European Journal of Medicinal Chemistry 45 (2010) 3219–3222

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Short communication

Synthesis and antitumor activity of novel 2′,3′-diethanethio-2′,3′,5′-trideoxy-5′-triazolonucleoside analogues

Jin-Lan Yu [a], Qin-Pei Wu [a,*], Qing-Shan Zhang [a], Xiao-Dong Xi [a], Ning-Ning Liu [a], Yun-Zheng Li [a], Yan-Hong Liu [b], Hong-Quan Yin [a]

[a] Department of Applied Chemistry and Pharmacy, Beijing Institute of Technology, Nandajie 5, Beijing 100081, P.R. China
[b] Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Beijing 100080, P.R. China

ARTICLE INFO

Article history:
Received 27 January 2010
Received in revised form
25 March 2010
Accepted 29 March 2010
Available online 3 April 2010

Keywords:
Antitumor
Nucleoside
Triazole
Targeted therapy
Cancer therapy

ABSTRACT

A series of novel 2′,3′-diethanethio-2′,3′,5′-trideoxy-5′-triazoloribonucleosides was synthesized in excellent yields and their antitumor activity was evaluated. These nucleoside analogues with aromatic substituted triazole rings showed significantly improved activity towards a broad range of tumor cell lines and those without arene substitutes were inactive.

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Numerous nucleosides and nucleotides analogues have been developed for medicinal purposes [1]. Many of which have been used in the clinic for the treatment of human immunodeficiency virus (HIV) [2], hepatitis B virus (HBV) [3], herpes simplex virus (HSV) [4], hepatitis C virus (HCV) [5] and various cancers [6] as anticancer and antiviral drugs.

Within the last 10 years, targeted therapy has been explored with the aim of developing highly specific inhibitors which act on a single target. After the emergence of serious drug resistance and the resulting relapse of one-target treatment plans in the clinic, there is now general knowledge that most tumors depend on more than one signaling pathway for their growth and survival. Thus, molecules interfering simultaneously with multiple targets might be more effective than single target agents [7]. A number of multi-targeted compounds have been developed and have entered clinical trials or clinical practice. These include both Gemcitabine and 2-chloro-2-deoxyadenosine 5′-triphosphate (CldATP) which inhibit DNA polymerase and potently inhibit ribonucleotide reductase (RDPR) as well as Fludarabine 5′-triphosphate (FaraATP) which inhibits DNA and RNA polymerases, RDPR, DNA ligase 1 and DNA primase [1d]. Clofarabine (Fig. 1), a next-generation deoxyadenosine analogue, is effective against various subtypes of leukemia and is currently being tested for combination therapy of both leukemias and solid tumors. The mechanisms of its anticancer activity involve a combination of direct inhibition of DNA synthesis and ribonucleotide reductase and induction of apoptosis [8].

Ribonucleotide reductase (RDPR) is a well-recognized target for cancer chemotherapeutic and antiviral agents [9]. RDPR inhibition precludes DNA transcription and repair, and results in cell apoptosis. The reduction of ribonucleotides into the corresponding 2′-deoxyribonucleotides is initiated by the conversion of cysteine residues positioned at the active site of this enzyme into a cysteinyl free radical. A series of 2′-modified nucleoside analogues such as 2′-methylene-2′-deoxycytidine [10], 2′-methylene-2′-deoxy-uridine [10], 2′-*O*-allyl-D-arabifuranosylcytosine [11] and 3′-*C*-methyladenosine [12] have been shown to be effective mechanism-based inhibitors of this enzyme and may be potential anticancer agents [13].

Furthermore, it is recognized that the replacement of the 2′,3′-hydroxy function of nucleosides by a thiol group able to react with reducing cysteine residues results in potent inhibitors of RDPR *in vitro* [14]. Some 2′,3′-dideoxy-3′-thionucleosides **2** (Fig. 1) [15] have shown good anti-HIV activity and 2′-deoxy-2′-thiocytidine has been proven to inhibit the proliferation of cancer cells [16]. A few S^6-nitrobenzyl mercaptopurine riboside analogues reported by Gupte and Buolamwini [17] were shown to be inhibitors of nucleoside transporters, which are potential targets for chemotherapy in cancer and viral infections [18].

* Corresponding author. Tel.: +86 10 68918511; fax: +86 10 68914009.
E-mail address: qpwu@bit.edu.cn (Q.-P. Wu).

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doi:10.1016/j.ejmech.2010.03.038

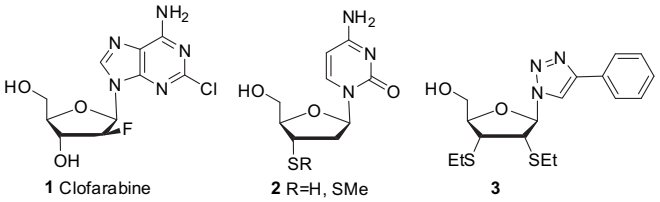


Fig. 1. Molecular structures of nucleoside analogues **1** Clofarabine, **2** and **3**.

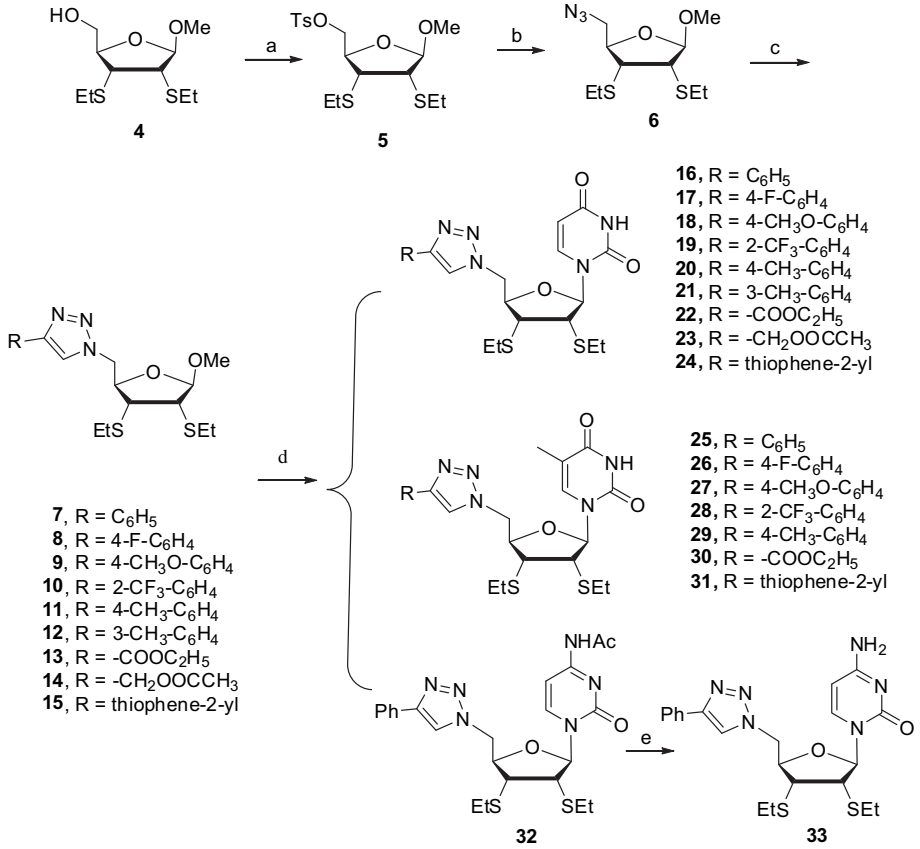
The structural diversity of nucleoside mimetics with antiviral and anticancer activity suggests that any new nucleoside analogue is worth exploring [19]. Recently, 1,2,3-triazoles have gained significant interest in fields of drug discovery and bioconjugation [20]. Introduction of a triazole ring into nucleosides to improve their bioactivity for antitumor and/or antiviral applications has become widespread in drug design practices [21].

Recently, we found that triazole nucleoside **3** showed enhanced bioactivity against a broad spectrum of cancer cell lines in comparison to the corresponding natural base nucleosides with an EC_{50} value of 5.96 μM in Hela cells [22]. Based on this interesting result, we further synthesized and evaluated the bioactivity of a series of novel 2′,3′,5′-trideoxy-5′-triazolonucleoside analogues **16**–**33** as described herein.

Compound **4** [22,23] effectively prepared in a large scale from D-xylose via a cascade reaction was smoothly converted into tosylate **5** [24] followed by treatment with sodium azide to give the expected azido ribofuranoside derivative **6** in 74% yield for two steps (Scheme 1). Under Huisge-Sharpless Azide–Alkyne cycloaddition reaction conditions, conversion of the azido group in **6** into the triazole ring with phenyl acetylene was initially carried out with CuCl as the catalyst. To improve the yield, CuBr or CuI were also employed as catalysts for this cycloreaction. However, the isolated yields were all lower than 50%. Fortunately, the yield for the desired product was higher than 80% when Cu–$CuSO_4$ was used to activate this 1,3-dipolar cycloaddition reaction at room temperature [25]. In addition, the triazole structure was identified to be an unambiguous 1,4-disubstituted cyclo-addition product according to the NOE spectrum data of the final product **18** (Fig. 2).

Under the Silyl-Hilbert-Johnson glycosylation conditions [22,26], trideoxy-D-ribofuranose derivative **6** was treated with trimethylsilylated uracil in the presence of trimethylsilyl trifluoromethanesulfate (TMSOTf) to give the corresponding nucleoside **16**, which was isolated using column chromatography to afford the β-isomer in 51% yield. Under the same reaction conditions, compounds **17**–**32** were also successfully prepared in quite good yields. To remove the acetyl protecting group in **32** methylamine was used to give the desired nucleoside **33** in 94% yield (Scheme 1).

The stereochemistry of the final products was further elucidated by NOE correlation experiments. In the NOE spectrum of **18**, strong NOE effects were observed between the anomeric proton H-1′ (at δ 5.97) and H-4′ (at δ 4.34) and H-6 (at δ 7.57) which suggests that the nucleoside is a β-isomer (Fig. 2). Moreover, it was also observed that the resonance signal of the triazole ring proton H-5″ (at δ 8.53) interacts with both H-4′ (at δ 4.34) and H-5′ (at δ 4.82) further providing evidence that the substitute groups are at the 1- and 4-positions in the 1,2,3-triazole ring. The NOE effect observed between the triazole ring proton H-5″ (at δ 8.53) and the benzene ring protons (at δ 7.78) might indicate that the triazole ring and the benzene ring are coplanar or nearly coplanar in space (Fig. 2). These



Scheme 1. Reagents and conditions: (a) TsCl, Et_3N, CH_2Cl_2, rt, 87%; (b) NaN_3, DMF, 105 °C, 85%; (c) Alkyne, Cu, $CuSO_4$, BuOH/H_2O (1:1, v/v); (d) CH_3CN, $CF_3SO_2OSiMe_3$, silylated bases; (e) $MeNH_2$, EtOH, rt, 94%.

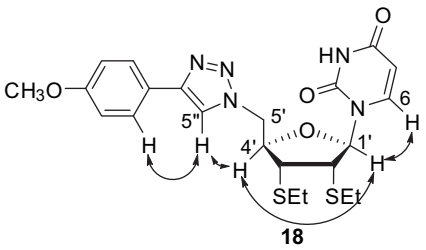


Fig. 2. Through space proton–proton interactions indicated by the NOE spectrum of compound **18**.

NOE spectroscopic data provide strong evidence for the β-anomeric configuration assignments, the triazole ring structure as well as the steric relationship between the triazole ring and the phenyl group.

The antitumor activity of these novel nucleosides devoid of hydroxy groups was tested *in vitro* towards the following human cancer cell lines: human hepatocellular liver carcinoma cell line ($HepG_2$), two types of non-small cell lung cancer: lung adenocarcinoma (LAC) and squamous subdivision of epithelial cells (A549), and human cervical carcinoma cell line (Hela). Cytotoxic activity was determined using the MTT assay, after exposure of cells to the test compounds for 72 h. 5-Fluorouridine was used as the reference compound and the results are summarized in Table 1.

As shown by the EC_{50} values listed in Table 1, most of these nucleoside mimetics had good or moderate activity against three or four of the tested tumor cell lines. Among these novel compounds, compound **16** proved to be the most active and was cytotoxic against three of the tested tumor cells, $HepG_2$, A549 and Hela, with EC_{50} values ranging from 3.04 to 8.38 μM. These EC_{50} values were at least 6-fold higher than those for the reference 5-FU against tumor cells (Table 1). The thymidine derivative **25** showed higher activity against Hela cells (1.89 μM) than against $HepG_2$ and A549 tumor cells. Compared with **16** and **25**, the cytosine compound **33** showed the least active towards the tested tumor cells. The results for nucleosides **17** and **26** bearing a *p*-fluorophenyltriazole residue indicated that the former had moderately active towards the four tested cell lines, while the latter was active towards both $HepG_2$ and Hela cells and inactive against lung A549 and LAC cells. EC_{50} values of **18**, **19**, **27** and **28** indicated that these compounds are potential cytotoxic agents against a broad spectrum of cancer cells and these compounds proved to be more active than 5-FU against these tested four cell lines. Both **20** and **29** with a *p*-methylphenyltriazole group displayed significant activity towards A549 cells (6.78 and 12.32 μM, respectively) while both were inactive against LAC cells. Additionally, **21** containing a *m*-methylbenzene group similar to **20** and **29** in molecular structure also showed remarkable activity against these four tested cell lines (Table 1). Thiophen-2-yl triazole nucleosides, **24** and **31** was mostly inactive towards these four cancer cell lines.

Table 1
Cytotoxicity of compounds **16**–**33** against cancer cell lines.[a]

Compound	EC_{50}[b] (μM)			
	$HepG_2$	A549	LAC	Hela
16	8.38	3.04	n/a	6.59
17	22.57	22.87	72.37	37.41
18	16.21	16.78	24.33	27.68
19	30.28	19.38	81.14	32.82
20	19.92	6.78	≥100	46.69
21	18.26	12.17	99.00	18.79
22	≥100	≥100	≥100	≥100
23	≥100	≥100	≥100	≥100
24	91.82	≥100	86.49	≥100
25	64.98	31.69	n/a	1.89
26	22.72	≥100	≥100	39.51
27	22.78	38.83	25.88	65.95
28	22.09	7.23	50.61	54.33
29	21.61	12.32	≥100	77.53
30	≥100	≥100	≥100	≥100
31	≥100	37.28	≥100	54.86
33	57.10	64.03	n/a	33.47
5-FU	52.43	≥100	43.73	79.79

n/a means the EC_{50} values were not recorded as the sample was contaminated by accident during testing.

[a] Cancer cells (2000 cells/0.1 mL) were cultured under standard conditions in 96-well plates. Twenty-four hours later, a series of concentrations of compounds was added and further incubated at 37 °C in 95% air and 5% CO_2 for 72 h. To the wells 20 μL of MTT reagent was added and further incubated for 4 h and the absorbance was measured at 490 nm. The fifty percent growth inhibitory concentration (EC_{50}) was calculated based on the observed growth inhibition.

[b] EC_{50} is the concentration of compound required to inhibit the cell growth by 50% compared with an untreated control. Compounds were tested up to a concentration of 100 μM.

Towards these four types of cancer cell lines evaluated, compounds **22**, **23** and **30** were inactive ($EC_{50} \geq 100$ μM). From the EC_{50} values shown in Table 1, it is worthwhile to note that all nucleosides bearing an aromatic triazole ring display anticancer activities and compounds lacking benzene substituents in the triazole rings are inactive. Additionally, it should also be noted that the anticancer activity of these analogues was improved compared with their parent compounds without the triazole ring at the 5′-position as reported previously [22]. It is reasonable to speculate that the substituents in the triazole ring play a pivotal role in the bioactivity, which may result from the conjugation effects between the benzene ring and the triazole moiety due to their coplanar relationship. Furthermore, this interesting structure–activity relationship was previously documented for 2′,3′-dideoxy-2′,3′-diethanthio-D-ribofuranoside analogues. For instance **3** was studied in which the natural base moiety was replaced by a series of triazoles substituted with various groups [22]. Moreover, conjugation effects might enhance the hydrophobic features of the triazole ring and might offer advantageous binding properties to the corresponding biological targets. The nature of this interaction between the arene substituted triazole groups in these trideoxy nucleoside analogues and biological targets may be electrostatic, hydrophobic and/or include aromatic ring stacking. Weak interactions such as these between agents and targets are the essential requirement for multi-target agents [27]. On the other hand, the nucleoside analogues without hydroxy groups cannot apparently be phosphorylated by deoxycytidine kinase to form natural nucleosides and thus they likely act as antimetabolic agents interacting with targets via specific modes of action [21c,28], but further studies will be needed to address these hypotheses.

In conclusion, a small library of novel 2′,3′,5′-trideoxy-2′,3′-diethanethio-5′- triazoloribonucleosides were prepared in 46–68% overall yields in four steps (Scheme 1). The molecular structure analysis indicated the potential coplanar relationship between the phenyl moiety and the triazole ring which results in the conjugate effects. Some of these compounds with aromatic substituents in the triazole ring showed excellent anticancer activity and most of them were potential inhibitory agents towards a broader range of tumor cell lines. Some trideoxy nucleoside analogues without the phenyl group were inactive against all four tested tumor cells. These results might suggest that the conjugation effects of the triazole ring with the aromatic system may be essential for bioactivity. Further structure–activity studies investigating the capacity of these compounds to act as multi-target candidates are currently underway in our laboratory.

Acknowledgments

We would like to thank Dr. Claire Simons (Cardiff University) for her useful advices. Financial supports of this work by the Ministry

of Science and Technology of China (2006AA100216) are appreciated.

Appendix. Supplementary material

Supplementary materials associated with this article can be found in the on-line version, at doi:10.1016/j.ejmech.2010.03.038.

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