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Novel synthetic routes to *N*-(2-amino-9*H*-purin-6-yl)-substituted amino acids

Alexey Yu. Vigorov, Viktor P. Krasnov,* Dmitry A. Gruzdev, Alisa A. Men'shikova, Alexander M. Demin, Galina L. Levit and Valery N. Charushin

I. Ya. Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 620990 Ekaterinburg, Russian Federation. Fax: +7 343 369 3058; e-mail: ca@ios.uran.ru

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Reaction of N^2-protected 2-amino-6-chloropurine with *tert*-butyl (*S*)-phenylalaninate, (*R*)- and (*S*)-valinates followed by deprotection affords 2-aminopurines bearing at 6-position the corresponding amino acid moieties, whose chiral centre is partially racemized.

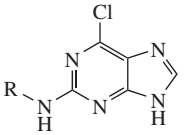
Currently a lot of attention is paid to the synthesis and study of nucleoside analogues, among which the compounds exhibiting antiviral and anticancer activity have been found.[1–3] For instance, Nelarabine [2-amino-9-(β-D-arabinofuranosyl)-6-methoxy-9*H*-purine][4] and Fludarabine [9-(β-D-arabinofuranosyl)-2-fluoro-adenine][5] are used for treatment of lymphoblastic leukemias.

Modification of various biologically active compounds by introduction of amino acid moieties into their structure is one of the most important approaches to achieve the optimal pharmacokinetic and pharmacodynamic characteristics of potential drugs.[6–14] The 9*H*-purine-based nucleoside analogues with amino acids fragments exhibit cytostatic,[15] antimicrobial[16] and antiviral[17,18] activity. The published synthetic routes to such compounds are based on the introduction of amino acid residues in N^9-substituted purines.[15,16,19,20] This approach makes it impossible to vary the structures of substituents in 9-position of purine fragment.

The purpose of this study was to develop the synthetic routes to the purine derivatives containing amino acid residues at C^6-position. Particular attention has been given to the preparation of purine derivatives with free functional groups in the amino acid and purine moieties available for further modification.

Attempted reactions of 2-amino-6-chloro-9*H*-purine **1** with *tert*-butyl (*S*)-phenylalaninate [(*S*)-PheOBu^t], (*R*)-valinate [(*R*)-ValOBu^t] and (*S*)-valinate [(*S*)-ValOBu^t] as well as methyl (*S*)-phenylalaninate [(*S*)-PheOMe] [Et_3N as the base, *N*,*N*-dimethylacetamide (DMA), 100 °C] did not afford the target products. Probably, a positive mesomeric effect of amino group at C^2 atom deactivated the purine derivative to attack by nucleophiles.[21]

Therefore, we turned to N^2-protected 2-amino-6-chloropurines **2**–**5**, such as *N*-acetyl, *N*-formyl, *N*-Boc and *N*-trifluoroacetyl derivatives. Reactions of compounds **2**–**5** with (*S*)-PheOBu^t hydrochloride were carried out at a 1:3 molar ratio in the presence of Et_3N in DMA at 100 °C for 12 h (Scheme 1). In the case of *N*-acetyl derivative **2** the product of nucleophilic substitution of chlorine; compound **7**,† was isolated as acetate in 63% yield.

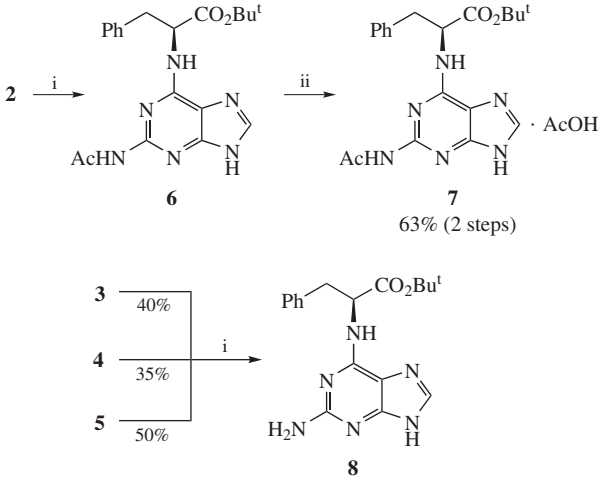


1 R = H
2 R = C(O)Me
3 R = CHO
4 R = C(O)OBu^t
5 R = C(O)CF_3

Reactions of derivatives **3**–**5** with (*S*)-PheOBu^t hydrochloride under the same conditions were accompanied by the removal of N^2-protection resulting in *tert*-butyl *N*-(2-amino-9*H*-purin-6-yl)-(*S*)-phenylalaninate **8**‡ in 40, 35, and 50% yields, respectively.

Methyl (*S*)-phenylalaninate proved to be less suitable for the preparation of *N*-(2-amino-9*H*-purin-6-yl) derivatives. For example, the nucleophilic substitution of chlorine in compound **2** under the action of (*S*)-PheOMe was complicated by formation of the corresponding diketopiperazine derivative as by-product.[22]

To obtain the unprotected C^6-derivatives of 2-amino-9*H*-purine, we carried out the hydrolysis of *tert*-butyl *N*-(2-acetamido-9*H*-

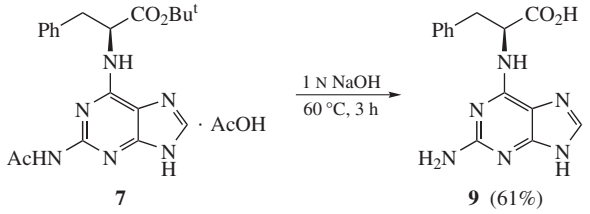


Scheme 1 *Reagents and conditions*: i, (*S*)-PheOBu^t·HCl, TEA, DMA, 100 °C, 12 h; ii, AcOH, hexane.

† tert-*Butyl* N-*(2-acetylamino-9*H*-purin-6-yl)-(*S*)-phenylalaninate acetate* **7**: colourless crystals, mp 118–125 °C, $[\alpha]_D^{20}$ –2.85 (*c* 1.0, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 100 °C) δ: 1.34 (s, 9H, Bu^t), 1.90 (s, 3H, *Me*CO_2H), 2.25 (s, 3H, MeCO), 3.21 (d, 2H, CH_2-Phe, *J* 6.5 Hz), 5.10 (br. s, 1H, CH-Phe), 6.92 (br. s, 1H, $C^{6'}$NH), 7.17 (m, 1H, Ph), 7.25 (m, 4H, Ph), 7.90 (s, 1H, $C^{8'}$H), 9.16 (s, 1H, N*H*Ac), 11.99 (br. s, 2H, $N^{9'}$H, MeCO_2*H*). ^{13}C NMR (DMSO-d_6) δ: 20.96 (*Me*CO_2H), 24.61 (*Me*CONH), 27.47 (C*Me*$_3$), 36.53 (CH_2-Phe), 54.95 (CH-Phe), 80.61 (*C*Me$_3$), 115.75 ($C^{5'}$), 126.31 (*p*-Ph), 128.08 (*o*-Ph), 129.11 (*m*-Ph), 137.78 and 138.39 ($C^{8'}$ and *i*-Ph), 150.70 and 152.39 ($C^{4'}$ and $C^{2'}$), 153.81 ($C^{6'}$), 169.40, 171.12 and 171.88 (C=O in AcNH, AcOH and CO_2Bu^t). Found (%): C, 58.06; H, 6.12; N, 18.60. Calc. for $C_{22}H_{28}N_6O_5$ (%): C, 57.89; H, 6.18; N, 18.41.

‡ tert-*Butyl* N-*(2-amino-9*H*-purin-6-yl)-(*S*)-phenylalaninate* **8**: yellowish powder, mp 123 °C, $[\alpha]_D^{25}$ –4.54 (*c* 1.0, $CHCl_3$). ^{1}H NMR (DMSO-d_6) δ: 1.33 (s, 9H, Bu^t), 3.03–3.23 (m, 2H, CH_2-Phe), 4.77 (br. s, 1H, CH-Phe), 5.69 (s, 2H, $C^{2'}NH_2$), 7.03 (br. s, 1H, $C^{6'}$NH), 7.20 (m, 1H, Ph), 7.24–7.31 (m, 4H, Ph), 7.68 (s, 1H, $C^{8'}$H), 12.12 (br. s, 1H, $N^{9'}$H). ^{13}C NMR (DMSO-d_6) δ: 27.52 (C*Me*$_3$), 36.97 (CH_2-Phe), 54.63 (CH-Phe), 80.46 (*C*Me$_3$), 112.68 ($C^{5'}$), 126.31 (*p*-Ph), 128.07 (*o*-Ph), 129.16 (*m*-Ph), 135.89 ($C^{8'}$), 137.72 (*i*-Ph), 152.46 and 153.75 ($C^{4'}$ and $C^{2'}$), 159.66 ($C^{6'}$), 171.36 (*C*O_2Bu^t). HRMS, m/z: 355.1877 $[M+H]^+$ (calc. for $C_{18}H_{23}N_6O_2$, *m*/*z*: 355.1882).

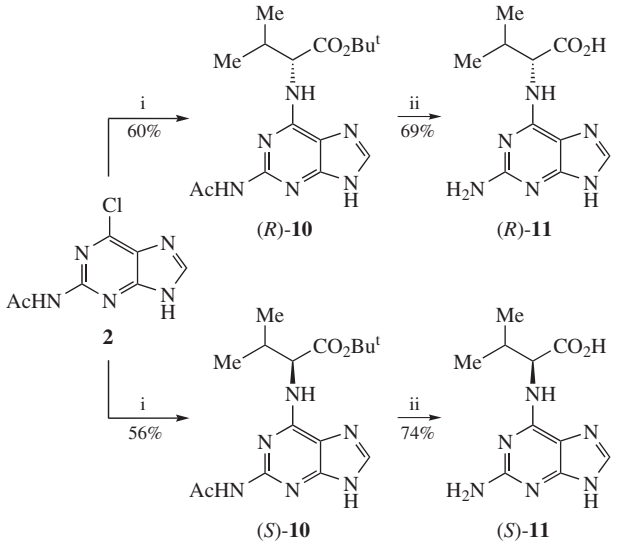
purin-6-yl)-(*S*)-phenylalaninate acetate **7** in 1 N NaOH at 60 °C (Scheme 2). Under these conditions the simultaneous removal of both N^2-acetyl and *tert*-butyl ester group occurred to yield *N*-(2-amino-9*H*-purin-6-yl)-(*S*)-phenylalanine **9**.§



7 **9** (61%)

Scheme 2

This approach is also suitable for the synthesis of other *N*-(2-amino-9*H*-purin-6-yl) amino acids, *e.g.*, *N*-(2-amino-9*H*-purin-6-yl)-(*R*)- and (*S*)-valines, (*R*)-**11** and (*S*)-**11** (Scheme 3).¶ Preparation of compounds (*R*)-**11** and (*S*)-**11** starting from compound **2** and (*R*)- or (*S*)-valinates **10**, respectively, made it possible to evaluate the degree of racemization of the chiral center in the amino acid moiety that occurred during the two-step process.



Scheme 3 *Reagents and conditions*: i, (*R*)- or (*S*)-ValOBu^t·AcOH, TEA, DMA, 100 °C, 12 h; ii, 1 N NaOH, 60 °C, 3 h.

§ N-*(2-Amino-9*H*-purin-6-yl)-(*S*)-phenylalanine* **9**: colourless solid, mp 234–236 °C (decomp.), $[\alpha]_D^{30}$ +14.6 (*c* 0.2, DMF). ^{1}H NMR (DMSO-d_6) δ: 3.20 (m, 2H, CH_2-Phe), 4.88 (br. s, 1H, CH-Phe), 5.75 (s, 2H, NH_2), 7.00 (br. s, 1H, C$^{6'}$NH), 7.17 (m, 1H, Ph), 7.26 (m, 4H, Ph), 7.67 (s, 1H, C$^{8'}$H), 12.2 (br. s, 2H, N$^{9'}$H and CO_2H). ^{13}C NMR (DMSO-d_6) δ: 36.57 (CH_2-Phe), 53.77 (CH-Phe), 112.23 (C$^{5'}$), 126.26 (*p*-Ph), 128.09 (*o*-Ph), 129.07 (*m*-Ph), 135.94 (C$^{8'}$), 138.06 (*i*-Ph), 152.22 (C$^{4'}$), 153.79 (C$^{2'}$), 159.57 (C$^{6'}$), 173.63 (CO_2H). HRMS, *m/z*: 299.1251 [M+H]$^+$ (calc. for $C_{14}H_{15}N_6O_2$, *m/z*: 299.1256).

¶ N-*(2-Amino-9*H*-purin-6-yl)-(*R*)-valine* (*R*)-**11**: colourless solid, mp 267–268 °C (decomp.), *ee* 81%. Chiral RP HPLC [ChiraDex, MeCN–H_2O (8:2), 0.8 ml min^{-1}] τ_R: 5.9 min. ^{1}H NMR (DMSO-d_6) δ: 0.96 (d, 3H, Me-Val, *J* 6.8 Hz), 0.97 (d, 3H, Me-Val, *J* 6.7 Hz), 2.22 (m, C$^{\beta}$H-Val), 4.64 (br. s, 1H, C$^{\alpha}$H-Val), 5.86 (s, 2H, NH_2), 6.68 (br. s, 1H, C$^{6'}$NH), 7.75 (s, 1H, C$^{8'}$H), 12.3 (br. s, 2H, N$^{9'}$H and CO_2H). ^{13}C NMR (DMSO-d_6) δ: 18.29 (Me-Val), 19.12 (Me-Val), 30.15 (C$^{\beta}$H-Val), 57.61 (C$^{\alpha}$H-Val), 112.15 (br. s, C$^{5'}$), 136.69 (C$^{8'}$), 152.68 and 153.72 (C$^{4'}$ and C$^{2'}$), 159.38 (C$^{6'}$), 173.66 (CO_2H). Found (%): C, 47.70; H, 5.59; N, 33.39. Calc. for $C_{10}H_{14}N_6O_2$ (%): C, 47.99; H, 5.64; N, 33.58.

N-*(2-Amino-9*H*-purin-6-yl)-(*S*)-valine* (*S*)-**11**: colourless solid, mp 270–272 °C (decomp.), *ee* 86%. Chiral RP HPLC [ChiraDex, MeCN–H_2O (8:2), 0.8 ml min^{-1}] τ_R: 6.8 min. NMR spectra were identical to those for compound (*R*)-**11**.

The enantiomeric excess (*ee*) of compounds (*R*)-**11** and (*S*)-**11** was 81 and 86%, respectively, according to the chiral HPLC.

The structures of the compounds obtained were confirmed by the ^{1}H and ^{13}C NMR spectroscopy, elemental analyses (or HRMS) and LC-MS.

In conclusion, the prepared *N*-(2-amino-9*H*-purin-6-yl) derivatives of amino acids, which are not substituted at N^9-position, can be suitable for further synthesis of novel nucleosides thereof. The starting material is readily available 2-amino-6-chloropurine.

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Online Supplementary Materials

Supplementary data associated with this article (details of synthetic procedures and characteristics of compounds) can be found in the online version at doi:10.1016/j.mencom.2013.12.011.

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