,4]diazepino[1,2,3-*g*,*h*]purine (16a). Diisopropyl azodicarboxylate (245 mg, 1.2 mmol) was added to a stirred solution of compound **15a** (180 mg, 0.6 mmol) and triphenylphosphine (331 mg, 1.26 mmol) in dry THF (10 mL) under an argon atmosphere. After 24 h the solvent was evaporated and the residue chromatographed under vacuum. Elution with ethyl acetate–methanol, 5:1, afforded compound **16a** (160 mg, 95%) as a colorless oil; ν_{max} ($CHCl_3$) 3018, 1672, 1597, 1208 cm^{-1}; δ_H (400 MHz, d_6-DMSO) 8.52 (1H, s, H-2), 8.42 (1H, s, H-5), 7.55 (2H, m, Ph*H*), 7.40 (3H, m, Ph*H*), 5.10 (2H, s, PhCH_2), 4.22 (2H, t, H-7), 3.78 (2H, t, H-9), 2.18 (2H, m, H-8); δ_C (100 MHz, d_6-DMSO) 159.6, 151.8, 151.7, 145.9, 135.9, 129.4, 128.3, 109.1, 75.8, 54.0, 46.9, 26.2; MS (CI) *m/z* (relative intensity): 282 (30, MH^+), 176 (85, $MH^+-C_7H_7O$), 107 (100, $C_7H_7O^+$); HRMS (CI): MH^+, found 282.1358, requires $C_{15}H_{16}N_5O$ 282.1355.

3.1.10. 7,8,9,10-Tetrahydro-10-benzyloxy-9-methyl-[1,4]diazepino[1,2,3-*g*,*h*]purine (16b). Compound **16b** was prepared from **15b** under the same procedure described for the preparation of **16a**. A mixture of diisopropyl azodicarboxylate (355 mg, 1.7 mmol), compound **15b** (110 mg, 0.35 mmol) and triphenylphosphine (475 mg, 1.7 mmol) in dry THF (10 mL) under an argon atmosphere was stirred for 1 h at 40°C and then kept at room temperature over night. VLC eluting with ethyl acetate–methanol, 6:1, afforded compound **16b** (70 mg, 68%) as a colorless oil; ν_{max} ($CHCl_3$) 3018, 1672, 1597, 1209 cm^{-1}; δ_H (400 MHz, d_6-DMSO) 8.50 (1H, s, H-2), 8.41 (1H, s, H-5), 7.53 (2H, m, Ph*H*), 7.40 (3H, m, Ph*H*), 5.11 (1H, d, J=10.2 Hz, PhCH_2), 5.10 (1H, d, J=10.2 Hz, PhCH_2), 4.38 (1H, m, H-7), 4.21 (1H, m, H-7), 4.08 (1H, m, H-9), 2.25 (2H, m, H-8), 1.23 (3H, d, 6.8 Hz, H-11); δ_C (100 MHz, d_6-DMSO) 159.3, 151.9, 150.8, 145.8, 136.0, 129.4, 128.1, 109.3, 76.2, 57.7, 41.7, 31.0, 13.7; HRMS (CI): MH^+, found 296.1511, requires $C_{16}H_{18}N_5O$ 296.1511.

3.1.11. 7,8,9,10-Tetrahydro-10-benzyloxy-9-heptyl-[1,4]diazepino[1,2,3-*g*,*h*]purine (16c). Compound **16c** was prepared from **15c** under the same procedure described for the preparation of **16a**. A mixture of diisopropyl azodicarboxylate (255 mg, 1.27 mmol), compound **15c** (170 mg, 0.42 mmol) and triphenylphosphine (350 mg, 1.33 mmol) in dry THF (5 mL) under an argon atmosphere was stirred for 4 h at 45°C and then kept at room temperature over night. VLC eluting with ethyl acetate–methanol, 10:1, afforded compound **16c** (130 mg, 80%) as a colorless oil; ν_{max} ($CHCl_3$) 3018, 1672, 1597, 1208 cm^{-1}; δ_H (400 MHz, d_6-DMSO) 8.46 (1H, s, H-2), 8.37 (1H, s, H-5), 7.51 (2H m, Ph*H*), 7.40 (3H, m, Ph*H*), 5.08 (1H, d, J=10.5 Hz, PhCH_2), 5.00 (1H, d, J=10.5 Hz, PhCH_2), 4.38 (1H, m, H-7), 4.12 (1H, m, H-7), 3.93 (1H, m, H-9), 2.36 (1H, m, H-8), 2.19 (1H, m, H-8), 1.71 (1H, m, H-11), 1.52 (1H, m, H-11), 1.19–1.34 (10H, m, $-CH_2-$), 0.82 (3H, t, J=6.5 Hz, CH_2CH_3); δ_C (100 MHz, d_6-DMSO) 159.0, 151.9, 150.3, 145.7, 136.0, 129.3, 128.4, 128.3, 109.1, 75.9, 61.5, 41.4, 39.8, 31.2, 28.7, 28.5, 27.4, 25.7, 22.1,

14.0; HRMS (CI): MH^+, found 380.2450, requires $C_{22}H_{30}N_5O$ 380.2450.

3.1.12. 7,8,9,10-Tetrahydro-10-hydroxy-[1,4]diazepino[1,2,3-*g*,*h*]purine (2). Compound **16a** (49 mg, 0.13 mmol) was dissolve in cold 30% HBr in glacial acetic acid (3 mL) and warmed to 100°C for 3.5 h. The cooled reaction mixture was then evaporated, the residue triturated twice with ether and the hydrobromide salt dissolved in methanol and basified with K_2CO_3. The remained gum after evaporation was chromatographed under vacuum. Elution with ethyl acetate–methanol, 7:3, afforded compound **2** (35 mg, 93%) as an amorphous solid; ν_{max} (KBr) 3412 (OH), 1607, 1559, 1345 cm^{-1}; δ_H (500 MHz, d_6-DMSO) 10.00 (1H, br s, O*H*), 8.31 (1H, s, H-2), 8.30 (1H, s, H-5), 4.28 (2H, t, H-7), 3.82 (2H, t, H-8), 2.24 (2H, m, H-9); δ_C (125 MHz, d_6-DMSO) 159.2, 152.3, 151.9, 145.4, 109.1, 56.0, 47.1, 26.7; MS (EI) *m*/*z* (relative intensity): 191 (18, M^+), 175 (100, M^+-100), 120 (78, $M^+-C_3H_5NO$); HRMS (EI): M^+, found 191.0803, requires $C_8H_9N_5O$ 191.0807.

3.1.13. 7,8,9,10-Tetrahydro-10-hydroxy-9-methyl-[1,4]diazepino[1,2,3-*g*,*h*]purine (3). Compound **3** was prepared from **16b** under the same procedure as described for the preparation of compound **2**. Compound **16b** (18 mg, 0.06 mmol) in 30% HBr in glacial acetic acid (3 mL) was warmed to 100°C for 3.5 h. VLC eluting with ethyl acetate–methanol, 7:3, afforded compound **3** (8 mg, 66%) as an amorphous solid; ν_{max} (KBr) 3412 (OH), 1607, 1559, 1345 cm^{-1}; δ_H (400 MHz, d_6-DMSO) 9.73 (1H, br s, O*H*), 8.33 (2H, br s, H-2 and H-5), 4.46 (1H, m, H-7), 4.13 (1H, m, H-7), 3.91 (1H, m, H-9), 2.22 (2H, m, H-8), 1.17 (3H, d, J=6.4 Hz, H-11); δ_C (100 MHz, d_6-DMSO) 159.4, 159.1, 151.9, 144.9, 109.7, 59.0, 41.8, 31.4, 14.2; MS (CI) *m*/*z* (relative intensity): 205 (7, M^+), 189 (M^+-16), 120 (16, $M^+-C_4H_7NO$), 84 (56, $C_4H_6NO^+$); HRMS (CI): MH^+, found 206.1037, requires $C_9H_{12}N_5O$ 206.1041.

3.1.14. 7,8,9,10-Tetrahydro-10-hydroxy-9-heptyl-[1,4]diazepino[1,2,3-*g*,*h*]purine (4). Compound **4** was prepared from **16c** under the same procedure as described for the preparation of compound **2**. Compound **16c** (14 mg, 0.04 mmol) in 30% HBr in glacial acetic acid (3 mL) was warmed to 100°C for 3.5 h. VLC eluting with ethyl acetate–methanol, 7:3, afforded compound **4** (8 mg, 67%) as an amorphous solid; ν_{max} (KBr) 3412 (OH), 1607, 1559, 1345 cm^{-1}; δ_H (400 MHz, d_6-DMSO) 9.79 (1H, br s, O*H*), 8.28 (2H, br s, H-2 and H-5), 4.33 (1H, m, H-7), 4.13 (1H, m, H-7), 3.91 (1H, m, H-9), 2.38 (1H, m, H-8), 2.26 (1H, m, H-8), 1.77 (1H, m, H-11), 1.52 (1H, m, H-11), 1.34–1.13 (10H, m, –CH_2–), 0.79 (3H, t, J=6.5 Hz, CH_2CH_3); δ_C (100 MHz, d_6-DMSO) 158.3, 151.7, 150.4, 144.8, 108.9, 63.0, 41.5, 31.2, 28.9, 28.7, 28.5, 27.7, 25.6, 22.0, 13.9; MS (CI) *m*/*z* (relative intensity): 290 (40, MH^+), 274 (100, MH^+-16); HRMS (CI): MH^+, found 290.1984, requires $C_{15}H_{24}N_5O$ 290.1980.

3.1.15. 7,8,10-Trihydro-10-(benzyloxy)-[1,4]diazepino[1,2,3-*g*,*h*]purin-9-one (18). A mixture of *N*-benzyloxyaminopurine (**17**)[17] (0.5 g, 2.1 mmol) and vinyl acrylate (0.4 g, 4.14 mmol) in dry DMSO (3 mL) under an argon atmosphere was heated to 80°C for 24 h. The solution was then cooled and the obtained solid filtered and washed with 2-propanol (3 mL) affording compound **18** (200 mg, 32%) as a white solid dec. 260°C; ν_{max} (KBr) 3092, 3039, 1695 (CO), 1618, 1554 cm^{-1}; δ_H (400 MHz, d_6-DMSO) 8.87 (1H, s, H-2), 8.65 (1H, s, H-5), 7.60–7.38 (5H, m, Ph*H*), 5.18 (2H, s, PhCH_2), 4.50 (2H, br t, H-7), 3.23 (2H, br t, H-8); δ_C (100 MHz, d_6-DMSO) 168.2, 161.8, 152.6, 147.7, 145.1, 135.6, 130.2, 129.5, 129.1, 113.5, 78.0, 42.3, 37.8; MS (EI) *m*/*z* (relative intensity): 295 (10, M^+), 278 (45, M^+-OH), 189 ($M^+-C_7H_7O$), 91 (100, $C_7H_7^+$); HRMS (CI): MH^+, found 296.1149, requires $C_{15}H_{14}N_5O_2$ 296.1148.

3.1.16. 7,8,10-Trihydro-10-hydroxy-[1,4]diazepino[1,2,3-*g*,*h*]purin-9-one (5). A solution of compound **18** (46 mg, 0.16 mmol), in methanol (2 mL) was hydrogenated over 10% Pd–C (42 mg) at atmospheric pressure at room temperature for 1.5 h. Removing the catalyst by filtration and evaporating the solvent left a crude gum. The residue was triturated with ether (5 mL) and ethyl acetate (5 mL) affording compound **5** (22 mg, 67%) as a white solid. The material was unstable while attempting crystallization; ν_{max} (KBr) 3379 (OH), 1669 (CO), 1619, 1559 cm^{-1}; δ_H (400 MHz, d_6-DMSO) δ 8.78 (1H, s, H-2), 8.60 (1H, s, H-5), 4.53 (2H, br t, H-7), 3.17 (2H, br t, H-8); δ_C (100 MHz, d_6-DMSO) 168.1, 161.1, 152.0, 147.0, 145.6, 113.1, 42.1, 37.2; MS (EI) *m*/*z* (relative intensity): 189 (65, MH^+-16), 135 (62, $C_5H_5N_5^+$); HRMS (EI): M^+-OH, found 188.0572, requires $C_8H_6N_5O$ 188.0572.

3.1.17. 3-[(3,4,5-Trimethoxyphenyl)methyl]-adenine (19). A mixture of adenine (4 g, 29 mmol) and 3,4,5-trimethoxybenzylbromide (9.25 g, 35 mmol) in DMF (50 mL) was heated to 70°C for 36 h. The cooled solution was then evaporated and the residue triturated with ethanol. The filtered hydrobromide salt was triturated with 10% aq. $NaHCO_3$, filtrated and washed with cold water. Recrystallization from ethanol gave **19** (3.9 g, 43%) as a white solid dec. 228°C; ν_{max} (KBr) 3005, 1672, 1618, 1127 cm^{-1}; δ_H (400 MHz, d_6-DMSO) 8.55 (1H, s, H-2), 8.22 (1H, br, N*H*), 8.10 (1H, br, N*H*), 7.80 (1H, s, H-8), 6.91 (2H, s, Ar*H*), 5.41 (2H, s, ArCH_2), 3.72 (6H, s, ArOCH_3), 3.61 (3H, s, ArOCH_3); δ_C (100 MHz, d_6-DMSO) 157.1, 155.1, 154.7, 151.9, 145.5, 139.5, 133.7, 122.6, 108.4, 62.1, 58.1, 54.6; MS (CI) *m*/*z* (relative intensity): 316 (100, MH^+), 183 (58, $C_{10}H_{15}O_3^+$), 136 (77, $C_5N_5H_6$); HRMS (CI): MH^+, found 316.1410, requires $C_{15}H_{18}N_5O_3$ 316.1410.

3.1.18. 3,7,8,9-Tetrahydro-3-[(3,4,5-trimethoxyphenyl)-methyl]-[1,4]diazepino-[1,2,3-*g*,*h*]purine (20). A mixture of compound **19** (1 g, 3.2 mmol), 1,3-dibromopropane (1.5 g, 7.4 mmol) and triethylamine (2 g, 19 mmol) in DMA (10 mL) was heated to 80°C for 36 h. The solution was then cooled and the triethylamine hydrobromide filtered off. The solvent was evaporated and the residue triturated with ether, leaving an oil which was dissolved in methanol and basified with K_2CO_3. The residue after evaporation was chromatographed under vacuum. Elution with ethyl acetate–methanol, 7:3, afforded compound **20** (0.9 g, 79%) as a white solid subl. 245°C; ν_{max} (KBr) 3125, 1655, 1591, 1397 cm^{-1}; δ_H (400 MHz, d_6-DMSO) 9.14 (1H, s, H-2), 8.76 (1H, s, H-5), 6.93 (2H, s, Ar*H*), 5.49 (2H, s, ArCH_2), 4.46 (2H, br t, H-7), 3.70 (6H, s, ArOCH_3), 3.64 (2H, m, H-9), 3.56 (3H, s, ArOCH_3), 2.23 (2H, br t, H-8); δ_C (100 MHz, d_6-DMSO) δ 155.1, 155.0, 152.2, 149.6, 149.5,

148.5, 139.7, 132.6, 113.6, 108.6, 62.2, 58.2, 54.3, 51.1, 46.3, 28.8; MS (CI) *m/z* (relative intensity): 356 (8, MH^+), 176 (100, $MH^+-C_{10}H_{13}O_3$); HRMS (CI): MH^+, found 356.1723, requires $C_{18}H_{22}N_5O_3$ 356.1724.

3.1.19. 7,8,9,10-Tetrahydro-[1,4]diazepino[1,2,3-*g*,*h*]purine (21). Compound **20** (140 mg, 0.39 mmol) was dissolved in 30% HBr in glacial acetic acid (5 mL) and warmed to 100°C for 1 h. The mixture was then cooled to room temperature and evaporated. The residue was triturated with ether, dissolved in methanol and basified with K_2CO_3. The residue after evaporation was chromatographed under vacuum. Elution with ethyl acetate–methanol, 8:2, afforded compound **21** (64 mg, 94%) as a white solid subl. 215°C; ν_{max} (KBr) 3125 (NH), 1635, 1399 cm^{-1}; δ_H (400 MHz, d_6-DMSO) 8.28 (1H, s, H-2), 8.16 (1H, s, H-5), 7.78 (1H, br s, N*H*), 4.23 (2H, t, H-7), 3.43 (2H, t, H-9), 2.13 (2H, m, H-8); δ_C (100 MHz, d_6-DMSO) 160.3, 153.6, 153.2, 145.9, 112.3, 49.7, 44.9, 29.9; MS (EI) *m/z* (relative intensity): 175 (100, M^+), 120 (65, $M^+-C_3H_5N$); HRMS (CI): MH^+, found 176.0936, requires $C_8H_{10}N_5$ 176.0933.

3.1.20. 7,8-Dihydro-[1,4]diazepino[1,2,3-*g*,*h*]purin-9(1H)-one (22). Compound **22** was prepared as described in the literature;[15] ν_{max} (KBr) 3417 (NH), 3100, 2885, 1680 (CO), 1631, 1574 cm^{-1}; δ_H (400 MHz, d_6-DMSO) δ 11.1 (1H, br s, N*H*), 8.58 (1H, s, H-2), 8.52 (1H, s, H-5), 4.48 (2H, br t, H-7), 3.07 (2H, br t, H-8); δ_C (100 MHz, d_6-DMSO) 172.2, 162.5, 152.2, 146.5, 145.2, 107.9, 41.7, 38.6; MS (EI) *m/z* (relative intensity): 189 (100, M^+), 161 (13, M^+-CO), 135 (35, $C_5H_5N_5^+$).

3.1.21. 1-Bromodecan-3-ol (24c). A solution of 3-bromopropanal (8 g, 60 mmol) in THF (10 mL) was added, over a period of 30 min. to a solution of heptylmagnesium bromide prepared from Mg (0.84 g, 35 mmol) and heptyl bromide (6.5 g, 35 mmol) in THF (20 mL), at 0°C under an argon atmosphere. The temperature was allowed to warm up to room temperature and the solution was stirred for another 2 h. The reaction mixture was then poured onto 10% aq. NH_4Cl and extracted twice with ether (30 mL). The combined organic layer was washed with brine and dried over magnesium sulfate. The residue after evaporation was chromatographed under vacuum. Elution with CH_2Cl_2–petroleum ether, 1:1, afforded compound **24c** as a colorless oil; ν_{max} ($CHCl_3$) 3400 (OH), 1450 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.83 (1H, m, H-3), 3.57 (2H, t, H-1), 1.97 (2H, m, H-2), 1.52–1.29 (12H, m, $-CH_2-$), 0.89 (3H, t, CH_2CH_3); δ_C (100 MHz, d_6-DMSO) 69.8, 39.9, 37.2, 31.8, 30.5, 29.5, 29.2, 25.5, 22.6, 14.0; MS (CI) *m/z* (relative intensity): 157 (100, MH^+-80).

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