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Synthesis of novel purin-6-yl conjugates with heterocyclic amines linked *via* 6-aminohexanoyl fragment

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Novel conjugates of purine and 2-aminopurine linked with heterocyclic amines, including chiral derivatives of 3,4-dihydro-2*H*-[1,4]benzoxazine, 3,4-dihydro-2*H*-[1,4]benzothiazine and 1,2,3,4-tetrahydroquinoline, by 6-aminohexanoyl fragment at the 6-position of purine moiety were obtained. For this purpose, replacement of the chlorine atom in 2-amino-6-chloropurine or 6-chloropurine by direct nucleophilic substitution reaction with 6-aminohexanamides or the coupling of 6-(purin-6-ylamino)-6-hexanoic acid with nitrogen heterocycles were used.

Purine derivatives with C-6-amino substituents have attracted considerable attention due to their physiological and pharmacological properties.[1–9] On the other hand, heterocyclic amines possess a wide spectrum of biological activity. However, there are only a few examples of synthesis of 2-aminopurine derivatives bearing the fragments of chiral amines.[10–12] Note that the introduction of linker/spacer fragments between a nucleobase and another part of the molecule appears to be a common approach in preparation of biologically active derivatives.[13–16] 6-Aminohexanoyl fragment was used as a linker in the synthesis of selective inhibitors of serine/threonine protein kinase Aurora A;[17] the antiproliferative activity of adenosine derivatives with 6-aminohexanoyl spacer was also reported.[18]

The purpose of this work was to obtain new 2-aminopurin-6-yl and purin-6-yl conjugates, in which the purine moiety is linked to heterocyclic amines **1–8** (Figure 1) *via* the 6-aminohexanoyl fragment. The presence of a free NH group at the 9-position of the purine system makes it possible to perform further transformations of the compounds obtained with the view of access to a new series of modified nucleosides. It should be emphasized that, since the biological activity of compounds depends substantially on their stereo configuration, the enantiomeric purity of the synthesized compounds is very important.

One of the most common approaches to introduction of amine residues at the 6-position of the purine system is the nucleophilic substitution of an appropriate good leaving group at C^6 in N^9-substituted purines with aliphatic or aromatic amines.[19–23] Most of the known preparative methods for 6-amino derivatives of (2-amino)purine with free NH group at the 9-position is based on the reaction of 6-chloropurine or its analogues with aliphatic or aromatic amines.[7,21,23–27] These reactions are usually carried out under drastic conditions, thus resulting in racemization of the target chiral compounds in those cases, when enantiopure amines are used as reactants. Thus, a partial racemization of (2-aminopurin-6-yl)amino acids was observed in nucleophilic substitution of chlorine in 2-acetamido-6-chloropurine under the treatment with *tert*-butyl esters of amino acids (as N-nucleophiles) followed by the removal of protecting groups.[28]

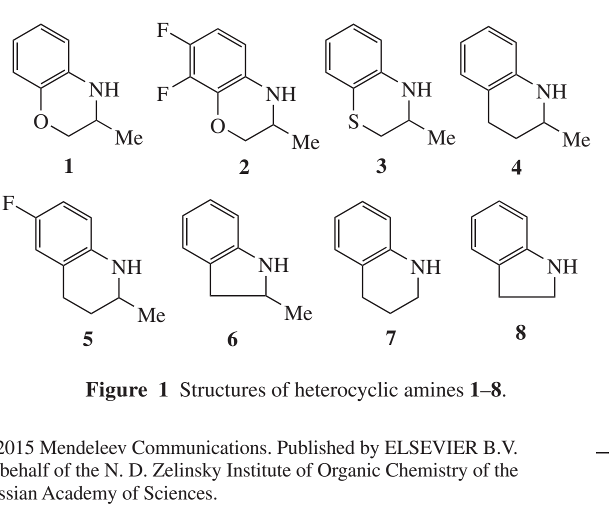
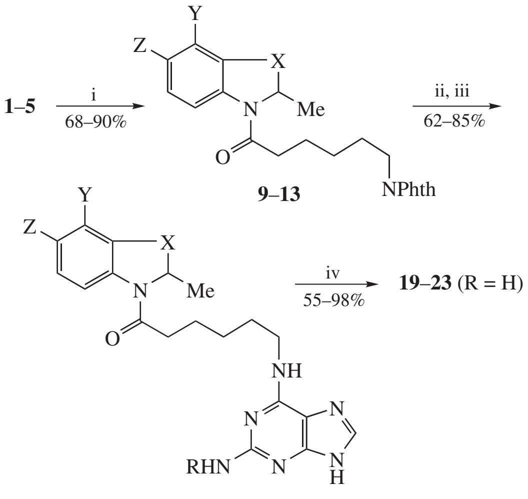


Figure 1 Structures of heterocyclic amines **1–8**.

Here we report the nucleophilic substitution of chlorine in 2-acetamido-6-chloropurine using enantiopure *N*-(6-aminohexanoyl) derivatives of heterocyclic amines **1–5**. To prepare the target compounds, we carried out the acylation of enantiopure amines **1–5** with 6-phthalimidohexanoyl chloride[29] in dichloromethane at room temperature in the presence of *N*,*N*-diethylaniline as a HCl acceptor and obtained the corresponding (*R*)- and (*S*)-amides **9–13** in 68–90% yields (Scheme 1).[†] Removal of the phthaloyl protection by hydrazinolysis in refluxing ethanol followed by the nucleophilic substitution of chlorine atom in 2-acetamido-6-chloropurine (TEA, DMA, 100 °C) similarly to the described method[28] afforded the corresponding (*R*)- and (*S*)-enantiomers of 2-acetamidopurin-6-yl derivatives **14–18** in 62–86% yields (relative to the starting 2-acetamido-6-chloropurine).[‡] Subsequent removal of the acetyl protecting group in amides **14–18** by alkaline hydrolysis under mild conditions afforded purine derivatives **19–23** containing unsubstituted 2-NH_2

[†] For procedures, see Online Supplementary Materials.

[‡] *Synthesis of 6-(2-acetamidopurin-6-yl)aminohexanoyl amines* **14–18** *(general procedure).* 64% Aqueous N_2H_4 (9.00 mmol, 0.44 ml) was added to a solution of corresponding amide **9–13** (5.00 mmol) in EtOH (30 ml). The reaction mixture was refluxed for 80 min, and then evaporated to dryness. 2 N HCl (30 ml) was added to the residue, the precipitate was filtered off; filtrate was alkalized with NaOH to pH 12 and extracted with diethyl ether (3×30 ml). Organic layers were dried (NaOH) and evaporated to dryness. The residue was re-dissolved in DMA (4.8 ml). 2-Acetamido-6-chloropurine (1.9 mmol, 0.402 g) and TEA (3.8 mmol, 0.53 ml) were added to the resulting solution. The reaction mixture was heated at 100 °C for 20 h, poured into water (50 ml), and kept at 5 °C for 16 h; the precipitate was separated by centrifuging, dried under reduced pressure and recrystallized from EtOH. The additional amount of the product was isolated from mother liquor by flash column chromatography. For characteristics of compounds **14–18**, see Online Supplementary Materials.



14–18 (R = Ac)

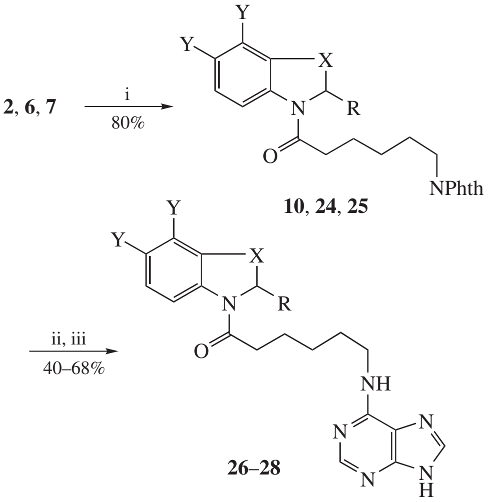
1, **9**, **14**, **19** X = OCH_2, Y = Z = H
2, **10**, **15**, **20** X = OCH_2, Y = Z = F
3, **11**, **16**, **21** X = SCH_2, Y = Z = H
4, **12**, **17**, **22** X = $(CH_2)_2$, Y = Z = H
5, **13**, **18**, **23** X = $(CH_2)_2$, Y = H, Z = F

Scheme 1 *Reagents and conditions*: i, $PhthN(CH_2)_5COCl$, $PhNEt_2$, CH_2Cl_2, room temperature; ii, N_2H_4, EtOH, Δ; iii, 2-acetamido-6-chloropurine, TEA, DMA, 100 °C; iv, 1 N NaOH, room temperature.

and 9-NH groups. No racemization of the chiral center at any step of the synthetic sequence was shown by chiral RP-HPLC.[§] Thus, *ee* values of 2-aminopurin-6-yl substituted (*R*)- and (*S*)-amides **14–18** and **19–23** were absolutely equal to those for the starting amines **1–5**.

The same approach was applied to the synthesis of racemic 6-purinyl derivatives **26–28** (Scheme 2). The reaction was carried out in *n*-BuOH at 85–90 °C similarly to the described procedure[7] and afforded the target compounds in 40–68% yields.[¶]

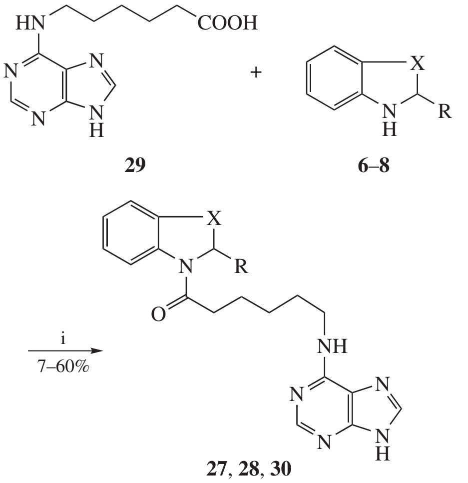
To obtain 6-purinyl derivatives **27**, **28**, **30** (Scheme 3) we used another protocol involving amidation of 6-(6-purinylamino)-hexanoic acid[30] **29** with racemic 2-methylindoline **6** and achiral amines **7** and **8** using *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(benzotriazol-1-yl)uronium tetrafluoroborate (TBTU) as a coupling agent in the presence of *N*,*N*-diisopropylethylamine (DIPEA).[††] However, the coupling of amines **6** and **7** with acid **29** afforded the target compounds **27** and **28** in lower yields (28 and ~7%, respectively) as compared with another approach (Scheme 2, yields of compounds **27** and **28** were 68 and 40%, respectively). Note that all attempts to perform the coupling of acid **29** with racemic 7,8-difluoro-3,4-dihydro-3-methyl-2*H*-[1,4]benzoxazine **2** and 2-methyl-1,2,3,4-tetrahydroquinoline **4** under the same conditions failed; only unreacted starting compounds were isolated from the reaction mixture.



2, **10**, **26** X = OCH_2, Y = F, R = Me
6, **24**, **27** X = CH_2, Y = H, R = Me
7, **25**, **28** X = $(CH_2)_2$, Y = R = H

Scheme 2 *Reagents and conditions*: i, $PhthN(CH_2)_5COCl$, $PhNEt_2$, CH_2Cl_2, room temperature; ii, N_2H_4, EtOH, Δ; iii, 6-chloropurine, *n*-BuOH, 90 °C, 12 h.

Thus, we applied two preparative approaches to the synthesis of purine and 2-aminopurine conjugates linked with heterocyclic amines *via* 6-aminohexanoyl fragment. When chiral amines are used, no racemization occurs during the synthetic sequence. All compounds obtained have free 9-NH group in the purine fragment,



27, **28**, **30**

6, **27** X = CH_2, R = Me
7, **28** X = $(CH_2)_2$, R = H
8, **30** X = CH_2, R = H

Scheme 3 *Reagents and conditions*: i, TBTU, DIPEA, DMSO/DMF.

[§] Analytical HPLC of compounds **10–13** was performed on a Knauer Smartline-1100 instrument using Chiralcel OD-H or Chiralpak AD (250×4.6 mm, 5 μm) columns, detection at 220 nm, 1 ml min^{-1} flow rate. HPLC of compounds **9**, **14–19** and **21–24** was performed on an Agilent 1100 instrument using a (S,S)-WHELK-O 1 (250×4.6 mm, 5 μm) column, detection at 254 nm, 0.8 ml min^{-1} flow rate. HPLC of compound **20** was performed on an Agilent 1200 instrument using a Kromasil Cellucoat column (150×4.6 mm, 5 μm), detection at 215 nm, 0.8 ml min^{-1} flow rate (for details, see Online Supplementary Materials).

[¶] *Synthesis of 6-(purin-6-yl)aminohexanoyl amines* **26–28** *(general procedure)*. Removal of *N*-phthaloyl protection in compounds **10**, **24**, **25** by hydrazinolysis was carried out as described above for preparation of compounds **14–18**. The residue was re-dissolved in BuOH (1 ml); 6-chloropurine (0.68 mmol, 0.11 g) and TEA (1.15 mmol, 0.16 ml) were added to the resulting solution. The reaction mixture was heated at 85–90 °C for 12 h, cooled to room temperature, washed subsequently with 1 N HCl (4×2 ml) and saturated aqueous NaCl (5×5 ml). Organic layer was dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography.

[††] *Synthesis of 6-(purin-6-yl)aminohexanoyl amines* **27**, **28**, **30** *(general procedure)*. Corresponding amine (0.80 mmol), DIPEA (2.47 mmol, 0.43 ml), and TBTU (0.88 mmol, 0.28 g) were added to a cold (0 °C) solution of acid **29** (0.80 mmol, 0.20 g) in a 4:1 mixture of DMSO/DMF (5 ml) at continuous stirring. The reaction mixture was stirred at 0 °C for 40 min, at room temperature for 48 h, and then poured into cold water (25 ml). The precipitate (in the case of compound **28**) was filtered off, washed with cold water (2×5 ml), and recrystallized from EtOH. In other cases, the reaction mixture was acidified to pH 3–5 with 1 N HCl and extracted with EtOAc (3×5 ml). Organic layers were dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography.

which makes it possible to carry out further transformations aimed at the preparation of modified nucleosides as a promising family of biologically active compounds.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.11.003.

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