
Mohamed A. El-Atawy1,2, Mohamed Nabil Abd Al-Moaty1, Adel Amer1,3,*

1Department of Chemistry, Faculty of Science, Alexandria University, Egypt
2Dipartimento Di Chimica, Universita Degli Studi Di Milano, Via C. Golgi 19, 20133 Milano, Italy
3Department of Applied Chemistry, Faculty of Applied Science, Taibah University, Madinah Munawwarah, Saudi Arabi

Abstract C-Nucleosides remain among the most challenging modified nucleosides to build for evaluation of their biological activities. This review includes a brief introduction of the C-Nucleosides classification and focuses on what has been done during a three year period (2009-2011) for their synthetic approaches and structural modifications. It spots locations of work and synthetic tactics, then correlate that to international vs. national transformation of methodologies. For sustainable developments science diplomacy may provide a forum for international collaborative research, which leads to intriguing topics of potential applications.

Keywords C-nucleosides, Synthetic Strategies, Global Perspective, Science Diplomacy

1. Introduction

Nucleosides are fundamental building blocks of biological systems. The natural nucleosides and their analogs find numerous applications as antibiotic, fungicidal, anti-tumor and anti-viral agents. Therefore, the chemistry of these compounds has been studied extensively and today nucleoside chemistry represents an important area of research for modern drug discovery. Vital elements of the structure of nucleoside are: 1) hydroxymethyl functionality; 2) spacer [e.g., sugar component] on which the hydroxymethyl group is a part; 3) heteroaryl base or aryl group attached to the sugar. C-Nucleosides are a subtype of these compounds in which the spacer and heteroaryl(aryl) groups are linked via C-C bond (Figure 1). The attractive feature of C-Nucleosides arises from the presence of this C-C glycosidic bond, which gives a greater resistance towards chemical and enzymatic hydrolysis than N-Nucleosides.

C-Nucleosides can be classified according to their sugar moiety into five different categories:
1- Cyclic C-Nucleoside
2- Acyclic C-Nucleoside
3- Homocyclic C-Nucleoside
4- Reverse C-Nucleoside
5- Carbocyclic C-Nucleoside
6- Heterocyclic C-nucleoside

These features have motivated organic chemists to develop efficient and practical synthetic methods, and numbers of strategies have been devised to design nucleoside analogues: 1) building up the heterocyclic unit on a suitably functionalized carbohydrate moiety; 2) building up a carbohydrate moiety on a suitably functionalized heterocyclic compound; 3) transformation of C-Nucleoside into another; 4) direct coupling between a suitably protected carbohydrate moiety with a preformed heterocyclic compound.

In this report we wish to view the latest development (2009-2011) with spotlighting on the tactics chemists deliberate based on their location(s).

2. Building up the Heterocyclic Unit on a Suitably Functionalized Carbohydrate Moiety

2.1. From Nitrile Terminal on C1 Atom

2.1.1. Cyclic C-Nucleosides

Functionalization of the carbohydrate moiety with nitrile group at the anomeric carbon gave an important precursor for synthesis of C-Nucleoside. Protected ribofuranosyl nitrile 5a-c was converted to the corresponding ribofuranosyl...
thioamide (6a-c), whose reaction with ethyl bromopyruvate gave the protected tiazofurin derivative 7a-c. Treatment of the latter with methanolic ammonia afforded the thiazole C-Nucleoside 8a-c (Scheme 1).

\[
\begin{align*}
\text{Scheme 1. Construction of C-nucleosides 7 from nitrile precursors}
\end{align*}
\]

2.1.2. Homocyclic C-Nucleosides

The homocyclic C-nucleoside analogue was also reported from the nitrile 9 using the same procedure already used for preparation of 8a-c to give the corresponding homo-C-tiazofurin analogue bearing 2,3-anhydro ribofuranosyl moiety 13 and 14, which represent the first biologically active tiazofurin analogue that demonstrate antiproliferative activity (Scheme 2).

\[
\begin{align*}
\text{Scheme 2. Construction of homocyclic C-nucleoside 13 from nitrile precursor}
\end{align*}
\]
2.2. From Alkynyl Terminal on C1 Atom

2.2.1. Cyclic C-Nucleosides

Another essential functional group for synthesis of heterocyclic moiety upon carbohydrate is the ethynyl group at the anomeric carbon. Sonogashira reaction of 1-ethynyldeoxyriboside $16\alpha$ or $16\beta$ with trifluoroacetanilide derivatives $15a-d$ furnished the corresponding alkynyldeoxyribose derivatives $17\alpha$ or $17\beta$, whose cyclization led to indolyl C-Nucleoside $18\alpha$ or $18\beta$ (Scheme 3). [3,  

\[ \text{Scheme 3. Synthetic steps to prepare C-nucleoside 18 from alkynyl precursor} \]

Monosubstituted ribosyl acetylene $19a-b$ was also used for a 1,3-dipolar cycloaddition with benzylazide in presence of copper catalysis to direct the formation of only 1,4 disubstituted regioisomer of 1,2,3-triazole C-Nucleoside $20a-b$ which is considered as carbonylated analogue of ribavirin (Scheme 4). [4,  

\[ \text{Scheme 4. Synthesis of 1,2,3-triazole C-nucleosides 20 from alkynyl precursor} \]

Disubstituted ribosyl alkyn $22$ obtained from riboside $21$ using indium(0)-mediated alkynylation reaction was also involved into 1,3-dipolar cycloaddition reaction with benzylazide to afford 1,4,5-trisubstituted triazole C-Nucleosides $23$ and $24$ (Scheme 5). [4,  

The reaction was conducted under micellar catalysis to improve the regioselectivity.
2.2.2. Heterocyclic C-Nucleosides

The same methodology of heterocyclization of ethynyl group into 1,2,3-triazole was used to prepare the aza-C-Nucleoside analogue 28 (Scheme 6) [5, 6, 7].

2.3. From Carboxyl Functionality on C1 Atom

2.3.1. Cyclic and Homocyclic C-Nucleosides

Hantzsch reaction on the aldehydo of 29a with β-ketoester 30 and enamine ester 31, under L-proline catalysis gave dihydropyridine C-Nucleoside 32a in stereoselective manner with (de 95%). The use of C-glycosyl aldehyde with elongated chain 29b-f extends the synthesis to the homo-C-Nucleoside analogue 32b-f (Scheme 7) [6, 7, 8, 9, 10, 11, 12].

Wittig type reaction of sugar functionalized with keto group at the 4-position 33 and stabilized phosphrane leads to 34 whose mild oxidation with pyridinium chlorochromate (PCC) afforded β-sugar-β-formy-α-β-unsaturated ester 35. Utilization of 35 in cyclocondensation reaction with hydrazine hydrate or its derivatives gave pyrazole, pyrazoline, pyridazinone pseudo C-Nucleoside (Scheme 8) [7, 9, 10].

2.3.2. Acyclic C-Nucleosides

Construction of the heterocyclic moiety on sugar can also be used for synthesis of acyclo C-Nucleoside analogs. Thus, the condensation of heterocyclic hydrazine derivatives with some monosaccharide gave the corresponding aldehydo sugar hydrazones, which on acetylation gave the o-acetylated sugar derivatives subsequent oxidative cyclization followed by de-α-acetylation afforded the 1,2,4-triazole C-nucleoside. Scheme 9 [8-14, 15].

In most cases acetylation of the sugar hydrazones (40 a, b, c, f, g) gave directly the O-acetylated cyclic C-nucleoside, on the other hand all attempts dehydrogeative cyclization of sugar hydrazone (40d) or its acetylated derivative (41d) failed. Competition between two ortho ring nitrogen (NH, =N) in the oxidative cyclization process such as in case of the O-acetylated hydrazone (41c, g, h) gave product corresponded to cyclization between the azomethine carbon and the hydrogenated nitrogen of the ring.
Reaction of acid hydrazides with some aldehydo sugars gave the corresponding sugar aroylhydrazones. When those hydrazones were heated in acetic anhydride at 100°C their corresponding 1,3,4-oxadiazoline acyclic C-nucleosides 46a-b were isolated (Scheme 10). [15-16].

Cyclocondensation of aldehydo sugar Schiff base 48 with thioglycolic acid in dry dioxane afforded the corresponding thiazolidinone a cyclic C-nucleoside 49 (Scheme 11). [17].

Following the Hantzch approach for synthesis of pyridine, treatment of D-glyceraldehyde 50 with methyl acetoacetate and dimedone 52 in presence of bentonite clay as a support, ammonium nitrate as source of ammonia, and HNO₃ as oxidant was furnished, after chromatographic purification, C-acyclic pyridine nucleoside 53 (Scheme 12). [18].

The Kidawaï’s method for synthesis of imidazole derivative via condensation of 1,2-dicarbonyl compound such as benzil with aldehyde in excess of ammonium hydroxide under microwave irradiation (MWI) was used for the synthesis of imidazole C-acyclic nucleoside 59 by utilizing the aldehydo functional group of protected D-glyceraldehyde 54. While condensation of 54 with ethyl acetoacetate and urea using natural phosphate doped with ZnCl₂ under MWI afforded acyclic C-nucleoside having dihydropyrimidinone 55. An efficient synthesis of the C-acyclic nucleoside of indeno[1,2-b]pyridine derivative 62 was accomplished using MWI treatment of 54 with 1,3-indeno-1,3-dione in presence of ammonium acetate (Scheme 13). [18].

Scheme 7. Construction of cyclic and homocyclic C-nucleosides 32 from carbonyl functionality on C1 of precursors.
Scheme 8. Syntheses of C-nucleosides 36-38

{\[\text{NH-NH}_2\] + CHO (CHOH)\_n \rightarrow \text{NH-NH}_2(CHOH)\_nCH\_2OH \text{ Aldohexoses or Aldopentoses} \rightarrow \text{NH-NH}_2(CHOH)\_nCH\_2OAc} \rightarrow \{\[\text{NH-NH}_2(CHOH)\_nCH\_2OAc\] + Ac\_2O + HCl \rightarrow \text{NH-NH}_2(CHOH)\_nCH\_2OAc (CHOAc)\_n\}

Scheme 9. Synthetic steps for the preparations of acyclic C-nucleosides 43 from the reactions of heterocyclic hydrazines with aldoses
Scheme 10. Synthetic approach to acyclic C-nucleosides 46 from hydrazides

Scheme 11. Synthetic approach to acyclic C-nucleosides 49 from aniline derivatives and aldoses

Scheme 12. Synthesis of acyclic C-nucleoside 53 from aldoses via multicomponent reaction (MCR)

Scheme 13. Synthetic approaches to acyclic C-nucleosides 56, 59 and 62
3. Direct Coupling between a Suitably Protected Carbohydrate Moiety with a Preformed Heterocyclic Compound

The direct attachment of a preformed glycon unit to an appropriate carbohydrate is one of the most important methods for synthesis of C-nucleoside. This strategy is based on ionic, free radical or metal mediated carbon-carbon bond formation.

Synthesis of nucleoside derivatives of quinuclidin-3-one 63 was achieved by the reaction of 63 with D-glucose in presence of catalytic amount of zinc chloride to give the cyclic C-nucleoside analogue 64a-d. This reaction involves nucleophilic displacement of the anomeric hydroxyl group which activated by Lewis acid catalysis. On the other hand condensation of 63 with D-glucose in sodium carbonate as basic catalyst instead of Lewis acid afforded the bis-quinclidine sugar 65. In addition the Mannich base analogue 66 was synthesized by treatment of 63 with glucose and morpholine under Mannich reaction condition (Scheme 14).

![Scheme 14. Construction of acyclic C-nucleosides 64-66](image)
Coupling of aryl or heteroaryl lithium reactants to protected sugar lactone gave hemiketal intermediate, which subsequent stereoselective reduction afforded the desired C-nucleoside with high β stereoselectivity. Thus, lithiating bromoheterocycle using n-butyl lithium at -78 °C afforded the lithio species in situ which reacted with the protected lactone to generate the hemiaketal. Subsequent anomeric reduction using triethylsilane and boron trifluoride etherate furnished Metobo et al. explain the stereoselectivity to β-anomer on the basis that the chelation of silicon to either 2- or 3-benzyl ether oxygen electron pair results in delivery of hydride anion from a favored face to furnish only the β-anomer or almost exclusively (Scheme 15).

**Scheme 15.** Reaction of heteroaryl lithium with sugar lactone to prepare C-ribonucleoside that bear amino pyrimidine or amino pyridine have been synthesized using the same synthetic approach, but it was found that protection of the amino group with benzyl bromide are more suitable for coupling with the sugar component. Also it was found that the dehydroxylation of hemiketal intermediate with Et₃SiH in presence of strong Lewis acid led to removal of the 2,3-O-isopropylidine group affording the corresponding C-nucleoside (Scheme 16).

**Scheme 16.** Reaction of heteroaryl lithium with sugar lactone to prepare C-nucleosides
The synthesis of 5-bromopyridin-2-yl and 6-bromopyridin-3-yl C-ribonucleosides was based on the regioselective lithiation of 2,5-dibromopyridine \( \text{79} \). In toluene the lithiation proceeded at position 2 leading to 5-bromo-2-lithiopyridine, whereas in Et\(_2\)O the lithiation took place at position 5 to furnish 2-bromo-5-lithiopyridine (Scheme 17).

![Scheme 17. Synthetic approaches to C-nucleosides 84 and 87 from 2,4-dibromopyridine](image)

4. Construction of the Spacer on the Base

A stereo-controlled synthesis via allylic substitution and ring closing metathesis sequence was reported to construct the sugar moiety of somearyl C-Nucleoside 108a-c. Where as the reaction of the enantiopure alcohol 88 with the enantiopure branched carbonated compounds 89a,b in presence of Ir(I) catalyst [23,24,25] afforded the respective enantiopure products 90-93 in good yields (Scheme 18). Ring closing metathesis of the bisallyl ethers 90-93 in presence of a catalyst led to the formation of the desired 1,5-dihydrofuran derivatives 94a,b-97a,b which were deprotected by treatment with Et\(_3\)N.HF to afford the corresponding alcohols 98a,b-101a,b (Scheme 19). Also vicinal dihydroxylation of the isolated cis-dihydrofuran derivatives 94a,b and 97a,b using either osmium tetroxide or ruthenium tetroxide as catalysts were performed to obtain compounds 102a,b and 103a,b in excellent yield.
Esterification of the tetrafluorinated alcohol 104 followed by cyclization and dehydroxylation was performed to yield the aryl C-nucleoside derivatives 108a-c (Scheme 20). [24] Thus, esterification of 104 using either acyl chlorides in CH$_2$Cl$_2$ in presence of Et$_3$N and 4-dimethylaminopyridine (DMAP), or carboxylic acids, which was performed in CH$_2$Cl$_2$ in presence of DCC and DMAP gave the desired esters 105a-c in good yields. The obtained esters are then cyclised using MeLi in THF to obtain the cyclised lactols 106a-c which underwent reductive dehydroxylation to give the protected derivatives 107a-c followed by debenzylation using either NaI in Me$_3$SiCl and MeCN or BBr$_3$ in CH$_2$Cl$_2$ to obtain aryl C-nucleoside derivatives 108a-c.
5. Transformation of the Existing C-nucleosides to Another Ones

Commonly, transformation of the C-nucleosides to other ones is carried out to improve the biological activity of the existing C-nucleosides without breaking the C-C bond between both the sugar and the base moieties.

Modification of the existing C-nucleosides occurred either in the sugar or base parts of the existing natural or synthetic C-nucleosides.

5.1. Modifications on the Base Moiety

Modifications on the heteroaryl (aryl)-C-nucleosides using organometallic catalysis were reported. In 2009 Hocek et al. described the aminocarbonylation of bromophenyl-C-ribonucleoside with CO (1 atm) with different amines in presence of lead acetate, xanthphos and potassium phosphate in toluene to give the corresponding amides (Scheme 21, Table 1). Deprotection of the silylated nucleosides using Et$_3$N.3HF at 40°C for two days followed by treatment with K$_2$CO$_3$ led to the formation of the desired free C-ribonucleosides.

Benzamide-C-ribonucleosides were found to have a biological character as to be a strong cytostatic agent including apoptosis in cancer cells.

The unprotected 5-bromofuran-C-nucleoside was used as a potential intermediate for aqueous phase cross coupling reactions. The Suzuki-Miyaura cross coupling reaction of this compound with different aryl boronic acids carried out in presence of lead acetate, tris(3-sulfophenyl)phosphine trisodium salt (TPPTS) ligand and Cs$_2$CO$_3$ as a base for 4h at 120°C yielded the biaryl β-C-nucleosides (Scheme 22). These nucleosides have high fluorescence properties that can be used as fluorescent labeling in biomolecules.

5.2. Modifications in the Spacer Part

The conversion of compounds into the hitherto unknown 2',3'-dideoxy- and 2',3'-dideoxy-2',3'-didehydro-C-nucleosides was performed (Scheme 23). Protection of the 5'-hydroxyl group in and using tert-butylidemethylsilyl chloride and imidazole in anhydrous dimethylformamide or pyridine gave and respectively. The 4-thione product was converted to the 4-methylthio derivative using methyl iodide in aqueous sodium hydroxide. Compounds and were then converted into 1,3-dioxolane-2-thione derivatives and followed by heating in presence of triethylphosphite to yield and. Deprotection of these products in presence of tetrabutyllammonium fluoride gave the amino derivatives and. Finally, hydrogenation of and using catalytic amount of Pd/C in ethanol yielded 2',3'-dideoxy-C-nucleosides and.
### Table 1. Aminocarbonylation of 3-bromophenyl-β-D-ribofuranoside

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>HN</td>
<td>—(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;y&lt;/sub&gt;—</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>HN</td>
<td>—(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;z&lt;/sub&gt;—</td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>HN</td>
<td>—(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;z&lt;/sub&gt;O(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;z&lt;/sub&gt;—</td>
<td></td>
</tr>
</tbody>
</table>

**Scheme 21.** Chemical reactions of modification to C-nucleosides 111

**Scheme 22.** Suzuki-Miyaura cross coupling reaction to prepare C-nucleosides 113
In order to incorporate $s^1\psi$C into triplex forming oligonucleotides [28, 29], S.-Q. Cao et al synthesized 3'-phosphoramidite derivative 131 starting from 128 (Scheme 24). There 128 was treated with 1.0 M tetrabutylammonium fluoride in THF followed by protecting the 5'-OH group using DMTr to give 129 in good yield. The 2'-OH protected derivative 130 was obtained by action of TBDMSCl on 129. Finally the reaction of 120 with NCCH$_2$CH$_2$OPClN(i-Pr)$_2$ in presence of 2,4,6-collidine and N-methylimidazole gave the phosphoramidite 131.
5.3. Cyclization of the Acyclic Analogue

Transformation of the di-O-isopropylidine acyclic C-nucleoside compound 132 to its O-mesityl derivative 133 was performed [29, 30] by addition of methansulfonyl chloride in pyridine at 0°C for 3 h, followed by deprotection and cyclization to yield the desired cyclic C-nucleoside 134 in good yield by refluxing compound 133 using 4% HCl in 1,2-dimethoxyethane (Scheme 25). The selective cyclization (C-4’-C-1’-1) and the configuration were confirmed using $^{13}$C-NMR and the nuclear overhauser effect (NOE) experiment. Similarly, the isopropylidine derivative 135 was transformed to the cyclic compound 137 under the same conditions through the formation of the tri-O-mesitylated derivative 136 (Scheme 26).

The reaction of the acyclic C-nucleoside 138 with 2,4,6-tri-isopropylbenzenesulfonyl chloride (TIBSCl) in pyridine gave the homo-C-nucleoside derivative 4-(2,5-anhydro-D-manno-pentitol-1-yl)-2-pheny-2H-1,2,3-triazole (Scheme 27) 139 [30, 31], where region-selectivity will occur due to the bulkiness of (TIBSCl). This dehydrative cyclization under basic conditions also yields a minor thermodynamically product 140 as a result of the 1,5-S_N^2 cyclization. During this reaction the intermediate 141 and the byproduct 142 were isolated from the reaction mixture.
Synthesis of 4-(5-deoxy-α- and β-L-arabinofuranosyl)-2-phenyl-2H-1,2,3-triazoles 144 and 145 were performed [31, ] and the anomeric configuration were determined by the CD and NMR spectroscopic measurements (Scheme 28). Acyclic 5-deoxy-L-manno-pentitol-1-yl nucleoside 143 was treated with methanolic sulfuric acid and subsequent reflux with copper sulphate yield the anomeric mixture of 144 and 145, which were separated by chromatography.

Similarly, the dehydrative cyclization of 4-(D-galacto-pentitol-1-yl)-2-phenyl-2H-1,2,3-triazole 146 catalyzed by acid gave the anomeric α,β-D-lyxopyranosyl and furanosyl derivatives 147-150 (Scheme 29). [32, ]
6. Miscellaneous Synthesis

The homo-coupled product 152 was obtained from the reaction of THF-alkyne 151 with different catalytic systems in dry DMF in order to obtain the optimized reaction conditions such as i) CuI, CsCO3 and NaI, ii) CuI and CsCO3 and iii) CuI only, to give the desired product in good yields. It was found that both CsCO3 and NaI have no effect in the reaction (Scheme 30). [33]

The reaction of butenonyl C-glycosides with cyanoacetamide via Michael addition followed by dehydrative cyclization and oxidative aromatization gave the corresponding glycosyl pyridines. These compounds are evaluated for their antidiabetic potential in vitro. (E)-1-(β-D-glucopyranosyl)-4-(aryl)but-3-en-2-ones 153a-c reacted with cyanoacetamide in DMSO, t-BuOK, N2 and O2 at room temperature followed by acetylation to give the respective 3-cyano-4-(aryl)-6-[(2",3",4",6"-tetra-O-acetyl-β-D-glucopyranosyl)methyl]pyridones 154a-c in good yields. Subsequently, deacetylation of these compounds with NaOMe/MeOH afforded the corresponding 3-cyano-4-(aryl)-6-[(β-D-glucopyranosyl) methyl]pyridones 155a-c (Scheme 31). [34]
7. Conclusions

This work highlights a recent progress in developmental strategies to build up C-nucleosides and analogues. It does not attempt to be comprehensive in particular, it intended to spot locations of work and synthetic tactics (Figure 2), then correlate that to international vs. national transformation of methodologies. From the Middle East, choosing Egypt as a model, it is clear that the internal transformation of research perspectives there dominates. However, science diplomacy may provide a forum for international collaborative research, which leads to intriguing topics of potential applications for sustainable developments.

Dedicated to the memory of Prof. Hans W. Zimmer

REFERENCES


