

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-ribose-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 antiviral⁵ activity, as cardiovascular agents⁶ 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-chloropurine⁸ (**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 afforded (Scheme 1).

The structure of products **3a–h** was elucidated by careful study of their IR absorption spectra which showed ν_{NH} and $\nu_{\text{C=O}}$ 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 Screening.—(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 procedure¹² 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. $\text{C}_{14}\text{H}_{13}\text{N}_5\text{O}_3$ requires C, 56.19; H, 4.35; N, 23.41%); $\nu_{\text{max}}/\text{cm}^{-1}$ 3413 (NH), 1718 (C=O), 1242 (COOH) δ_{H} 3.84 (s, 3 H, OCH₃), 4.18 (s, 2 H, α -CH₂), 7.14 (d, 2 H,

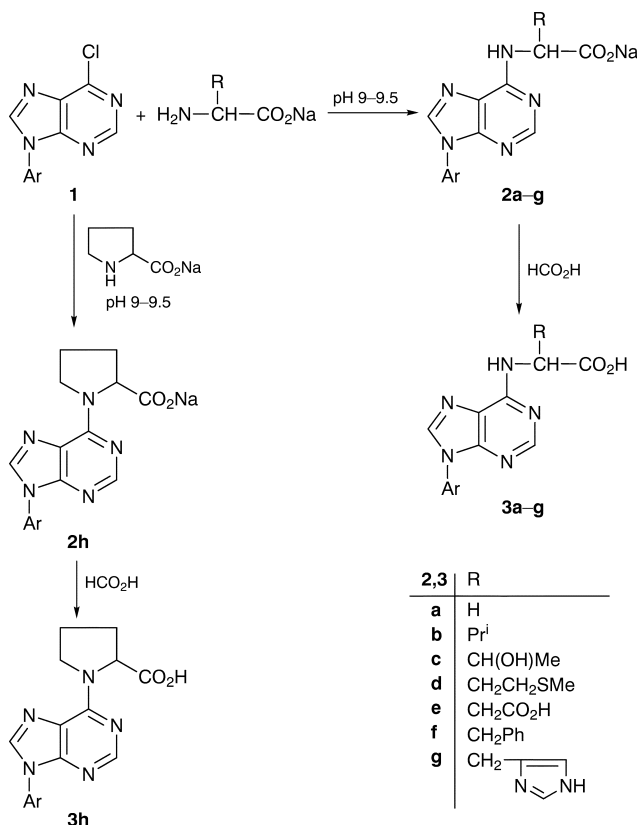
ArH), 7.76 (d, 2 H, ArH), 8.05 (br, 1 H, NH, D₂O-exchangeable), 8.28 (s, 1 H, 8-H), 8.52 (s, 1 H, 2-H); m/z 299 (M^+).

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. $\text{C}_{17}\text{H}_{19}\text{N}_5\text{O}_3$ requires C, 59.82; H, 5.57; N, 20.53%); $\nu_{\text{max}}/\text{cm}^{-1}$ 3293 (NH), 1718 (C=O); 1251 (CO₂H); δ_{H} 1.02 (t, 6 H, γ -CH₃), 2.32 (m, 1 H, β -CH), 3.84 (s, 3 H, OCH₃), 4.05 (m, 1 H, α -CH), 7.15 (d, 2 H, ArH), 7.53 (br, 1 H, NH, D₂O-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. $\text{C}_{16}\text{H}_{17}\text{N}_5\text{O}_4$ requires C, 55.98; H, 4.96; N, 20.41%); $\nu_{\text{max}}/\text{cm}^{-1}$ 3363 (NH), 1706 (C=O), 1252 (CO₂H); δ_{H} 1.22 (d, 3 H, γ -CH₃), 3.84 (s, 3 H, OCH₃), 4.35 (m, 1 H, β -CH); 4.75 (d, 1 H, α -CH); 5.56 (br, 1 H, NH, D₂O-exchangeable), 7.07 (br, 1 H, NH, D₂O-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. $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_3\text{S}$ requires C, 54.69; H, 5.09; N, 18.77%); $\nu_{\text{max}}/\text{cm}^{-1}$ 3302 (NH), 1718 (C=O), 1249 (CO₂H); δ_{H} 2.05 (s, 3 H, SCH₃), 2.20 (m, 2 H, β -CH₂), 2.60 (m, 2 H, γ -CH₂), 3.85 (s, 3 H, OCH₃), 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, D₂O-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. $\text{C}_{16}\text{H}_{13}\text{N}_5\text{O}_5$ requires C, 53.78; H, 4.20; N, 19.61%); $\nu_{\text{max}}/\text{cm}^{-1}$ 3383 (NH), 1710 (C=O); δ_{H} 2.93

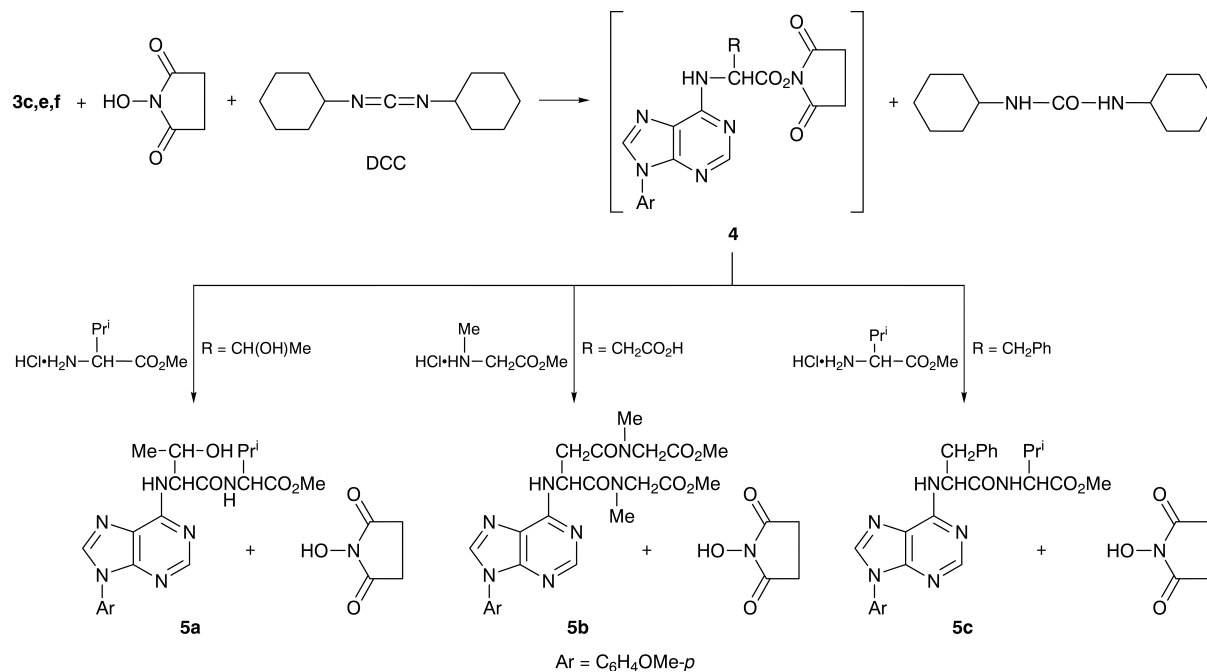


Ar = C₆H₄OMe-p

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 -CH₂), 3.84 (s, 3 H, OCH₃), 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, D₂O-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. C₂₁H₁₉N₅O₃ requires C, 64.78; H, 4.88; N, 17.99%); $\nu_{\max}/\text{cm}^{-1}$ 3281 (NH), 1716 (C=O), 1251 (CO₂H); δ_{H} 3.27 (d, 2 H, β -CH₂), 3.83 (s, 3 H, OCH₃), 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, D₂O-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. C₁₈H₁₇N₇O₃ requires C, 56.99; H, 4.49; N, 25.86%); $\nu_{\max}/\text{cm}^{-1}$ 3380 (NH), 1728 (C=O), 1254 (CO₂H); δ_{H} 3.80 (d, 2 H, β -CH₂), 3.86 (s, 3 H, OCH₃), 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, D₂O-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. C₁₇H₁₇N₅O₃ requires C, 60.18; H, 5.01; N, 20.65%); $\nu_{\max}/\text{cm}^{-1}$ 1728 (C=O), 1248 (CO₂H); δ_{H} 2.05 (m, 2 H, γ -CH₂), 2.34 (m, 2 H, β -CH₂), 3.78 (m, 1 H, δ -CH₂), 3.84 (s, 3 H, OCH₃), 4.23 (m, 1 H, δ -CH₂), 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-[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. C₂₂H₂₈N₆O₅ requires C, 57.89; H, 6.14; N, 18.42%); $\nu_{\max}/\text{cm}^{-1}$ 3327 (NH), 1741 (C=O ester), 1624 (C=O amide); δ_{H} (CDCl₃) 0.70–1.40 (m, 9 H, 3 \times CH₃), 1.90 (m, 1 H, β -CH val.), 3.80 (m, 1 H, β -CH thr.); 3.85 (s, 6 H, 2 \times OCH₃), 4.20 (m, 1 H, α -CH thr.), 4.32 (m, 1 H, α -CH val.), 5.15 (br, 1 H, OH, D₂O-exchangeable), 6.15 (br, 1 H, NH, D₂O-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. C₂₄H₂₉N₇O₇ requires C, 54.65; H, 5.50; N, 18.60%); $\nu_{\max}/\text{cm}^{-1}$, 3320 (NH), 1684 (C=O

ester), 1654 (C=O amide); δ_{H} (CDCl₃) 2.67 (d, 6 H, 2 \times NCH₃), 3.10 (m, 2 H, β -CH₂ asp.), 3.45 (m, 2 H, CH₂ sar.), 3.70 (m, 2 H, CH₂ sar.), 3.86 (d, 6 H, 2 \times OCH₃), 4.20 (m, 1 H, α -CH asp.), 6.05 (br, 1 H, NH, D₂O-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. C₂₇H₃₀N₆O₄ requires C, 64.54; H, 5.98; N, 16.73%); $\nu_{\max}/\text{cm}^{-1}$ 3326 (NH), 1738 (C=O ester), 1622 (C=O amide); δ_{H} 1.05 (m, 6 H, 2 \times CH₃), 2.20 (m, 1 H, β -CH val.), 3.30 (s, 2 H, CH₂), 3.80 (d, 6 H, 2 \times OCH₃), 4.15 (m, 1 H, α -CH val.), 5.55 (d, 1 H, α -CH phe.), 5.80 (br, 1 H, NH, D₂O-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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