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A simple perspective of glycosciences†

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Carbohydrates are a very large class of family of organic compounds. Carbohydrates and its derivatives are widely found in nature, especially in plants and are constituents of several essential organic compounds. Till now several derivatives has been isolated from nature and or synthesized by scientists. These carbohydrates and its derivatives have found wide application in the development of drugs as well as in biology and medicinal science communities. This mini-review focuses on the important progress in the area of glycosciences which includes glycoconjugates, glycolipids and glycotargeting.

Keywords: Carbohydrates, glycosciences, glycoconjugates, glycolipids, glycotargeting.

1. Glycoconjugates

Glycoconjugates are derivatives of carbohydrates which is covalently linked with other chemical species, such as, proteins, peptides, lipids and saccharides. These glycoconjugaes are biologically important molecules with different functions, and plays a vital role in several normal and pathological processes[1–4]. It is formed by the processes named "*glycosylation*". It consists of carbohydrates of variable size and complexity, covalently attached to a non-sugar moiety such as a lipid or a protein[5]. They consist of several different categories such as glycoproteins, glycopeptides, peptidoglycans, glycolipids, glycosides and lipopolysaccharides. In general, carbohydrates are attached to various conjugates like lipids and proteins by *N* (nitrogen)-glycosidic, *O* (oxygen)-glycosidic or *S* (sulphur)-glycosidic linkages. These glycoconjugates are useful in elementary activities of research. Carbohydrate moieties present in the naturally occurring glycoconjugates plays major role in the clinical research and diagnostic medicine and also in clinical pharmacology and therapeutics. Beyond the preference for the more abundant native *O*- and *N*-linked glycoconjugates, *S*-linked glycoconjugates are also attractive and synthetic targets as a result of their greater chemical stability and enzymatic resistance[6]. Structures of glycoconjugate are often very complex and its overexpression is very difficult and it is because of their complex biosynthetic pathway. This leads to the isolation of pure, structurally defined compounds from natural sources unwieldy. Therefore, to better address demands in glycobiology, synthetic glycoconjugates are an alluring alternative. Synthetic glycoconjugates, materials that are often referred to as neoglycoconjugates, were first implemented 70 years ago as products of an intellectual exercise[7]. Synthetic methods allow for the preparation of non-natural glycoconjugates that can enhance the understanding of the influence of structural features on the biological responses. The future of carbohydrate science will be polished by the application of its products; therefore the applications of glycoconjugates are very important. Glycobiology, and the chemistry of glycoconjugates, has gained massive attention over the past few years owing to the understanding of the role played by carbohydrates in many biological events, such as cell growth, inflammation, and immune responses, field of drug delivery and targeting etc.[8]. Analysis of glycoconjugates is very difficult because of its high molecular weight. Analytical ultracentrifugation (AUC) is a powerful characterization method used for the characterization of large carbohydrate-based polymers. These materials still represent a substantial challenge, because of their polydispersity, great

†Review.

variety of conformation types, and large non-idealities. One of the ultimate impacts is the development of software for the handling of both sedimentation velocity and sedimentation equilibrium data, greatly enhancing the resolving power of the instrument[9].

Glycoconjugates and its applications

Carbohydrates and its derivatives are the major and essential vitality hotspots for all the living life forms and are required in the formation of nucleic acids, polysaccharides, glycoproteins, glycopeptides etc.[10]. Among those glycopeptides are well recognized for its antibiotic and antibacterial activities[11,12]. In recent times, researchers have developed a number of glycoconjugates derived from amino acid **(1)**, that exhibit a fair amount of anti-inflammatory and analgesic properties (Fig. 1)[13]. Another interesting filed of research is '*Neuroimmunology*'. Nowadays plenty of researches are working in this field to develop specific and effective antiglycoconjugate antibodies that can be used in neuropathy i.e. neuroimmunology[14]. Quite of evidence has shown that antiglycoconjugate based antibodies play vital roles in several pathogenesis of autoimmune neuropathies, such as Guillain-Barre syndrome (GBS), Fisher syndrome and multifocal motor neuropathy (MMN)[15]. The pathogenic actions of these antiganglioside antibodies are governed by their voracity, which are influenced by binding specificity, specific localization in the peripheral nervous system, glycolipid environment and internalization on nerve membranes. The detection of antibodies to ganglioside complexes improves the detection rate of antibodies in Guillain-Barre syndrome. Antibodies to glycoconjugates are infrequent in chronic inflammatory demyelinating patients, and their pathogenic roles are uncertain[14].

One more interesting field of research is the development of carbohydrate conjugated vaccine for various diseases. Homo- and heteropolysaccharides are major components of the bacterial cell wall and capsule. Polysaccharides present in the bacterial cell surfaces provide mechanical protection and also can act as protective antigens. Carbohydrate structures situated on the bacterial cell surface generally differ from those on the host cell surface. Therefore, the recognition of carbohydrates located on the bacterial cell surface by cells of the immune system is essential for the host, resulting in the elimination of bacteria from the host organism. It is seen that some bacteria bear carbohydrates structurally similar to surface components of mammalian and human tissues, thus deterring their recognition by the immune system in infected cells[16]. Studies show that oligosaccharide ligand is largely responsible for antigen specificity of the immune response to the conjugate. Thus synthetic oligosaccharide ligand is an important step in the construction of antibacterial conjugate vaccines[17].

Glycoconjugates derived from microalgaes

Microalgae are attracting major attention due to the potential of their practical applications as valuable food constituents, raw material for biofuels, drug candidates, and components of drug delivery systems. Most of the microalgae are capable of executing photosynthesis, and every year they harvest globally half of oxygen and all organic substances[18]. Glycoconjugates are known as bioactive metabolites with various biological properties. Recently, new evidence has appeared on the exciting biological activities of microalgal glycoconjugates forms of sterols and sphingolipids. Sterols in microalgae are found as conjugated and also in free forms. Microalgal based sterols are well known as the main source of steroidal materials of many other marine organisms, which obtain these compounds through their diet. Steryl glycoconjugates **(2)** are known for their bioactivity and these metabolites have been found many times in nature, being isolated from different plants, such as olives, soybeans, potatoes, and algae. An example of glycoconjugated sterols from higher plants are given in Fig. 1[19]. Glycosylated sterols play important roles in their producers and exhibit different bioactivities, making them promising agents for applications in medicine and as auxiliary components to healthy food. Sphingolipids, found in almost all animals, plants, and fungi, as well as in some viruses, are an important part of the corresponding lipidomes. These compounds perform important structural and intracellular functions and participate in extracellular signaling. Along with sterols, they form the specialized micro domains in plasma membranes which are involved in a great variety of cellular processes. It was found that glycosphingolipids and sterol conjugates are regulators of membrane functions. Some of them are significant for the interactions of their producers with pathogens, and may induce apoptosis in microalgae[18].

Transition metal ions and glycoconjugates

Transition metal ions are found in all living organisms, coordinated to different biomolecules and contributing in many biochemical reactions where they play a vital role. Carbohydrates, although involved in many biochemical processes, immunological events, and pathological conditions, exhibit relatively deprived coordinating properties and form weak complexes with metal ions[20], though, an increased metal-binding ability has been linked to the glycosylated proteins formed in Maillard reaction[21]. There is storing evidence for the ability of Maillard reaction products to complex metal ions[22]. Due to the importance of the transition metals like copper, aluminium, calcium, zinc[23] etc., in human bodies, for example copper involved in the oxidative processes[24], there is no known physiological part for aluminium within the body and hence this metal may strongly alter normal cellular metabolic pathways and produce adverse physiological effects[25]. Calcium is important for healthy bones, but it is responsible for kidney stones formation, and calcification of blood vessels. Thus, investigation of difference in complexation ability for these metal ions of natural peptides and their Maillard reaction products **(3)** is of essential importance. A representative example of glycosylated product formed through Maillard reaction has been given in Fig. 1[20].

Recently, platinum(IV) prodrugs have been designed, synthesized and evaluated as antitumor agents.[26] Most platinum(IV) drugs are used in tumour targeting, or drug delivery.[27] One auspicious strategy for targeting the cancer cells

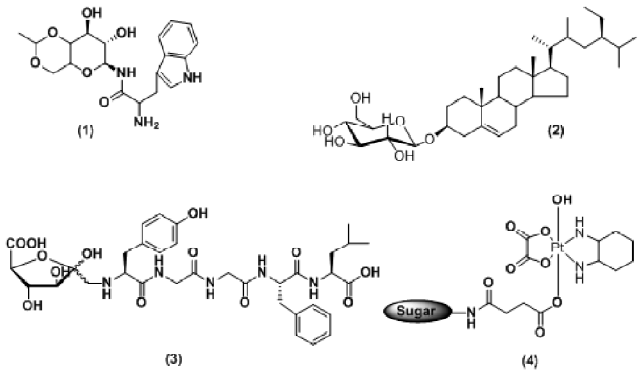


Fig. 1. Representative example of (**1**) amino acid derived glycoconjugate, (**2**) glycoconjugated sterol, (**3**) glycosylated product formed through Maillard reaction and (**4**) platinum(IV) glycoconjugate[13,19,20,30].

in cancer therapy is glycoconjugation and the details about the action is discussed in Section 3 under glycotargeting, in which incorporated glucose and other monosaccharides of the drug can efficiently improve cancer targeting selectivity and decrease the toxicity[28,29]. Due to the manifestation of platinum(IV) complexes, unwanted side reactions with biological nucleophiles reduce undesired side effects and increase the lifetime in biological fluids. A representative example of platinum(IV) glycoconjugate precursor for cancer targeting **(4)** has been given in Fig. 1[30].

Triazoles and glycoconjugates

Synthesis of medium sized heterocyclic systems especially 1,2,3-triazoles which can show excellent biological activities shows potential scope in medicinal chemistry[31–35]. Cu(I)-catalyzed 1,3-dipolar cycloadditions (i.e. *click reaction*) of organic azide and terminal alkyne has been widely used in adjoining of two entirely different building blocks having azide and alkyne groups[36]. Hence enabling an easy access of simple to complex molecular architectures containing 1,4-disubstituted triazole skeleton. Carbohydrate-based triazole containing molecules in combination of standard drugs and other biologically relevant molecules are always symbolized itself as remarkable drug candidate which show their effect with increased therapeutic efficacy. Morpholine, has been found to be an admirable pharmacophore in medicinal chemistry. A number of drugs including morpholine as a constituent are available in the market. Therefore, many new approaches toward the synthesis of morpholine derivatives **(5)** have been reported in the literature (Fig. 2)[37,38]. Nowadays a large number of biologically active glycosylated 1,2,3-triazole moieties have been synthesized which showed good pharmacokinetic properties. A number of carbohydrate based 1,2,3-triazole core containing drug like molecules with good pharmacokinetic properties have been synthesized and evaluated till now, and the molecular structure of representative examples **(6-8**) are provided in Fig. 2. DNA is a nucleic acid composed of proteins, lipids and polysaccharides. It is one of the primary targets in drug development strategies that are designed to produce novel therapeutics for diseases such as cancer. For the better understanding of the molecular mechanism of drug action and designing of specific DNA targeted drugs, it is important to study the drug-DNA interaction. In general, DNA molecule is a target for anticancer and

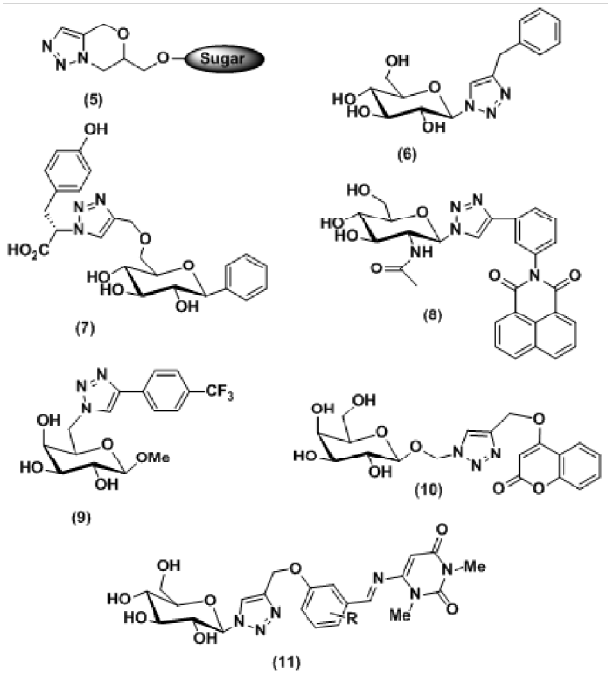


Fig. 2. A representative examples of triazole based glycoconjugates compounds, (**5**) morpholine derivative, (**6**) potential inhibitor of glycosidases, (**7**) potential (PTP) 1B inhibitor, (**8**) sialyltrans-transferase inhibitor, (**9**) biologically active glycosylated triazole, (**10**) antifungal triazolyl glycoconjugate, (**11**) uracil appended triazole based sugar-iminederivative[39–43,46].

antiviral drugs that form covalent and non-covalent adducts with DNA. It has been reported that glucopyranosyl based triazoles exhibit various biological activities, such as anti-tumor, anti-viral and anti-tuberculosis agents[44] and *N*-substituted-uracil derivatives possess biological activity, which is widely used in therapy, mainly as antiviral and antineoplastic agents[45]. It has been already proved that uracil appended triazole based sugar-imine derivatives that exhibit DNA binding properties. Representative example is given in the Fig. 2[46,47]. Usually DNA binding studies are done using electronic absorption spectroscopy. This is one of the most useful techniques used commonly because the observed changes in the spectra may give evidence of existing interactions and their mode[48].

Docking methods are used to study the binding of the synthesized conjugate ligand molecules to DNA. Here the structures of the ligands were optimized using density functional theory (DFT)[46], docked pose of derivatives of **k** with CT-DNA and it is given in the Fig. 3.

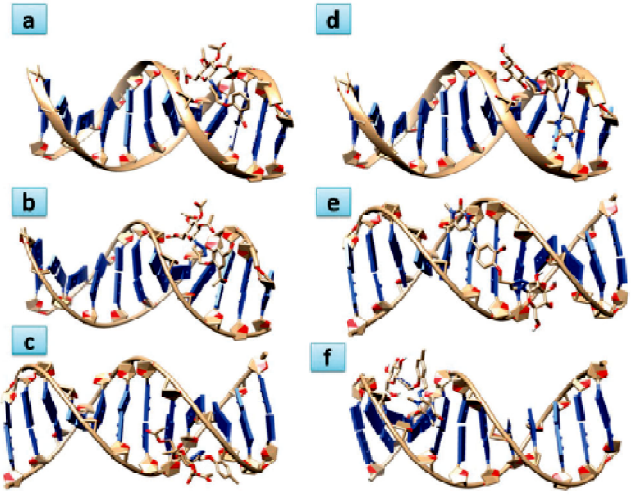


Fig. 3. Docked pose of sugar derivative with CT-DNA[46].

2. Glycolipids

In general glycolipids are composed of two different segments viz. hydrophilic carbohydrate and hydrophobic aliphatic groups and it possess an extensive variety of biological activities. Natural occurring glycolipids are known to be very complex and heterogeneous in nature. Presence of lipophilic contaminants creates confusion in the understanding of their original functions in several biological processes. In order to understand their role in several biological processes at the molecular level, structurally defined glycolipids are very much needed. A suitable chemical synthetic methodology may be adopted to understand the problem. Thus, the design, synthesis and characterization of synthetic glycolipids become one of the important fields of research in glycosciences.

Carbohydrates covalently attached to proteins and lipids which establish three different types of glycoconjugates, such as proteoglycans, glycoproteins, and glycolipids. Though in the first two classes, the types of linkages are the same, chemically proteoglycans behave as polysaccharides and glycoproteins having much less carbohydrate content as proteins. The third important class of glycoconjugates viz. glycolipids consists of carbohydrate residues which are covalently attached to lipidic components.

Glycolipids are broadly classified into four different types and it is based on the lipidic nature, i.e. glycoglycerol, glycosyl polyisoprenol pyrophosphates, fatty acid esters, and glycosphingolipids. Representative examples of simple and important lipids are triglycerides (triacylglycerols), steryl es-

ters, and wax esters. Hydrolysis of these lipids results in the formation of the corresponding alcohol and the acid i.e. glycerol and fatty acids, sterols and fatty acids, respectively.[49] In general, the main functions of lipids are storing energy, signaling, and acting as structural constituents of cell membranes. Details about the different types and its source are given in Table 1.

Table 1. Different types of glycolipids and its source

Glycolipid type	Micro organism
Rhamnolipids	*Pseudomanas* sp.
Sophorolipids	*Sacchromyces* sp.
Trehalolipids	*Mycobacterium* sp.

Based on the nature of the groups present, the lipids can be classified into hydrophobic or amphiphilic lipids. Due to the amphiphilic properties, these classes of lipids are useful as vesicles, multilamellar/unilamellar liposomes, or membranes in an aqueous environment. Lipids may be divided into eight classes, such as fatty acids, glycerol-lipids, glycerol-phospholipids, sphingo-lipids, saccharo-lipids (glycolipids), polyketides (derived from condensation of ketoacyl subunits), sterol lipids and prenol lipids (derived from condensation of isoprene subunits)[50]. Carbohydrate moiety linked to the long-chain aliphatic acids or hydroxyl-aliphatic acids by an ester group. Though these glycolipids found several applications in different areas of research, it has been used in the field of surfactants. Among the glycolipids, the important well known classes (Table 1) are rhamno-lipids, trehalo-lipids and sophoro-lipids[51]. Details about each of the naturally occurring lipids along with the synthetically known are discussed in the following sections.

Rhamnolipids

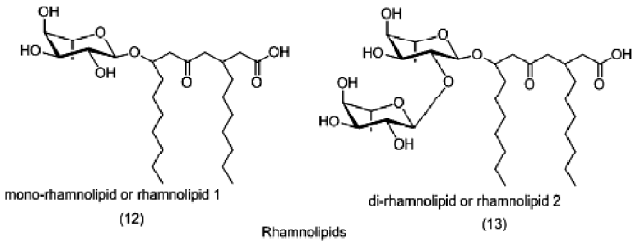


Fig. 4. Molecular structure of naturally occurring mono- and di-rhamno-lipids **12** and **13**.

In rhamno-lipids, one or two molecules of rhamnose moieties are linked to one or two molecules of hydroxy-decanoic acid. Molecular structure of the naturally occurring monorhamno-lipid and dirhamno-lipids are shown in Fig. 4. Among the different classes of lipids, these classes of lipids are extensively studied as bio-surfactant and these glycolipids are produced by *P. aeruginosa*[52].

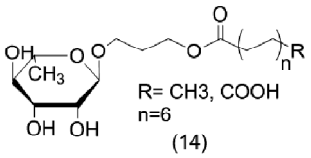


Fig. 5. Representative examples of synthetic rhamnolipids **14**[53].

The defence mechanisms that already exist in plants are able to stimulate by some of the natural and synthetic amphiphilic molecules includes lipopeptides, lipopolysaccharides, and glycolipids. Biological and biophysical approaches were adopted to understand the two synthetic C14 rhamnolipids (Alk-RL and Ac-RL). Synthetic rhamnolipids are different and it varies only at the level of the terminal group i.e. -CH_3 group in case of alkylated rhamnolipids (Alk-RL) and carboxylic acid group at the end of the carbon chain in the case of acylated rhamnolipids (Ac-RL) (Fig. 5). The Ac-RL was enthused from the carboxylic acid function which is present in natural rhamnolipids, however Alk-RL mimics the surfact in fatty acid chain. It has been reported in the literature that among the two derivatives, Alk-RL induces a stronger primary signaling response in tobacco cell suspensions. Both experimental and computational studies were reported on understanding the relations between synthetic rhamnolipids and basic biomimetic membranes. Molecular level studies shows that the synthetic rhamnolipids could be easily correlated very well with the lipid-driven process which is liable on the organization of the membrane and also the orientation of the rhamnolipids within the membrane and is interrelated with the induction of early signaling responses in tobacco cells[53].

Trehalose lipids

Trehalose lipids are present with the maximum species of *Mycobacterium, Nocardia* and *Corynebacterium*. The lip-

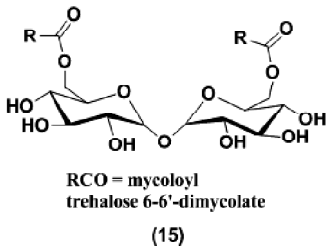
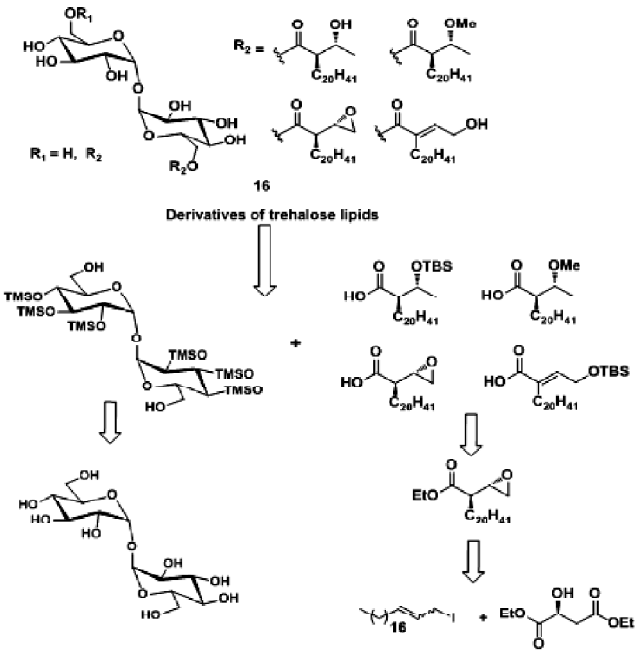


Fig. 6. Structure of naturally occurring trehalolipid **15**.

ids produced from *Rhodococcus erythropolis* and *Arthrobacter* sp. possess the property which can able to lower the surface and interfacial tension in culture broth from 25–40 and 1–5 mNm, respectively[54]. Molecular structure of a representative example of trehalose lipid (**15**) is shown in Fig. 6.

Retrosynthetic analysis for the trehalose glycolipids[55] involves the simple condensation of trehalose monoesters and trehalose diesters. These mono and diester synthons were produced via the coupling of TMS-protected trehalose to one or two of the mycolic acid groups (Scheme 1)[56,57]. Key steps in this synthetic strategy involves a Fráter-Seebach α-alkylation to incorporate the C_{20} aliphatic lipid on a malic acid derivative, and the development of a β,γ-epoxide as an intermediate from which modifications to the β-position of the lipid can be made. Biological evaluation of the derivatives using nuclear factor of activated T cells-green fluorescent protein reporter cell lines expressing mMincle or hMincle exposed that the hMincle agonist activity of all diesters was superior to that of the current lead trehalose glycolipid adjuvant trehalose dibehenate[58].



Scheme 1. Retrosynthetic approach for the synthesis of modified trehalose based glycolipids (**16**)[57].

Sophorolipids

Sophorolipids are produced by yeasts and it contains a dimeric carbohydrate sophorose linked to a long-chain hydroxyl fatty acid through glycosidic linkage (Fig. 7). In general, it is a mixture of at least six to nine different hydrophobic sophorolipids[59]. Lactone form of the sophorolipid are reported to have several applications[60].

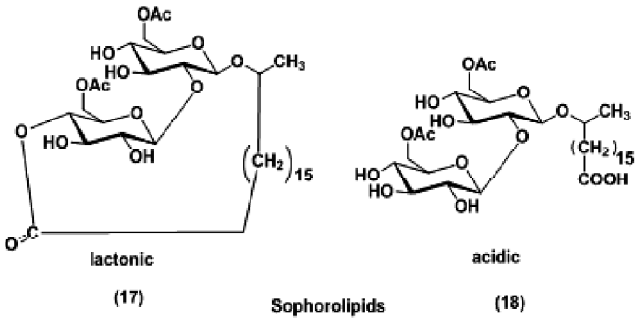


Fig. 7. Structure of a representative sophorolipids containing different functional groups (a) lactone (**17)** and (b) acid (**18**).

Naturally occurring sophorolipids possesses interesting biological activities, such as anticancer, antimicrobial, dermatological, immunoregulatory, spermicidal, and antiviral activity[61,62]. Moreover, they have self-assembly properties with a high variety in the type of nanostructures formed from different sophorolipid derivatives[63–66]. Recently, the fermentative production of sophorolipid based bolaamphiphiles with two sugar heads has also been reported in the litrature[67,68]. Microbial glycolipids, also known as "*biosurfactants*", have a good biodegradability, low cytotoxicity, and several applications as antimicrobial, antibiofilm, anticancer, emulsifying, and stabilizing agents[69,70].

The different classes of microbial glycolipid compounds (Fig. 8) have been reported in the literature[71,72]. Even though the structures of different sophorolipids[73] are comparable (apart from the type of sugar-lipid linker), the self-assembly properties were not known much in the literature. In contrast, between their self-assembly behavior with sophoro-

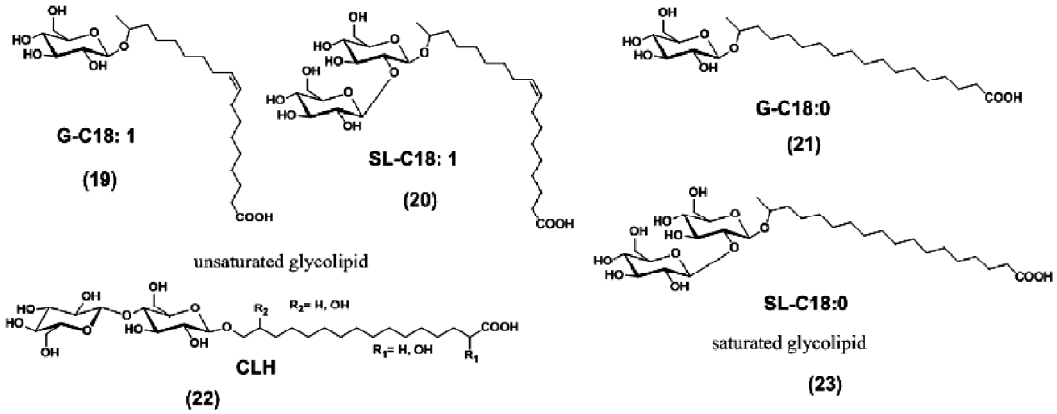


Fig. 8. Representative examples of microbial based sophorolipids (**19-23**)[71,72].

lipids has been reported to understand the self-assembly and in particular, the role of both the sugar head group and the fatty acid chain in the assembly. Another form of glycolipid which was reported in the literature is the acidic form of cellobiose lipids. Due to the structural similarities that exist between the unsaturated and saturated sophorolipids, the self-assembly has been compared in the literature.

Monounsaturated glucolipids, G-C18:1 (**19)**, form vesicles at pH < 6.2 and the corresponding saturated glucolipids, G-C18:0 (**21)**, form infinite sheets at pH < 7.8. Thus by changing the pH, the morphology of the glucolipids changes and it is due to the change in the self-assembly phenomenon. Glycolipids containing familiar chemical groups (glucose, fatty acid) were selected to compare with the more common amphiphiles (phospholipids, anionic and neutral surfactants, fatty acid salts and alkyl polyglycosides). However, their corresponding bolaform structure i.e. the unfamiliar nature of sugars (via oriented hydrogen bonding) and pH-responsive properties are features which were unpredictably influence the self-assembly[74]. At basic pH, most of the selected composites form micelles as a major constituent and the presence of additional aggregates, such as platelets, bilayers, ill-defined structures could not be ruled out[75]. At acidic pH, SL-C18:1 (**20)** and SL-C18:0 (**23)** sophorolipids correspondingly accumulate into micelles[76] and twisted ribbons[77] in addition, G-C18:1 (**19)** glucolipids form vesicles while G-C18:0 (**21)** forms infinite bilayer sheets[78].

Mannosylerythritol and other mannose-containing lipids

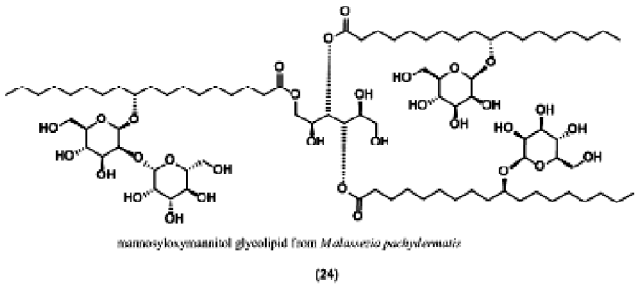
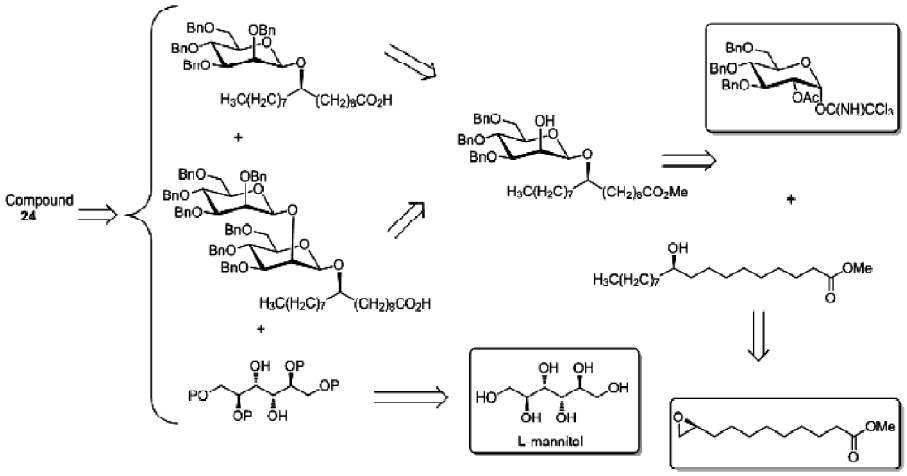


Fig. 9. Structure of mannose-containing lipids **24**[79].

Mannosylerythritol lipids are produced in large quantities by yeast strains of the genus *Pseudozyma*; they consist of fatty acids linked to either 4-*O*-β-D-mannopyranosylerythritol or 1-*O*-β-D-mannopyranosylerythritol as hydrophilic head group (Fig. 9). One or two of the hydroxyls (4′ and/or 6′) on the mannose residue are acetylated, and there are one to three esterified fatty acids, which are both odd- and even-numbered from C_8 to C_{12} in chain-length (longer in related species).

Mannolipid **24** possesses a remarkable, triol-triester architecture comprising an L-mannitol core adorned with unusual β-mannosylated lipids (Scheme 2). The β-mannosyl-1,2-β-mannoside motif found within one of these is especially rare in nature, aside from within this mannolipid, it has been observed in the cell wall of fungi (e.g. *C. albicans*)[80]

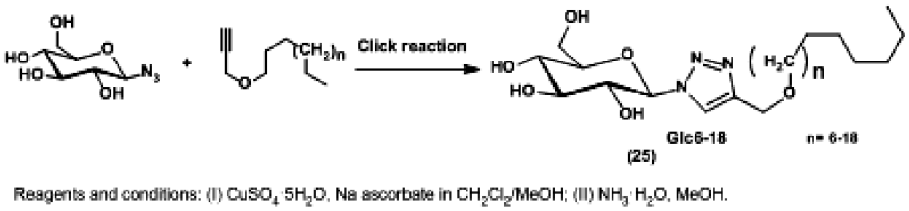


Scheme 2. Retrosynthetic approach of β-1,2-mannosyloxymannitol glycolipid **24**[79].

and the soluble intracellular carbohydrate reserve of *Leishmania*[81]. Total synthesis of **24** that takes advantage of the symmetry inherent in this class of molecules. As the stereochemistry of the 10-hydroxystearic acid group is unknown, attempts were made to synthesise the molecules and it has been confirmed NMR data and also compared with the naturally occurring derivatives.

Triazole based glycolipids

The series of triazolyl glycolipid derivatives **25** has been synthesized by a "click" reaction (Scheme 3).



Scheme 3. Synthetic scheme of triazole based glycolipids via click reaction[82].

They have the capability to increase the susceptibility of a drug-resistant bacterium to β-lactam antibiotics. Moreover, they determined that the glycolipids can defeat the minimal inhibitory concentration of a number of ineffective β-lactams, upward of 256-fold, for methicillin-resistant *Staphylococuss aureus*. The mechanism of action has been preliminarily investigated and discussed[82]. Our research group also reported the stereoselective synthesis of sugar based β-lactam from the reaction between sugar imine derivative and ketenes through cycloaddition reaction and we also studied the biological evaluation[83].

A novel class of gelators have been designed and synthesized in such a way that they can form gels with different organic solvents. The structure of the above compound (Fig. 10) has three different parts to improve the gelating ability in different solvents. The three parts are long alkyl chain (like lipid), benzohydrazide and protected D-glucose moiety. The long alkyl chain has hydrophobic nature and so it has been introduced to increase solubility in organic solvents. Benzohydrazine has an aromatic ring as well as an amide group. As per the literature, that π-π stacking of aromatic ring and amide group possess the ability to gelate organic solvents[84].

Our group has reported the design, synthesize and char-

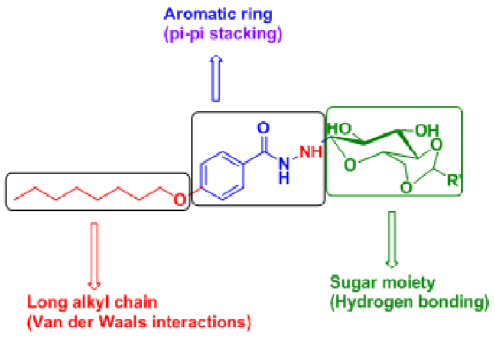


Fig. 10. Design of gelating ability glycolipids.

acterization of novel class of glycolipids (Fig. 11) by incorporating the structural features, such as hydroxyl groups, amide, aromatic and hydrophobic moieties that are known to promote molecular assembly.

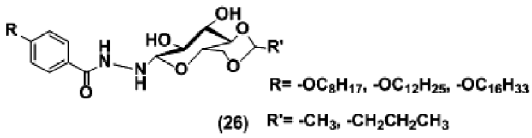


Fig. 11. Representative examples of synthetic glycolipids[84].

A new and novel class of glycolipid based surfactant from renewable feed stocks, monosaccharide and cashew nut shell liquid (Fig. 12) has been reported in the literature[84]. Under the enhanced reaction condition, glycolipid derived from glucose exhibited cyclic structure, however in the instance of galactose derived glycolipids, the existence of ring chain tautomerism, caused in the formation of both cyclic and acyclic structures. Supramolecular self-assembly of these glycolipids forms gel in highly hydrophobic solvents and vegetable oils, and foam in water.

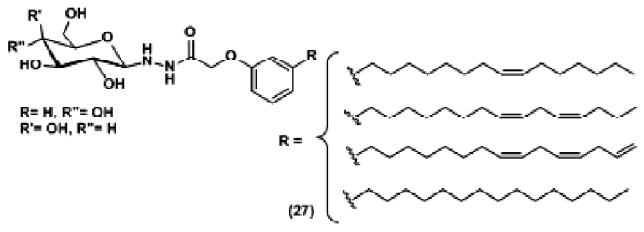


Fig. 11. Representative examples of synthetic glycolipids[85].

Formation of 3-dimensional fibrous network in gel and micellar structure in water has been identified using optical microscopy and HR-TEM. Rheological studies demonstrated the thermo-reversibility and thixotropic nature gel. Critical micellar concentration of glycolipids and surfactant behaviour was investigated using pendant drop method and rheological measurements, respectively. They have demonstrated the use of these self-assembled glycolipids in disassembling the pathogenic biofilms. Less hydrophobic glycolipid, showed higher potential in eradicating the Gram-positive *S. aureus* and *Listeria* biofilms, whereas glycolipid with more hydrophobicity is effective in disrupting the Gram-negative biofilm formed by the two related organisms *E. coli* and *Salmonella*. The report emphasizes the potential of supramolecular self-assembled materials derived from renewable resources to be useful in washing hands for clinicians, surface cleansing in hospitals and eradicating preformed biofilm in food processing industries[85].

3. Glycotargeting

Mutation in cancer cell metabolism is an emerging cause of cancer. Nowadays various clinically permitted drugs have enormous side effects results in higher toxicities and it is due to lack of selectivity towards cancer cells. In order to avoid the researchers have tried to develop targeted drugs having high absorption properties towards cancer cells than normal cells so as to improve efficiency and reduce toxicity. Selectively, targeted drugs do not involve only a carrier uptake pathway but also hinders the passive diffusion. Metabolic process of cancer cells differ significantly from normal cells, because the possibility to target cancer cells is to improve the selectivity of anticancer therapeutics[86,87]. Various metabolic alterations shown by tumour cells are identified as prerequisite for cancer transformation, which is necessary in order to adapt the microenvironment which is found in solid tumors[88]. Recent methods have been developed in order to target the metabolic alterations of cancer cells specially conjugation of folate, glucose to exploit the improved consumption of these nutrients by diseased cells[89–91]. Generally, normal cells differ from cancer cell by generating energy during mitochondrial oxidative phosphorylation whereas cancer cells produce energy by the process called “Glycolysis”. Otto Warburg was the first researcher who described the importance of glucose metabolism that occurs in tumor cells with their association towards cancer cells and altered mechanism[92,93] and he got Nobel prize for this work in a year 1931

which indicates that the glycolysis is the major anaerobic glucose metabolism which takes place within the tumor cells, however still not clear that weather the change in metabolism is cause or consequences of cancer. Due to the higher consumption of glucose by cancer cells than by normal cells the cancer cells are more "hungry" than normal cells because of lower energy production by glycolysis and also due to very less amount of energy is being produced by glycolysis and also due to the high generation of lactic acid and other acidic species. This metabolic modification protects an massive and quick supply of energy and biosynthetic intermediates from glucose, due to insufficient level of oxygen in hypoxic areas of cancer tissues[94]. There are various advantages of targeted drugs over the non-targeted analogous and are discussed in the following sections:

(1) It can carry their therapeutic payloads selectively into cancer cells, thereby evading nonspecific uptake with their related toxicity to normal cells.

(2) It can permit the use of highly powerful therapeutic missiles that display little or no efficiency when administered in non-targeted form at the extreme tolerated dose.

(3) The targeting ligands can be concurrently oppressed to create a companion diagnostic agent that can be used to select patients whose pathological cells overexpress the targeted receptor[95]. In the case of limited targeted drugs that target the folate receptor folate-linked, folate-linked 99mTc and 68Ga radio imaging agents that have been successfully used to recognize patients whose tumors express adequate folate receptors to permit uptake of a therapeutic quantity of drug[96].

(4) It can be administered at lesser doses compared to their non-targeted counterparts, because receptor binding and internalization can effort the conjugates which is present inside the receptor-positive pathological cells[97].

Metabolic programming in tumors

Glucose metabolism and tumor hypoxia are the two most important aspects which describes the metabolic programming in tumors. Reduction of oxygen supply which is also called as "Hypoxia" is a main cause of several cancer tissues. The major components which are responsible for these tumors are a family of hypoxia inducible factor (HIF). Hypoxia-inducible factor-1 (HIF-1) is formed by two components HIF-1α and HIF-1β. Majority of human tumors was found in the overexpression of HIF-1. The most important consequence of this resulted in the abnormal promotion of glycolytic flux[98]. HIF-1 is an important targeting tumor glycolysis in cancer chemotherapy and it is due to its low activity in normal tissues which makes it more attractive towards tumor cells with negligible side effects. In other words, all the tumor glycolysis whose overexpression is promoted by HIF-1, may be considered as a suitable catalysts for the "*development of anticancer agents*". Very few anticancer agents

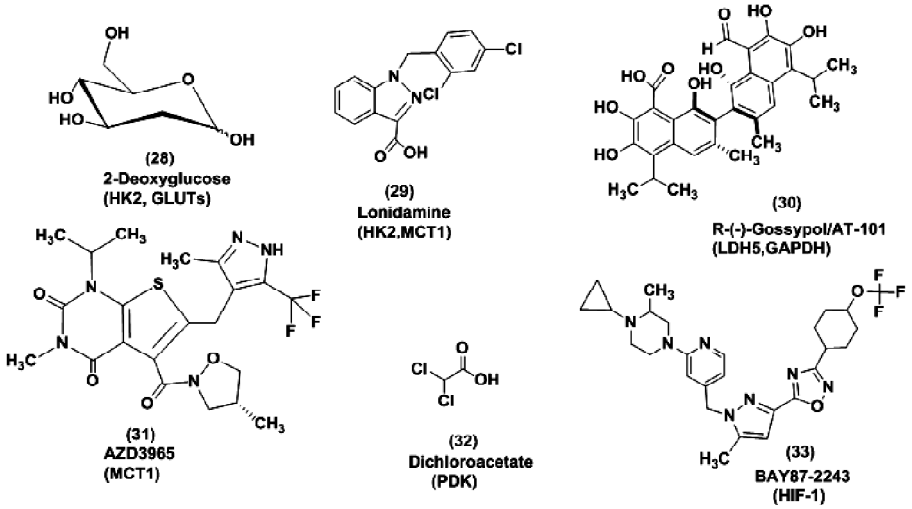


Fig. 12. Representative examples of drugs targeting tumor glycolysis currently undergoing clinical trials (alleged target(s) in brackets)[101].

pointing to give response in tumor glycolysis have entered in phase 1-3 clinical trials (Fig. 12) and many others undergoing preclinical evaluation[99,100].

Glycoconjugation as an anticancer strategy

Glycoconjugation is one of the important and also more useful strategies for designing the targeted drug delivery. For glycoconjugation to be effective one for the targeted anticancer strategy, glucose transporters (GLUT) must be overexpressed in cancer cells when compared to the normal tissues. There are three classes of GLUT having specific-tissue distribution and discrete affinity towards glucose and other carbohydrates which are finding in the literature[92,99,125]. Class 1 comprises of four members (GLUT-1 to GLUT-4), whose special substrate is glucose, whereas classes 2 (GLUT 5) and class 3 (GLUT 6, 8,10, HMIT) are highly effective for other types of sugars. Similar to FR-a overexpression in cancer, GLUT-1 has been demonstrated to be overexpressed in a large percentage of cancers from various tissues of origin. In particular, human class 1 GLUTs are 48–63% identical, and have been extensively studied in the litrature[102]. Action of GLUTs in tumors is 10–12-fold higher than the normal cells, whicn demonstrates that the cancer cells are more reliant on glucose transporters for their survival[103]. Numerous studies have shown the importance of C-2 modification of D-glucose for enhanced GLUT mediated uptake and cellular retention of glycoconjugates[105,106], with the addition of bulky substituents in this position generally well tolerated.

C-2 Modified glucose moieties are used to increase GLUT absorption and remains as a GLUT substrate and also important for Hexokinase recognition (Fig. 13). The polyethylene glycol linker attached to glucose moiety decrease the lipophilicity and also reduces the steric interferences. In addition the presence of amine group is used for conjugation with a variety of compounds. Some more C-2 modified glucose analogues for GLUT-1 has been synthesised from 1,2:5,6-di-*O*-isopropylidene-D-glucofuranse by protection and deprotection strategies in three steps (Scheme 4)[92].

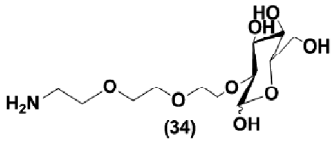


Fig. 13. Molecular structure of C-2 modified glucose derivative[92].

Some of the mannose and its derivatives show high targeting affinity towards various kinds of tumours. Most likely mannose-6-phosphate can able to target the hepatocellular carcinoma cells and it prevents the hepatic fibrosis[107a].

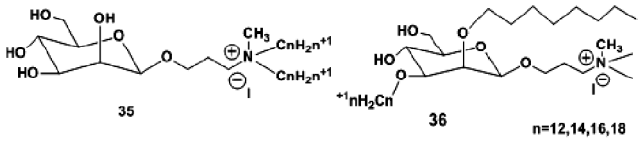
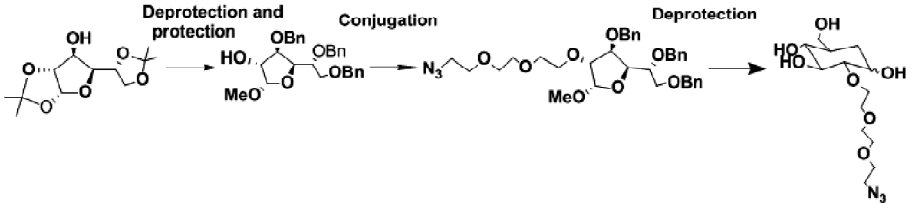


Fig. 14. Molecular structures of representative *O*-glycosides[107a].

While discussing the basic role of these transporters used for glycolytic tumour cells, GLUT and HK may also represents an efficient process in order to attack tumor cells. The main role of GLUT and HK are to block the pathways upon which nutrient absorption takes place, which resulted in the reduction of glycolytic flux and leads to cell death. However, it is not an easy task to inhibit the activity of cancerous cells without affecting the functioning of normal cells. This can be explained with very few GLUT which is being developed still now. Inhibition of this target by means of antibodies[107b] and antisense nucleic acids[108–110], either alone or in combination with chemotherapeutic drugs, has been reported in the literature. Furthermore, some synthetic and natural organic molecules having affinity towards GLUT-inhibition have been discovered recently.



Scheme 4. Synthesis of novel C-2 modified glucose analogue for GLUT-1[92].

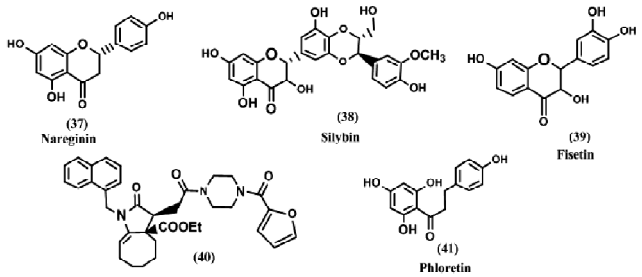


Fig. 15. Molecular structure of the natural products that inhibit GLUT[94].

A class of natural product i.e. flavonoids (Fig. 15) shows strong affinity to inhibit the proliferation and survival of cancer cells. For example *Silybin* is a natural flavonoid which shows direct interaction that exists in GLUT-1 and GLUT-4 resulted in the inhibition of tumor cells. In particular, the oxidised form of silybin prevents cellular absorption of glucose by direct interaction with GLUT-4[111]. Moreover, *Naringenin* is another natural flavonoid present in grapes shows a strong binding affinity towards estrogen receptor b[110], and also inhibits glucose uptake in breast cancer cells by the process of disruption of insulin induced GLUT-4 from intracellular compartment to the plasma membrane. *Myricetin* **2**, *Fistein* **3**, *Quercetin* **4**, and *Isoquercitrin* **5** are some of the other naturally occurring flavonois which can able to inhibit the GLUT-2.

Synthetic flavonoid i.e. *Fasentin*, (Fig. 16) possessing *meta*-trifluoro methyl and *para*-chloro groups on its phenyl ring were found to have more sensing towards the prostate cancer cells. It has a capability to alter expression of genes which is involved in metabolism of glucose and to hinder glucose absorption process[112]. *Glucose phosphamide* is a glucose containing cytotoxic agent, whose action is enhanced in cancer cells by overexpressing GLUTs[113]. One of the best examples of this class of synthetic flavonoid which is reported in the literature is *glucose-chlorambucil* which can directly inhibit the glucose uptake by GLUT-1. The hydroxyl group present at the second position of the sugar moiety is being replaced by *S*-nitroso-*N*-acetyl penicillamine (SNAP), which leads to the formation of the sugar derivative (2-Glu-SNAP)[111]. This glucose-derivative is more effective in the ovarian carcinomas than that of its non-conjugated analogue of SNAP[114]. In addition, two synthetic sugars (*O*-protected cyclohexane polyols) has been reported to possess inhibition of glucose uptake which is in a dose dependent manner[99].

Hexokinase inhibition studies

Hexokinase (HK) acts as a rate determining step of glycolysis, which is used to convert glucose into glucose-6-phosphate (Glu-6-P) with an expense of ATP i.e. an irreversible phosphorylation that occurs during the cycle. Subsequently the negatively charged phosphorylated form of glucose, is trapped inside the cell which can be metabolized further by the process of glycolysis to generate ATP, or by the pentose phosphate pathway which is normally used for biosynthetic reactions. The inhibition of HK glucose phosphorylation by glucosamine hydrochloride, the aglycone 2-[2-(2-aminoethoxy)ethoxy]ethanol has been investigated using a glucose (HK) assay reagent containing HK, ATP, NAD^+ and glucose-6-phosphate dehydrogenase (G-6-PDH). Following the addition of a glucose solution, a series of enzyme catalyzed reactions occur that enable quantification of the rate of HK glucose phosphorylation by monitoring the conversion of NAD^+ to NADH using the absorption spectroscopy. However there are four different isoforms of hexokinase, namely HK1, HK2, HK3, and HK4 (or glucokinase, GK), having different kinetic properties subcellular localization, and tissue expres-

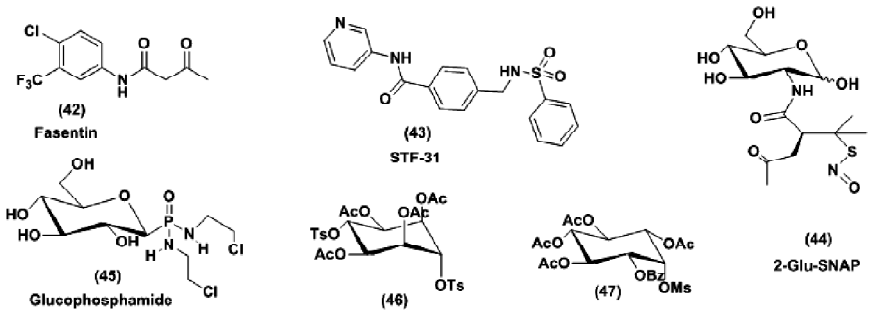


Fig. 16. Molecular structure of GLUT-interacting agents[94].

sion. Isoforms, HK1 to 3 possess significantly higher affinities for glucose when compared to other forms. The *N*-terminal portion of the HK3 and HK1 proteins shows a regulatory function, which is more sensitive to feedback regulation by Glu-6-P, ADP, and inorganic phosphate. The two types does not play a catalytic role, whereas, HK2 retains catalytic activity in both *C*- and *N*-terminal portions and it can double the rate of glucose phosphorylation and considerably speeding up the glycolytic process[115,116]. Thus the HK2 plays a pivotal role in inhibiting the tumor cell growth and it is bound to *trans* membrane *voltage-dependant anion channels* (VDACs) located within the outer mitochondrial membrane[117]. This strategic localization blocks the release of *cytochrome c* from mitochondria, thus protecting the cancer cell from apoptosis. Considering the fundamental role played by these HK2 in highly malignant tumors it is the fact that this enzyme, together with GLUT-1, shows main role towards the glycolytic flux[118]. Thus, it is strong evidence that this enzyme signifies an attractive target for therapeutic approaches to suppress tumour development.

member of this HK family is 5-thio-D-glucose[124] which can inhibit and radio sensitize chronically hypoxic cells[125] through *in vitro* process.

In case of 2-halo-2-deoxy-D-glucose, fluorine containing glucose unit is an important member of this class which is highly effective than the rest of the two members and more potent[126] than non-halogenated counterparts of 2-deoxy-D-glucose. 2-Fluoro-2-deoxy-D-glucose is harmless and less toxic than 2-deoxy-D-glucose, because of absence of side chains found in 2-deoxy-D-glucose.

Metal based drug delivery

Sugars are the most important target group and it has been extensively used for the alteration of anti-cancer drugs and also as drug transfer materials. These drugs have immense targeting properties. Synthesize involves the reaction of active amino group containing biomolecule such as proteins and amino rich liposomes with sugar molecules. This reaction is called "Millard reaction". Synthesis of two mannose-based platinum complex[127,128] (*trans*-*R*,*R*-cyclo-hex-

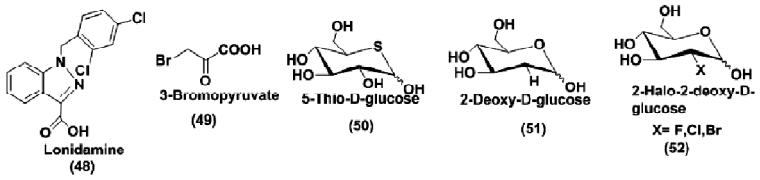


Fig. 17. Molecular structure of different hexokinase inhibitors[99,92].

One of the most widely used HK inhibitor in which OH group at position second is replaced by H viz. deoxy derivative[119]. Thus the 2-deoxy-D-glucose can undergo phosphorylation and the product formed 2-deoxy-D-glucose-6-phosphate cannot undergo further metabolic process so it can only diffuse outside the cell and prevents the glycolysis[120]. This prevention phenomena blocks the generation of energy, with ATP depletion, cell cycle inhibition, which ultimately results in cell death[121]. However, in case of normoxic cancer cells, heterokinase inhibition does not result by the prevention of glycolysis but it is due to the abnormal *N*-linked glycosylation of proteins[122]. 2-Deoxy-D-glucose-6-phosphate in combination with 2-methaoxy estradiol-3,17-*O*,*O*-bis-sulfamate are used for the treatment of breast and prostate cancer by reducing the volume of tumor cells[123]. Another

ane-1,2-diamine)-2-malonatoplatinum(II)-α-D-mannose exhibited excellent anticancer activity. The conformational studies have shown that the compound **1** was transported across the cell membrane was mediated by GLUT, which is extensively overexpressed in cancer cells[129]. This property helps to improve its tumor selectivity and reduce side effects. Compared to oxaliplatin and related compounds, compound **1** was found to be safe and can exhibit better antileukemia activity (Table 2).

Table 2. Water solubilities of (*trans*-*R*,*R*-cyclohexane-1,2-diamine)-2-malonatoplatinum(II)-α-D-mannose conjugates at 25°C

Compd.	*Cis* platin	Carboplatin	Oxaliplatin	Compound **1**	Compound **2**
Solubility (mg/mL) at 25°C	1.0	17.3	6.1	58	63.9

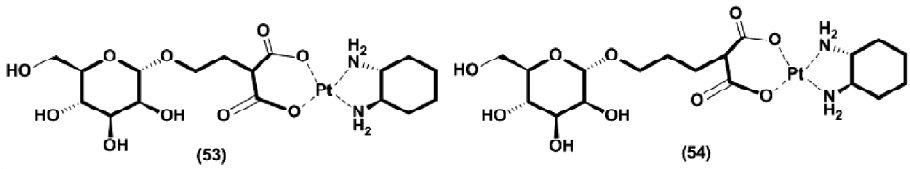


Fig. 18. Molecular structure of (*trans*-R,R-cyclohexane-1,2-diamine)-2-malonatoplatinum(II)-α-D-mannose conjugates[129].

GLUT-1-dependent antiproliferation activity studies on human colon cancer (HT29) 293FT cells shows that the *in vitro* inhibition of platinum complex **1** depends on GLUT-1 expression. Mannosyl based platinum glycoconjugate motif is suitable for GLUT mediated drug delivery and it can selectively target the tumor and the mannose-derived platinum complex **1** has great potential as a new anticancer agent.

Metal-based antibody drug conjugates

Antibody-drug conjugate is an important therapeutic tool to approach cancer through chemotheraptically. These drug molecules are used to treat solid and blood tumors[131]. These drug conjugates are combined with monoclonal antibodies to bind antigens (Fig. 19). Huge number of anticancer drugs has been reported in the literature[130] and it cannot distinguish between tumor and normal cells, but the use of monoclonal antibodies as a targeting tool can able to deliver cytotoxic payload to a tumor cell to give rise to more selectivity towards the tumor cells.

Use of cis-platin for treatment of other cancers

Though some anti-cancer drugs are known, the *cis*-platin derivative is one of the most widely used drug for the treatment of lung, bladder, head, neck, ovarian, cervical and testicular cancers. It is also used for the treatment of child brain tumors[134], gastric[135], leukaemia[136] and anal[137] tumors. It has also been reported that *cis*-platin is used to enhance life span of patient[138]. However, due to drug resistance and side effects of *cis*-platin which inhibits its applications. Attempts were made by different researchers to synthesise several *cis*-platin derivatives containing organic ligands to overcome the side effects. Thus, the antibody drug conjugates of platinum come into existence. The conjugation of antitumor antibodies with platinum-based drugs was reported in 1982 by Wilchek and co-workers[139]. *Cis*-platin were directly (Fig. 20) bonded with different immunoglobin antibodies. The platinum immunoglobin molecules possess affinity towards mice tumor cell to inhibit DNA synthesis and it is more efficient

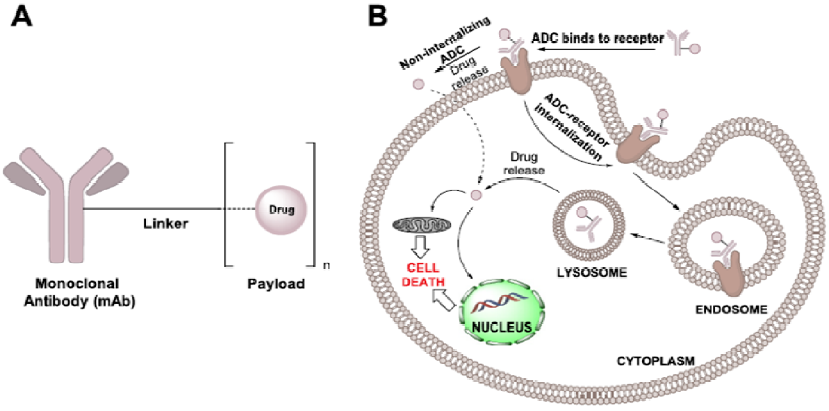


Fig. 19. Action of metal-based antibody drug conjugates: (**A**) Scheme of an antibody-drug conjugate with the three main components and (**B**) schematic view of the mode of action of antibody-drug conjugate[132].

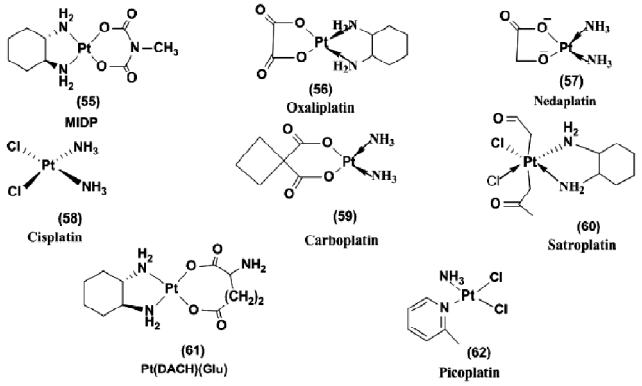


Fig. 20. Different platinum compounds used as cytotoxic payloads and conjugated to or encapsulated in delivery vehicles conjugated to antibodies[141b].

compared to the corresponding platinum compound conjugated to non-tumor reactive antibody[139,140]. Researchers have synthesised murine monoclonal antibody having strong binding with 1,2-diamine cyclohexane side chain of methyliminodiacetato-*trans*-*R*,*R*-1,2-diamminocyclohexane (MIDP) platinum complex at low concentration. The antibody-Pt derived conjugate 1C1-MIDP shows similar cytotoxicity to free Pt derivative MIDP in MCF-7 breast cancer cells. The conjugation of antibodies with that of platinum(II) compounds can be obtained by using water soluble carriers so that it may dissociate from the carriers in order to release the platinum(II) drug with moderate to low stability[141].

Cis-platin and its associated platinum analogous which are approved by Food and Drug administration as a chemotherapeutic antitumor drug for the treatment of solid cancers viz. lung, bladder, head, neck, ovarian, cervical, testicular and bladder cancers[104]. C*is*-platin and its second-generation compounds, such as carboplatin, satroplatin, picoplatin, oxaliplatin and methyliminodiacetato-*trans*-*R*,*R*-1,2-diamminocyclohexane induces a considerable number of toxicities[142]. To overcome these challenges advanced methods[142] are being emerged, such as use of bioactive targeted therapies non-platinum drugs, transition metal-based drugs with intercalating domains which could interact with myriad targets viz. proteins, enzymes, DNA, RNA, etc.

Recent advances in metallo drug-like molecules targeting non-coding RNAs in cancer chemotherapy

It is being reported[143] that several metal-based RNA interactions that are unfamiliar as compared to the corresponding metal-based DNA interactions. Currently a number of RNA tertiary structures are known which can divert the attention of researchers. From the last two decades, much interest has been applied in the growing of RNA therapeutics, and many literature reviews[144] have appeared to highlight the importance of many small molecules viz. antibiotics, inorganic metal complexes in RNA and organic cations[133]. One of the best examples of this category is bleomycin, tobramycin and enediyne etc. All of them act as antitumor antibiotics and possess high affinity towards RNA structures[145]. NMR and X-ray studies[146], shows that the two ring cores of tobramycin (Fig. 21) which is 4,6-linked aminoglycosides makes very parallel contact with phosphate backbones and RNA bases. Bleomycin A2 was used for specific sequence cleavage of tRNA yeast through phosphodiester linkage in the absence of transition-metal ions[147].

Doxorubicin is one of the most effective chemotherapeutic anticancer, anthracycline drugs and is crucial for the treatment of different types of cancers viz. acute leukaemia, malignant lymphoma and breast cancers. Tobramycin shows strong affinity to the HIV frame shift signals. All bleomycin-

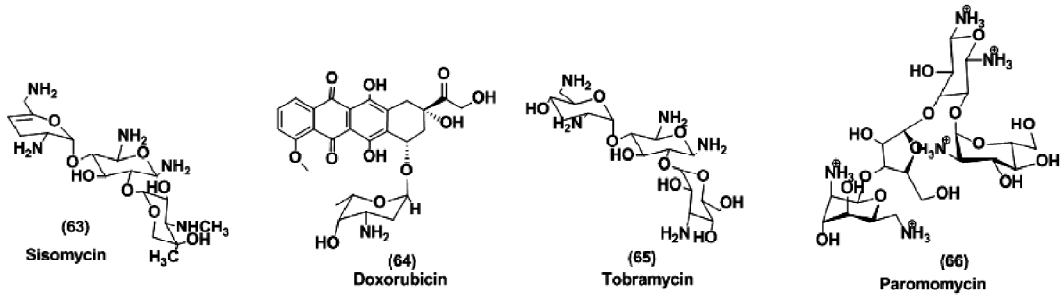
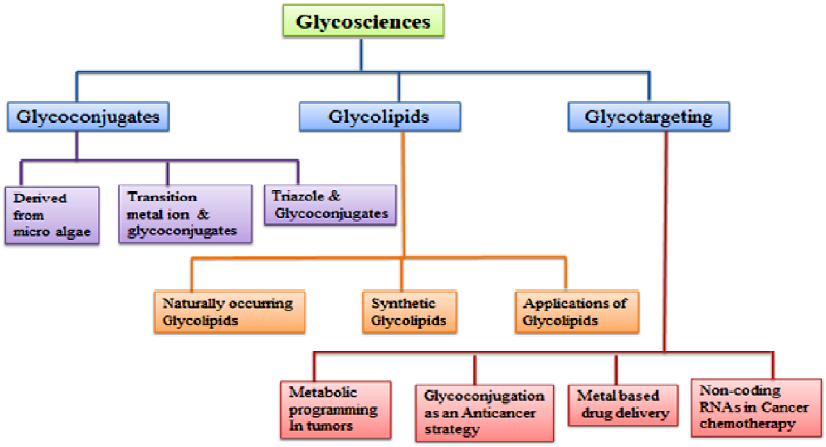


Fig. 21. Molecular structure of representative aminoglycosides.



Flow chart. Glycosciences.

RNA tobramycin-RNA and enediyne-RNA and their subsequent analogous-RNA cleavage and binding interaction require further understanding to confirm their significance in cancer therapies[148].

Conclusion

A great number of previous reports have shown that a sugar derivative plays an important role in the complement activation of several biological phenomenon. Recent development of research on glycosciences suggests that a complement-independent mechanism plays a key role in the development of antibody based drug molecules for several life-threatening diseases. Though several reports are available on glycosciences, the chemistry used in this field of research needs to be efficient enough to solve several of the problems. All these findings summarized in the review provide a better understanding of the structures and functional features of glycosciences in general and sugar derivatives in particular and it is expected to lead to a new direction for the future design and synthesis of sugar-based drugs. Details about the different aspects on glycosciences that are discussed in this mini-review is summarized in the following flow chart.

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