# Aspects of the Stability and Bioavailability of Carbohydrates and Carbohydrate Derivatives

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**Abstract:** Carbohydrates play a critical role in many biological processes and disease states including cancer, inflammation and infection. The development of carbohydrates as therapeutics continues to gain interest, as the biological roles of these biopolymers are further elucidated and understood. However, many carbohydrates display poor affinity, stability and bioavailability characteristics, which has led to a widely held view that this class of molecules make poor drugs. As there are already a significant number of carbohydrate-based drugs presently being employed by physicians, it is clear that some carbohydrates do make effective drugs. Recent advances in (a) the understanding of carbohydrate specific transport mechanisms, and (b) the development of novel carbohydrate based bioactives which may overcome many of the previous limitations of stability and bioavailability, suggest that carbohydrate-based compounds may provide a rich source of new drug candidates for a variety of diseases.

## INTRODUCTION

The physico-chemical properties that make a substance a good drug, have been studied for some time and considerable knowledge has been garnered on this front. Admittedly, drugs in the clinic display an extraordinary array of physico-chemical properties, with vast ranges in molecular weight, solubility, net charge, polarity and stability. To assist drug design, it is commonly considered a viable process to statistically analyse physico-chemical properties, in an effort to determine the nature of kinetic/functional trends existing in drugs in the clinic, such as exemplified by the research of Lipinski [1, 2].

Carbohydrate based drugs are typically seen to fall outside the statistical means provided by this kind of analysis. Regardless, there are numerous carbohydrate-based drugs already in the clinic and in a variety of different therapeutic categories. There has been long and consistent interest shown by pharmaceutical companies to develop drugs from carbohydrate related biological interactions, and it is now well evidenced that new developments in carbohydrate chemistries are capable of providing exciting lead compounds that are more typically of a drug-like profile. Unlike proteins or nucleic acids carbohydrates can form, from a relatively limited set of sugars, an immense number of complex branching structures. These structures exhibit a vast complexity of form and function and can confer cell-type specificity or provide a crucial cell-signalling component. Although too numerous to detail in their entirety, following is a brief discussion of a number of different biological indications which specifically relate to carbohydrates.

Cell surface carbohydrates are known to interact with infectious particles; mechanisms of infection for both viruses and bacteria often involve a carbohydrate-binding event. Carbohydrates therefore represent a target to inhibit interactions such as bacterial cell or bacterial toxin binding, and viral infection. Carbohydrates are able to successfully act as vaccines as demonstrated by action of a vaccine against *Haemophilis Influenza* type b (Hib). Hib caused bacterial Meningitis in 60% of children that were infected. The advent of the sugar based vaccine all but eliminated this disease from much of Europe and the United States [3].

Carbohydrates also make up part of a cell's identity profile, and are therefore of significance in immunological and auto-immune events. They have for some time been known to play a role in the inflammation cascade, particularly via interactions with a subclass of carbohydrate binding proteins, the selectins.

Certain cell surface carbohydrate structural motifs have been implicated in promoting metastasis of oncogenic cells. Further, in tumorigenic neoplasia, aberrant glycosylation takes place providing uncommon and cryptic cell surface motifs, which provides medicinal chemists with predominantly cancer specific structures for anticancer vaccine development [4]. It is also commonly held that the neoplastic glycosylation of metastatic cells assists in immune system evasion by masking immunogenic peptidic epitopes [5-7].

In another well-known indication, the involvement of carbohydrate structures in inhibiting blood clotting has been therapeutically exploited for over 65 years in the form of various heparinoid molecules. There is also an obvious carbohydrate involvement in diabetes, and there have been some recent successes with α-glucosidase inhibition in this respect. In addition, there are numerous carbohydrate processing enzymes, involved in the synthesis and trimming of glycoforms that are recognised therapeutic targets.

With so many varied and important processes involving carbohydrates, why is it that we are not flooded with a plethora of carbohydrate based therapeutics? By comparison one could also argue that peptide based drugs are relatively

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rare, although becoming increasingly important in drug discovery programs, despite the fact that there is a detailed understanding of myriads of protein-protein interactions at a structural level. In the next phase of drug discovery we can expect a significant increase of medically relevant proteins used in the treatment of disease. There are already a large number of clinically relevant proteins including Filgrastim, Erythropoietin, and Herceptin [8-11]. If complex molecules such as these are effective drugs, why are there such diminished expectations for the potential of carbohydrate-based compounds?

There are three commonly considered damning aspects of carbohydrates molecules, poor stability *in vivo*, poor bioavailability, and poor affinity for their target. These problems are not inherent for all sugars, there are numerous examples where carbohydrates can be used to act as drugs themselves or improve the action of other drugs. Admittedly many, although not all, carbohydrate-protein interactions are weak, relying on substrate avidity binding as opposed to affinity. Further, some, but not all carbohydrate structures, display poor biological uptake. Some carbohydrates do display lability due to enzymatic action and physiological pH's, but this is by no means an intrinsic characteristic of all carbohydrates.

Spectacular failures can also reduce the boldness of investigators. In the early 1990's several sugar-based drugs were progressed to the point of late-stage clinical trials, where they failed [12]. The purpose of this review is to highlight some of the physicochemical characteristics of carbohydrate based drugs being employed as therapeutics, to draw attention to some promising candidates in clinical trials, and to bring remark on some synthetic developments that auger new roles for carbohydrates in drug development.

## ANTI-DIABETIC DRUGS

One consideration during development of a particular drug is the nature and environment of the target. Not all therapeutics are required to be systemically available and therefore low systemic bioavailability is not necessarily an impediment to drug development. This is particularly the case where the point of action is in the gastrointestinal tract. Carbohydrates are involved in a number of indications in the GI including diabetes and intestinal bacterial toxin binding. Inhibition of intestinal α-glucosidases is a relatively new approach to the treatment of diabetes mellitus, although development in carbohydrate based α-glucosidase inhibitors has been on-going for some time. Required activity of these therapeutics is within the gastrointestinal tract and so low systemic activity can be considered desirable. Below are given examples of some carbohydrate based anti-diabetes drugs.

The pseudo tetrasaccharide Acarbose Fig. (**1**), a competitive inhibitor of α-glucosidase, acts through slowing down digestion and prolonging the time of conversion of carbohydrates into glucose. It thus reduces the post-prandial hyperglycemia that normally occurs in diabetics, it acts by inhibiting the degradation of disaccharides and higher oligosaccharides, but not monosaccharides. Acarbose was shown to have low systemic bioavailability after oral delivery, less than 2% found as active drug in urine. It is metabolised exclusively in the gut (intravenous injection provided ~90% of the active drug in the urine within 48 hours), predominantly by intestinal bacteria [13]. Low systemic bioavailability is certainly not in this case, an impediment to therapeutic efficacy.

Another α-glucosidase inhibitor Voglibose Fig. (**1**), similarly acts through slowing down enzyme activity, thus reducing acute post-prandial hyperglycemia. It has been reported to show 23-33 times more potent inhibition of hydrolysis of semi-purified porcine small intestine disaccharides than acarbose. Voglibose suppressed elevation of the blood glucose concentration after oral sucrose, maltose, and starch, but not after oral glucose, fructose, and lactose. Voglibose is useful as an adjunct to the dietary management of obesity and diabetes [13]. The potential of this agent is considered promising, although further investigations related to its clinical efficacy and safety, pharmacokinetics and possible adverse reactions seem to be necessary to expand the current knowledge of Voglibose [14, 15]. As can be seen this compound is not a pyranose and in fact more closely shares structural features with inositols, or aminocyclitols. The primary structural point of divergence between pyranoses and inositols is the absense of a ring oxygen, it is still has a highly hydroxylated cyclohexyl moiety. Due to the heavily hydroxylated nature of these molecules they are often considered under the general aegis of carbohydrate chemistry, and these types of rings are commonly encountered in naturally occuring glycoforms. Voglibose can probably be considered a disaccharide mimetic.

The azasugar Miglitol Fig. (**1**), another α-glucosidase inhibitor, was developed for the treatment of Type II diabetes. Absorption of Miglitol is saturable at high doses: a dose of 25 mg is completely absorbed, whereas a dose of 100 mg is only 50%-70% absorbed. For all doses, peak

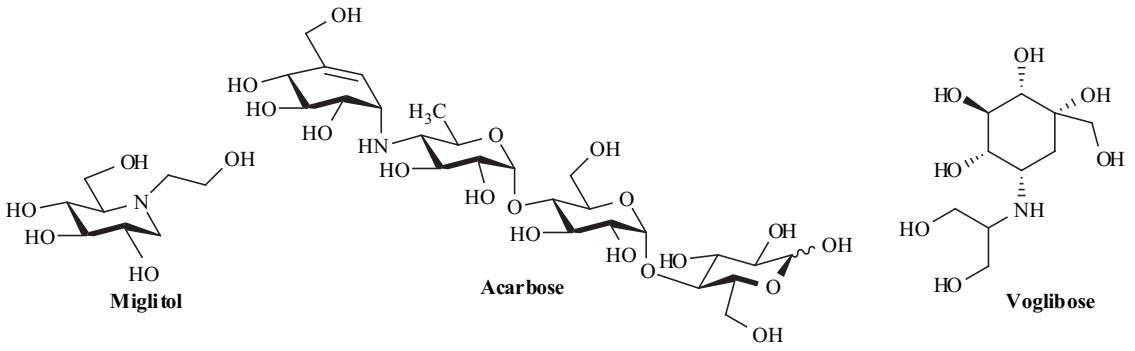
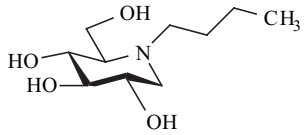



**Fig. (1).** Clinically employed, carbohydrate derived anti-diabetic drugs.

concentrations are reached in 2-3 hours. As expected, there is no evidence that systemic absorption of Miglitol contributes to its therapeutic effect. The protein binding of Miglitol is negligible (<4.0%). Miglitol was determined to be not metabolized in man or in any animal species studied. Miglitol is eliminated by renal excretion as unchanged drug, over 95% of a 25mg dose of the is recovered in the urine within 24 hours. The elimination half-life of miglitol from plasma is approximately 2 hours [16]. The lack of metabolites for this antidiabetic compared with acarbose for example, is likely a result of the absence of any glycosidic linkages. Miglitol has no aglycon (therefore no acetal functionality), and has a nitrogen heteroatom in the ring. This is not to say that all carbohydrates are necessarily going to be metabolised due to possesion of these more labile structural features. A good example of lack of gut metabolism of carbohydrates is exemplified by milk oligosaccharides. Studies have indicated that the bulk of antipathogenic milk oligosaccharides such as the fucosyl-lactoses, survive transit through the gut [17].

## GLYCOLIPID STORAGE DISORDERS

Structurally very similar to Miglitol, *N*-butyldeoxynojiromycin Fig. (**2**) is an orally administered small-molecule glucosylceramide glucosyl transferase inhibitor, for the treatment of glycolipid storage disorders including Gaucher, Tay-Sachs, Fabry and Niemann-Pick Type C diseases. As might be expected, it is not highly specific, it also inhibits α-glycosidase I and II as well as glycosphingolipid synthesis. *N*-Butyldeoxynojiromycin's predominant therapeutic indication, is the inhibition of glucosylceramide synthase (GCS), the enzyme that catalyzes the first glycosylation step leading to the formation of higher order glycosphingolipids. The initial target validation was accomplished through demonstration of inhibition of glycosphingolipid biosynthesis in mice, indicating that the compound could cross the blood brain barrier in sufficient quantities to prevent storage disorders [18].



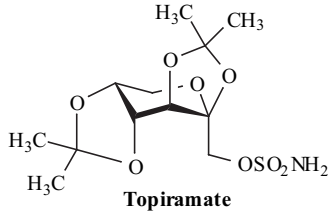

***N*-Butyldeoxynojiromycin**

**Fig. (2).** Structurally related to Miglitol, the more hydrophobic *N*-butyldeoxynojiromycin displays adequate bioavailability for the treatment of storage related disorders.

## ANTI-SEIZURE

### Topiramate

The indications for the orally available Topiramate (2,3:4,5-bis-*O*-(1-methylethylidene)-β-D-fructopyranose sulfamate) Fig. (**3**) are various; diabetic neuropathy, migraine, obesity, manic depression, seizure, epilepsy & convulsion and tremor. The drug displays a good pharmacological profile, it has a long plasma elimination half-life, linear pharmacokinetics (suggesting passive transport), predominantly renal clearance, absence of significant protein binding and lack of clinically relevant active metabolites. It is not a potent inducer of drug metabolising enzymes, and is rapidly and well absorbed and distributed. Based on $^{14}C$ studies the extent of absorption was at least 81% (major route of elimination is 81% via the kidneys), a mean peak plasma concentration of 2μg/mL achieved within 2-3 hours. 13-17% bound to plasma protein, ~20% metabolised in healthy volunteers [13].




**Topiramate**

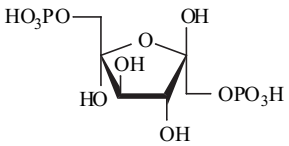
**Fig. (3).** The acid stable, bis-isopropylidene derivatised fructopyranoside anticonvulsive, Topirimate.

The isoprolylidene ring system is generally considered quite chemically labile to acidic conditions and so it comes as somewhat of a surprise to find that the bis-isopropylidene structure of topiramate demonstrates such good stability. The isopropylidene rings are certainly likely to improve bioavailability and appear necessary for therapeutic efficacy. It is unlikely that this compound uses glucose active transport mechanisms to cross the blood brain barrier, particularly as it is predominantly unmetabolised in active form. The anomeric methylenesulphonamide functionality is also unusually stable under physiological conditions. Topiramate is an example of a very simply derivatised carbohydrate ring structure with an effective therapeutic profile and lauditory pharmacokinetics.

## ISCHEMIA

### Fructose 1,6-Diphosphate

The naturally occurring fructose disphosphate (FDP) Fig. (**4**) is a cytoprotective currently under development for the potential treatment of cardiovascular ischemia, sickle cell anemia and adult respiratory distress syndrome. It is a glycolytic intermediate which has been used in intervention in various ischemic conditions for two decades. Pharmacokinetics studies showed that the highest FDP blood concentrations were obtained at 10 min after injection [19]. FDP (0.5 to 50 mM) dose-dependently crossed the cell membrane intact in artificial membranes (lipid vesicles) and endothelial cells *in vitro*. The results indicated that FDP diffuses through the membrane bilayer in a dose-dependent fashion [20, 21].

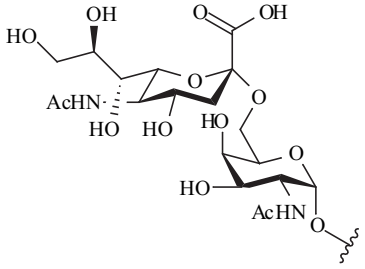



**Fructose-1,6-diphosphate**

**Fig. (4).** The high polarity would seem to preclude passive membrane transport, which might suggest FDP is actively transported by one of the small charged molecule, transport systems.

## IMMUNITY AND VACCINATION

As alluded to in the introduction, carbohydrates are critical in the formulation of some vaccines that are currently in clinical use. In the field of vaccine development, there is much interest in the role that *O*-Linked glycans play on the cell surface in tumorogensis and inflammatory diseases as specific structures appear to be associated with a particular disease state [22]. The persual of strategies to either vaccinate against the implicated structure or to produce a structural analog as an inhibitor, hold some promise for drug development. When embarking upon a research program aimed at identifying potential leads, it is important to realise the endpoint, identifying such important considerations as the effect the method of administration has on "overall" therapeutic success. For example, for a drug to treat a disease in the third world, such as malaria, it is advisable that you have a compound that requires little in the way of patient compliance. Alternatively, for an anti-cancer therapeutic, route of administration may be of far less significance. An example of a carbohydrate anticancer vaccine currently under development is Theratope. Theratope is a synthetic Sialyl-Tn antigen Fig. (**5**), linked to the keyhole limpet hemocyanin protein carrier, and is administered with Corixa's Detox-B adjuvant, an oil droplet emulsion containing monophosphoryl lipid A and cell wall skeleton from Mycobacterium phlei.




**STn Antigen**

**Fig. (5).** Abherrant sialylation of the cryptic α-*N*-acetyl galactosamine moiety provides the STn antigen, one promising epitope for the development of anti-cancer vaccines.

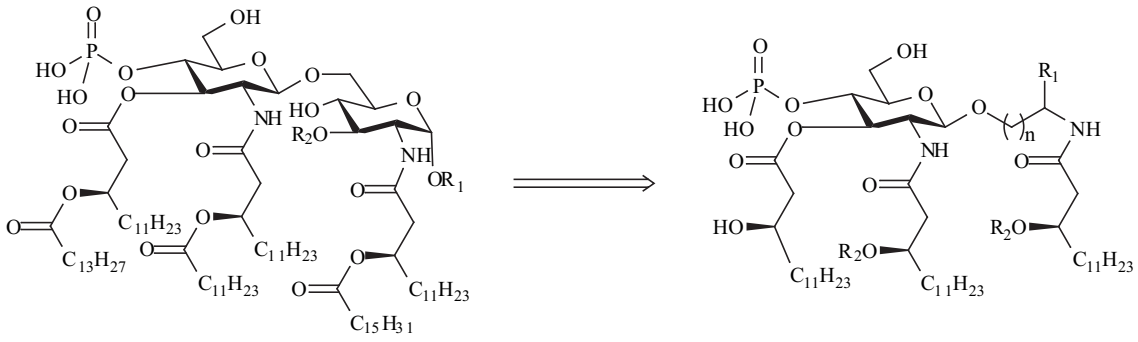
Theratope elicits a T-cell dependent antibody response to the STn antigen. There is an apparent correlation between this antibody response generated by the vaccine and improved survival. The vaccine also induces STn-specific T-cell responses in patients with high-risk or metastatic cancer of the ovary or breast. The Theratope vaccine was developed by generating a synthetic mimic (STn-crotyl) of the natural O-linked epitope of mucins (STn-serine). The STn-crotyl was then conjugated to keyhole limpet hemocyanin (KLH), which serves as a carrier through the crotyl linker arm. This has the effect of creating a hapten-carrier complex. The vaccine is administered subcutaneously in the adjuvant Detox-B.

### Immunomodulators

Generally, when trying to employ a carbohydrate to activate an immune recognition, it will be presented in the form of a conjugate vaccine, with the relatively poorly immunogenic carbohydrate entity conjugated to an immunogenic carrier protein to enhance overall immunity [3]. As mentioned, such vaccines have had a significant impact in the extremely successful immunisation strategies that have been employed to combat *Haemophilus Influenzae* induced disease in children. However, the use of the capsular polysaccharides as vaccines has often induced poor immunity in infants or very young children [23]. As a potential ameliorator of such induction problems, it has been demonstrated that glycoconjugates themselves can act in an adjuvant capacity to successfully amplify the activity of the immune system. There are a number of carbohydrate immunomodulators that have been discovered which may serve as the basis for a whole range of therapies in the treatment and or prevention of autoimmune disease, infection or cancer. Discussion of some of these compounds is presented here.

#### *Lipid A Analogues*

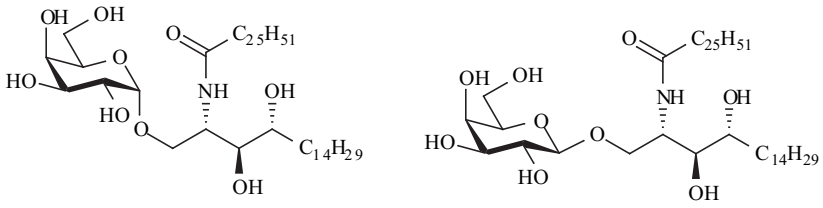
Lipid A analogues (**1**) are examples of compounds that demonstrate such potential as immunomodulators. Derivatives of these molecules have been synthesized and examined, for example, the 1-*O*-phosphono and (*R*)-3-hydroxytetradecanoyl moieties of native *Salmonella minnesota* R595 lipid A have been replaced with hydrogen and the length of the normal fatty acyl residues has been systematically varied. Normal fatty acid chain length in the 3-*O*-desacyl monophosphoryl lipid A (MLA) series was found to be a critical determinant of inducible nitric oxide synthase gene expression in activated mouse macrophages, and in the induction of proinflammatory cytokines in human peripheral monocytes. Examination of pyrogenicity in rabbits and lethal toxicity in D-galactosamine-treated mice with these analogues, showed that toxic effects in the MLA




**1**. $R_1 = PO_3H_2$, $R_2$ = (*R*)-3-hydroxytetradecanoyl

**2**

**Fig. (6).** The glucosaminoyl moiety of compound **1** is replaced with a carbon spacer providing derivative **2**.



**KRN7000** **AGL-583**

**Fig. (7).** Chemical structures of the active immunomodulator **KRN7000** (α-GalCer) and the inactive **AGL-583** (β-GalCer).

series can be ameliorated by modifying fatty acid chain length. When used as an adjuvant for tetanus toxoid vaccines, certain MLA derivatives were shown to enhance the production of tetanus toxoid-specific antibodies in mice [24].

Aminoalkyl glucosaminide 4-phosphates **2** are formally further derivatives of the Lipid A analogues, Fig. (**6**). Compounds **2** demonstrate a reduced structural complexity over the parent compound. One glucosaminyl ring was found to be non-essential, and was effectively replaced with a carbon tether. Several derivatives of this compound were able to enhance antibody responses to tetanus toxoid vaccines as well as augment vaccine induced cytotoxic T lymphocytes (CTLs) against EG.7-ova target cells. Studies showed that $n$-$C_9H_{19}CO$ at $R_2$ gave the best adjuvant activity [25]. Certain of these compounds not only enhance humoral and cellular mediated responses in murine models but also exhibit low pyrogenicity in rabbits.

### *Acemannan*

Acemannan, a naturally occuring potent immunostimulant isolated from aloe vera, is a water soluble complex polysaccharide consisting of long-chain, 4-*O*-acetylated β-linked mannose monomers interspersed with galactose moieties. The pharmacological properties of acemannan are predominantly mediated through its activation of monocytes and macrophages, a known biological activity of the class of mannans is the stimulation of both macrophages and T-cells. It appears that acemannan may be synergistically useful when employed in conjunction with anti-viral treatments. Pharmacokinetic studies of the oral administration of radioactive acemannan in beagle dogs (20 mg/kg) showed that the compound was absorbed from the gut and reached peak blood levels within 4 to 6h ($t_{1/2}$ > 48h) [26]. No toxicity was demonstrated in 40 normal healthy males administered oral acemannan (up to 3200 mg/day for 6 days).

### *KRN7000*

Six types of agelasphins having α-galactosylceramide structure have been isolated from the marine sponge *Agelas mauritianus*. Concurrent injection of these compounds prolonged the life of mice inoculated intraperitoneally with B16 melanoma cells [27].

The *in vitro* and *in vivo* effects of α-, β-galactosylceramide (GalCer) and α-, β-glucosylceramide (GluCer) which have the same ceramide moiety were compared for their tumour growth inhibitory effects on mice after subcutaneous inoculation with B16 melanoma cells. The α-GalCer showed stronger suppressive activity than its β-type paralleling their enhancing effects on NK cell activity [28].

Analogues of the galactosylceramide were synthesised and tested for their anti-tumour and immunostimulatory properties. Of the ten monoglycosylceramides synthesised, the α-D-sugar monoceramides demonstrated stronger activities than the β-anomers. It was determined that the orientation of certain hydroxyl groups of the pyranose ring, as presented in the α-stereoorientation, were critical for effective binding. Further confirmatory studies were able to determine the optimal length of the fatty acid side chain in the ceramide portion [29, 30].

One analogue, the α-galactosylceramide (2S,3S,4R)-1-*O*-(α-D-galactopyranosyl)-2-(*N*-hexacosanoyl-amino)-1,3,4-octadecanetriol (KRN7000) Fig. (**7**), was chosen as the candidate for clinical application [31]. This molecule was also shown to have adjuvant properties. Adoptively transferred KRN7000-treated dendritic cells markedly prolonged the survival time of mice bearing B16 pulmonary metastases. These results demonstrate that KRN7000 may be useful for cancer therapy not only as an anti-tumour agent but also as an activator of antigen-presenting cells such as dendritic cells, which can be used for adoptive cellular therapy.

It has also been demonstrated that α-galactosyl ceramide is a ligand that activates natural killer T cells if presented on CD1d molecules. It is thought that these cells have a crucial role in modulating and augmenting protective immune responses by contributing to the generation of specific cytotoxic T cells and activation of NK cells [32]. KRN7000 activated T cells protected mice against the development of the intra-hepatic phase of the rodent malaria parasites *Plasmodium yoelli* and *Plasmodium berghei* [33] and galactosylceramide administration also enhances the protective immunity induced by experimental malarial vaccines [34]. A phase one clinical trial has recently been completed in patients with solid tumours. KRN7000 is well tolerated in cancer patients over a wide range of doses, biological effects were observed in several patients [35].

### *Amiprilose*

1,2-*O*-Isopropylidene-3-*O*-3'(*N',N'*-dimethylamino-(*n*-propyl))-D-glucofuranose hydrochlo-ride (Amiprilose HCl) is a synthetic D-glucofuranose derivative, Fig. (**8**). It has been reported to possess numerous immunomodulatory properties both *in vitro* and *in vivo* experiments, It has been suggested that amiprilose HCl acts by interacting with macrophage 'sugar receptors', lectin-like molecules on the surface of the macrophage, used to detect molecules on Mycobacterial cell walls. Amiprilose HCl has been found to possess a broad

range of potentially useful immunomodulatory and other properties *in vitro*. In addition, clinical studies have described a favourable safety profile. The two issues remaining are its efficacy, particularly in rheumatoid arthritis, and its mechanism of action.

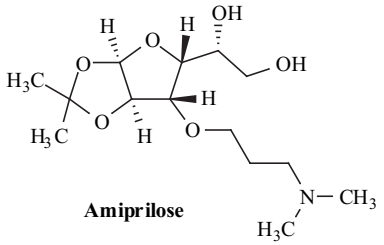



**Fig. (8).** Chemical structure of the potential furanoside immunomodulator, amiprilose.

Despite an apparently good safety profile and some encouraging results in 1993 and 1994, the FDA declared the drug 'not approvable' for the treatment of rheumatoid arthritis (RA), in a decision which attracted some controversy. It is stable in 0.1*N* NaOH at 60 degrees where its acid solvolysis product, 3-O-3'-(N',N'-dimethylamino-n-propyl)-D-glucose is readily degraded. In human volunteers over 90% of the drug was recovered intact in the urine, indicating relatively limited metabolism. The major metabolite, desmethyl amiprilose, was examined in *in vitro* immunological assays, and was found to be relatively inactive. Plasma protein binding of amiprilose HCl was negligible in humans. Orally administered, amiprilose showed a rapid absorption ($t_{1/2}$ = 10 min) after a lag time of 23 min, and a terminal plasma half-life of 344 min. The erythrocyte/plasma water partition coefficient was close to unity [36]. Once again we see an isopropylidene derivatised monosaccharide structure displaying good stability, less unusual in this instance where we have stabilisation derived from the presence of two *cis* fused 5-membered rings.

## ANTI-THROMBOTICS

Heparin, a powerful anticoagulant has been used since the late 1930's in the treatment of thrombosis [37]. In its original implementation, tolerance problems were noted and so reduced dosage was suggested to reduce bleeding and improve efficacy. In the early 1970's clinical trials did indeed indicate acceptable tolerance was obtainable, whilst still preserving antithrombotic activity. Unfractioned heparin (UFH) is primarily used as an anticoagulant for both therapeutic and surgical indications, and is usually derived from either bovine lung or porcine mucosa. Amongst the modern uses of unfractioned heparin are the management of unstable angina, an adjunct to chemotherapy and anti-inflammatory treatment, and as a modulation agent for growth factors and treatment of haemodynamic disorders [38-42]. In the late 1980's, the development of low molecular weight heparins (LMWHs) led to improvements in antithrombotic therapy [43]. LMWHs are derived from UFH by such processes as; chemical degradation, enzymatic depolymerisation and γ-radiation cleavage. Heparins have recently been used for treatment of trauma related thrombosis. This drug in its various forms is not orally bioavailable.

### Fondaparinux Sodium

One synthetic derivative of heparin recently marketed is known as Fondaparinux Sodium, Fig. (**9**). The pharmacokinetics of Fondaparinux have been determined in healthy human volunteers [44]. Fondaparinux sodium administered by subcutaneous injection is rapidly and completely absorbed. Pharmacokinetics of fondaparinux, determined after intravenous and subcutaneous injections, showed elimination half lives of 0.7 and 1.0h respectively [45].

Drug not bound to AT-III (anti-thrombin III) is rapidly eliminated by the kidneys, in individuals with normal kidney function fondaparinux is eliminated in urine mainly as unchanged drug. In healthy individuals up to 75 years of age, up to 77% of a single subcutaneous or intravenous Fondaparinux dose is eliminated in urine as unchanged drug in 72 hours. The urinary excretion was 53 to 84% of the injected dose in 24 h at steady state [44]. In healthy adults, intravenously or subcutaneously administered Fondaparinux sodium distributes mainly in blood and only to a minor extent in extravascular fluid.

### Idraparinux Sodium

Another synthetic heparin pentasaccharide, Idraparinux sodium, has currently entered phase III clinical trials. Idraparinux sodium is a partially methylated pentasaccharide with the indications of deep vein thrombosis and

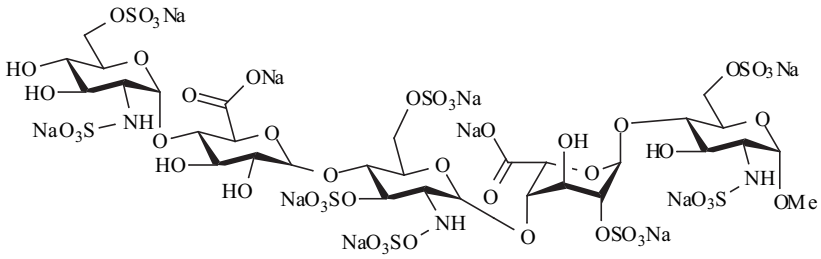
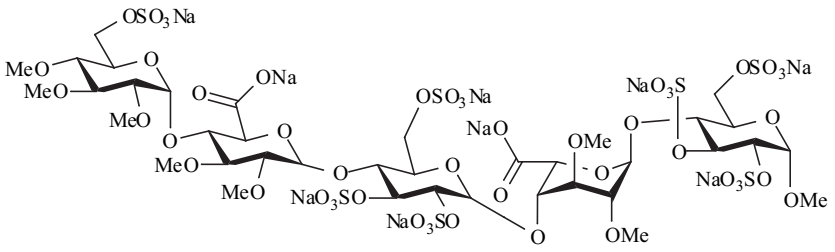



**Fig. (9).** The highly charged decavalent heparinoid Fondaparinux is essentially an exact copy of a naturally occuring AT-III binding pentasaccharide sequence found in heparin. The compound is likely stabilised in the α-methyl glycoside form, as opposed to the hemiacetal.



**Idraparinux Sodium**

**Fig. (10).** The Introduction of multiple methyl ethers as well as a slightly altered charge distribution pattern distinguish this Idraparinux from its parent compound Fondaparinux. The penta-pyranosyl skeleton is still identical and makes possible much of the observed activity of this potential drug.

thrombosis, it is a potent and selective factor Xa inhibitor [46]. It shows linear pharmacokinetics and a complete subcutaneous bioavailability. Elimination half life was a remarkable 120 hours. The major structural changes of Idraparinux from Fondaparinux sodium, are replacement of hydroxyl groups with methoxy functions, and exchange of *N*-sulfates for *O*-sulfates. From a purely synthetic point of view this reduces synthetic complexity significantly. There is also a modified, and simpler, sulfation pattern on idraparinux as opposed to fondaparinux sodium. Through further structural modification to the natural heparin AT-III binding fragment, it is conceivable that a orally bioavailable heparin therapeutic could eventually be developed, without loss of efficacy.

In contrast to unfractionated and low molecular weight heparins, the above pentasaccharides represent single molecular entities with well-defined pharmacological targets, and more specific pharmacokinetic profiles.

## CARBOHYDRATE MIMETICS

The diverse range of biological functions ascribed to oligosaccharides and glycoconjugates has prompted the development of compounds which can potentially block their formation and/or function. These inhibitors can be divided into those which block glycoconjugate biosynthesis and those that interfere with recognition of the target carbohydrate. Synthesis of these kinds of molecules is proving to be useful for researchers trying to ascertain the role of specific glycoconjugates in health and disease, and is thus leading to exciting therapeutic candidates.

### Anti-Inflammatory Drugs

The homing receptors on lymphocytes, which interact with tissue specific adhesion molecules on high endothelial venules direct the recirculation of lymphocytes in a tissue specific fashion. Determinants specifically recognised by these lectin-like receptors include phosphorylated and sulphated mannose, fucose and fructose moieties such as mannose-6-phosphate, fucose-4-sulphate, fructose-1-phosphate, fucoidin and phosphomannan [47, 48].

Terminal saccharide structures assist in increasing the specificity of glycoprotein-receptor interactions. The sialic acid-binding lectins (Siglecs) are transmembrane glycoproteins that function in cellular recognition events. They have restricted distribution and expression, with characteristic profiles within leukocyte sub-populations. L, E and P-selectins are early signal molecules in the recruitment of neutrophils into inflammatory sites. The essential recognition structure enabling the selectin ligand, P-selectin glycoprotein ligand-1, to be recognised by the selectin is the O-glycosylated amino terminus [49]. However, the structures involved in these interactions are complex and may rely more on avidity than affinity for their binding potential. As previously mentioned, recent trends in carbohydrate chemistry have seen numerous positive developments in terms of the ability to manipulate structural and stereochemical aspects of carbohydrate moieties. There are now a number of chemistries available that can generally be effected in a simpler manner than previously possible. Focus on ameliorating structural lability has revolved around the interglycosidic linkages of carbohydrates and the reducing end lactol functionality. It has been demonstrated that in many instances, successful chemical modification can be effected without any change in biological properties. Development of synthetic ligands that can interact with the selectins could lead to useful therapies for treating inflammation. Considered as a particularly promising target to develop potential drug like molecules, the naturally occurring ligand sLeX can now be considered a valid starting point for a drug development program[50].

The following Fig (**11**). demonstrates the kinds of measures that can be effectively employed to reduce structural complexity whilst improving the physico-chemical properties of an interesting bioactive molecule.

The sLeX (**3**) ligand itself displays binding to target with numerous weak handholds, it is expensive to make, and is poor at crossing cell membranes. It contains a fucose glycosidic linkage that is particularly acid sensitive. In the hypothetical sequence Fig. (**11**), it is shown how non-essential structural features may be removed, structural lability ameliorated, and ligand affinity improved, to provide a substance with greater stability and efficacy than the parent molecule with an accompanied reduced synthetic cost [51, 53, 56, 57] Structure **7** actually displays greater selectin affinity than structure **8**, but structure **8** has led directly to the development of a clinical candidate. The above scheme shows compounds taken from a variety of different research projects and is far from exhaustive. Other programs worthy of mention synthesized compounds that

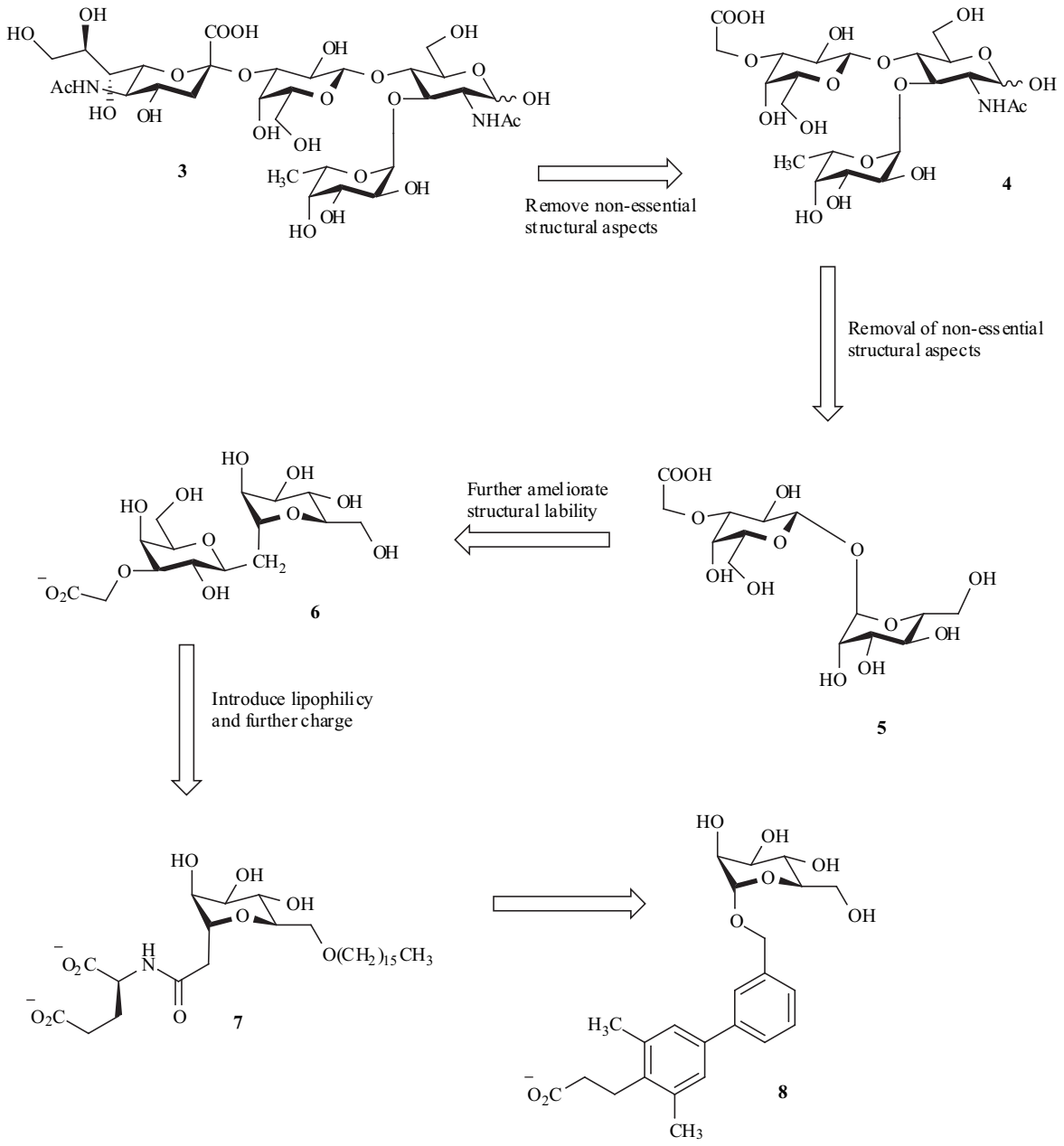



**Fig. (11).** The above scheme shows in a stepwise fashion, sequential structural changes that are possible that can effectively create an active viable drug candidate from a target that shows less than desirable qualities. (This scheme is hypothetical, each of these compounds derives from a different primary source, **4** [51], **5** [52, 53], **6** [54], **7** [52], and **8** [55].

have incorporated peptidic backbones to correctly orient the required functional groups for binding [58-60].

### *Bimosiamose*

One compound with particular mention is Bimosiamose, a potent E-, P- and L-selectin antagonist which inhibits HL60 cells binding to recombinant E-, P- and L-selectin-IgG fusion proteins bound to magnetic beads with an $IC_{50}$ of 0.5, 0.07 and 0.56 mM respectively. By comparison, the natural ligand $sLe^x$ oligosaccharide has an $IC_{50}$ of 0.7, 8.0 and 4.0 mM on E-, P-, and L-selectin respectively. Bimosiamose is a dimeric derivative of an earlier potential drug candidate (see compound **8**, Fig. (**11**)) Although active the original molecule was not developed as a drug as it displayed very low bioavailability. One reason the dimeric compound bimosiamose was developed, was to specifically to increase bioavailability [55].

In developing the dimeric compound it was found that analogues with 2 acids and 2 sugars and 1 acid and 2 sugars were found to be active, while analogues with 2 acids and 1 sugar were found to be inactive. Bimosiamose, is now a lead compound of a series of low molecular weight E-, P- and L-selectin antagonists, for the potential treatment of acute asthma (as an inhaled formulation) and psoriasis (as a topical formulation). By November 2002, Bimosiamose was in phase I trials for psoriasis and phase II trials for asthma were ongoing. No bioavailability data is currently available for this compound. Bimosiamose compares well against range of potential selectin antagonists in research.

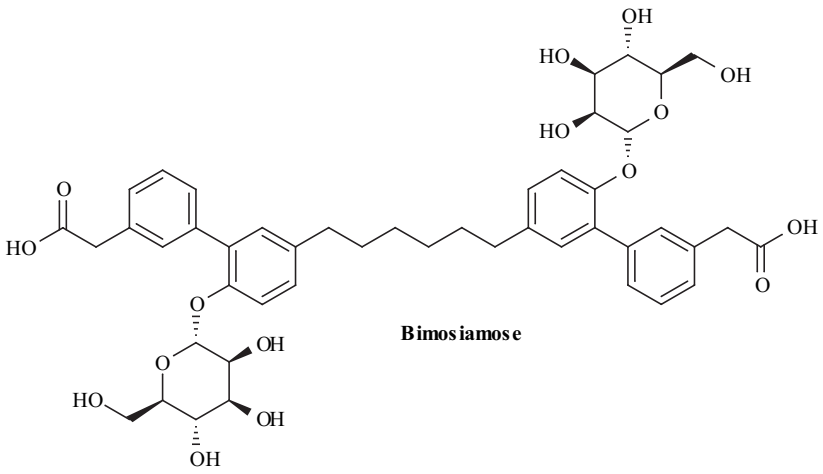



**Fig. (12).** Bimisiamose, a dimeric sialyl Lewis X mimetic based on compound **8** (Fig. (**11**)).

## Neuraminidase Inhibitors

Influenza viral replication in known to occur in the superficial epithelium of the respiratory tract. The activity of both Zanamivir and Oseltamivir Fig. (**13**) is extracellular in nature, influenza viral infection is mediated via a neuraminidase enzyme. Both of these therapeutics act as specific inhibitors of this enzyme by mimicking a cell-surface sialic acid molecule during the neuraminidase transition state, thereby reducing the propagation of both influenza A and B viruses, with varying degrees of success.

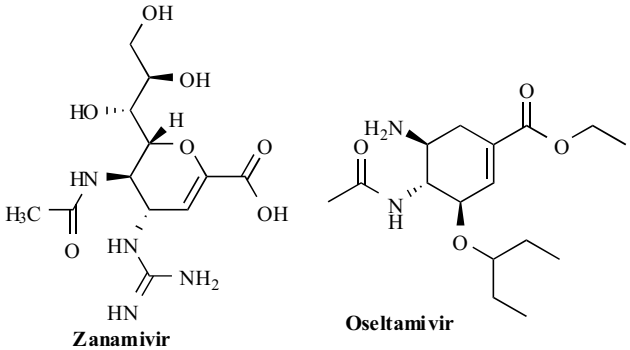


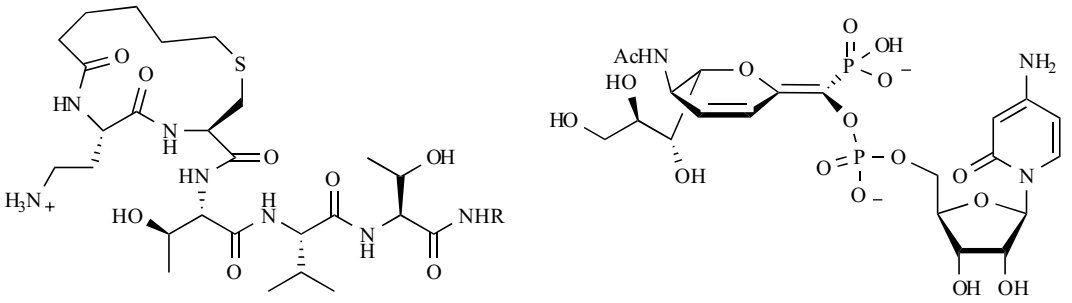

**Fig. (13).** The structures of two neuraminidase inhibitors. Influenza viral particles use a neuraminidase as a part of their mechanism of entry, or infection, of a healthy human cell.

For Zanamivir, oral bioavailability is low (about 2%), so ingested drug does not appear to contribute greatly to systemic exposure. Zanamivir is not metabolised [61]. After inhaled administration of Zamamivir, approximately 13% of the drug is deposited in the bronchi and lung, 77% in the oropharynx and 1% in the trachea. A mean serum concentration of 30 to 40 microg/l is achieved after 1.5 h, high concentrations of drug are delivered to the respiratory system but not to other organs [62]. Conversely, Oseltamivir is absorbed from the gastrointestinal tract after oral administration and is converted predominantly by hepatic esterases into the active metabolite. Peak concentration reached 2-3 hours after dosing. At least 75% of an oral dose reaches systemic circulation as the active metabolite. Metabolite reaches all keys sites of infection. Binding to human plasma proteins is negligible (less than 3%). The prodrug is 90% eliminated by conversion to the active metabolite. The active metabolite is not further metabolised, and is eliminated entirely by renal excretion [63]. Both laboratory strains and clinical isolates, were all found to be susceptible to inhibition by Olsetamivir with respect to enzyme inhibition ($IC_{50}$ values < 2 nM) and inhibition of replication in cell culture ($IC_{50}$ values = 0.6 to 155 nM [64]. In comparison to the ethyl ester prodrug, the parent guanidino analog of olsetamivir exhibited poor oral bioavailability (2 to 4%) and low peak concentrations in plasma [65].

## Glycosyltransferase Inhibitors

There have been several reports of inhibitors of the carbohydrate modifying enzymes, enzymes such as fucosyl-, galactosyl- and sialyltransferases. Inhibition of specific glycotransferases could have an important role in modifying the metastatic potential of certain cancers [66, 67], in inflammation [68, 69] and in certain disease states where elevation of sialic acid results in disease [70]. Sialic acids are monosaccharides that attach to the terminal galactose, *N*-acetylgalactosamine, or other sialic acids in carbohydrate chains of glycoproteins or glycolipids [71]. By virtue of their terminal location, sialic acids on the cell surface are among the first molecules encountered by another cell when cell to cell contact occurs [71].

An example of a sialyltransferase inhibitor is compound **10**, Fig. (**14**), a potent inhibitor of α2,6 sialyltransferase [72]. As can be seen, this type of compound is highly charged which may effect its ability to cross cell walls. There are specific CMP-sialic acid transporter proteins which may be exploited although this is not of any consequence when considering the initial molecular crossing of intestinal membranes. Phosphate bridges, as seen in compound **10**, have a pH dependent stability that may prove problematic in the gut. Non-carbohydrate compounds such as **2** which are capable of being transported into the endoplasmic reticulum have been designed and synthesised [73]. Other compounds have been reported that have efficacy in inhibiting other glycosyltransferases in a mouse model of Tay Sachs disease [18]. Therefore the probabilities of the development of stable drugs that can inhibit this important biosynthetic pathway seem quite promising.



**9** **10**

**Fig. (14).** Compound **9** is an inhibitor of oligosaccharyl transferase that is capable of permeating the endoplasmic reticulum membrane. A potent sialyltransferase inhibitor **10** (inhibition constant $K_i$ = 40 nM); its polar charged nature may preclude activity in cellular systems.

An example of cell surface glycan suppression using metabolic decoys is provided by the "oligosaccharide primers" described by Esko and co-workers. Hydrophobic disaccharides were incorporated during the biosynthesis of sLeX, and cells treated in this manner displayed a diminished E-selectin binding activity [74]. Likewise, hydrophobic glycosides of xylose can subvert the biosynthesis of glycosaminoglycan, temporarily reducing the density of these chains on cell surfaces [75].

The pathway for sialic acid biosynthesis is amenable to biosynthetic modulation using precursors derived from metabolism of *N*-acetylmannosamine (Man*N*Ac), Fig. (**15**). The sialic acids are known to participate in myriad cell surface recognition events, including selectin mediated

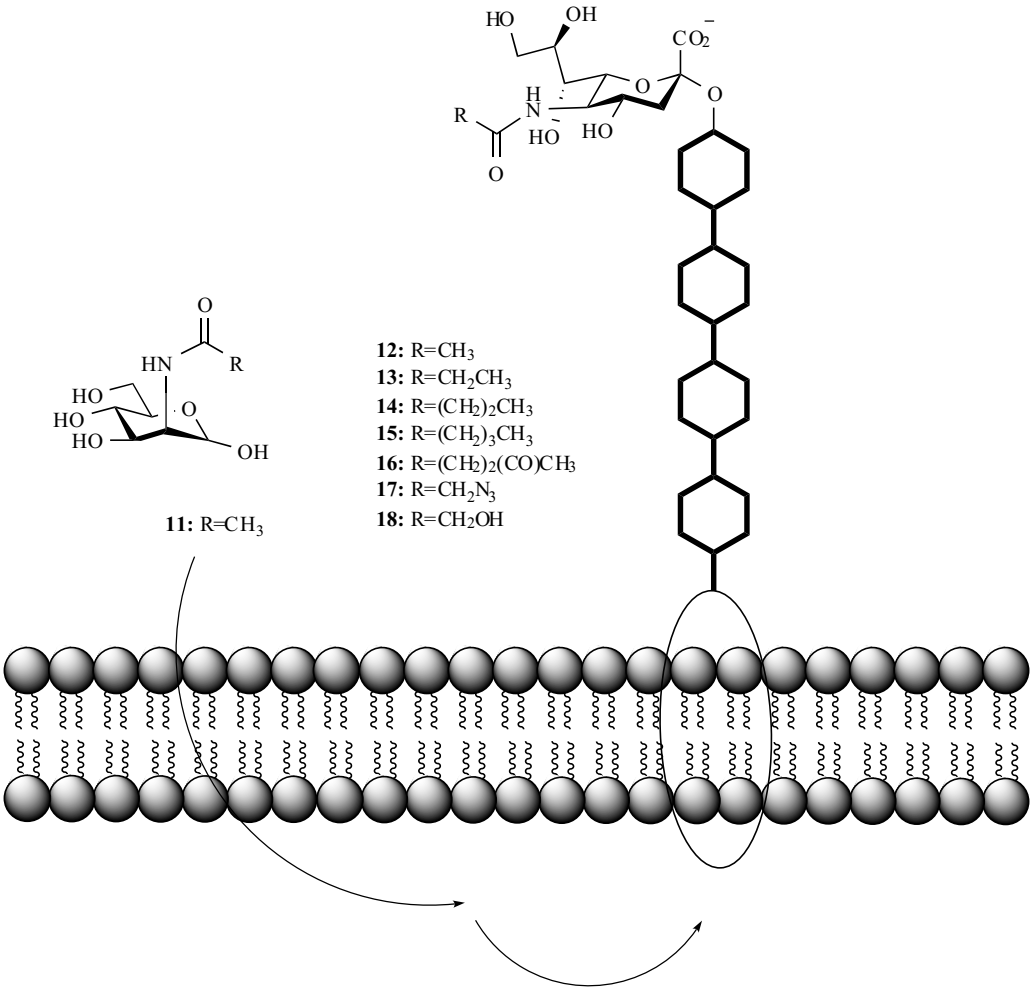



**Fig. (15).** Biosynthetic engineering of unnatural sialic acids on cell surface glycoconjugates. Man*N*Ac (**11**) is converted to sialic acid (**12**) by cellular metabolism. Unnatural *N*-acyl groups are tolerated by the biosynthetic enzymes and transport proteins, enabling the display of myriad unnatural sialosides on cells (**13** through **18**). Sialic acides bearing ketones **16** or azides **17** can be further elaborated by reaction with complementary functional groups.

leukocyte adhesion and influenza virus binding. Culturing cells in the presence of synthetic analogs of ManNAc bearing *N*-acyl groups not known to occur in nature produce unnatural sialic acids on cell surface glycoconjugates Fig. (**15**) [76]. The expression of these types of sialic acids can inhibit or enhance viral infection, depending on the physical interaction of the unnatural moiety with the viral receptor [77, 78]. They can also disrupt contact inhibition of cell growth [79], and block the binding of myelin-associated glycoprotein to neurons [80].

## CARBOHYDRATE BASED ANTIBIOTICS

### Aminoglycosides

Aminoglycosides are a well-known group of clinically important antibiotics. They function by inhibiting protein synthesis in susceptible bacteria through binding to specific sites in the prokaryotic ribosomal RNA, therefore interfering with the reproduction of the bacterial genetic code. Their use is restricted to gram-negative bacteria. There are some serious side effects, notably ototoxicity and nephrotoxicity associated with these molecules, as well as poor oral bioavailability and biostability.

On a more positive note, aminoglycosides do exhibit very high bioavailability when administered by their usual route, that is intramuscularly or intravenously, and stand as a good example of an extremely effective treatment that is not orally bioavailable. The aminoglycosides are highly polar and relatively high molecular weight molecules, their high polarity derived from the numerous amino and hydroxyl functions that adorn their structures Fig. (**16**). Most of the common aminoglycosides appear to be excreted unmetabolised.

All of the aminoglycosides have similar pharmacokinetic properties and all are toxic; they are generally used parenterally for systemic infection but are also used topically for eye and ear infections. One immediate distinction to this is neomycin which is used to kill intestinal flora prior to surgery and so is therefore administered orally, once again point of delivery is to the GI tract. After injection, the aminoglycosides are distributed mainly in the ECF. Protein

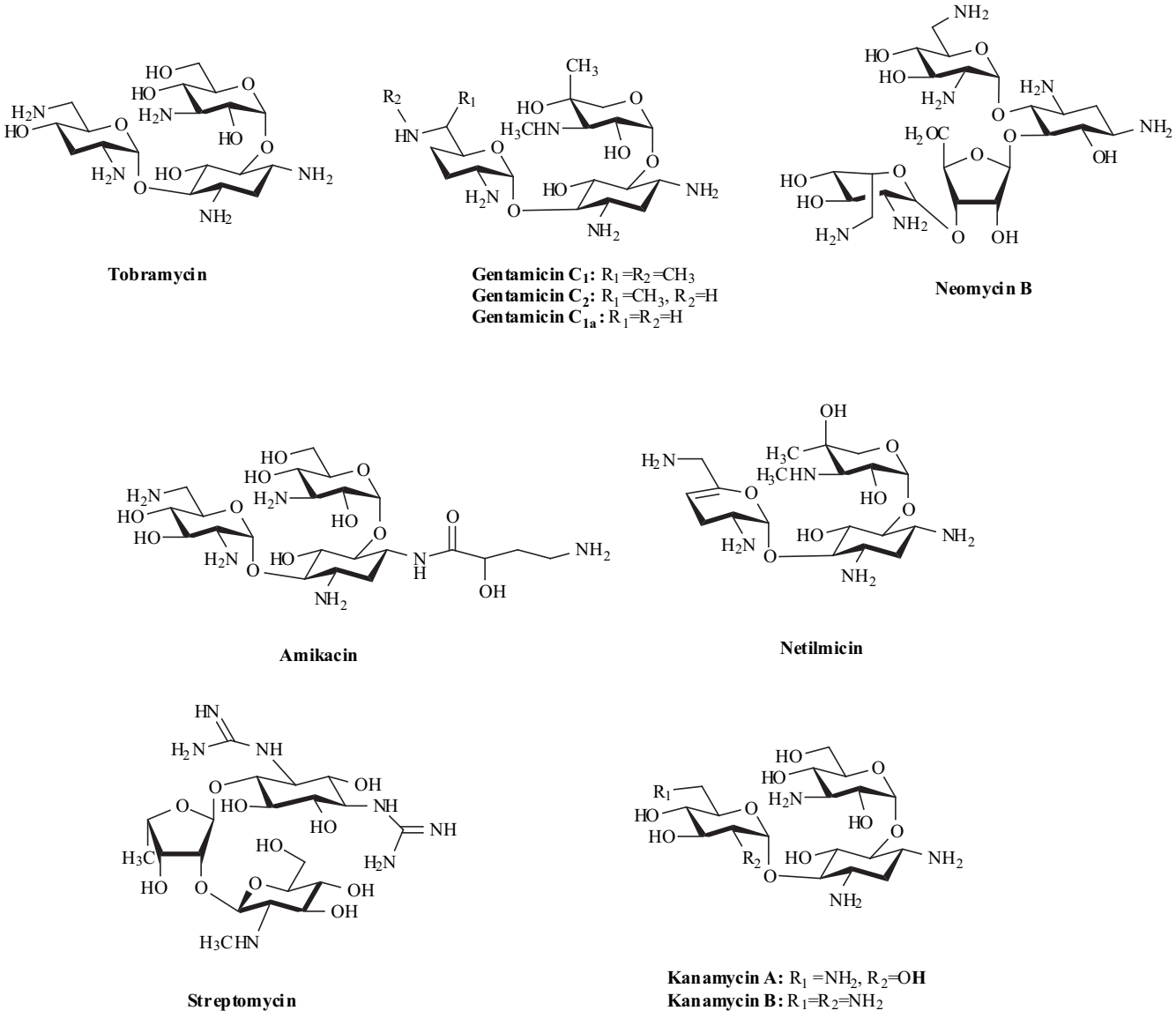
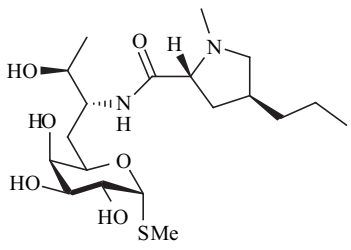
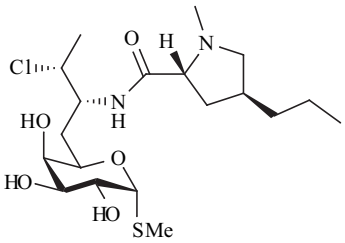



**Fig. (16).** Selected common aminoglycoside antibiotics.



**Lincomycin**



**Clindamycin**

**Fig. (17).** The α-thioglyosides lincomycin and clindamycin.

binding is generally low, even with inflammation concentrations in tissues and secretions are much less than those in plasma levels. In the absence of renal insufficiencies, they all have the same half-life in plasma of about 2 to 3 hours [81]. Due to their inherent activity they offer themselves as model compounds from which to base an antibiotic drug discovery program and such programs have been undertaken [82].

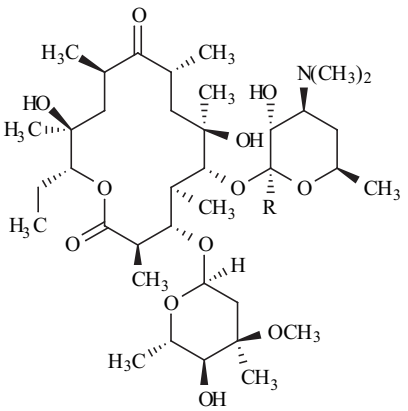
## Lincomycin, Clindamycin and the Macrolides

The macrolides are very similar in structure and activity Fig. (**18**), as are Lincomycin and Clindamycin Fig. (**17**). All the macrolides, Lincomycin, and Clindamycin are absorbed when taken orally, and Erythromycin, Lincomycin, azithromycin, and clindamycin can also be given parenterally. All are primarily bacteriostatic and bind to the 50S subunit of the ribosome, thus inhibiting bacterial protein synthesis [83].

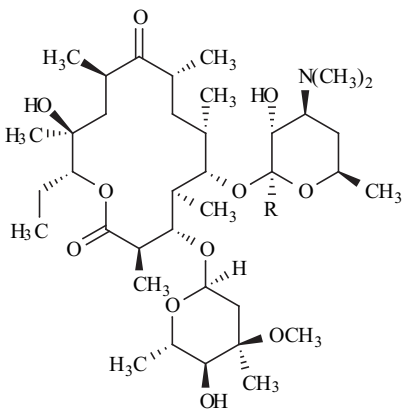
Clindamycin and Lincomysin are good examples of thiopyranosides with excellent pharmacokinetic properties. Clindamycin is an antibiotic used to treat anaerobic infections and is rapidly absorbed after oral administration. Absorption of an oral dose is virtually complete (90%). It is widely distributed in body fluids and tissues, with the average biological half-life about 2.4 hours. The drug is predominantly metabolised to inactive metabolites with only about 15% of active drug excreted [84]. Active against a range of microorganisms, lincomycin is also rapidly orally absorbed reaching average peak serum levels of approximately 3 μg/mL in 2 to 4 hours. Following oral administration, therapeutic levels of lincomycin are maintained for 6 to 8 hours for most susceptible gram-positive organisms. Administration intramuscularly or by intravenous administration of a single dose of 600 mg of Lincomycin provides a therapeutically effective level of the antibiotic for 14 to 20 hours. The biological half-life after oral, intramuscular or intravenous administration is 5.4 ± 1.0 hours. Lincomycin is clinically effective against *Staphylococcus aureus* (penicillinase- and non-penicillinase producing strains) and *Streptococcus pneumoniae* [85].

A member of a class of antibiotics known as the macrolides, Erythromycin is similarly active against a range of infections. Orally administered Erythromycin base and its salts are generally readily absorbed in the microbiologically active form. Erythromycin is largely bound to plasma proteins, and the freely dissociating bound fraction after administration of Erythromycin base represents 90% of the total Erythromycin absorbed. After absorption, erythromycin diffuses readily into most body fluids, about 95% of the dose is completely metabolised. To ameliorate problems of stability in the stomach, the drug is delivered in a pellet with an enteric coating. After administration of a single dose of a 250-mg Erythromycin delayed-release capsules, peak serum levels in the range of 1.13 to 1.68 μg/ml are attained in approximately 3 hours and decline to 0.30-0.42 μg/ml in 6 hours [86].

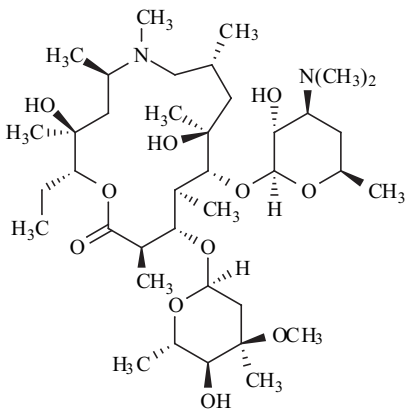
Another macrolide Clarithromycin, is active against a range of anaerobic and aerobic bacterium as well as most avium mycobacterium complex microorganisms. It is



**Erythromycin A**



**Clarithromycin**



**Azithromycin**

**Fig. (18).** The macrolide antibiotics.

rapidly absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability of 250-mg Clarithromycin tablets was approximately 50%. In fasting healthy human subjects, peak serum concentrations were attained within 2 hours after oral dosing. Steady-state peak serum Clarithromycin concentrations were attained in 2 to 3 days and were approximately 1 mcg/ml with a 250-mg dose administered every 12 hours, 2 to 3 μg/ml with a 500 mg dose administered every 12 hours, and 3 to 4 mcg/ml with a 500-mg dose administered every 8 hours. The elimination half-life of Clarithromycin was about 3 to 4 hours with 250 mg administered every 12 hours but increased to 5 to 7 hours with 500 mg administered every 8 to 12 hours. Similarly, to its sister compounds the macrolide Azithromycin is also rapidly absorbed and widely distributed throughout the body following oral administration.

## FUTURE DIRECTIONS

### Transport

Although incompletely explored, the availability of endocytic receptors for sugars may allow transport of carbohydrate-based drugs to target specific areas, for example hepatic sinusoids, despite relatively poor inherent drug bioavailability. These receptors can be utilised to provide explicit and site directing ligands to target drugs (or functional groups with drug like effects) to various cell types. A suitably active carbohydrate structure conjugated to a drug may be transported after interaction with a specific carbohydrate receptor thereby enhancing delivery of the drug to a target organ or tissue. A drug can also utilise a carbohydrate specific ligand or receptor when conjugated to a carbohydrate moiety as a prodrug. However in that case the carbohydrate moiety needs to be chemically cleaved in order for the drug to have its effect

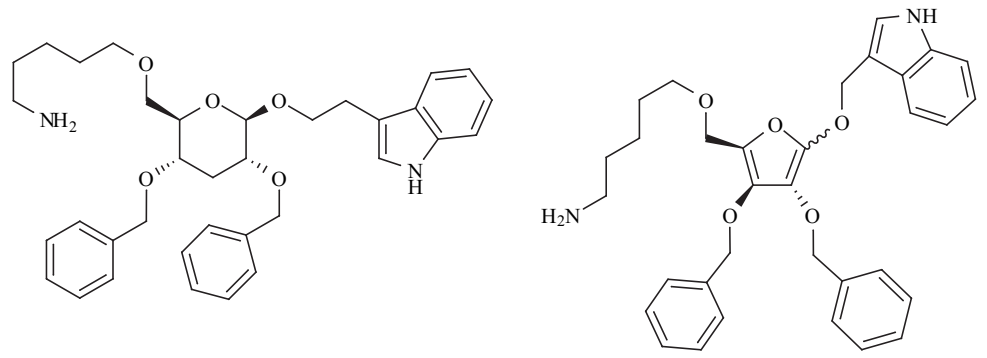
There are numerous receptors for the active transport of saccharides into cells and across cell membranes, which can be exploited for targeting including the glucose receptors, GLUT 1 to 12 [87, 88]. These receptors are pivotal in maintaining mammalian cell function, as glucose is the predominant source of ATP generation and substrate storage. Glucose is hydrophilic and requires active transport to facilitate its movement into cells. These are serpentine proteins with 12 membrane-spanning helices and they have different tissue distributions (GLUT1- erythrocytes, brain, microvessels; GLUT2 -liver, pancreatic islets; GLUT3 – neuronal cells) and different affinities for glucose with some members having a higher affinity for fructose. Studies in which glucose was conjugated to dopamine, [89] and the anti-HIV agents Saquinavir, Indinavir and Nelfinavir [90, 91] have been reported. The dopamine studies concluded that although the compounds were active *in vitro*, the glycosyl dopamine did not have anti-parkinsonian properties, probably due to slow bioconversion of the pro-drug into dopamine. The *in vivo* activities of the anti-HIV drugs were not reported although the more labile of the glucose containing pro-drugs had demonstrated improved anti-HIV activity *in vitro*. However, metabolically stable glucosidic pro-drugs that could cross the blood brain barrier have been described. The administration of certain Deltomorphin and Dermorphin analog glycopeptides led to dose dependent antinociception in tail flick tests while being more potent than the equivalent parent peptides. The gylco-analogs modified at position 4 displayed low opioid properties while $Thr^7$ glycosylated peptides displayed remarkable activity *in vivo* being 20 and 6 times more potent than Morphine and Dermorphin, respectively [92].

There are numerous other receptors that can be targeted by sugar moieties including mannose receptors (nonparenchymal liver cells) and the asialoglycoprotein (galactose) receptor. The asialoglycoprotein receptor can bind molecules with highly clustering galactose residues and these receptors are expressed exclusively on hepatocytes [93]. However although a useful indication, the galactose receptor is often reduced in liver disease making this a less attractive target for the development of hepatic disease therapies.

The mannose receptor (MR) is an endocytic receptor for glycans expressed in a number of tissues, including the hepatic sinusoids. The MR contains eight tandem carbohydrate recognition domains that bind terminal mannose, fucose and *N*-acetylglucosamine residues [94]. The mannose receptor also contains an N-terminal cysteine rich domain that binds sulfated sugar moieties including N-acetylgalactosamine, chondroitin sulphates A and B and sulphated Lewis$^a$ and $^b$ groups [48, 95]. A study of the serum of MR deficient mice revealed that there was an elevated level of several inflammatory proteins in the serum. This indicated that MRs played an essential role in the clearance of serum glycoproteins and possibly offers an opportunity to regulate serum levels of inflammatory response proteins in health and disease [96]. Blocking the function of the receptors with a mannose mimetic may help prolong to serum half-life of glycoproteins which are being used in the treatment of disease (eg. Antibodies). Conversely, activation of these receptors utilising a mannose binding lectin can mimic many of the functional characteristics of IgM, IgG and C1q and activate a range of activities spanning from defence against bacteria *via* complement activation, to disease modulation. Indeed, when levels of this lectin are low there is an increased incidence of infection and an association with autoimmune rheumatic diseases [49].

### Carbohydrate Based Peptidomimetics

Not only are carbohydrates pharmaceutically useful as drugs in themselves, and as targets for the development of carbohydrates based mimetics, they also demostrate untapped potential as scaffolds for drug discovery. There are several reasons that monosaccharide rings are potentially interesting templates: (i) there is a wide variety of structural diversity available, there are numerous different monosaccharides each with a fixed ring that allow access to different regions of molecular space, Fig (**19**), (ii) a high degree of oxygenation contributes to end-product water solubility, important when establishing viable drug candidates, and (iii) monosaccharides are highly functionalised, with each functional group able to be distinguished, thus allowing for dense structural and functional diversity to be implemented around a simple core scaffold. Interest began in the use of monosaccharides as



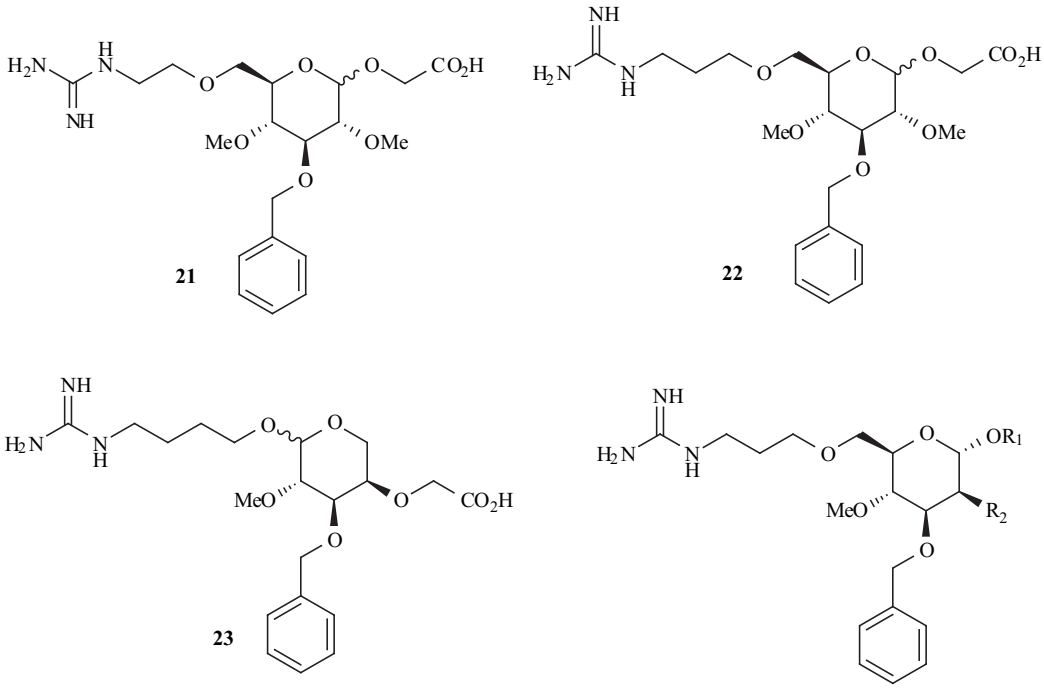
**19** **20**

**Fig. (19).** Two early examples of somatostatin mimetics. Incorporation of benzyl substituents increases lipophilicity whilst the ether functions maintain some level of water solubility.

drug discovery scaffolds over ten years ago [97] and there has been consistent research undertaken in this challenging area since that time. Examples of somatostatin mimetics are compound **19** [98] and **20** [99] one exploiting a 3-deoxy-glucopyrano ring system and the other a xylofurano ring system.

These early example were more concerted syntheses as opposed to being generated from a combinatorial drug discovery methodology. It was evident alternate chemistries were required to effect synthetic processes that allowed access to a vast array of structural and functional diversity. A slightly more discovery based approached saw the synthesis of a small library of 9 compounds Fig. (**20**) [100]. Whilst there were some common intermediates, essentially each member of this library was prepared in a separate linear synthesis, an arduous and time consuming way to obtain structural and functional diversity.

The above mentioned methodology, when used in conjunction with molecular modelling allows for prediction of which scaffold to use and in which positions to couple which isostere. Recently another small very simple, peptidomimetic library was synthesised based this time on a mannose scaffold [101] Fig. (**21**). The investigators were attempting to mimic a Leu-Asp-Thr (LDT) motif of the MAdCAM-1 ligand, a ligand recognised as a potent and selective inhibitor of MAd-CAM-1/$\alpha_4\beta_7$ ligand integrin

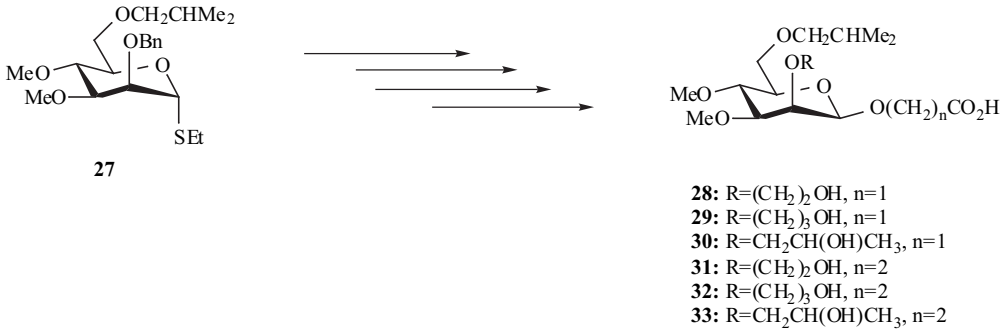


**21** **22**

**23**

**24:** $R_1$=Me, $R_2$=$OCH_2CO_2H$
**25:** $R_1$=$OCH_2CO_2H$, $R_2$=H
**26:** $R_1$=$OCH_2CO_2H$, $R_2$=1

**Fig. (20).** An example of a small array of potential peptide mimetics, each compound is essentially an amino acid, containing a amine or a guanidino group, and a carboxylate function. The molecules also contain a phenylalanine isostere. The capping of the hydroxyl groups with a methyl group further increases lipophilicity.




**27**

**28:** R=$(CH_2)_2OH$, n=1
**29:** R=$(CH_2)_3OH$, n=1
**30:** R=$CH_2CH(OH)CH_3$, n=1
**31:** R=$(CH_2)_2OH$, n=2
**32:** R=$(CH_2)_3OH$, n=2
**33:** R=$CH_2CH(OH)CH_3$, n=2

**Fig. (21).** A mannose building block provides a scaffold for a range substances designed to mimic a Leu-Asp-Thr motif.

interaction [102]. Molecular modelling studies (Insight II, DISCOVER, CVFF) confirmed that the mannose scaffold was the most appropriate to use for correct presentation of a LDT mimetic sequence.

The investigators noted that all compounds synthesised have the requirements necessary for orally available drugs, and further that the active compound **32** fulfilled Lipinski's rules for bioavailability. It does not require too much of an intuitive leap to see that derivatives of structures such as licomycin, clindamycin, zanamivir, oseltamivir and amiprilose could be accessed in a combinatorial fashion using such a methodology. Of course the use of such an approach is far wider reaching, particularly as already detailed, in regard to molecular mimicry of protein turns and cyclic peptides.

## CONCLUSION

Advances in oligosaccharide synthesis and the application of new chemical tools have resulted in the availability of many potential new drug-like carbohydrate based compounds. It is well known that there is a sometimes complicated relationship between a given drug's physical properties and the disease state which it targets. For example, gastro-intestinal stability may not be an issue if the preferred route of administration is subcutaneous, and similarly, degree of plasma protein plasma binding may be irrelevant if the site of action of the drug is the intestine.

It can be seen that for carbohydrate based therapeutics, both those in the clinic and those under development, that the degree of oral bioavailability is varied and thus bioavailability should be considered in the context of use. There are positive signs that within the future generations of carbohydrate based therapeutics being developed, bioavailability can be tailored. In general, for carbohydrate therapeutics the pharmacokinetics, $t_{1/2}$ etc., are good. Drug excretion is predominantly *via* usual pathways and in most cases unmetabolised, which is a positive indication. Additionally, several examples of carbohydrate based therapeutics cross the blood-brain barrier.

It has long been recognized that drugs can be conjugated to a sugar molecule to improve targeting, solubility, stability. It is now well evidenced that carbohydrates themselves can act as biological response modifiers. Recent advances in the understanding of the myriad of enzymes that regulate carbohydrate synthesis and processing will enable selection of clinically relevant targets for inhibitor design and metabolic deviation. This combined with the potential for oligosaccharides, with physico-chemical characteristics tailored for *in vivo* stability to target cell surface interactions, represents a potential vast new area for medicinal chemistry research.

A diversity of therapeutic indications has been discussed suggesting a general utility of this class of molecules.

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