Bioactive Carbohydrates and Recently Discovered Analogues as Chemotherapeutics

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Abstract: Infectious diseases such as tuberculosis, malaria, the "simple flu" or HIV and HBV, are killing more than 50,000 people a day according to estimations by the World Health Organisation (WHO). Consequently, the development of biologically active agents in general, such as antibiotics and chemotherapeutics, is of great importance. Hand in hand with the understanding of the mechanisms of biological agents, structures carrying sugar moieties have become increasingly important during the last decades. This review will cover the most recent developments in the field of new antibiotics and synthetic agents containing carbohydrates which are active against tuberculosis and malaria. In addition, compounds having antiviral, antibacterial and anticancer properties will be examined. Compounds such as aminoglycosides, iminosugars, carbacycles, nucleosides, and other selected substance classes will be considered.

Keywords: Carbohydrates, nucleosides, carbasugars, antibiotics, glycopeptide conjugates, chemotherapeutics.

INTRODUCTION

Tuberculosis (TB) has long been a cause of morbidity and mortality worldwide. The new fight against TB has resulted from several factors including the growing incidence of multi-drug resistant forms of *Mycobacterium tuberculosis* as well as the prevalence of tuberculosis in the AIDS community [1].

Malaria is a life-threatening parasitic disease transmitted by mosquitoes, an infection due to protozoan parasites, which causes approximately 300 million acute illnesses and at least one million deaths per year. Current malaria prophylaxis based on heteroaromatic systems containing nitrogen suffer from the development of resistant microbial strains. Consequently, safe and cost-efficient drugs for the treatment of this disease caused by these multidrug resistant strains are urgently needed. Targeting enzymes that are only found in bacteria, yeast and protozoa, but not in mammals, for example nucleoside hydrolases or glycolytic enzymes such as glyceraldehyde-3-phosphate dehydrogenase are, subsequently, worthwhile for the development of corresponding inhibitors.

Influenza is nowadays still one of the largest health concerns and the major cause of mortality and morbidity among patients with respiratory diseases. Before 1999 there were two drugs available on the market, apart from vaccines which require a new formation every year, namely the antiviral drugs amantadine and rimantadine, these being limited to influenza virus A. Recently, neuraminidase, which is one of the two glycoproteins expressed on the viral surface responsible for the cleavage of sialic acid residues, was found as a new drug target. Indeed, two neuraminidase inhibitors have been available on the market since 1999.

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Bacteria are often the causes of human and animal disease. Gram-positive and gram-negative bacteria require different structures on the cell surface to interact with and, therefore, this research field is wide-spread and many different approaches have been made to treat diseases induced by bacteria.

Antibiotics are bacterial or fungal metabolites that inhibit the growth of other organisms. Over many years, antibiotics such as penicillins, aminoglycosides, macrolide structures, glycopeptide antibiotics and β-lactams, just to mention a few, have been extensively investigated. Whereas in the beginning, work was focused on the search for new structures, these days investigations concentrate on understanding biosynthesis [2] and resistance formation [3]. This, in turn, leads to the design of new structures, as well as their synthesis and investigation of their biological activities. Carbohydrate-based antibiotics promise to be a new approach of tackling the problem of resistance [4].

The discovery of safe and effective antiviral drugs has also become a big challenge, because only very few virus-specific molecular targets have been identified that can specifically be subjected to antiviral intervention. This is because viral metabolic processes closely resemble host cellular processes. In addition, the rapid emergence of resistance to antiviral drugs is a major problem. Clearly, there exists a substantial need for antiviral drugs with different structures and specific mechanisms of action. In addition, pro-drug concepts [5] have become increasingly important during the past decades, because pro-drugs have only little or no cytotoxicity, whereas the drug itself being released at the place of action exhibits high activity.

There are many different approaches for the treatment of cancer known to date. Consequently, many different substance classes have been examined in order to find new agents. In this research field, carbohydrates have also become significant in the development of approaches to combat this illness.

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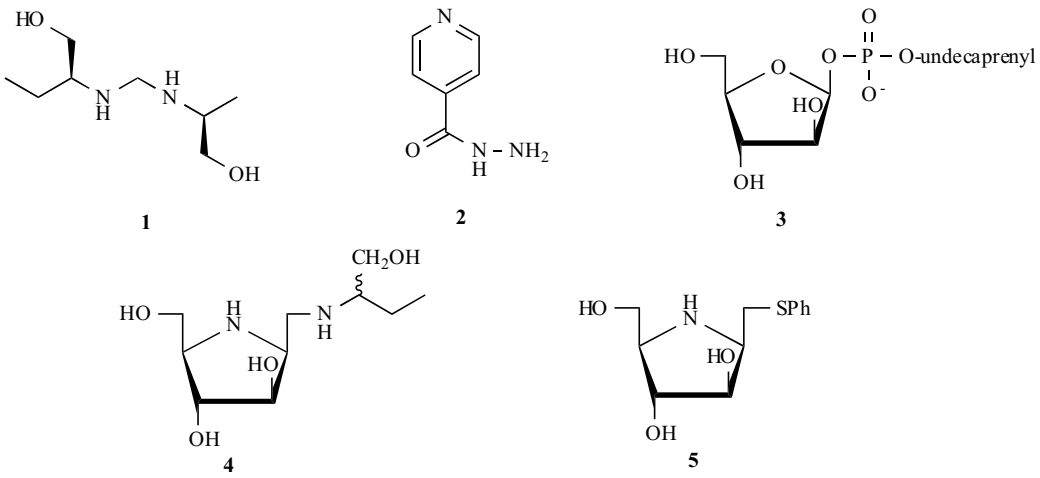


Fig. (1).

"Long avoided by chemists and biologists, sugar-based drugs are suddenly on medicine's menu and garnering impressive early reviews," says J. Alper in his comments on the searching for Medicine's "sweet spots" and early sugar chemistry as well as the recent acceptance of this research field by the chemical community [6].

TUBERCULOSIS

A large proportion of the mycobacteria cell wall consists of arabinofuranose containing polysaccharides. Suitable and selective inhibitors of the corresponding arabinofuranosyl transferases necessary to build up these polymers are interesting and offer leads for antimycobacterial chemotherapy. The arabinogalactan consists of arabinofuranose and galactofuranose, both sugars are not found in humans, thus making the biochemistry and attendant enzyme pathways ideal targets for the development of new, selective anti-tuberlucosis agents. Clinical drugs such as ethambutol (**1**) and isoniazid (**2**) (Fig. **1**) target two essential cell wall components, the arabinogalactan [7] and the mycolic acids, respectively [8]. Iminosugars such as 1,2,5-trideoxy-1-{[1-hydroxymethyl)-propyl]amino}-2,5-imino-D-mannitol (**4)** (Fig. **1**) resemble both ethambutol and β-D-arabinofuranosyl undecaprenylphosphate (**3**) (Fig. **1**), the latter being the natural substrate of this enzyme. Such iminosugars have recently been synthesised but did not exhibit any appreciable inhibitory activity [9]. Interestingly, 1,2,5-trideoxy-1-phenylthio-2,5-imino-D-mannitol (**5**) (Fig. **1**) was found active against the *Mycobacterium avium*

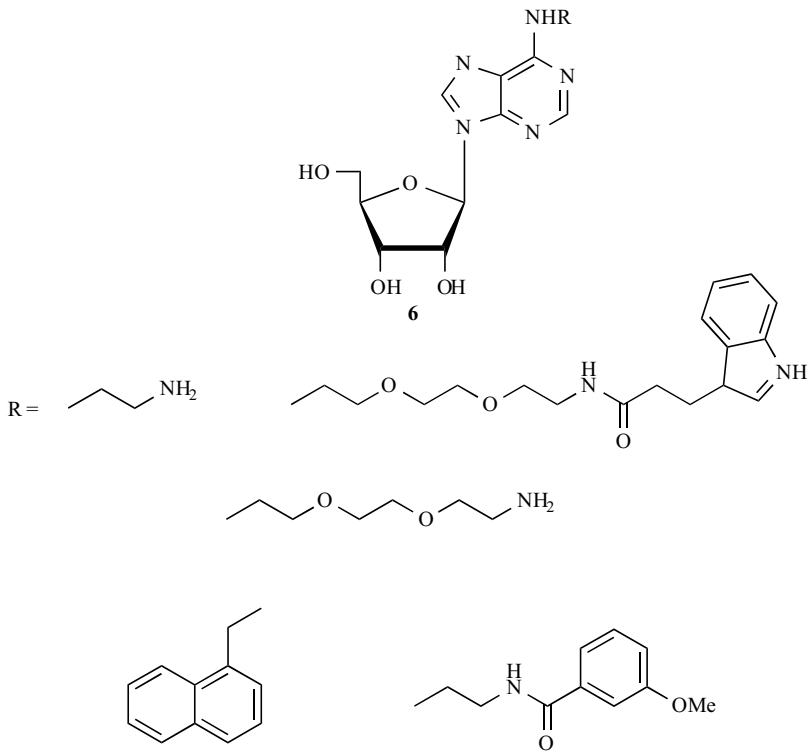


Fig. (2).

complex in an infected macrophage model at 4 μg/ml [10]. Furthermore, this compound increased tumour necrosis factor α (TNFα) production in the infected cells. Despite all efforts, several other compounds such as acyclic nitrogen containing deoxy sugars [11], arabinofuranosyl- and glacatofuranosyl [12] disaccharides as well as arabinosyl-β-D-galactofuranosides [13] did not show significant activities against mycobacterial glycosyltransferases.

MALARIA

The nucleoside transporter of parasites exhibits broad substrate specificity for purine nucleosides. Substituted adenosine derivatives are therefore prone to selective uptake by the parasite. N^6-Substituted adenosine derivatives based on structure (**6**) (Fig. **2**), carrying different primary aliphatic amines, were synthesised and their anti malarial activity tested [14] and some of them were found to have IC_{50} values in the low micromolar range.

In addition, *S*-adenosyl-L-homocysteine hydrolase, an enzyme responsible for the hydrolysis of *S*-adenosyl-L-homocysteine to adenosine and L-homocysteine, has been found as an inhibitor target because of its specificity for parasites. Carbacyclic nucleoside antibiotics such as neplanocin A (**7**) (Fig. **3**) and (6'*R*)-6'-*C*-methylneplanocin A (**8**) (Fig. **3**) were found to be effective inhibitors of this enzyme. While the inhibitory effect of (**8**) against *S*-adenosyl-L-homocysteine hydrolase is weaker than (**7**) *in vitro*, its antimalaria activity *in vivo* is superior to that of (**7**). This effect can be explained because compound (**8**) is completely resistant against adenosin deaminase. This fact allows for relatively high concentrations *in vitro* and the compound *in vivo* and it is less toxic to host cells because it is not phosphorylated by adenosine kinase [15].

The concept of targeting the binding sites of coenzymes rather than the often well-conserved active site of an enzyme was used in case of glyceraldehyde-3-phosphate dehydrogenase, one of the seven glycolytic enzymes involved in the conversion of glucose to 3-phosphoglycerate. 2'-Amido-2'-deoxy-N^6-(1-naphthylmethyl)-adenosine derivatives (**9**) (Fig. **3**), having different 2'-amido substituents, were tested with respect to their activity against these

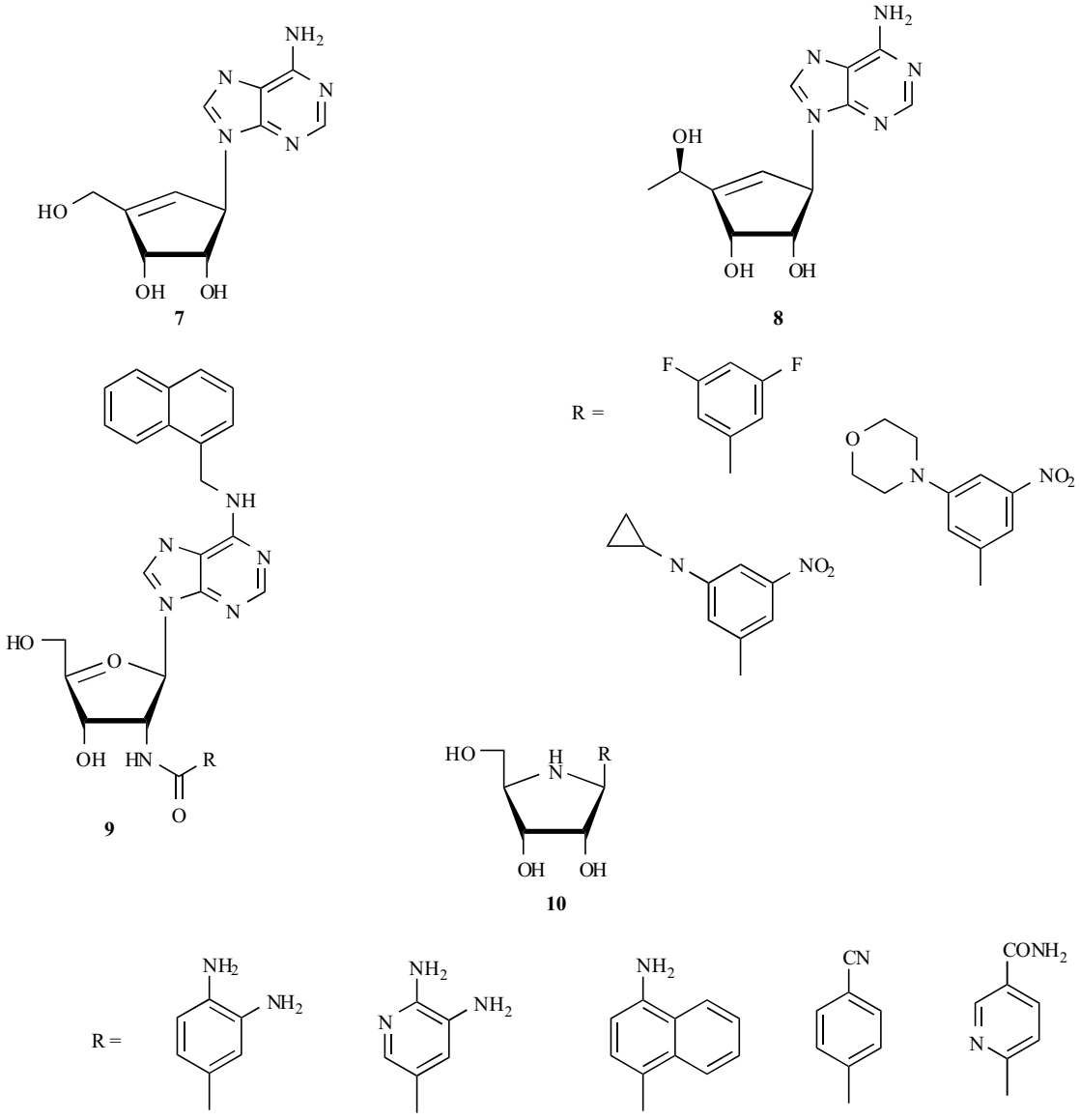


Fig. (3).

enzymes and some of them have been found to be very active in the submicromolar range [16].

Iminosugars, such as substituted 1,4-dideoxy-1,4-imino-D-ribitol derivatives (**10**) (Fig. **3**), were found to be active transition state analogue inhibitors against nucleoside hydrolases in protozoa. These enzymes catalyze the *N*-ribosidic bond of purine and pyrimidine nucleosides [17]. Compounds (**10**), when tested against nucleoside hydrolase, showed K_i values from 2-5 μM.

INFLUENZA

Neuraminidase, which is one of the two glycoproteins expressed on the virus surface and catalyzes the cleavage of sialic acid residues (**11**) (Fig. **4**) was found as new drug target a few years ago. The catalytic activity of this enzyme is essential for influenza virus replication and infectivity. Two neuraminidase inhibitors zanamivir (**12**) (Fig. **4**) and oseltamivir (**13**) (Fig. **4**) have been available on the market since 1999. Zanamivir (**12**) was shown to be active against influenza viruses A and B. However, because its highly polar nature, (**12**) requires oral inhalation [18]. Oseltamivir (**13**), an unsaturated carbacycle, is also effective against influenza A and B and has the big advantage of oral application, but the disadvantage of serious side effects such as vomiting and nausea [19].

Babu and co-workers reported several carbacyclic structures such as (**14**) (Fig. **4**) having IC_{50} values in the

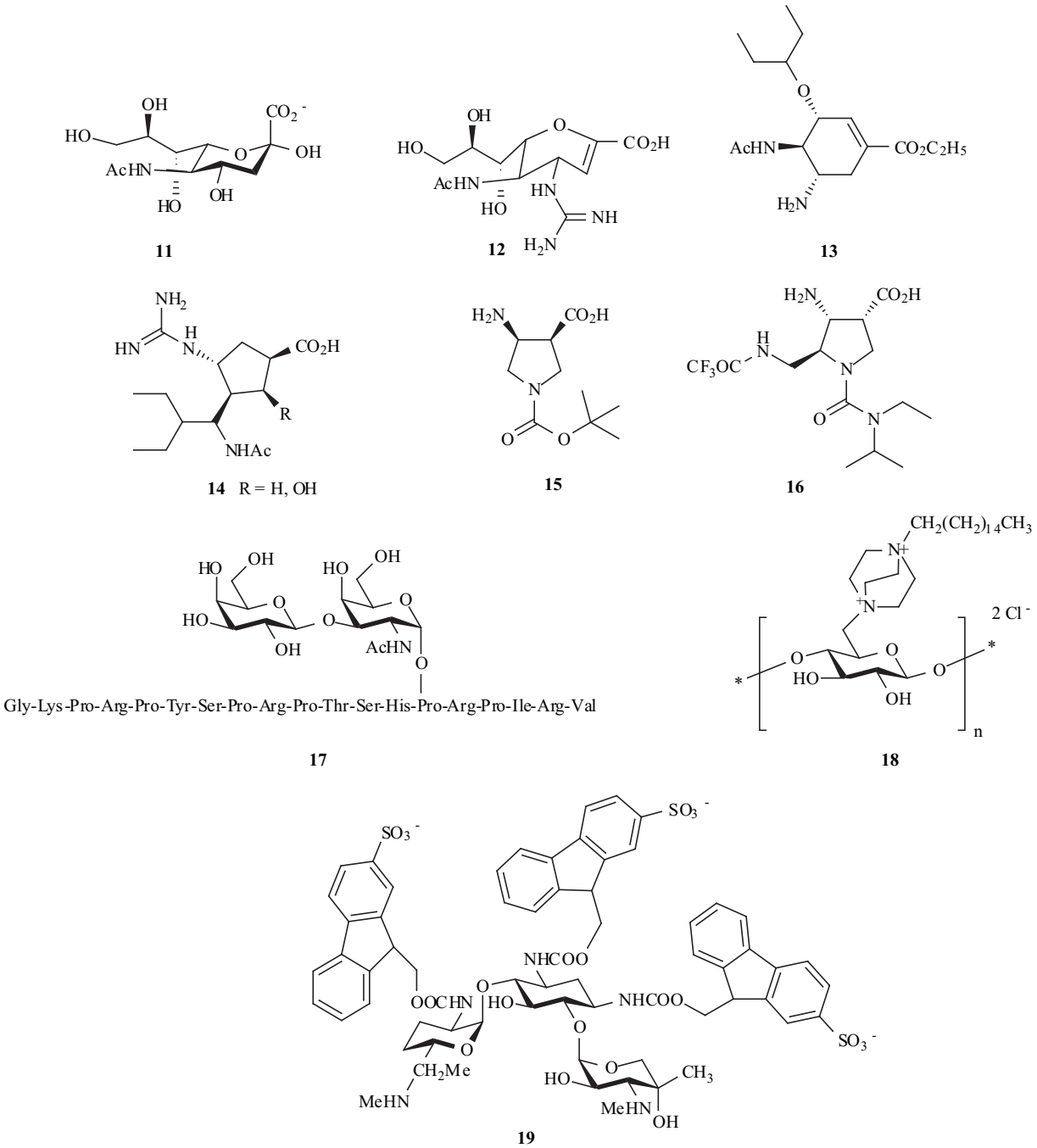


Fig. (4) .

nanomolar range against influenza neuraminidase. These orally active compounds [20] are now in clinical trials phase III. A different approach was taken by Wang [21], who identified *cis*-*N*-Boc-3-aminopyrrolidine-4-carboxylic acid (**15**) (Fig. **4**) as a neuraminidase inhibitor with an IC_{50} value of 50 μM. Employing a combination of structure based drug design and combinatorial chemistry, they synthesised a series of compounds of which (**16**) (Fig. **4**) was the most active representing a 250-fold improvement in terms of activity against neuraminidase A exhibiting an IC_{50} of 0.28 μM.

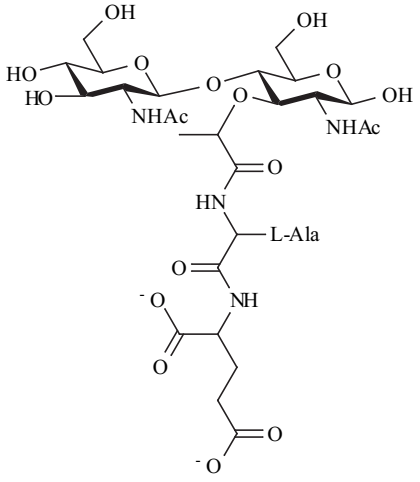
ANTIBACTERIAL SUGAR CONTAINING AGENTS

Insects show remarkable resistance against bacterial infection due to their ability to synthesize small-sized cationic antibacterial peptides. These are proline rich and glycosylated at one, two or three glycan moieties on conserved threonine residues such as drosocin (**17**) (Fig. **5**), formeacins, diptericin and lebocins. The significance of the carbohydrate moiety is still unknown, and only hypotheses can be made, but is has been shown that deglycosylation significantly reduces antimicrobial activity. Such glycosylated peptides are the target for the search of novel antibacterial agents. However, the lack of *in vivo* activity was attributed to the high degradation rate of the peptide in mouse serum in contrast to the considerable stability in insect hemolymph. In an attempt to improve the features of compound (**17**), structure-activity relationship studies were undertaken [22] to make it a suitable drug by testing different glycosylated peptide analogues of (**17**). It could be shown that the antimicrobial activity against several gram-negative bacteria is affected by the shape of sugar and the type of the glycosidic linkage.

It has also been recognized that cationic surfactants in combination with a significantly lipophilic component bear antibacterial activity. The mechanism of action of such compounds on bacteria is understood to be one of electrostatic interaction and physical disruption, rather than interference with a metabolic pathway. The cationic site of the agent is able to bind to anionic sites of the cell-wall surface whereas the lipophilic part is able to diffuse through the cell wall and bind to the membrane. As a surfactant it is able to disrupt the membrane and nucleic material, leading to cell death. Polyammonium units having lipohilic adjuncts were attached to carbohydrates leading to structures such as (**18**) (Fig. **5**). Several bacterial strains, gram-negative as well as gram-positive, were investigated in continued growth experiments. It could be shown that broad activity can be imparted to those carbohydrate surfaces, such as cotton cloth, through the covalent attachment of cationic agents with lipohilic adjuncts. Maximal antibacterial activity is observed towards both gram-negative and gram-positive bacteria with a chain length of 16 carbon atoms in the lipophilic moiety [23].

Most low-molecular-weight drugs are short lived species in the circulatory system, being rapidly eliminated by glomerular filtration in the kidneys. However, binding to human serum albumin (HAS) can slow down clearance and prolong life time *in vivo*. This approach was introduced on peptide and protein drugs such as insulin and interferon α2 employing 2-sulfo-9-fluorenylmethoxycarbonyl moieties because of its affinity to HAS [24]. Gentamicin, an example of such low-molecular-weight class of compounds used for treatment of many serious gram-negative bacterial infections, was also investigated in this manner. It could be shown that introduction of two to three 2-sulfo-9-fluorenylmethoxy-carbonyl units to gentamicin lead to structures such as *N*-[(2-sulfo)-9-fluorenylmethoxycarbonyl]$_3$-gentamicin C_1 (**19**) (Fig. **5**) which showed sufficient affinity to HAS and, consequently, a significant life time extension in situ could be observed [25].

In gram-negative bacteria, the outer membrane, the cytosolic membrane as well as the murein (peptidoglycan) layer are simultaneously involved in cell division. Lytic transglycosylases catalyze the cleavage of the β-1,4-glycosidic bond between *N*-acetylmuramic acid and D-acetylglucosamine residues in peptidoglycans such as **20** (Fig. **5**) [26]. Consequently, these bacterial enzymes play a role in peptidoglycan metabolism. Because such peptidoglycans are unique to and essential for bacteria, lytic transglycosylases (LT) may be effective targets for drug design [27]. Bulgecins, such as (**21**) (Fig. **5**) [28] are a family of antibiotics inhibiting this bacteria-specific enzyme



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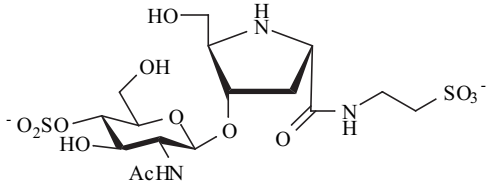

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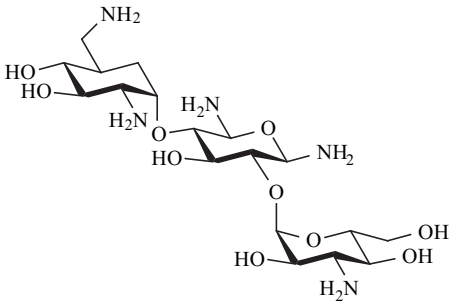
Fig. (5).



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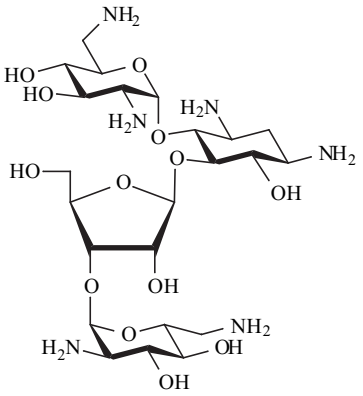

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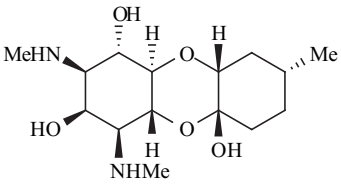

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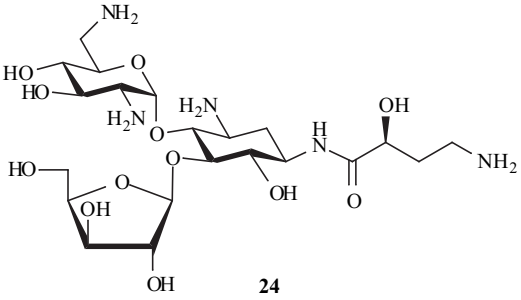

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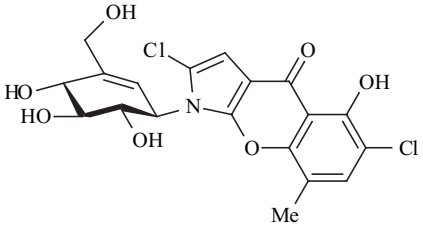
Fig. (6).

acting on murein. Interestingly, an X-ray crystallographic study of the structure of LT has recently become available [29]. It could be demonstrated to closely resemble the structure of lysozymes [30]. Remarkably, in this context, no significant sequence homology of amino acid residues could be detected. This successful structure elucidation should allow the design of non-natural specific inhibitors of this enzymes on the basis of the structural information known from available bulgecins (**21**).

ANTIBIOTICS

Aminoglycosides, a family of polycationic pseudo-oligosaccharides, have been shown to be one of the clinically most important groups of antibiotics for a long time. Classification of aminoglycoside antibiotics can be made into two groups based on their chemical structures. One has, as aglycon, a substituted aminocyclitol, whereby streptomycin, fortimicin and spectinomycin (**25**) (Fig. **6**) are the best investigated structures in this group [31]. The other group has as common aglycon 2-deoxystreptamine (DOS) and numerous important compounds are in this category such as neomycin (**23**), kanamycin (**22**), ribostamycin, butirosin (**24**) (Fig. **6**), gentamicin, tobramycin and sisomicin. They are employed to combat gram-negative bacterial infections because of their ability to interfere with protein translation in prokaryotes as a consequence of binding to the A-site decoding region of rRNA [32]. This mechanism was recently investigated employing a fluorescent A site rRNA model [33]. The possible binding of such structures to tRNA [34] and their interaction with DNA triple helix strains [35] could lead to the development of new treatments. This is necessary because the emergence antibiotic resistance. This has become a serious problem in the treatment of bacterial infections [36] because bacteria have often acquired the ability to modify the structures of the drugs in a manner that renders them ineffective as therapeutic agents [37].

A few years ago, pseudo-aminosugars such as pyralomicins and valienamine as well as validamine [38] were found as novel structural types of antibiotics also exhibiting antitumour activities. Pyralomicins such as (**26**)



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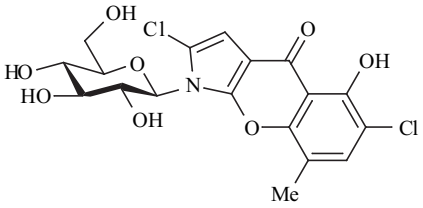

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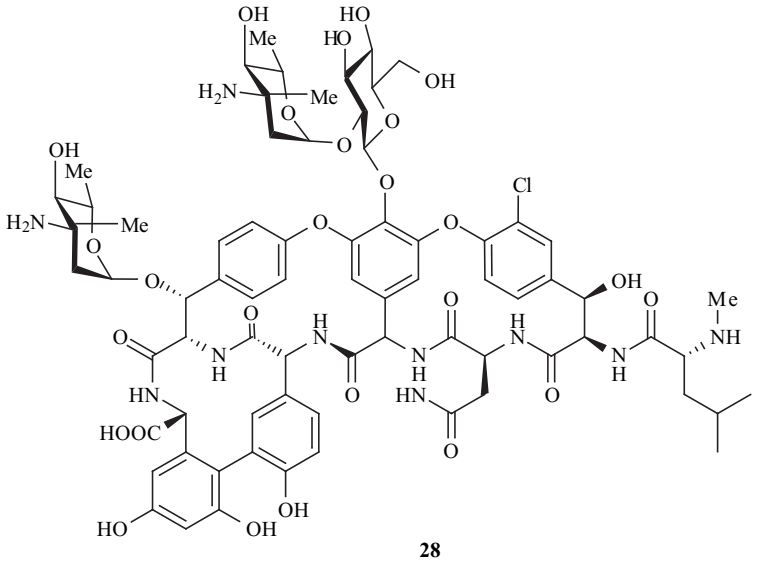
Fig. (7).

and (**27**) (Fig. **7**) were found in the culture broth of *Microtetraspora spiralis* [39], its biosynthesis was elucidated [40] and a total synthesis has been published [41].

Glycopeptide antibiotics are another important group of compounds displaying high activities against gram-positive bacteria including pathogens resistant to β-lactams, tetracyclines, and fluoroquinolones. The antibacterial activity of natural glycopeptide antibiotics is based on their ability to bind peptidoglycan precursors terminating in the sequence D-Ala-D-Ala [42]. In the past decade the use of glycopeptide antibiotics such as vancomycin and teicoplanin in clinical practice and usage of avoparcin in agriculture has given rise to bacterial strains resistant to these antibiotics by replacing the terminal D-Ala unit with D-lactate, leading to a 1000-fold decrease in affinity of glycopeptides to its target [43]. Thus, the design of new semisynthetic glycopeptides that would be especially active against vancomycin-resistant enterococci was necessary. Eremomycin (**28**) (Fig. **8**) is related to vancomycin, but has several different structural features and consequently the biological properties are different. It is several times more active than vancomycin and even exhibits a different mechanism of inhibition. It does not bind to the D-Ala-D-Ala cell wall intermediates but inhibits the transglycosylase catalysed step of peptidoglycan bio-synthesis [44]. Several differently substituted eremomycin structures such as (**29**) (Fig. **8**) were synthesised and their antibacterial activities investigated against several strains of bacteria [45].

Süssmuth and co-workers presented the first *in vivo* modified glycopeptides with non-natural fluorine substituents such as fluorobalhimycin. They exploited mutagenesis for creating a set of new glycopeptide antibiotic building blocks with a perspective towards antimicrobial activity including vancomycin-resistant organisms [46].

Yet another candidate for treatment of antibiotic-resistant gram-positive infections is ramoplanin (**30**) (Fig. **9**) [47], a lipoglycodepsipeptide antibiotic, which is more active than



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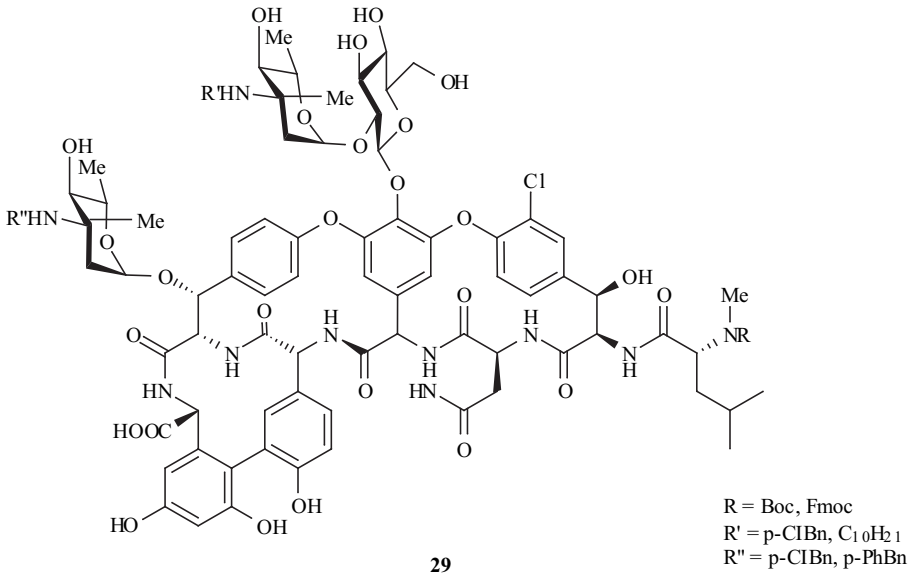

R = Boc, Fmoc
R' = p-ClBn, $C_{10}H_{21}$
R" = p-ClBn, p-PhBn

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Fig. (8).

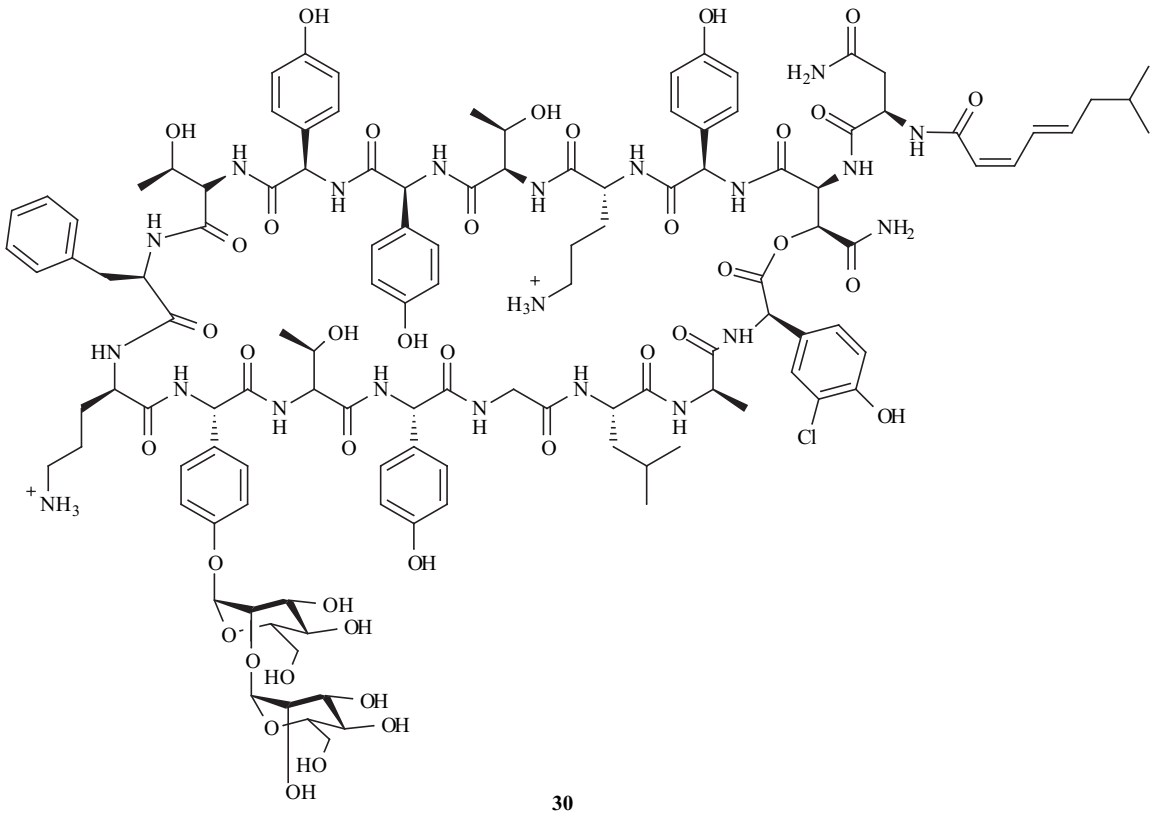

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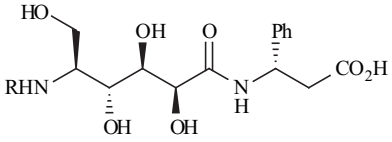
Fig. (9).

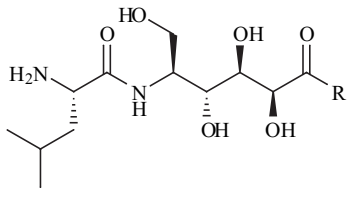
vancomycin. No cases of clinical or laboratory-generated resistance have been reported thus far to date. Currently in phase III clinical trials, (**30**) does not target an enzyme directly, but rather sequesters the substrates of peptidoglycan biosynthesis enzymes. As a result, bacteria produce a weaker cell wall [48]. Due to its complex structure attempts have been made to reduce its structure to the minimum bioactive pharmacophore [49].

A different type of antibiotic was found by Hasuokaand and his group in 2001, who isolated pyloricidin A (**31**), B (**32**) as well as C (**33**) (Fig. **10**) from the fermentation broth of a *Bacillus* sp. These compounds have a new structural feature, (2S,3R,4R,5S)-5-amino-2,3,4,6-tetrahydroxyhexanoic acid, in addition to several amino acids [50]. They were found to have potent and highly selective anti-*Helicobacter pylori* activity [51]. *H. pylori* is a gram-negative bacterium which causes gastric as well as duodenal ulcers, and its association with gastric cancer has been recently revealed. Consequently, several derivatives of pyloricidin such as (**34**) (Fig. **10**) were synthesized and tested on their biological activity, some of them showing promising results [52].

Macrolide antibiotics such as erythromycin A (**35**) (Fig. **11**) have been used excessively in the last 45 years and are considered for the treatment of upper and lower tract infections. However they lose their antibacterial activity very easily under acidic conditions due to degradation [53]. Derivatives such as clarithromycin and azithromycin were widely prescribed due to their efficacy and lack of side effects. However, this has also caused rapid increase of resistant strains. Consequently, a group of so called "next generation" macrolide antibiotics was created and showed good antibacterial activities against gram-positive pathogens including macrolide-lincosamides-streptogramin-resistant strains, compound (**36**) (Fig. **11**) showing the best activity in a series of derivatives [54].

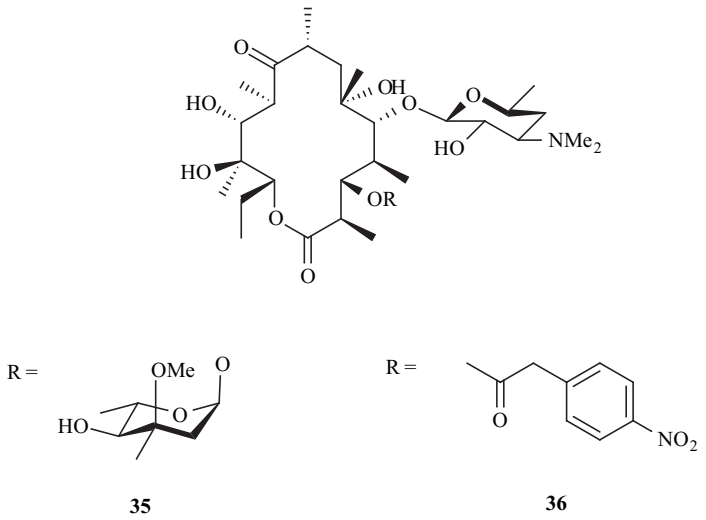


31 R = L-Val-L-Val-L-Leu A
32 R = L-Val-L-Leu B
33 R = L-Leu C



34 R = Gly-OH, β-Ala-OH, $_{DL}$-Phg-OH, D-Phe-OH, β-D-Phe(4-Me)-OH, β-L-Phe-OH

Fig. (10).

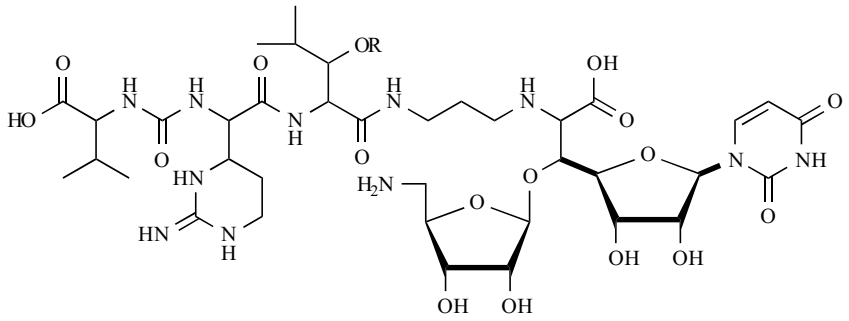


35 **36**

Fig. (11).

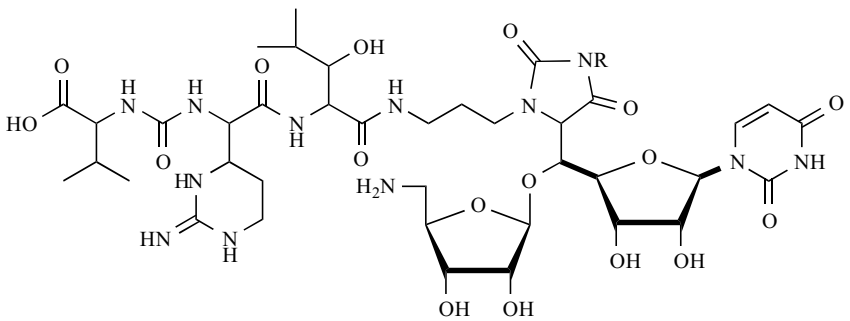
Since peptidoglycans are essential bacterial cell wall polymers, their biosynthesis provides an excellent target for antibiotic action. MraY, an enzyme located in the membrane, was thought to be such a good drug target. Thus, muraymycins A1 (**37**) and C1 (**38**) (Fig. **12**) were found to be very good inhibitors of this enzyme, and of gram-positive bacteria *in vitro* as well as *in vivo*. To improve the activity and decrease the toxicity of these compounds, many derivatives such as (**39**) as well as (**40**) (Fig. **12**) were synthesized, some of them showing as good activities, comparable to muraymycin C1 [55].

Calicheamicin (**41**) (Fig. **13**) is one of the secondary metabolites of the enediyne family, a class of naturally occurring antitumour antibiotics that include neocarzinostatin, esperamicin, dynemicin and kedarcidin. Results of *in vitro* experiments suggest that these compounds elicit their effects by promoting DNA strand scission through their sequence selectivity and in their ability to invoke either single- or double-strand breaks. Calicheamicin is one of the most sequence selective of this class and has a strong preference reported for TCCT and poly-A/T sequence [56] (in naked DNA).



37 R = $COC_{11}H_{22}N(OH)C(NH_2)=NH$
38 R = H

muraymycin Al
muraymycin Cl



39 R = $C_{12}H_{25}$
40 R = $PhCH_2$

Fig. (12).

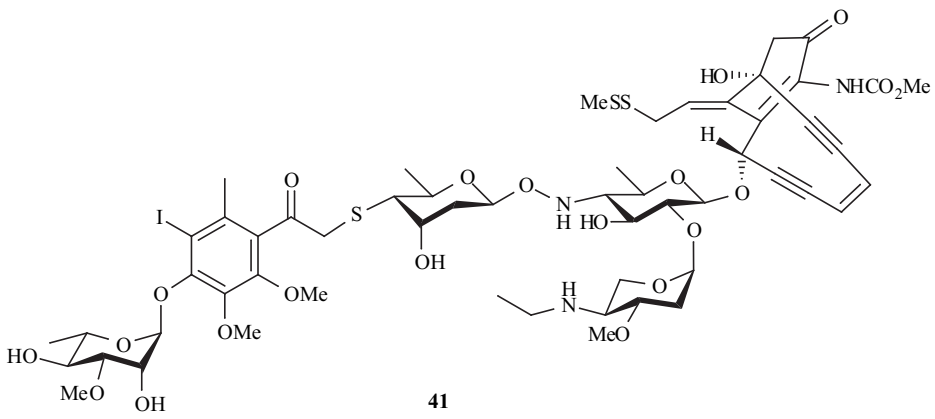


Fig. (13).

SUGAR CONTAINING COMPOUNDS EXHIBITING ANTIVIRAL ACTIVITIES

For decades, nucleosides have been traditional antiviral agents due to the fact that most small molecule-type targets are enzymes such as proteases, polymerases and neuraminidase these requiring nucleosides as their donor compounds. As mentioned above, the pro-drug concept gained more and more importance during the past years. One approach to this concept employing nucleosides as active structures is to synthesize the corresponding monophosphates of a known active structure. This permits the kinase activation step to be avoided, because nucleoside kinases are often the rate-limiting step in the activation of nucleoside analogues used in the treatment of cancer [57]. Secrist and co-workers synthesized the derivatives of the pro-drug (**43**) (Fig. **14**) from known weakly cytotoxic versions of compound (**42**) (Fig. **14**) and could successfully show the viability of this approach [58].

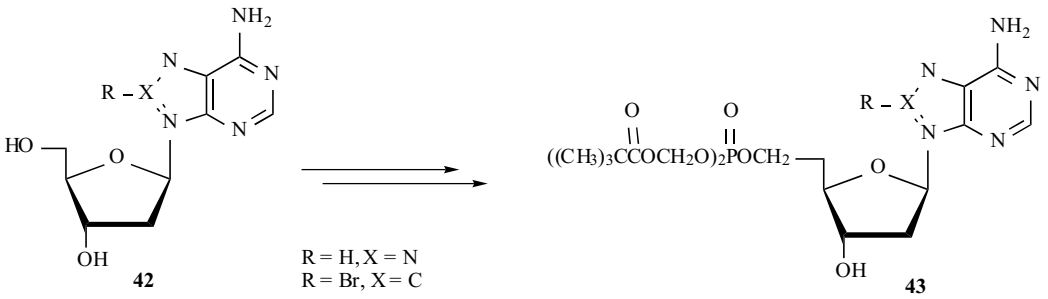


Fig. (14)

The same concept but a different approach was published by Borch and his group, who synthesized the corresponding

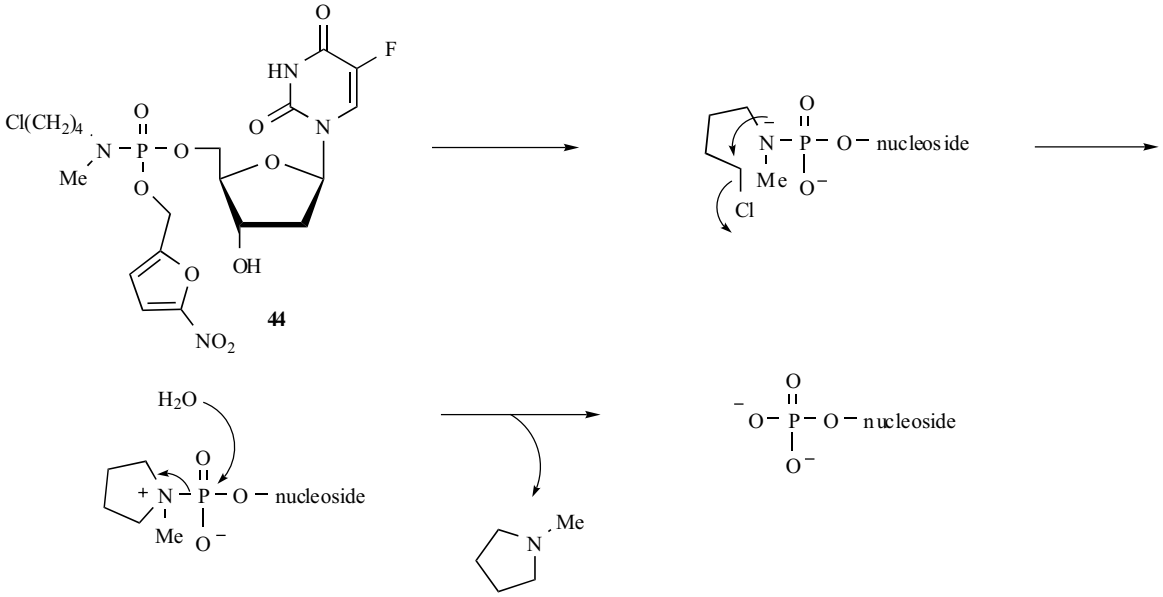


Fig. (15).

phosphoramidate compounds of known active nucleosides. Pro-drugs such as structure (**44**) (Fig. **15**) contain an ester group that undergoes intracellular activation liberating phosphoramidate anion, which undergoes spontaneous cyclisation and P-N bond cleavage to yield the nucleoside monophosphate quantitatively (Fig. **15**) [59].

Other attractive targets are *S*-adenosylhomocystein hydrolase inhibitors because of their important role in viral replication. Structures such as fluoroneplanocins (**45**) (Fig. **16**) [60] and 5`-*S*-propynyl-5'-thioadenosine (**46**) (Fig. **16**) [61] were found to be irreversible inhibitors active in this manner.

Hepatitis B virus (HBV), an incomplete double-stranded DNA virus, is a causative agent of acute and chronic hepatitis and is the world's ninth-most leading cause of death. Chronic HBV infection leads to liver damage, cirrhosis and heptatocellular carcinoma. New infection can be prevented by vaccination, but this is not effective for chronic carriers. Antiviral therapy can help to clear the virus load in body fluids of infected people and reduces the risk of viral transmission to other. DNA replication includes reverse transcriptase, which is quite different from human DNA polymerase and is therefore a target for nucleoside type inhibitors. Open chain acyclic sugar moieties were found to be promising nucleoside analogue chemotherapeutics [62]. Kumar and his group found a series of such compounds such as 5-substitued acyclic pyrimidine nucleosides (**47**), (**48**) as well as (**49**) (Fig. **16**) showing potent and selective anti DHBV (duck hepatitis B virus, closely related to human HBV) activity [63].

Jeong and co-workers synthesized a different class of compounds, namely dideoxyisonucleosides, which feature an exocyclic methylene group. This idea was based on the finding that compound (**50**) (Fig. **16**) showed very good activity against HBV, this compound being hundred times more potent than clinically available lamivudine (**52**) (Fig. **16**) [64]. Several D- and L-nuleosides were synthesized and compounds (**51**) (Fig. **16**) showed an EC_{50} value of 1.5 μM against HBV (lamivudine exhibits an EC_{50} of 0.05 μM) [65].

Thionucleosides, having sulphur instead of an oxygen in the ring, have been known as antiviral agents for more than 10 years [66]. To this end, 2'-deoxy-2`-fluoro-4`-thioarabinofuranosylpyrimidine and –purine nucleosides were found to have potent and selective antiherpes simplex virus HSV–1 and HSV–2 activities. Some of these compounds such as 2'-deoxy-2'-fluoro-4'-thioarabinofuranosylpyrimidine (**53**) (Fig. **16**) even show antitumor properties against both leucemia and solid tumours [67].

Another nucleoside-based class of substances was investigated by Sartorelli's group who synthesized D- and L-configurated 1,3-dioxolane-5-azacytosin and -6-azathymine

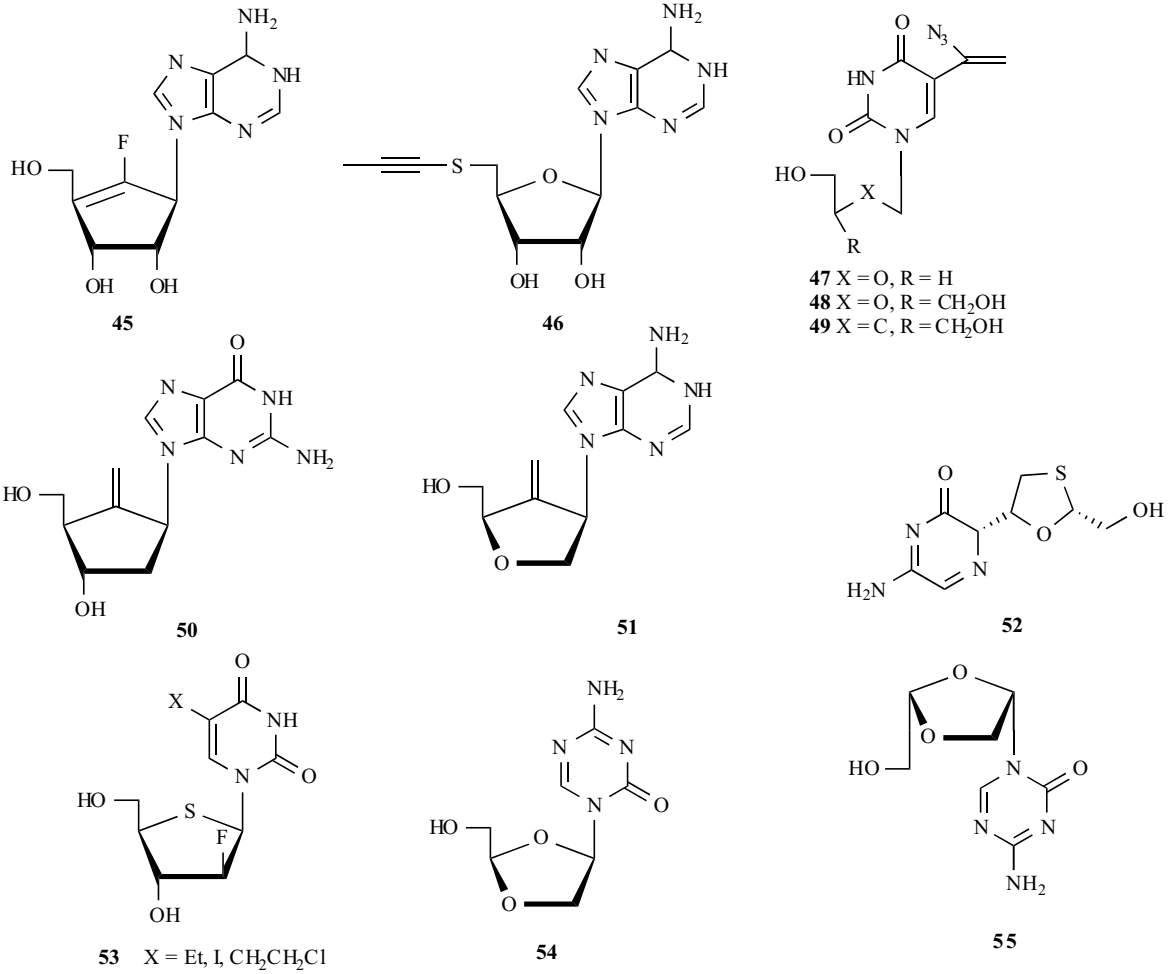
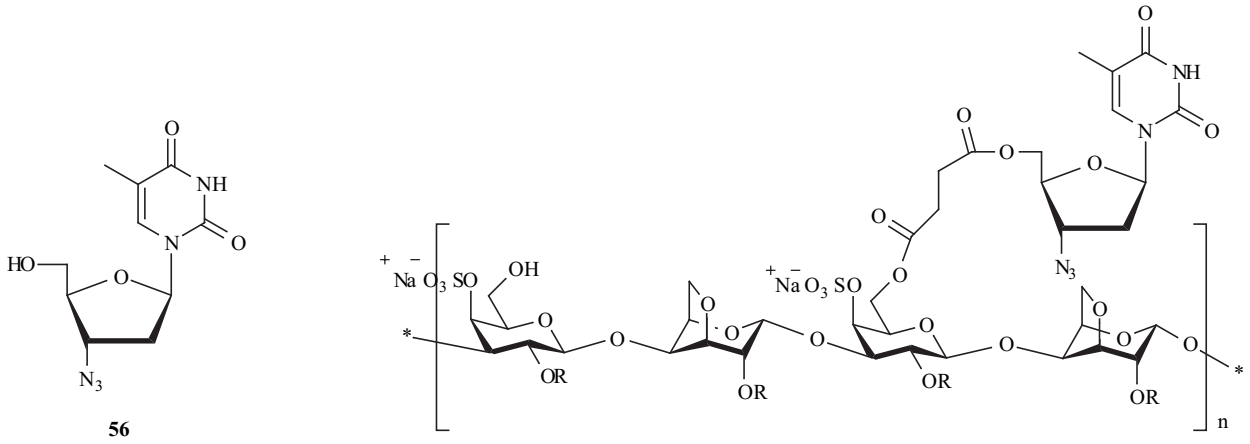


Fig. (16).



56

57 R = 5'-*O*-(succinate)

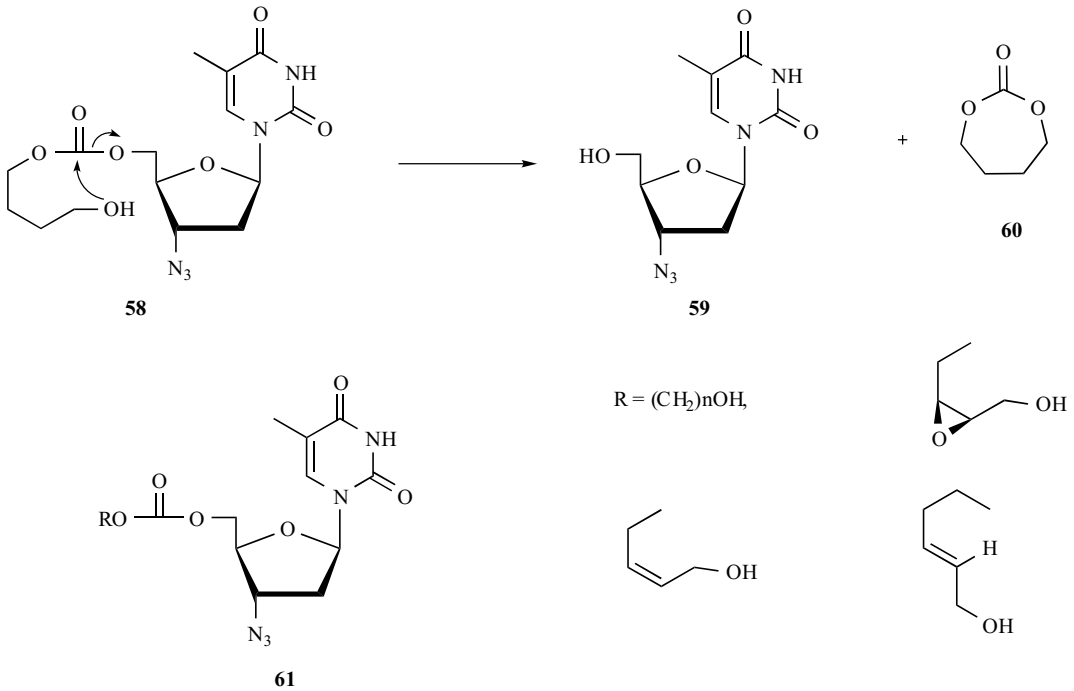
Fig. (17).

derivatives and screened them for activity against HIV and HBV. Interestingly, L-configurated 1,3-dioxolane 5-azacytosin (**55**) (Fig. **16**) showed significant activity against HBV, whereas the D-configured analogue (**54**) (Fig. **16**) was found to exhibit potent anti-HIV activity [68].

Human immunodeficiency virus (HIV), the ethiological agent of the acquired immunodeficiency syndrome (AIDS), is one of the prominent targets in drug development worldwide. The search for an effective chemotherapeutic treatment against HIV infection has led to compounds that target specific and critical events in the HIV replicate cycle. The most extensively studied compound is 3'-azido-3'deoxy-thymidine (**56**) (Fig. **17**) [69] (AZT, zidovudine, retrovir) and was also the first agent which was approved by the Food and Drug Administration for the treatment of AIDS [70]. The major limitations of AZT are clinical toxicities, a short half-time in plasma, high susceptibility to catabolism and to the development of AZT resistance by HIV. In attempts to overcome these problems many different derivatives of AZT have been synthesized during the last years, the most recent are listed below.

Kraus and his group synthesised a covalently bound κ-carrageenan-AZT conjugate. The κ-carrageenan is expected to act not only as drug carrier, but also as an anti-HIV agent by itself, which could act synergistically with AZT. The effect of pre treatment of MT-4 cells with κ-carrageenan-succinate diester-AZT conjugate (**57**) (Fig. **17**) was found to be four times more potent (EC_{50} 6.8 nM) than AZT itself (EC_{50} 25 nM) [71].

The same group also developed a pro-drug system when they synthesized 5'-yl-*O*-(hydroxyalkyl), –alkenyl and –alkylepoxide carbonate derivatives such as 3'-azido-3'-deoxythymidin-5'-yl-O-(4-hydroxybutyl) carbonate (**58**) (Fig. **18**) of AZT. The mechanism of release of the active component (**59**) (Fig. **18**) was shown to be the same for all derivatives, depending on the thermodynamic stability of the



58 **59** **60**

61

Fig. (18).

released component **60** and, therefore, dependent on the substituent. Especially derivatives 3`-azido-3'-deoxythymidine-5'-yl-O-hydroxyalkyl, -alkenyl, and –alkylepoxide carbonate (**61**) (Fig. **18**), carrying different substituents on the carbonate, turned out to be a good example in this series, being twice as active on HIV-1 (III)B replication as AZT (EC_{50} 6 and 12 nM respectively). All compounds showed reduced cytotoxicity as compared to AZT (four to six times) [72].

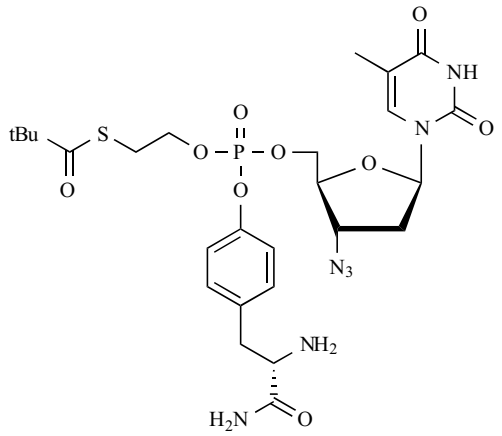
Mixed phosphotriester derivatives of AZT tethering polar but not anionic residues were synthesized by Perigaud in order to study the influence regarding anti-HIV activities, kinetic decomposition parameters, and lipophilicity. It could be shown that these compounds are releasing the 5'-monophosphoester of AZT inside infected cells and they displayed activity against HIV-1 which was comparable to that of AZT [73]. *O*-[L-Tyrosinamide]yl-*O*-(*S*-pivaloyl-2-thioethyl)-3'-azido-3'-deoxythymidine-5'-yl phosphate (**62**) (Fig. **19**) turned out to be the most active in this series.

Recently, highly active anti-retroviral therapy, which involves a combination of HIV protease (HIV PR) and reverse transcriptase (RT) inhibitors, has become the clinical practice for the treatment of AIDS or HIV infections [74]. A different approach was investigated by Kiso and co-workers, when they designed an inhibitor which inhibits both enzymes. This hybrid-type pro-drug contains both the RT inhibitor AZT (**56**) (Fig. **17**) as well as the HIV PR inhibitor, usually a dipeptide HIV PR inhibitor, in one conjugate such as structure (**63**) (Fig. **19**). The anti-HIV activities of these "double-drugs" were found to be more potent than those of AZT and the HIV PR inhibitor itself. For example, AZT conjugate **64** (Fig **19**)**,** in which AZT is linked to the dipeptide HIV PR inhibitor by a glutarylglycine, exhibited anti-HIV activity which was 920 and 62 times more potent than those of the parent compounds, respectively [75].

The same approach was persued by Tamaura and Fujii who synthesised conjugates of AZT (**56**) (Fig. **17**) with selected proteins, these containing up to 14 amino acids known to be HIV PR inhibitors [76].

A great variety of other nucleoside type structures were synthesized such as L- and D-2',3'-didehydro-2'-fluoro-4'-thionucleosides (**65**) and (**66**) (Fig. **20**) respectively [77], 2'-fluoro-2',3'-unsaturated D-nucleosides [78], [2',5'-bis-*O*-(tert-butyldimethylsilyl)-β-ribofuranosyl]-3'-spiro-5''-(4''-amino-1'',2''-oxathiole-2'',2''-dioxide) nucleosides (TSAO-T) such as (**67**) (Fig. **20**) and derivatives thereof [79]. Other recent examples include carbacyclic structures such as dinucleoside polyphosphonate (**68**) (Fig. **20**) [80] as well as D- and L-cyclopentenyl nucleosides such as (1'*R*,2'*S*,3'*R*)-1-[2,3-Dihydroxy-4-hydroxymethyl-4-cyclopenten-1-yl] nucleosides (**69**) (Fig. **20**) [81], 9-(3,5-Di-*O*-benzyl-2-deoxy-4-*C*-ethynyl-β-D-ribo-pentofuranosyl)adenine and –thymine (**70**) (Fig. **20**), this having pyrimidines and purines as the base component [82] as well as oligodeoxyribonucleotides (**71**) (Fig. **20**) [83]. All these examples showed potent anti-HIV activity.

Another class of carbohydrate based structures was synthesized by Samuelsson and co-worker who found that C_2-symmetric diols containing a 2,5-difluoro motif, such as structures (**72**) and (**73**) (Fig. **21**), showed very potent activity against HIV-1 protease [84].



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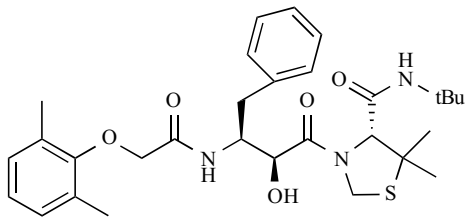

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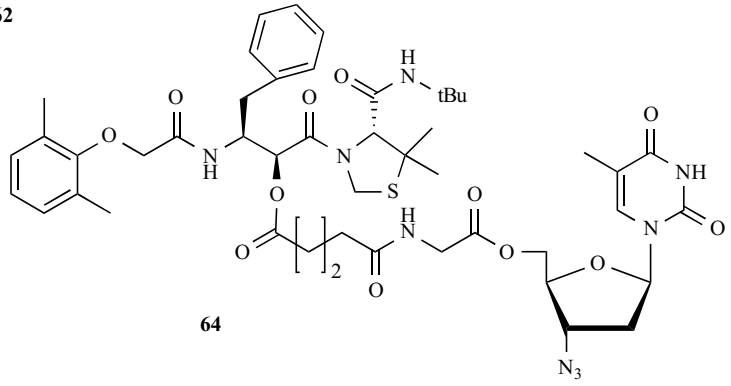

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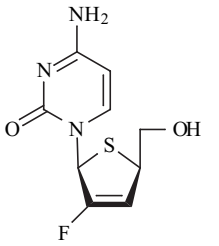
Fig. (19).



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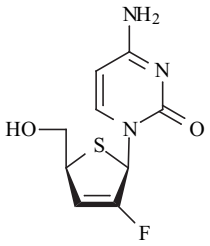

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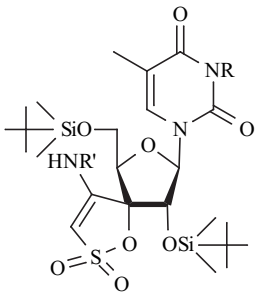
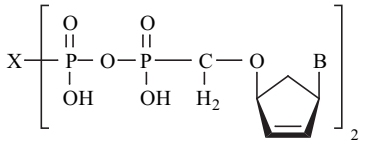
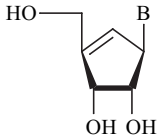


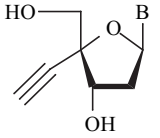
67 R = allyl, H, CH_2CONH_2
R = H, allyl, CH_2CONH_2



68 X = O, CF_2, CBr_2
B = Ade, Gua



69 B = Ade, Cyt,
5-F-Cyt, F-F-Ura



70 B = Ade, Thy

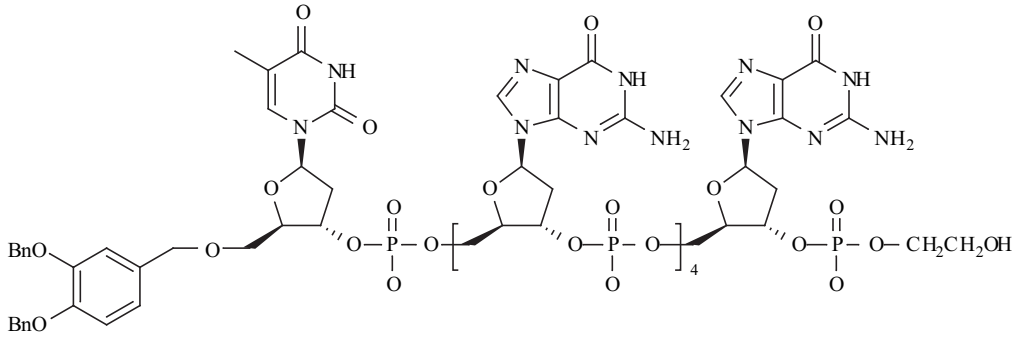


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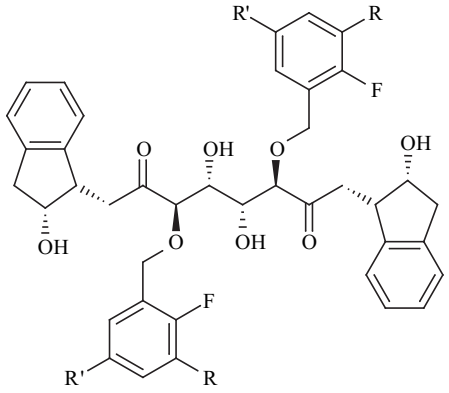
Fig. (20).



72 R = F, R' = H
73 R = H, R' = F

Fig. (21).

Vierling and his group investigated the anti-HIV properties of galactosylceramide (**74**) (Fig. **22**) and amphiphilic analogues thereof. Such compounds consist of single and double-chain amphiphiles containing one or two galactose residues as well as amino groups and anionic groups to favour their clustering into galactosyl-rich microdomains. Their anti-HIV activity is believed to rely on binding to HIV-1 gp 120 [85].

Non-natural glycosphingolipids carrying a biotin moiety were investigated with respect to their binding to HIV-1 recombinant gp120. These were shown to serve as recognition elements for rgp 120, although interactions turned out not to be highly specific [86].

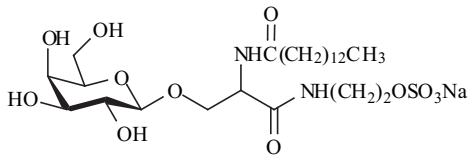


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Fig. (22).

SUGAR CONTAINING COMPOUNDS HAVING ANTICANCER ACTIVITIES

Tubercidine, 7-deaza-adenosine (**75**) (Fig. **23**) and related compounds thereof showed a mild effect on protein kinase A [87]. These enzymes, as mentioned before, are involved in the cyclic adenosine monophosphate dependent pathway, this being one of the major signal transduction pathways in mammalian cells. Recently, hydrophobic alkynyl residues were introduced into such structures leading to compounds such as (**76**) (Fig. **23**). These compounds activated protein kinase A in a concentration range of 0.1 – 10 μM, tubercidin

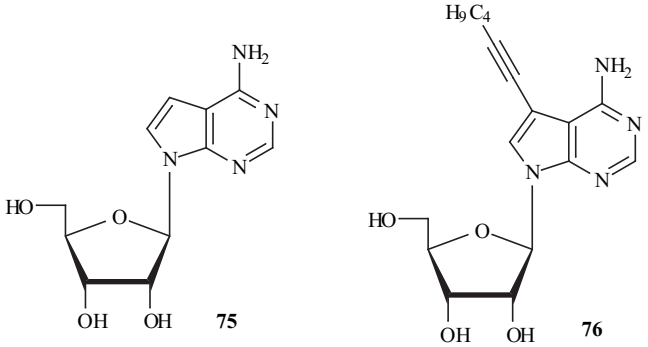


Fig. (23).

showed an IC_{50} of 20 to 100 μM, indicating that (**76**) is active but by a different mechanism [88].

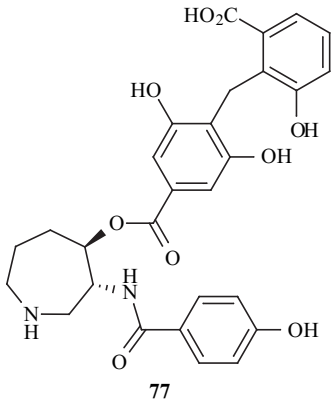


Fig. (24).

Protein kinase C (PKC) is another enzyme which plays important roles in cellular growth control, regulation and differentiation. It is a family of phospholipid-dependent serine/threonine specific protein kinases and its activation has been implicated in a number of diseases such as cancer, cardiovascular disorders, HIV, only to mention a few. Selective inhibitors of PKC isozymes might have wide ranging therapeutic potential [89]. The discovery of the PKC-inhibitory fungal metabolite balanol (**77**) (Fig. **24**) [90] provided a new motif to the PKC inhibitor area. The novelty of its structure as well as the possibility that it could be a new therapeutic agent has resulted in a great deal of efforts in terms of synthetic approaches to balanol and related structures as well as the investigation of their biological properties [91].

Inhibition of DNA biosynthesis has become a key objective in the design of anticancer chemotherapeutic agents. In this manner, inhibitors for the enzyme thymidylate synthase (TS), which is responsible for the endogenous production of thymidine 5'-monophosphate, have been developed. Amino acid phosphoramidate derivatives of antiviral and antitumour nucleosides have been demonstrated to be potential pro-drug systems because of easy P-N bond hydrolysis following intracellular activation to liberate the known nucleotide TS inhibitor, 5-fluoro-2'-deoxyuridine 5'-monophosphate. In this context, Borch and co-workers synthesized compounds bearing benzotriazolyl and nitrofuryl esters such as compound (**78**) (Fig. **25**) which showed potent inhibition of cell proliferation [92]. 1-(β-D-2-Deoxyribofuranosyl)-4-hydroxyaminopyrimidin-2(1H)-one

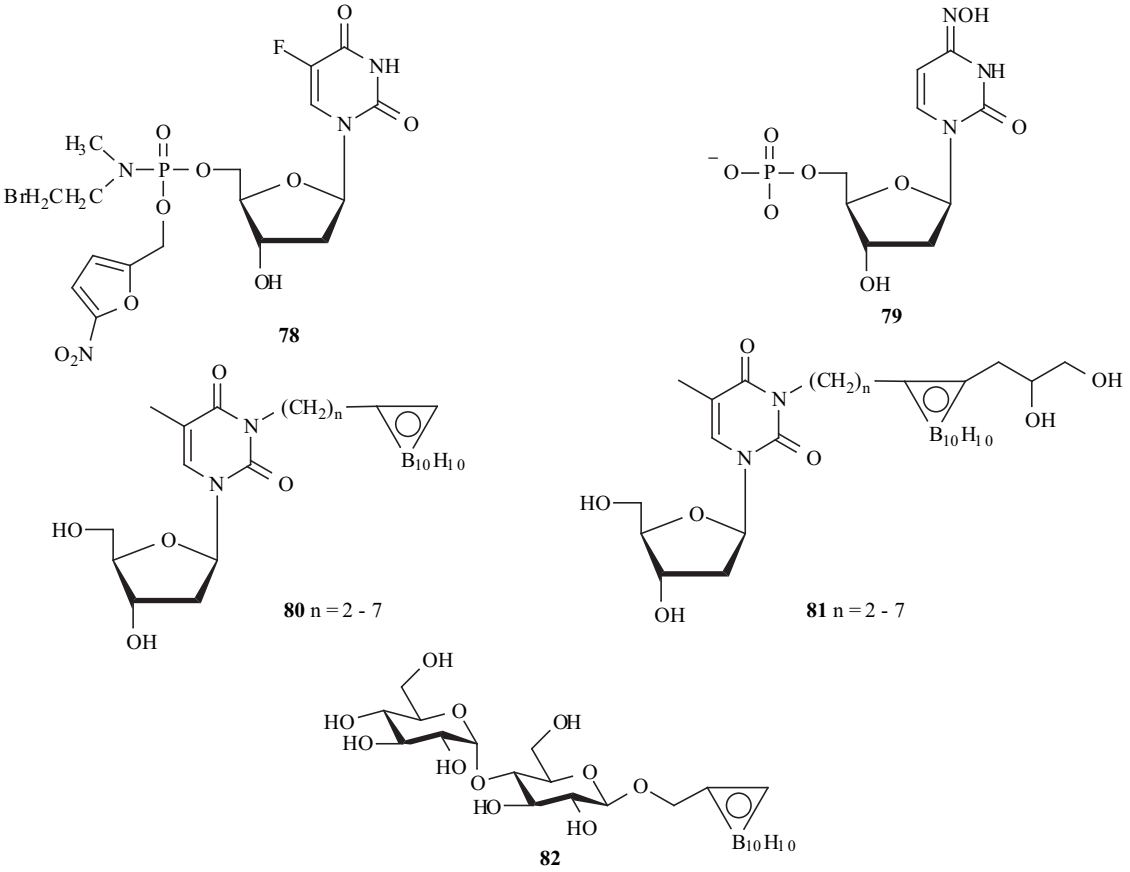


Fig. (25).

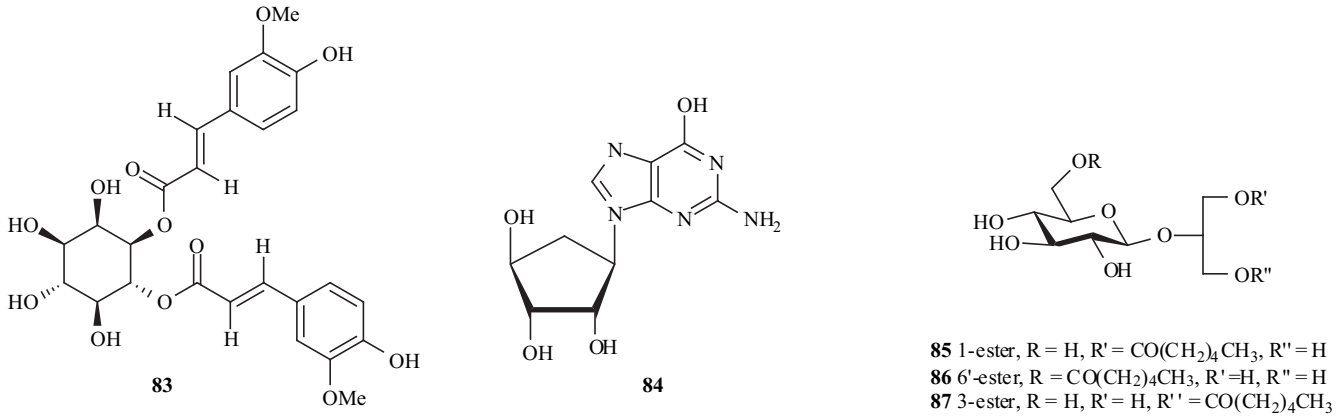


Fig. (26).

5'-monophosphate (**79**) (Fig. **26**) were also found to inhibit TS [93].

The boron neutron capture therapy (BNCT) for the treatment of cancer has gained intense interest during the last years [94]. This chemotherapy is based on the capture of thermal neutrons with nonradioactive ^{10}B to produce unstable ^{11}B by irradiation, which subsequently undergoes fission generating cytotoxic α-particles and lithium nuclei. These high linear energy transfer particles have a limited range in biological tissue ensuring that their destructive effects are restricted only to boron-containing cells in which the capture reaction occurs. In order for this therapy to be effective, ^{10}B has to be delivered selectively to the targeted tumour cells. It was found that boronated nucleosides are good candidates for BNCT because of their metabolic potential for incorporation into rapidly diving cells [95]. Different compounds such as (**80**) [96] and (**81**) (Fig. **25**) or ortho-carboranyl glycosides (**82**) (Fig. **25**) [97]**,** carrying a boron substituent, were found to act as suitable agents for this therapy.

In the search for cancer chemo preventive agents, the inhibitory effects on Epstein-Barr virus early antigen (EBV-EA) induction by the tumour promoter, 12-*O*-tetradecanoylphorbol-13-acetate (TPA), have been conducted as a primary screening test [98]. Results of studies on antitumour promoting activities of several natural products [99] using this *in vitro* assay have been in very good correlation with animal models.

Ferulic acid has attracted considerable attention in the field of chemotherapeutic study [100]. *Myo*-Inositol, on the other hand, plays an important role in biological systems, its exaphosphate is known to have anticancer action [101]. Taniguchi and his group could show that a combination of these two structures, feruloyl-*myo*-inositol derivatives show activity in this assay, compound **(83**) (Fig. **26**) being the most active one [102].

The antiviral properties of carbocyclic structures such as (**84**) (Fig. **26**), a derivative of 5'-noraristeromycin, on the EBV-EA was shown by Schneller [103].

A different substance class was found to be active in the EBV-EA assay by Colombo and co-workers. They investigated differently substituted glycosylglycerols and glycoglycerolipids, and found that the activity followed the

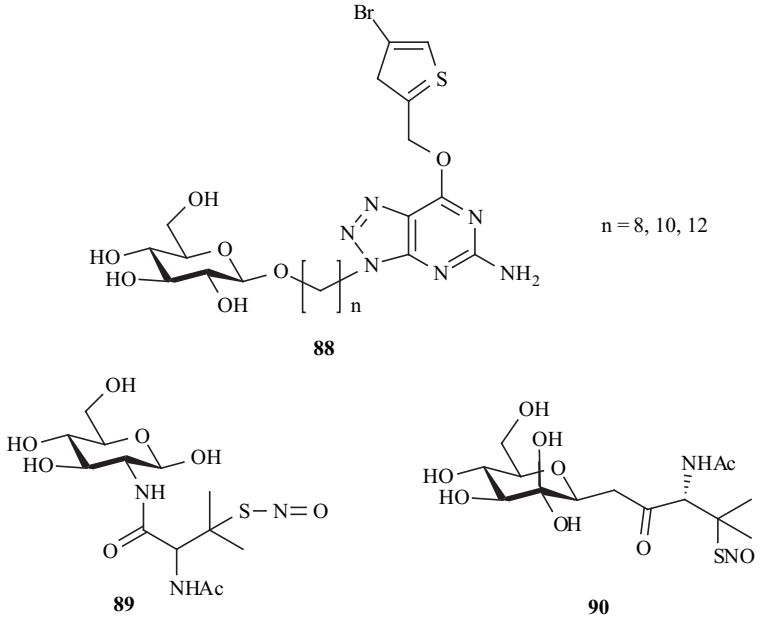


Fig. (27).

order: 1-esters (**85**) >6'esters (**86**) >3esters (**87**) (Fig. **26**) [104].

The human DNA repair protein *O*-6-methylguanine-DNA methyltransferase (MGMT) plays a critical role in cancer therapy with alkylating reagents. Among the resulting DNA adducts, *O*-6-alkylguanines are considered to be of major importance for the induction of cancer, mutation, and cell death. These adducts direct the incorporation of either thymine or cytosine without blocking DNA replication, resulting in GC to AT transition mutations. Although potent inhibitors of MGMT have been found and introduced into adjuvant therapy, they all have major disadvantages such as poor water solubility limiting their application, or short half life *in vivo*. Wiessler and his group consequently designed monosaccharide-linked inhibitors having a spacer between the purine *N*9 and β-D-glucose. The best inhibitors exhibiting the strongest protein-spacer interaction turned out to have a spacer length of 8 – 12 carbons such as compounds (**88**) (Fig. **27**) [105].

Several studies have shown that nitric oxide (NO)-releasing agents can kill tumour cells. Unfortunately, currently available NO delivery molecules do not target tumour cells preferentially. To exploit the over expression of glucose transport proteins and the high level of glucose transport characteristics of tumour cells, glucose as well as mannose were conjugated to *S*-nitro-*N*-acetyl-penicillamine (SNAP) which turned out to be much more stable than SNAP and exhibit much stronger effects in killing cancer cells [106]. 2-GluSNAP (**89**) (Fig. **27**) [107, for example, has been shown to be 5000-fold more potent than SNAP in killing human ovarian cancer cells. Man-1-SNAP (**90**) (Fig. **27**) [108] appears to be potent against cancer cells and it is believed that the potency of these compounds is correlated to both NO releasing efficacy and steric configuration, which may affect its interaction with sugar transport.

Sialyltransferase, a family of membrane bound enzymes located in the endoplasmatic reticulum and Golgi apparatus, catalyze the transfer of sialic acid to acceptor hydroxyl groups located on carbohydrate regions of glycoproteins and glycolipids [109]. Beside their biological role in cell adhesion and inflammation processes, different studies could show that there is a link between sialyltranferase activity and the growth of metastasis of certain tumour cells [110]. Many inhibitors of such enzymes have been synthesized, mainly sialic acid derivatives and their biological activities were investigated [111].

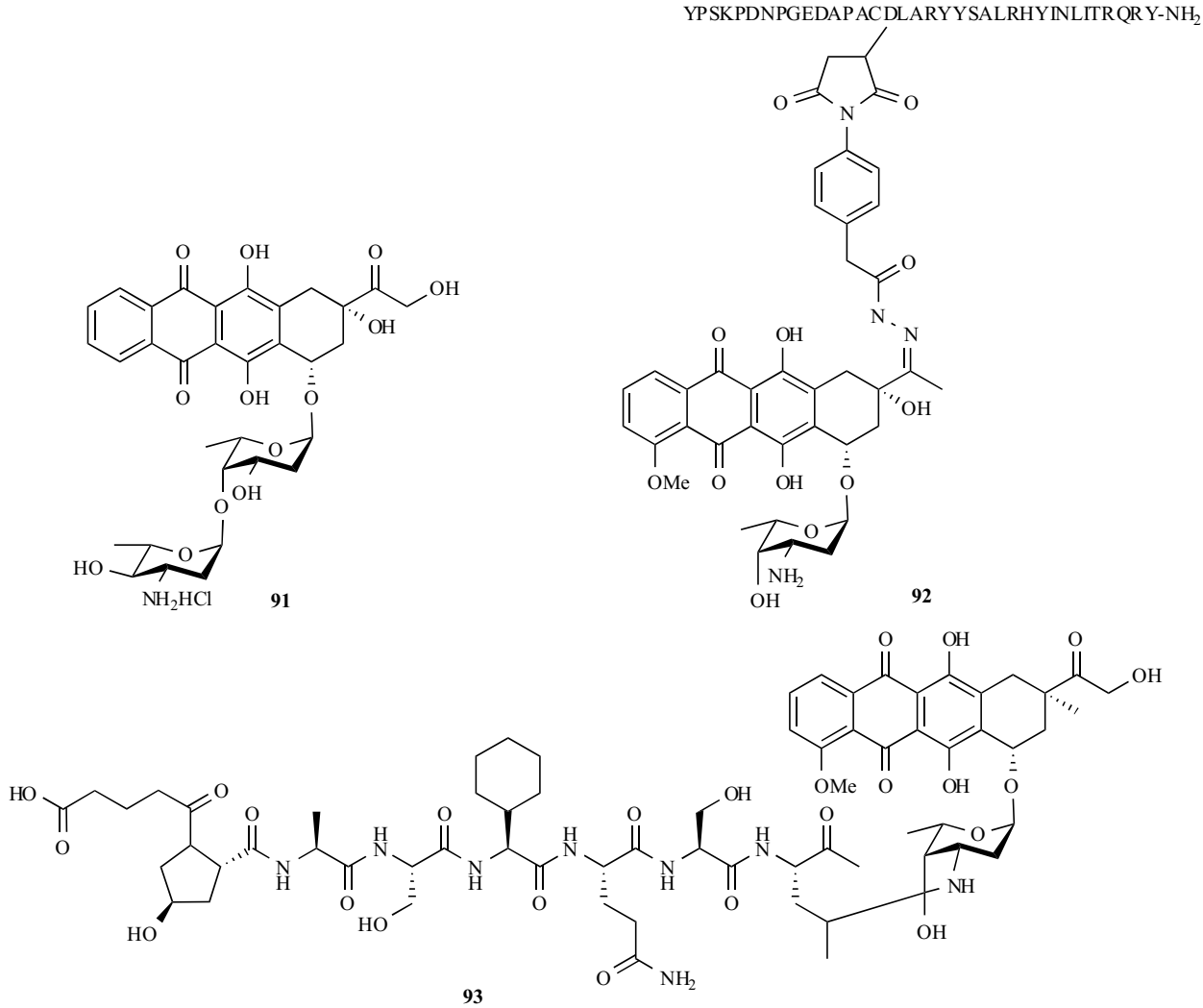
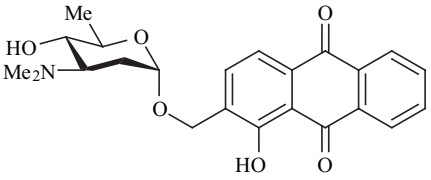


Fig. (28).



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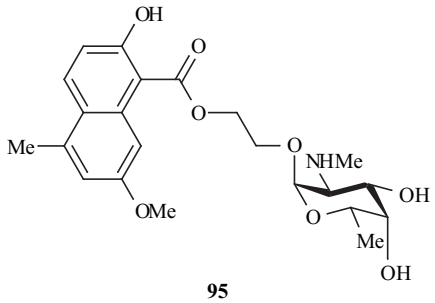


95

Fig. (29).

Anthracycline antibiotics are still amongst of the most useful drugs in cancer therapy because of their clinical efficacy against a broad spectrum of solid tumours and leukemias. Their interference with the catalytic cycle of the enzyme topoisomerase II is considered to be the main biological event responsible for the cytotoxic effect [112]. Moreover, experimental results demonstrate that chemical modification in the carbohydrate moiety of the molecule can determine changes in the drug preferred base sequence at the cleavage site [113]. Based on the known activity of daunomycin and doxorubicin [114], Cipollone and his group investigated novel oligosaccharide analogues thereof containing chemical and configurational modifications in the carbohydrate moiety. Disaccharidic compounds such as (**91**) (Fig. **28**) turned out to be as cytotoxic as the reference compound whereas the corresponding trisaccharide showed a lack of activity [115].

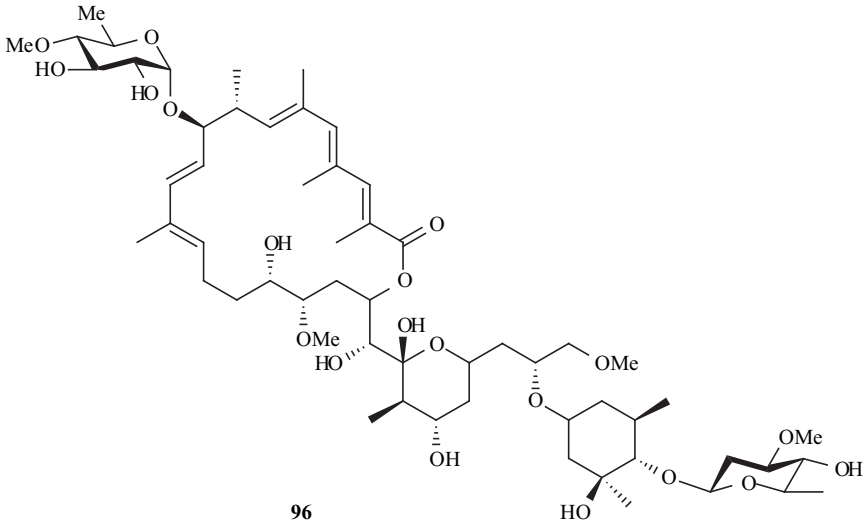
To increase the therapeutic index of daunomycin and doxorubicin, which have serious dose-based toxic side effects drug delivery systems were also designed. Beck-Sickinger and co-workers studied peptide carriers such as neuropeptide (**92**) (Fig. **28**), a 36-amino acid peptide, which are covalently linked to the drug. This structure containing an acid-sensitive bond showed cytotoxic activity comparable to free daunorubicin. It is believed that the conjugate releases the active agent within the cell [116].

Another pro-drug approach was presented by Garsky who synthesized peptide-doxorubicine conjugate (**93**) (Fig. **28**) which remained bioinactive whereas, converted by PSA, the active drug was set free at the place of action [117].

The same approach was investigated by Fernandez who found that the *N*-succinyl-(β-alanyl-L-leucyl-L-alanyl-L-leucyl)doxorubicin has an increased uptake in tumours then doxorubicin itself [118].

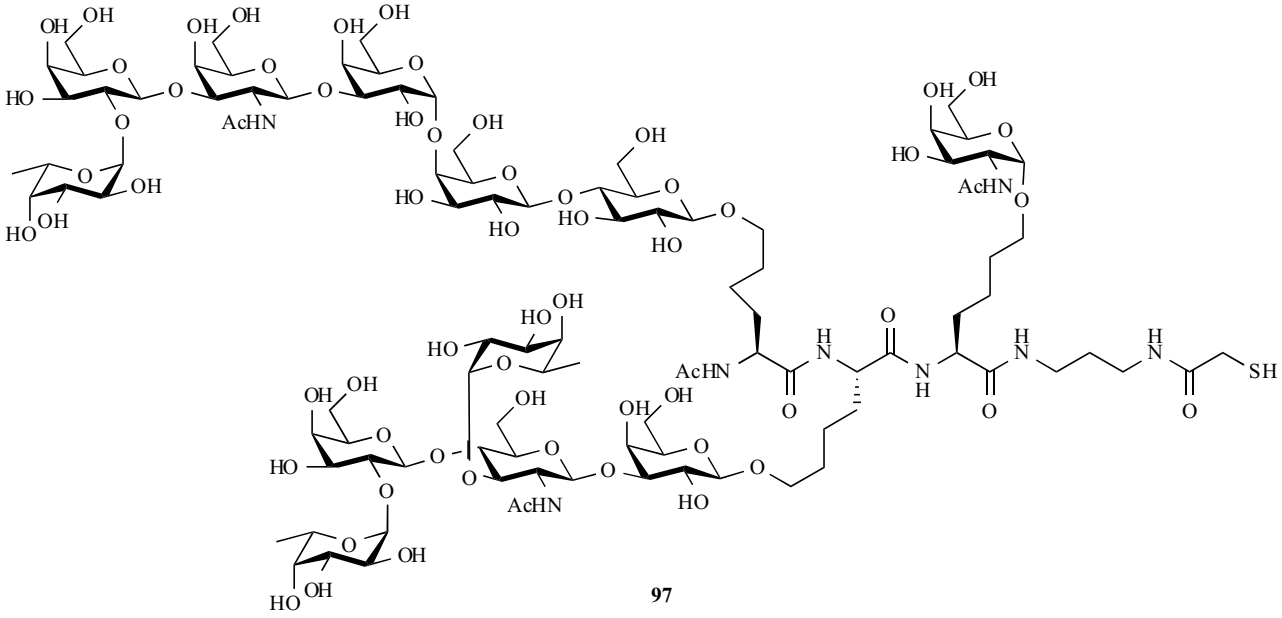
The development of photochemical DNA cleaving agents, which selectively cleave DNA by irradiation with a specific wave length under mild conditions an without any additives such as metals or reducing agents, offers considerable potential in medicine. Furthermore, photo-dynamic therapy using photosensitizing drugs has recently emerged as a promising modality against cancer and allied diseases. Recently, Toshima and his group showed two different compound groups to be suitable for this approach. Both intercalator-carbohydrate hybrids, anthraquinone-carbohydrate hybrids such as (**94**) (Fig. **29**) [119] as well as neocarzinostatin derivative (**95**) (Fig. **29**) [120], where the aromatic and sugar moiety were linked by only an ethylene glycol unit, showed DNA cleavage activity initiated by photoirradiation.

Apoptolidin (**96**) (Fig. **30**) was isolated by Seto and co-workers from *Nocardiopsis* sp. and was found to selectively induce apoptosis in cancer cells such as E1A and E1A/E1B19K [121]. This fucosylated macrolide became an exciting new lead for the treatment of cancer. The Khosla group recently identified mitochondrial F0F1-ATPase as a cellular target of apoptolidin and further demonstrated that



96

Fig. (30).



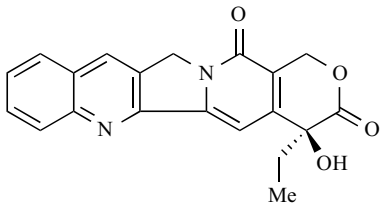
97

Fig. (31).

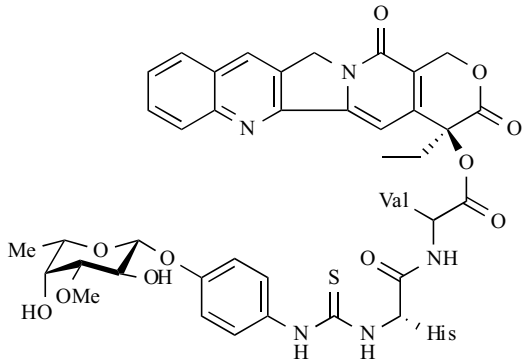
cell lines which were unresponsive to treatment with apoptolidin could be sensitized by co treatment with either oxamate or 2-deoxyglucose [122]. The biological importance of this complex compound made it popular for total synthesis [123].

Synthetic carbohydrate cancer vaccines have been shown to stimulate antibody-based immune response in both preclinical and clinical trials. The antibodies have been observed to react *in vitro* with the corresponding natural carbohydrate antigens expressed on the surface of tumour cells and are able to mediate complement-dependent and/or antibody-dependent cell mediated cytotoxicity. Furthermore, these vaccines have proven to be safe when administrated to cancer patients. Therefore, the syntheses of such glycosyl amino acids is of great interest and the results demonstrate that single vaccine constructs bearing several different carbohydrate antigens such as compound (**97**) (Fig. **31**), a carbohydrate-based antitumour vaccine containing Globo-H-, Tn- and Lewis Y-antigen, have the potential to stimulate a multifaceted immune response [124].

A different approach to antitumour vaccines was made by Nicotra's group who synthesized Tn antigen-containing neoglycopeptides. One or two *N*-acetylgalactosamine moieties were conjugated by a non-natural oxime bond to the segment peptides 327 – 339 and 328 - 339 of ovalbumin. They found that such structures could be



98



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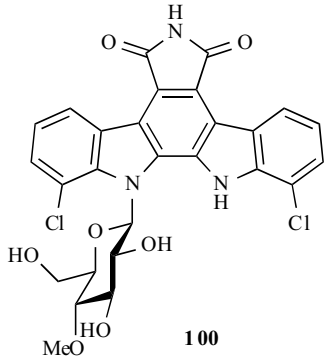
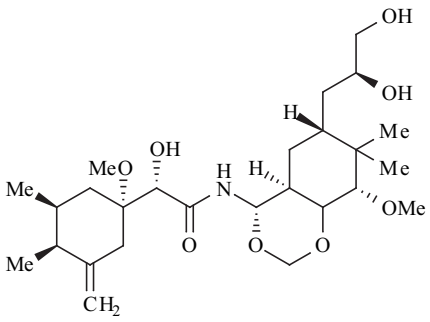
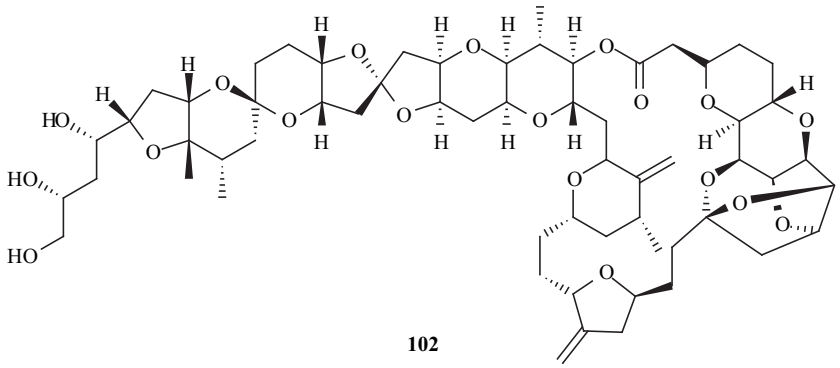


100

Fig. (32).



101



102

Fig. (33).

recognized by the T cell receptor. Efficiency was even higher when they carried two B-epitops [125].

Camptothecin (**98**) (Fig. **32**) is a pentacyclic alkaloid isolated from *Camptotheca acuminate* and showed impressive activity against leukemias and a certain variety of solid tumours [126]. It acts by binding to the topoisomerase I-DNA complex, leading to an accumulation of DNA strand breaks upon replication, ultimately causing cell death [127]. A number of pro-drugs and delivery systems have been developed [128] to date. Conjugates with sugars such as (**99**) (Fig. **32**) have been synthesized for preferential receptor-mediated uptake into tumour cells compared to liver cells utilizing neoglycoconjuates of bovine serum albumine. The sugar moiety, together with the spacer, is responsible for criteria such as efficacy, stability, solubility and reduced toxicity against thematopoietic stem cells and hepatocytes [129].

Indolopyrrolocarbazoles are a class of compounds showing a wide range of biological activities such as antibacterial, antifungal, and antitumour properties [130]. Usually, they contain a sugar moiety linked to the nitrogen of the indolocarbazole core. Some of them, such as rebeccamycin (**100**) (Fig. **32**) [131], are DNA damaging agents capable of inducing topoisomerase I mediated DNA breaks. This antitumour antibiotic, produced by the actinomycete *Saccarothrix aerocolonigenes,* shows antibacterial activity against gram-positive bacteria and it also inhibits the growth of some tumour cell lines in addition to displaying activity against several types of tumours implanted in mice [132]. Consequently, there is a considerable effort placed on the design and synthesis of new rebeccamycin analogues and derivatives with enhanced activity [133].

Mycalamides A (**101**) (Fig. **33**) and B were isolated from a sponge of the genus *Mycale* collected from the Otago Harbour in New Zealand [134]. The mycalamides reveal extremely potent *in vitro* cytotoxicity and *in vivo* antitumour efficacy against several leukaemia and solid tumour model systems as well as antiviral activity. In addition, mycalamide A blocks T-cell activation in mice and is 10-fold more potent than FK-506 and 1000 fold more potent than cyclosporin A in this model. The promising biological activity of the mycalamides and their congeners led to many synthetic approaches and severed biological investigations of this substance class [135].

Another carbohydrate related class of compounds is the halichondrine family, large polyether marcrolides, of which Halichondrine B (**102**) (Fig. **33**) is the most potent one and was found in a variety of marine sponges, such as *Halichondria okadai*, *Axinella* sp., *Phakellia carteri*, and *Lissodendryx* sp. [136]. Halichondrine B was shown to have remarkable *in vitro* and *in vivo* anticancer activities against murine melanomas and leukemias. Its sub-nanomolar *in vitro* potency was identified as a tubulin-based antibiotic mechanism. Several groups have studied halichondrine B [137] as well as macrocyclic ketone analogues thereof [138] with respect to such anticancer properties.

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