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An efficient synthesis tetrazole and oxadiazole analogues of novel 2′-deoxy-C-nucleosides and their antitumor activity

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Introduction

Unlike natural and synthetic N-nucleosides, C-nucleosides\textsuperscript{1,2} are stable to enzymatic and acid-catalyzed hydrolysis of the glycosidic bond. Therefore, C-nucleosides offer a distinct advantage over the N-nucleosides for design of biologically active molecules. C-Nucleosides\textsuperscript{3–5} have also attracted the interest of researchers looking for hydrogen-bond interactions alternative to those produced in the classical Watson–Crick model. Among well-known antitumor C-nucleosides, pyrazofurin,\textsuperscript{6} showdomycin\textsuperscript{7} and tiazofurin\textsuperscript{8} are five-membered heterocyclic structures showing excellent biological activity (Fig 1). Despite of their remarkable activity profile, lack of specificity and neurotoxicity prohibited the clinical progress of these nucleosides. More recently, remdesivir (GS-5734)\textsuperscript{9,10} has shown promise for the treatment of COVID-19. Immucillins is yet another important class of C-nucleosides advancing into clinical trials as inhibitor of purine nucleoside phosphorylase. These observations have motivated us to revisit the study of C-nucleosides with a particular interest of designing 2′-deoxyribose analogues of various five membered heterocycle and their antiviral and antitumor activity.

The presence of five-membered heterocyclic system is also a common feature in raltegravir,\textsuperscript{11} an antiviral drug for treatment of HIV. Interestingly, the oxadiazole ring system is also present in ataluren\textsuperscript{12} and zibotentan\textsuperscript{13} used for the treatment of Duchenne muscular dystrophy (DMD) and prostate cancer, respectively (Fig 2). These facts and other reports on the promising biological activity of various regioisomeric oxadiazoles inspired us to synthesise and evaluate the biological activity of novel C-glycosides assembled from 2′-deoxyribose and oxadiazoles.

In particular, the oxadiazole ring\textsuperscript{14} is an essential part of the pharmacophore favouring ligand binding, act as a flat aromatic linker to place substituents in the proper orientation and finally mimics as bioisoster of esters, amides, carbamates, and hydroxamic esters. The 1,2,3-oxadiazole ring is unstable. 1,2,4-oxadiazole, 1,2,5-oxadiazole, and 1,3,4-oxadiazole are well known and appear in numerous marketed drugs. We have chosen 1,2,4-oxadiazole and 1,3,4-oxadiazole moiety for C-nucleoside synthesis. We envisioned the synthesis of a common building block by C–C bond formation at C1 and further integration of the heterocycle to assemble these C-nucleosides. We utilized the glycosyl cyanide as the key starting material which is obtained as mixture of α/β-cyanide anomers from 1-chloro carbohydrate by reaction with trimethyl silyl cyanide in the presence of a Lewis acid as catalyst. These two anomers of glycosyl cyanide were transformed into tetratoazole nucleosides followed by acylative rearrangement to furnish 1,3,4-oxadiazoles in high yields. These protocols offer an easy access to otherwise difficult to synthesize C-nucleosides in good yield and protecting group compatibility. These C-nucleosides were evaluated for their antitumor activity. This work paves a path for facile assembly of library of new chemical entities useful for drug discovery.

Various tetrazole and oxadiazole C-nucleoside analogues were synthesized starting from pure α- or β-glycosyl-cyanide. The synthesis of glycosyl-cyanide as key precursor was optimized on gram-scale to furnish crystalline starting material for the assembly of C-nucleosides. Oxadizole C-nucleosides were synthesized via two independent routes. First, the glycosyl-cyanide was converted into an amidoxime which upon ring closure offered an alternative pathway for the assembly of 1,2,4-oxadizoles in an efficient manner. Second, both anomers of glycosyl-cyanide were transformed into tetratoazole nucleosides followed by acylative rearrangement to furnish 1,3,4-oxadizoles in high yields. These protocols offer an easy access to otherwise difficult to synthesize C-nucleosides in good yield and protecting group compatibility. These C-nucleosides were evaluated for their antitumor activity. This work paves a path for facile assembly of library of new chemical entities useful for drug discovery.

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stereochemically pure glycosyl cyanide that is transformed into C-nucleosides without anomerization at the C1 position. The C-nucleosides of both anomers of 2′-deoxyriboside of tetrazoles and oxadiazoles synthesised are reported for the first time and the methodologies developed are general, which can be applied to construct other structurally diverse anomerically pure C-nucleosides.

**Result and discussion**

Herein, we describe a modular synthesis approach allowing rapid assembly of C-nucleoside library in an efficient manner. Synthesis of a common building block by C–C bond formation at C1 and further integration of the heterocycle was the key feature of our approach. We have divided our study in three parts: (i) synthesis and separation of glycosyl cyanine anomers on multigram scale, (ii) synthesis of 1,2,4-oxadiazole C-nucleoside via amidoxime intermediate and (iii) synthesis of 1,3,4-oxadiazole via acylative rearrangement of tetrazole.

(i) Synthesis and separation of glycosyl cyanine anomers on multigram scale:

The glycosyl cyanine is one of the most important type of C-glycosyl intermediate, which is usually obtained as mixture of cyanine anomers from commercially available Hoffer’s chloro sugar by reaction with trimethyl silyl cyanide in the presence of a Lewis acid as catalyst (Scheme 1). Synthesis of 2′-deoxy glycosyl cyanine anomers (1a and
Table 1
Screening of Lewis acid for cyanation of Hoffer's chloro sugar in DCM at −78 °C.

| Entry | Lewis Acid | Anomeric ratio (β/α) | Isolated Yield (%) |
|-------|------------|----------------------|-------------------|
| 1     | SnCl4      | 3:1                  | 93                |
| 2     | BF3.OEt2   | 2:1                  | 70                |
| 3     | TMSOTf     | 0.59:1               | 60                |
| 4     | CeCl3      | No Reaction          | (Starting material remains intact) |
| 5     | ZnCl2      | 2:1                  | 55                |
| 6     | Mg(Clo4)2  | No Reaction (Insoluble in DCM) | –          |
| 7     | FeCl3      | 5.7:1                | 70                |

1b) have been reported16 only on small-scale. Since 2′-deoxy glycosyl cyanine anomers (1a and 1b) are the key starting materials for our study, it was essential to optimize the yield and anomeric ratio with an ultimate objective of making it in hundred-gram quantity. Because chloro-sugar is devoid of neighbouring group participation, selective stereochemical outcome is challenging. Hence development of process which is robust and greener was undertaken. We screened several Lewis acids and solvents to improve yield and obtain better ratio of anomers in favour of β-selectivity. β-Anomer 1b is desirable to produce C-nucleoside having resemblance to the naturally abundant 2′-deoxy-nucleosides.

Upon screening of various Lewis acids, FeCl3 afforded best β:α = 5.7:1 ratio in 70% yield (entry 7 Table 1). Next solvent screening using nitromethane, toluene, 1,2-dichlorooethane, tetrahydrofuran, acetonitrile, 1,2-dimethoxyethane, acetone and dimethyl formamide failed to improve the β:α ratio and yield compared to the reaction performed in dichloromethane. Considering desired β:α ratio, yield (93%) and scalability, SnCl4 was chosen as preferred Lewis acid for the present study. It is important to note that low temperature is essential for β-selectivity and high yield. Further optimization effort is underway in our laboratory to find a robust process with non-toxic Lewis acid.

The two anomers of glycosyl cyanide were easily separated by silica gel column chromatography and anomeric configuration was established by 1H NMR experiments. The SnCl4 protocol (entry 1 Table 1) was scaled-up to furnish 366 g of the pure β-anomer required for the transformation into various C-nucleosides containing five membered heterocycles. This route is the largest scale synthesis of glycosyl cyanide 1b reported to date in high yield.

(ii) Synthesis of 1,2,4-oxadiazole C-nucleoside via amidoxime intermediate:

Nitrile functional group has served as an excellent handle to install several heterocyclic rings. Separately, both anomers of glycosyl cyanide (1a and 1b) were converted into amidoxime (2a and 2b) following Tiemann protocol17 using hydroxylamine hydrochloride under basic condition. Reaction was performed with NH2OH.HCl in presence of Hüning’s base, instead of using NH2OH.HCl and Na2CO3 was reported by Adelfinskaya et al.18 Excellent yields were obtained for both anomers. These amidoxime derivatives were then converted into 1,2,4-oxadiazoles derivatives (5–6 and 7–11) following two distinct protocols (Scheme 2). First, sequential synthesis of O-acylated amidoximes using acetyl chloride followed by cyclization to 1,2,4-oxadiazole ring (5–6) using alkaline DMSO solution. Whereas the second protocol involves direct cyclization of amidoximes19 to 1,2,4-oxadiazoles20–27 using orthoformate or acid anhydride in presence of BF3.Et2O as Lewis acid. The later protocol is shorter and offered higher yields compared to the first route. Deprotection of p-tolyl group was accomplished using NaOMe in methanol at room temperature in excellent yield except for 7a and 7b. Multiple product formation was observed on TLC for 7a and 7b. This phenomenon of multiple product formation can be attributed to the deprotonation28,29 of acidic CS-H of 1,2,4-oxadiazole by NaOMe followed by ring opening and rearrangement.

(iii) Synthesis of 1,3,4-oxadiazole via acylative rearrangement of tetrazole:

In 1994, Kobe et al.30 synthesised 5-β-u-ribofuranosyl-1H-tetrazole from allononitrile using NaN3 and AlCl3 in excellent yield. Our attempt to utilize same protocol starting with glycosyl cyanide 1a or 1b resulted in low yield of tetrazole derivative along with other unidentified products. Therefore, tetrazole derivatives31–33 (18a and 18b) were successfully synthesized in good yield from both anomers of glycosyl cyanide (1a and 1b) using azide click reaction with copper and cupric sulphate in DMF at 120 °C. Unprotected tetrazole nucleosides (19a and 19b) were obtained by cleaving tolyl protecting group using sodium methoxide in methanol at room temperature (Scheme 3). The conversion of tetrazole to 1,3,4-oxadiazole derivatives34–38 was achieved either by reacting tetrazole derivatives with carboxylic acid anhydride in presence of hydroquinone under reflux or by reacting with carboxylic acid chloride in pyridine.39–42 The Deprotection of p-tolyl group was executed using NaOMe in methanol at room temperature in excellent yield. However, the deprotection protocol suffers from a drawback for CS-unsubstituted and CS-substitution with electron withdrawing groups. In both cases, multiple product formation was observed due to the ring opening of the oxadiazole ring. This decomposition can be explained by the nucleophilic addition of NaOMe to CS-carbon and ring opening.43–45

The postulated mechanism46 of this conversion is illustrated in Scheme 4. 5-Substituted tetrazole undergoes N2-acylation upon treatment with acylation reagent due to steric bulk of 5-substitution. This unstable intermediate (INT-1) then ring opens via nitroen extrusion and formation of N-acyl nitrolime as putative intermediates (INT-2 and INT-3). These intermediates are then cyclized to form 1,3,4-oxadiazoles (20–25) in good yield. Structural elucidation of the new compounds described in this study was based on NMR and mass spectral data.

Biological activity

We tested a set of 12 C-nucleosides both α- and β-anomers for their in-vitro cytotoxicity activity in five tumor cell lines,45 namely HeLa, MDA-MB-231 (breast cancer), Panc-1 (pancreatic cancer), PC3 (prostate cancer) and SK-OV-3 (ovarian cancer) using the MTT (3-(4,5-dimethyl thiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay. Doxorubicin was used as a positive control to validate the MTT assay.46 Majority of the compounds failed to exhibit significant cytotoxicity against five cell lines tested at 10 μmol concentration. The results are summarized in the graph shown below. Compounds 15b and 28a exhibited modest (9–11%) inhibition of breast cancer cell line MDA-MB-231. Whereas in case of SK-OV-3, we observed 10–14% inhibition exerted by five C-nucleosides (19b, 17b, 12b, 14b & 14a) (Fig. 3).

Summary

Various regio-isomeric five-membered oxadiazoles based 2′-deoxy-C-nucleosides were synthesized for the first time in good yield and high purity. All C-nucleosides were assembled from pure α- or β-anomer of glycosyl cyanide. The synthesis of glycosyl cyanide as key starting material was established on large-scale and in excellent yield. The easy accessibility of glycosyl cyanide further allows its utility in design of therapeutic oligonucleotides.47 The synthetic methodologies developed in this study are general and offer future scope to generate other nucleoside analogues for SAR study. Biological evaluation was carried out for synthesised compounds and shows reasonable cytotoxicity in five different tumor cell lines. Studies on antiviral activity of these compounds is in progress and it will be published elsewhere.
Scheme 2. (Reagents and Conditions): (i) NH₂OH.HCl, DIEA, EtOH, reflux, 1 h (92–96%); (ii) Acyl chloride, 1,4-dioxane, RT, 16 h (73–97%); (iii) Trimethyl orthoformate, BF₃.Et₂O 110 °C, 3 h (or) Acid anhydride, BF₃.Et₂O, 110 °C (or) Trifluoroacetic anhydride, DCM, RT, 5 h (80–98%); (iv) KOH, DMSO, RT, 6 h (72–98%); (v) NaOMe, DCM:MeOH (3:2), RT, 16 h (48–97%).

Scheme 3. (Reagents and Conditions): (i) NaN₃, Cu, CuSO₄, DMF, 120 °C, 16 h (87–90%); (ii) (R₂CO)₂O, hydroquinone, reflux, 1 h (or) R₂COCl, Pyridine, 90 °C, 2 h (78–97%); (iii) NaOMe, DCM:MeOH (3:2), RT, 16 h (46–97%).

Scheme 4. Plausible reaction mechanism for 2-substituted 1,3,4-oxadiazole ring formation from 18a or 18b.
Fig. 3. Inhibition profile for 12 C-nucleosides against 5 cell lines. Doxorubicin was used as a control which exhibited >90% inhibition at 2 μM.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data (experimental data and product characterization) to this article can be found online at https://doi.org/10.1016/j.bmcl.2020.127612.

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16. Qian W, Kuncich KM, Markella K, Svilana VS, Dömling A. 1,3,4-Oxadiazoles by
15. Qian W, Kuncich KM, Markella K, Svilana VS, Dömling A. 1,3,4-Oxadiazoles by
14. Qian W, Kuncich KM, Markella K, Svilana VS, Dömling A. 1,3,4-Oxadiazoles by
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6. Qian W, Kuncich KM, Markella K, Svilana VS, Dömling A. 1,3,4-Oxadiazoles by
5. Qian W, Kuncich KM, Markella K, Svilana VS, Dömling A. 1,3,4-Oxadiazoles by
4. Qian W, Kuncich KM, Markella K, Svilana VS, Dömling A. 1,3,4-Oxadiazoles by
3. Qian W, Kuncich KM, Markella K, Svilana VS, Dömling A. 1,3,4-Oxadiazoles by
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