1,3-Dipolar cycloadditions: applications to the synthesis of antiviral agents†

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In the present perspective the advances and real possibilities of 1,3-dipolar cycloadditions as key steps in the total synthesis of virus inhibitors are described. Azides, nitrones, and azomethine ylides are the most appropriate 1,3-dipoles for the synthesis of privileged structures with the highest biological responses against viruses.

1. Introduction

Newly emerging viral infections represent the major threat to human health. If we analyze the data concerning only the people killed by the influenza pandemics during the last century, we notice that this number goes beyond the deaths caused by other natural or man-made disasters. World Health Organisation (WHO)[1] alerts on viral outbreaks announce the spreading ways of the virus, urging all governments to step up surveillance.

Apart from the three more extended global virus infections, namely human immunodeficiency virus (HIV, 35 millions approximately), hepatitis C virus (HCV, more than 190 millions) and influenza A and B viruses, Ebola, Marburg, dengue, yellow fever, nipah, enterovirus 71 and oncoviruses are the most dangerous viruses causing many human fatalities.[2] An additional drawback of these microorganisms is their fast mutation rates because a small genetic variation in an, *a priori*, inoffensive virus can originate a new strand with increased capacity to cause disease (virus with increased virulence).

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† Dedicated to Prof. Benito Alcaide on the occasion of his 60th birthday

Vaccine development is an extremely effective strategy to protect people from specific virus infections. However, an appropriate vaccine cannot be developed before a virus can be replicated in sufficient quantities to manufacture it. In fact, vaccines are very effective on stable viruses but difficult to apply to rapidly mutating viruses such as influenza, HCV, *etc.* This last situation, and obviously when the patient has already been infected, is when antiviral drugs became crucial. An antiviral drug does not kill the virus, but acts by interfering with one step of the viral replication process. This lowering in the replication frequency allows the body's immune system to destroy the virus using many natural defences.

Researchers working on strategies for developing antivirals have tried to attack viruses at every stage of their life cycles, namely attachment to a host cell, replication of viral components, assembly of viral components into complete viral particles and release of viral particles able to infect new host cells. The present and the future of these antiviral tools has been reported from the pharmacological point of view of pathogenic specific drugs such as amantidine, Tamiflu®, and Relenza® or ribavirin and interferons targeted against influenza or hepatitis C viruses, respectively.[3] Unfortunately, extensive data on their efficacy are not available and recent reports of drug resistance in patients infected with, for

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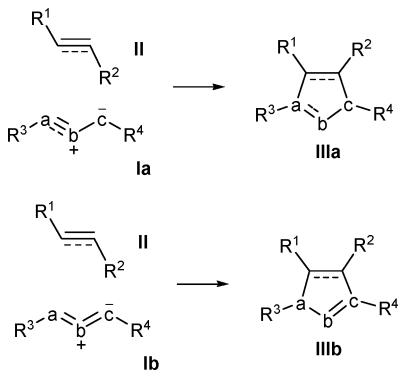
example, H5N1 raise serious concerns.[4] So, new broad-spectrum antivirals must be developed because the cost and the risk of rapid drug resistance to the antivirals targeted against single viruses are very elevated.

Genomics helps scientists to find targets at every viral stage and also provides crucial data for understanding the drug–virus effective interaction. Accordingly, the organic synthetic chemists are dedicating much effort to designing and preparing potential drugs once targets have been identified. From all of the resources, methodologies, reactions, *etc.*, put into service for the preparation of antiviral agents,[5] 1,3-dipolar cycloaddition (DC) (Hüisgen cycloadditions)[6] constitutes a powerful classical synthetic tool and is one of the most productive fields in modern organic chemistry.[7]

The reaction between 1,3-dipoles and alkenes or alkynes is very versatile, allowing the presence of many functional groups in both components, namely 1,3-dipole **I** and dipolarophile **II** (Scheme 1). Yields of heterocycles **III** are high, with few and easily removable impurities. The available precursors of dipole **I** can be, basically, divided into two groups: the allyl anion-type **Ia** such as nitrones, azomethine ylides, azomethine imines, carbonyl ylides and carbonyl imines, and the linear propargyl/allenyl anion-type **Ib** such as nitrile oxides, nitrile imines, nitrile ylides, diazoalkanes and azides (Fig. 1).



Scheme 1 General 1,3-DCs of alkenes and alkynes.

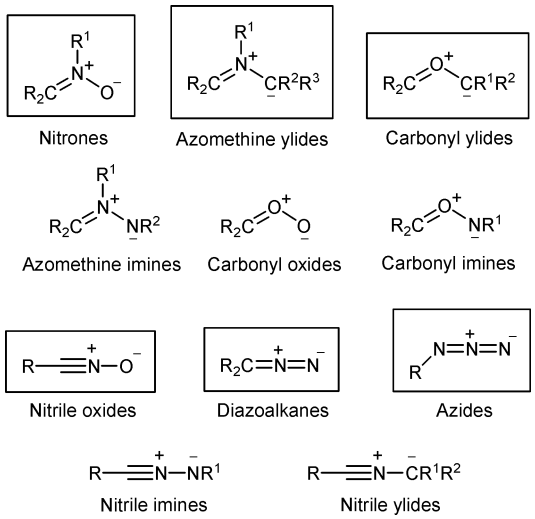


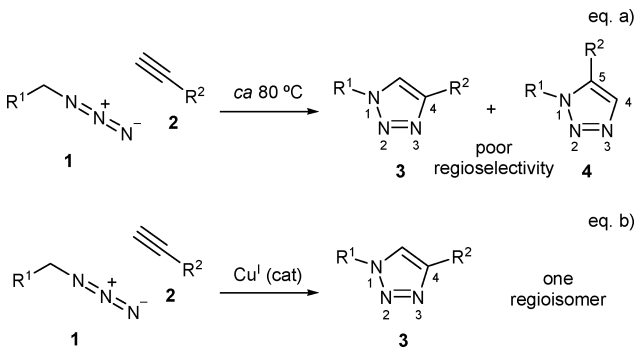
Fig. 1 Most important 1,3-dipoles in the synthesis of heterocycles **III**.

This [2s+4s] addition is stereoconservative (suprafacial) and stereospecific, and the six π-electrons participate in a concerted or non-concerted reaction pathway controlled by the HOMO–LUMO interaction rules.[7c,8] This elevated stereocontrol is responsible for the high diastereo- and regioselectivity (and also enantioselectivity in asymmetric synthesis examples) achieved in an impressive number of heterocycles **III**.[7,9] Another important feature of this transformation[10,11] is that up to four stereogenic centres can be unambiguously generated in only one reaction step whether a diastereo- or enantioselective approach is performed.

The general interest of these broad series of cycloadducts **III** as potential antiviral drugs[12] will be the focus of this perspective. For convenience, the examples will be classified on the basis of the 1,3-dipole involved, which are highlighted in the frames in Fig. 1.

2. Azides

Organic azides **1** are readily available and potentially explosive compounds. Although the 1,3-DC between azides **1** and alkynes **2** (also with nitriles)[7d] has been known for years, it has been extensively employed since 2001.[11,13] The interest of this process was the transformation of the purely thermal procedure[13] to a 1,3-DC catalysed by metal salts [mostly copper(I) salts], which dramatically accelerated the reaction even at room temperature (Scheme 2).[14] Under these catalysed reaction conditions, the process becomes nearly solvent insensitive, it shows an extremely high tolerance of functional groups and affords 1,2,3-triazoles **3** in excellent chemical yields with few by-products.[15] 1,2,3-Triazoles are exceedingly stable to acidic and basic hydrolysis as well as severe reductive/oxidative conditions, and are also capable of active participation in hydrogen bonding as well as dipole–dipole and π-stacking interactions. The other important feature concerns the high regioselectivity achieved (1,4-addition over 1,5-addition) (Scheme 2b), unlike the thermal procedure which exhibits very poor regioselectivity (Scheme 2a). The resulting 1,2,3-triazole moiety[16] is a likely candidate for small molecule drugs compatible with the side chain of all of the amino acids and the molecular dimensions of these heterocycles are somewhat similar to the amide bonds in terms of distance and planarity. These last two properties of **3** are closely related with successful interaction with enzymes or even DNA or RNA strands of the viruses in order to deter their proliferation.



Scheme 2 Cu-catalysed *versus* thermal 1,3-DC of azides and alkynes.

Many works focused on this 1,3-DC of azides and alkynes had, unfortunately, no marked biological activity. The most productive

results are shown as follows on the basis of the type of virus inhibited.

There is no vaccine or cure for HIV, and the most employed treatment consists of highly active antiretroviral therapy. Many compounds derived from AZT (a reverse transcriptase inhibitor) and others were prepared through a 1,3-DC between organic azides and alkynes with the objective of decreasing the viral replication and lowering their cytotoxicity (Fig. 2). Nucleosidic molecules **5–7** and **9**, and the non-nucleosidic structures **8** and **10** are examples of triazole-containing entities able to inhibit HIV proliferation. One of the first contributions in this area was published in 1989, but nucleoside **5** showed moderate activity in HIV-1 infected cells.[17] The same author used hydrazoic acid as 1,3-dipole and a carbodiimide as dipolarophile, generated from AZT, for the elaboration of compound **6**, which also exhibited moderate activity against HIV-1.[18] The series of products **7** were prepared and tested as antiviral HIV agents, the most active being $R^1 = Bu^t(Me)_2Si$-, R^2, $R^4 = H$, $R^3 = CONMe_2$.[19] Phosphasugar

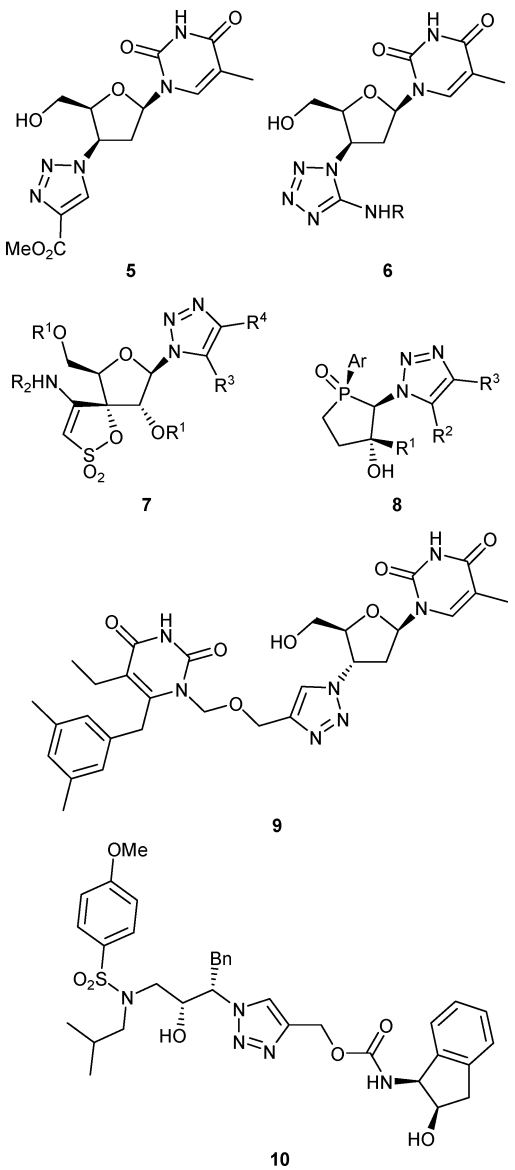
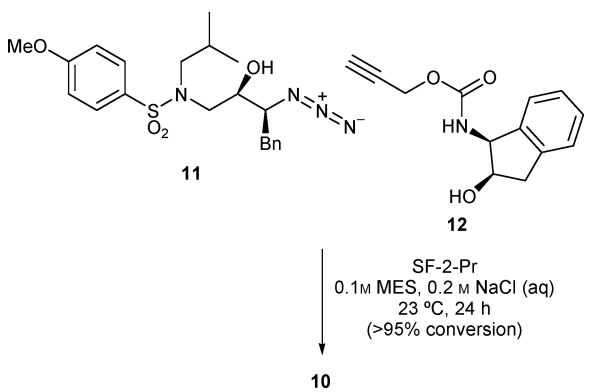


Fig. 2 Important inhibitors of HIV.

N-nucleoside derivatives were prepared to be antiviral agents but no data from biomedical studies was described.[20] Compound **9** showed an interesting activity against wild type HIV-1 and mutant strains, which is comparable with other nucleoside reverse transcriptase inhibitors such as MKC-442.[21] Molecules **5–9**, as surrogates of AZT, function as analogues for thymidine and this means that AZT and its mimetics have the same shape as it, and therefore can be incorporated into the developing nucleic acid in place of a thymidine molecule. The phosphate group attached to thymidine or AZT forms a bond with the 3′-OH group of the preceding nucleotide in the developing DNA chain. When thymidine is incorporated into the DNA chain, its 3′ -OH becomes the binding site for the next nucleotide's phosphate group. However, AZT and its mimetics lack the -OH functional group that is necessary to form a bond with the next nucleotide; in its place is an azido ($-N_3$) group. Because the azido group cannot form a bond with a phosphate group, no additional nucleotides can be added once AZT is incorporated into the DNA chain. Hence, reverse transcription stops after AZT is incorporated.

The non-nucleosidic product **10** (obtained by a conventional 1,3-DC) was revealed as an important inhibitor of the wild type HIV1 (IC_{50} = 6 nM) and also of several mutant strains.[22] This molecule inhibits certain proteases, which are enzymes used by the viruses to cleave nascent proteins needed for the final assembly of new virions, and their inhibition also prevents viral replication. The authors observed that with incubation of the azide **11** and alkyne **12** in the presence of the HIV-1-PrSF-2WTQ74-Pr protease (henceforth simply denoted SF-2-Pr, 15 μM) in 2-morpholinomethanesulfonic acid (MES; 0.1 M) NaCl (0.2 M) buffer solution at 23 °C for 24 h, acceleration (ten fold) of the reaction occurred enhancing the regioisomeric ratio in favour of the 1,4-isomer **10** (18:1). The target protease itself acted as a template for the reaction (Scheme 3) that forms its own inhibitor.[23]



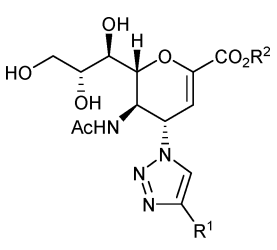
Scheme 3 Synthesis of product **10**.

A recent contribution demonstrated that compound **10** retains high affinity for both wild-type and PR_{6x} multidrug resistant (MDR) protease viruses as the result of interactions with selected residues and maintenance of hydrogen bonding to main chain atoms. Thus, compound **10** binds to the protease that promotes multidrug resistance, the triazole moiety forms a precise hydrogen bonding network and the carbamate accepts a hydrogen bond from the amide of Gly48. Both of these interactions feature a conserved element of protease structure. The 1,3-DC of modified starting materials **11** and **12** will also allow the evaluation of whether

such changes improved the antiviral performance against newly appearing multidrug-resistant viruses.[24]

The employment of the catalysed 1,3-DC of azides and alkynes contributes to the formation of novel templates based on oligosaccharide[25] or peptide[26] clusters. The incorporation of several units of triazole derivative in these natural or synthetic polymers is responsible for their increased binding affinity and antiviral activity against multiple strands of HIV-1. This strategy allows optimization of the size and nature of the substituents in both dipole and dipolarophile to achieve the best efficiency with the smallest structure. For example, the successful construction of fully synthetic immunogens that contain novel oligosaccharide clusters has laid the foundation for further immunisation studies in animals to evaluate whether the vaccine candidates are able to elicit carbohydrate-specific neutralising antibodies against HIV,[25] constituting a very exciting research area. Particularly, it is known that sugar chains are crucial for high affinity binding to the antibody 2G12. This human monoclonal antibody potently and broadly neutralizes primary and T-cell line-adapted clade B strains of HIV-1 in a peripheral blood mononuclear cell-based assay and inhibits syncytium formation in the AA-2 cell line.

Worldwide extended influenza viruses caused seasonal epidemic. Vaccinations against influenza are usually given to people, the most common being trivalent influence vaccine (TIV). It contains purified and inactivated material for two influenza A virus subtypes and one influenza B strain. In spite of this advantage, several specific antiviral drugs have been designed to inhibit the most aggressive influenza virus types. The most active synthetic compound corresponded to the series of non-nucleosidic molecules **13** (Fig. 3), whose structure is very similar to zanamivir. In fact, compound **13** [$R^1 = CH(OH)C_2H_5$, $R^2 = H$) is almost as active as zanamivir against avian influenza virus (AIV) H5N1.[27] In this work molecular modelling provided very reliable information about the binding model between inhibitors and neuraminidase, which was in a good agreement with the observed *in vivo* activity of the inhibitors. To better understand the activity discrepancy between synthesised new inhibitors and zanamivir, the study was based on the crystal structure of neuraminidase-inhibitors derived from docking simulation. Whilst carboxylic acid group of zanamivir formed strong hydrogen bonds with two arginine residues (Arg118, Arg371) in the S1 region and five hydrogen bond interactions in the S2 region through the guanidinyl moiety, inhibitor **13** [$R^1 = CH(OH)C_2H_5$, $R^2 = H$) moved up forming exclusively a hydrogen bond with residue Arg152 in the S2 region. Other molecules of **13**, with large substituents with different electronic properties, could not be accommodated in the subsite S2, and hence the six membered ring flipped, resulting in a drop of inhibitory activity.[27]

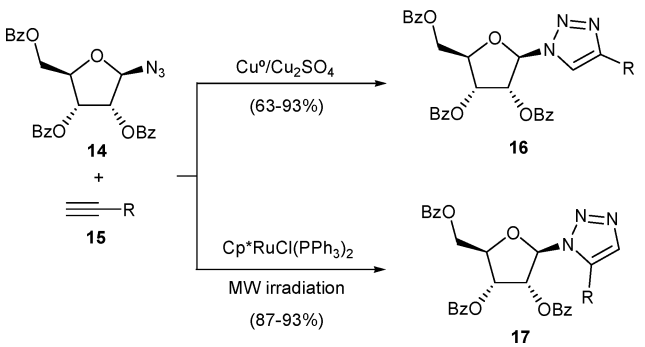


13

Fig. 3 Compound inhibitors of influenza virus.

The neuraminidase enzymes (also called sialidases) are glycoside hydrolase enzymes that promote the mobility of virus particles through the respiratory tract mucus and in the elution of virion progeny from the infected cell. In this line, multivalent 1,3,5-triazine or sialic acid containing-scaffolds have been designed incorporating structures **13**, which have been shown to have stable structures in solution and be well suited for functionalisation with relevant antiviral ligands *versus* influenza viruses.[28,29]

Ribavirin and its analogues are widely used for treating HCV infections. Searching for the highest inhibition of the HCV and lowest cytotoxicity, 1,2,3-triazole derivative families such as **16** and **17** were prepared. Although the antiviral activity of their dibenzoylated surrogates was moderate, it is worth noting the high regioselectivity achieved with $Cu^0/CuSO_4$ couple (favouring the 1,4-regioisomer), and the reverse regioselectivity (favouring the 1,5-regioisomer) obtained when $Cp^*RuCl(PPh_3)_2$ complex was employed. Protected β-azidoribose **14** reacted with alkynes **15** under a copper(I)-catalysed 1,3-DC affording triazoles **16** in very good yields and with total 1,4-regioselectivities (>99:1) (Scheme 4). Highest conversions and chemical yields were generated upon microwave radiation, in the presence of the above mentioned ruthenium catalyst, furnishing compound **17** with a high 1,5:1,4 regioisomeric ratio (up to 97:3).[30]



Scheme 4 Regioselective synthesis of compounds **16** and **17**.

There is currently substantial interest in the use of nucleic acids for modifying gene expression for therapeutic purposes. The lipid-conjugation (*via* 1,3-DC) of oligonucleotides potentiates the cellular uptake of oligonucleotides and allows their intracellular delivery. These non-toxic lipid conjugates **18** (Fig. 4) efficiently inhibit HCV internal ribosome entry site-mediated translation in human hepatic cells. The specific target was the subdomain IIId of the mentioned internal ribosome entry site at the 5′ end of the viral RNA.[31]

Through a similar mechanism, oligonucleotides bearing the *p*-tolyl-group as a substituent of both the oxygen atoms in **19** afforded better interactions with the virus. In addition, this protecting group decreased notably their cytotoxicity. Particularly active were the newly synthesized compounds **19** bearing a 6-chloro-7-deazapurine or 2-amino-6-chloro-7-deazapurine (Fig. 4).[32]

Less aggressive hepatitis B virus (HBV) has also been moderately inhibited by 1,2,3-triazoles **20** and **21** (Fig. 5) obtained as cycloadducts by reaction of 1-propargyl pyrimidines with 5-azido-5-deoxyribofuranoside or 1-azido-1-deoxytetra-*O*-acetylglucose. The most active structures were the pyrimidine derivatives rather than the pyridine analogues, obtained from 1-propargyl

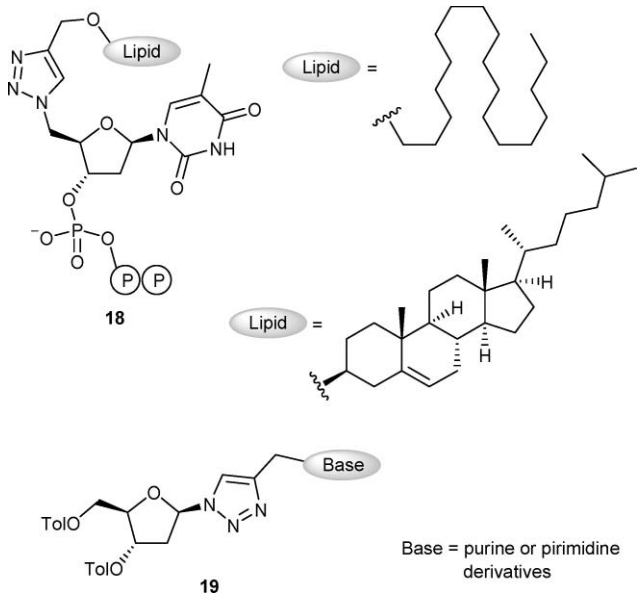


Fig. 4 Antivirals against HCV.

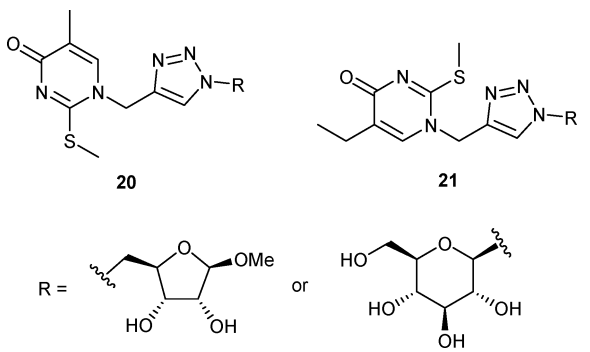


Fig. 5 Bioactive compounds against HBV.

pyridinium salts. Presumably, this anti-HBV activity originates from inhibition of viral replication by degrading HBV pregenomic RNA and message RNAs.[33,34]

Acyclonucleosides **22** and **23**, with the alkylating chain of acyclovir, were prepared and evaluated against tuberculosis virus and showed moderate activity.[35,36] Carbanucleosides **24** gave very low levels of inhibition of small pox, vaccinia or cowpox viruses.[37] However, 1,2,3-triazole carbanucleosides **25** and more specifically iodide **26** (Fig. 6) exhibited an elevated inhibitory potential against thymidine kinase varicella-zoster virus (TK^+VZV).[38]

Another application of 1,3-DC of azides and alkynes or alkenes concerns the construction of biomolecular prototypes. For example, it was observed that degradation of the viral particles occurred during the 1,3-DC of the corresponding alkyne and the azide derived from the icosahedral cowpea mosaic virus (CPMV). Molecules **27** (Fig. 6) incorporate an aliphatic chain with a 1,2,3-triazole unit. This carbonous structure is bonded to the virus through an amino group of the native reactive lysines, and genetically inserted cysteines of the protein subunits arranged helically around genomic single RNA strand.[39] This binding caused degradation or variation of the stability of the viral peptides, which has been considered of great interest for future investigations.[39-41]

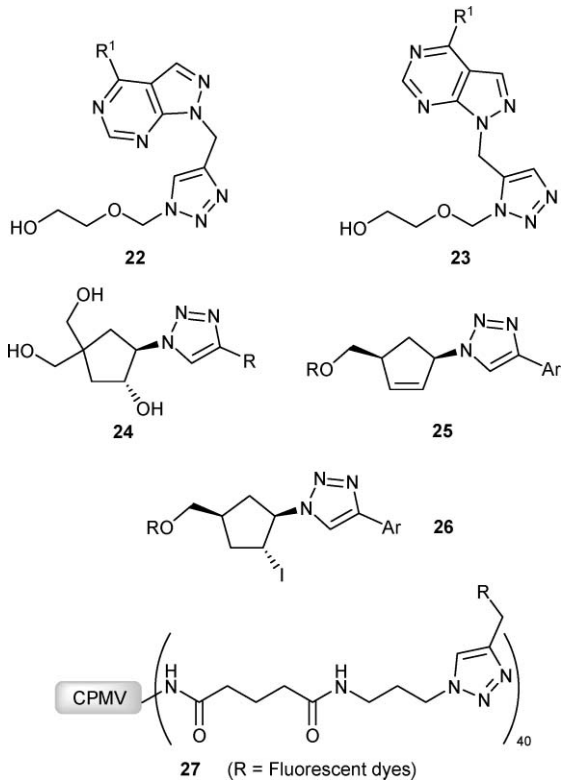
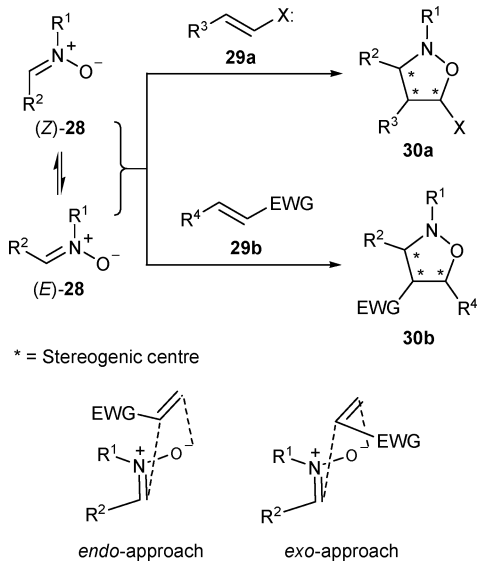


Fig. 6 Several antiviral inhibitors prepared by 1,3-DC of azides and alkynes.

Although they are not considered antiviral agents, there are other contributions dealing with the synthesis of very interesting useful molecules for the study of biomolecular recognition, binding mechanisms, *etc.* For example, the synthesis of radiolabelled peptides (^{18}F or ^{11}C), incorporating 1,2,3-triazole units, which have been used as diagnostic agents, for example, as radiopharmaceuticals for several purposes, and also served as a vector to direct a small drug to the virus.[42] As well, azides and alkynes are easily transformed into the corresponding 1,2,3-triazoles in the synthesis of ligands for the preparation of antiviral drugs,[43] in the preparation of sensors on oligo- or poly(ethylene glycol) films on silicon surfaces that possess a structural portion capable of being recognised by a biological specimen (including viruses),[44] and finally, in the elaboration of cross-linked polymeric multilayers, interesting for the fields of drug delivery directed towards viruses and tissue engineering.[45]

3. Nitrones

Nitrones **28** or azomethine oxides were first prepared by Beckman in 1890. Their chemistry is hugely varied,[46] but is ultimately dominated by their use as 1,3-dipoles for cycloaddition reactions.[7,47] The most common 1,3-DC involving nitrones is the formation of isoxazolidines **30**[48] using alkenes **29** as dipolarophiles (Scheme 5), although other different multiply bonded systems such as alkynes, allenes, isocyanates, nitriles, thiocarbonyls, *etc.,* may also be used. The isoxazolidine adduct **30** contains up to three new stereogenic centres and the reaction products can be predictable according to experience, results and frontier molecular orbital (FMO) theory.[7c] The *E*/*Z*-interconverting nitrones **28** reacted with electron-rich



Scheme 5 General 1,3-DC of nitrones.

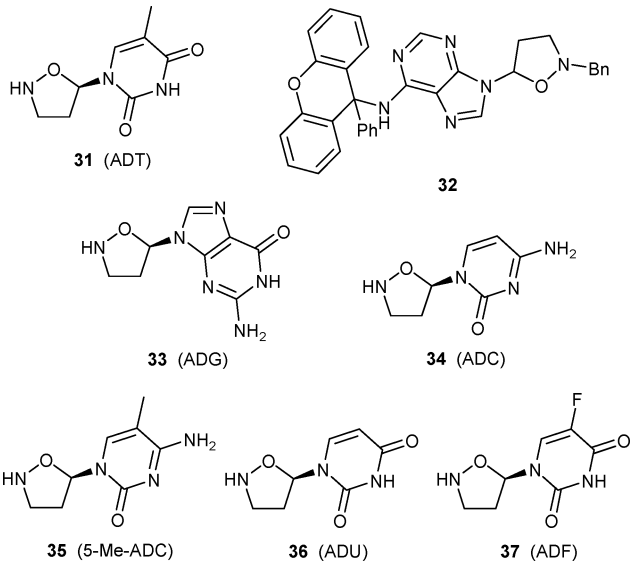


Fig. 7 Inhibitors of HIV from nitrones and *N*-vinylpurines or *N*-vinylpyrimidines.

alkenes **29a** firstly through a nitrone oxygen atom attack on the α-position of the electron-rich alkene, however, this oxygen atom react with the β-position of the electron-poor alkenes **29b** (Scheme 5). Often, diastereomeric pairs of *exo*- and *endo*-adducts are formed under thermal conditions. However, steric hindrance is of importance in controlling the approach of the alkenes towards the nitrones. Operating under metal-catalysed or organocatalysed processes, run at lower temperatures, overall control of the absolute configuration of each stereogenic centre can be achieved. The diastereoselective processes are also efficient at furnishing optically enriched heterocycles.[7d]

This cycloaddition has been applied (to a lesser extent than the above mentioned azides) to the elaboration of inhibitors of RNA viral strands. For example, it was found that derivatives of natural nucleic acids play an important role in current chemotherapy as potent and selective antiviral agents in AIDS treatment. The ribose ring surrogates depicted in Fig. 7 are considered as active inhibitors of HIV. Especially active was product ADF **37**, which was a good inducer of cell death by apoptosis in Molt-3-cells, a continuous line of human lymphoblasts.[49] In previous works some isoxazolidines **31–35** (also called aza-dideoxynucleosides) were synthesized through the same route with an identical objective, but the inhibition of HIV was only moderate.[50-53] In all cases, products **31–37** were obtained through 1,3-DC of the nitrone with the corresponding *N*-vinylpurine or *N*-vinylpyrimidine by heating the mixture for approximately 4 h, obtaining only the desired regioisomer. Azanucleosides can act as intercalating drugs avoiding the reverse transcription or can induce a different new double-stranded RNA (dsRNA), which effectively inhibits expression of the HIV genes.

The herpes simplex virus (HSV) type 1 and 2 are very extended viruses causing different pathologies. The inhibition of them can be achieved by the use of molecule **38a** (B = 5-fluorouracyl) rather than other isoxazolic nucleosidic bases **38** (Fig. 8). Again, *N*-vinylpurines or *N*-vinylpyrimidines were employed as dipolarophiles.[54] Bicyclic *N*,*O*-nucleoside analogues **39** showed an interesting inhibition of HSV-1 replication in the range of 100 μM. The particular conformation of **39** reduces the probability of puckering interconversion, which justifies strongly the conserved DNA-like shape and therefore they could be considered for optimisation studies for designing more potent HCV reverse transcriptase inhibitors.[55] Phosphonated carboxylic-2′-oxa-3′-azanucleosides **40** were obtained according to the already mentioned thermal 1,3-DC. Reaction of the nitrone-phosphonate and vinyl acetate

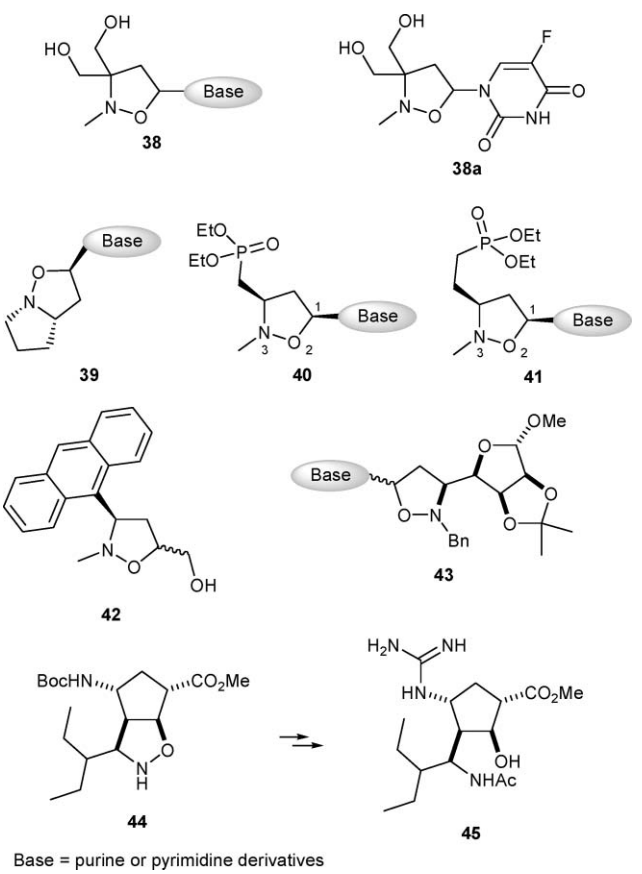


Fig. 8 Thermally-generated isoxazolines with noticeable inhibition of different virus types.

was followed by attack of the purine or pyrimidine moiety at the anomeric carbon. The resulting nucleosidic derivatives **40** were tested and low levels of cytotoxicity were detected, but most important was their activity as inhibitors of reverse transcriptase in virus. In fact, it was as powerful as AZT and one of the most effective known inhibitors of the hepatitis B virus.[56] The ability of the newly synthesized compounds to inhibit retroviral RNA-dependent DNA polymerase (reverse transcriptase) activity was determined by means of a novel cell-free assay, originally developed for preliminary screening of potential inhibitors of reverse transcriptase. In this assay, RNA isolated from stable transfectants, constitutively expressing the glycoprotein D (gD) of HSV-1, was used as a template for the reversal transcriptase activity of commercial avian myeloblastosis virus reverse transcriptase (AMV-RT) and moloney murine leukemia virus reverse transcriptase (MLV-RT).[56] The postulated mechanism of the inhibition of the reverse transcriptase was identical to that already described for AZT surrogates (see earlier).

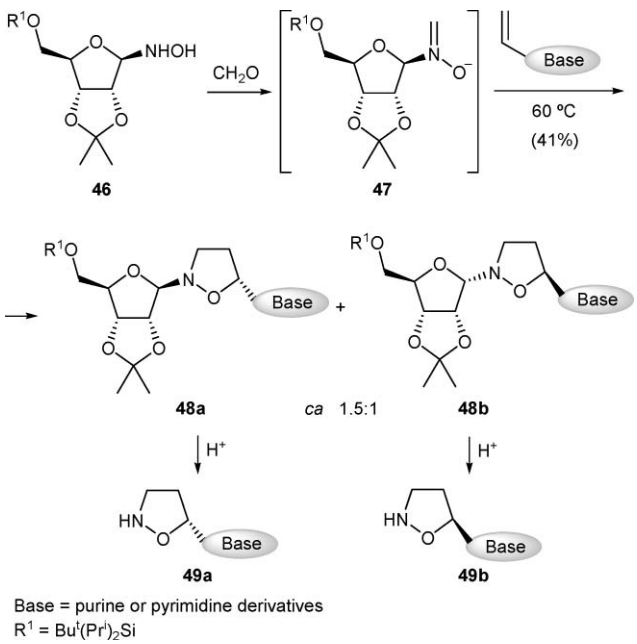
The homologous series of azanucleosides **41** were prepared by the same chemical route but using microwave radiation (100 W, 20 min) for the obtention of a 1.8:1 *endo*:*exo* ratio of the precursor isoxazoline in 65% yield. Their activity as inhibitors of HIV or HBV was moderate and lower than homologous structures **40**. However, compounds **41** contributed to the research of the structural features, which concur to determine the biological activity of the *N*,*O*-nucleoside system.

The insertion of nucleotides in the growing nucleic acid chain, operated by polymerases, is assisted by bivalent metallic ions that facilitate the transfer of nucleotide units. It was speculated that the nitrogen atom of the heterocycle would facilitate the breaking between P_α and P_β in the nucleotide triphosphate structure and, in this way, allows the transfer of a diphosphoryl or a nucleotidyl group. The nitrogen atom is probably responsible for metal-ion coordinations and, in this context, while the distance P_α–N_3 in compounds **40** promotes the formation of 6-membered chelates, for compounds **41** the distance P_α–N_3 is not compatible with a stable 7-membered chelate and, consequently, any antiviral activity is forbidden.[57]

Compound **42**, obtained by reaction of the corresponding nitrone and allyl alcohol at 160 °C, was active against the bunyavirus punta toro virus (PTV) for which the cytotoxic/antiviral ratio was virtually 10-fold. This PTV is one of eight members of the family *Bunyaviridae*, which produce disease in man through accelerated apoptosis of hepatocytes *in vivo*. Preliminary docking studies of this compound **42** to the B-DNA fragment $d(CGCAATTGCG)_2$ show that it preferentially intercalates in the DNA AT region, and the resulting complex is further stabilised by a hydrogen bond between the hydroxyl group of the hydroxymethyl moiety and an oxygen of a phosphate group.[58]

Whilst potential inhibitors of virus *endo*- and *exo*-**43** are currently being evaluated *in vivo*,[59] the formation of isoxazole **44** was the key step in the total synthesis of racemic BCX-1812(RWJ-270201) **45**. The 1,3-DC was performed at room temperature in the presence of sodium hypochlorite with an isolated yield of 61%. Compound **45** is in clinical phase due to its notable selectivity and potency against neuraminidase of a wide range of influenza A and B viruses. The strong interaction between **45** and the S2 region of neuraminidase ensures a high inhibition. However, this agent may not confer ideal therapeutic characteristics due to several side effects. The establishment of a practical, efficient, and versatile synthetic route would contribute to further the structure–activity relationship (SAR) studies needed for the development of safe and potent neuraminidase inhibitors.[60]

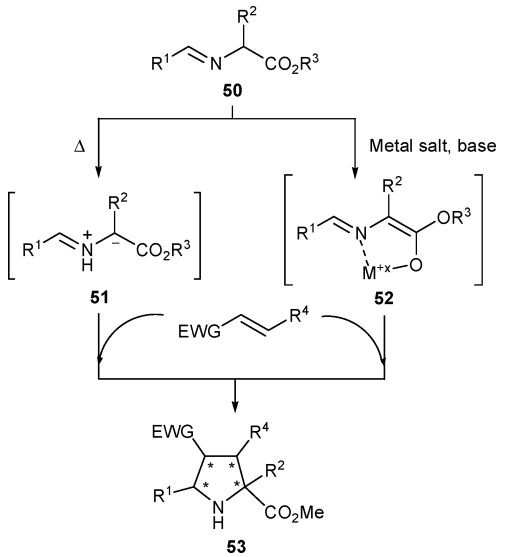
The diastereoselective synthesis of *N*,*O*-nucleosides **48** was achieved in 41% yield by the reaction of intermediate nitrone **47**, obtained from *N*-ribosylhydroxylamine **46**, with *N*-vinylpurines or *N*-vinylpyrimidines. The diastereomeric ratios were moderate (1.5:1), furnishing compound **48a** as the major stereoisomer (Scheme 6). Nucleoside analogues **48** exhibited low levels of cytotoxicity, however, heterocycles **49a** and **49b** (base = fluorouracil, FU) caused very fast cell death by apoptosis in lymphoid cells. These investigations opened new perspectives on their possible use as therapeutic antiviral agents. To obtain further information on the mechanisms regulated by AdFU-induced apoptosis, the possible involvement of the caspase-cascade was confirmed after culture tests and calorimetric assays.[61]



Scheme 6 Synthesis of antiviral compounds **48** and **49**.

4. Azomethine ylides

Azomethine ylides are 1,3-dipoles very frequently generated *in situ*, by a thermal 1,2-prototropy shift in iminoesters **50** or by a base-assisted formation of a metallo-dipole also from **50**. Although many other methods are known, the metallo-dipole route is the most employed due to its simplicity and the mildness of the reaction conditions required.[7,62] According to the stereochemical point of view, metallo-dipoles **52** are crucial species because their geometry is perfectly controlled, which allows the formation of highly diastereoselective 1,5-*cis*-adducts. The frontier orbital theory (FOT) explains the high regioselectivity and very important *endo*/*exo* diastereoselection achieved in the preparation of proline derivatives **53**[63] (Scheme 7), following the identical dipole–dipolarophile approach depicted for nitrones (see Scheme 5). All these features are appropriate to run a catalytic enantioselective version,[64] which would generate up to four stereogenic centres

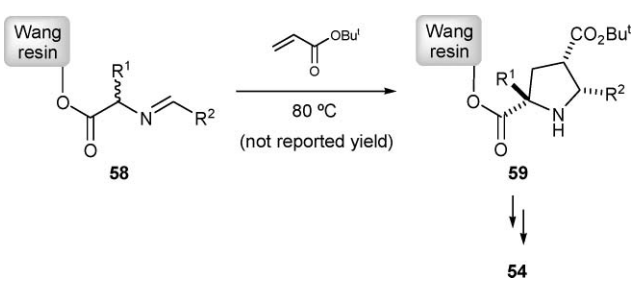


Scheme 7 General 1,3-DC using azomethine ylides.

in the resulting pyrrolidines **53**.[65] The 1,3-DC using azomethine ylides is only productive when electron-deficient alkenes are employed.

One of the most relevant applications of these cycloadditions is generation of the key intermediate in the preparation of potent and promising inhibitors of the HCV polymerase. This enveloped single-stranded RNA virus (belonging to the *Flaviviridae* family) is present in six major genotypes in the world's industrialized nations, genotype 1 being the most prevalent, followed by genotypes 2 and 3. Inside the infected hepatocyte, structural E1 and E2 and non-structural proteins such as NS2, NS3 (which bears serine proteinase, helicase, and NTPase activities), NS4A, NS4B, NS5A (regulators of RNA replication), and NS5B (the RNA-dependent RNA polymerase) are generated.[66,67] So, their high replication rates (billions of copies per day) can be drastically suppressed by inhibition of the NS5B RNA-dependent RNA polymerase enzyme, which is the primary target for oral antiviral agents **54–57** (Fig. 9).[68]

The preparation of racemic *N*-acylpyrrolidine **54** was accomplished by means of a concerted thermal 1,3-DC between supported Wang resin-azomethine ylides **58** and *tert*-butyl acrylate (Scheme 8). The pure enantiomers were separated by preparative chiral HPLC, after amidation and hydrolysis of both ester groups.[69] In this way, many *N*-acyl pyrrolidines were designed, with heterocyclic compound **57** found to be the most promising candidate to help infected people.



Scheme 8 Synthesis of the racemic *endo*-**54**.

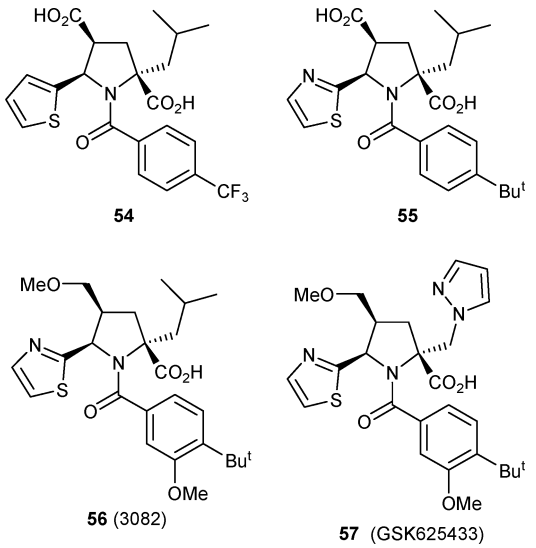
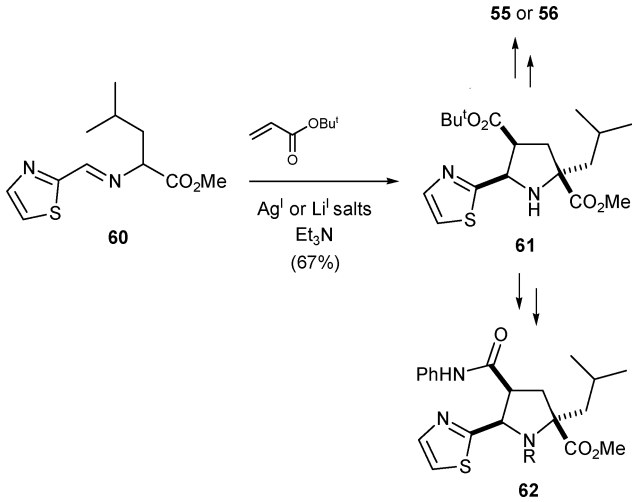


Fig. 9 Proline inhibitors of the HCV.

The potent activity of these series of products was correlated with the binding site identification and genotypic profiling of HCV polymerase inhibitors.[70] The search for hepatitis C virus polymerase inhibitors has resulted in the discovery of several non-nucleoside binding pockets. The shape and nature of these binding sites differ across and even within diverse hepatitis C genotypes. These differences confront antiviral drug discovery with the challenge of finding compounds that are capable of inhibition in variable binding pockets. It was demonstrated that the recombinant P495L, M423T, M414T, and S282T mutant enzymes could be used to identify the binding site of the acyl pyrrolidine inhibitors. For these prolines it was found that Phe415 is crucial for genotype 1a coverage. Hydrogen bonding and contacts with the polypeptide backbone are rare. To best adapt to the highly variable binding sites of NS5B, small molecules ideally used hydrophobic interactions with the residue placed at the α-position of the heterocycle. The hydrophobic arylcarbonyl group is important in order to ensure or increase the permeability through the lipidic membranes. This property is transformed into good replicon potency and good pharmaco-kinetics for future developments of new drugs. The α-epimers are more potent than the corresponding β-epimers.[70]

The first synthesis of racemic product **55**, and other derivatives including compound **54** was achieved in several steps using in the key reaction a silver(I) or lithium-metalloazomethine ylide, generated from iminoester **60** under basic conditions, and *tert*-butyl acrylate. The resulting cycloadduct **61** was obtained in 67% yield through a non-concerted mechanism (Scheme 9). The enantiomeric samples were isolated from semi-preparative chiral HPLC. A small modification on the side chain of the heterocycle (amido group instead of carboxylic group) gave raise to product **62**, which in its (+)-form exhibited superior activity in both the enzyme and the replicon assays (Scheme 9).[71]

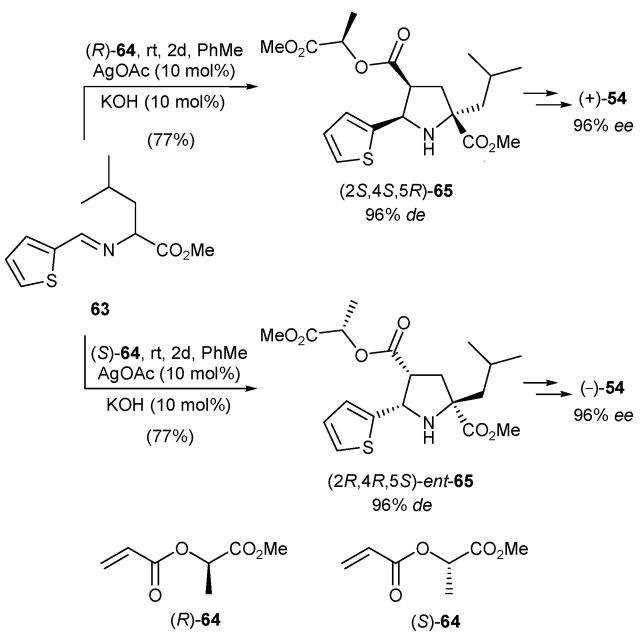
Molecule **56** (3082) was obtained through the analogous key intermediate **61** (Scheme 9). These 3-methoxyarylamides had superior solubility properties and lower molecular weights than other precedent antiviral agents. On this occasion, to resolve the racemic mixtures of compound **61**, (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl-hydrogen phosphate was employed providing the required



Scheme 9 Synthesis of several racemic HCV inhibitors.

diastereomeric salt in good yield and excellent enantiomeric excess at the end of the process (98.8%). In this work, a comparison of the X-ray structures of dicarboxylic acid **55** and the binding site of the HCV polymerase was surveyed. The bulkier *tert*-butyl substituent on the benzamide caused movement in the side chain of Leu384 allowing inhibitors to bind deeper into the pocket and increase their antiviral power.[72] This result was in total agreement with those previously reported (see earlier).

The first *endo*-diastereoselective 1,3-DC of the key precursors of these antiviral agents was achieved *via* silver(I)-metalloazomethine ylide in the presence of acrylates derived from (*R*)- or (*S*)-methyl lactate **64** (Scheme 10). The diastereoselection was very high (96% *de*) and the chemical yield was 77%. Enantiomerically enriched (+)-**54** and (–)-**54** forms were finally isolated in 96% *ee* and in 51–54% yield (overall yield from iminoester **63**), after successive amidation and double hydrolytic process. In spite of the small size of the substituents bonded around the stereogenic centre, it was

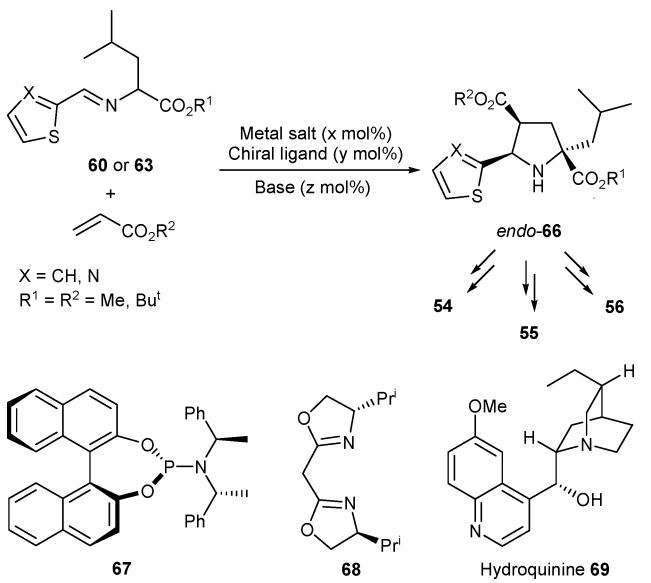


Scheme 10 Diastereoselective synthesis of key compounds **65**.

demonstrated that the excellent stereocontrol originated from the interaction of the lactate methyl groups and the aryl or heteroaryl residue of the starting material.[73]

The more straightforward and faster approach to the enantiomeric forms of these non-nucleosidic antiviral agents is based on a catalytic enantioselective 1,3-DC as the key step.[64] The asymmetric reaction was pioneered by Grigg and Allway in 1991 using stoichimetric amounts of chiral bases or chiral metal complexes.[74] However, it was in 2002 when the first substoichiometric catalytic (3 mol%) enantioselective transformation was successfully reported by Zhang and coworkers using a chiral diphosphane/silver(I) complex.[75] At that time, this cycloaddition became a fascinating transformation and many contributions appeared with outstanding results. Chiral metal complexes, chiral bases, and chiral organocatalysts have been tested, obtaining the best results, in terms of diastereo- and enantioselectivities, and wider general scope when chiral metallodipoles were generated as intermediate products. Silver(I)[76] and copper(I)[77] catalytic complexes afforded the most efficient and attractive processes.[78,79]

The first enantioselective synthesis of the five-membered core of these structures was performed by using a chiral phosphoramidite **67** and $AgClO_4$ (both in 5 mol% amounts) as catalyst. The reaction run at –20 °C furnishes a good yield of compound *endo*-**66** with high enantioselection (Scheme 11, and Table 1, entry 1). In this work, the synthesis of enantiomerically enriched product **54** (82% *ee*) was also reported after amidation and double hydrolytic sequence involving TFA/0 °C followed by KOH–MeOH/80 °C.[76j,80] Box ligand **68** and calcium isopropoxide formed a chiral complex, which was used to catalyse the process at –44 or –30 °C in THF as solvent. The yields are high and the enantioselectivities are the highest reported to date for compound **66** (85 and 88% *ee*) (Scheme 11 and Table 1, entries 2 and 3).[78d] Apart from the Lewis acid-catalysed 1,3-DC the concept of organocatalysis was applied to the synthesis of **66** using hydroquinine **69** as chiral base (6 mol%) together with a 3 mol% amount of silver acetate. Although chemical yields were very good, the enantioselection was moderate (74% *ee*) (Scheme 11, and Table 1, entry 4). In fact, a further



Scheme 11 Enantioselective synthesis of intermediate **66**.

Table 1 Catalytic enantioselective synthesis of compound **66**

X	R^1	R^2	Salt[a]	L[a]	Base[a]	T(°C)	Yield (%)[b]	*ee* (%)
CH	Me	Bu^t	$AgClO_4$ (5)	**67** (5)	Et_3N (5)	–20	70	82
CH	Bu^t	Bu^t	$Ca(OPr^i)_4$ (10)	**68** (10)	—	–44	83	85[c]
N	Bu^t	Bu^t	$Ca(OPr^i)_4$ (10)	**68** (10)	—	–30	83	88[c]
N	Bu^t	Me	AgOAc (3)	**69** (6)	—	0 or –10	84	74

[a] In brackets (x, y or z mol%). [b] Isolated yield. [c] *ent*-**66** was obtained.

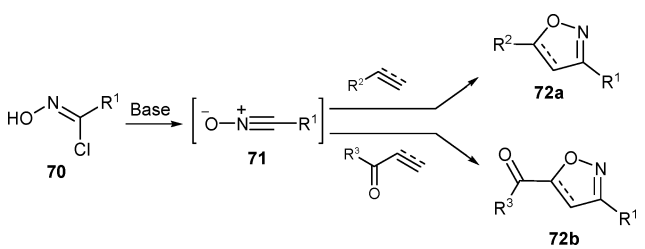
1,1′-binaphthyl-2,2′-dihydrogen phosphate assisted chiral resolution of **66** was performed in order to obtain pure compound *endo*-**66** with a 99.8% *ee*.[79g]

To the best of our knowledge the synthesis of antiviral agent **57** has not been reported yet,[81] and it has appeared as a consequence of evolutive structural modifications of the precedent inhibitors. Product **57** (GSK625433) is the most potent and selective drug having a good pharmacokinetic profile in phases I and II. This last compound does not inhibit human DNA polymerases, can be administrated in low concentrations and no significant cytotoxicity was observed.[82] The discovery of the active specific interaction site polymerase-receptor for the inhibitors supports this new trend of therapy. A small modification in the final structure of **57** can be translated into a more potent inhibition of the named viral polymerase, the highest optical purity of intermediate **66** being modulated by selecting the most appropriate solvent, silver salt, chiral ligand, temperature, and base.

This alternative therapy is orally administrated in smaller amounts, it is cheaper and causes a lot fewer side effects and complications than the current subcutaneous pegylated α-interferon treatment combined with oral ribavirin. In addition, RNA-polymerase inhibition is much more effective than the inhibition of other structural and non-structural viral proteins in the fight against HCV.

5. Nitrile oxides

Similarly to azomethine ylides, nitrile oxides **71** have to be generated *in situ*. There are many methods described for their preparation,[7d] dehydrohalogenation of hydroxymoyl chlorides **70** and dehydration of nitroalkanes being the most frequently used strategies. The regioselectivity of the 1,3-DC of nitrile oxides and alkenes or alkynes is easily predictable. For monosubstituted alkenes and electrophilic olefins the major regioisomers isoxazoles or isoxazolines[48] **72a** and **72b**, respectively, are isolated as pure compounds (Scheme 12). As a maximum, only two stereogenic centres can be generated employing catalytic enantioselective synthesis.



Scheme 12 Synthesis of the major regioisomers **72**.

As it was described previously for azides, nitrile oxides are used to strategically modify several parts of the molecule with the aim of increasing its antiviral potency. Initial contributions were designed for studying the antiviral activity of a series of products, but no biological assay results were detailed.[83] This was the case for C-nucleoside analogues **73**,[84] and isoxazolines **74**[85] (Fig. 10), which were obtained following the conditions depicted in Scheme 12 but using an α-bromoacrylic system.[86] They have potential activity against varicella-Zoster virus (VZV), cytomegalovirus (CMV), and herpes simplex virus (HSV). Particularly, compound **73**, obtained from *N*-vinylpurines, was moderately effective against HIV-1 in acutely infected primary human lymphocytes.[84] *N*-Oxide carbonocyanidic acid ethyl ester reacted with benzodiazepines to yield compounds **75** that are considered as HIV reverse transcriptase inhibitors.[87] *N*-Adamanthyl isoxazoline **76** is a very simple structure that showed a slight inhibition of HIV.[88] Since this publication, several articles reported modified structures able to hamper the development of HIV. For example, nucleoside and

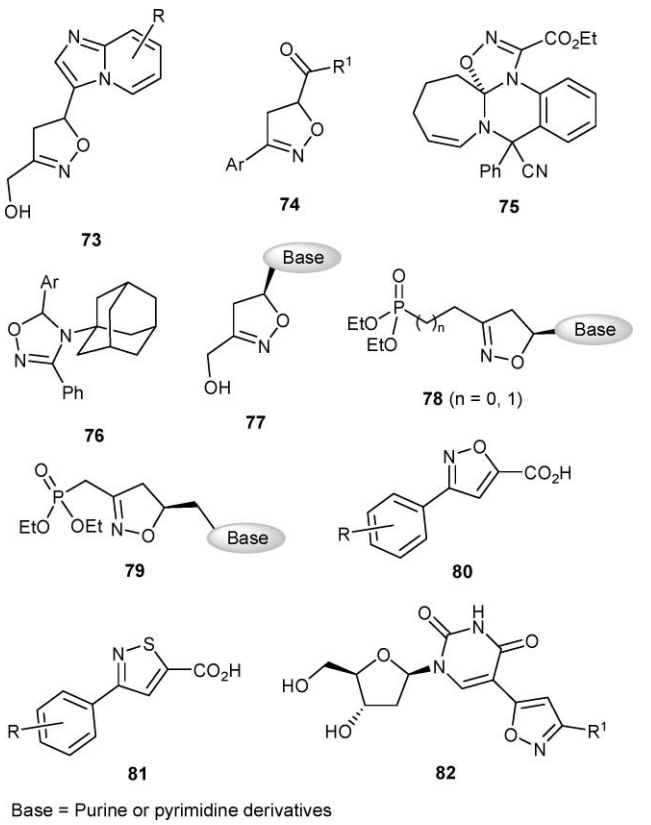


Fig. 10 Antiviral products derived from 1,3-DC between nitrile oxides and alkenes.

nucleotides **77** and **78** (n = 1) (Fig. 10) were obtained from the nitrile oxide and the corresponding *N*-vinylnucleo-base. The results were very promising against HIV, **78** (n = 1) being the most effective and less cytotoxic drug.[89] The connection of oxygen and nitrogen atoms provided the possibility to introduce the nucleophilic nitrogen into the furanose ring with a minimum of steric manipulation, providing opportunities to modify the furanose ring of nucleoside analogues with novel structural features. Consequently, it became possible to design other related *N*,*O*-containing derivatives for biological studies.

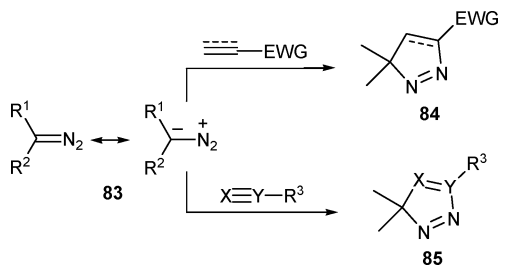
However, homologue compounds **78** (n = 0) (Base = thymine, fluorouracil, or cytosine) and **79** (Base = thymine) (Fig. 10) completely inhibited the reverse transcriptase activity of the avian myeloblastosis retrovirus at 10 μM concentration. These isoxazolines, **78** and **79**, exhibited lower potency with respect to isoxazolidine derivatives **40** and **41** (Fig. 8).[90] The lesser ability to elicit recognition by the reverse transcriptase, due to the insertion of a double bond in the five-membered heterocycle, can be attributed to a lower molecular flexibility and a lower basicity of the nitrogen atom. Such as it was already mentioned, the bivalent metallic ions assisted the insertion of nucleotides in the growing nucleic acid chain. In this particular case, Mg^{+2} could form a six-membered chelate with the nitrogen atom and the oxygen of the phosphorous group as well.[90]

The 1,3-DC involving nitrile oxides and alkynes (methyl propiolate) was studied in the generation of isoxazoles and isothiazoles **80** and **81**, respectively. These aryl-substituted heteroaromatic carboxylic acids (when R = 3-BnO in **80**, and R = 4-NO_2 in **81**) afforded the advantageous features of improvement of antiviral potency against HIV-1 integrase and decreased cytotoxicity with high therapeutic index. The good antiviral potency of the heteroaromatic carboxylic acid series could be attributable to the improved bioavailability of the bioisosteres. On the other hand, the inconsistency between integrase inhibitory activity and the antiviral effect might involve multiple targeting in the HIV-1 life cycle.[91]

Finally, 2-deoxyuridine derivatives **82** (Fig. 10), formed by 1,3-DC of nitrile oxides and 5-alkynyluridines showed a poor affinity for HSV-1-specific thymidine kinase.[92,93]

6. Diazoalkanes and carbonyl ylides

For a long time diazo-compounds **83** have been one of the most synthetically useful classes of 1,3-dipoles because they could be prepared and isolated in pure form in contrast to other 1,3-dipoles that are generated as transient species.[7d] The cycloadditions with double or triple bonds (including heteroatoms) have been widely surveyed (Scheme 13).[7] The reaction with electrophilic olefins occurred such as it is depicted in Scheme 13, the carbon atom

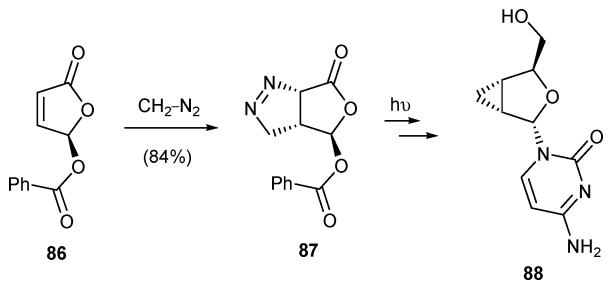


Scheme 13 General 1,3-DC promoted by diazoalkanes.

reacted at the 4-position of the electrophile with almost total selectivity to yield pyrazoline or pyrazole derivatives **84** and **85**, nevertheless, some mixtures are obtained by reaction with electron-rich alkenes. In addition, the reaction of diazoalkanes with nitriles also gives good regioselectivities of the corresponding compounds **85** (Scheme 13).

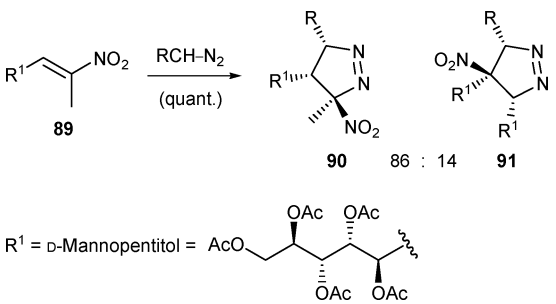
The commercially available diazo(trimethylsilyl)methane is a safe, non-explosive and non-mutagenic substitute of diazomethane, and its cycloaddition can be greatly expanded by metallation with butyllithium. In general, Δ^1-pyrazolines or pyrazoles **84** or **85**[94] were regioselectively obtained at very low or room temperature (Scheme 13). On some occasions, the five membered ring is not the active substance but the corresponding cyclopropane, generated *via* photoinduced elimination of molecular nitrogen.

Thus, 2′,3′-dideoxy-2′,3′-α-methanocytidine **88** was prepared following this last mentioned sequence where the key intermediate **87** was regioselectively obtained in 84% yield and almost total diastereoselection. Product **88** only exhibited weak to moderate activity against the HIV[95] (Scheme 14).



Scheme 14 Synthesis of antiviral agents **87** and **88**.

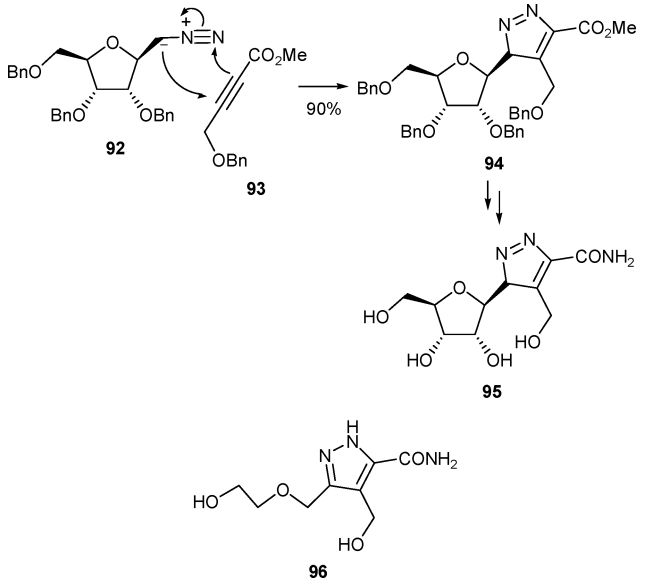
Δ^1-Pyrazoline **90** was diastereoselectively obtained (>99:1 *dr*) in quantitative yield. This heterocycle was aromatised to yield the corresponding pyrazole unit with some interesting weak inhibition of several types of viruses (Scheme 15).[96]



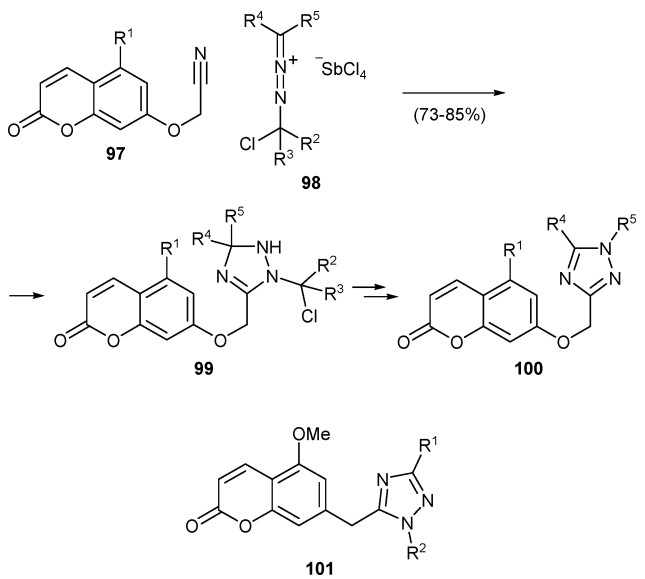
Scheme 15 Synthesis of heterocycle **90**.

The synthesis of pyrazole-5-carboxamide **95** started with the 1,3-DC between 1-(diazomethyl)-D-allitol derivative **92** and butynoate **93**. Compound **94** underwent very simple and standard reaction transformations to yield finally carboxamide **95** (Scheme 16). Analogously, amide **96**, possessing the truncated acyclic side chain of acyclovir, was prepared in a similar manner. Both pyrazoles **95** and **96** demonstrated weak biological activity against HIV, yellow fever virus, and vaccine virus.[97]

Diazo-compounds **98** were allowed to react with coumarins **97**, bearing a nitrile functional group, yielding products **99** in very good yields (73–85%) (Scheme 17). After several steps coumarins



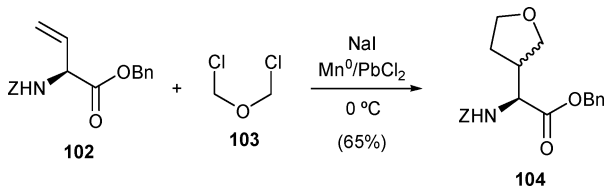
Scheme 16 Synthesis of pyrazoles **94–95**.



Scheme 17 Synthesis of series of compounds **100** and **101**.

100 and the analogous adducts **101** were isolated. Compounds **101** showed encouraging results by inhibition of HIV-1 with an IC_{50} value >0.17 μM, whilst none of the tested compounds **100** was found to inhibit HIV-1 or HIV-2 replication. The structure–activity relationship (SAR) suggested that molecules incorporating the carbon–coumarin linkage manifested higher HIV inhibition activity than did the corresponding analogues having the oxygen linkage as in structures **100**.[98] These results would lead to modification of the target molecules by the introduction of more potential groups with a carbon linkage.

To the best of our knowledge only one example of compounds with antiviral activity has been published employing a 1,3-DC between *in situ* generated carbonyl ylides and alkenes. In this work tetrahydrofuranyl glycine **104** have been obtained in 65% yield from L-vinylglycine **102** through a 1,3-DC reaction using the non-stabilised carbonyl ylide, prepared from carcinogenic bis(chloromethyl) ether **103**. The reaction was run at 0 °C, achieving better chemical yield of a 57:43 mixture of diastereoisomers (Scheme 18).[99] The resulting polypeptides, incorporating this α-amino acid **104**, acted as substrate-based inhibitors of HIV-1 protease. The inhibitory action of these macromolecules was probably due to the favourable interactions at the S2 region of neuraminidase (see earlier). This strategy proved to be very valuable to medicinal and peptide chemistry due to the numerous modifications to essay.



Scheme 18 1,3-DC involving a carbonyl ylide as the 1,3-dipole.

7. Conclusions

After more than a century after their discovery, these 1,3-DCs represent a powerful tool in modern synthetic chemistry whose limits are still being explored. According to the previously described contents and in search of drugs with a wider spectrum of activity, a clear perspective can be defined: the 1,3-DCs allow structurally simple modifications, which fit to Lipinki's rules, facilitating the interaction of drug–virus at different stages. Ylides are easily generated, the reactions involved are highly regio- and diastereoselective, even with elevated enantioselection for enantioselective processes. The reaction conditions are usually very mild and the atom economy is almost total. Azides, nitrones, and azomethine ylides are the most employed dipoles giving rise to nitrogenated five membered ring heterocycles. Particularly interesting is the enantioselective approach to them using substoichiometric amounts of chiral catalysts.

The most promising methodology is based on the azomethine ylide and its reactions with alkenes. In fact, this cycloaddition is a ray of hope for the more than 190 million people having chronic hepatitis C in the world. This asymmetric reaction could allow the preparation of multiple libraries of chiral molecules able to inhibit the HCV replication. The scope of these products can be also applied to the single or combined treatment of the HIV/HCV coinfected people (15 million of patients in a critical situation) or for the treatment of influenza or other devastating viruses; however, we do not have any data about all these ambitious goals.

Acknowledgements

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