New *N*-(Purin-6-yl)-amino Acid and -Peptide Derivatives; Synthesis and Biological Screening†

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N-(Purin-6-yl)-amino acids and -peptides were synthesized from 9-(*p*-anisyl)-6-chloropurine; selected examples from the synthesized products were screened as antitumour and antiviral (HIV-1) agents.

The naturally occurring *N*-(purin-6-yl)amino acids[1,2] are important intermediates in biochemical processes. Adenylsuccinic acid (9-ribosyl-6-aspartopurine-5′-monophosphate) is an intermediate product in the amination of inosinic acid (IMP) to adenylic acid (AMP).[2]Also, synthetic 6- and 9-substituted purine derivatives have been previously reported for their antitumour[3,4] and antiviral[5] activity, as cardiovascular agents[6] and for their use as hepadnaviride-active antiviral agents.[7]

Therefore, the present work was aimed at synthesizing new *N*-(purin-6-yl)-amino acid and -peptide derivatives expected to have antitumour and antiviral activity.

When 9-(*p*-anisyl)-6-chloropurine[8] (**1**) was allowed to react with the sodium salt of various amino acids under reflux at pH 9–9.5, the corresponding *N*-[9-(*p*-anisyl)purin-6-yl]amino acid derivatives **3a**–**h** were affored (Scheme 1).

The structure of products **3a**–**h** was elucidated by careful study of their IR absorption spectra which showed ν_{NH} and $\nu_{C=O}$ in the 3413–3281 and 1728–1706 cm^{-1} regions respectively, in addition to another band in the 1254–1242 cm^{-1} region for a CO_2H group.[9]

The *N*-[9-(*p*-anisyl)purin-6-yl]peptides **5a**–**c** were synthesized from reaction of **3c**, **e** and **f** with the appropriate amino acid ester hydrochloride.

Biological Screeening.—(1) *Antitumour screening*. Antitumour activity screening of products **3a**, **b**, **d**, and **f** and **5c** was carried out against 60 human tumour cell lines derived from nine cancer types (leukaemia, non-small cell lung, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer) according to a well known procedure.[10,11] All the compounds tested showed no significant activity against the tested tumour cell lines.

(2) *Anti-HIV screening*. The products **3a**, **b**, **d** and **f** and **5c** were evaluated for *in vitro* anti-HIV-1 activity. The procedure[12] used for agents active against human immunodeficiency virus (HIV) is designed to detect agents acting at any stage of the virus reproductive cycle. The tested compounds showed no significant activity.

Experimental

N-(*Purin-6-yl*)*amino Acids* **3a**–**h**: *General Procedure*.—The amino acid (9.60 mmol) and sodium carbonate (5.40 mmol) were dissolved in water (10 ml), then adjusted to pH 9–9.5. The 6-chloropurine **1** (4.80 mmol) was added and then the mixture was stirred at 100 °C for 6 h with control of pH. The reaction mixture was left overnight at room temperature, then treated with formic acid (88%). The solid product obtained was filtered off, washed with water and purified using preparative silica gel TLC plates to give **3a–h**.

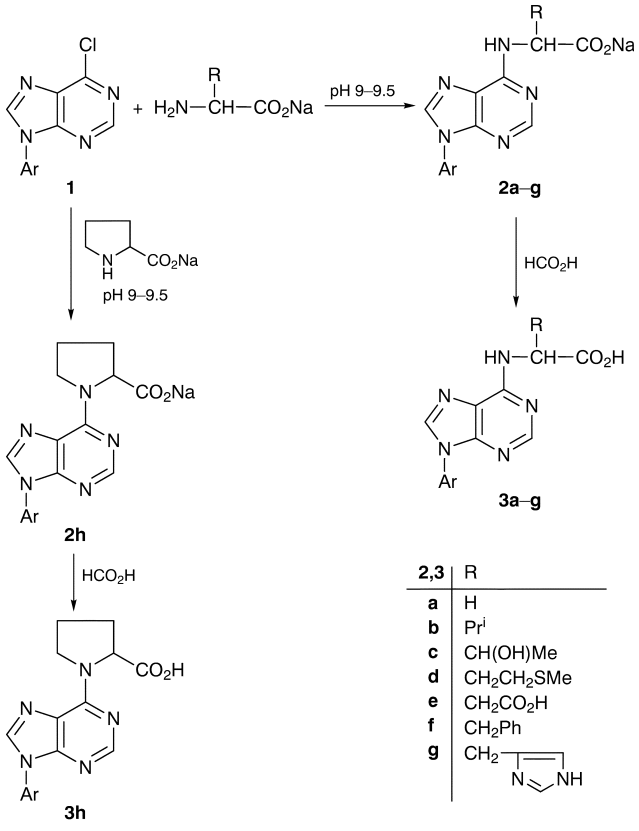
N-[9-(p-*Anisyl*)*purin-6-yl*]*glycine* **3a** (70%): mp 251–253 °C (Found: C, 56.3; H, 4.2; N, 23.2. $C_{14}H_{13}N_5O_3$ requires C, 56.19; H, 4.35; N, 23.41%); ν_{max}/cm^{-1} 3413 (NH), 1718 (C=O), 1242 (COOH) δ_H 3.84 (s, 3 H, OCH_3), 4.18 (s, 2 H, α-CH_2), 7.14 (d, 2 H, ArH), 7.76 (d, 2 H, ArH), 8.05 (br, 1 H, NH, D_2O-exchangeable), 8.28 (s, 1 H, 8-H), 8.52 (s, 1 H, 2-H); *m*/*z* 299 (M^+).

N-[9-(p-*Anisyl*)*purin-6-yl*]-L-*valine* **3b** (62%): mp 115–117 °C (Found: C, 59.7; H, 5.7; N, 20.7. $C_{17}H_{19}N_5O_3$ requires C, 59.82; H, 5.57; N, 20.53%); ν_{max}/cm^{-1} 3293 (NH), 1718 (C=O); 1251 (CO_2H); δ_H 1.02(t, 6 H, γ-CH_3), 2.32 (m, 1 H, β-CH), 3.84 (s, 3 H, OCH_3), 4.05 (m, 1 H, α-CH), 7.15 (d, 2 H, ArH), 7.53 (br, 1 H, NH, D_2O-exchangeable), 7.76 (d, 2 H, ArH), 8.28 (s, 1 H, 8-H), 8.55 (s, 1 H, 2-H); *m*/*z* 341 (M^+).

N-[9-(p-*Anisyl*)*purin-6-yl*]-L-*threonine* **3c** (67%): mp 207–209 °C (Found: C, 56.1; H, 5.0; N, 20.3. $C_{16}H_{17}N_5O_4$ requires C, 55.98; H, 4.96; N, 20.41%); ν_{max}/cm^{-1} 3363 (NH), 1706 (C=O), 1252 (CO_2H); δ_H 1.22 (d, 3 H, γ-CH_3), 3.84 (s, 3 H, OCH_3), 4.35 (m, 1 H, β-CH); 4.75 (d, 1 H, α-CH); 5.56 (br, 1 H, OH, D_2O-exchangeable), 7.07 (br, 1 H, NH, D_2O-exchangeable), 7.16 (d, 2 H, ArH), 7.77 (d, 2 H, ArH), 8.30 (s, 1 H, 8-H), 8.50 (s, 1 H, 2-H); *m*/*z* 343 (M^+).

N-[9-(p-*Anisyl*)*purin-6-yl*]-L-*methionine* **3d** (71%): mp 147–149 °C (Found: C, 54.5; H, 5.0; N, 19.0. $C_{17}H_{19}N_5O_3S$ requires C, 54.69; H, 5.09; N, 18.77%); ν_{max}/cm^{-1} 3302 (NH), 1718 (C=O), 1249 (CO_2H); δ_H 2.05 (s, 3 H, SCH_3) 2.20 (m, 2 H, β-CH_2), 2.60 (m, 2 H, γ-CH_2), 3.85 (s, 3 H, OCH_3), 4.40 (m, 1 H, α-CH), 7.10 (d, 2 H, ArH), 7.75 (d, 2 H, ArH), 8.10 (br, 1 H, NH, D_2O-exchangeable), 8.25 (s 1 H, 8-H), 8.52 (s, 1 H, 2-H); *m*/*z* 373 (M^+).

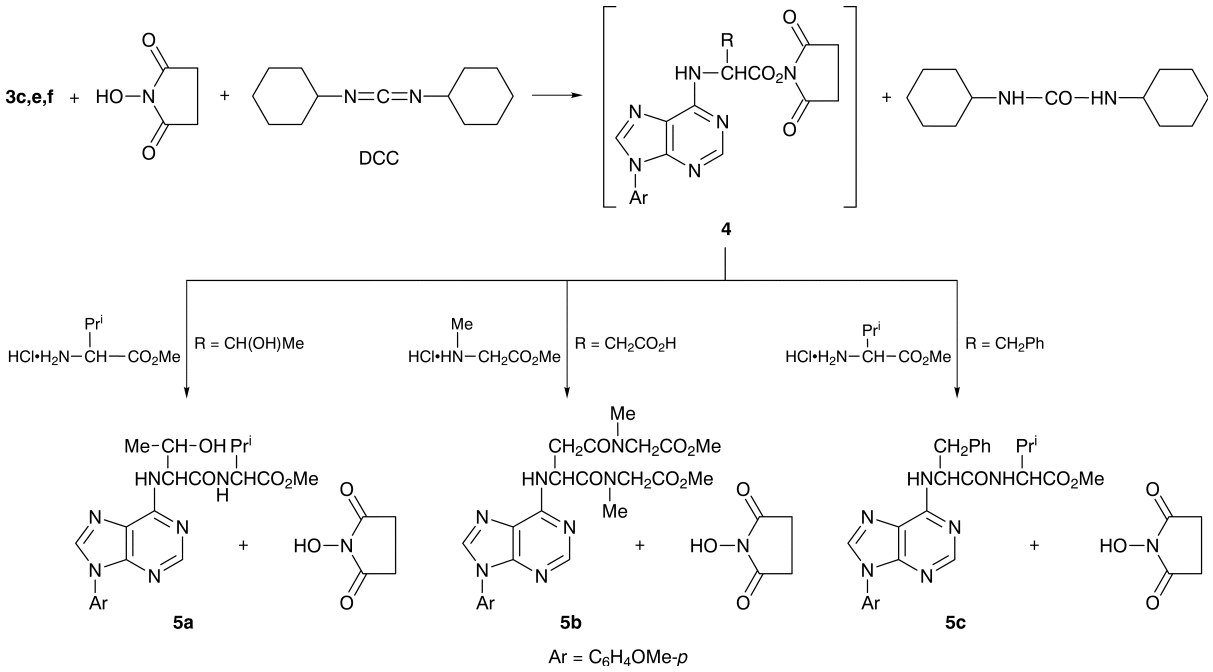
N-[9-(p-*Anisyl*)*purin-6-yl*]-L-*aspartic* **3e** (68%):, mp 197–199 °C (Found: C, 54.0; H, 4.1; N, 19.5. $C_{16}H_{15}N_5O_5$ requires C, 53.78; H, 4.20; N, 19.61%); ν_{max}/cm^{-1} 3383 (NH), 1710 (C=O); δ_H 2.93



Scheme 1

*To receive any correspondence.

†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.



Scheme 2

(d, 2 H, β-CH_2), 3.84 (s, 3 H, OCH_3), 5.14 (m, 1 H, α-CH), 7.15 (d, 2 H, ArH), 7.76 (d, 2 H, ArH), 7.96 (br, 1 H, NH, D_2O-exchangeable), 8.31 (s, 1 H, 8-H), 8.55 (s, 1 H, 2-H); *m*/*z* 357 (M^+).

N-[9-(p-*Anisyl*)*purin*-6-*yl*]-L-*phenylalanine* **3f** (69%): mp 122–124 °C (Found: C, 64.8; H, 5.0, N, 18.1. $C_{21}H_{19}N_5O_3$ requires C, 64.78; H, 4.88; N, 17.99%); ν_{max}/cm^{-1} 3281 (NH), 1716 (C=O), 1251 (CO_2H); δ_H 3.27 (d, 2 H, β-CH_2), 3.83 (s, 3 H, OCH_3), 4.95 (q, 1 H, α-CH), 7.00–7.40 (m, 7 H, Ph, ArH), 7.75 (d, 2 H, ArH), 7.85 (br, 1 H, NH, D_2O-exchangeable), 8.24 (s, 1 H, 8-H), 8.85 (s, 1 H, 2-H); *m*/*z* 389 (M^+).

N-[9-(p-*Anisyl*)*purin*-6-*yl*]-L-*histidine* **3g** (60%): mp 257–259 °C (Found: C, 57.1; H, 4.6; N, 26.0. $C_{18}H_{17}N_7O_3$ requires C, 56.99; H, 4.49; N, 25.86%); ν_{max}/cm^{-1} 3380 (NH), 1728 (C=O), 1254 (CO_2H); δ_H 3.80 (d, 2 H, β-CH_2), 3.86 (s, 3 H, OCH_3), 4.60 (m, 1 H, α-CH), 7.15 (d, 2 H, ArH), 7.67 (d, 2 H, ArH), 7.80 (d, 1 H, 4-H, his.), 8.10 (s, 1 H, 2-H, his.), 8.37 (s, 1 H, 8-H), 8.49 (s, 1 H, 2-H), 9.01 (br, 1 H, NH, D_2O-exchangeable); *m*/*z* 379 (M^+).

N-[9-(p-*Anisyl*)*purin*-6-*yl*]-L-*proline* **3h** (60%): mp 132–134 °C (Found: C, 60.3; H, 5.0; N, 20.5. $C_{17}H_{17}N_5O_3$ requires C, 60.18; H, 5.01; N, 20.65%); ν_{max}/cm^{-1} 1728 (C=O), 1248 (CO_2H); δ_H 2.05 (m, 2 H, γ-CH_2), 2.34 (m, 2 H, β-CH_2), 3.78 (m, 1 H, δ-CH_2), 3.84 (s, 3 H, OCH_3), 4.23 (m, 1 H, δ-CH_2), 4.68, 5.41 (2d, 1 H, α-CH), 7.15 (d, 2 H, ArH), 7.75 (d, 2 H, ArH), 8.29 (d, 1 H, 8-H), 8.51 (d, 1 H, 2-H); *m*/*z* 339 (M^+).

N-(*Purin*-6-*yl*)*peptides* **5a–c**: *General Procedure*.—To a stirred cold (ice-bath) solution of **3c**, **e** or **f** (5 mmol) and *N*-hydroxysuccinimide (5 mmol) in THF (20 ml) dicyclohexylcarbodiimide (DCC) (5 mmol) was added. Stirring was continued for 2 h at 0–5 °C. The *N*,*N*′-dicyclohexylurea which separated was removed by filtration and the solvent was evaporated *in vacuo* to give the active esters **4**.

To a stirred cold (ice-bath) solution of **4** (4 mmol) in THF (20 ml), the desired amino acid ester hydrochloride (4 mmol) and triethylamine (4 mmol) in tetrahydrofuran (20 ml) were added. Stirring was continued for 4 h while cooling and the pH was adjusted to 8–9. Stirring was continued at room temperature for a further 3 h and then the mixture was filtered.

N-[9-(p-*Anisyl*)*purin*-6-*yl*]-L-*threonyl*-L-*valine methyl ester* **5a** (46%): mp 159–161 °C (Found: C, 58.1; H, 6.3; N, 18.2. $C_{22}H_{28}N_6O_5$ requires C, 57.89; H, 6.14; N, 18.42%); ν_{max}/cm^{-1} 3327 (NH), 1741 (C=O ester), 1624 (C=O amide); δ_H ($CDCl_3$) 0.70–1.40 (m, 9 H, 3 × CH_3), 1.90 (m, 1 H, β-CH val.), 3.80 (m, 1 H, β-CH thr.); 3.85 (s, 6 H, 2 × OCH_3), 4.20 (m, 1 H, α-CH thr.), 4.32 (m, 1 H, α-CH val.), 5.15 (br, 1 H, OH, D_2O-exchangeable)), 6.15 (br, 1 H, NH, D_2O-exchangeable); 7.05 (d, 2 H, ArH), 7.40–7.70 (m, 3 H, ArH, CONH), 8.55 (d, 1 H, 8-H), 8.85 (d, 1 H, 2-H).

N-[9-(p-*Anisyl*)*purin*-6-*yl*]-L-*aspartylsarcosine methyl ester* **5b** (40%): oil (Found: C, 54.5; H, 5.3; N, 18.8. $C_{24}H_{29}N_7O_7$ requires C, 54.65; H, 5.50; N, 18.60%); ν_{max}/cm^{-1}, 3320 (NH), 1684 (C=O ester), 1654 (C=O amide); δ_H ($CDCl_3$) 2.67 (d, 6 H, 2 × NCH_3), 3.10 (m, 2 H, β-CH_2 asp.), 3.45 (m, 2 H, CH_2 sar.), 3.70 (m, 2 H, CH_2 sar.), 3.86 (d, 6 H, 2 × OCH_3), 4.20 (m, 1 H, α-CH asp.), 6.05 (br, 1 H, NH, D_2O-exchangeable), 7.06 (d, 2 H, ArH), 7.50 (m, 3 H, ArH, CONH), 8.60 (s, 1 H, 8-H), 8.80 (s, 1 H, 2-H).

N-[9-(p-*Anisyl*)*purin*-6-*yl*]-L-*phenylalanyl*-L-*valine methyl ester* **5c** (42%): mp 194–196 °C (Found: C, 64.7; H, 6.1; N, 17.0. $C_{27}H_{30}N_6O_4$ requires C, 64.54; H, 5.98; N, 16.73%); ν_{max}/cm^{-1} 3326 (NH), 1738 (C=O ester), 1622 (C=O amide); δ_H 1.05 (m, 6 H, 2 × CH_3), 2.20 (m, 1 H, β-CH val.), 3.30 (s, 2 H, CH_2), 3.80 (d, 6 H, 2 × OCH_3); 4.15 (m, 1 H, α-CH val.), 5.55 (d, 1 H, α-CH phe.), 5.80 (br, 1 H, NH, D_2O-exchangeable), 7.00–7.90 (m, 10 H, Ph, ArH, CONH), 8.70 (s, 1 H, 8-H), 8.80 (s, 1 H, 2-H); *m*/*z* 502 (M^+).

Biological Screening.—The biological activity screening was carried out at the National Cancer Institute, Bethesda, Maryland, USA.

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