

Carbohydrate based Potential Chemotherapeutic Agents: Recent Developments and their Scope in Future Drug Discovery

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Abstract: In addition to being valuable source of energy, carbohydrates, one of the main dietary components, are integral parts of the cell. As extra- & intracellular molecules they act as cell surface receptor and also as signaling molecules playing predominant role in molecular recognition and many other cellular processes. The clear understanding of their role in the various important biological events has led to the demand for easy access of diverse glycoconjugates for their complete chemical and biological investigations. Several carbohydrate-based molecules both of synthetic and natural origin are known for their wide range of pharmacological activities and even many of them are clinically used to treat different ailments. Due to their structural diversity in terms of functional groups, ring size and linkages they are valuable scaffolds in drug discovery processes. Because of the hydrophilic nature of monosaccharides they offer good water solubility, optimum pharmacokinetics and decreased toxicity. These naturally occurring molecules have therefore been extensively used to access diverse library of compounds with great chemotherapeutic importance. This review highlights an overview of development of carbohydrate-based molecules from others and our lab which have shown promising biological activity against front line diseases.

Keywords: Glycoconjugates, Antitubercular agent, Antibiotics, NIDDM, Glycopeptides, Carbohydrates, Drug development.

1. INTRODUCTION

Carbohydrates, one of the most abundant biomolecules in nature are essential molecules for sustaining and survival of the living beings [1]. As the main dietary components in the form of table sugar, starches and fibers they are useful to control the body weight, and sometimes to treat diverticulosis, diabetes, and heart disease. The primary function of carbohydrates is to provide energy for the body, especially the brain and the nervous system. An enzyme called amylase helps in breakdown of carbohydrates into glucose (blood sugar), which is used for energy by the body. In addition to energy source, carbohydrates as extra- and intracellular molecules are involved in molecular recognition as cell surface receptors, signaling molecules and many other biochemical reactions including the immune reactions [2-7]. Several glycoconjugates such as glycolipids, glycoproteins or glycopeptides & glycosylated natural products are frequently being used as antimicrobial drugs and also emerging as anti-cancer drug candidates. The glycosylation of many biologically active natural products is known to decrease toxicity, increase water solubility and improve pharmacokinetics. Moreover, in several cases the presence of sugar component is essential for the observed biological activity. Several simple carbohydrate-based molecules are known for their remarkable pharmacological activities and even some of them are currently being clinically used [8-15].

In view of the above there is an increasing demand for the carbohydrate based compounds in drug discovery and development involving different molecular events such as inter-and intracellular recognition, adhesion, migration, invasion, communication, bacterial and viral infection, and tumor metastasis etc [16-19]. Towards this end, tremendous efforts have been made to access a large variety of carbohydrate based molecules involving new and innovative techniques. This review highlights an overview of development of carbohydrate-based molecules by our group and others showing promising biological activity against different parasitic, microbial and metabolic diseases.

2. CARBOHYDRATES: CLASSIFICATION

Depending on the chemical structure of the food and how quickly the sugar is digested and absorbed, carbohydrates can be classified as simple or complex. Examples of simple single sugars from foods include Fructose (found in fruits), Galactose (found in milk products); and double sugars such as Lactose (found in dairy), maltose (found in beer and some vegetables), sucrose (table sugar), etc. Honey is also double sugar, but unlike table sugar, it contains a small amount of vitamins and minerals. Complex carbohydrates, referred to as 'starchy' foods include legumes, starchy vegetables, cereals, and whole-grain breads. The polysaccharides can be further classified into homopolysaccharide and heteropolysaccharide.

Chemically carbohydrates are polyhydroxy aldehydes or ketones or their derivatives containing carboxyl, amino or other groups. These molecules can be classified according to

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the number of carbohydrate unit in each chemical structure namely monosaccharides, disaccharide, oligosaccharides and polysaccharides. Monosaccharides have been classified as tetroses, pentoses (D-ribose (**1**), D-arabinose), hexoses (*e. g.* D-glucose (**2**), D-galactose, D-mannose, etc), heptoses, octoses and nonoses (neuraminic acid) etc (Fig. 1) depending upon the number of carbon atoms present in the molecule. Furthermore, they can also be classified as reducing or non-reducing sugars. L-ascorbic acid (**3**), a very important naturally occurring molecules can be placed in the category of six carbon containing sugar [20]. Sialic acids contain a 9-carbon backbone and are more structurally complex molecules as compared to five- or six- carbon monosaccharides, but known for the most important recognition elements as terminal sugars [21]. They have been predominantly found as the terminal carbohydrate units on glycoproteins, glycolipids of vertebrates, components of capsular polysaccharides, or lipo-oligosaccharides of pathogenic bacteria. The three basic forms of sialic acids includes *N*-acetylneuraminic acid (**4**, Neu5Ac), *N*-glycolylneuraminic acid (**5**, Neu5Gc), deaminoneuraminic acid (**6**, KDN), and their structural modifications with different substitutions (at *C*-4, *C*-5, *C*-7, *C*-8, and/or *C*-9 positions) lead to more than 50 different sialic acids in nature that further increase the complexity of sialic acid-containing structures [22].

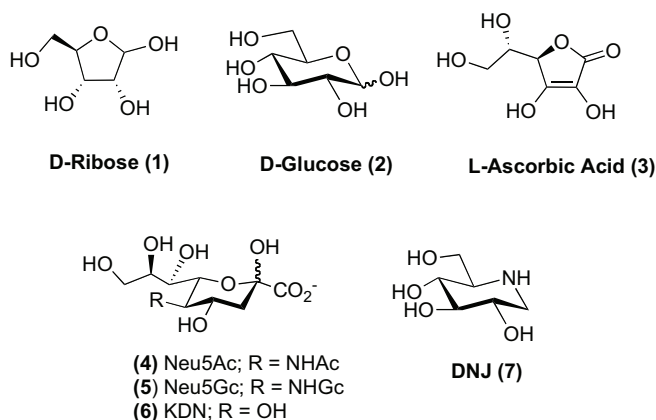


Fig. (1). Biologically important monosachharides.

Iminosugars, for example deoxynojirimycin (DNJ, **7**), where the ring substitution of the endocyclic oxygen of carbohydrate is replaced by nitrogen atom, form undoubtedly the most fascinating and attractive class of carbohydrate mimics [14,23,24]. Since the discovery of their biological activity as glycosidase inhibitors in the 1970's, they have progressively made their way from the laboratory to the clinic. These molecules have potential to act as new tools for studying the biological functions of oligosaccharides, and also as new generation of emerging carbohydrate-based therapeutics for the control of wide range of diseases including diabetes, HIV, hepatitis, cancer, Gaucher's disease, and viral infections such as influenza [14].

The role of carbohydrates in the body is well understood as they supply energy; provide fuel for the Central Nervous

System (CNS) and also for the muscular system. They are known to spare proteins, and finally supply 'Dietary Fiber'. Several simple carbohydrate-containing molecules are known for their great chemotherapeutic potential. Carbohydrates with sialic acid backbone play pivotal roles in many of the pathologically and physiologically important biological processes. Several sialic acid-containing molecules including Relenza, Tamiflu etc are known for their great chemotherapeutic potential.

3. IMPORTANCE OF FURANOSE SUGAR IN DRUG RESEARCH

Furanose sugars as the essential component of the genetic material, the nucleic acids, (RNA and DNA) play important roles in living organisms. It is speculated that sugars in furanose form offer the better fit conformation for eliciting the biological response. Several other biologically active compounds found in nature do also possess furanose skeleton. A study on gluconic and mannonic amino acids where furanoid form incorporated into Leu-enkephalin (**8**), replacing its Gly-Gly portion has been shown to provide flexible and amenable conformations depending on the binding environment. Among the above carbopeptides, one with furanose sugar (**9**) exhibited analgesic activity similar to that of Leu-enkephalin methyl ester while carbopeptide derived from mannonic amino acid did not show any significant activity (Fig. 2) [25]. It is explained on account of the presence of pre introduced folded conformations that are absent in the biologically inactive pyranoid GAA (Glycosyl amino acid) containing Leu-enkephalin analogous. The above finding indicates that furanoid sugar amino acid can serve as useful templates to induce secondary structure in peptides.

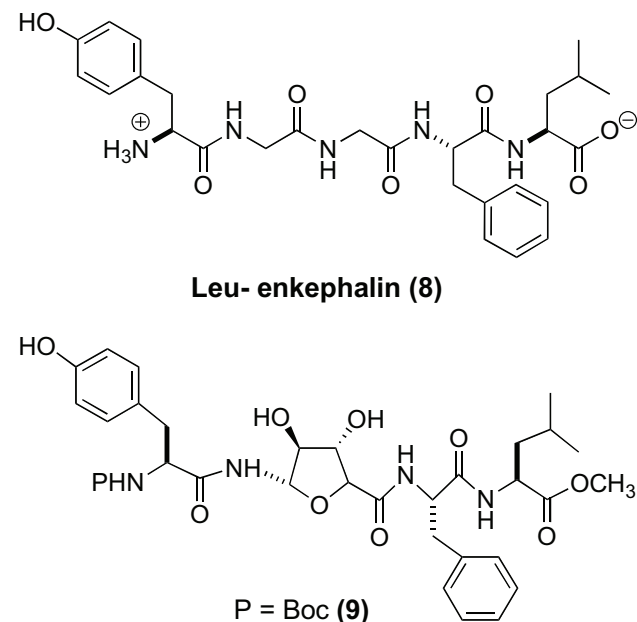


Fig. (2). Replacement of two amino acids in Leu-enkephaline with furanose sugar.

4. CARBOHYDRATE DERIVATIVES AS CHEMOTHERAPEUTIC AGENTS

4.1. Carbohydrate based Antibiotics

Several carbohydrate based antibiotics have been isolated from different sources of flora and fauna. Plants, microbes and marine organisms have been a continuous source of several antibiotics of carbohydrate origin (Fig. 3, 4 and 5) [26a]. Recently, Singh *et al.* have reviewed the natural products as source of antibacterial agents with broad spectrum of activities [26b]. The majority of the known carbohydrate-containing drugs are antibiotics, which are bacterial or fungal products or synthetic antibacterial substances that inhibit the growth of other organisms [27]. The cell wall of bacteria is largely composed of an array of oligosaccharides which are required for the integrity of the cell wall and also responsible for the transport of nutrients and drugs. Several classes of nucleoside antibiotics including liposidomycin (**12**), tunicamycin (**13**), mureidomycins (**14**) *etc.* (Fig. 3). are known to inhibit the biosynthesis of peptidoglycan layer by inhibiting the phospho-MurNAc-pentapeptide translocase [28]. Till date, Ramoplanin (**38**) is the only clinically used antibiotic which is known to inhibit the GlcNAc transferase [29].

The macrolides erythromycin A (**10**), isolated from *Streptomyces erythreus*, is primarily used against the major respiratory pathogens and widely prescribed for children. Its limited spectrum of antibacterial action and limited solubility in acidic medium is concerning. Due to the higher potency, broader spectrum of activity, improved physicochemical and pharmacokinetic profiles, and attenuated side effects, the second generation macrolide antibiotics such as clarithromycin (**11**), roxithromycin (**15**), azithromycin (**16**), dithromycin (**17**), telithromycin (**18**) have gradually been added in the arsenal of anti-infectives to replace erythromycin A [30]. Telithromycin (**18**) was approved for the once daily oral dose for treatment of respiratory tract infections in USA, Europe and some Asian countries. However, the second generation variants also have poor activity against macrolide resistant pathogens. This compound displays bactericidal activity by blocking the progression of the growing polypeptide chain through binding with the 50S subunit of ribosome.

Erythromycin (**10**) exerts antibacterial activity through inhibition of protein synthesis by binding to peptidyltransferase site of 50S subunit [31]. Among other derivatives, cethromycin (**19**), EP-420 (**20**) and BAL-19403 (**21**) are currently in clinical development [32]. Cethromycin (**19**) has demonstrated clinically and statistically significant survival rate in placebo-controlled non-human primate studies with anthrax, plague and tularemia. FDA has recently given orphan drug designation to compound **19** for the treatment of plague and tularemia. Likewise, EP-420 (**20**), a bridged bicyclic derivative of Erythromycin is currently under Phase II clinical development by Enanta and Shionogi for treatment of CAP (Community-Acquired Pneumonia) [33]. BAL-19403 (**21**), a macrolide antibiotic significant against clinical isolates of *Propionibacterium acnes* with mutations in the 2057 to 2059 region of 23S rRNA

conferring resistance to Erythromycin (**10**), is under clinical development for the treatment of acne [34].

Mitemincin (**22**) has successfully completed Phase-I trial by Chugai while Phase II trials in US are still running against diabetic reflux oesophagitis and idiopathic gastroparesis [35]. Phase-II trials of **22** against irritable bowel syndrome is also under process by Chugai Pharma. This compound is an agonist of motilin that lacks the antibiotic properties of erythromycin (**10**) and increases the amplitude & frequency of antral contractions and initiates gastric contractions.

The mode of action of the macrolide antibiotics involves the inhibition of bacterial protein biosynthesis through binding to the 23S ribosomal RNA of the 50S subunit and interfering with the elongation of nascent peptide chains during translation [36].

Tiacumicin B (**23**), a macrolactone isolated from actinomycetes, inhibits RNA synthesis and is under phase III clinical development by Optimer Pharmaceuticals for the treatment of *Clostridium difficile*-associated diarrhea (CDAD) [37]. Tobramycin (**24**) belongs to aminoglycoside family of antibiotics and it inhibits the protein synthesis in bacteria.

The lincomycin (**25**), obtained by fermentation of *Streptomyces lincolnensis* and its semi synthetic derivative clindamycin (**26**), were successfully used in clinics as oral antibiotics [38]. The mode of action of lincosamine involves binding to the ribosome and inhibiting bacterial protein synthesis. Specifically, macrolides, lincosamides, and streptogramin B type antibiotics bind to adjacent sites on the 50S ribosomal subunit [39]. Aminoglycoside antibiotics such as neomycin (**27**), streptomycin (**28**), and gentamycin (**29**) are among the oldest known class of antibiotics.

Moenomycin A (**30**) is a potent naturally occurring antibiotic inhibiting the bacterial cell wall synthesis by binding to the transglycosylases; which are responsible for the formation of the carbohydrate chains of peptidoglycan. Its distinctive mechanism of action is matched by its unusual structure and this is the only natural product inhibitor known which directly binds to transglycosylase enzymes [40].

Telavancin (**32**), a semisynthetic derivative of vancomycin (**31**), a FDA approved drug is being used for use against Gram-positive bacteria. Teicoplanin, an additional member of Vancomycin (**31**), the first glycopeptide introduced into clinical practice in 1959, is now available for human use. This class of compound is known to inhibit bacterial cell wall biosynthesis by recognizing and binding to the L-Lys-D-Ala-D-Ala termini of peptidoglycan precursor strands at the external side of the membrane. In this way, transpeptidases are prevented from executing their cross linking. This class of antibiotics are restricted to treat only Gram-(+) infections as they cannot penetrate the outer membrane of Gram(-) bacteria [41]. Dalbavancin (**33**), a semi-synthetic derivative of the teicoplanin analogue A40926 (**34**), was discovered by Biosearch Italia and being developed by Pfizer for the treatment of bacterial infections [42].

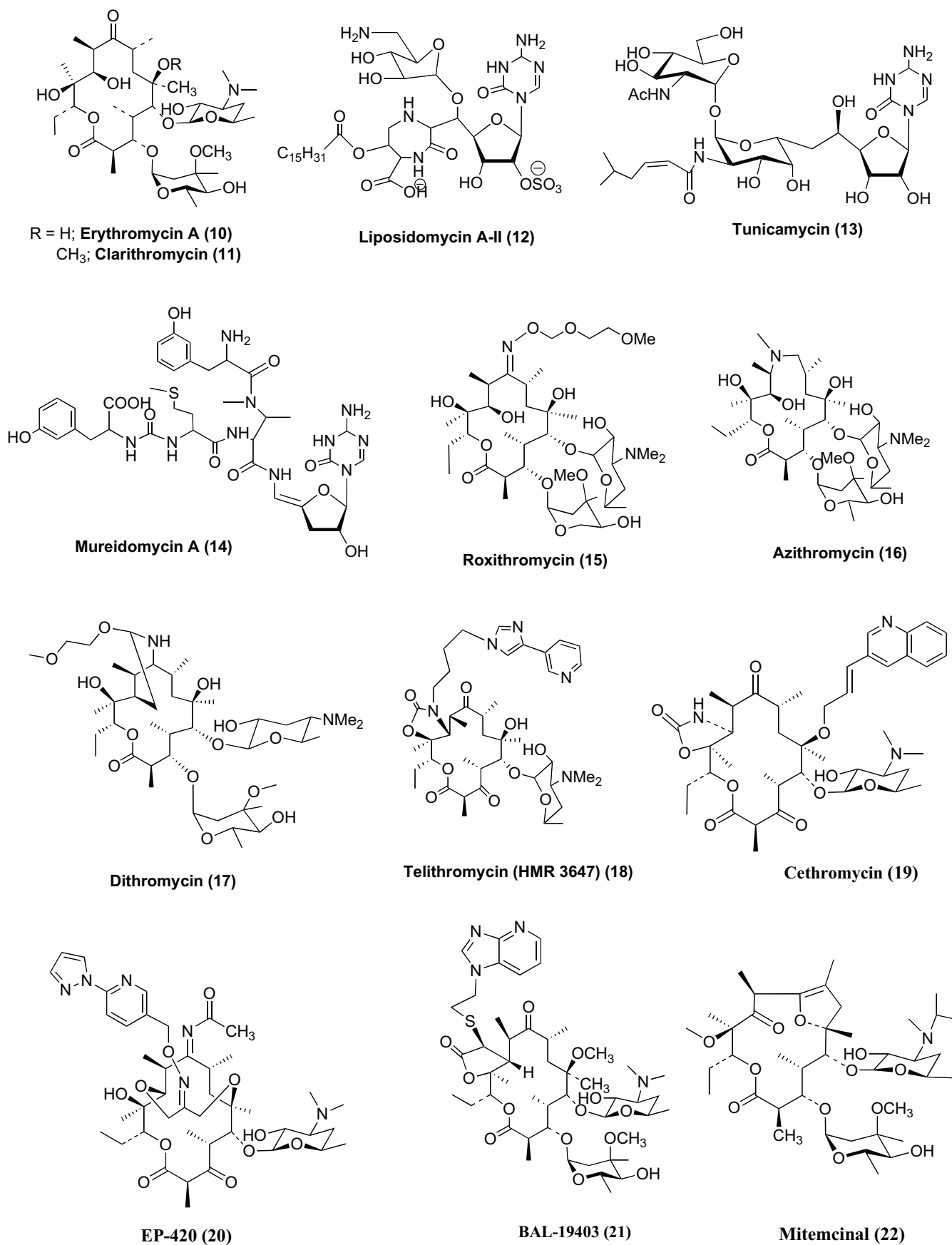


Fig. (3). Antibiotics with glycosidic linkages and macrolide glycosides as antibiotics.

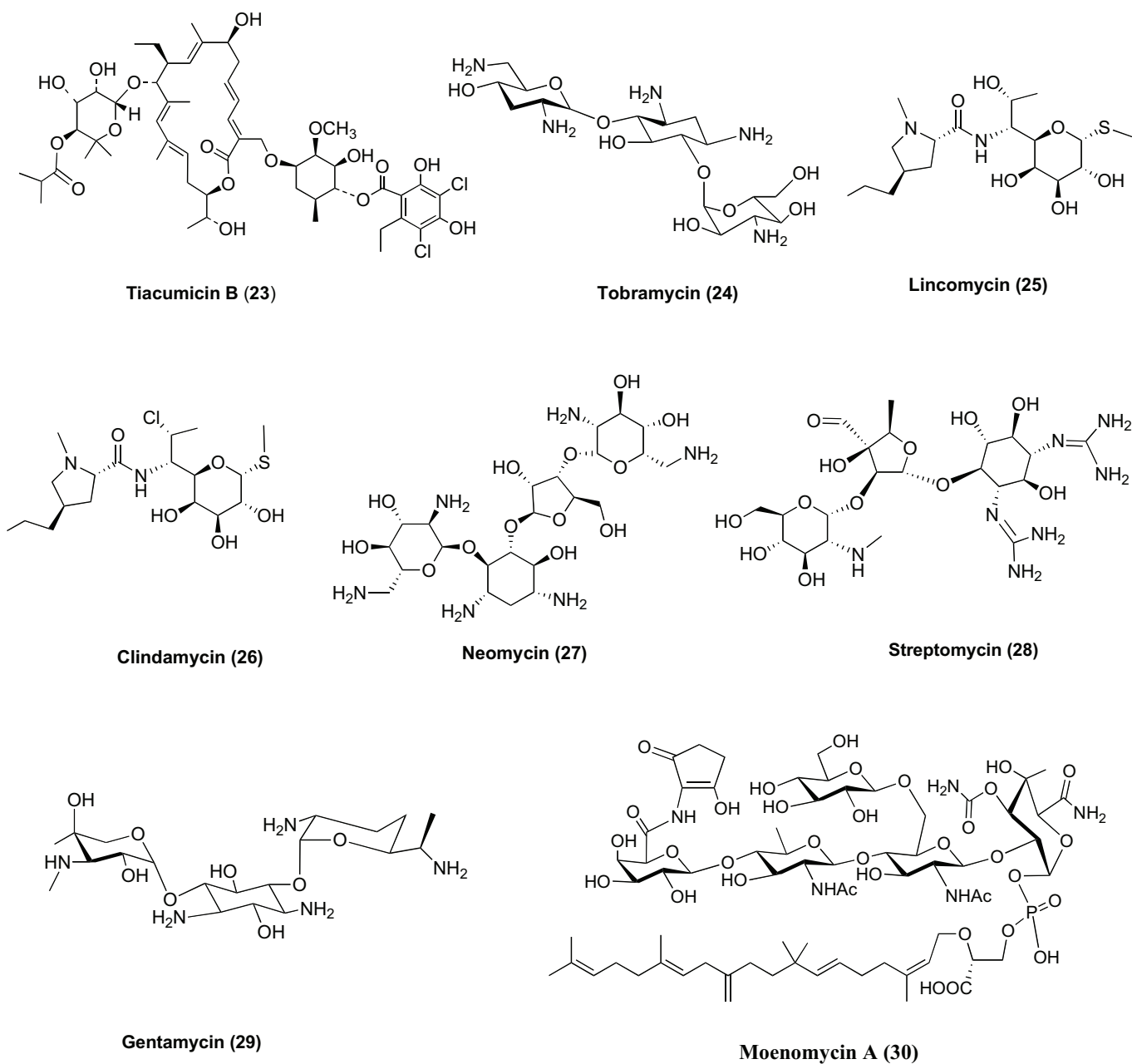


Fig. (4). Aminoglycoside antibiotics.

Oritavancin (**35**), a derivative of chloroeremomycin (**36**) known to inhibit cell-wall biosynthesis was developed by Eli Lilly and acquired by InterMune in 2001. Later on in 2005 it was transferred to Targanta Therapeutics and in 2008, an NDA for **35** was submitted to the FDA that unfortunately couldn't be approved due to insufficient data. TD-1792 (**37**), a vancomycin-cephalosporin heterodimer successfully evaluated by Theravance in Phase-II trials against cSSSIs including MRSA and it satisfied the primary and secondary endpoints of non-inferiority trial compared to vancomycin. This compound has been designed to target two key targets in bacterial cell wall synthesis.

Ramoplanin (**38**), the major component of the lipopeptide antibiotics is known to inhibit the cell wall synthesis in bacteria by forming U-shaped structures that are able to bind

and capture Lipid II (C35-MurNAc-peptide-GlcNAc), a specific intermediate in membrane formation [43]. Oscient Pharmaceuticals is evaluating orally active doses of **38** in Phase-II trials against *Clostridium difficile* associated GI tract infections [44].

4.2. Carbohydrate based Molecules Known as Potential Glycosidase Inhibitor

Many carbohydrate mimics including iminosugar- and aminoglycoside-based glycosidase inhibitors have been used as drugs to treat diabetes, viral infections, cancers, and Gaucher's disease. Iminosugars have emerged as versatile tools to develop new therapeutic agents [14]. The easy access of these sugars has led to the evolution of new anti-diabetics, antivirals and also agents to treat genetic disorders.

Biochemistry of D-iminosugar is well explored, whereas relatively little attention has been paid to the corresponding L-enantiomers. Recently, D'Alonzo *et al.* presented the biochemistry of L-iminosugar and their role in the inhibition mechanisms of specific enzymes and enzyme-inhibitor interactions, which led to reconsideration of the therapeutic skills of L-iminosugars in recent years [45].

Inhibition of all or some of the intestinal glycosidases and pancreatic α -amylase enzymes by inhibitors could regulate the absorption of carbohydrates and these inhibitors could be used therapeutically for the oral treatment of non-insulin dependent diabetes mellitus II [46]. Acarbose (**39**), a pseudotetrasaccharide anti-diabetic drug, was the first marketed α -glucosidase inhibitor used to treat type 2 diabetes mellitus. Later on, several carbohydrate mimics appeared and have been marketed for the treatment of NIDDM type II [47]. Miglitol (**40**), an oral anti-diabetic drug acts by inhibiting the breakdown of complex carbohydrates into glucose. It is primarily used in diabetes mellitus type 2 for establishing greater glycemic control by preventing the digestion of carbohydrates (such as disaccharides, oligosaccharides, and polysaccharides) into monosaccharides which can be absorbed by the body. Acarbose is also shown to inhibit enzyme such as glycoside hydrolases to be specific α -glucosidase in the brush border of the small intestines and pancreatic α -amylase. Pancreatic α -amylase hydrolyzes complex starches to oligosaccharides in the lumen of the small intestine, whereas the membrane-bound intestinal α -glucosidases hydrolyzes oligosaccharides, trisaccharides, and disaccharides to glucose and other monosaccharides in the small intestine. Inhibition of these enzymes reduces the rate of digestion of complex carbohydrates. Voglibose (**41**), a product of Takeda Pharma Company, Japan, delays the absorption of glucose thereby reducing the risk of macrovascular complications. The acarbose, miglitol and voglibose may decrease the carbohydrate digestion rate and thus can reduce postprandial hyperglycemia. Since compound **39** prevents the degradation of complex carbohydrates into glucose, some carbohydrate will remain in the intestine and be delivered to the colon. In the colon, bacteria digest the complex carbohydrates, causing gastrointestinal side-effects such as flatulence and diarrhea.

Several glycosidase inhibitor-based molecules (Fig. 6) are shown to possess anticancer activity. Miglustat (*N*-butyl-deoxynojirimycin, **42**), a synthetic analogue of D-glucose, is the first iminosugar which is used primarily to treat Type 1 Gaucher disease under the trade name Zavesca. Miglustat inhibits glucosylceramide synthase, an essential enzyme for the synthesis of most glycosphingolipids (GSL). Miglustat is used to treat adults with mild to moderate type 1 Gaucher patients for whom enzyme replacement therapy is unsuitable and it is the first treatment to be approved for patients in the European Union for the treatment of progressive neurological manifestations in adult or pediatric patients with Niemann-Pick type C disease (NPC).

Since carbohydrates play a vital role in living organism, a slight defect in their metabolism can have disastrous consequences *e.g.* Gaucher's and Fabry's diseases. This

inherited mutations in carbohydrate-processing enzymes cause glycosphingolipids to accumulate leading to the damage of kidneys, heart and brain [48,49]. Some carbohydrate mimics including *N*-butyl-1-deoxy-nojirimycin (**42**), *N*-methyl-1-deoxy-nojirimycin (**43**) and *N*-butyl-1-deoxy-galactonojirimycin (**44**) are known for the treatment of Gaucher's and Fabry's diseases [50]. Other bicyclic iminosugars for example swainsonine (**45**) and castanospermine (**46**) are at present under clinical trials for anticancer drug candidate. They are shown to be inhibitors of catabolic glycosidase associated with cancer progresses.

Neu5Ac2en (**47**), a dehydrated neuraminic acid derivative, is a transition state analog inhibitor of sialidases. In recent years, two such competitive inhibitors namely Relenza (**48**) and Tamiflu (**49**) were developed for the viral disease with an aim to overcome the low efficacy and poor selectivity of Neu5Ac2en for the inhibition of neuraminidases, an influenza virus. Well-known neuraminidase inhibitor Reneza (**48**) has successfully been used in the treatment of both influenza A and influenza B and it acts by inhibition of influenza virus neuraminidase with the possibility of alteration of virus particle aggregation and release [51].

The highly selective Cu(I)-catalyzed 1,3 dipolar cycloaddition of organic azides and terminal alkynes (click reaction) has extensively been applied to get a variety of products including a library of sixteen C-4 triazole substituted zanamivir analogues. One of the triazole based zanamivir analogue (**50**) substantially showed maximum anti-AIV activity ($IC_{50} = 6.4 \mu M$) comparable to zanamivir ($IC_{50} = 2.8 \mu M$) [52].

4.3. Development of Sugar based Potential α -glucosidase Inhibitor

We have developed selective, novel and potent glycosyl ureas and evaluated their α -glucosidase inhibitory activity. The glycosyl ureides (**51-53**) (Fig. 7) have shown very good α -glucosidase inhibitory activity and provided lead for further exploration as new class of anti-diabetic agents [53].

7-*O*- α -(2,3,5,6-bis-*O*-isopropylidene-1-*O*- α -D-mannofuranosyl)-4-propyl-coumarin (**54**) and ethyl 2-cyano-3-[3'-methoxy-4'-*O*-(2,3,5,6-bis-*O*-isopropylidene-1-*O*- α -D-mannofuranosyl)-phenyl] propenoate (**55**) (Fig. 7) have been synthesized and screened for α -glucosidase inhibitory activity. Both compounds **54** and **55** inhibited rat intestinal α -glucosidase more effectively than a standard drug acarbose (**39**) [54].

Recently, we have developed a series of 1,2,3-*H*-triazolyl glycohybrids with two or more than two sugar units or a chromenone moiety *via* CuAAC reaction of glycosyl azides to 2,3-unsaturated alkynyl glycosides or propargyloxy coumarins [55]. These hybrid molecules were screened for their α -glucosidase, glycogen phosphorylase, and glucose-6-phosphatase inhibitory activities. Few of these triazolyl glycohybrids (**56-59**) (Fig. 7) have shown promising inhibitory activities against these enzymes at 100 μM conc. as compared to acarbose and sodium-*ortho*-vandate (Table 1).

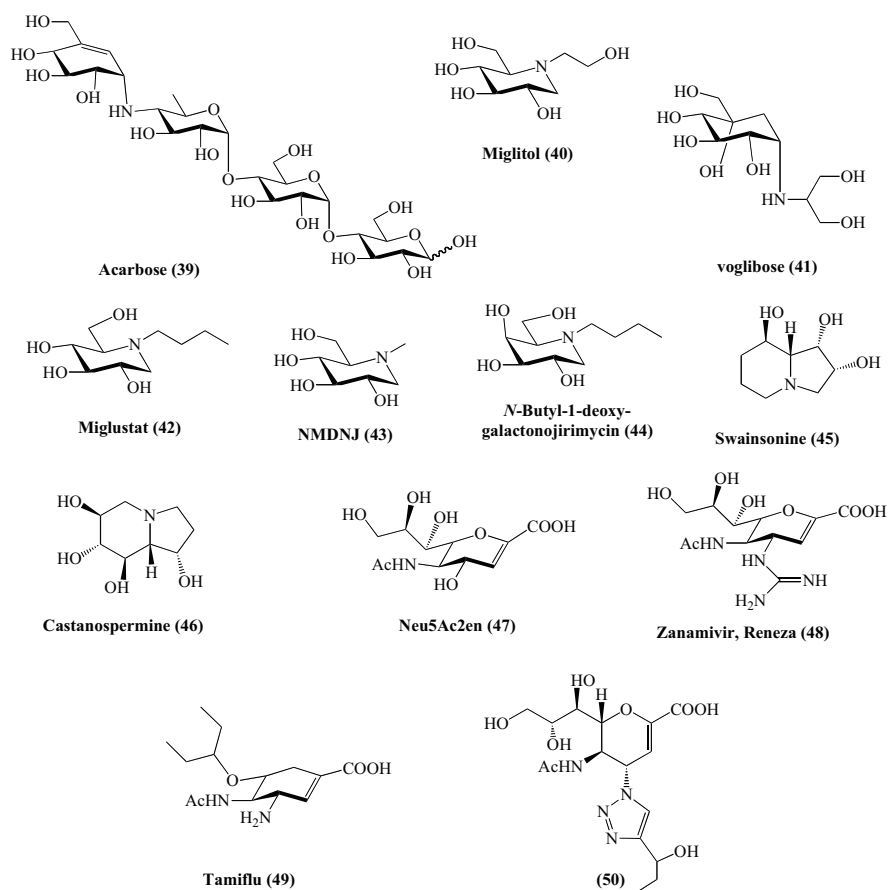


Fig. (6). Glycosidase inhibitors used clinically to treat diseases.

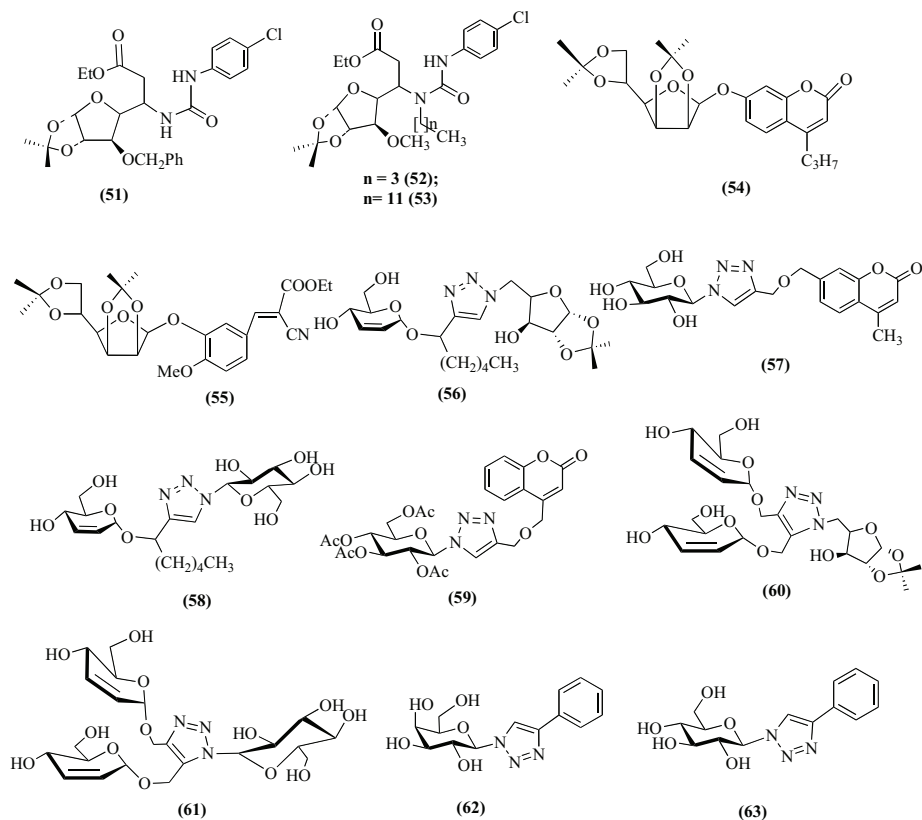


Fig. (7). Glycoconjugates with α -glucosidase inhibitory activities.

Table 1. Comparison of α -glucosidase, glycogen phosphorylase, and glucose-6-phosphatase inhibitory activities of 1,2,3-1H-triazolyl glycohybrids (56-59)

1H-triazolyl glycohybrids	α -glucosidase Inhibitory Activities	Glycogen phosphorylase Inhibitory Activities	Glucose-6-phosphatase Inhibitory Activities
Acarbose	60%	-	-
Sodium-ortho-vandate	-	-	36%
56	-	47.7%	up to 25%
57	-	34.1%	-
58	29.6%	20.0%	up to 25%
59	31.4%	-	-

In the above synthesis, triazolyl glycohybrids with one or two sugar unit(s) and coumarins were also prepared using thermal 1,3-dipolar cycloaddition reaction of corresponding sugar azides with different alkynes. The glycohybrids (**60** and **61**) have shown promising α -glucosidase, glucose-6-phosphatase and glycogen phosphorylase inhibitory activities [55a].

1- β -D-glucosyl-4-phenyl triazole (**62**) and 1- β -D-galactosyl-4-phenyl triazole (**63**) were recently reported as aglycone-modified inhibitors of β -glycosidase enzyme. They were screened against three β -glycosidase enzymes, the sweet almond glucosidase (SAG), *Escherichia coli* galactosidase (ECG), and bovine liver galactosidase (BLG). Triazolyl glycoside **62** showed moderate inhibition of ECG as compared to standard glycosidase inhibitors deoxygalactonojirimycin and deoxynojirimycin, whereas triazole **63** proved to be better inhibitor of BLG than the triazole **62**, but none of them showed good activity for SAG inhibition [56].

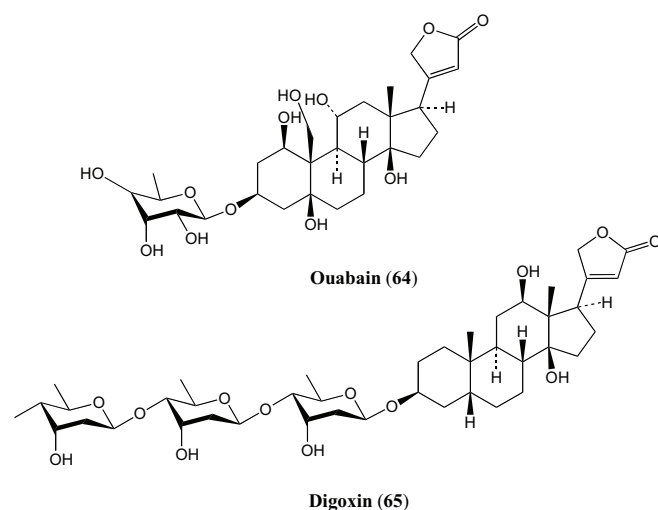
4.4. Cardiac Glycosides

Ouabain (**64**), (Fig. 8) a cardiac glycoside from ripe seeds of *Strophanthus gratus* and bark of *Acokanthera ouabaio*, is known to inhibit the plasma membrane Na^+/K^+ -ATPase *in vitro* or with intravenous dosage [57]. Well-known drug digoxin (**65**), also known as digitalis, a purified cardiac glycoside extracted from the foxglove plant, *Digitalis lanata*, is widely used for the treatment of various heart conditions, namely atrial fibrillation, atrial flutter and sometimes heart failure, which cannot be controlled by other medications. Its corresponding aglycone is digoxigenin, and the acetyl derivative is known as acetyldigoxin. Although the exact mechanism of action of this drug is not completely understood; yet it is expected to involve the Na^+/K^+ ATPase pump in the membranes of heart cells (myocytes) [58,59].

4.5. Drugs with Simple Carbohydrate Moieties

The structures of compounds with simple carbohydrate moieties important for medicinal used are depicted below (Fig. 9). Topiramate (**66**), an epilepsy drug for both children and adults has also been approved by the Food and Drug Administration (FDA) for the prevention of migraines [60]. Auranofin (**67**), an oral carbohydrate-containing gold compound is used in the treatment of rheumatoid arthritis.

This compound is under investigation as means of reducing the viral reservoir of HIV that lies latent in the body's T-cells despite treatment with antiretroviral therapy [61].

**Fig. (8).** Structure of some Cardiac glycosides.

A naturally occurring compound streptozotocin (**68**), having toxic effects on insulin-producing beta cells of the pancreas in mammals, is also being used for treating certain cancers of the Islets of Langerhans. Streptozotocin is approved by the FDA for treating metastatic cancer of the pancreatic islet cells [62]. As compound **68** received a substantial risk of toxicity and rarely cures the cancer, thus its use is generally limited to patients whose cancer cannot be removed by surgery. Vidarabine (**69**), arabinosyl nucleoside is clinically used drug for infections caused by herpes simplex and varicella zoster viruses [63]. Lactulose (**70**) is a synthetic disaccharide used in the treatment of constipation and hepatic encephalopathy, a complication of liver disease [64].

4.6. Carbohydrate-Containing NP-Antibody Anticancer Conjugates

Anticancer agents conjugated with various supports such as antibodies, polymers, liposomes and nanoparticles have extensively been explored in medicinal chemistry. For

example, Zinostatin stimalamer, conjugated with neocarzinostatin chromoprotein and polystyrene-co-maleic acid is useful against hepatocellular carcinoma. Gemtuzumab ozogamicin (**71**) linked to calicheamicin (**72**), obtained from *Micromonospora echinospora*, was co-developed by Wyeth and UCB Pharma. Likewise, inotuzumab ozogamicin (CMC-544), a calicheamicin-antibody conjugated with CalichDMH and hydrazone linker attached to humanized IgG4 anti-CD22 [65], is being developed by Wyeth and UCB Pharma in Phase II/III trials against non-Hodgkin's lymphoma in combination with rituximab, a chimeric human IgG1 antibody that targets another B-lymphoid lineage-specific molecule, CD20 (Fig. 10) [66].

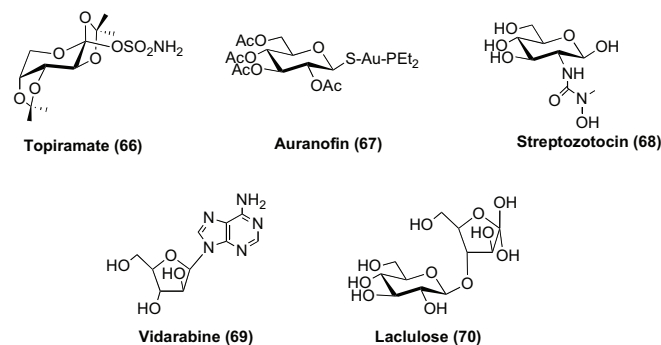


Fig. (9). Simple carbohydrate derivatives used as drugs.

4.7. Carbohydrate-based Vaccine Useful Against Meningitis, Malaria and Cancer

Because of development of resistance with known antibiotics, the carbohydrate vaccines were perused to cure against bacterial infection. It is known that the carbohydrates present on the cell surface of parasites are different from the host and these specific carbohydrate antigens may provide the way to develop effective natural as well synthetic vaccines. Several vaccines based on the purified cell-wall polysaccharides (CPS) or neoglycoconjugates (Fig. 11) are now commercially available [67] to treat several infections. The fragment of the Hib capsular polysaccharide is used in some of the licensed vaccines with a short five ribosylribitolphosphate repeating unit oligosachharides. The synthetic carbohydrate vaccine *Haemophilus influenzae* type b (Hib) is now commercially available as Quimi-Hib (**73**) to fight against meningitis caused by *Neisseria meningitides*, a Gram-negative in humans [68].

The malaria parasite initially infects the liver cells and then initiates blood-stage infection. The emergence of resistant forms of parasites and poor eradication of mosquitoes may lead to the basis for development of a vaccine against malaria [69,70]. Seeberger *et al.* have developed a glycoconjugate vaccine candidate by conjugating a hexasaccharide containing glycosylphosphatidylinositol (GPI) with keyhole limpet haemocyanin (KLH) protein through a spacer linker (**74**) [71].

Carbohydrate-based vaccines are widely used to prevent infectious diseases since long back, but their use to treat cancer has been known recently [72,73]. Carbohydrates, predominant over the surfaces of human cells, coordinate

several essential functions ranging from protein transport and cell-cell recognition to signal transduction and cell adhesion. The cancer cell surface saccharides are different from those on normal cells and thus making it possible to distinguish the cancerous ones. The carbohydrate based vaccines have been used to enhance the immune system to fight the cancerous cells involving different sets of mechanism. The ways to raise the immune response to carbohydrates, the efficient strategies may include engineering cancer cells to display carbohydrates that are more likely to trigger an immune response; devising new types of carriers, ranging from polysaccharides to nanoparticles, that enhance a carbohydrate antigen's immune response; using additives known as adjuvants to boost the immune response to antigens conjugated to conventional carrier proteins and constructing polyvalent vaccines that include multiple carbohydrate antigens. Carbohydrate vaccines based on strategies like these are being recently tested and presently in human clinical trials for ovarian cancer. This vaccine **75** contains five sugar units found on the surface of tumor cells such as Globo-H, sTn, Tn, GM2 and TF [73].

Carbohydrates involved in post-translational modifications of protein (protein glycosylation) play crucial role in drug development research. Nowadays these carbohydrate-based active proteins are recognized as an attractive target in several important diseases including anti-inflammatory, anti-cancer, anti-infective, anti-viral, antibiotic etc. The carbohydrate-protein conjugation is able to elicit immune response and allow generating antibodies recognising the glycidic entity. Thus the synthetic vaccines may be prepared which can develop immune response against specific bacterial polysaccharides, or to generate antibodies that recognise tumour associated glycidic antigens.

4.8. Carbohydrate based Anti-Tubercular Agents

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis* affects nearly 33% of the world's population and remains a leading cause of death worldwide even today [74,75]. A number of targets are known to develop new and novel antitubercular drugs. Among these targets, the genes and enzymes responsible for the biosynthesis of carbohydrate based molecules in the mycobacterial cell wall play a dominant role in antitubercular drug discovery and a number of groups are currently engaged to find out new drugs [76].

Mycobacterial cell wall biosynthesis is a unique and attractive target for development of new class of anti-mycobacterial agents because of the several reasons and prominent one being its absence in host cell. Further, an impressive and attractive feature of *M. tuberculosis* is that they synthesize cell wall polysaccharides with sugars predominantly in furanose form. Since the ability to synthesize arabinogalactan (AG) and lipoarabinomannan (LAM), where galactose and arabinose residues exist in furanose form, is critical to its survival, interference in the biosynthesis of these polysaccharides will be an ideal and novel approach for development of new chemical entities against this disease [74-78]. Our Research Group at CDRI

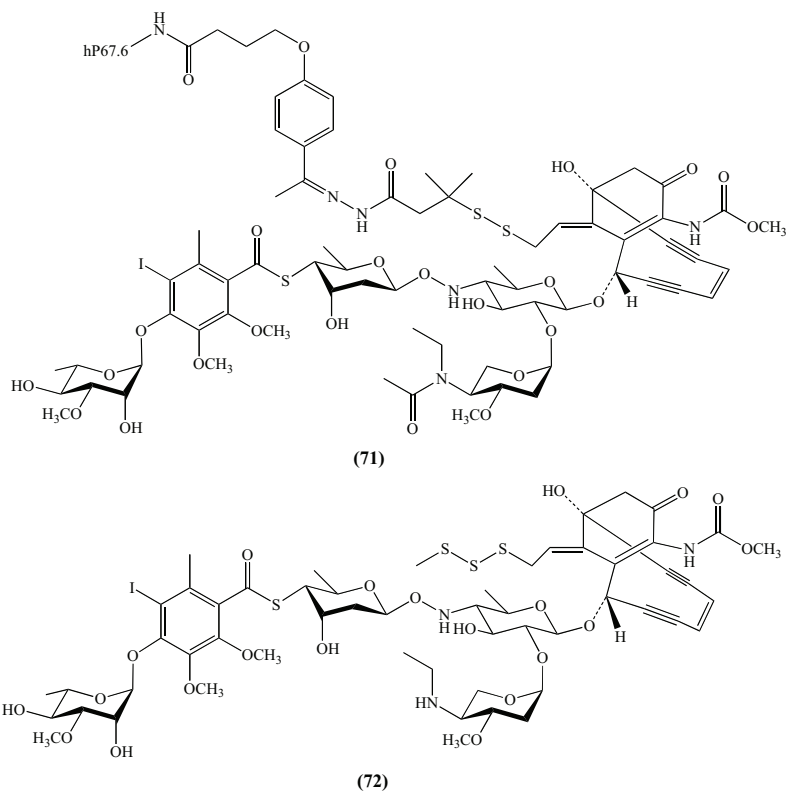


Fig. (10). Carbohydrate-containing NP-antibody anticancer conjugates.

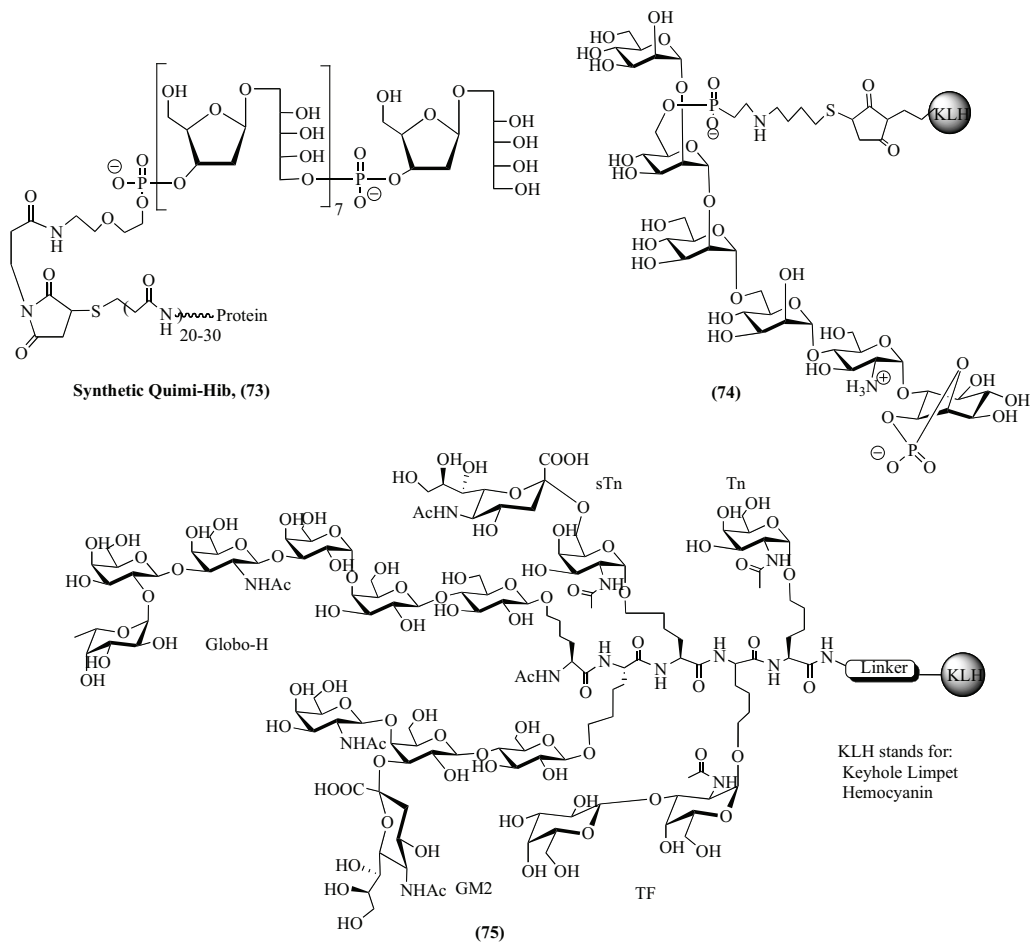


Fig. (11). Structures of few carbohydrate-based vaccine.

has been working on this aspect for quite sometime and has synthesized a number of simple carbohydrate derivatives (Fig. 12) possessing potent antitubercular activities.

In this context, conjugate addition of several primary and secondary amines to the glycosyl olefinic esters (**76**, **77**) has yielded a number of β -glycosyl amino acid derivatives [79,80]. These compounds have displayed interesting and potent antitubercular activities *in vitro*. Best compound of the series (**78**) having *S*-configuration at C-5 has MIC value of 3.12 $\mu\text{g/mL}$ whereas '*R*' isomer has MIC value of 100 $\mu\text{g/mL}$. The compounds were designed to mimic the enzyme *D-alanine racemase* and *glycosyl transferase* involved in the biosynthesis of essential cell wall components, peptidoglycan and arabinogalactan [78]. However, these compounds on *in vivo* studies could not protect the mice against mycobacterial infection [79].

The glycosyl amino acids showed poor activity as compared to the esters. Further formylation of NH with a formyl group using ammonium formate gave the corresponding *N*-formyl derivatives which were less active against *M. tuberculosis* as compared to unprotected amines [80, 81].

Ethambutol (EMB, **81**), a β -amino alcohol, is a well known antitubercular drug which is known to inhibit the biosynthesis of arabinan in both AG and lipoarabinomannan (LAM) [82]. The latter is predominant in wide variety of biologically active molecules, apart from their role as synthons for the synthesis of many chemotherapeutic agents. Several β -glycosyl amino alcohols (**82**) [83] and *N*^l, *N*^m-diglycosylated diaminoalcohols (**85**) [84] were also synthesized and evaluated for antitubercular activity against *Mycobacterium tuberculosis* H37Ra and H37Rv. Few of them exhibited antitubercular activity with MIC values as low as 6.25–3.12 $\mu\text{g/mL}$ in virulent and avirulent strains, and one was found to be active against MDR strain and showed mild protection in mice. Several others compounds of this series exhibited antitubercular activities with MIC ranging from 6.25 to 3.12 $\mu\text{g/mL}$ [83,84].

In another attempt a series of galactopyranosyl amino alcohols were synthesized by regioselective oxirane ring opening of 6-*O*-(3'-epoxypropan-1'-yl) galactopyranosyl derivative with variety of amines and screened for their antitubercular activity, where one of the *N*^l, *N*^m-digalactopyranosylated amino alcohols (**86**) showed potent activity (MIC 1.58 $\mu\text{g/mL}$) against *M. tuberculosis* H37 Rv *in vitro* and also displayed activity in MDR TB. The compound was found to be superior to ethambutol, the clinically used anti TB drug in *in vitro* [85].

During 1,4-conjugate addition of imidazole, a well known pharmacophore, to the above glycosyl olefinic esters (**76** & **77**) in presence of a DBU base was accompanied with an unusual observation where the β,γ -unsaturated product emerges (**87**) apart from the usual conjugate addition product [86]. The imidazolyl glycohybrids (**88**) and bis-imidazolyl derivatives (**89**) showed interesting antitubercular activity [87].

Replacement of '*N*' with '*S*' in some biologically active compounds alters the activity profile and sometimes results

in improvement in the activity. Further, keeping in mind the antitubercular activity of '*S*' alkyl (isoxyl) and other compounds with '*S*' as integral part of the molecule, we have synthesized some *S*-alkylated glycosyl acid derivatives and screened. One of the compounds (**91**) diglycosylated dithioalkane was found active at 12.5 $\mu\text{g/mL}$ [88].

We have further prepared glycosylated phenyl cyclopropyl methanone (**92**) and identified as a very good anti-tubercular agent active even against MDR strains of *M. tuberculosis* and *in vivo* too [89,90]. Based on the above findings we have developed an efficient, high yield and one-pot synthesis of phenyl cyclopropyl methanones (**93**) by the reaction of different aryl alcohols with 4'-fluoro-4-chlorobutyrophenone in the presence of NaH/TBAB [90]. All the compounds were evaluated for their anti-tubercular activities against *M. tuberculosis* H37Rv *in vitro* displaying MICs ranging from 25-3.12 $\mu\text{g/mL}$. The most active compounds showed activity against MDR strains and *in vivo* studies showed marginal enhancement of MST (Median survival time) in mice [91]. The compound has shown very good pharmacokinetic parameters. Based on this HIT we are developing a new class of antitubercular agents from benzyl alcohols.

NAD^+ -dependent DNA ligases (LigA), found only in bacteria and some virus species have recently drawn attention as novel drug targets. Based on the crystal structure of the NAD^+ binding domain of the *M. tuberculosis* enzyme (*MtuLigA*) and virtual screening our research group have recently identified some novel carbohydrate based molecules such as urea, thiourea, and amino alcohols as inhibitors for this enzyme. These molecules bind to the adenylation domain and compete with the co-factor NAD^+ [92].

We have undertaken virtual screening program using the modeled domain from *MtuLigA* and identified compounds with the potential to bind to this domain. These molecules will be evaluated in an ongoing program. As part of a long range program to develop anti-TB therapies based on *MtuLigA* inhibition, we have in the first instance searched for diverse compound families which inhibit *MtuLigA* with several fold specificity compared to ATP-dependent ligases including for the human DNA ligase I (Table 2). These compounds possess IC_{50} values in the low μM range. Bacterial growth inhibition studies using specific LigA deficient strains suggest that their observed antibacterial activity is most likely due to inhibition of the LigA in the bacteria [93-96].

Detailed molecular docking studies involving *MtuLigA* BRCT domain with Glycosyl uriedes and amines (Fig. 11) demonstrated that mimicking the interactions of NAD^+ with the enzyme improves the specificity/distinguishing ability of the compounds for LigA. These studies also suggested that the inhibitors should interact with conserved residues in the binding site and thus can be exploited in rational inhibitor design (Fig. 13).

4.9. Carbohydrate Derivatives as Antiparasitic Agents

Diamines and polyamines are well known antiparasitic agents. We have synthesized a series of *N*^l, *N*^m-glycosylated

diaminoalkanes (97) (Fig. 14) by reductive amination of glycosyl aldehydes with different diamines. These compounds were screened for their interference with filarial worm's glutathione metabolism. The compounds affected

intracellular glutathione, γ -glutamyl cysteine synthetase, glutathione reductase and glutathione-S-transferase(s) of bovine filarial worms to varying degrees [97]. One of the compounds (97) though effected the motility and MTT

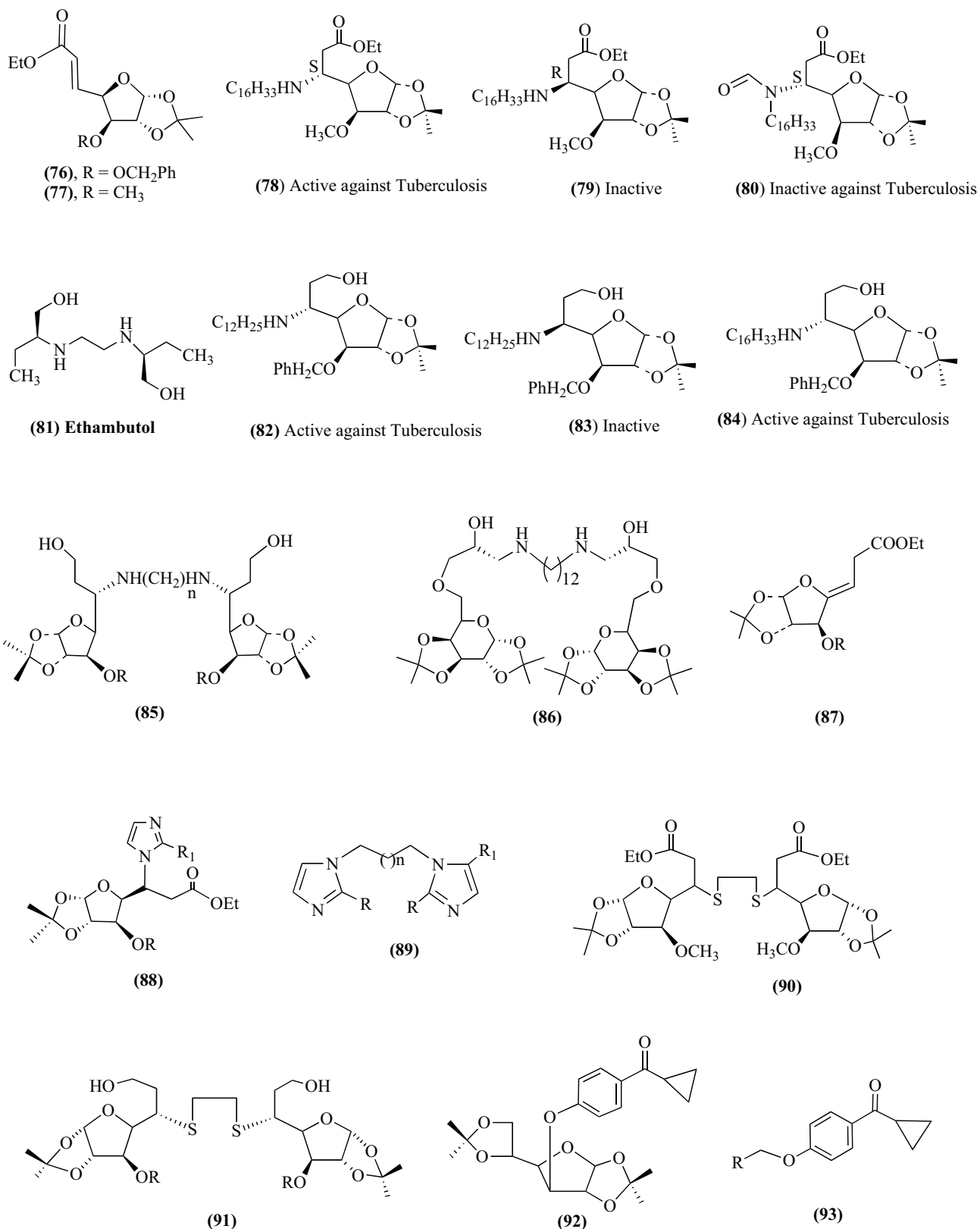


Fig. (12). Chemical structures of carbohydrate based antitubercular agents.

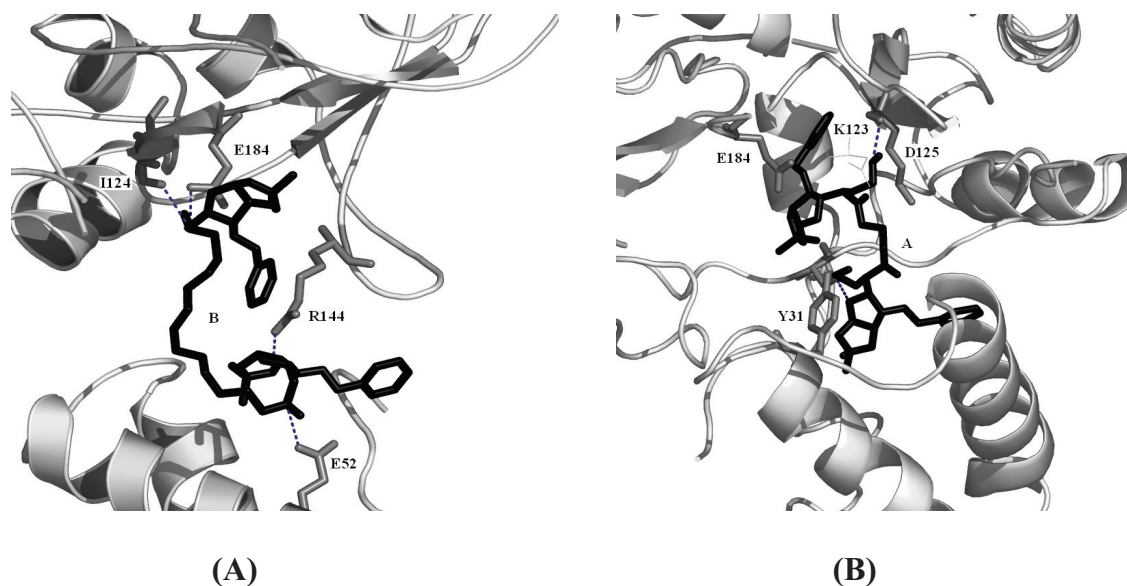


Fig. (13). Glycosyl amines: compound **A** can distinguish between *MtuLigA* and ATP-dependent ligase whereas compound **B** whose modeled interactions extend beyond the NAD^+ binding site cannot.

Table 2. *MtuLigA* inhibitors with corresponding IC_{50} values in μM . Representative structures from each compound class are depicted.

Class	Structure	IC_{50} (μM)
Glycosyl ureide	 94	9.65 ± 0.5
Glycosyl thioureide	 95	4.0 ± 0.3
Glycosyl amino alcohol	 96	46.2 ± 1

reduction potential of filarial worms *Brugia malayi*, however, little microfilaricidal and macrofilaricidal were noted with these compounds at 50 mg/kg oral dose. Three compounds were evaluated also for *in vivo* activity [97b].

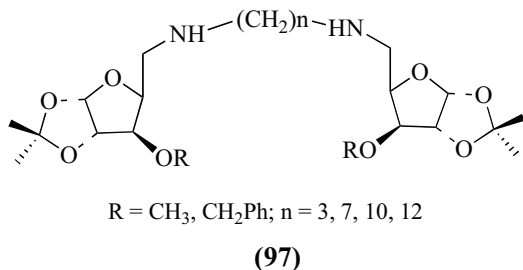


Fig. (14). N¹,Nⁿ-diglycosyl diaminoalkanes with antiparasitic activity.

Since some of the amino alkyl derivatives of sugars known for their immuno-modulatory and antiviral activities, [98] a series of *bis*-xylofuranosylated N¹,Nⁿ-diaminoalkanes (**98-100**) (Fig. 15) were synthesized by conjugate addition of diamines to glycosyl olefinic esters (**76 & 77**) [97b].

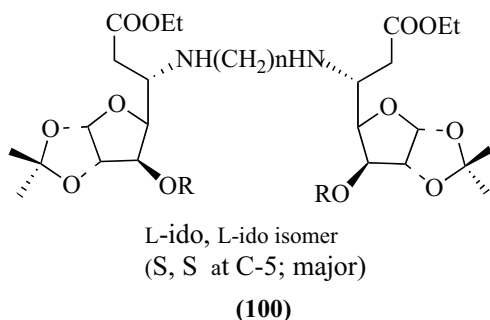
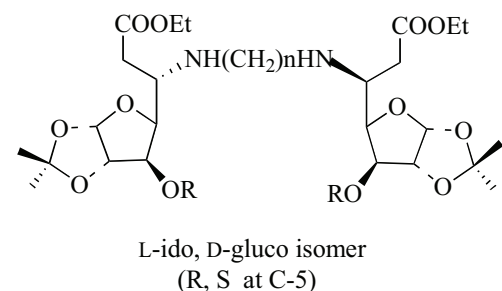
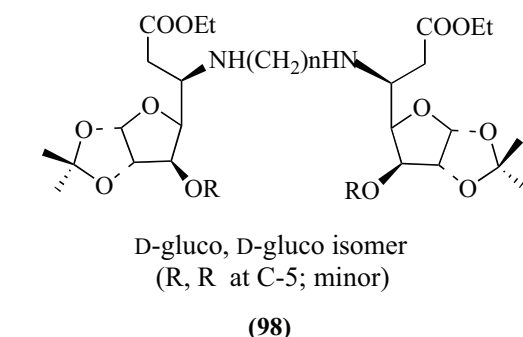


Fig. (15). N¹,Nⁿ-diglycosyl diaminoalkanes with antifilarial activity.

Filarial worms are sensitive to oxidative stress and rely on the Glutathione (a tri-peptide) for their long term survival inside the host. Glutathione guards them from oxidative stress and reactive oxygen species, metabolic pathway of which is now a well-known target for design and development of anti-filarial compounds. Compound **101**, with a glycosyl hydantoin skeleton has been found to be effective against glutathione metabolizing enzymes, GCL (Glutamate cysteine ligase) and GR (Glutathione reductase) [99,100].

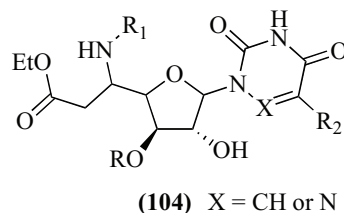
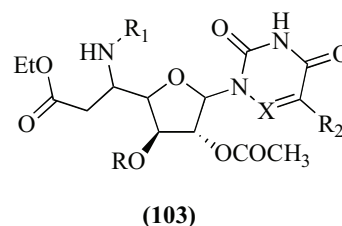
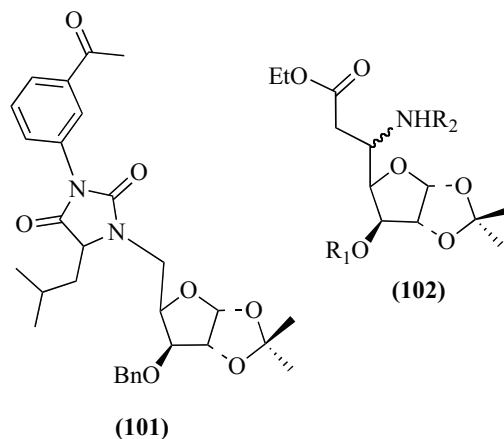


Fig. (16). Simple sugar derivatives with modulation glutathione enzyme activities.

Glycosylated amino esters (**102**), described above, were also evaluated for their DNA-topo-II inhibition. Some of these compounds showed marked inhibition of DNA-topo-II [80].

We have also synthesized a series of unnatural nucleoside analogs with modified sugar and aza-pyrimidine bases (Fig. 16) for further study in this direction. The synthesized compounds were screened against DNA-topo-II of *S. cervi* *in vitro*. Compounds showed prominent inhibition of the enzyme in *in vitro* studies. The results of the enzyme inhibitory activity showed that only one of the compounds was active against the DNA-topo-II. Some of the unnatural nucleosides were found to cause degradation or cleavage of DNA in treated cells which indicated that they were acting as antineoplastic agents [101].

Leishmaniasis, a group of tropical diseases caused by protozoan parasites of genus *Leishmania*, is a major health problem worldwide. In another study we have prepared a series of glycosyl and galactosyl dihydropyridines (**105**, **106**) (Fig. 17) and evaluated for their pteridine reductase inhibitory activity in detail. The compounds inhibited the enzyme and showed very good antileishmanial activity [102,103].

Keeping in view the antileishmanial activity associated with several alkaloids [104], we have also synthesised a series of *bis*-glycosyl ureide derivatives (**107**) flanked by phenylene ureidyl moiety with C2 symmetry. These compounds exhibited significant *in vitro* antileishmanial activities against promastigote and amastigotes of Leishmanial parasite [105]. Few of them showed interesting antileishmanial activity *in vivo* too. In general, the acids and esters have shown more antileishmanial activity active than the corresponding alcohols. *Bis*-glycosyl ureides with more hydrophobic 3-*O*-benzyl substituent are found to be more potent than 3-*O*-methyl substituent. Further, as adjunctive to SSG (Sodium stibogluconate), the glycosyl ureides with carboxylic acid moieties are enhancing the efficacy of standard drug SSG to a greater extent than the corresponding esters [105]. The lower doses of the toxic drugs with such adjunctive agents may be beneficial to minimise the side effects and thus with the use these molecules dose of SSG may be reduced, which may be quite helpful in reducing toxicity of the drugs.

4.10. Novel Anti Malarials: Hydroxamic Acid Derivatives of Carbohydrates

In one of our research programmes towards development of antiparasitic agents, we took up the design of novel

antimalarial agents. Iron uptake in many microorganisms is performed via chelation using siderophores which contain hydroxamic acid functionality (Fig. 18) [106].

Availability of Iron-(III) is crucial for the growth of malarial parasite in human during its intra erythrocytic phase and hydroxamates enhance the clearance of the parasite in mild malaria. Hydroxamates are also known to act on recently discovered target Peptidyl deformylase (present only in parasite) for antimalarial therapy [91]. Glycosyl hydroxamates (**113**) were synthesized by the reaction of hydroxyl amine hydrochloride with glycosylated beta amino acids. Another series of glycosyl hydroxamates (**114**) was prepared where the sugar counterpart was derived from galactose and is present in pyranose form (Fig. 18). The biological data suggested that presence of a long chain (C-16) as the amine substituent contributed most to the anti-malarial activity and at the same time compounds with glucofuranose sugar were comparatively better than their galactopyranose analogs [107].

4.11. Antiviral and Antifungal Aminoalkyl Gluco-Furanoses and Glycosylated Isoxazolines

Isoxazolines are special five membered heterocyclic compounds having both nitrogen and oxygen in the ring. These compounds can be prepared by cycloaddition reactions. These heterocyclic compounds possess intrinsic biological activity against different mycelia and thus exhibit antifungal properties. Isoxazoline system was constructed on glucofuranose system via its aldoxime. A [3+2] cycloaddition approach was used; where sugar derived nitron was formed in situ by the reaction of *N*-chlorosuccinimide on oxime in presence of DBU. Different alkenes were used as dipolarophile to prepare a series of the

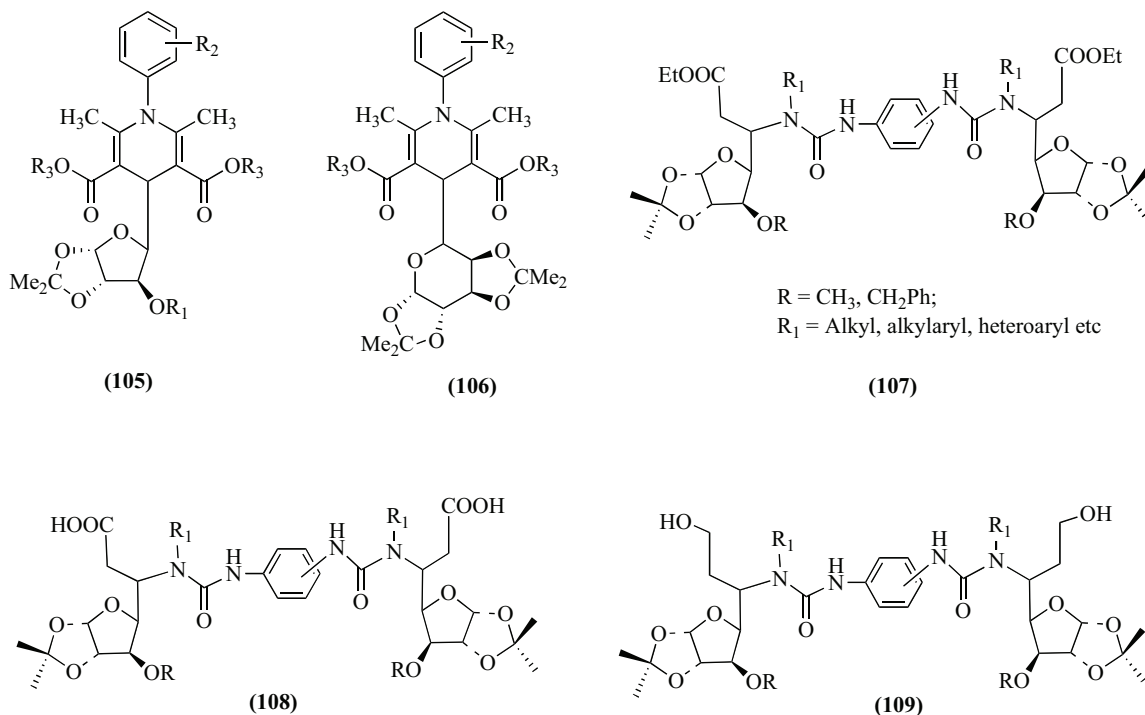


Fig. (17). Sugar derivatives with potent antileishmanial activities.

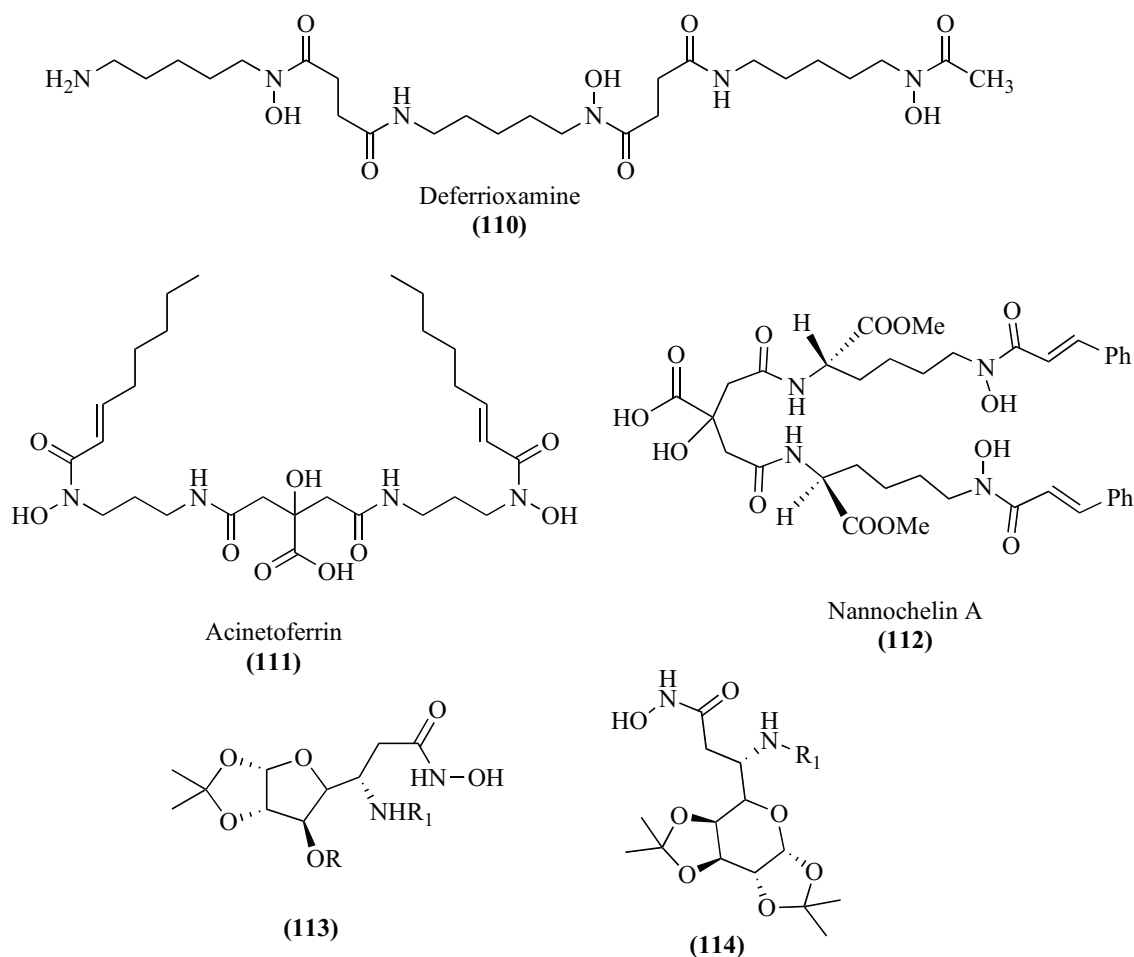


Fig. (18). Hydroxamates and glycosyl hydroxamates with antimalarial activities.

glycosyl isoxazolines (115). Apart from desired product an intermolecular dimerization product of the intermediate nitrile oxide was also isolated in some reactions. Another series, starting with galacto-pyranosyl oxime (116) was also prepared and the compounds were evaluated for their antifungal activity, where some of these glycosyl isoxazolines were shown promising activity (Fig. 19) [108].

Because 2-deoxy-D-glucose, D-glucosamine and other modified monosaccharides have antiviral activity against influenza virus and exhibit very less side effect, we have also synthesized a series of 3-O-(aminoalkyl)-1,2-O-isopropylidene- α -D-gluco(xylo) foranoses (117) and evaluated their antiviral activity against EMCV (encephalomyocarditis virus) and SFV (semliki forest virus). One of the compounds (118) of the series shows very promising antiviral activity and protects the infected mice to an extent of 60% and 70% against EMCV and SFV respectively [109].

4.12. Heparin in Medicinal Chemistry

Heparin and their analogs have been used as drugs of choice for the management of thrombosis since since long back [110]. Heparin activates antithrombin III, a serine protease inhibitor blocking thrombin and factor Xa in coagulation cascade [111]. Discovery of the antithrombin binding domain in heparin (119) (Fig. 20), a critical element

in the anticoagulant activity of this polysaccharide, allowed a rational approach based on medicinal carbohydrate chemistry in the design of new anticoagulants. Important neurobiological roles for heparin sulfate proteoglycans, which include neuroepithelial growth and differentiation, neurite outgrowth, nerve regeneration axonal guidance and branching, and the deposition of amyloidotic plaques in Alzheimer's disease and astrocyte proliferation have been well documented [112].

Hadri *et al.* reported a synthetic pentasaccharide fondaparinux, which selectively targets blood coagulation factor Xa. Various heparin mimicking oligosaccharides were prepared with an aim to replace the low molecular weight heparins and polydisperse heparin by structurally-defined anticoagulants without any unwanted side-effects [113].

4.13. Synthesis of Versatile Carbohydrate based Scaffold for Combinatorial Synthesis

5-Amino- 5,6-dideoxy-1, 2-O-isopropylidene-3-O-methyl/benzyl- α -D-gluco- and β -L-ido heptofuranuronic acids (120) were successfully been used in our lab as organo catalyst in asymmetric aldol reaction [114]. The scaffold was used in solid phase combinatorial synthesis to achieve a diverse range of pharmacologically active compounds. Solid phase combinatorial synthesis *via* loading of combinatorial

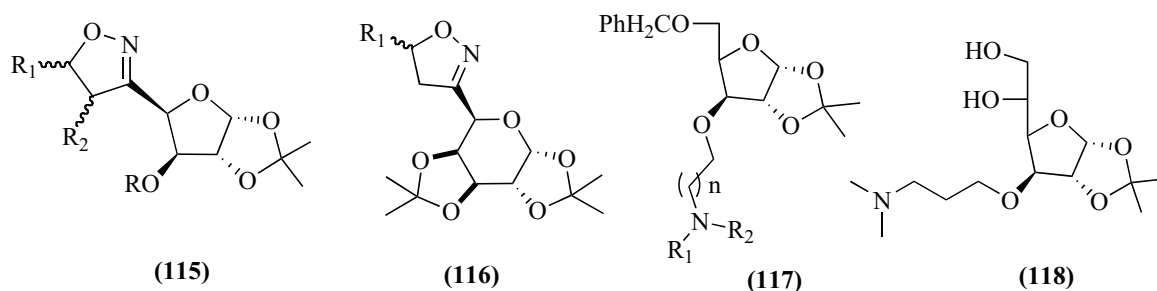


Fig. (19). Simple sugar derivatives with antiviral activities.

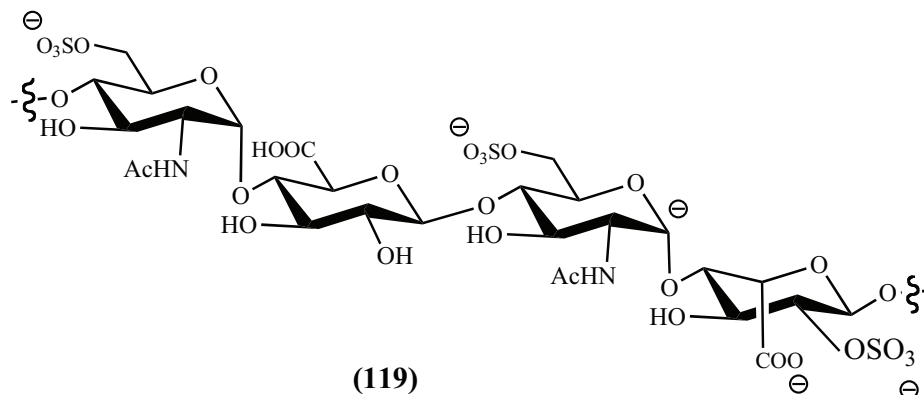


Fig. (20). Heparin a well known anticoagulant.

scaffold glycosyl amino acid with Siber amide resin in presence of DIC/HOBT/TBTU as coupling agent, followed by different set of reaction such as reductive amination, followed by reaction with different isocyanate and finally removal of polymer support using 2% TFA in CH_2Cl_2 afford a glycosyl ureas (**121**) in flexible form in good yield. A library of 48 members of glycosyl ureas in rigid form have been reported *via* loading of scaffold glycosyl amino acid with Wang resin in presence of appropriate coupling agent, followed by different set of reaction through cyclo release strategy in high yield and with excellent purity [115].

These C-Nucleoside were screened for filarial activities and few of them were found to be moderately active. Larger amount of these compounds were successfully prepared via an efficient and versatile method for introducing dihydropyrimidinone skeleton on protected glucofuranose derivative by reacting glycosyl ureas with DBU as catalyst and TBAB as co-catalyst in 4A^0 MS [116-118].

Glycosyl enaminones, obtained in good yields from corresponding glycosylated amino ester on Amberlite IR-120 resin, were used for introducing dihydropyridinone skeleton on protected glucofuranose (**123**) and galactopyranose derivative (**124**) [119a]. The protocol is extended by one-pot reaction of beta-glycosyl amino acids with beta ketoesters in the presence of Amberlite IR-120 resin and 4A^0 molecular sieve in refluxing toluene [119b]. The β , γ -unsaturated glycosyl urines (**125**), obtained from DBU catalyzed reaction of glycosyl olefinic ester, have been successfully converted to corresponding glycosyl dienes through the DBU catalyzed aldol type reaction with aldehydes followed

by subsequent E2 reaction [120]. Tetrabutylammonium hydrogen sulphate mediated eco-friendly protocol for pharmacologically promising carbohydrate-containing 1,4-dihydropyridines (**126**, **127**) and dihydropyrimidinones (Fig. **21**) has been achieved from corresponding uloses [121].

Several pharmacologically active skeletons including nucleoside, tetramic acid, and 4-(butenolide-5-methylidene)-1,4-dihydropyridines were achieved starting from Ascorbic acid [122-124]. Some of the L-ascorbic acid based nucleoside analogs have shown promising antitubercular activity [124].

From a synthetic library of glycoconjugates using glycosyl amino acid as combinatorial scaffold and sieber amide resin on solid support, we have identified inhibitors of DNA Topoisomerase-II [125].

A combinatorial library of 28 members of carbapeptide analogues using glycosyl amino ester scaffold (**128** and **129**) on solid support was developed previously, where these compounds *in vitro* displayed moderate anti-fungal, anti-tubercular and general antibacterial activities [126a]. For detailed biological investigation, recently the solution phase synthesis of these carbapeptides analogues has also been achieved [126b]. The most active compound against tuberculosis was further tested for *in vivo* too and no significant protection was achieved. Furthermore reverse docking calculations involving over 841 protein drug targets have identified two potential targets for these compounds [126b]. Thus, these observations form the basis for synthesizing second-generation antimicrobial compounds. The exact mode for the activity of these glycoconjugates

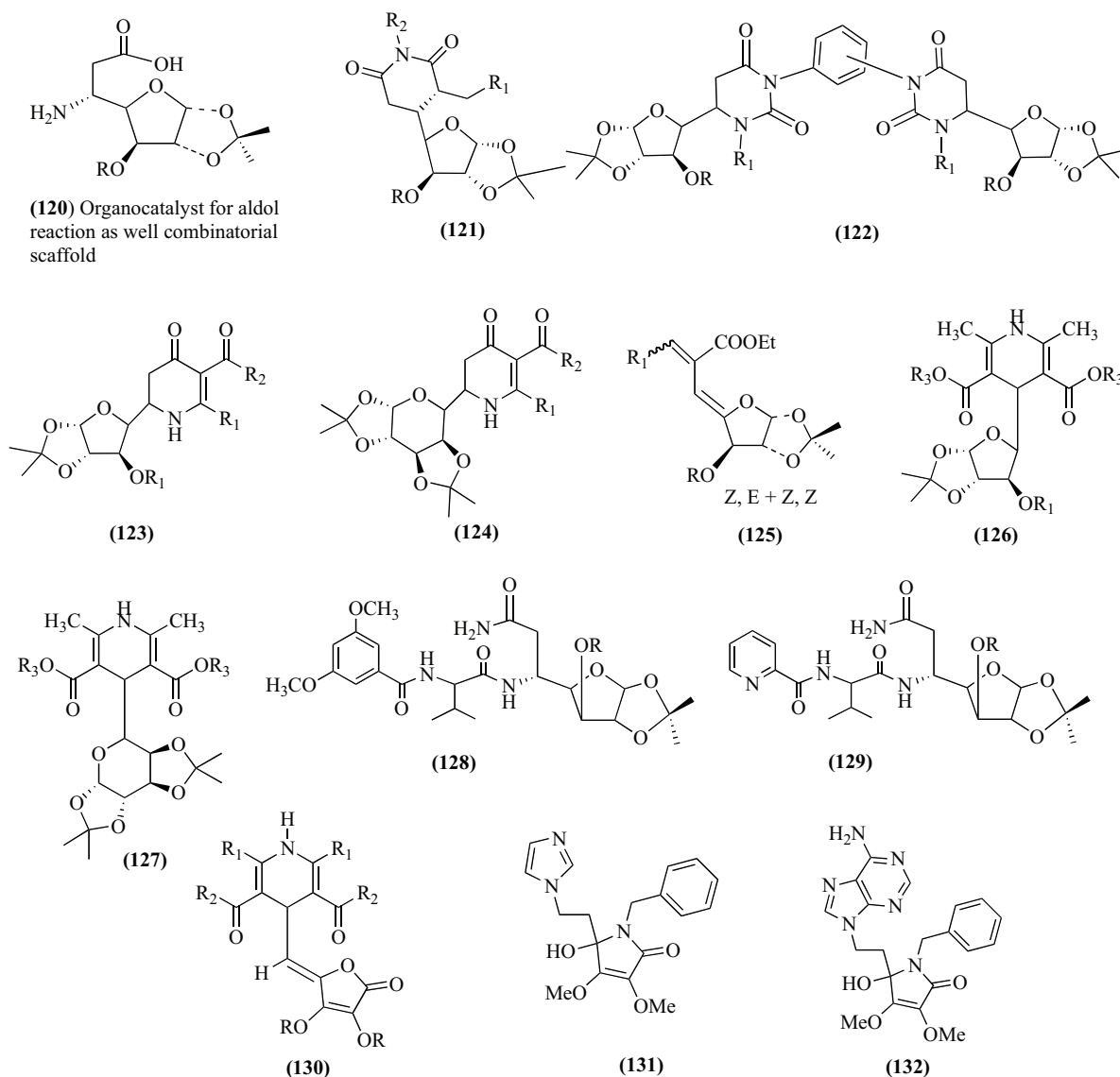


Fig. (21). Glycoconjugates synthesized by solid phase and conventional synthesis with promising biological activities.

including glycosyl amino ester, glycosyl amino alcohols, glycosyl thiols, carbapeptides, and unnatural nucleosides against the *Mycobacteria* is unclear. Yet it is speculated that these compounds might be acting either by interfering in the cell wall biosynthesis by inhibiting the crucial enzymes or through some immune modulation mechanism.

CONCLUSIONS

Carbohydrates because of structural diversity and functional groups are being used to develop new and novel therapeutic agents due to their natural abundance, good pharmacokinetics and low toxicity. Recent developments in synthetic capabilities have enabled us to add new arsenals in the chemotherapeutic armory. Molecules based on carbohydrate skeletons have shown a wide spectrum of activities against parasitic as well as microbial infections. The developments in chemistry and biochemistry of carbohydrates have led to evolution of new molecules involving several cellular and biochemical events such as

such as transport, modulation of protein function, energy storage, intercellular adhesion, signal transduction, malignant transformation, viral and bacterial cell surface recognition, as well as involvement in selective binding and molecular recognition. In addition, inhibition of carbohydrate processing enzymes is a topic of great interest in medicinal chemistry, since they are involved in a plethora of key biochemical events such as digestion, lysosomal catabolism of glycoconjugates and post-translational glycoprotein processing. Availability of sophisticated tools to understand the chemistry of complex carbohydrates has led to better molecular understanding and thus convince the scientific community to work on these molecules. We hope to see many more molecules reaching the phase II and III stages in clinical trials with carbohydrate derived skeleton.

CONFLICT OF INTEREST

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

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ABBREVIATIONS

AG	=	Arabinogalactan
BLG	=	Bovine liver galactosidase
CPS	=	Cell-wall polysaccharides
CNS	=	Central nervous system
CDAD	=	<i>Clostridium difficile</i> -associated diarrhea
CAP	=	Community-Acquired Pneumonia
cSSSIs	=	Complicated skin and skin structure infections
CuAAC	=	Cu(I) catalyzed alkyne-azide cycloaddition
KDN	=	Deaminoneuraminic acid
DNJ	=	Deoxynojirimycin
DNA	=	Deoxy ribonucleic acid
DBU	=	Diazabicyclo[5.4.0]-undec-7-ene
DIC	=	Diisopropyl carbodiimide
EMCV	=	Encephalomyocarditis virus
ECG	=	<i>Escherichia coli</i> galactosidase
EMB	=	Ethambutol
FDA	=	Food and Drug Administration
GCL	=	Glutamate cysteine ligase
GR	=	Glutathione reductase
GSL	=	Glycosphingolipids
GAA	=	Glycosyl amino acid
GPI	=	Glycosylphosphatidylinositol
IC50	=	Half maximal inhibitory concentration
HOBt	=	1-Hydroxybenzotriazole
KLH	=	Keyhole Limpet Hemocyanin
LAM	=	Lipoarabinomannan
MST	=	Median survival time
MRSA	=	Methicillin resistant <i>Staphylococcus aureus</i>
MIC	=	Minimal inhibitory concentration
MDRTb	=	Multi drug resistant tuberculosis
Neu5Ac	=	N-Acetylneuraminic Acid
NCE	=	New chemical entities
NDA	=	New Drug Application
NAD	=	Nicotinamide adenine dinucleotide

NPC	=	Niemann-Pick type C disease
NIDDM	=	Non-insulin dependent diabetes mellitus
SFV	=	Semliki forest virus
SSG	=	Sodium stibogluconate
SPCS	=	Solid phase combinatorial synthesis
SAG	=	Sweet almond glucosidase
TBAB	=	Tetrabutylammonium bromide
TFA	=	Trifluoroacetic acid
TBTU	=	<i>N,N,N',N'</i> -tetramethyl- <i>O</i> -(Benzotriazol-1-yl)-uronium tetrafluoroborate

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