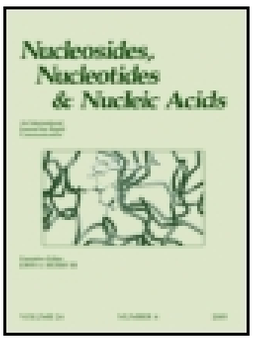

Nucleosides, Nucleotides and Nucleic Acids

ISSN: 1525-7770 (Print) 1532-2335 (Online) Journal homepage: http://www.tandfonline.com/loi/lncn20

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To cite this article: Yi-Ning Wen, Zhi-Feng Zhang, Ning-Ning Liu, Yu-Hong Xiang, Zhuo-Yong Zhang, Graciela Andrei, Robert Snoeck, Dominique Schols, Qing-Shan Zhang & Qin-Pei Wu (2016): Synthesis and Bioactivity of Novel Trisubstituted Triazole Nucleosides, Nucleosides, Nucleotides and Nucleic Acids, DOI: 10.1080/15257770.2015.1115523

To link to this article: http://dx.doi.org/10.1080/15257770.2015.1115523

Published online: 08 Feb 2016.

NUCLEOSIDES, NUCLEOTIDES AND NUCLEIC ACIDS
http://dx.doi.org/10.1080/15257770.2015.1115523

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Synthesis and Bioactivity of Novel Trisubstituted Triazole Nucleosides

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ABSTRACT
A series of novel trisubstituted 1,2,3-triazole purine nucleosides were efficiently synthesized via Huisgen 1,3-dipolar cycloaddition in good yields. Bioactivity against cytomegalovirus (CMV) and varicella-zoster virus (VZV) in human embryonic lung cell cultures was evaluated and all compounds show low antiviral activity.

ARTICLE HISTORY
Received 25 October 2015
Accepted 26 October 2015

KEYWORDS
triazole; nucleosides; Huisgen 1,3-dipolar cycloaddition; antiviral

Introduction

More than half of the clinic drugs for treating viral disease are nucleoside analogues.[1] Certain acyclic nucleosides, in which the ribose sugar is replaced with a chain structure, have outstanding biological activity,[2] an example is acyclovir, the first acyclic nucleoside drug approved for treating HSV-1, HSV-2 and VZV.[1,3] Other acyclic nucleoside drugs include ganciclovir-treating cytomegalovirus (CMV),[4] penciclovir-treating varicella-zoster virus (VZV),[4] adefovir-treating herpesviruses, retroviruses and HBV,[5] tenofovir used as an anti-HIV and anti-HBV agent,[6] cidofovir-treating herpesviruses (CMV), and adenoviruses (Figure 1).[7]

Ribavirin, the first example of atriazole-containing nucleoside drug, presents a broad spectrum of antiviral activity against many DNA and RNA viruses.[8] Among various structural modifications of nucleosides, 1,2,3-triazole-nucleoside analogues have been extensively studied and exhibit broad bioactivity,[9] such as antibacterial[10], antifungal[10b,10c,11], anticancer[12], and antiviral[13].These compounds include the replacement of sugar[9b,14] or nucleobases[15] with a 1,2,3-triazole moiety as well as an additional linker of 1,2,3-triazoles between a phosphonoalkyl unit and a nucleobase.[16]

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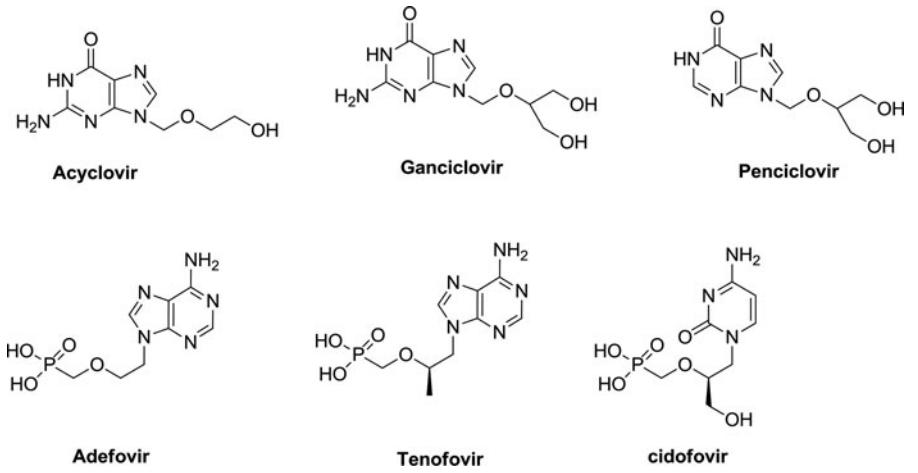


Figure 1. Antiviral acyclic nucleoside drugs.

In view of the fact that moderate activity is shown by compounds PTriaT, PTriaU, and PtriaA[16h] against HCV and by compound PTriaP towards HSV-1 and HSV-2 (Figure 2),[16j] we assumed that 4,5-double substituted 1,2,3-triazole-nucleoside analogues might be biologically active.

Results and Discussion

Chemistry

Azidation of ethyl bromoacetate **1** with NaN_3 gave ethyl 2-azidoacetate **2**, which was directly used to be cyclized with 1,4-butynediol at 110°C without any catalysts and the corresponding 4,5-bis(hydroxymethyl)-1,2,3-triazole **3** was formed in 51% yields.[17] Then selectively protecting one hydroxyl group in **3** was successfully performed in 73% yield via treatment with triphenylmethyl chloride. **4** was mesylated with methanesulfonyl chloride and then treated with nucleobases in DMF at room temperature to give the expected product **5** in good yields.[18] Removal of the trityl group was smoothly carried out in the presence of trifluoroacetic acid (TFA) to give the product **6a** and **6b** (Scheme 1).

The structures of target compounds **6a** and **6b** were proven on the basis of ^{1}H NMR and ^{13}C NMR spectroscopic analysis. The ^{1}H NMR spectrum of **6a** showed singlets at δ 8.80 and 8.67 ppm for CH of the 6-chloropurine group, with signals

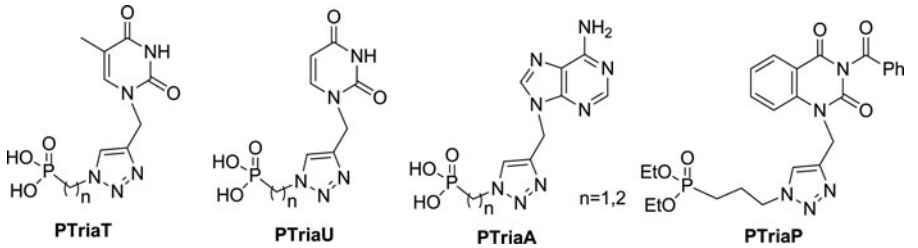
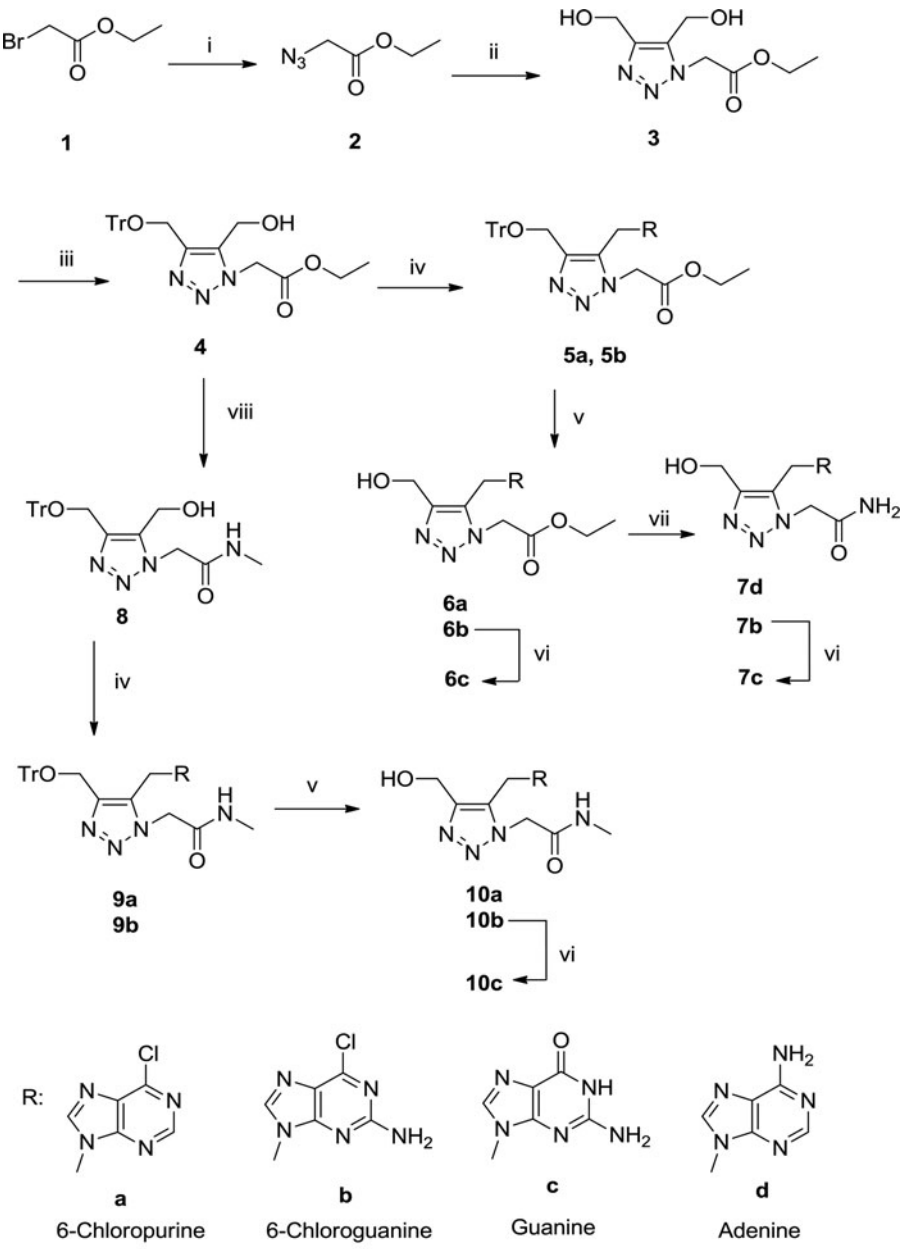


Figure 2. Structures of PTriaT, PTriaU, PtriaA, and PtriaP.



Reagents and conditions: (i) NaN_3, Acetone/H_2O, 60°C; (ii) 1,4-Butynediol,110°C; (iii) TrCl, Et_3N, 0°C, 5h; (iv) a. MsCl, Et_3N, 0°C; b. nucleobase, K_2CO_3,DMF,rt; (v) TFA, 0°C; (vi) TFA/H_2O=3:1;(vii) $NH_3 \cdot H_2O$, r.t.; (viii) CH_3NH_2, r.t.;

Scheme 1. Synthesis of 1,2,3-triazole-nucleosides.

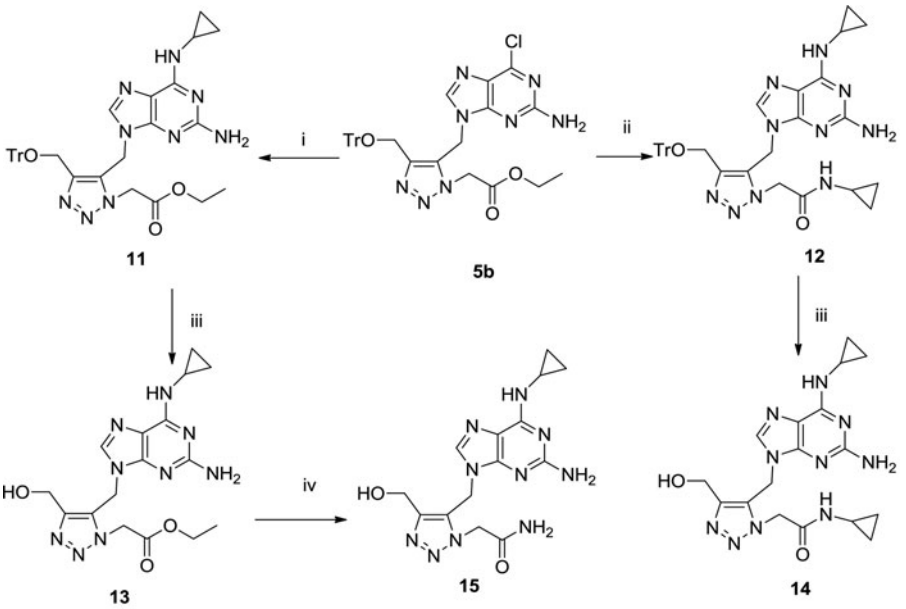
at δ 3.79 and 1.03 ppm as quartet and triplet for CH_2 and CH_3 of the ethoxycarbonyl group, in addition to singlets at δ 5.78, 5.57 and 4.74 ppm for three other CH_2, respectively. Its ^{13}C NMR spectra showed the characteristic signals at δ 166.82, 61.56 and 13.63 ppm corresponding to C=O, $\underline{C}H_2CH_3$ and $CH_2\underline{C}H_3$ of the ethoxycarbonyl group, signals at δ 151.72, 151.67, 149.12, 147.13, 146.87, 130.58, and 130.01 ppm for the 6-chloropurine group and triazole ring, in addition with signals

at δ 54.63, 49.20 and 34.54 ppm for three methylene groups, respectively. The spectroscopic analysis for **6b** was similar with that of **6a** and the data was in agreement with the structure.

After treatment of **6a** or **6b** with aqueous ammonia, the ester group was converted into the corresponding amides and the 6-chloropurine group was transformed into adenine, e.g. **6a** converted to **7d**. The 6-chloro atom in **6b**, however, is intact under this condition. In aqueous TFA solution (V(TFA)/V(H_2O) = 3:1), compounds **6b** and **7b** were converted to the corresponding guanine nucleosides **6c** and **7c**, respectively.[19] The ^{1}H NMR spectrum of **6c** showed the characteristic signal at δ 10.67 ppm as a singlet, which could prove this conversation.

Treatment of ester **4** with methylamine at room temperature formed the amidic compound **8**, which converted to nucleoside **9** in a good yield under similar condition for compound **5**. The ^{1}H NMR spectrum of **8** showed the characteristic signals at δ 8.28 and 2.66 ppm corresponding to the presence of the CH_3NH group. After deprotecting the trityl group of **9a** and **9b** in TFA-CH_2Cl_2 solution, **10a** and **10b** were obtained, respectively. The conversion of 6-chloroguanine **10b** to guanine **10c** was smoothly performed in TFA aqueous solution at room temperature.

Selective substitution of the chlorine atom in **5b** by amine was efficiently conducted via treatment with cyclopropylamine at 0°C to form **11**(**Scheme 2**). At 60°C, however, both the chlorine atom and the ester group were transformed to give **12**. The ^{1}H NMR spectrum of **11** showed signals at δ 3.19–3.17, 0.68–0.62, and 0.61–0.54 ppm as multiplets for the CH and CH_2 of the cyclopropyl group, with signals at δ 3.01 ppm as singlet for the NH of cyclopropylamino group, respectively. Its ^{13}C



Reagents and conditions: (i) Cyclopropylamine, K_2CO_3, DMF, 0°C; (ii)Cyclopropylamine,60°C, seal tube; (iii) TFA, 0°C; (iv) $NH_3 \cdot H_2O$, r.t.

Scheme 2. Synthesis of N^6-cyclopropyl-9*H*-purine-2,6-diamine1,2,3-triazole-nucleosides.

NMR spectrum showed the characteristic signals at δ 24.17 and 6.80 ppm corresponding to $\underline{C}H$ and $\underline{C}H_2$ of the cyclopropyl group, respectively. ^1H and ^{13}C NMR spectra of **12** showed the characteristic signals corresponding to the presence of two cyclopropylamino groups.

The final product **14** was obtained after treating **12** with TFA to remove the trityl group. Under similar deprotecting conditions, **13** was formed. Treatment of **13** with aqueous ammonia gave the target compound **15**.

Antiviral activity evaluation

All the synthesized compounds **6a–c, 7b-d, 10a-c**, and **13–15** were evaluated for antiviral activities against herpes viruses, using human embryonic lung (HEL) cell-based assays, cytomegalovirus (AD-169 strain and Davis strain), varicella-zoster virus (TK^+ VZVstrain and TK^- VZV strain). Ganciclovir, cidofovir, acyclovir, and brivudin were used as the reference compounds. The antiviral activity was expressed as the EC_{50}: the compound concentration required to reduce virus plaque formation by 50%. Unfortunately, none of these compounds demonstrated activity against these tested viruses as shown by the EC_{50} values (>20 μM, Table 1).The cytotoxicity of the tested compounds toward the uninfected host cells was defined as the minimum cytotoxic concentration (MCC) that causes a microscopically detectable alteration of normal cell morphology.

Table 1. Anti-CMV and anti-VZV activities of the synthesized compounds.

	CMV			VZV		
	EC_{50} (μM)[a]		Cytotoxicity (μM)	EC_{50} (μM)[a]		Cytotoxicity (μM)
Compound	AD-169	Davis	Cell morphology (MCC)[b]	TK^+ VZV	TK^-VZV	Cell morphology (MCC)[b]
6a	>20	>100	≥100	>100	>100	>100
6b	>20	100	≥100	>100	>100	>100
6c	>20	>100	≥100	>100	>100	>100
7b	>20	>100	≥100	>100	>100	>100
7c	>20	>100	≥100	>100	100	>100
7d	>20	>100	≥100	>100	>100	>100
10a	ND	ND	ND	ND	ND	ND
10b	>20	>100	≥100	>100	>100	>100
10c	>20	>100	≥100	>100	>100	>100
13	>20	>100	≥100	>100	>100	>100
14	>100	>100	≥100	>100	>100	>100
15	>100	>100	>100	>100	>100	>100
Ganciclovir	7.0	7.0	>350	ND	ND	ND
Cidofovir	0.70	1.02	>300	ND	ND	ND
Acyclovir	ND	ND	ND	1.78	53.8	>440
Brivudin	ND	ND	ND	0.036	60	>300

[a]Effective concentration required to reduce virus plaque formation by 50%. Virus input was 100 plaque forming units (PFU) for HCMV. Virus input was 20 plaque forming units (PFU).
[b]Minimum cytotoxic concentration that causes a microscopically detectable alteration of cell morphology.
[c]Not determined.

Conclusion

In conclusion, a number of1,4,5-trisubstituted 1*H*-1,2,3-triazole purines were effectively synthesized. Antiviral activity against CMV and VZV in human embryonic lung (HEL) cell cultures was evaluated and none show significant activity towards these selected virus.

Experimental

^{1}H NMR, ^{13}C NMR spectra were recorded on a Bruker AM-400 nuclear magnetic resonance spectrometer. Chemical shifts (δ) are reported in ppm relative to the TMS peak. Melting points are uncorrected and were determined on a XT4A type melting point apparatus. High-resolution mass spectra were acquired with an Agilent Accurate-Mass-Q-TOF MS 6520 system equipped with an electrospray ionization (ESI) source. Thin-layer chromatography (TLC) was carried out on silica gel precoated plates purchased from Yantai Institute of Chemical Industry. Column chromatography separation was carried out on silica gel (40∼50 μm, Yantai Institute of Chemical Industry). All the chemical reagents were analytical or chemical pure reagents.

Ethyl 2-(4,5-bis(hydroxymethyl)-1H-1,2,3-triazol-1-yl)acetate(3)

A solution of ethyl 2-bromoacetate **1** (11.40 mL, 100 mmol) and NaN_3 (8.60 g, 100 mmol) in acetone / H_2O (50 mL, V/V = 3:2) was heated at 60°C overnight. The residue was dissolved in EtOAc and washed with brine, the organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure to afford ethyl 2-azidoacetate **2** (9.67 g, 75%) as an colorless oil, which was used in the next step without being further purified.

A solution of **2** (9.67 g, 75 mmol) and 1,4-butynediol (5.86 g, 68 mmol) was stirred at 110°C overnight. The reaction was monitored by TLC (stained with iodine). When the reaction was completed, the mixture was cooled to room temperature and diluted in EtOAc. The organic layer was evaporated under reduced pressure. The residue was purified by silica gel column chromatography using petroleum ether—ethyl acetate (3:7, v/v) as an eluent to afford compound **3** (7.20 g, 51%) as a white solid, m.p.105°C ∼ 107°C.^{1}H NMR (400 MHz, DMSO-*d6*) δ 5.38 (t, J = 5.5 Hz, 1 H), 5.12 (t, J = 5.5 Hz, 1 H), 4.58 (d, J = 5.3 Hz, 2 H), 4.51 (d, J = 5.4 Hz, 2 H), 4.17 (q, J = 7.0 Hz, 2 H), 1.21 (t, J= 7.2 Hz, 3 H).^{13}C NMR (400 MHz, DMSO-*d6*) δ 167.16, 144.36, 134.71, 61.38, 54.12, 51.19, 49.24, 13.96. HRMS calculated for $[C_8H_{14}N_3O_4+H]^+$: 216.0984, Found: 216.0987.

Ethyl 2-(5-(hydroxymethyl)-4-((trityloxy)methyl)-1H-1,2,3-triazol-1-yl)acetate (4)

To a solution of **3** (4.30 g, 20 mmol) in CH_2Cl_2 (25 mL) was added TEA (2.90 mL, 22 mmol) and triphenylmethyl chloride (6.05 g, 22 mmol) at 0°C. The mixture was

stirred at 0°C for 5 h and subsequently quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using the mixture petroleum ether—ethyl acetate (1:1, v/v) as an eluent to afford compound **4** (6.67 g, 73%) as a white solid, m.p.107°C ~ 109°C.^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.44 –7.26 (m, 15H), 5.42 (t, *J*= 5.4 Hz, 1 H) 5.38 (s, 2 H), 4.47 (d, *J*= 5.3 Hz, 2 H), 4.17 (q, 7.0 Hz, 2 H), 4.05 (s, 2 H), 1.21 (t, *J*= 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-*d6*) δ 167.05, 143.47, 140.76, 135.55, 128.27, 127.99, 127.15, 86.55, 61.41, 56.71, 51.17, 49.38, 13.92. HRMS calculated for $[C_{27}H_{28}N_3O_4+H]^+$: 458.2080, Found:. 458.2078.

Ethyl 2-(5-((6-chloro-9H-purin-9-yl)methyl)-4-((trityloxy)methyl)-1H-1,2,3-triazol-1-yl)acetate (5a)

To a solution of **4** (4.57 g, 10 mmol) in CH_2Cl_2 (25 mL) was added TEA (1.46 mL, 11 mmol) and methanesulfonyl chloride (850 µL, 11 mmol) at 0°C. The mixture was stirred at 0°C for 10 min and subsequently quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure afforded crude product **4**. A mixture of crude methane sulfate **4** (4.16 g, 8.0 mmol), K_2CO_3 (1.32 g, 9.60 mmol) and 6-chloropurine (1.47 g, 9.6 mmol) in DMF (20 mL) was stirred at room temperature for 5 h. The reaction mixture was quenched with distilled water. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with H_2O (80 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified on a silica gel column using petroleum ether – EtOAc (1:1, v/v) as eluent, giving pure compound **5a** (3.32 g, 70%) as a white solid, m.p.110°C ~ 111°C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.66 (s, 1 H), 8.46 (s, 1 H), 7.35 – 7.25 (m, 15 H), 5.64 (s, 4 H), 4.23 (s, 2 H), 3.97 – 3.90 (m, 2 H), 1.09 (t, *J*= 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-*d6*) δ 166.82, 151.63, 151.58, 149.18, 146.60, 143.29, 130.69, 130.60, 128.18, 127.93, 127.12, 86.77, 61.69, 56.96, 49.34, 34.95, 13.66. HRMS calculated for $[C_{32}H_{29}ClN_7O_3+H]^+$: 594.2020, Found: 594.2025.

Ethyl 2-(5-((2-amino-6-chloro-9H-purin-9-yl)methyl)-4-((trityloxy)methyl)-1H-1,2,3-triazol-1-yl)acetate (5b)

Compound **5b** was synthesized from **4** by a similar procedure to that described for **5a** as a white solid (3.6 g, 69%), m. p. 115°C ~ 117°C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.76 (s, 1 H), 7.34 – 6.90 (m, 15 H), 5.76 (s, 2 H), 5.62 (s, 2 H), 5.33 (s, 2 H), 4.15 (s, 2 H), 3.99 (q, *J*= 7.1 Hz, 2 H), 1.14 (t, *J*= 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-*d6*) δ 166.87, 159.67, 153.69, 149.52, 143.30, 142.89, 141.92, 131.13, 128.20, 127.89, 127.08, 122.99, 86.72, 61.65, 56.73, 49.46, 34.23, 13.67. HRMS calculated for $[C_{32}H_{30}ClN_8O_3+H]^+$: 609.2129, Found: 609.2130.

Ethyl 2-(5-((6-chloro-9H-purin-9-yl)methyl)-4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)acetate (6a)

To a solution of **5a** (3.00 g, 5.06 mmol) in CH_2Cl_2 (15 mL) at 0°C (ice bath) was added TFA (2.28 mL, 25.30 mmol). After stirred 7 h at 0°C, the mixture was neutralized to pH 7 with saturated aqueous $NaHCO_3$. The residue was concentrated in vacuo and purified on a silica gel column using petroleum ether – EtOAc (2:3, v/v) as eluent to afford compound **6a** (0.78 g, 74%) as a white solid, m.p.172°C ~ 173°C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.80 (s, 1 H), 8.67 (s, 1 H), 5.78 (s, 2 H), 5.57 (s, 2 H), 4.74 (s, 2 H), 3.79 (q, J = 7.2 Hz, 2 H), 1.03 (t, J= 7.1 Hz, 3 H). ^{13}C NMR (400 MHz, DMSO-*d6*) δ 166.82, 151.72, 151.67, 149.12, 147.13, 146.87, 130.58, 130.01, 61.56, 54.63, 49.20, 34.54, 13.63. HRMS calculated for $[C_{13}H_{14}ClN_7\ O_3+H]^+$: 352.0918, Found:. 352.0919.

Ethyl 2-(5-((2-amino-6-chloro-9H-purin-9-yl)methyl)-4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)acetate (6b)

Compound **6b** was synthesized from **5b** by a similar procedure to that described for **6a** as a white solid (0.94 g, 81%), m.p.185°C ~ 187°C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.64 (s, 1 H), 6.52 (s, 2 H), 5.08 (d, J= 15.4 Hz, 2 H), 5.01 (s, 2 H), 4.23 (s, 2 H), 3.39 (q, J= 7.1 Hz, 2 H), 0.62 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-*d6*) δ 166.80, 159.79, 153.79, 149.47, 146.69, 142.69, 130.42, 122.95, 61.65, 54.62, 49.31, 33.90, 13.67. HRMS calculated for $[C_{13}H_{15}ClN_8O_3+H]^+$: 367.1028, Found:. 367.1028.

Ethyl 2-(5-((2-amino-6-oxo-9H-purin-9-yl)methyl)-4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)acetate (6c)

To a solution of **6b** (183 mg, 0.50 mmol) in CH_2Cl_2 at room temperature was dropwise added TFA/H_2O = 3:1 (4 mL, v/v) and stirred overnight. The residue was concentrated in vacuo and purified on a silica gel column using CH_3OH – CH_2Cl_2 (1:9, v/v) as eluent to afford compound **6c** (78 mg, 45%) as a white solid, m. p. 175°C ~ 177°C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.67 (s, 1 H), 7.68 (s, 1 H), 6.48 (s, 2 H), 5.53 (s, 2 H), 5.40 (t, J = 5.5 Hz, 1 H), 5.34 (s, 2 H), 4.66 (d, J= 5.5 Hz, 2 H), 3.93 (q, J= 7.1 Hz, 2 H), 1.11 (t, J= 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-*d6*) δ 166.81, 156.74, 153.63, 150.84, 146.29, 137.08, 130.82, 116.11, 61.62, 54.54, 49.22, 33.56, 13.73. HRMS calculated for $[C_{13}\ H_{16}\ N_8\ O_4+H]^+$: 349.1367, Found: 349.1369.

2-(5-((6-Chloro-9H-purin-9-yl)methyl)-4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl) acetamide (7d)

A solution of **6a** (121mg, 0.35 mmol) and $NH_3{\cdot}H_2O$ (10.00 mL) was stirred at room temperature overnight. The residue was concentrated in vacuo and purified with

CH_3OH to give pure **7d** (73 mg, 65%) as a white solid, m.p.189°C ~ 191°C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.15 (s, 2 H), δ7.78 (s, 1 H), 7.39 (s, 1 H), 7.27 (s, 2 H), 5.58 (s, 2 H), 5.44 (m, 1 H), 5.29 (s, 2 H), 4.62 (s, 2 H). ^{13}C NMR (100 MHz, DMSO-*d6*) δ 167.62, 156.44, 152.95, 149.62, 146.50, 141.08, 131.36, 118.84, 54.98, 50.62, 34.61. HRMS calculated for $[C_{11}H_{13}N_9O_2+H]^+$: 304.1270, Found: 304.1272.

2-(5-((2-Amino-6-chloro-9H-purin-9-yl)methyl)-4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)acetamide (7b)

Compound **7b** was synthesized from **6b** by a similar procedure to that described for **7d** as a white solid (75 mg, 67%), m.p. 215°C ~ 217°C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.11 (s, 1 H), 7.78 (s, 1 H), 7.45 (s, 1 H), 6.98 (s, 2 H), 5.37 (s, 2 H), 5.29 (s, 2 H), 4.60 (s, 2 H). ^{13}C NMR (400 MHz, DMSO-*d6*) δ 167.34, 159.69, 153.81, 149.41, 146.19, 142.85, 130.44, 123.06, 54.61, 50.38, 34.36. HRMS calculated for $[C_{11}H_{13}N_9O_3+H]^+$: 338.08752, Found: 338.08765.

2-(5-((2-Amino-6-oxo-9H-purin-9-yl)methyl)-4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)acetamide (7c)

A solution of **7b** (188 mg, 0.56 mmol) and TFA/H_2O = 3:1 (4 mL, v/v) was heated to 60°C and stirred overnight. The residue was concentrated in vacuo and purified with CH_3OH to give pure **7c** (72 mg, 41%) as a white solid, m.p. 237°C ~ 239°C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.72 (s, 1 H), 7.77 (s, 1 H), 6.48 (s, 2 H), 5.44 (s, 2 H), 5.40 – 5.31 (m, 3 H), 4.62 (s, 2 H). ^{13}C NMR (100 MHz, DMSO-*d6*) δ 168.32, 156.57, 153.68, 150.81, 146.16, 137.08, 130.49, 115.72, 54.56, 49.40, 33.89. HRMS calculated for $[C_{11}H_{13}N_9O_3+H]^+$: 320.1214, Found: 320.1216.

2-(5-(Hydroxymethyl)-4-((trityloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-methylacetamide (8)

To a solution of **4** (914 mg, 2.0mmol) in CH_2Cl_2 at 0°C (ice bath) was added methylamine (2 mL) and stirred for 10 min. The residue was concentrated in vacuo and purified on a silica gel column using petroleum ether – EtOAc (3:7, v/v) as eluent to afford compound **8** (831 mg, 94%) as a white solid, m.p.109°C ~ 110°C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.28 (d, J = 4.5 Hz, 1 H), 7.52 – 7.26 (m, 15 H), 5.34 (t, J = 5.4 Hz, 1 H), 5.13 (s, 2 H), 4.48 (d, J = 5.4 Hz, 2 H), 4.07 (s, 2H), 2.66 (d, J = 4.6 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-*d6*) δ 166.43, 144.02, 141.43, 136.22, 128.79, 128.46, 127.62, 87.04, 57.29, 51.57, 50.80, 26.13. HRMS calculated for $[C_{26}H_{27}N_4O_3+H]^+$: 443.2083, Found: 443.2084.

2-(5-((6-Chloro-9H-purin-9-yl)methyl)-4-((trityloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-methylacetamide (9a)

Compound **9a** was synthesized from **8** by a similar procedure to that described for **5a** as a white solid (464 mg, 68%), m.p. 105°C ~ 106°C. ^{1}H NMR (400 MHz,

DMSO-*d6*) δ 8.65 (s, 1 H), 8.47 (s, 1 H), 8.28 (d, *J*= 4.6 Hz, 1 H), 7.31 – 7.22 (m, 15 H), 5.59 (s, 2 H), 5.31 (s, 2 H), 4.08 (s, 2 H), 2.54 (d, *J*= 4.5 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-*d6*) δ 166.05, 152.04, 151.96, 149.52, 147.16, 143.72, 143.29, 131.44, 131.09, 128.59, 128.33, 127.54, 87.14, 57.41, 50.90, 35.75, 26.02. HRMS calculated for $[C_{31}H_{28}ClN_8O_2+H]^+$: 579.2024, Found: 579.2023.

2-(5-((2-Amino-6-chloro-9H-purin-9-yl)methyl)-4-((trityloxy)methyl)-1H-1,2,3-triazol-1-yl)-N-methylacetamide (9b)

Compound **9b** was synthesized from **8** by a similar procedure to that described for **5a** as a white solid (456 mg, 65%), m.p.112°C ~ 114°C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.29 (d, *J*= 4.6 Hz, 1 H), 7.79 (s, 1 H), 7.33 – 7.24 (m, 15 H), 6.86 (s, 2 H), 5.34 (s, 2 H), 5.31 (s, 2 H), 4.01 (s, 2 H), 2.62 (d, *J*= 4.5 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-*d6*) δ 166.21, 160.16, 154.22, 149.94, 143.76, 142.99, 142.52, 131.75, 128.63, 128.33, 127.51, 123.54, 87.14, 57.27, 51.03, 35.19, 26.11. HRMS calculated for $[C_{31}H_{29}ClN_9O_2+H]^+$: 594.2133, Found: 594.2136.

2-(5-((6-Chloro-9H-purin-9-yl)methyl)-4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)-N-methyl acetamide (10a)

Compound **10a** was synthesized from **9a** by a similar procedure to that described for **6a** as a white solid (129 mg, 70%), m.p.168°C ~ 169°C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.76 (s, 1 H), δ 8.63 (s, 1 H), 8.14 (d, *J*= 4.4 Hz, 1 H), 5.72 (s, 2 H), 5.30 (t, *J*=5.2 Hz, 1 H), 5.24 (s, 2 H), 4.64 (d, *J*= 5.2 Hz, 2 H), 2.42 (d, *J* = 4.4 Hz, 3 H). ^{13}C NMR (400 MHz, DMSO-*d6*) δ 165.92, 152.26, 151.96, 149.35, 147.63, 146.93, 131.07, 130.60, 55.04, 50.77, 35.33, 25.90. HRMS calculated for $[C_{12}H_{13}ClN_8O_2+H]^+$: 337.0923, Found: 337.0922.

2-(5-((2-Amino-6-chloro-9H-purin-9-yl)methyl)-4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)-N-methylacetamide (10b)

Compound **10b** was synthesized from **9b** by a similar procedure to that described for **6a** as a white solid (148 mg, 65%), m.p.175°C ~ 177°C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.12 (d, *J* = 4.3 Hz, 1 H), 8.02 (s, 1 H), 6.87 (s, 2 H), 5.35 (s, 2 H), 5.25 (s, 2 H), 5.21 (t, *J*= 5.4 Hz, 1 H), 4.54 (d, *J*= 5.2 Hz, 2 H), 2.49 (d, *J*= 4.4 Hz, 3 H).^{13}C NMR (100 MHz, DMSO-*d6*) δ 165.71, 159.67, 153.78, 149.36, 146.24, 142.79, 130.42, 123.03, 54.61, 50.49, 34.27, 25.62. HRMS calculated for $[C_{12}H_{14}ClN_9O_2+H]^+$: 352.1037, Found: 352.1033.

2-(5-((2-Amino-6-oxo-9H-purin-9(6H)-yl)methyl)-4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)-N-methylacetamide (10c)

Compound **10c** was synthesized from **10b** by a similar procedure to that described for **6c** as a white solid (68 mg, 42%), m.p. 159°C ~ 161°C. ^{1}H NMR (400 MHz,

DMSO-*d6*) δ 10.78 (s, 1 H), 8.24 (s, 1 H), 7.84 (s, 1 H), 6.56 (s, 2 H), 5.64 – 4.96 (m, 5 H), 4.59 (s, 2 H), 2.61 (s, 3 H). ^{13}C-NMR (100 MHz, DMSO-*d6*) δ 165.78, 156.42, 153.78, 146.05, 130.67, 115.17, 54.55, 50.46, 34.14, 25.68. HRMS calculated for $[C_{12}H_{15}N_9O_3+H]^+$: 334.1371, Found: 334.1373.

Ethyl 2-(5-((2-amino-6-(cyclopropylamino)-9H-purin-9-yl)methyl)-4-((trityloxy) methyl)-1H-1,2,3-triazol-1-yl)acetate (11)

To a solution of **5b** (1.15 g, 1.89 mmol) in DMF (5 mL) was added cyclopropylamine (654 µL) and K_2CO_3 (312 mg, 2.23 mmol) at 0°C. The mixture was stirred at 0°C for 7 h and subsequently quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using the CH_3OH – CH_2Cl_2 (5:95, v/v) as eluent to afford compound **11** (816 mg, yield 69%) as a white solid, m.p.123°C ~ 125°C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.44 – 7.22 (m, 16 H), 5.78 (s, 2 H), 5.62 (s, 2 H), 5.19 (s, 2 H), 4.16 (s, 2 H), 3.99 (q, *J*= 7.1 Hz, 2 H), 3.19 – 3.17 (m, 1 H), 3.01 (s, 1 H), 1.13 (t, *J* = 7.1 Hz, 3 H), 0.68 – 0.62 (m, 2 H), 0.61 – 0.54 (m, 2 H). ^{13}C NMR (101 MHz, DMSO-*d6*) δ 167.29, 160.61, 156.33, 143.86, 143.08, 136.34, 132.35, 128.76, 128.44, 127.60, 113.43, 87.23, 62.07, 57.20, 49.94, 33.87, 24.17, 14.15, 6.80. HRMS calculated for $[C_{35}H_{36}N_9O_3+H]^+$: 630.2941, Found:. 630.2944.

2-(5-((2-Amino-6-(cyclopropylamino)-9H-purin-9-yl)methyl)-4-((trityloxy) methyl)-1H-1,2,3-triazol-1-yl)-N-cyclopropylacetamide (12)

A solution of **5b** (383 mg, 0.63 mmol) and cyclopropylamine (3 mL) was heated at 60°C overnight in a seal tube. The residue was concentrated under reduced pressure and purified by silica gel column chromatography using the CH_3OH – CH_2Cl_2 (5:95, v/v) as eluent to afford compound **12** (290 mg, 72%) as a white solid, m.p.167°C ~ 169°C.^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.49 (d, *J*= 3.9 Hz, 1 H), 7.42 – 7.21 (m, 16 H), 5.84 (s, 2 H), 5.42 (s, 2 H), 5.18 (s, 2 H), 4.06 (s, 2 H), 3.19 – 3.17 (m, 1 H), 3.01 (s, 1 H), 2.68 – 2.61 (m, 1 H), 0.68 – 0.62 (m, 4 H), 0.60 – 0.54 (m, 2 H), 0.49 – 0.44 (m, 2 H). ^{13}C NMR (100 MHz, DMSO-*d6*) δ 166.96, 160.60, 156.35, 143.84, 142.80, 136.41, 132.47, 128.73, 128.41, 127.56, 113.46, 87.17, 57.21, 51.06, 34.33, 22.84, 6.83, 6.09; HRMS calculated for $[C_{36}H_{37}N_{10}O_2+H]+$: 641.3101, Found:.641.3108.

Ethyl 2-(5-((2-amino-6-(cyclopropylamino)-9H-purin-9-yl)methyl)-4-(hydroxy methyl)-1H-1,2,3-triazol-1-yl)acetate (13)

Compound **13** was synthesized from **11** by a similar procedure to that described for **6a** as a white solid (67 mg, 35%), m.p.165°C ~ 167°C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.98 (s, 1 H), 7.39 (s, 2 H), 5.55 (s, 2 H), 5.44 (s, 2 H), 4.67 (s, 2 H), 3.95 (q, *J*= 7.1 Hz, 2 H), 2.88 (m, 1 H), 1.12 (t, *J*= 7.1 Hz, 3 H), 0.91 – 0.80 (m, 2 H), 0.77 – 0.67 (m, 2 H). ^{13}C NMR (100 MHz, DMSO-*d6*) δ 166.82, 158.10, 157.79, 146.26,

130.98, 118.74, 115.76, 112.78, 61.55, 54.54, 49.25, 33.26, 21.13, 13.69, 6.48. HRMS calculated for $[C_{16}H_{21}N_9O_3+H]^+$: 388.1846, Found: 337.1848.

2-(5-((2-Amino-6-(cyclopropylamino)-9H-purin-9-yl)methyl)-4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)-N-cyclopropylacetamide (14)

Compound **14** was synthesized from **12** by a similar procedure to that described for **6a** as a white solid (105 mg, 65%), m.p.178°C ~ 180°C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.43 (d, J =4.0 Hz, 1 H), 7.73 (s, 1 H), 7.37 (s, 2 H), 5.40 (s, 2 H), 5.31 (s, 2 H), 4.61 (d, J =5.3 Hz, 2 H), 3.01 (s, 1 H), 2.60–2.66 (m, 1 H), 0.66 – 0.63 (m, 4 H), 0.58 – 0.57 (m, 2 H), 0.48 – 0.44 (m, 2 H).^{13}C NMR (100 MHz, DMSO-*d6*) δ 166.50, 160.09, 155.94, 145.88, 136.81, 131.15, 112.94, 54.60, 50.43, 33.58, 22.34, 6.38, 5.62. HRMS calculated for $[C_{17}H_{22}N_{10}O_2+H]^+$: 399.2000, Found: 399.2000.

2-(5-((2-Amino-6-(cyclopropylamino)-9H-purin-9-yl)methyl)-4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)acetamide (15)

Compound **15** was synthesized from **13** by a similar procedure to that described for **7d** as a white solid (66 mg, 60%), m.p. 202°C ~ 204°C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.46 (s, 1 H), 7.74 (s, 1 H), 7.40 (s, 1 H), 5.95 (s, 2 H), 5.48 (s, 2 H), 5.31 (s, 2 H), 4.62 (s, 2 H), 2.99 (s, 1 H), 2.63 (m, 1 H), 0.65 – 0.61 (m, 2 H), 0.57 – 0.46 (m, 2 H). ^{13}C NMR (100 MHz, DMSO-*d6*) δ 166.56, 160.13, 155.96, 145.91, 136.82, 131.21, 112.95, 54.62, 50.46, 33.59, 22.38, 6.41. HRMS calculated for $[C_{14}H_{18}N_{10}O_2+H]^+$: 359.1690, Found: 359.1687.

Acknowledgments

Financial support of this work by the National Natural Science Foundation of China (Grant No. 21172019) is appreciated.

References

1. De Clercq, E. Antiviral drugs in current clinical use. *J. Clin. Virol*. **2004**, *30*, 115–133.
2. a) De Clercq, E. The acyclic nucleoside phosphonates from inception to clinical use: Historical perspective. *Antiviral Res*. **2007**, 75, 1–13. b) De Clercq, E.; Holy, A. Acyclic nucleoside phosphonates: a key class of antiviral drugs. *Nat. Rev. Drug Discov*. **2005**, 4, 928–940.
3. a) De Clercq, E. Strategies in the design of antiviral drugs. *Nat. Rev. Drug Discov*. **2002**, *1*, 13–25. b) Schaeffer, H. J.; Beauchamp, L.; de Miranda, P.; Elion, G. B.; Bauer, D. J.; Collins, P. 9-(2-Hydroxyethoxymethyl)guanine activity against viruses of the herpes group. *Nature* **1978**, *272*, 583–585.
4. a) De Clercq, E. Antivirals: Past, present and future. *Biochem. Parm*. **2013**, *85*, 727–744. b) Antonelli, G. Turriziani, O. Antiviral therapy: old and current issues. *Int. J. Antimic. Agent*. **2012**, *40*, 95–102.
5. a) Danta, M.; Dusheiko, G. Adefovir dipivoxil: a review of novel acyclic nucleosideanalogue *Int. J. Clin. Pract*. **2004**, *58*, 877–886. b) Cundy, K. C. Clinical pharmacokinetics of the antiviral nucleotide analogues cidofovirand adefovir *Clin. Pharmacokinet*. **1999**, *36*, 127–143.

6. a) Srinivas, R. V.; Fridland, A. Antiviral activities of 9-(*R*)-2-phosphonomethoxypropyladenine (PMPA) and bis(isopropyloxymethylcarbonyl)PMPA against various drug-resistanthuman immunodeficiency virus strains. *Antimicrob. Agents. Chemother*. **1998**, *42*,1484–1487. b) Ayoub, W. S. Tenofovir: A new option for treatment of chronic hepatitis B *Virus Adaptation Treatment* **2009**, *1*, 5–10.
7. a) Safrin, S.; Cherrinton, J.; Jaffe, H. S. Cidofovir: Review of current and potential clinical uses *Adv. Exp. Med. Biol*. **1999**, *458*, 111–120. b) De Clercq, E. Towards an effective chemotherapy of virus infections: Therapeutic potential of cidofovir [(*S*)-1-[3-hydroxy-2-(phosphonomethoxy)propyl]cytosine, HPMPC] for the treatment of DNA virus infections. *Collect. Czech. Chem. Comunn*. **1998**, *63*, 480–506.
8. Sidwell, R. W.; Huffman, J. H.; Khare, L. G. P.; Allen, B.; Witkowski, R. J. T.; Robins, K. Broad-spectrum antiviral activity of virazole: 1-beta-D-ribofuranosyl-1,2,4-triazole -3- carboxamide. *Science* **1972**, *177*, 705–706.
9. a) Glowacka, I. E.; Balzarini, J.; Andrei, G.; Snoeck, R.; Schols, D.; Piotrowska, D. G. Design, synthesis, antiviral and cytostatic activity of omega-(1H-1,2,3-triazol-1-yl) (polyhydroxy)alkylphosphonates as acyclic nucleotide analogues. *Biorg. Med. Chem*. **2014**,*22*, 3629–3641. b) Tron, G. C.; Pirali, T.; Billington, R. A.; Canonico, P. L.; Sorba, G.; Genazzani, A. A. Click chemistry reactions in medicinal chemistry: Applications of the 1,3-dipolar cycloaddition between azides and alkynes. *Med. Res. Rev*. **2008**, *28*, 278–308.
10. a) Lolk, L.; Pohlsgaard, J.; Jepsen, A. S.; Hansen, L. H.; Nielsen, H.; Steffansen, S. I.; Sparving, L.; Nielsen, A. B.; Vester, B.; Nielsen, P. A click chemistry approach to pleuromutilin conjugates with nucleosides or acyclic nucleoside derivatives and their binding to the bacterial ribosome. *J. Med. Chem*. **2008**, *51*, 4957–4967. b) Moustafa, A. H.; Haggam, R. A.; Younes, M. E.; El Ashry, E. S. H. The synthesis of triazolothiadiazines and thiadiazoles from 1,2-bis-(4-amino-5-mercapto-1,2,4- triazol-3-yl)-ethanol and ethane. *Phosphorus, Sulfur Silicon Relat. Elem*. **2006**, *181*, 2361–2371. c) Kotb, E. R.; Anwar, M. M.; Abbas, H.-A. S.; Abd El-Moez, S. I. A concise synthesis and antimicrobial activity of a novel series of naphthylpyridine-3-carbonitrile compounds. *Acta Pol. Pharm*. **2013**, *70*, 667–679.
11. Moustafa, A. H.; El-Sayed, H. A.; Haikal, A. E.-F. Z.; El Ashry, E. S. H. Synthesis of acyclovir and HBG analogues having nicotinonitrile and its 2-methyloxy 1,2,3-triazole. *Nucleos. Nucleot. Nucl. Acids* **2011**, *30*, 340–352.
12. a) El Sadek, M. M.; Abd El-Dayem, N. S.; Hassan, S. Y.; Mostafa, M. A.; Yacout, G. A. Antioxidant and antitumor activities of new synthesized aromatic C-nucleoside derivatives. *Molecules* **2014**, 19, 5163–5190. b) Tuyet Anh Dang, T.; Nguyen Thi Kim, T.; Chinh Pham, T.; Ha Thanh, N.; Cham Ba, T.; Tien Doan, D.; D'Hooghe, M.; Tuyen Van, N. Synthesis and cytotoxic evaluation of novel ester-triazole-linked triterpenoid-AZT conjugates. *Bioorg. Med. Chem. Lett*. **2014**, 24, 5190–5194. c) Wang, M.; Xia, Y.; Fan, Y.; Rocchi, P.; Qu, F.; Iovanna, J. L.; Peng, L. A novel arylethynyltriazole acyclonucleoside inhibits proliferation of drug-resistant pancreatic cancer cells. *Bioorg. Med. Chem. Lett*. **2010**, 20, 5979–5983. d) Romeo, R.; Giofre, S. V.; Carnovale, C.; Chiacchio, M. A.; Campisi, A.; Mancuso, R.; Cirmi, S.; Navarra, M. Synthesis and biological activity of triazole-appended N,O-nucleosides. *Eur. J. Org. Chem*. **2014**, *25*, 5442–5447.
13. a) Vernekar, S. K. V.; Qiu, L.; Zacharias, J.; Geraghty, R. J.; Wang, Z. Synthesis and antiviral evaluation of 4′-(1,2,3-triazol-1-yl)thymidines. *MedChemComm* **2014**, *5*, 603–608. b) Bernardino, A. M.; Azevedo, A. R.; Pinheiro, L. C.; Borges, J. C.; Paixao, I. C.; Mesquita, M.; Souza, T. M.; Dos Santos, M. S. Synthesis and anti-HSV-1 evaluation of new 3H-benzo[b]pyrazolo[3,4-h]-1,6-naphthyridines and 3H-pyrido[2,3-b]pyrazolo [3,4-h]-1,6-naphthyridines. *Org. Med. Chem. Lett*. **2012**, *2*, 3–9. c) Wu, J.; Yu, W.; Fu, L.; He, W.; Wang, Y.; Chai, B.; Song, C.; Chang, J. Design, synthesis, and biological evaluation of new 2′-deoxy-2′-fluoro-4′-triazole cytidine nucleosides as potent antiviral agents. *Eur. J. Med. Chem*. **2013**, *63*, 739–745.

14. a) Amblard, F.; Cho, J. H.; Schinazi, R. F. Cu(I)-catalyzed Huisgen azide-alkyne 1,3-dipolar cycloaddition reaction in nucleoside, nucleotide, and oligonucleotide chemistry. *Chem. Rev*. **2009**, *109*, 4207. b) Najera, C.; Sansano, J. M. 1,3-Dipolar cycloadditions: applications to the synthesis of antiviral agents. *Org. Biomol. Chem*. **2009**,*7*, 4567.
15. a) Saito, Y.; Escuret, V.; Durantel, D.; Zoulim, F.; Schinazi, R. F.; Agrofoglio, L. A. Synthesis of 1,2,3-triazolo-carbanucleoside analogues of ribavirin targeting an HCV in replicon. *Bioorg. Med. Chem*. **2003**, *11*, 3633. b) Yu, J.L.; Wu, Q.P.; Zhang, Q.S.; Liu, Y. H.; Li, Y. Z.; Zhou, Z. M. Synthesis and antitumor activity of novel 2′,3′-dideoxy-2′,3′-diethane thionucleosides bearing 1,2,3-triazole residues. *Bioorg. Med. Chem. Lett*. **2010**, *20*, 240–243. c) Holy´, A.; Dvorˇakova, H.; Jindrˇich, J.; Masojidkova, M.; Budeˇšinsky´, M.; Balzarini, J.; Andrei, G.; De Clercq, E. Acyclic Nucleotide Analogs Derived from 8-Azapurines: ; Synthesis and Antiviral Activity. *J. Med. Chem*. **1996**, *39*, 4073.
16. a) Diab, S. A.; Hienzch, A.; Lebargy, C.; Guillarme, S.; Pfund, E.; Lequeux, T. Synthesis of fluorophosphonylated acyclic nucleotide analogues via copper(I)-catalyzed Huisgen 1–3 dipolar cycloaddition. *Org.Biomol. Chem*. **2009**, 7, 4481. b) Głowacka, I. E.; Balzarini, J.; Wroblewski, A. E. Design, Synthesis, Antiviral, and Cytotoxic Evaluation of Novel Phosphonylated 1,2,3-Triazoles as Acyclic Nucleotide Analogues. *Nucleosid. Nucleotid. Nucl. Acid* **2012**, 31, 293. c) Koszytkowska-Stawin´ ska, M.; Mironiuk-Puchalska, E.; Rowicki, T. Synthesis of 1,2,3-triazolo-nucleosides via the post-triazole N-alkylation. *Tetrahedron***2012**, 68, 214. d) Koszytkowska-Stawin´ ska, M.; Sas, W. Synthesis of novel NH-1,2,3-triazolo-nucleosides by the Banert cascade reaction. *Tetrahedron* **2013**, 69, 2619. e) Ganesan, M.; Muraleedharan, K. M. Synthesis of β-Hydroxyphosphonate and 1,2-Dihydroxy Acyclic Nucleoside Analogs via 1,3-Dipolar Cycloaddition Strategy. *Nucleosid. Nucleotid. Nucl. Acids* **2010**,29, 91. f) Głowacka, I. E.; Balzarini, J.; Wroblewski, A. E. Synthesis and Biological Evaluation of Novel 1,2,3-Triazolonucleotides. *Arch. Pharm. Chem. Life Sci*. **2013**, 346, 278. g) Piotrowska, D. G.; Balzarini, J.; Głowacka, I. E. Design, synthesis, antiviral and cytostatic evaluation of novel isoxazolidine nucleotide analogues with a 1,2,3-triazole linker. *Eur. J. Med. Chem*. **2012**, 47, 501. h) Elayadi, H.; Smietana, M.; Pannecouque, Ch.; Leyssen, P.; Neyts, J.; Vasseur, J.-J.; Lazrek, H. B. Straightforward synthesis of triazoloacyclonucleotide phosphonates as potential HCV inhibitors. *Bioorg. Med. Chem. Lett*. **2010**,20, 7365. i) Głowacka, I. E.; Balzarini, J.; Wroblewski, A. E. Synthesis of a New Series of Phosphonylated 1,2,3-Triazoles as Acyclic Analogs of Ribavirin. *Arch. Pharm. Chem. Life Sci*. **2013**,346, 677. j) Głowacka, I. E.; Balzarini, J.; Wroblewski, A. E. The synthesis, antiviral, cytostatic and cytotoxic evaluation of a new series of acyclonucleotide analogues with a 1,2,3-triazole linker. *Eur. J. Med. Chem*. **2013**, 70, 703.
17. a) Huisgen, R. Kinetics and mechanism of 1,3-dipolar cycloadditions. *Angew. Chem. Int. Ed. Engl*. **1963**, *2*, 633–645. (b) Chen, Y.; Liu, Y.; Petersen, J. L.; Shi, X. Conformational control in the regioselective synthesis of N-2-substituted-1,2,3-triazoles. *Chem. Commun*. **2008**, 3254–3256.
18. Garcia, M. D.; Caamano, O.; Fernandez, F.; Lopez, C.; De Clercq, E. Synthesis of purinyl homo-carbonucleoside derivatives of 2-benzylcyclopenta[c]pyrazol. *Synthesis-Stuttgart* **2005**, 925–932.
19. Barral, K.; Courcambeck, J.; Pèpe, G.; Balzarini, J.; Neyts, J.; De Clercq, E.; Camplo, M. Synthesis and antiviral evaluation of cis-substituted cyclohexenyl and cyclohexanyl nucleosides. *J. Med. Chem*. **2005**, *48*, 450–456.