Pergamon

Tetrahedron 55 (1999) 549–560

TETRAHEDRON

Intramolecular Hydrogen Bonding Studies For a Series of Dipurinyl-2,6-pyridinedicarboxamides

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Received 25 August 1998; revised 21 October 1998; accepted 5 November 1998

Abstract: A series of potential receptor molecules based on the dipurinyl-2,6-pyridinedicarboxamide motif has been prepared and the intramolecular hydrogen bonding characterised by ^{1}H NMR and FT-IR spectroscopies. The hydrogen bonding gives rise to a preferential planar, cis conformation for the molecules. The planar nature of the unit also gives rise to π–π stacking as shown by ^{1}H NMR dilution experiments. © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

Molecular recognition studies of nucleoside bases provide useful information in the search for pharmacologically active compounds[1,2] and the selective cleavage of DNA.[3] Specific hydrogen bonding interactions of the Hoogsteen-type and Watson-Crick type are the dominant interactions in the recognition of single base pairs,[2, 4-6] along with the π-π stacking of the aromatic base pairs.[1, 7]

Amide derivatives of pyridine-2,6-dicarboxylic acids have been used previously to study the intramolecular hydrogen bonding of amido carbohydrates,[8] the self assembly of macrocyclic porphyrins[9] and for the directed macrocyclisation of host molecules.[10] In addition, such derivatives have been used to assist the synthesis of metallohelices based on Ni(II) and Cu(II) complexes where deprotonation of the amide nitrogens allows ready coordination of the metal.[11] The intramolecular hydrogen bonding between the pyridinyl nitrogen and the amide hydrogens enables the molecules to adopt a preferential cis conformation (Figure 1).[10]

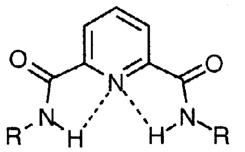


Figure 1

Molecular modelling of simple dipurinyl-2,6-pyridinedicarboxamides showed that the planar conformation stabilised by the intramolecular hydrogen bonding would give rise to potential hosts for a

PII: S0040-4020(98)01053-9

variety of guests (Figure 2).[12] We report in this paper the intramolecular hydrogen bonding exhibited by these structures and in a later paper will discuss the host-guest interactions.

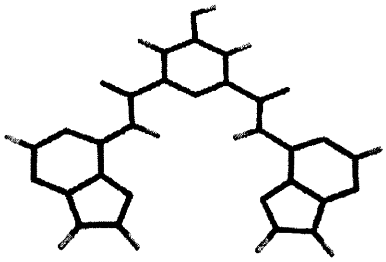
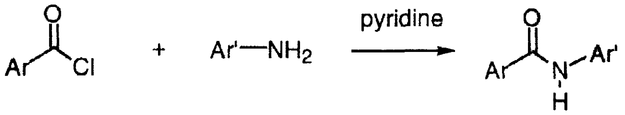


Figure 2

RESULTS AND DISCUSSION

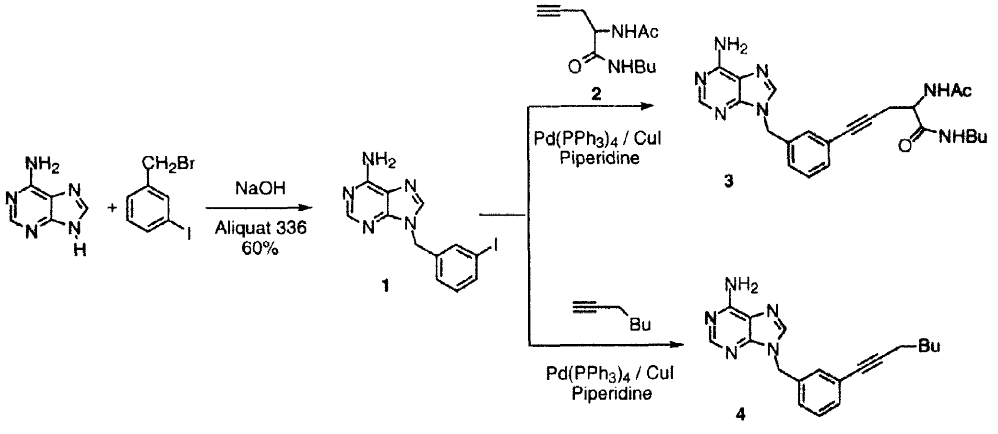
Synthesis

In order to probe the intramolecular hydrogen bonding occurring within the cavity of dipurinyl-2,6-pyridinedicarboxamides (Figure 2) a series of analogues was required which incrementally established the final structural motif (Figure 3). The structures were assembled by the reaction of the appropriate acid chloride and primary amine in pyridine (Eq1).[13]



Eq 1

The required 9-substituted adenines were prepared as outlined in Scheme 1. Adenine was alkylated at the 9 position with 3-iodobenzylbromide to give **1** in 60% yield. The iodo function of **1** then underwent a palladium-catalysed coupling with either a propargylglycine derivative (**2**) to give **3** (93%) or with 1-heptyne to give **4** (99%), (Scheme 1).[14] These 9-substituted adenines were then used as amine coupling partners in reactions with the appropriate acid chlorides (Eq 1) to give the compounds **7-9** and **11-16** (Figure 3).



Scheme 1

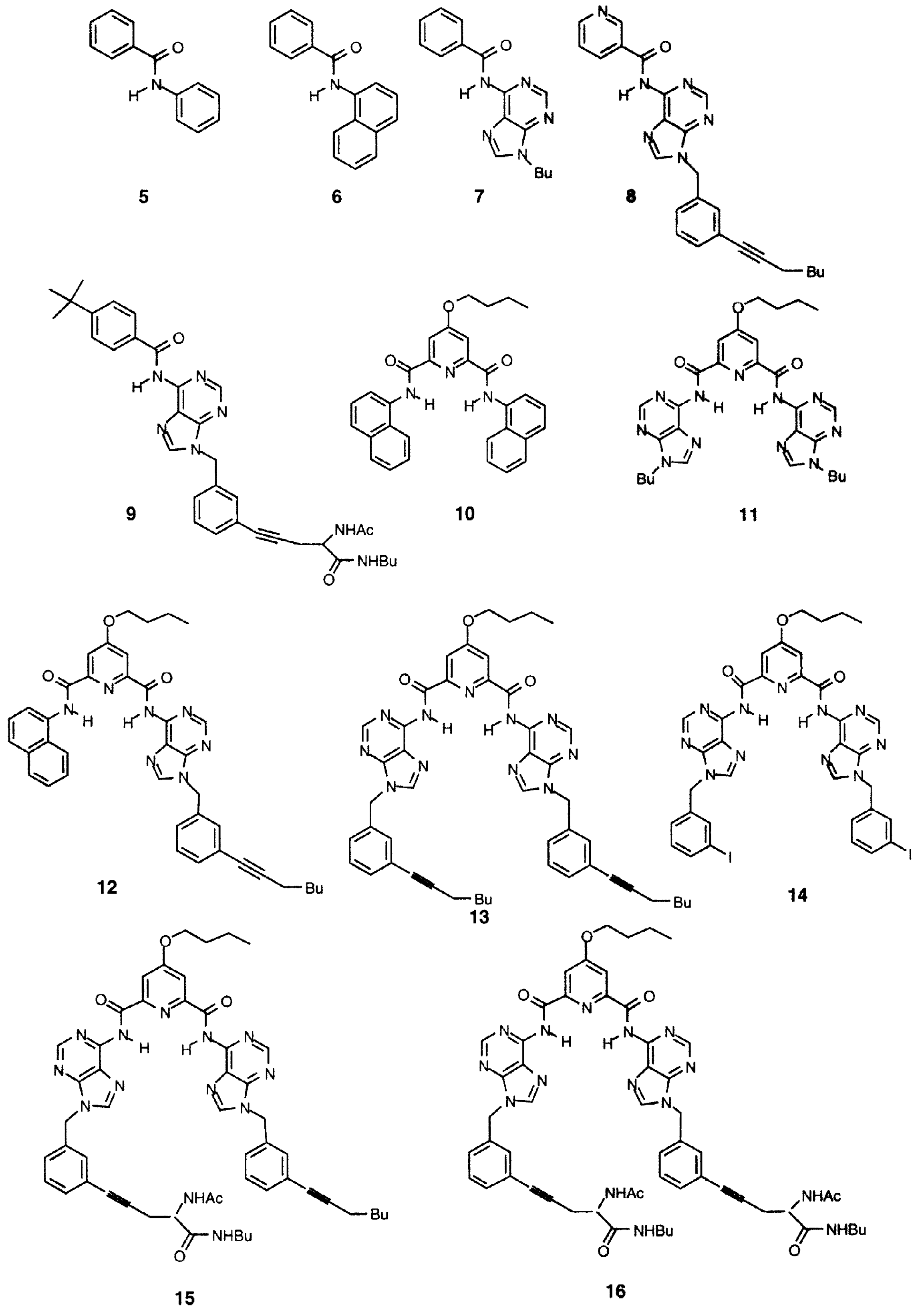


Figure 3

Hydrogen Bonding

Inter- and intramolecular hydrogen bonding interactions for NH groups can be measured by ^{1}H NMR and FT-IR spectroscopy with intramolecular hydrogen bonding being determined in dilute solutions (≤ 2mM).[15,16] Selected ^{1}H NMR and FT-IR data for the 6' and 6" NH (Figure 4) resonances and absorptions for amides **5-16** in 1.9mM solution in $CDCl_3$ are listed in Table 1. Since there can be no intramolecular hydrogen bonding for compounds **5** and **6** the data for these compounds will serve as a reference. The 6' NH in compounds **7** and **8** can form intramolecular hydrogen bonds with N7' of the adenine ring and there is a significant downfield shift for these protons in the ^{1}H NMR spectrum and a shift to lower wavenumber in the FT-IR spectrum (Table 1). These observations are consistent with significant intramolecular hydrogen bonding[17] as indicated in Figure 4.

Table 1. ^{1}H NMR and FT-IR data for 6' and 6" NH groups in **5-16** in $CDCl_3$ (1.9mM)

compound	δ NH (ppm)	ν_{max} (cm^{-1})	compound	δ NH (ppm)	ν_{max} (cm^{-1})
5	7.78	3437	**11**	11.08	3370
6	8.19	3434	**12**	11.05, 10.40	3359
7	8.89	3409	**13**	11.04	3359
8	8.91	3399	**14**	11.07	3360
9	8.91	3414	**15**	11.06, 11.07	
10	10.32	3389	**16**	11.30	

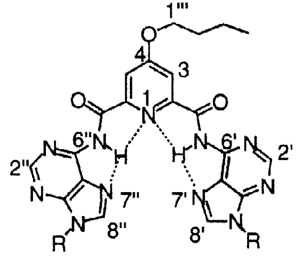


Figure 4

Compound **10** showed a further downfield shift compared to **7** and **8** indicating that the nitrogen of the pyridine can also form strong hydrogen bonds with the 6' and 6" NH of the amide. Furthermore, the chemical shifts of the 6' and 6" NH's in compounds **12-16** shift further downfield, suggesting that these amide hydrogens can form hydrogen bonds to the nitrogen atoms on both the adenine and pyridine rings. As expected, one of the NH groups in compound **12** can form one intramolecular hydrogen bond with the nitrogen on the pyridine ring, whereas the other NH group can form intramolecular hydrogen bonds to both the adenine and pyridine rings. This is clearly evident from the chemical shifts observed for the two different NH groups, one at 10.40 ppm, which is similar to compound **10** and the other at 11.05 ppm, which is similar to compound **11** and supports the concept of cooperative hydrogen bonding.[18]

Dilute solutions (≤ 2mM) of amide compounds in which the NH groups are involved in intramolecular hydrogen bonding display broad absorptions in the FT-IR spectrum between 3300-3400 cm^{-1}, whereas dilute solutions possessing only intermolecular hydrogen bonding to the solvent display sharp absorptions between 3400-3500 cm^{-1}.[19] The data presented in Table 1 are consistent with this general observation in that compounds **5** and **6** showed absorptions above 3400 cm^{-1} while compounds **10-14** all showed absorptions between 3359-3389 cm^{-1}.

The temperature dependence of the chemical shift for the 6' and 6" NH protons of compound **11** is shown in Figure 5 and it is evident that as the temperature is increased there is a rapid upfield shift in the NH resonance as the strong intramolecular hydrogen bonds are disrupted. Hydrogen bonding reaches a maximum around –50 to -60°C as further reductions in temperature have very little effect on the chemical shift. The temperature dependence of the ^1H NMR chemical shifts of NH protons can be used indicate the extent of hydrogen bonding such that values of $\Delta\delta NH/\Delta T$ significantly greater that 3ppb are indicative of intramolecular hydrogen bonding.[19] Table 2 contains selective $\Delta\delta NH/\Delta T$ data from variable temperature ^1H NMR spectra of compounds **11** and **14**. The chemical shift changes for the 6' and 6" NH protons are significantly larger than for other protons in the molecules and confirm that a strong intramolecular hydrogen bond is present.

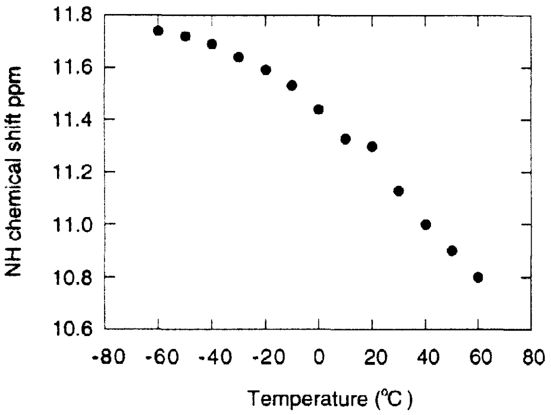


Table 2. $\Delta\delta NH/\Delta T$ in ppb/K for **11** and **14**.

Compound	6'(6")-NH	2'(2")-H	8'(8")-H
11	10.5	0.8	0.4
14	11.4	0.7	0.4

Figure 5. Temperature dependence of δNH for amide protons 6' and 6" for compound **11**.

π-π Stacking

Concentration dependent ^1H NMR chemical shift changes have been used to identify π-π stacking of nucleic acid bases.[20] Organic solvents tend to enhance the formation of hydrogen bonds compared to aqueous solvents whereas π-π stacking is often enhanced in aqueous solvents because of the favourable hydrophobic interactions which result when water molecules are excluded from close proximity to the stacked bases. ^1H NMR resonances are normally shifted upfield as the concentration is increased due to π-π stacking.[20] In order to probe the ability of the dipyridinyl-2,6-dicarboxamides to undergo π-π stacking the changes in chemical shifts of the NH and aromatic protons were monitored as the concentration was increased (Table 3). Compound **7** exhibited a significant downfield shift (+0.94 ppm) in the proton resonance for the NH group as the concentration was increased from 0.0184 to 0.461M in $CDCl_3$ (Table 3).

This was indicative of the formation of intermolecular hydrogen bonds[21] and as a consequence the chemical shift changes for the aromatic protons cannot be used to determine π-π stacking since any shift changes may be due to changes in electron density due to hydrogen bonded dimers rather than the stacking of the aromatic rings.

Table 3. Selected ^1H chemical shift (ppm) changes with concentration for **7**, **10** and **13** in $CDCl_3$.

compound	(mM)	NH	3-CH	2'-CH	1'''CH
7	461 to 18.4	+0.935		-0.099	
10	50.0 to 1.6	-0.017	-0.183	-0.166	-0.121
13	64.1 to 1.1	-0.048	-0.031	-0.061	-0.016

For compound **13** there is minimal change in the amide NH chemical shift (small upfield shift) when the concentration was increased over a wide range which was indicative of strong intramolecular hydrogen bonding. The upfield shifts in the aromatic protons are small but significant which could indicate a moderate degree of π–π stacking present between the aromatic rings at higher concentrations in $CDCl_3$. The change (Δδ) of 8'-CH in the adenine ring is about -0.061ppm and for 3-CH in the pyridine ring -0.031ppm. During the determination of the dimerisation constants of 9-butyladenine and **4** by dilution experiments with NMR, little or no change (±0.003ppm) in the chemical shifts of 8'-CH or 2'-CH was observed as the concentration was increased.[22]

Compound **10** also showed minimal change in the amide NH chemical shift (small upfield shift) when the concentration was increased over a wide range, indicative of strong intramolecular hydrogen bonding. The large upfield shifts of the 8'-CH in the adenine ring and 3-CH in the pyridine ring was consistent with π-π stacking of the aromatic rings (Figure 6). The intramolecular hydrogen bonding of N-H to 1-N in pyridine would also increase the stability of π-π stacking[23] and promote the formation of the stacking interactions, because the pyridine ring becomes electron-deficient after the formation of the intramolecular hydrogen bonding. The butoxy groups on stacked pyridine rings could then aggregate together through van de Waals interactions.[24]

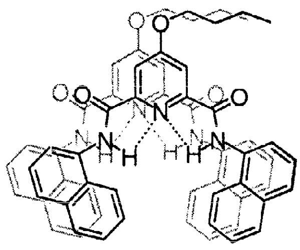


Figure 6

Hydrogen bonding interactions of amino acid amides with nucleobases

Previous reports of metal complexes derived from disubstituted-2,6-pyridinecarboxamides have shown that supramolecular assemblies containing helical motifs are possible.[11] In order to provide additional binding sites for potential guest molecules or metals we prepared *N*9 derivatives of the *N*2,*N*6-dipurinyl-2,6-pyridine carboxamides containing amido acid amide groups and examined the hydrogen bonding effects of these additional NH groups.

The chemical shift values in dilute solution (therefore minimum intermolecular hydrogen bonding) for the model compound **9** showed typical values[14] of δ 6.11 for CONHBu and δ 6.36 for NHAc. In contrast, the chemical shift values for **15** (δ 6.56 for CONHBu and δ 6.53 for NHAc) and **16** (δ 6.60, 6.73 for CONHBu and δ 6.61, 6.64 for NHAc) were shifted downfield and indicated intramolecular hydrogen bonding. Compound **16** consists of a pair of diastereoisomers and the ^{1}H NMR spectrum showed a doubling of many of the signals in a 1:1 ratio. The fact that the chemical shifts for **16** were further downfield compared to **15** would indicate stronger intramolecular hydrogen bonding. Further evidence for this intramolecular hydrogen bonding for **16** was obtained from the variable temperature ^{1}H NMR spectra that are shown in Table 4. The Δδ/ΔT (ppb/K) values of 8.40/6.18 for CONHBu and 5.73/5.63 for NHAc confirm the strong intramolecular hydrogen bonding.[19] It would appear that the CONHBu group forms a stronger hydrogen bond compared to NHAc, as the chemical shift changes more rapidly with temperature. Assuming that the mixture of diastereoisomers is responsible for the two sets of amido acid amide NH signals of **16** (Figure 7), the more rapid change in the chemical shift of CONHBu (triplet) compared to NHAc (doublet) is clearly evident. What was not clear from the 2D (COSY, ROESY) spectra of **16** was definitive proof for the origins of the two sets of signals, whether they were arising from two separate compounds (ie the diastereoisomers) or from non-equivalent purinyl groups on the one compound due to conformational restrictions. This is under further investigation.

Table 4. (Δδ/ΔT in ppb/K) from 20°C to 60°C for selected protons of **16**.

6'(6")-NH	3-CH	8"(8")-CH	2"(2")-CH	CONHBu	NHAc
10.15	2.73	1.13	0.43	8.40/6.18	5.73/5.63

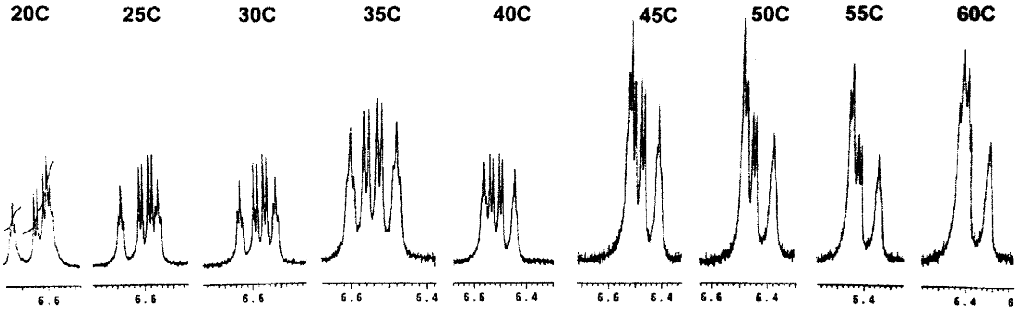


Figure 7. The ^{1}H NMR signals for CONHBu and NHAc of **16** from 20°C to 60°C

It is possible that a helical arrangement is evolving in **15** and **16** involving hydrogen bonding between either or both of the CONHBu and NHAc groups with the adenine groups or it is also possible for **16** that the two amido acid amide groups could engage in intramolecular hydrogen bonding with each other.

Conclusion

This study of dipurinyl-2,6-pyridinedicarboxamides has confirmed that strong intramolecular hydrogen bonding is incrementally established with the final structural motif and that for the dinaphthyl-2,6-pyridinedicarboxamides π–π stacking is apparent at high concentrations. The ability of these complexes to act as hosts for organic guests and as ligands for metal cations will be reported in a separate paper.

EXPERIMENTAL SECTION

All melting points are recorded on a Reichhert hot stage apparatus and uncorrected. Reagents were used as obtained from commercial supplies or purified according to standard literature procedures.[25] All reactions were performed in oven dried glassware under a nitrogen atmosphere unless otherwise stated. ^1H and ^{13}C NMR spectra were recorded on a Bruker ACP-300 or a Varian 600 spectrometer in $CDCl_3$ (dried with 4Å molecular sieves) as solvent with TMS as an internal standard. Chemical shifts were reproducible within a ±0.002 ppm range. Mass spectra were recorded on a VG ZAB 2HF mass spectrometer with either electron impact (EI) or fast atom bombardment (FAB) ionisation, or on an AEI-GEC MS 3074 instrument with EI ionisation. High resolution mass spectra were obtained using either electron impact $[M]^+$ or LSIMS $[M + H]^+$. FT-IR spectra were recorded on ATI Mattison Genesis Series spectrometer. Analytical thin layer chromatography was carried out using Merck aluminium sheets precoated with Kieselgel 60 F_{254}, and visualized at 250 or 365 nm. Flash chromatography was performed using Merck Kiesegel 60 (230-400 mesh).

9-Butyladenine and compounds **1**,[26] **3**[11] and **6**[27] were prepared by literature methods. Compound **5** was obtained from Aldrich.

2-(Acetylamino)-*N*1-butyl-5-{3-[(6-amino-9*H*-9-purinyl)methyl]phenyl}-4-pentynamide 3

To a stirred solution of **1** (0.351 g, 1.0mmol) and **2** (0.210 g, 1mmol) in piperidine (5 mL) under nitrogen, was added $Pd(PPh_3)_4$ (0.052 g, 0.05mmol), PPh_3 (0.026 g, 0.1mmol) and copper iodide (0.015 g, 0.1mmol) respectively. The clear, dark red solution was heated at reflux for 45 min. The solvent was evaporated under vacuum and the residue was purified on silica gel (20% CH_3OH/CH_2Cl_2). The product **3** was obtained as a white solid in 93% (0.40g). Mp 188-190°C. ^1H NMR δ : 0.84(t, 3H, J=7.1Hz, CH_3); 1.26-1.48(m, 4H, CH_2); 2.04(s, 3H, CH_3); 2.75-2.99(m, 2H, CH_2); 3.29(m, 2H, CH_2); 4.53(m, 1H, CH); 5.34(s, 2H, CH_2); 6.32(bs, 1H, NH); 6.57(d, 1H, J=6.5Hz, NH); 7.29(m, 4H, Ar); 7.78(s, 1H, 8'-CH); 8.41(s, 1H, 2'-CH). Calc. for $[M + H]^+$ $C_{23}H_{28}N_7O_2$: 434.2304. Found: 434.2300.

9-[3-(1-Heptynyl)benzyl]-9*H*-6-purinamine 4

Prepared as described for compound **3** from **1** and 1-hexyne. Eluant was 7% CH_3OH/CH_2Cl_2, yield 99% as a white solid. M.p. 147-148°C. ^1H NMR δ : 0.91(t, 3H, J=7.1Hz, CH_3); 1.38-1.57(m, 6H, CH_2); 2.38(t, 2H, J=6.5Hz, CH_2); 5.69(s, 2H, NH_2); 7.20-7.31(m, 4H, Ar); 7.77(s, 1H, 8'-CH); 8.41(s, 1H, 2'-CH). ^{13}C δ: 13.9, 19.2, 22.1, 28.2, 31.0, 46.8, 73.8, 79.8, 91.6, 119.0, 125.1, 126.9, 129.1, 130.8, 131.7, 135.7, 140.5, 153.4, 155.6. Calc. for $C_{19}H_{21}N_5$: 319.1797. Found: FAB mass spectrum $[M + H]^+$ 320.

***N*1-(9-Butyl-9*H*-6-purinyl)benzamide 7**

9-Butyladenine (0.143 g, 0.75mmol) and benzoyl chloride (0.105 g, 0.75mmol) and anhydrous pyridine (1 mL) were stirred together at 100°C for 1h. The pyridine was removed under vacuum and the residue purified on silica gel, ($CH_3OH/CH_3COCH_3/CH_2Cl_2$:1/8.6/26.5). Yield 74% (0.164g) as a white solid. M.p. 119-120°C. ^1H NMR δ: 0.99(t, 3H, J=7.2Hz, CH_3); 1.44(sextet, 2H, J=7.2Hz, CH_2); 1.93(pentet, 2H, J=7.2Hz, CH_2); 4.30(t, 2H, J=7.1Hz, CH_2); 7.51(dd, 2H, J=7.0, 7.2Hz, Ar); 7.63(dd, 2H, J=7.0, 7.2Hz, Ar); 8.01(s, 1H, 8'-CH); 8.04(d, 2H, J=7.2Hz, Ar); 8.83(s, 1H, 2'-CH); 8.89(s, 1H, NH). ^{13}C NMR δ: 13.3, 19.8, 31.9, 43.9, 123.2, 127.9, 129.0, 132.8, 143.0, 149.6, 152.7, 161.30, 164.7. Calc. for $[M + H]^+$ $C_{16}H_{17}N_5O$: 295.1433. Found: 295.1424.

***N*3-{9-[3-(1-Heptynyl)benzyl]-9*H*-6-purinyl}nicotinamide 8**

Nicotinic acid (0.083 g, 0.75mmol) and $SOCl_2$ (0.5 mL) were heated at reflux for 4 hr. The $SOCl_2$ was then removed under vacuum. To the residue was added **3** (0.123 g, 0.375mmol) and pyridine (1 mL) and the mixture was stirred at 90°C for 1h. Purification on silica gel ($CH_3OH/CH_3COCH_3/CH_2Cl_2$:1/13.4/13.4) gave **8** in 30% (0.048g) as a pale yellow solid. M.p. 143.5-144°C. ^1H NMR δ : 0.92(t, 3H, J=7.2Hz, CH_3); 1.38-1.59(m, 6H, CH_2); 2.38(t, 2H, J=6.9Hz, CH_2); 5.42(s, 2H, CH_2); 7.24-7.47(m, Ar); 7.50(dd, 1H, J=4.5, 7.8Hz, pyridyl); 8.01(s, 1H, 8'-CH); 8.33(dt, 1H, J=1.8, 6.0Hz, pyridyl), 8.84(d, 1H, J=1.5Hz, pyridyl); 8.85(s, 1H, 2'-CH); 8.95(s, 1H, NH); 9.25(d, 1H, J=2.0Hz, pyridyl). Calc. for $[M]^+$ $C_{25}H_{24}N_6O$: 424.2011. Found: 424.2002.

***N*1-(9-{3-[4-(Acetylamino)-5-(butylamino)-5-oxo-1-pentynyl]benzyl}-9*H*-6-purinyl)-4-(tert-butyl)benzamide 9**

Compound **9** was prepared according the procedure above for **7** using 4-(*tert*-butyl)benzoyl chloride and **3**. The product was applied twice to a silica gel column (7% CH_3OH/CH_2Cl_2) and obtained in a yield of 20% as a pale yellow solid. M.p. 162-164°C. ^1H NMR δ : 0.87(m, 6H, CH_3); 1.24(m, 4H, CH_2); 1.37(s, 9H, CH_3); 2.04(s, 3H, CH_3); 2.79-2.96(m, 2H, CH_2), 3.32(m, 2H, CH_2); 4.54(m, 1H, CH), 5.42(s, 2H, CH_2); 6.11(t, 1H, J=7.0Hz, $NHCH_2$); 6.36(d, 1H, J=7.2Hz, NHAc); 7.31(m, 4H, Ar); 7.55(d, 2H, J=9.0Hz, Ar); 7.98(d, 2H, J=9.0Hz, Ar); 7.99(s, 1H, 8'-CH); 8.84(s, 1H, 2'-CH); 8.92(s, 1H, NH). Calc. for $C_{34}H_{39}N_7O_3$: 593.3114. Found: FAB mass spectrum $[M + H]^+$ 594.1.

4-Butoxy-*N*2,*N*6-di(1-naphthyl)-2,6-pyridinedicarboxamide 10

4-Butoxypyridine-2,6-dicarboxylic acid[10] (0.478 g, 2mmol) and $SOCl_2$ (2 mL) were heated at reflux on an oil bath for 0.5 h, the excess $SOCl_2$ was removed under vacuum. To this residue was added 1-naphthylamine (0.572 g, 4mmol) and pyridine (2 mL) and the mixture stirred at 90°C for 1h. The pyridine was removed under vacuum and the solid residue was washed with methanol (5 mL) then $CHCl_3$ (5 mL). The product was obtained in 36% (0.35g) as an off-white solid. M.p. >230°C. ^1H NMR δ : 1.03(t, 3H, J=7.5Hz, CH_3); 1.55(m, 2H, CH_2); 1.90(m, 2H,); 4.28(t, 2H, J=6.3Hz, CH_2); 7.36(ddd, 1H, J=1.0, 6.9,7.5Hz, Ar); 7.51(ddd, 1H, J=0.9, 6.9,8.4Hz, Ar); 7.59(t, 1H, J=7.8Hz, Ar); 7.77(d, 1H, J=8.4Hz, Ar); 7.93(d, 1H, J=8.1Hz, Ar); 8.1(d, 1H, J=7.5Hz, Ar); 8.10(s, 1H,3-CH); 8.39(d, 1H, J=7.5Hz, Ar); 10.32(s, 1H, NH). ^{13}C NMR δ: 13.6, 19.0, 30.7, 69.0, 112.0, 119.6, 120.0, 125.8, 126.0, 126.1, 126.6, 126.8, 129.1, 131.9, 134.2, 151.1, 161.6, 168.64. Calc. for $[M]^+$ $C_{31}H_{27}N_3O_3$: 489.2052. Found: 489.2069.

4-Butoxy-*N*2,*N*6-di(9-butyl-9*H*-6-purinyl)-2,6-pyridinedicarboxamide 11

Prepared according the procedure for **10**. The pyridine free product was dissolved in CH_2Cl_2 and purified on silica gel ($CH_3OH/CH_3COCH_3/CH_2Cl_2$:1/8.6/26.5). Yield 38% as a white solid. M.p. 81-82°C. ^1H NMR δ : 1.02(m, 6H, CH_3); 1.43-1.56(m, 8H, CH_2); 1.89(m, 4H, CH_2); 4.23(t, 2H, J=6.3Hz, CH_2); 4.32(t, 2H, J=7.5Hz, CH_2); 8.07(s, 1H, 8'-CH); 8.12(s, 1H, 3-CH); 8.88(s, 1H, 2'-CH); 11.07(s, 1H, NH). ^{13}C NMR δ : 13.5, 14.7, 19.0, 19.9, 30.7, 32.0, 43.9, 69.0, 113.2, 143.1, 149.0, 150.3, 152.4, 152.7, 161.3, 168.3. Calc. for $[M]^+$ $C_{29}H_{35}N_{11}O_3$: 585.2924. Found: 585.2918.

4-Butoxy-*N*2-{9-[3-(1-heptynyl)benzyl]-9*H*-6-purinyl}-9-*N*6-(1-naphthyl)-2,6-pyridinedicarboxamide 12

Prepared according to the procedure above for **10**. The pyridine free product was dissolved in warm methanol and CH_2Cl_2 and purified on silica gel ($CH_3OH/CH_3COCH_3/CH_2Cl_2$:1/2/13.4). The product was recrystallized from methanol, yield 37% (0.124 g) as a pale fawn solid. M.p. 174-175°C. ^1H NMR δ: 0.90(t, 3H, J=8.0Hz, CH_3); 1.03(t, 3H, J=8.0Hz, CH_3); 1.32-1.60(m, CH_2); 1.89(m, 2H, CH_2); 2.37(t, 2H, J=7.0Hz, CH_2); 4.26(t, 2H, J=6.6Hz, CH_2); 5.43(s, 2H, CH_3); 7.23(m, 4H, Ar); 7.54-8.34(m, 6H, Ar); 7.89(s, 1H, 8'-CH); 8.12(s, 1H, 3-CH); 8.44(d, 1H, J=7.5Hz, Ar); 8.94(s, 1H, 2'-CH); 10.40(s, 1H, NH); 11.05(s, 1H, NH). Calc. for $[M]^+$ $C_{40}H_{39}N_7O_3$: 665.3114. Found: 665.3128.

4-Butoxy-*N*2,*N*6-di{9-[3-(1-heptynyl)benzyl]-9*H*-6-purinyl}-2,6-pyridinedicarboxamide 13

Prepared according to the procedure for **12**. Yield 43% as an off-white solid. M.p. 172-174°C. ^1H NMR δ : 0.91(t, 3H, J=7.5Hz, CH_3); 1.01(t, 3H, J=7.5Hz, CH_3); 1.38-1.59(m, 12H, CH_2); 1.87(m, 2H, CH_2); 2.37(t, 4H, J=7.0Hz, CH_2); 4.23(t, 2H, J=6.6Hz, CH_2); 5.43(s, 2H, CH_2); 7.23-7.35(m, 4H, Ar); 8.00(s, 1H, 8'-CH); 8.11(s, 1H, 3-CH); 8.90(s, 1H, 2'-CH); 11.04(s, 1H, NH). ^{13}C NMR δ : 13.6, 13.9, 19.0, 19.3, 22.2, 28.3, 30.7, 31.1, 47.1, 69.2, 79.8, 91.9, 113.2, 123.7, 125.3, 126.9, 129.1, 130.8, 131.8, 135.3, 143.0, 148.9, 150.3, 152.7, 153.0, 160.7, 168.6. Calc. for $[M + H]^+$ $C_{49}H_{52}N_{11}O_3$: 842.4254. Found: 842.4237.

4-Butoxy-*N2*,*N6*-di[9-(3-iodobenzyl)-9*H*-6-purinyl]-2,6-pyridinedicarboxamide 14

4-Butoxypyridine-2,6-dicarboxylic acid[10] (0.36 g, 1.5mmol) and $SOCl_2$ (4 mL) were heated at reflux on an oil bath for 6 hr. The $SOCl_2$ was removed under vacuum and to the residue was added compound **1** (0.95 g, 3.0mmol) and anhydrous pyridine (5 mL), and the mixture was stirred at 90°C overnight. The pyridine was removed under vacuum and residue submitted twice to a flash column separation with silica gel (7% CH_3OH/ CH_2Cl_2). Yield 68% (0.74g) as a pale yellow solid. M.p. 221-223°C. ^{1}H NMR δ: 1.01(t, 3H, J=7.0Hz, CH_3); 1.55(m, 2H, CH_2); 1.87(m, 2H, CH_2), 4.23(t, 2H, J=6.3Hz, CH_2); 5.42(s, 2H, CH_2); 7.11-7.69(m, 4H, Ar); 8.04(s, 1H, 8-CH); 8.12(s, 1H, 3-CH); 8.90(s, 1H, 2-CH); 11.07(s, 1H, NH). ^{13}C NMR δ: 13.6, 19.0, 27.7, 30.6, 46.6, 69.1, 113.3, 123.5, 127.2, 130.9, 136.8, 137.3, 138.0, 142.8, 149.3, 150.3, 152.7, 153.0, 161.4, 168.5. Calc. for $[M + H]^+$ $C_{35}H_{30}I_2N_{11}O_3$: 906.0626. Found: 906.0626

***N2*-(9-{3-[(Acetylamino)-5-(butylamino)-5-oxo-1-pentynyl}-9*H*-6-purinyl)-4-butoxy-*N6*-{9-[3-(1-heptynyl)benzyl]-9*H*-6-purinyl}-2,6-pyridinedicarboxamide 15**

Prepared according to the procedure for **12** and purified on silica gel using 7% CH_3OH in CH_2Cl_2. Yield 5.3% as an off-white solid. M.p. 200-202°C. ^{1}H NMR δ : 0.80(t, 3H, J=7.5Hz, CH_3); 0.91(t, 3H, J=7.0Hz, CH_3); 1.01(t, 3H, J=7.5Hz, CH_3); 1.25-1.86(m, CH_2); 2.38(t, 2H, J=7.0Hz, CH_2); 2.72-2.99(m, 2H, CH_2); 3.30(m, 2H, CH_2); 4.22(t, 2H, J=6.3Hz, CH_2); 4.64(m, 1H, CH); 5.52(s, 2H, CH_2); 6.10(t, 1H, J=6.0Hz, $NHCH_2$); 6.32(d, 1H, J=5.8Hz, NHAc); 7.20-7.40(m, 4H, Ar); 8.08(s, 2H, 8'-CH); 8.08(s, 2H, 3-CH); 8.90, 8.91(s, 2H, 2'-CH); 11.06, 11.07(s, 2H, NH). Calc. for $[M + H]^+$ $C_{53}H_{58}N_{13}O_5$: 956.4683. Found: 956.4697.

***N2*, *N6*-di(9-{4-[(Acetylamino)-5-(butylamino)-5-oxo-1-pentynyl]benzyl}-4-butoxy-9*H*-6-purinyl)-2,6-pyridinedicarboxamide 16**

Prepared according the procedure for **12** and purified on silica gel using 11% CH_3OH in CH_2Cl_2. Yield 18% as a pale yellow solid. M.p. 222-224°C. ^{1}H NMR δ : 0.83(m, 6H, CH_3); 1.03(t, 3H, J=7.2Hz, CH_3); 1.31-1.56(m, CH_2); 2.75-3.30(m, CH_2); 4.66(m, 2H, CH); 5.44(s, 4H, CH_2); 6.64(m, 1H, NH); 6.73(m, 1H, NH); 7.29(m, 8H, Ar); 8.11(s, 2H, 8'-CH); 8.12(s, 2H, 3-CH); 8.91(s, 2H, 2'-CH); 11.27(s, 2H, NH). Calc. for $[M + H]^+$ $C_{57}H_{64}N_{15}O_7$: 1070.5112. Found: 1070.5098.

Acknowledgement: We would like to thank the Australian Research Council for the award of an Overseas Postgraduate Research Scholarships to Y.-L. J.

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