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Spirocyclic Nucleosides in Medicinal Chemistry: An Overview

Raquel G. Soengas* and Sandrina Silva

Department of Chemistry, QOPNA, University of Aveiro, 3810-193 Aveiro, Portugal

Abstract: This review describes some spiro- and pseudospironucleoside derivatives as well as their biological and pharmacological applications.

Keywords: Spironucleosides, Pseudospironucleosides, Carbohydrates, Antiviral, Antitumoral.

1. INTRODUCTION

Nucleosides are structural subunits of nucleic acids, the macromolecules that convey genetic information in living cells. In fact, they embrace a large family of great structural diversity and wide biological activity spectrum [1]. Human creativity has been put to light in the ability of drug researchers to draw on an understanding of the biochemistry of naturally occurring nucleosides and to build up synthetic nucleoside analogs, which belong to the most important class of antiviral drugs and are extensively used as anticancer agents and in the treatment of other diseases [2].

Nucleoside analogs prepared so far can be divided into three categories: 1) phosphate-modified, 2) base-modified, and 3) sugar-modified; most of the commonly known active compounds belong to the two latter groups. Base- and sugar-modified nucleosides are valuable constituents of potent medicinal artificial oligonucleotides.

The ability to functionalize either the heterocycle or the sugar portion of a nucleoside has led to their use in antisense [3] and RNA interference [4] strategies. In these processes, specifically functionalized nucleotides are incorporated into oligodeoxyribonucleotides (ODN's) targeted to specific RNA or DNA. The sugar portion of the nucleoside has become an important region for modifications, since the conformation of the sugar ring appears to control whether the ODN binds to RNA or DNA.

Conformationally restricted nucleoside analogs known as LNA's (locked nucleic acids) have been synthesized to lock the sugar conformation in either the N or S conformation [5], enhancing base stacking and backbone pre-organization. Accordingly, conformational restriction of the furanose ring of nucleosides, nucleotides and oligonucleotides has been intensively pursued in recent years, stimulated by the potential application of these molecules as therapeutic agents [6]. Among those, spiro-functionalized nucleosides have recently gained more interest.

The term "spironucleoside" is used to designate a type of sugar derivative in which the anomeric carbon belongs simultaneously to a pyranoid or furanoid sugar ring and to an aza-heterocyclic moiety [7]. The term "spiropseudonucleoside" is used when the spiranic carbon atom is not the anomeric carbon. The first natural spironucleoside known was (+)-hydantocidin **1**, isolated in 1991 from culture broths of *Streptomyces hygroscopicus*.

The observation that hydantocidin shows potent plant-growth regulatory activities and low toxicity to microorganisms and mammals prompted the synthesis of spiro-functionalized nucleosides as conformationally restricted molecules [8]. Considerable attention has thereafter been paid to structural modifications of nucleosides [9]. The syntheses of spiro-derivatives including C-1'-spiro, C-2'-spiro, C-3'-spiro, and C-4'-spironucleosides, as well as conformationally restricted/based analogs, have subsequently appeared in the literature.

Considering the biological relevance of spiro-functionalized nucleosides and the considerable synthetic efforts devoted to their preparation, the lack of a recent revision on this matter is somehow surprising. The aim of this mini-review is then to present an overview on the different types of spiro-functionalized nucleosides and their use as drug candidates.

2. SPIRONUCLEOSIDES (C-1'-SPIRO-FUNCTIONALIZED NUCLEOSIDES)

As mentioned in the introduction, spironucleosides are defined as structurally modified nucleosides in which the base unit at the anomeric position is spiro to the sugar moiety [10], which means when the anomeric carbon belongs to both the sugar and the heterocyclic base. Spironucleosides have gained in importance with the discovery of hydantocidin, a natural spironucleoside isolated from fermentation broths of *Streptomyces hygroscopicus* SANK 63584 [11], Tu-2474 [12], and A1491 [13], which exhibits potent herbicidal activity with high selective toxicity between plants and animals. Biochemical studies have shown that hydantocidin is a proherbicide that inhibits adenylosuccinate synthetase, an enzyme that plays an important role in purine biosynthesis [14]. These observations have understandably stimulated considerable interest, not only in the synthesis of **1** [15], but also in a variety of its analogs, with the notion that important pharmaceutical leads can be found among modified nucleoside analogs. Included in this group are several hydantoin-type

*Address correspondence to this author at the Department of Chemistry, QOPNA, University of Aveiro, 3810-193 Aveiro, Portugal;
Tel:/Fax: +351(234)370084; E-mail: rsoengas@ua.pt

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analogs as well as diketopiperazines, barbiturates and more diverse spiroheterocyclic subunits.

2.1. Hydantoines

First of all, some spirohydantoins from other sugars than D-ribose were synthesized with a view to discovering novel compounds with interesting biological properties. In 1995, Fleet *et al.* synthesized epimeric spirohydantoins based on glucopyranose **2** and **3** and biological results have shown that spirohydantoin **2** was the most active inhibitor of glycogen phosphorylase known to date, whith a K_i value of 3.1 μM [16].

Glycogen phosphorylase (GP; α-1,4-glucan: orthophosphate glycosyl transferase) [17] is a key enzyme in the regulation of muscle and hepatic glycogen metabolism, and catalyzes the first step in the intracellular degradation of glycogen [18]. Inhibition of glycogen phosphorylase [19] is believed to assist in shifting the equilibrium between glycogen degradation and glycogen synthesis in favor of the latter in both muscle and liver. Therefore, GP inhibitors may be clinically useful for the treatment of diabetes mellitus, especially the non-insulin dependent diabetes mellitus (NIDDM or type II diabetes). Diabetes, a disorder of chronically elevated blood glucose levels (hyperglycemia), is one of the most dangerous diseases killing people throughout the world [20]. Over 75% of patients suffering from this illness have type II form, also known as non-insulin-dependent diabetes mellitus (NIDDM) [21] [22]. Hyperglycemia is a consequence of inadequate insulin release or insulin resistance [23], which results in increased glucose levels in the blood stream. Therefore, inhibition of glycogen phosphorylase (GP) enzymes can assist the regulation of blood sugar level in type II diabetes patients.

The activity of **2** as a potent inhibitor of glycogen phosphorylase has therefore stimulated the synthesis of hexose analogs of spirohydantoins as the anomeric spirohydantoins of glucofuranose **4** and **5** [24]. Analogs from other hexoses were also synthesized, as L-rhamnose derivatives **6** and **7** [25], or 6-deoxy-L-lyxose-derived spironucleoside **8** [26] (Fig. **1**).

In the quest for glycogen phosphorylase inhibitors, a number of deoxyspironucleoside analogs were also synthesized. For example, **9**-**12** were prepared from 2-deoxy-D-ribose and screened *in vitro* against rabbit muscle glycogen phosphorylase b (GPb). Compounds **10** and **12** were found to be weak competitive inhibitors of the enzyme (K_i = $8.2x10^{-3}$ and $2.2x10^{-1}$ M, respectively), while the remaining two were inactive [27]. 2'-Deoxyhydantocidin **13** and its 1'-epimer **15** as well as trityl derivatives **14** and **16** were also described [28] (Fig. **2**).

Some thiohydantoin derivatives have also been synthesized, mainly in connection with their potent biological activity. For example, it is known that changing the C-8 carbonyl in **2** by a thiocarbonyl group as in **17** (Fig. **3**, K_i = 5.1 μM), brings about practically no change in the inhibition of muscle GPb. In contrast to **2**, compound **17** can advantageously be synthesized in a simple and highly stereoselective six-step route, starting from D-glucose, allowing **17** to be prepared in gram quantities [29]. Glucopyranosylidene-spiro-thiohydantoin (G-TH) **17**, which was extensively studied as an inhibitor of glycogen

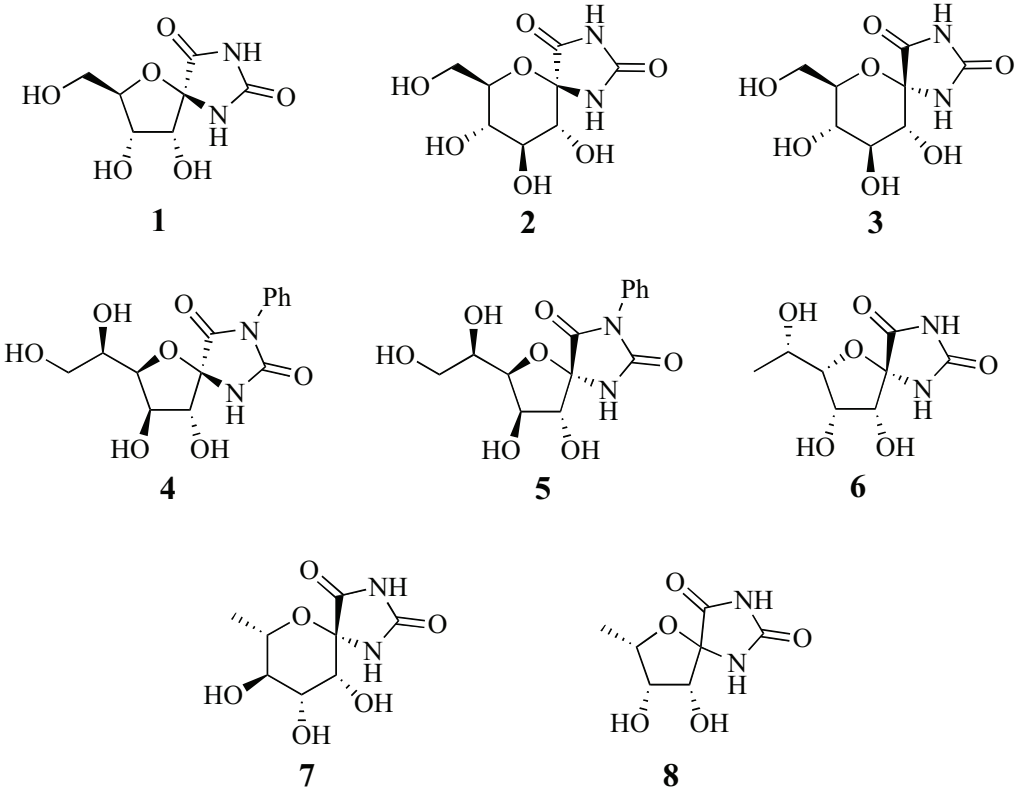


Fig. (1). Epimeric spirohydantoins.

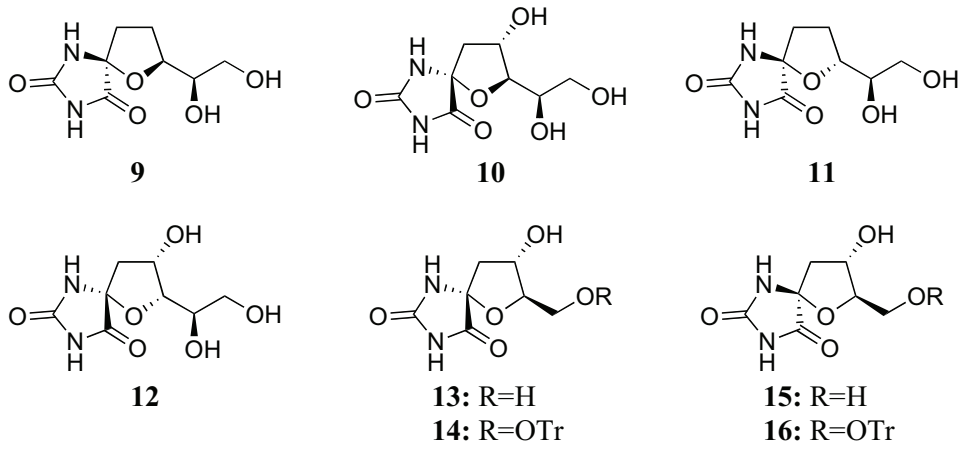


Fig. (2). Deoxy analogues of epimeric spirohydantoins.

phosphorylases [30], is also inhibitor of salivary amylase. For this reason, G-TH represents a new concept since this drug might be used successfully, not only for the prevention of dental caries but also as a supplementary drug for the treatment of sugar metabolic disorders [31].

Fuentes *et al.* have developed a useful strategy for the syntheses of 7-thio analogs of hydantocidin. This procedure, based on the use of glycosyl isothiocyanates as intermediates [32], was employed for the synthesis of several thioderivatives, as for example **18** and **19** [33].

Recent modifications of the nucleoside structure consist in the introduction of a selenium atom, an essential trace element [34], either by replacing the endocyclic oxygen atom of the carbohydrate residue [35] or as part of the nucleobase, leading to potent anti-HIV and anti-HBV activities [36]. Derivatives **20** and **21** were the first described selenium-containing spironucleosides, incorporating an imidazoline-2-selone unit in a fixed conformation around the glycosidic bond [37] (Fig. **3**).

2.2. Diketopiperazines

Cyclic dipeptides or diketopiperazines are among the most common peptide derivatives found in Nature. In fact, naturally occurring [38] as well as synthetic diketopiperazines [39] have a wide range of potential biological applications [40] and this feature has not escaped to the attention of researchers. Fleet *et al.* prepared several anomeric spirodiketopiperazines [41] from D-mannose (**22** [41a, c], **23** [41a, b, c], **24** [41d,e]), D-glucose (**25** [41f]), L-rhamnose (**26** [41g], **27** [41g], **28** [41h]) and 6-deoxy-L-lyxofuranose (**29** [41i], **30** [41i]) in order to find potential drug candidates (Fig. **4**). Among them, the glucopyrano-derived spirodiketopiperazine **25** showed to be a strong and specific inhibitor of glycogen phosphorylase (K_i = 59.7 μM), although less effective than its spirohydantoin analog **2**. After the pioneering work of Fleet's group, other synthetic procedures have been developed in order to prepare different anomeric spirodiketopiperazines. For example, 2,3-deoxy derivatives **31** and D-lyxose derivative **32** were synthesized using a procedure featuring an acid-catalyzed rearrangement of a 3-hydroxy β-lactam and the ammonolysis of a spiro keto lactone [42].

Structurally related to spirodiketopiperazines are the spirodihydrouracil derivatives, which formally result from the insertion of a methylene group between the anomeric carbon and the nitrogen of the *N*-glycosidic bond. The hydantocidin-related spirodihydrouracil **33** [43] was synthesized to study the direction of the hydrogen bonding of the hydantoin part in the natural parent molecule. Also related to the spirodiketopiperazine skeleton is the spiro-derivative **34**, recently prepared from carbohydrate lactones. The synthetic route involves *N*-glycosylation of ulosonic acid esters, easily obtained via an indium-mediated Reformatsky reaction of aldonolactones with an alkyl α-bromoisobutyrate [44] (Fig. **5**).

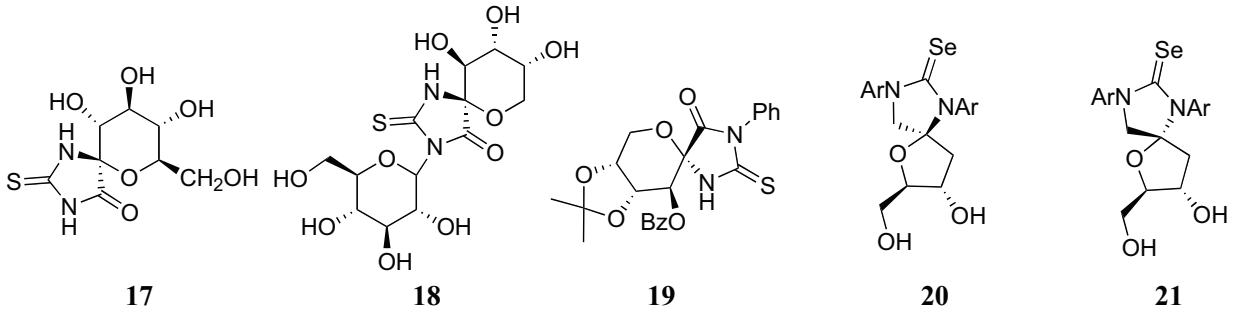


Fig. (3). Thiohydantoin derivatives.

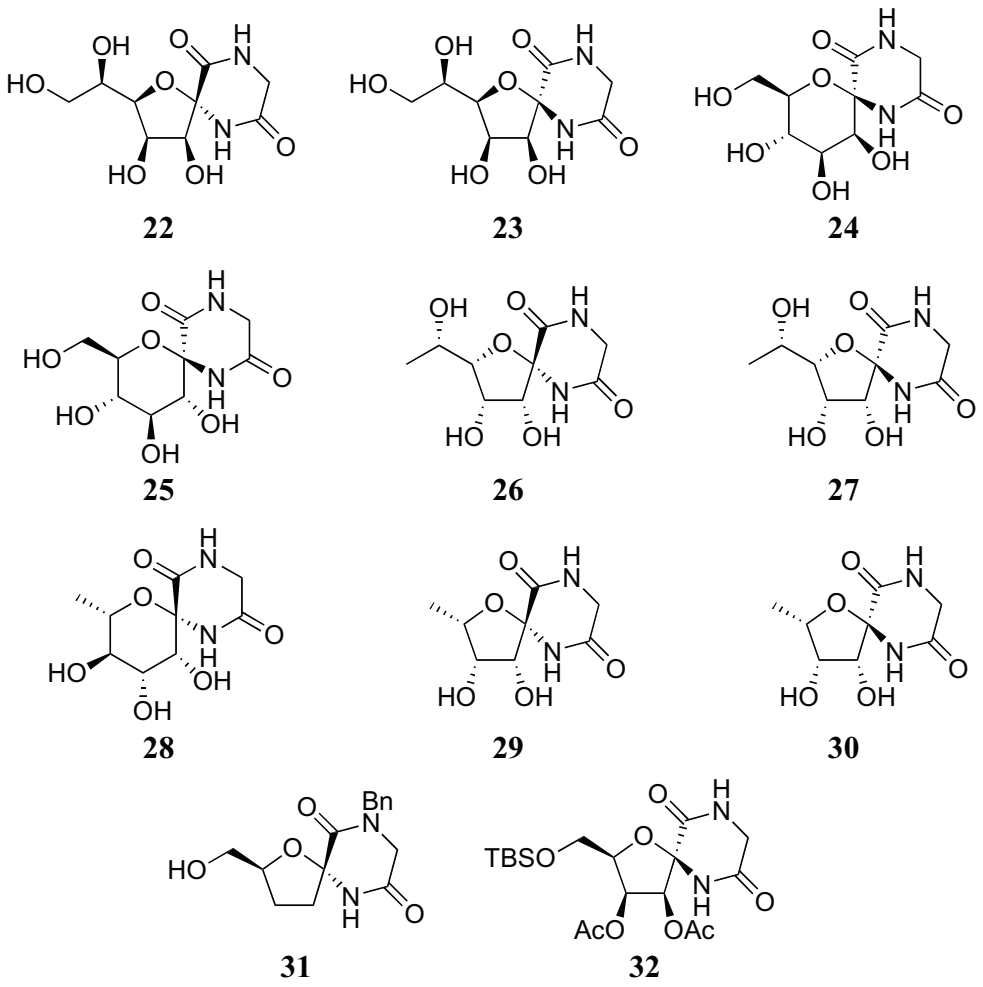


Fig. (4). Anomeric spirodiketopiperazines.

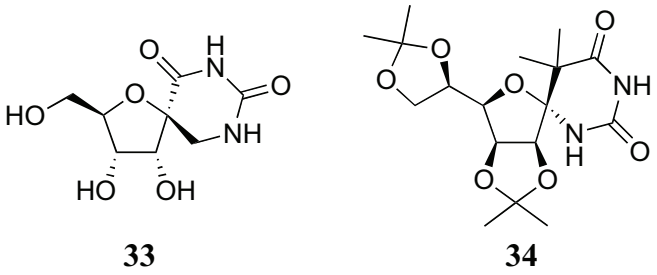


Fig. (5). Anomeric spirodihydrouracil derivatives.

2.3. Barbiturates

Similarly to the hydantoin ring, the barbiturate ring system is known to possess thymine-like hydrogen bonding capacity against adenine derivatives [45] and is found in many pharmaceutically important molecules [46]. The main problem with hydantoins and diketopiperazines is their instability, due to anomeric epimerization in basic media. To avoid epimerization around C-1', hydantoin or diketopiperazine rings can be replaced by a barbiturate ring as exemplified by compound **35** [47] (Fig. **6**).

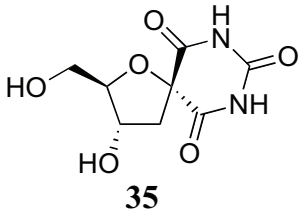


Fig. (6). Anomeric barbiturate.

2.4. Polycyclic spironucleosides

A number of spironucleosides in which the base is attached to the anomeric position of the sugar giving rise to a polycyclic system have been described. Such molecules provide conformationally fixed models, which can be useful to elucidate the glycosidic torsion angle of nucleosides. The most common procedures to prepare this type of derivatives are radical reactions on the C-1' position [48]. Following this procedure, several spironucleosides have been prepared, as 6,l'-propanouridine **36** [49], 2-deoxy-6,1'-ethanouridine **37** and 2-deoxy-6,1'-ethenouridine **38** [50], 6,1'-ethenopurines **39** and **40** [51], oxygenated derivatives **41** and **42** [52] and aza-pyrimidine nucleosides **43** and **44** [53] (Fig. **7**).

3. SPIROPSEUDONUCLEOSIDES

In the search for new antiviral and anticancer agents, a large number of spiropseudonucleosides have been prepared and biologically evaluated over the last decade. This strategy allowed the discovery of new drugs of great importance, as the 3'C-spiropseudonucleoside TSAO-T, with potent anti-HIV-1 activity. The most relevant spiropseudonucleosides synthetized to date are mentioned in this chapter.

3.1. 2'C-Spiropseudonucleosides

The first synthesized spiropseudonucleoside were 2'C-derivatives **45** and **46** [54]. Taking into account that 6-deoxy-L-ketohexopyranosyl nucleosides exhibit significant activity against L1210 leukaemia *in vivo*[55] and that the epoxy group constitutes the critical moiety in the structure of important classes of antitumour compounds [56], spiroepoxy nucleosides **45** and **46** were prepared on account of their potential antineoplastic properties.

Later on, 2'-spirocyclopropane derivatives of 2'-deoxyadenosine **47** and **48** have been synthesized [57] as a mechanistic probe for ribonucleotide reductases [58] (Fig. **8**). As inhibition of these reductases interferes with the replication of genetic material required for cancer cell division or viral genome biosynthesis [59], the study of this process is of great interest in the quest for new drug candidates.

Since then, other 2'-spironucleoside derivatives have been synthesized: 2'-*C*, 2'-*O*-propanonucleosides **49** and **51** and 2'-*C*, 2'-*O*-ethanonucleosides **50** and **52** were developed as novel conformationally restricted probes [60]; 2'-deoxy-2'-spirocyclopropylcytidine **53** is an inhibitor of the HCVNS5BRNA-dependent RNApolymerase displaying an

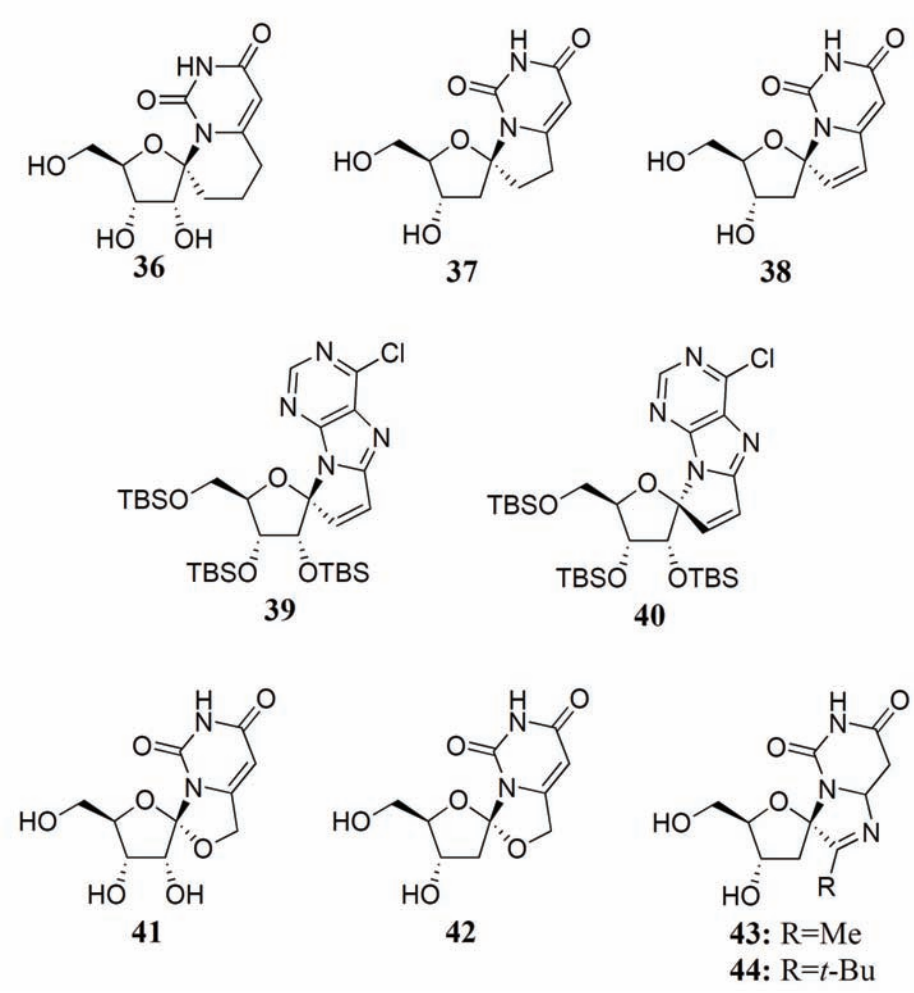


Fig. (7). Polycyclic spironucleosides.

EC_{50} of 7.3 μM and no cytotoxicity associated and thus clinically valuable for HCV (hepatitis C virus) treatment [61], and 2'-spiroisoxazolidine nucleoside analogs **54** and **55** are of potential interest for its use in antisense and RNA interference strategies [62] (Fig. **9**).

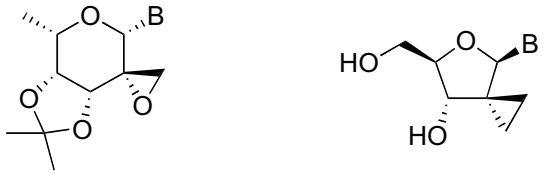
3.2. 3'C-Spiropseudonucleosides

Searching for new nucleoside derivatives as inhibitors of HIV replication, Camarasa *et al.* synthesized 3'C-spironucleosides **56-63** [63]. While *xylo* derivatives or *ribo*-nucleosides with none or only one silyl group were shown to be inactive towards HIV-1, 3'-spiro *ribo*-nucleosides containing two silyl groups such as [1-[2',5'-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyllthymine]-3'-spiro-5''-[4''-amino-1" ,2"-oxathiole 2",2"-dioxide] (TSAO) **60a** exhibited potent (EC_{50} = 0.034 μg/mL, CC_{50} = 7.7 μg/mL) and selective inhibition on HIV-1 replication [64] (Fig. **10**).

As consequence of TSAO highly interesting biological activity, great efforts were devoted to the development of analogs in which the cytotoxicity is decreased without compromising the antiviral activity and the most common strategy is the introduction of slight modifications either in base or in sultone moiety [65]. Examples of sultone-modified derivatives are compounds **64-70** [66] and **71-72** [67], nevertheless, no antiviral activity at subtoxic concentration was achieved. Other 3'C-spiropseudonucleosides are lactone **73** [68] and 3'-spirooxirane derivative **74** [69] (Fig. **11**).

2.4. 4'C-Spiropseudonucleosides

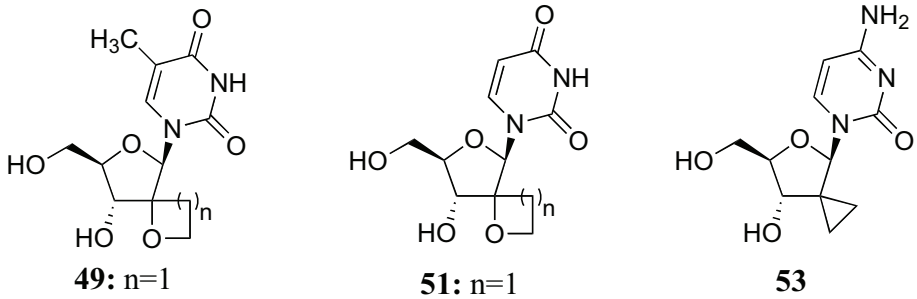
Since the first example of a C4'-homologated nucleoside reported in 1992 [70], molecules of this class have attracted much interest [71], motivated by several factors. In a first hand, the glycosyl torsion angle about the C4'-C5'-bond is now fixed, such that positioning of the hydroxyl functionality at R_1 or R_2 results in the adoption of rather different spatial orientations. Beyond this, DNA and RNA fragments have a considerably large void space in the region below C4', which can accommodate several methylene groups [72]. Finally, DNA strand cleavage has been shown to occur due to the action of C4'-radicals. However, in 4'C-branched nucleosides, the 4'-hydrogen is no longer present.



45: B= purinyl
46: B= pyrimidyl

47: B= adenyl
48: B= uracyl

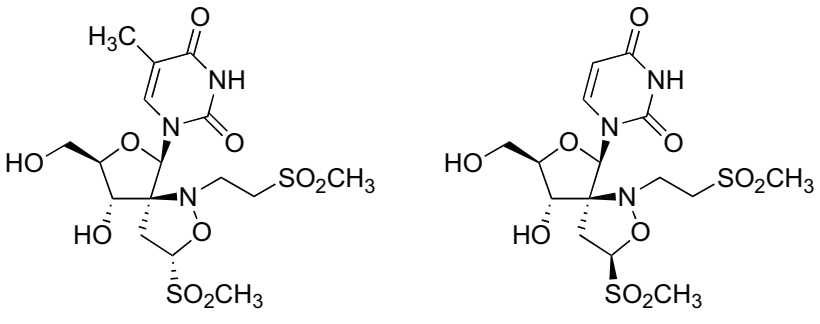
Fig. (8). Spiroepoxide and spirocyclopropane nucleosides.



49: n=1
50: n=2

51: n=1
52: n=2

53



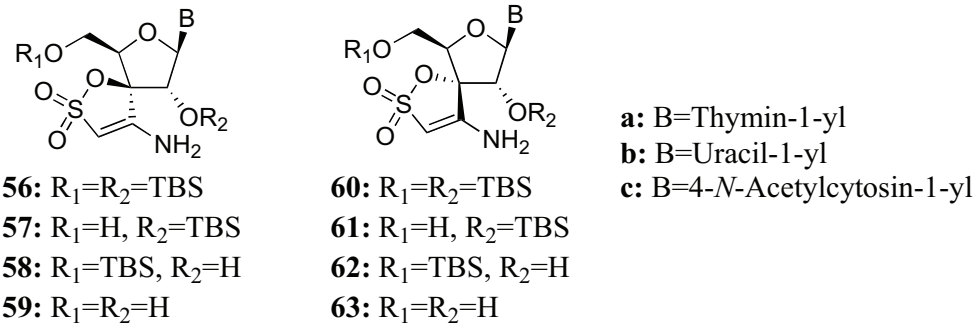
54 **55**

Fig. (9). Miscellaneous 2'-spironucleoside derivatives.

Of all the possibilities of substitution at C4'-position, the spirocyclization is particularly interesting, mainly due to conformational restrictions inherent to the spiro system. Paquette *et al.* carried out extensive research in this field, preparing several spirocyclic nucleosides (**75** and **76** [73], **77** and **78** [73a], **79** [73a] and **80** [74], **81** and **82** [75]) which were shown to display significant antiviral activity. Among them, the most relevant for its biological activity is **78**, which displays strong inhibitory effect against human coronavirus. High selectivity and low cytotoxicity are additional characteristics of this substance. Closely related to those derivatives reported by Paquette's group, nucleosides **83** and **84** were developed using a completely different synthetic strategy [76] (Fig. **12**).

As a direct consequence of potent antitumor and antiviral properties of several naturally occurring carbocyclic nucleosides [77], many efforts have been dedicated into the preparation of different types of those nucleoside analogs [78]. In order to achieve rigidification of the molecular architecture, the use of a spirocyclic restriction has been considered. Thus, carbocyclic analogs such as **85 a**-**e** and **86 a**-**e** [79], have been built up (Fig. **13**).

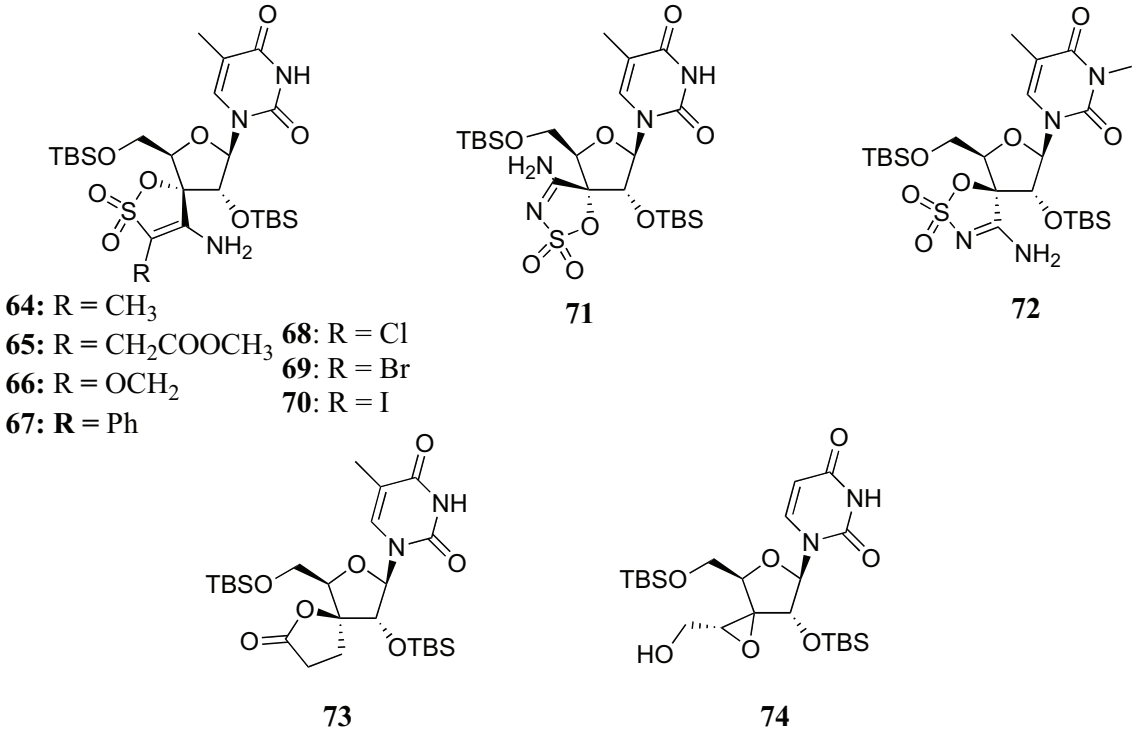
Heterosubstitution of the furanoid ring can provoke a profound effect on biological activity. For example, several sulfur mimics have been recognized as potent antiviral and anticancer agents [80]. These findings have ignited the interest for the synthesis of spirocyclic thionucleosides to use as biochemical probes, as C4'-spiropseudonucleosides **87**, **88** and **89** [81] (Fig. **14**).



56: R_1=R_2=TBS
57: R_1=H, R_2=TBS
58: R_1=TBS, R_2=H
59: R_1=R_2=H

60: R_1=R_2=TBS
61: R_1=H, R_2=TBS
62: R_1=TBS, R_2=H
63: R_1=R_2=H

Fig. (10). 3'C-spironucleosides.



64: R = CH_3
65: R = CH_2COOCH_3
66: R = OCH_2
67: R = Ph
68: R = Cl
69: R = Br
70: R = I

71

72

73

74

Fig. (11). TSAO analogues.

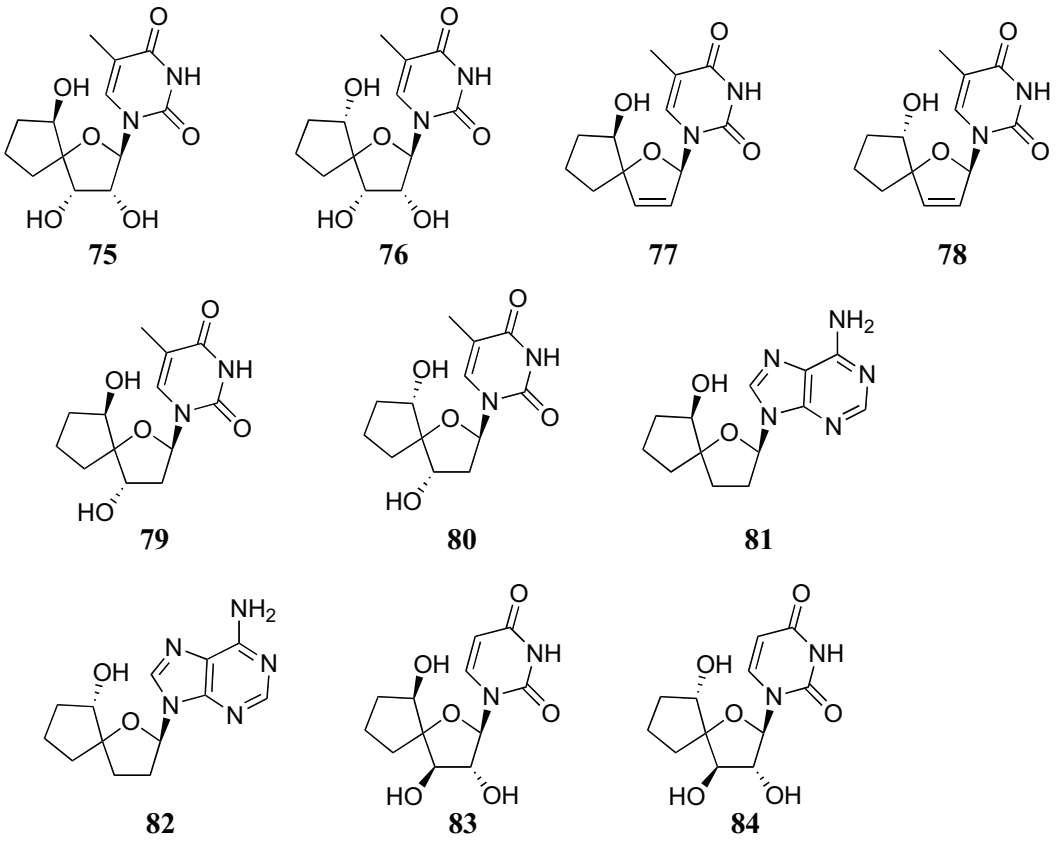


Fig. (12). C4'-spirocyclized nucleosides.

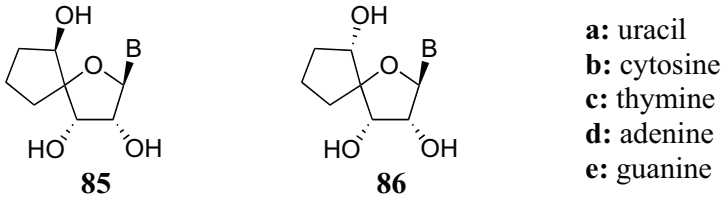


Fig. (13). 4'C-Spiropseudonucleoside analogues.

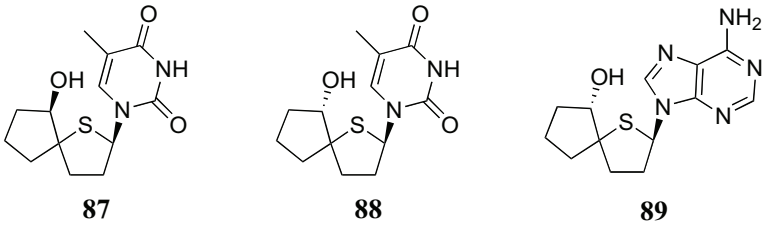


Fig. (14). 4'C- spirocyclic thionucleosides.

4. CONCLUSIONS

The past several years have witnessed explosive developments in spiro- and pseudospironucleoside chemistry, targeting many biological applications. Revising the existent world of those nucleosides, we can find many more extensive pharmaceutical applications, namely as antidiabetic, antiviral and antitumoral agents. Thus, looking to the future, the widespread and wide field of application of nucleosides in medicinal chemistry, and the emergence of increasingly sophisticated structures, seems certain to ensure continued interest in the development of this class of "synthetic" nucleosides. We thus hope that this review will provide a useful aid to medicinal chemists dealing with nucleosides and heterocyclic systems on a daily basis.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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