Triazole Nucleoside Derivatives Bearing Aryl Functionalities on the Nucleobases Show Antiviral and Anticancer Activity

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Abstract: Synthetic nucleoside mimics are important candidates for antiviral and anticancer drugs. Ribavirin, the first antiviral nucleoside drug, is unique in its antiviral activity with mutilple modes of action, which are mainly due to its special triazole heterocycle as nucleobase. Additionally, introducing aromatic functionalities to the nucleobase is able to confer novel mechanisms of action for nucleoside mimics. With the aim to combine the special characteristics of unnatural triazole heterocycles with those of the appended aromatic groups on the nucleobases, novel 1,2,4-triazole nucleoside analogs bearing aromatic moieties were designed and developed. The present short review summarizes the molecular design, chemical synthesis and biological activity of these triazole nucleoside analogs. Indeed, the discovery of antiviral and anticancer activities shown by these triazole nucleosides as well as the new mechanism underlying the biological activity by one of the anticancer leads has validated the rationale for molecular design and impacted us to further explore the concept with the aim of developing structurally novel nucleoside drug candidates with new modes of action.

Keywords: Triazole nucleosides, nucleoside analogs, HCV, TMV, pancreatic cancer.

INTRODUCTION

Ribavirin (Fig. **1A**), with its unnatural 1,2,4-triazole heterocycle able to mimic the nucleobase, was the first synthetic triazole nucleoside analog to show antiviral and anticancer activity, discovered 40 years ago [1]. Since then, numerous nucleoside drugs have been developed [2-3] and approved for clinical treatments, mainly of various viral infections [4] and cancers [5]. Well-known antiviral nucleoside drugs consist of ribavirin, zidovudine, lamivudine, emtricitabine, abacavir and acyclovir (Fig. **1A**), and the most commonly used anticancer nucleoside drugs include gemcitabine, floxuridine, capecitabine, cladribine, fludarabine and clofarabine (Fig. **1B**). These nucleoside drugs are able to mimic natural nucleosides and as such serve as building units or inhibitors that interfere in nucleic acid synthesis or block nucleos(t)ide-dependent biological processes [4-8]. Consequently, they can inhibit rapidly replicating viruses and uncontrolable cancer cell proliferation, leading to potent and effective antiviral and anticancer activity, respectively.

The importance of nucleoside drugs for clinical use and the clear-cut molecular mechanisms underlying their biological activities [4-8] alongside the increasing concern about drug resistance encountered with antiviral and anticancer chemotherapy, has led to an intensified search by bio-organic and medicinal chemists for novel nucleoside analogs as more efficacious drug candidates. Many efforts have been directed towards the design and synthesis of nucleoside mimics based on natural nucleosides, with modifications introduced to either the nucleobase and/or the sugar part, as shown in Fig. (**1**) and detailed elsewhere [1-5].

The use of unnatural heterocycles as nucleobases in the design of novel nucleoside analogs not only enhances *in vivo* stability but also confers novel biologically interesting activities. Ribavirin constitutes one of the best examples in this regard. With the special triazole heterocycle as nucleobase, ribavirin is unique in treating hepatitis C virus (HCV) infection [1,9-11]. Ribavirin exerts its biological acivity possibly by several modes of action including the inhibition of viral RNA polymerases and viral capping enzymes, the lethal mutagenesis of viral RNA genomes, the interference of host inosine monophosphate dehydrogenase and the modulation of the host immune responses [9-11]. Shortly after its discovery, considerable work was directed towards designing and synthesizing ribavirin analogs with modifications either on the triazole nucleobase and/or on the ribose [12-17]. However, even small structural modifications on the ribavirin led to important alterations (often a decrease) in biological activity. Viramidine (Fig. **2**), which has the carboxylamide function of ribavirin replaced by an amidine group, is an exception and can act as a prodrug of ribavirin with anti-HCV activity [12-13]. It is worth noting that structural modifications involving the triazole heterocycle in a ribavirin analog mainly focus on the transformation of the exocyclic carboxylamide functionality (Fig. **2**) [12-17]. This is in large part due to the limited synthetic methods available for creating structural diversity of the triazole ring in triazole nucleoside analogs [12-17].

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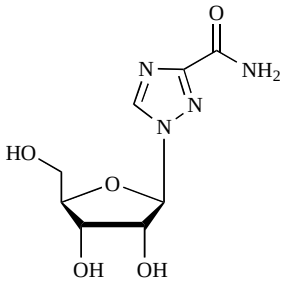
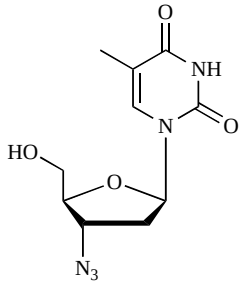
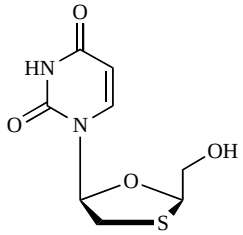
(A) Antiviral nucleoside drugs



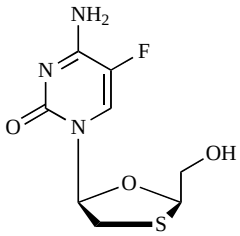
Ribavirin



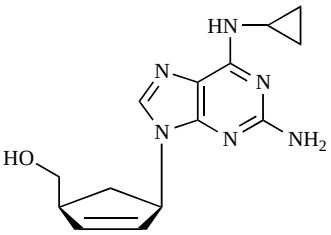
Zidovudine



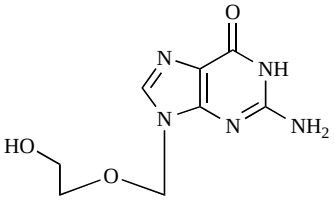
Lamivudine



Emtricitabine

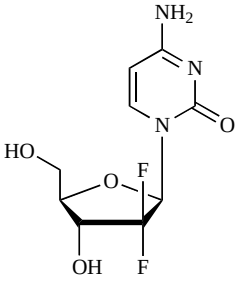


Abacavir

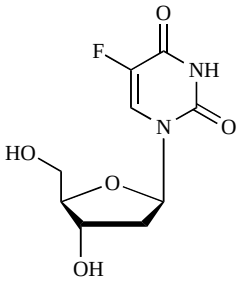


Acyclovir

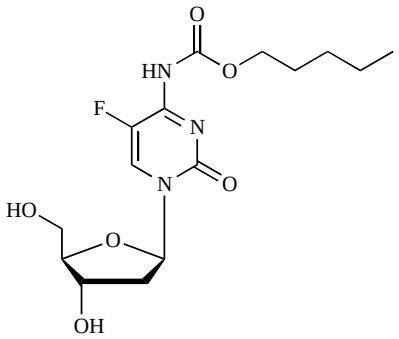
(B) Anticancer nucleoside drugs



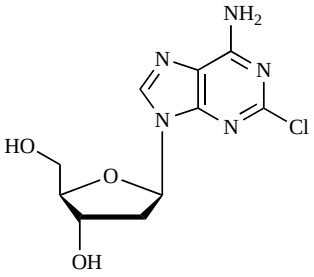
Gemcitabine



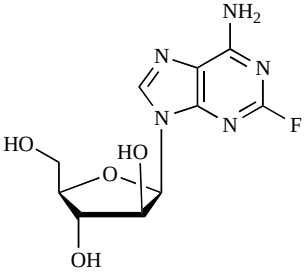
Floxuridine



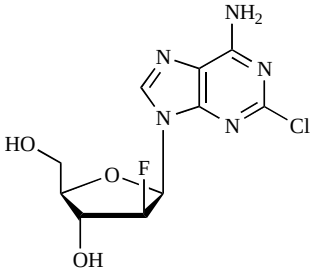
Capecitabine



Cladribine



Fludarabine



Clofarabine

Fig. (1). Examples of nucleoside drugs used in antiviral and anticancer chemotherapy.

Introducing various aromatic functionalities to the nucleobase constitutes an interesting strategy of developing new nucleoside mimics with novel modes of action. A successful example of a natural nucleobase bearing an aromatic moiety is HEPT (Fig. **3**), an acyclonucleoside analog with a phenylthio group anchored at the 6-position of the pyrimidine nucleobase [18]. HEPT exhibits potent and selective anti-HIV activity by acting as a non-nucleoside reverse-transcriptase inhibitor [18-20], a different mode of action to that of conventional nucleoside drugs. Of particular importance is the appended phenylthio group which interacts with the amino acid residues Tyr188 and Leu100 of the HIV reverse transcriptase enzyme [20], leading to the conformational change and consequent inhibition of HIV replication. Recently, 6-arylpurine nucleosides (Fig. **3**), with aromatic moieties introduced on the 6-position of adenine [21-22], have been shown to elicit effective anti-HCV and anticancer activity. These nucleoside analogs are believed to act *via* completely novel mechanisms of action.

With the above-mentioned rationales in mind, we wished to create 1,2,4-triazole nucleoside analogs bearing aromatic

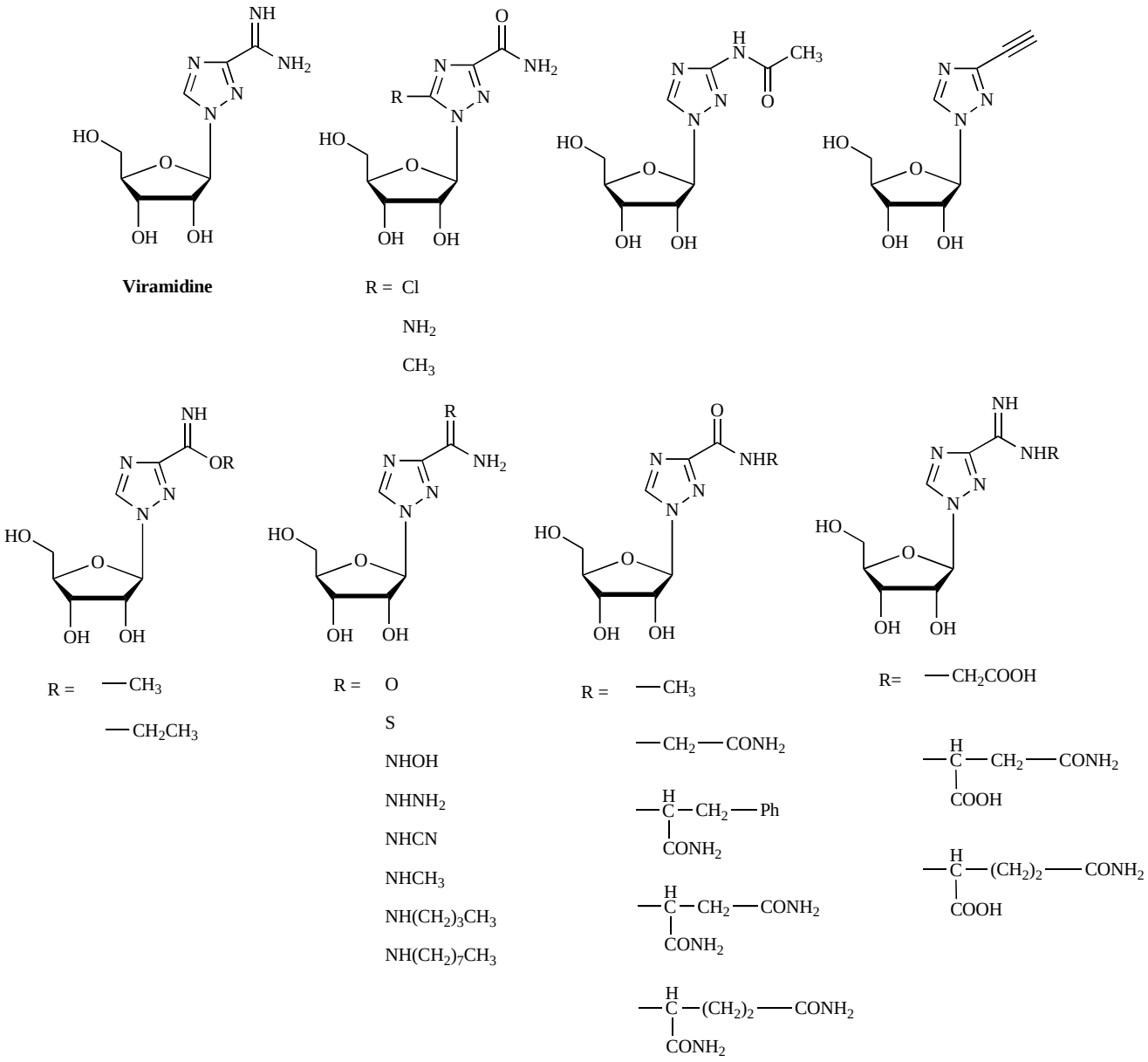


Fig. (2). Base-modified triazole nucleoside analogues based on ribavirin [12-17].

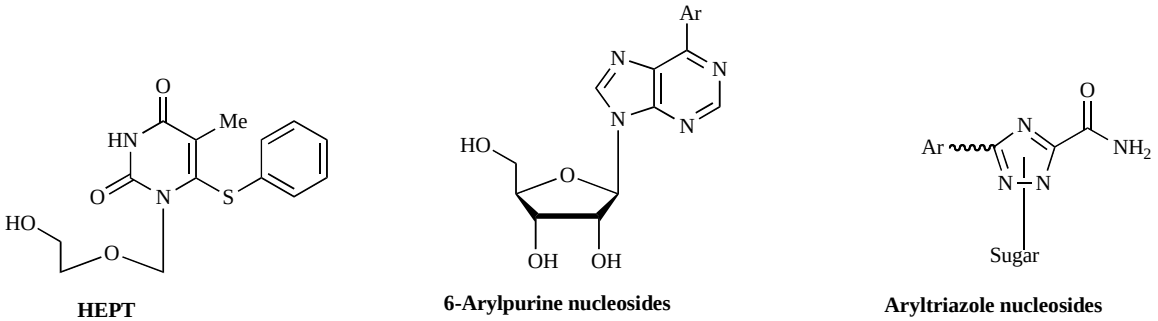


Fig. (3). HEPT and 6-arylpurine nucleosides are examples of natural nucleobases bearing aromatic moieties [18-19, 21-22]. Novel 1,2,4-triazole nucleosides bearing aromatic functionality on the nucleobase have been proposed and developed recently.

moieties which may confer biologically interesting activity with possibly new modes of action (Fig. **3**). We expected that by appending aromatic systems to the triazole nucleobase we may combine the special characteristics of unnatural triazole heterocycles [1, 23] with those of expanded and enlarged aromatic nucleobases thus leading to stronger and more efficient binding to biological targets *via* the larger aromatic systems. Triazole is also considered as a universal base capable of forming base-pairs with all five natural nucleobases [23] and thus potentially confers an increased interacting ability of triazole nucleosides with their biological receptors.

Accordingly, we developed several types of 1,2,4-triazole nucleoside derivatives bearing aromatic moieties on the triazole nucleobase (Fig. **4**) [24-34]. By using modern synthetic reactions such as Suzuki coupling, Sonogashira reaction, Huisgen cycloaddition and N-arylation, the aromatic functionalities were introduced directly onto the triazole ring of the readily accessible pure triazole nucleosides precursors (Fig. **4**) [35-36]. Among the various triazole nucleoside analogs developed, some displayed very interesting antiviral activity against either hepatitis C virus (HCV) [30-31], a life-threatening pathogenic agent in humans, or tobacco mosaic virus (TMV) [27-29], an important pathogenic virus affecting agricultural plants; whereas others exhibited potent and effective anticancer activity against pancreatic cancer [31-32], one of the most aggressive and lethal human cancer forms. The chemistry and biological activity of these nucleoside analogs can not be deduced from any known nucleoside derivatives. As such they may constitute new antiviral and anticancer agents with possible novel modes of action. Here, we present a brief overview of the molecular design, chemical synthesis and biological activity of these triazole nucleoside analogs as well as the results from the preliminary investigation on the structure-activity relationship.

MOLECULAR DESIGN

Based on the available starting materials as well as simple and convenient synthetic methods in organic chemistry, we have designed 4 different types of triazole nucleosides with aromatic moieties introduced on the triazole ring *via*, respectively, a direct connection (**I**), a triple bond bridge (**II**), a triazolyl ring linker (**III**) or N-arylation (**IV**) (Fig. **4**). The aryl moieties were anchored either at the 3- or at the 5-position of the triazole nucleosides; and the sugar part varied between being a ribose or an acyclic sugar component (Fig. **5**).

Appending aromatic moieties directly on the triazole ring yields a biaryl motif as the nucleobase in **I**. Since biaryl motifs [37] have important uses in medicinal chemistry, their presence within the nucleobases in nucleoside analogs is of great interest with respect to designing new nucleoside mimics. It should be noted that, due to the steric constraint between the aromatic moiety and the triazole ring, the biaryl motif in **I** will not be coplanar and is thus unable to yield a conjugated nucleobase. By inserting a slim and rigid triple bond between the aromatic moiety and the triazole ring as in **II**, the corresponding steric hindrance can be considerably released, leading to a conjugated nucleobase. Replacing the triple bond with the triazolyl ring as in **III** can further in-

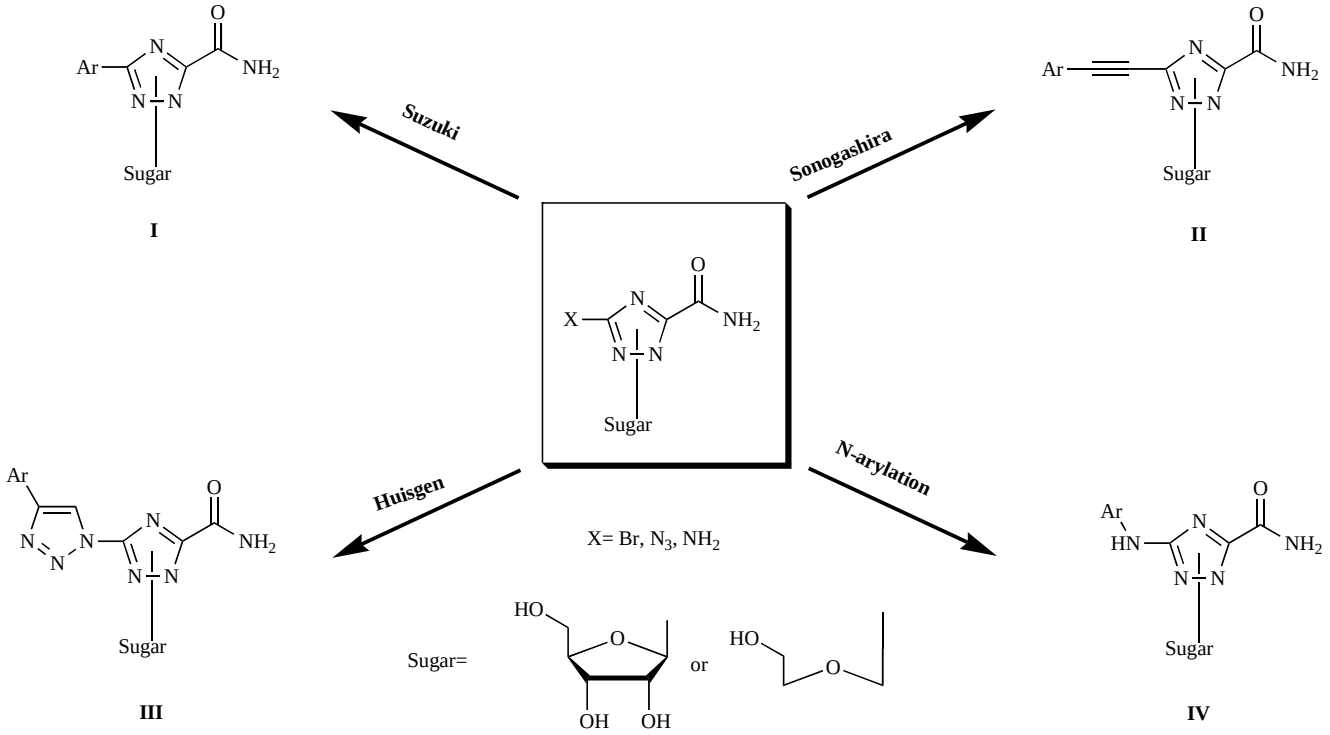


Fig. (4). Novel triazole nucleoside analogs, with various aromatic functionalities being introduced onto the triazole heterocycles *via*, respectively, a direct connection (**I**), a triple bond bridge (**II**), a triazolyl ring linker (**III**) or N-arylation (**IV**) by using readily available triazole nucleosides as starting materials and employing modern organic reactions of Suzuki coupling, Sonogashira reaction, Huisgen cycloaddition and N-arylation, respectively.

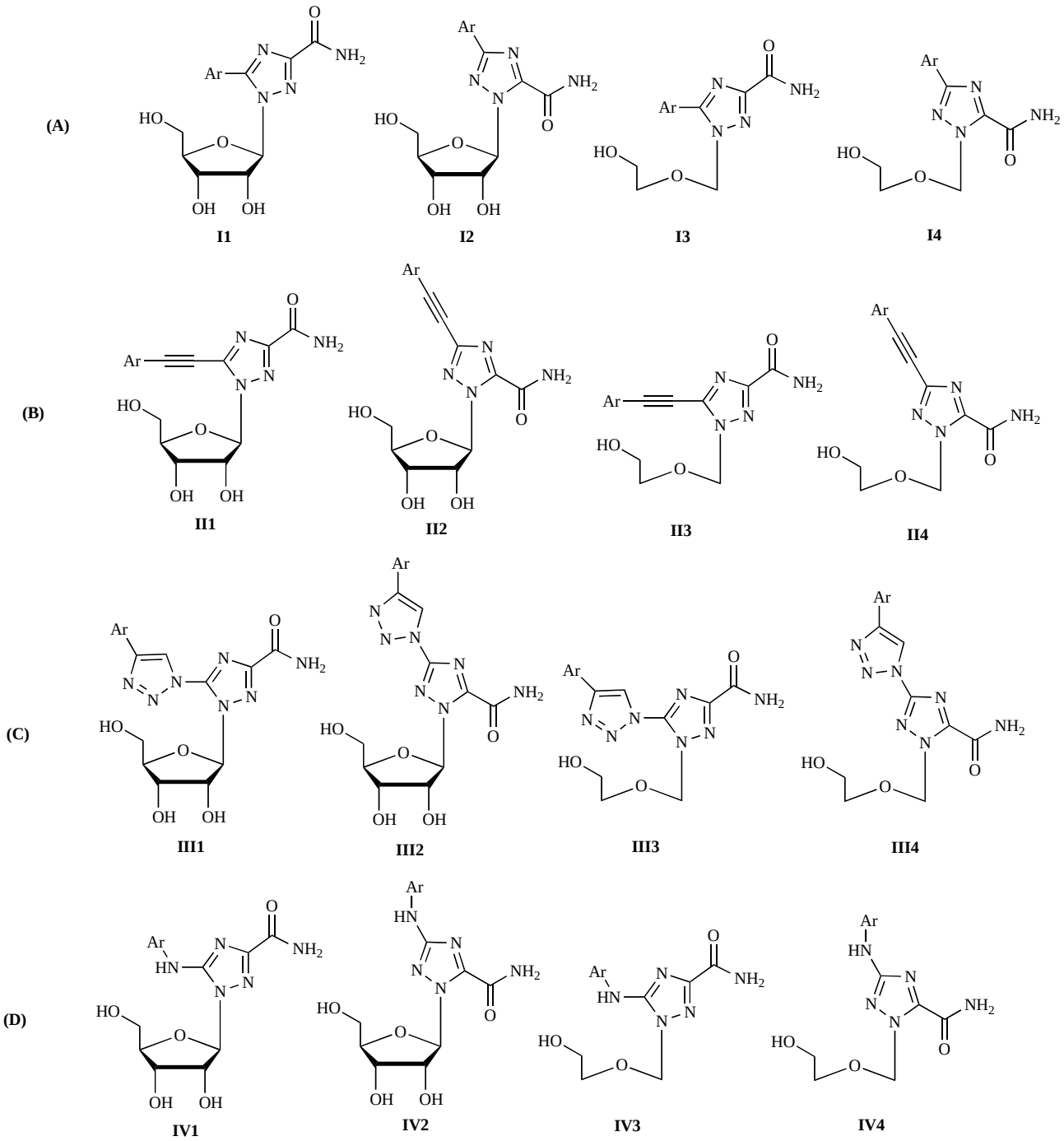


Fig. (5). Triazole nucleoside derivatives (**I**-**IV**) with aryl moieties being introduced at either 3- or 5-position of the triazole nucleobase, and the sugar component being either ribose or acyclic.

crease the overall aromatic surface and rigidity of the nucleobase, which may result in better and stronger binding with biological targets. Finally, the N-aryl motif is frequently presented in many natural products and synthetic drugs [38]. The presence of the flexible amine linkage between aromatic moieties and the triazole ring in **IV** is expected to provide not only a certain amount of flexibility within the corresponding nucleobase, but also confer biologically interesting activity. Collectively, all four types of triazole nucleosides offer structural diversity with respect to the nucleobase, and therefore represent a good starting point in the search for novel triazole nucleoside analogs with potent biological activity.

CHEMICAL SYNTHESIS

The conventional synthesis of 1,2,4-triazole nucleosides involving acid- or base-catalyzed condensation between triazole heterocycles and sugar components [3, 17] often yields several isomeric products (Scheme **1**), making the separation and purification process extremely difficult and leading to

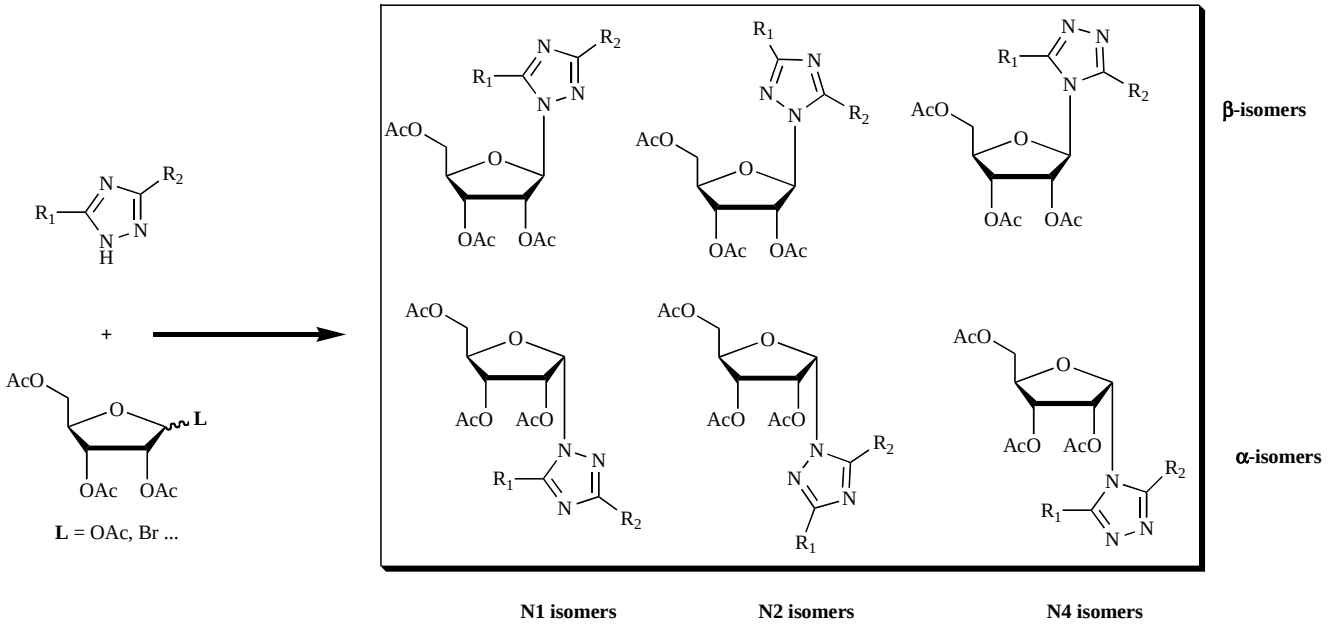
very low yields of the desired products. In certain cases, 1,2,4-triazole nucleosides can be obtained *via de novo* synthesis of the 1,2,4-triazole heterocycles [17b]. However, the synthesis of many base-modified triazole nucleoside derivatives relies on the direct chemical transformation of the existing 1,2,4-triazole nucleoside precursors, which have very limited functionalities on the triazole ring for derivatization [17]. In addition, the triazole heterocycle rings often show limited reactivity in many conventional reactions. Consequently, developing novel triazole nucleosides using modern organic chemistry methods and easy-to-perform convenient synthetic procedures constitutes not only a considerable interest in medicinal chemistry, but also a synthetic challenge in triazole nucleoside chemistry.

We have elaborated several strategies in our laboratories to prepare triazole nucleoside analogs **I-IV** (Fig. **4**). Their synthesis was carried out, respectively, *via* the Suzuki reaction [24-25], Sonogashira coupling [30-32], Huisgen cycloaddition [26-29] and N-arylation [33], using various triazole nucleoside precursors [35-36] previously developed in our laboratories (Fig. **4**).

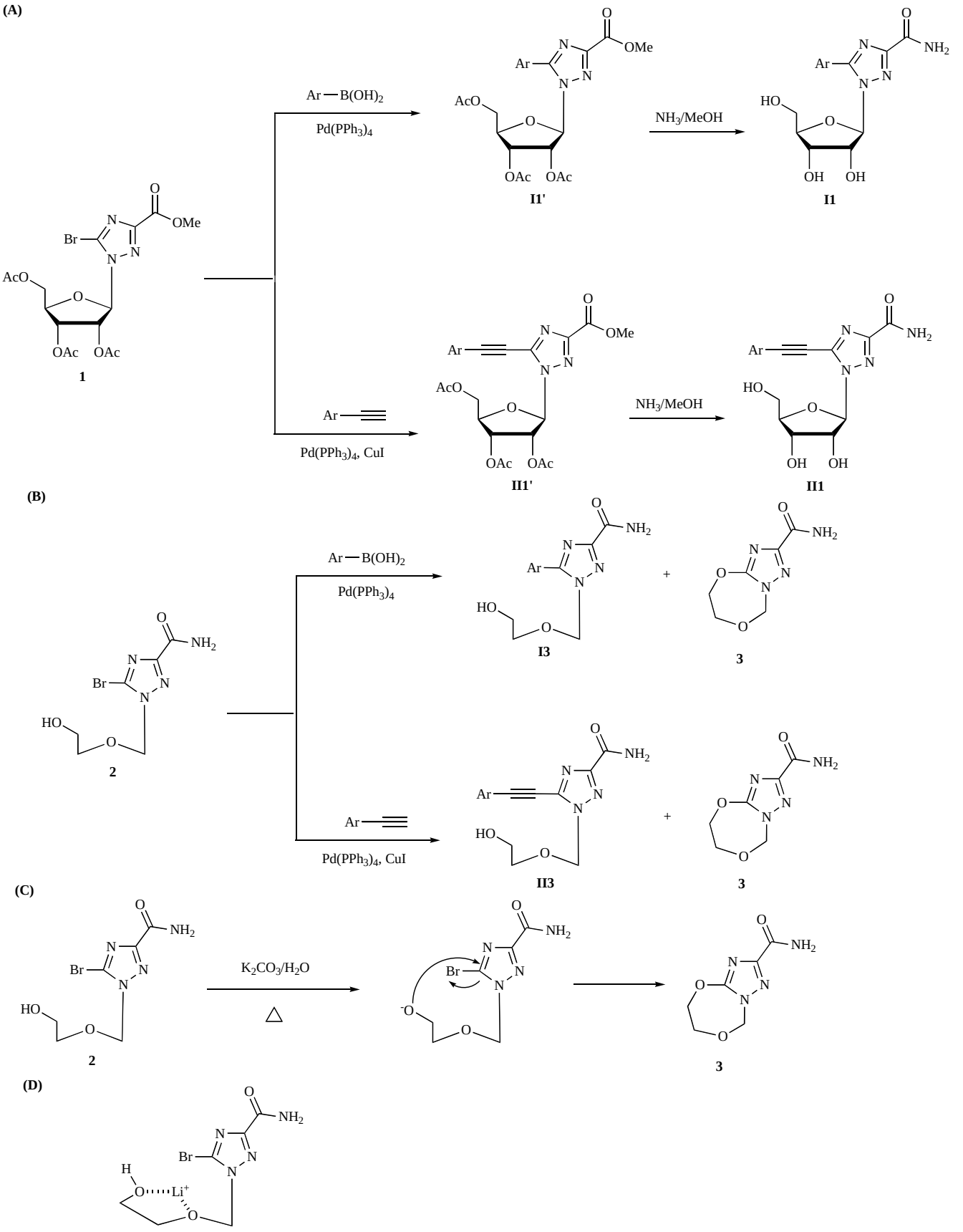
Both 3- and 5-aryl triazole ribonucleoside analogs **I1-I2** and **II1-II2** were obtained, *via* the corresponding Suzuki and Sonogashira reactions (Scheme **2A**) followed by subsequent ammonolysis [24, 31-32]. Under conventional heating conditions, neither the Suzuki nor the Sonogashira reaction gave good yields of the corresponding products, likely due to the electron-deficient nature of the triazole ring and the formation of Pd-triazole complexes. Under microwave irradiation and our optimized conditions, both the Suzuki and Sonogashira reactions were significantly improved, giving clean products with good to excellent yields [24, 31-32]. The significant improvement brought about by microwave irradiation [39] may be a direct consequence of the destabilization of the Pd-triazole complex. Furthermore, starting with unprotected triazole acyclic nucleoside precursors, the corresponding products **I3-I4** and **II3-II4** could be obtained in good to excellent yields using a simple one-step procedure *via*, respectively, Suzuki and Sonogashira reactions in aqueous solution and under microwave irradiation (Scheme **2B**) [25, 30], thereby constituting interesting green and atom-economic synthetic procedures. It should be mentioned that a side product of **3** was observed during the preparation of **I3** and **II3** (Scheme **2B**). This side product resulted from an intra-molecular cyclization of 5-bromotriazole acyclonucleoside **2** (Scheme **2C**), which could be completely suppressed by carefully choosing the reaction conditions, namely, using Li_2CO_3 to chelate with the side chain of triazole nucleoside (Scheme **2D**) thus impeding the intra-molecular cyclization reaction [25, 30].

The nucleoside analogs **III2** and **III4** could be obtained with high yields in a straightforward manner *via* Huisgen reaction using 3-azidotriazole nucleosides and various alkynes, followed by ammonolysis (Scheme **3A** and **3B**) [28-29]. The synthesis of 5-bitriazole nucleosides **III1** and **III3** was, however, problematic: the 5-azidotriazole ribonucleoside **6** yielded no corresponding Huisgen reaction products but was instead rapidly reduced to amine **7** and, at the same time, underwent cycloaddition-rearrangement to give **8** [28]; whereas Huisgen reactions with 5-azidotriazole acyclonucleoside **9** gave very low yields of the corresponding products **III3'** and considerable levels of **10** resulted from the reduction of **9** (Scheme **3C**) [29]. All these findings are the direct consequence of the unfavorable steric and electronic properties of 5-azidotriazole nucleosides which prevent them from undergoing Huisgen cycloaddition in the presence of ascorbate/Cu(II) [28-29]. We are currently searching for alternative methods of synthesizing the triazole nucleoside analogs **III1** and **III3**.

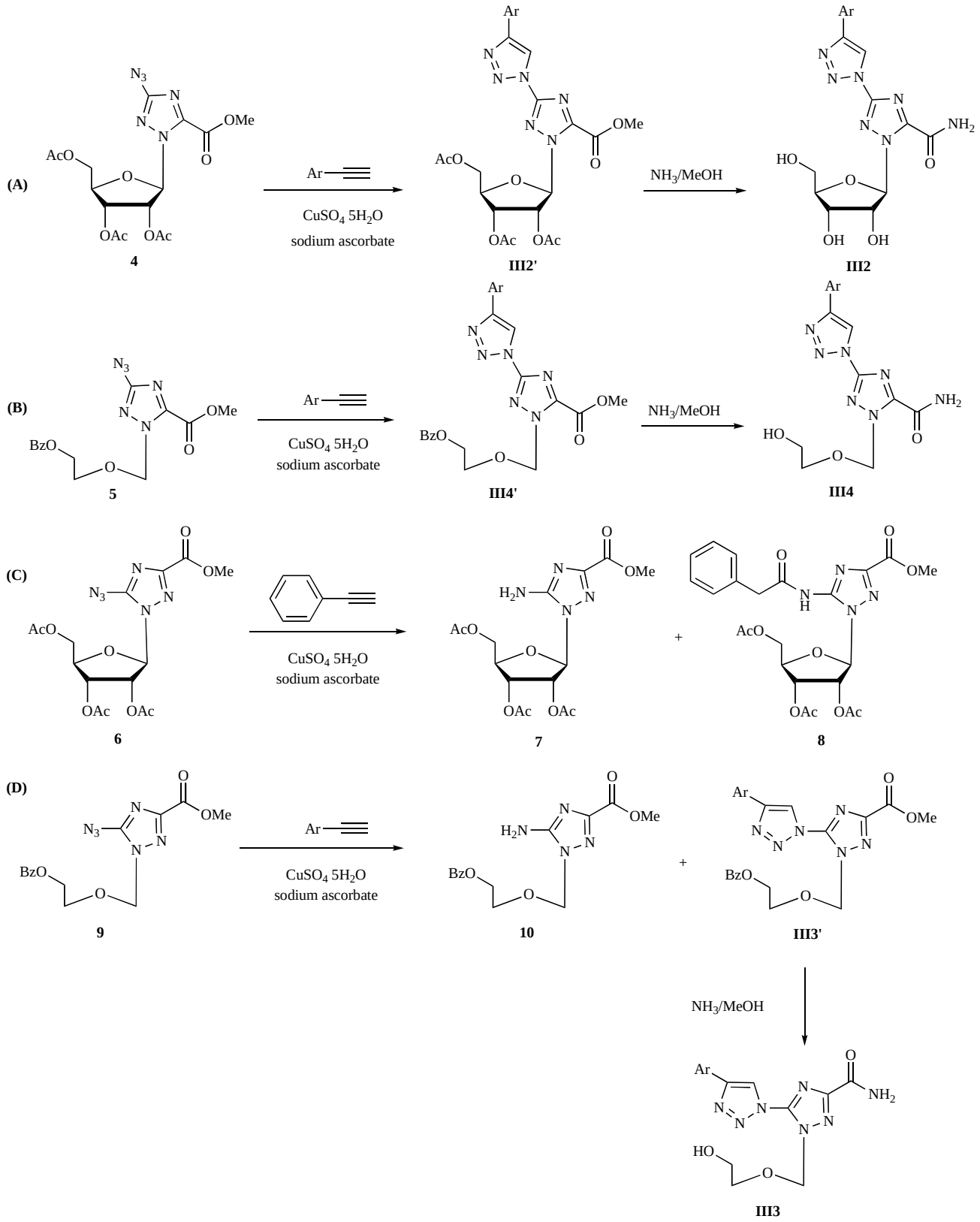
Our current method for synthesizing triazole nucleoside analogs **IV** is far from satisfactory [33]: only **IV2** and **IV4** could be obtained in low and moderate yields *via*



Scheme 1. Synthesis of 1,2,4-triazole nucleosides *via* condensation of triazole heterocycle and sugar precursor.

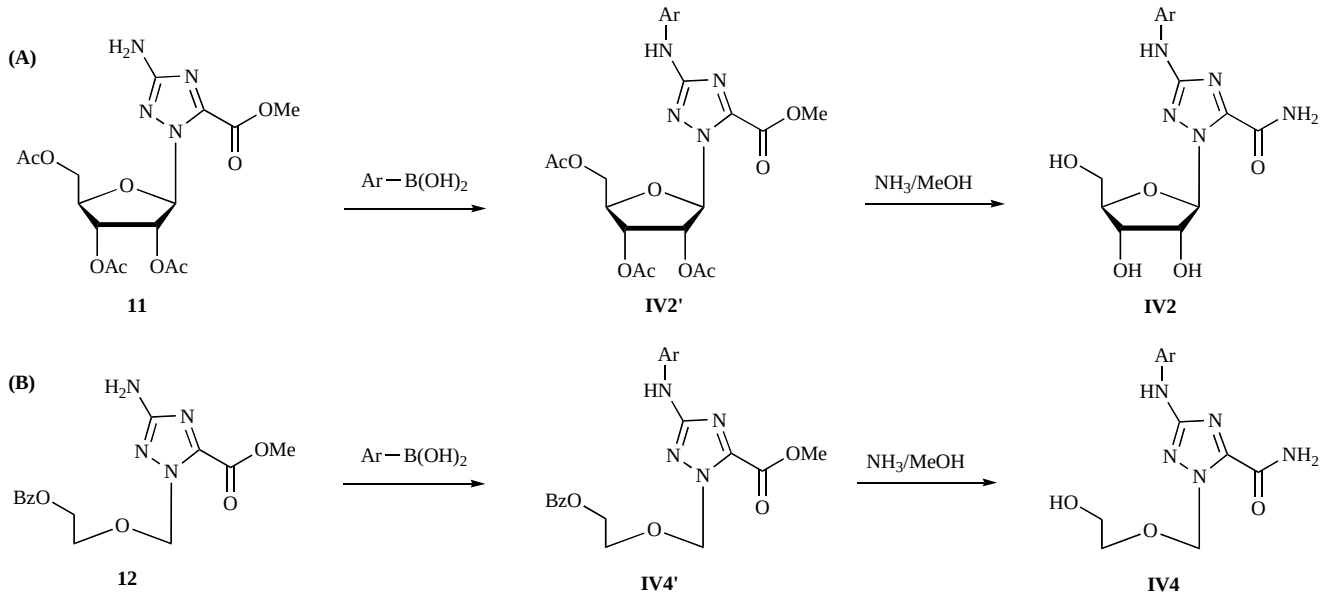


Scheme 2. Synthesis of triazole nucleoside analogs **I** and **II** using Suzuki and Sonogashira reactions respectively [24-25, 30-32].



Scheme 3. Synthesis of bitriazole nucleoside analogs **III** using Huisgen cycloaddition [28-29].

Cu-mediated N-arylation by coupling 3-aminotriazole nucleosides with a large excess of boronic acids (Scheme **4**). Despite trying a number of different experimental conditions, neither Pd-catalyzed nor Cu-mediated N-arylation delivered the corresponding products **IV1** and **IV3** in reasonably acceptable yields [33]. This is probably due to the lim-



Scheme 4. Synthesis of *N*-aryltriazole nucleoside analogs **IV2** and **IV4** using Cu-mediated *N*-arylation [33].

ited reactivity of the triazole nucleosides and/or the fact that triazole heterocycle may complex with the Pd- and Cu-catalysts, leading to inactivation of the catalytic reaction. We are actively searching for a suitable catalyst/ligand system and the corresponding feasible reaction conditions that would allow an efficient, atom-economic and green synthetic procedure for synthesizing N-arylated triazole nucleoside derivatives **IV**.

STRUCTURAL FEATURES

The structural features of the triazole nucleosides bearing various aromatic moieties were studied using X-ray crystallographic analysis. As shown in Fig. (**6**), the sugar moieties in triazole nucleosides adopt the N-type conformation (C2'-exo—C3'-endo) [24, 28, 31], similar to that observed with ribavirin [40]. For the triazole nucleosides **I**, the phenyl ring forms a dihedral angle with the triazole plane (ϕ = 41.2°), as displayed in **13** (Fig. **6A**). In this way, the steric hindrance resulting from the two hydrogen atoms located in the *ortho*-positions on the phenyl ring with respect to the triazole ring is released [24]. Concerning the triazole nucleosides **II**, the phenyl ring is extended out of the triazole ring plane *via* the triple bond linkage as shown in **14** (Fig. **6B**), which can significantly reduce the steric hindrance between the two aromatic moieties and act as a bridge within a conjugated aromatic system [31], differing considerably from those observed for aryltriazolyl nucleoside **13**. It is interesting to note that the overall structure of the nucleobase in nucleoside analog **15** becomes almost co-planar [28], which is a direct consequence of the small size of the triazole ring and the favorable geometry of the bitriazole motif. The quasi coplanar bitriazolyl unit may therefore be an interesting motif for mimicking conjugated or enlarged nucleobases. As yet, we unfortunately have no X-ray structure for the triazole nucleosides **IV**. This is partly due to our small supply of compounds for crystallization experiments as a result of the low synthetic yields mentioned above.

BIOLOGICAL ACTIVITY

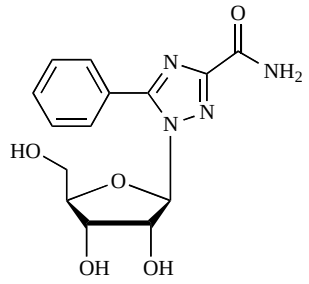
Antiviral Activity Against Hepatitis C Virus

Hepatitis C virus (HCV) constitutes a major public health issue with a heavy social burden [41]. WHO estimates that 170 millon people worldwide, 3% of the world population, are infected by HCV [41b]. The current treatment for HCV infection is based on the nucleoside drug, ribavirin, in combination with pegylated interferon-α [11]. Unfortunately, this therapy is not very effective, has a response rate of 40% - 60% (depending on the genotype) and is often associated with serious side effects. Therefore, the development of new drug candidates with improved efficacity and tolerance to treat HCV infection is urgently needed [42].

The type **II** triazole nucleosides **16, 17** and **18** (Fig. **7**) showed potent anti-HCV activity [30-31, 43]. Since **18** exhibited a low improbability of having carcinogenic toxicity according to the computer prediction programs CISOC-PSMT [44] and CISOC-PSCT [45], no further structure/activity relationship study was conducted on this compound.

It is worth mentioning some interesting observations made during the structure/activity relationship studies on **16** and **17**. The a*cyclo*nucleoside **19** (Fig. **8**) displayed effective anti-HCV activity on Huh-5-2 and Huh-6 cells, which was, however, not reproducible on Huh-9-13 cells [30]. By introducing one F atom at the *p*-position of **19**, the corresponding analog **16** resulted in stable anti-HCV activity in all three cell lines [30]. Removing the triple bond linkage (**20** in Fig. **8**) or replacing it with either a more flexible sulfur linkage [46] (**21** in Fig. **8**) or a more rigid triazole ring (**22** in Fig. **8**) led to a decrease in activity. Further altering the position of the F group at the *ortho*- and *meta*-position (**23** and **24** in Fig. **8**) also resulted in reduced activity. However, replacing the F atom in **16** with the CF_3 functionality giving analog **25** (Fig. **8**), which exhibited an improved anti-HCV activity [30]. Unfortunately, **25** also showed increased

(A)



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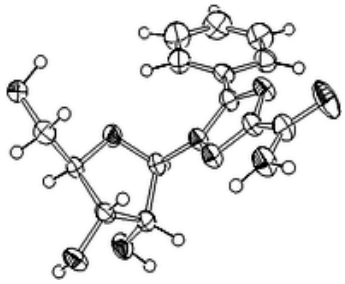
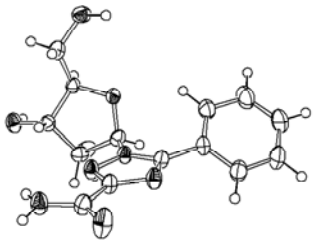
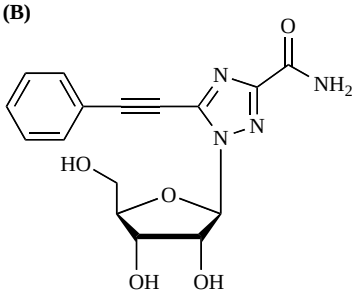




(B)



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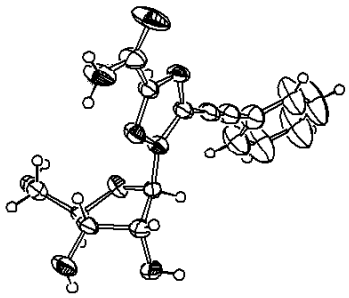

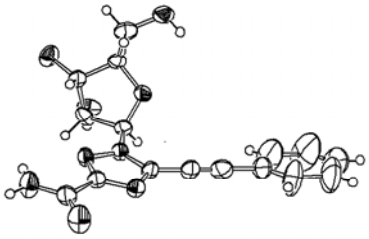

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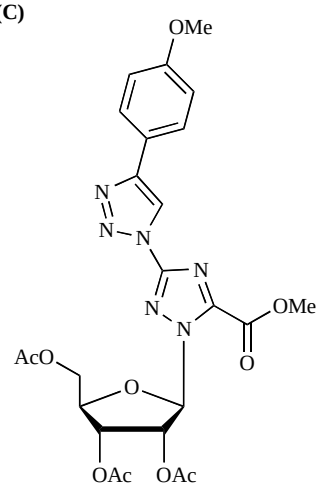

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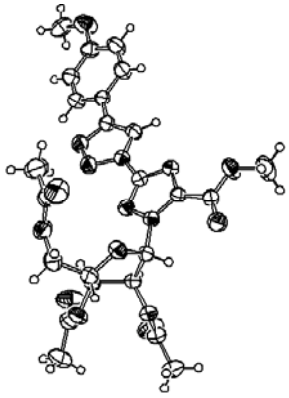


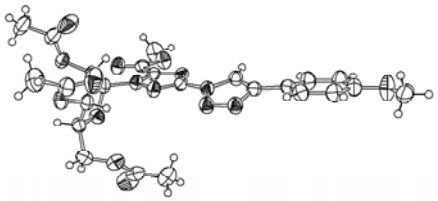
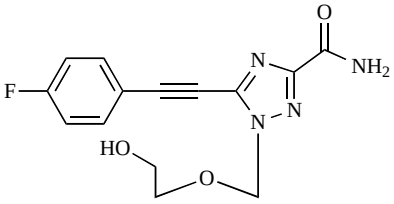


Fig. (6). X-ray structures of triazole nucleosides **13** (**A**) [24], **14** (**B**) [31] and **15** (**C**) [28].



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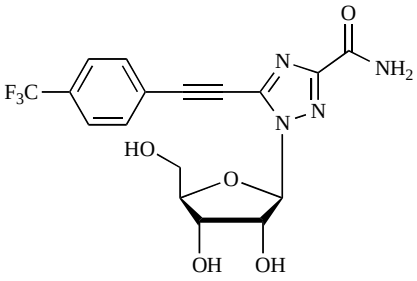

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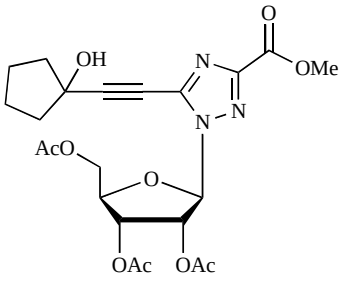

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Fig. (7). Triazole nucleoside compounds with anti-HCV activity [30-31, 43].

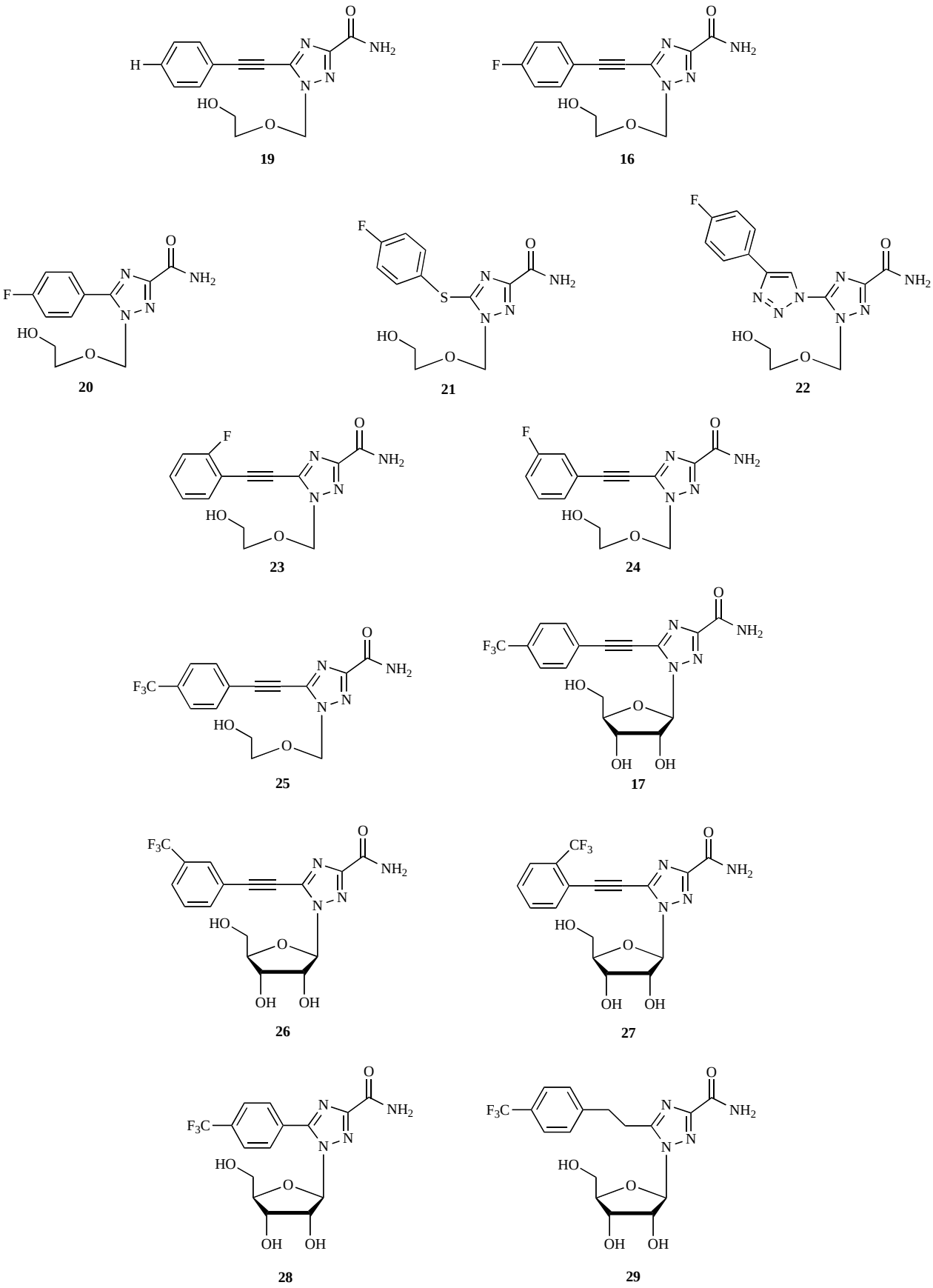

Fig. (8). Structural analogs of **16** and **17** for the structure/activity relationship analysis related to their anti-HCV activity [30-31].

toxicity [30]. Substituting the acyclic sugar part in **25** with the cyclic ribose sugar moiety yielded the *ribo*nucleoside **17**, which had an antiviral potential similar to **25** though a markedly reduced cytotoxicity [31]. These data demonstrate the importance of the ribose sugar component in compound **17** in terms of enhancing anti-HCV activity and reducing the associated toxicity. Further amending the position of the CF_3 group at the *meta*- and *ortho*-position of the phenyl ring (**26** and **27** in Fig. **8**) greatly reduced activity. In addition, either removing the rigid ethynyl triple bond in **17** (**28** in Fig. **8**) or replacing it with a more flexible ethylene group (**29** in Fig. **8**) completely abolished the antiviral activity. Therefore, both the CF_3 group at the *p*-position of the phenyl ring and the triple bond linker appear to be essential for the observed anti-HCV activity. A lead optimization based on **17** is currently underway in our laboratories.

Antiviral Activity Against Tobacco Mosaic Virus

Tobacco mosaic virus (TMV) belongs to the family of RNA viruses and is the most prevalent pathogen affecting tobacco plants. When a tobacco plant is infected by TMV, the virus rapidly multiplies leading to the development of a "mosaic" pattern on the leaves. Large dead areas on the leaves subsequently develop and the plants are stunted. As one of the most important causes for massive crop losses, TMV has established itself as an economically significant

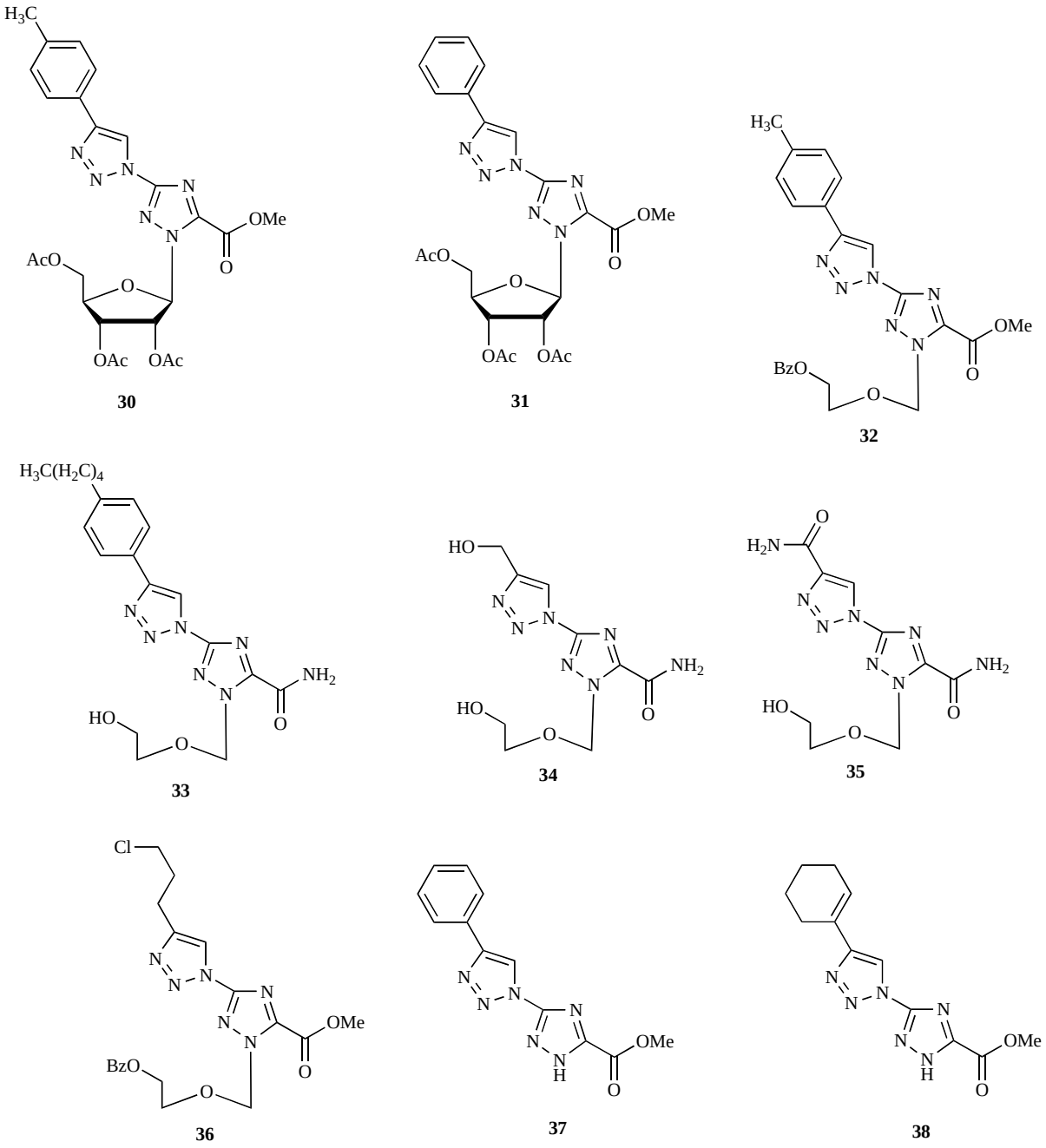

Fig. (9). Bitriazolyl compounds with anti-TMV activity [27-29, 48].

virus and has become also a typical model for studies in plant virology [47]. Development of efficient means of managing TMV is important for both agriculture and plant phytopathology.

It is interesting to note that some triazole nucleosides of type **III** displayed potent antiviral activity against TMV (Fig. **9**) [28-29, 48]. These active compounds have chemically and structurally diverse substituents acting on the bitriazolyl unit. The active ribonucleoside **30** showed exactly the same bitriazolyl structural motif as the corresponding active acyclonucleoside **32** [28-29]. This finding suggests that the bitriazolyl scaffold may be a potentially useful structural motif for designing candidates with antiviral activity against TMV, regardless of whether the sugar moiety is an acyclic or cyclic ribose. Indeed, two bitriazolyl compounds **37** and **38** bearing no sugar component exhibited potent anti-TMV activity [27] with improved efficiency compared to the nucleosides **30**-**36**. We are currently exploring new bitriazolyl motifs in the search for improved antiviral activity against TMV and other viruses.

Anticancer Activity Against Pancreatic Cancer

Pancreatic cancer belongs to an extremely aggressive form of human cancers and is highly resistant to chemotherapy [49-50]. The current first-line treatment based on the nucleoside drug, gemcitabine, results in only a 12% response and 3% overall survival rate [49-52]. Therefore, there is an urgent need to develop new drug candidates with effective anticancer potency.

More than 30 compounds among the triazole nucleoside analogs **I**-**IV** showed effective antiproliferative activity against drug-sensitive pancreatic cancer Capan-2 cells,

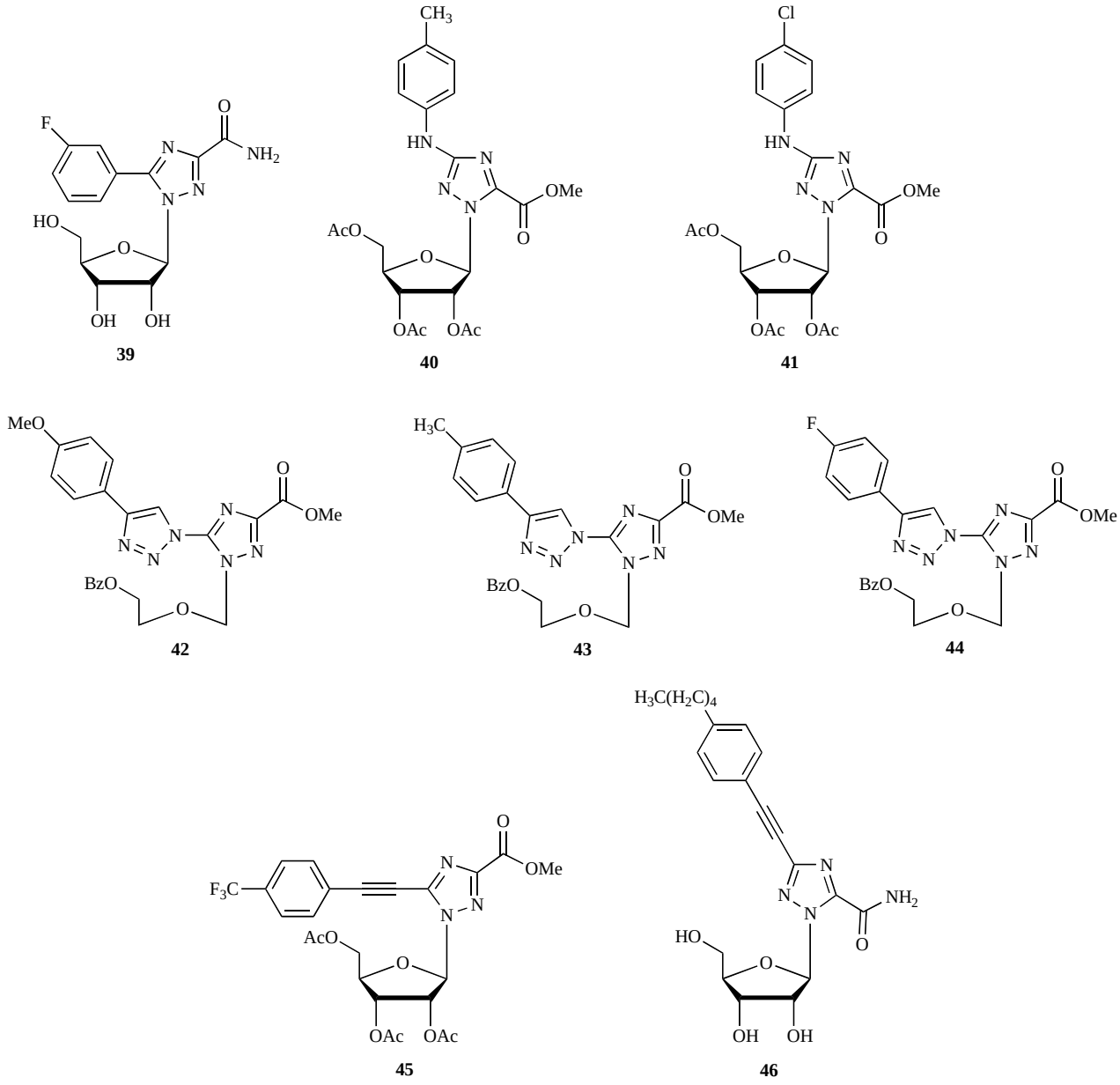

Fig. (10). Triazole nucleoside compounds with anticancer activity [31-32, 33b, 53].

whereas several triazole nucleoside derivatives (Fig. **10**) demonstrated activity against drug-resistant pancreatic cancer MiaPaCa-2 cells, with a potency equal to or higher than that of gemcitabine [53]. We have mainly concentrated on the latter group since we are particularly interested in identifying leads against drug-resistant pancreatic cancer, for which there is currently no effective treatment.

Some interesting structural features can be noted among the identified hits listed in Fig. (**10**). **39** has the phenyl ring directly linked to the triazole nucleobase, whereas **40** and **41** bear the aryl moiety linked to the triazole ring *via* structurally flexible N-linkage [33b], and **42**-**46** are triazole nucleosides with aromatic moieties connected to the triazole ring *via* rigid linkers, either through a slim triple bond or a planar triazolyl ring. Interestingly, hits **42**, **43** and **44** share very similar structural features with bitriazolyl acyclonucleoside, the only difference being the substituent at the phenyl ring. However, no further SAR or *in vivo* studies were carried out due to the short supply of this family of compounds as a result of the low synthetic yields.

Among the triazole nucleoside hits with aromatic moieties connected to the triazole ring *via* a triple bond linker, a large structural diversity can be observed. The aromatic functionalities can either be at the 5- or at the 3-position of the triazole ring (**45** and **46** in Fig **10**). SAR and *in vivo* studies were carried out with the most promising active compounds **45** [31] and **46** [32], which both exhibited effective anticancer activity by inhibiting tumor growth in MiaPaCa-2-xenograft nude mice after only two weeks of treatment with no notable adverse effects [31-32]. It is important to note that neither **45** nor **46** inhibited DNA synthesis, which is different from gemcitabine [54]. Moreover, **46** significantly down-regulated Hsp27, a novel target for anticancer therapy which plays an important role in the drug-resistance observed in certain cancers [55-57]. The triazole nucleoside **46** thus represents the first small molecule with such a mechanism of action and may offer a new avenue in the search for novel nucleoside analogs with novel modes of action.

CONCLUSION AND PERSPECTIVES

Based on the rationale to combine the special features of unnatural triazole heterocycles with those of the appended aromatic groups on the nucleobases, a series of triazole nucleoside analogs bearing aromatic moieties on the triazole nucleobase have been developed in the view to create new nucleoside analogs with novel modes of action. The synthesis of these nucleosides was achieved *via* modern organic reactions starting with readily available triazole nucleoside precursors, and the synthetic procedures developed are simple and easy to perform. Among the identified active triazole nucleoside analogs, some showed interesting antiviral activity against either HCV or TMV, whereas others demonstrated potent anticancer activity against pancreatic cancer *in vitro* and *in vivo*. Most importantly, one of the hit compounds exhibited a novel mechanism of action through down-regulation of Hsp27, a novel target for anticancer therapy related to many drug-resistant cancer forms. Collectively, the discovery of antiviral and anticancer activities shown by the triazole nucleosides bearing aromatic moieties has inspired us to further explore and validate our concept with the aim of developing structurally novel triazole nucleoside analogs in our continuing search for biologically active compounds with novel modes of action. Future work has been directed to further develop synthetic strategies using modern organic chemistry for the synthesis of novel triazole nucleoside analogs. Additional aims include optimizing the identified antiviral and anticancer leads, undertaking detailed structure/activity relationship studies and investigating the precise mechanisms underlying their biological activity.

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