REVIEW

Carbohydrate-based drugs launched during 2000−2021

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Abstract   Carbohydrates are fundamental molecules involved in nearly all aspects of lives, such as being involved in formating the genetic and energy materials, supporting the structure of organisms, constituting invasion and host defense systems, and forming antibiotics secondary metabolites. The naturally occurring carbohydrates and their derivatives have been extensively studied as therapeutic agents for the treatment of various diseases. During 2000 to 2021, totally 54 carbohydrate-based drugs which contain carbohydrate moities as the major structural units have been approved as drugs or diagnostic agents. Here we provide a comprehensive review on the chemical structures, activities, and clinical trial results of these carbohydrate-based drugs, which are categorized by their indications into antiviral drugs, antibacterial/antiparasitic drugs, anticancer drugs, antidiabetics drugs, cardiovascular drugs, nervous system drugs, and other agents.

1. Introduction

Carbohydrates and carbohydrate-containing molecules are involved in almost every aspect of living organisms and perform various important biological functions[1-3]. Thus, the study of carbohydrate-based molecules has long been an important area of drug research[4-7]. For examples, carbohydrate-based antibiotics, including streptomycin, neomycin, and gentamicin were discovered as anti-infectives in 1940s; adriamycin was isolated and developed as one of the most widely prescribed anticancer drugs; ganglioside GM1 was extracted and developed as an acute stroke drug; and the polysaccharide hyaluronic acid was investigated for arthritis treatment. In fact, the broad biological functions of carbohydrates lay the basis for the development of carbohydrate-based drugs.

D-Glucose is a energy source for most living organisms[8], accordingly, the conjugates or derivatives of D-glucose can be used to treat metabolic disorders such as diabetes. Since D-ribose and -deoxyribose are the building blocks of RNA and DNA[9], their derivatives are wiedely used to insert and interrupt the replication processes of pathological cells as well as viruses. Also prominent are the various glycans presenting on the surface of viruses, bacteria, and eukaryotic cells, which are responsible for recognition, communication, and invasion, therefore can be used as candidates for diagnosis and treatment of diseases[10-12]. In addition, microorganisms and plants secrete a large variety of carbohydrate-based secondary metabolites as defense or signaling moleculars[13], which can be used as leads for drug development[14].

Since 2000, great progresses have been achieved in the fields of carbohydrate chemistry[15-21], glycobiology[22,23], and chemical glycobiology[24,25], bringing numerous opportunities for carbohydrate-based drug discovery[26-28]. A number of innovative carbohydrate-based drugs were designed, evaluated, and developed in the past twenty years[29-33]. For example, with a new mechanism of action, the sodium-glucose cotransporter type 2 (SGLT2) inhibitors bring great benefits to the type 2 diabetes mellitus (T2DM) patients, not only in blood glucose control, but also in kidney and heart functions[34,35].

There have been excellent reviews and book chapters updating the research progresses on topics relevant to carbohydrate-based drugs, diagnostic agents, and vaccines during the past years[36-55]. Aiming to provide a comprehensive vision of the latest advances in the carbohydrate-based drugs and diagnostics, here we summarize the carbohydrate-based drugs and diagnostic agents approved during the period 2000−2021 around the world, including the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), the National Medical Products Administration of China (NMPA), as well as in Japan, South Korea, and India, etc.

2. The approved carbohydrate-based drugs during 2000−2021

Over the past two decades, 54 carbohydrate-based new chemical entities (NCEs) have been launched worldwide (Table 1 and Fig. 1). Here we classify them into seven major categories based on their therapeutic indications, those include antiviral drugs, antibacterial/antiparasitic drugs, anticancer drugs, antidiabetic drugs, cardiovascular drugs, nervous system drugs, and other drugs. While the R&D of carbohydrate-based drugs is a continuous process, there have been a few explosive breakthroughs (Fig. 2A). Thus, the first SGLT2 inhibitor Dapagliflozin was launched in 2012 for T2DM treatment; then from 2012 to 2014, five analogues with the same mechanism, canagliflozin, empagliflozin, ipragliflozin, luseogliflozin, and tofogliflozin were successively approved, bringing more choices for T2DM patients. The top four categories, including antiviral drugs (10), antibacterial/antiparasitic drugs (9), anticancer drugs (8), and antidiabetic drugs (8), account for more than 60% of all CBNCEs (Fig. 2B). Prominently, all these CBNCEs are either natural products or derived from the natural carbohydrate scaffolds, among them 37% are nucleosides (Table 1 and Fig. 3).

3. Carbohydrate-based antiviral drugs

Viral pathogens have been one of the great threats to public health throughout human history, accounting for more than 60 percent of the past pandemics, including the outbreaks of severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002−2003, Asian hghly pathogenic avian influenza (HPAI) A (H5N1) in 2009 and 2010, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, Ebola virus in West Africa in 2014−2016, as well as the ongoing coronavirus disease 2019 (COVID-19)[56-58]. Besides, there is still no complete cure for acquired immune deficiency syndrome (AIDS) caused by human immunodeficiency virus (HIV) and hepatitis B disease caused by hepatitis B virus (HBV). Current treatments of HIV and HBV can only maintain low levels of the virus through lifelong antiviral therapy[59,60].

The carbohydrate-based molecules show unique advantages in antiviral drug discovery. Nucleoside and nucleotide could selectively interrupt the replication of the viral RNA or DNA[61]. Eight new antiviral drugs have been developed based on this mechanism, including remedesivir (**1**), molnupiravir (**2**), azvudine (**3**), entecavir (**4**), telbivudine (**5**), clevudine (**6**), sofosbuvir (**7**), and maribavir (**8**). Some sugar moieties of glycoproteins on mammalian cell membrane can be hijacked by viruses and act as anchor receptors for host cell invasion. For example, the influenza A and B viruses infect host cells through binding to the α-2,3-linked sialic acid (N-acetyl-neuraminic acid, zanamivir)[62], which is an important terminal sugar moiety of mammalian glycoproteins. For this reason, sialic acid analogues, including peramivir (**9**) and laninamivir octanoa (**10**), have been developed as neuraminidase inhibitors to block the invasion of influenza A and B. Moreover, since the natural carrageenans prevent viruses' attachment to host cells and infection, the Iota-carrageenan carragelose (**11**) was approved as an OTC drug recently.

3.1. Drugs for COVID-19

Since late 2019, the world has been shaken by the ongoing COVID-19 pandemic. Though several inactivated, recombinant, and mRNA vaccines have been emergently authorized, the specific antiviral medicines are still in demand to stop the pandemic[63]. Rapid compound screenings have provided numerous potential antiviral agents for urgent clinical trials, such as chloroquine, hydroxychloroquine, favipiravir, lopinavir, ritonavir, and remdesivir (**1**)[64-69].

Remdesivir (**1**) is an AMP (55) nucleotide analogue (Fig. 4A), originally developed by Gilead and purposed for treatment of Ebola virus (IC$_{50}$ = 100 nmol/L) and MERS-CoV (IC$_{50}$ = 340 nmol/L). This compound, containing a necessary 1-β-cyano-ribose scaffold and a 1-α-C-nucleobase unit, is a phosphate prodrug, which can be readily hydrolysed into

Table 1 The carbohydrate-based drugs launched during 2000−2021.

No.	Generic name	Indications	Year	Country	Chemical category
1	Remedesivir	Antiviral	2020	USA	Nucleoside
2	Molnupiravir	Antiviral	2021	UK	Nucleoside
3	Azvudine	Antiviral	2021	China	Nucleoside
4	Entecavir	Antiviral	2005	USA	Nucleoside
5	Telbivudine	Antiviral	2006	USA	Nucleoside
6	Clevudine	Antiviral	2006	South Korea	Nucleoside
7	Sofosbuvir	Antiviral	2013	USA	Nucleoside
8	Maribavir	Antiviral	2021	USA	Nucleoside
9	Peramivir	Antiviral	2010	Japan	Nucleoside
10	Laninamivir octanoate	Antiviral	2010	Japan	Nucleoside
11	Carragelose	Antiviral	2013	Europe	NP-derived[a]
12	Telithromycin	Antibacterial	2001	USA	NP-derived
13	Cethromycin	Antibacterial	2009	USA	NP-derived
14	Carrimycin	Antibacterial	2019	China	NP-derived
15	Fidaxomicin	Antibacterial	2011	USA	NP-derived
16	Telavancin	Antibacterial	2009	USA	NP-derived
17	Oritavancin	Antibacterial	2014	USA	NP-derived
18	Dalbavancin	Antibacterial	2014	USA	NP-derived
19	Plazomicin	Antibacterial	2018	USA	NP-derived
20	Paromomycin	Antiparasitic	2006	India	NP-derived
21	Azacitidine	Anticancer	2004	USA	Nucleoside
22	Decitabine	Anticancer	2006	USA	Nucleoside
23	Clofarabine	Anticancer	2004	USA	Nucleoside
24	Nelarabine	Anticancer	2005	USA	Nucleoside
25	Forodesine	Anticancer	2017	Japan	Nucleoside
26	Amrubicin	Anticancer	2002	Japan	NP-derived
27	Midostaurin	Anticancer	2017	USA	NP-derived
28	Mifamurtide	Anticancer	2009	Europe	NP-derived
29	Dapagliflozin	Antidiabetic	2012	Europe	NP-derived
30	Canagliflozin	Antidiabetic	2013	USA	NP-derived
31	Empagliflozin	Antidiabetic	2014	Europe	NP-derived
32	Ipragliflozin	Antidiabetic	2014	Japan	NP-derived
33	Luseogliflozin	Antidiabetic	2014	Japan	NP-derived
34	Tofogliflozin	Antidiabetic	2014	Japan	NP-derived
35	Ertugliflozin	Antidiabetic	2017	USA	NP-derived
36	Sotaglifozin	Antidiabetic	2019	Europe	NP-derived
37	Remogliflozin etabonate	Antidiabetic	2019	India	NP-derived
38	Tinzaparin sodium	Cardiovascular/anticoagulant	2000	USA	NP-derived
39	Fondaparinux sodium	Cardiovascular/anticoagulant	2001	USA	NP-derived
40	Ticagrelor	Cardiovascular	2010	Europe	Nucleoside
41	Cangrelor	Cardiovascular	2015	USA	Nucleoside
42	Sodium oligomannate	Alzheimer disease	2019	China	NP-derived
43	Sugammadex	Anesthesia	2008	Europe	NP-derived
44	Diquafosol tetrasodium	Dry eye disease	2010	Japan	Nucleoside
45	Lactitol	Chronic idiopathic constipation	2020	USA	NP-derived
46	Magnesium isoglycyrrhizinate	Anti-inflammatory	2005	China	NP-derived
47	Miglustat	Gaucher disease	2002	Europe	NP-derived
48	Migalastat	Fabry disease	2016	Europe	NP-derived
49	Uridine triacetate	Hereditary orotic aciduria	2015	USA	Nucleoside
50	Regadenoson	Myocardial perfusion imaging	2008	USA	Nucleoside
51	[99mTc]Tilmanocept	Contrast media	2013	USA	NP-derived
52	Givosiran	siRNA for AHP	2019	USA	Glycoconjugate
53	*S. Pneumoniae* vaccines	*S. Pneumoniae* prevention	2000−2021	USA, Europe, etc.	Glycoconjugate
54	Typhim Vi vaccine	Typhim prevention	2014	USA	Glycoconjugate

[a]NP-derived: derived from natural product.

remdesivir-MP (**56**) and further converted to remdesivir-TP (**57**). The latter form can be incorporated into the nascent viral RNA to prevent viral replication[70,71]. However, it failed in a phase II anti-Ebola clinical trial conducted in West Africa in 2016[72].

In vitro experiments revealed that remdesivir (**1**) could protect the Vero E6 cells against the infection of COVID-19 with an IC_{50} value of 770 nmol/L and IC_{90} value of 1760 nmol/L based on the

qRT-PCR quantification of viral copy number in infected cells[73−75]. Several emergent large scale randomized, double-blind, placebo-controlled trials were conducted to evaluate the safety and efficacy of remdesivir (**1**) for severe COVID-19 patients[76,77]. The results showed that the patients receiving remdesivir (**1**) recovered 31% faster than those in the placebo group (11 *vs.* 15 days)[69,70]. A downtrend of mortality was also observed, although not
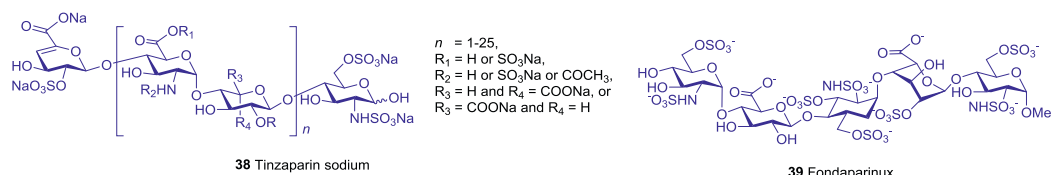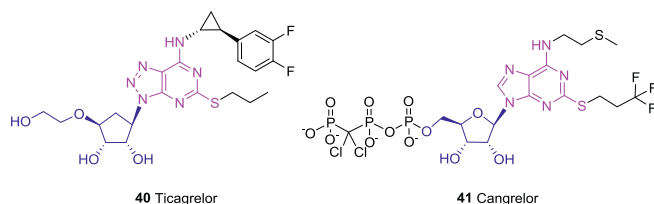
statistically significant (8.0% *vs.* 11.6%). Therefore, remdesivir (**1**) was authorized by FDA for the treatment of hospitalized patients with severe COVID-19 under an Emergency Use Authorization (EUA)[69,77,78].

Molnupiravir (**2**), also named EIDD-2801, is a prodrug of the cytidine nucleoside β-D-*N*-4-hydroxycytidine (NHC, **58**) developed by Merck (Fig. 4B)[79]. This molecule was found effective in

reducing nasopharyngeal COVID-19 virus and viral RNA, with good safety and tolerability[80]. Among 202 participants in a phase II clinical trial (NCT04405570), the viral load in the 800 mg molnupiravir (**2**) group (1.9%) was significantly inhibited compared with the placebo group (16.7%) after 3−5 days' treatment. A more recent phase III clinical trial (MOVe-OUT) indicated that molnupiravir (**2**) reduced the risk of hospitalization or
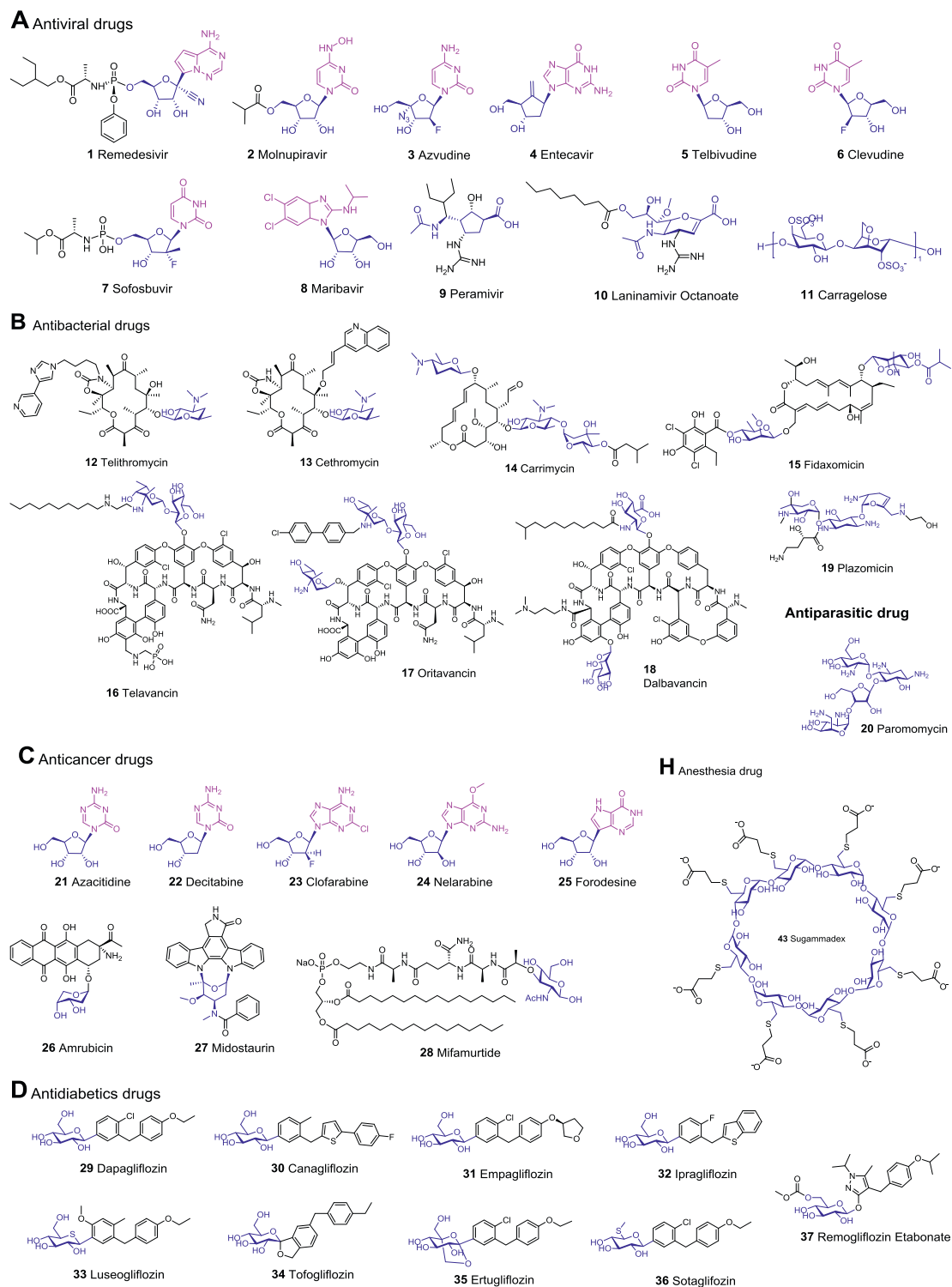
Figure 1 The chemical structures of carbohydrate-based drugs launched during 2000−2021.

E Anticoagulant drugs

n = 1–25,
R_1 = H or SO_3Na,
R_2 = H or SO_3Na or $COCH_3$,
R_3 = H and R_4 = COONa, or
R_3 = COONa and R_4 = H

38 Tinzaparin sodium

39 Fondaparinux

F Antiplatelet Drugs

G Alzheimer disease drug

40 Ticagrelor

41 Cangrelor

42 Sodium Oligomannate (*n* = 2–8)

I Other drugs

44 Diquafosol tetrasodium

45 Lactitol

46 Magnesium isoglycyrrhizinate

49 Uridine tricetate

50 Regadenoson

47 Miglustat

48 Migalastat

J Contrast agent

51 [^{99m}Tc]Tilmanocept

K siRNA drug

Modified strand

52 Givosiran
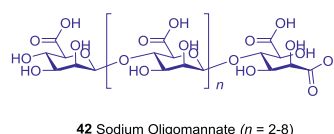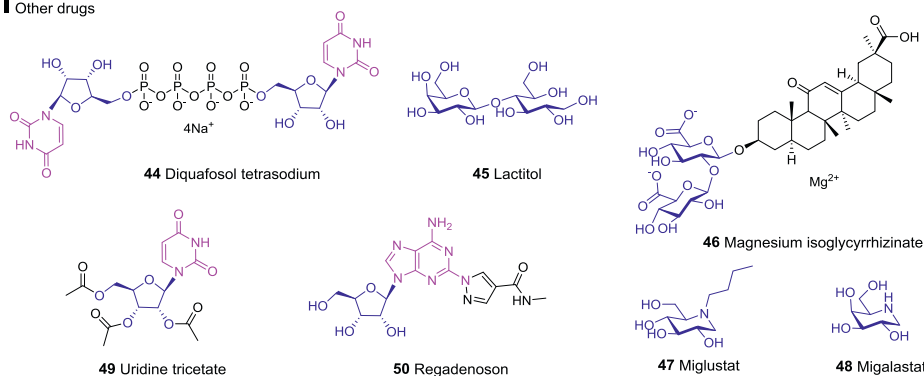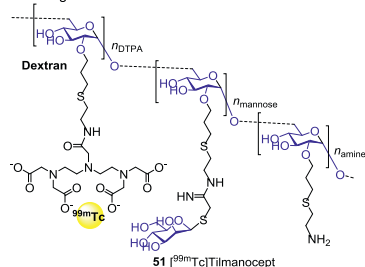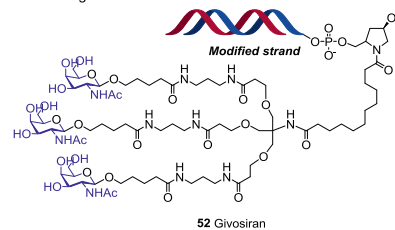
Figure 1 *(continued)*

death by about 50% in non-hospitalized adults with mild to moderate COVID-19[80]. Accordingly, molnupiravir (**2**) was approved in UK, becoming the first oral antiviral drug for the treatment of COVID-19.

There are other antiviral nucleosides which have shown promise when repurposed to treat COVID-19. Azvudine (**3**), the 2′-deoxycytidine (**59**) anaologue developed by Genuine Biotech, is an oral effective 2′-deoxy-2′-β-fluoro-4′-azidocytidine (FNC) antiviral nucleoside (Fig. 4B)[81]. Azvudine (**3**) demonstrated highly potent replication inhibition against both HIV-1 and HIV-2 virus (EC$_{50}$: 0.018−6.92 nmol/L). In phase II and III clinical trials, azvudine (**3**) displayed desirable pharmacokinetics, excellent efficacy, and safety for HIV treatment[82], thus was approved as an anti-HIV drug in China in 2021. Azvudine (**3**) was found to be also effective in inhibiting COVID-19. A randomized, open-label, controlled clinical trial showed that Azvudine treatment significantly reduced the mean time of the first nucleic acid negative conversion (NANC) compared with standard antiviral treatment

(2.6 *vs.* 5.6 days, $P = 0.008$)[83]. Such a convenient and inexpensive oral medicine could greatly benefit the treatment of mild to moderate COVID-19[84].

3.2. Antiviral nucleosides and nucleotides

Nucleoside/nucleotides have been widely used to treat viral infections besides the COVID-19[62]. For example, idoxuridine (**60**), vidarabine (**61**), and ribavirin (**62**) were developed before 2000 (Supporting Information Fig. S1)[85]. In the past twenty years, four more nucleoside/nucleotide antiviral drugs, *i.e.*, entecavir (**4**), telbivudine (**5**), clevudine (**6**), and sofosbuvir (**7**), have been marketed. All these four drugs are used for HBV treatment, with Sofosbuvir (**7**) originally used for hepatitis C virus (HCV).

Chronic HBV infection causes Hepatitis B and puts people at high risk of death from cirrhosis and liver cancer[60]. The FDA has approved a total of seven anti-hepatitis B drugs, including
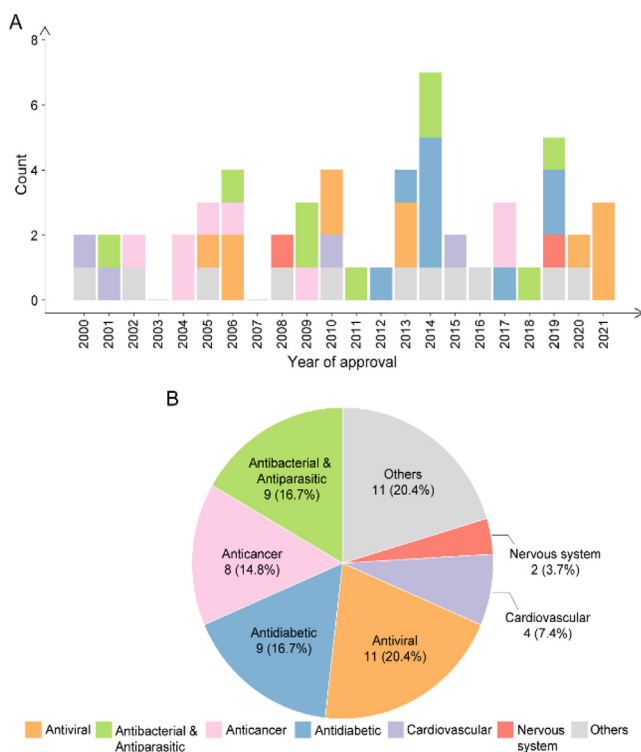
Figure 2 Statistics of carbohydrate-based drugs by launched year (A) and their medical indications (B).

interferon α (IFNα), PEG-IFNα, lamivudine (**63**), entecavir (**4**), telbivudine (**5**), adefovir dipivoxil, and tenofovir disoproxil. However, none of them could eliminate HBV due to the occuurence of covalently closed circular DNA (cccDNA) of HBV[86].

Entecavir (ETV, **4**) is a novel carbocyclic nucleoside drug developed by Bristol-Myers Squibb (BMS). The cyclopentane pseudo sugar moiety mimics 2′-deoxyguanosine (**64**, Fig. 5)[87]. The corresponding triphosphate (entecavir-TP) can compete with the natural nucleotide deoxyguanosine triphosphate (dGTP) to inhibit HBV DNA polymerase with a K_i value of 1.2 nmol/L. The

inhibition of mammalian DNA polymerase α, β, or γ isoforms is relatively weak, with a K_i of 18−40 μmol/L[88]. In phase II and III clinical trials, entecavir (**4**) demonstrated superior advantages over lamivudine for all primary endpoints evaluated in both nucleoside-naive and lamivudine-resistant patients[89]. Since it was highly effective in both HBeAg-positive and HBeAg-negative nucleoside-naive patients, entecavir (**4**) was approved for the treatment of HBV in 2005.

Telbivudine (**5**), a ʟ-enantiomer of the natural ᴅ-thymidine (**65**), is developed by Idenix and Novartis (Fig. 5)[90]. The triphosphate form of telbivudine (telbivudine-TP) can compete with natural thymidine triphosphate to inhibit HBV DNA duplication with EC$_{50}$ of 1.3 ± 1.6 μmol/L for the first strand (RNA-dependent) DNA synthesis and a preferential EC$_{50}$ of 0.2 ± 0.2 μmol/L for the second strand (DNA-dependent) synthesis, wheras it does not inhibit mammalian DNA polymerases at concentrations up to 100 μmol/L[91]. In a 52-week phase III trial, the telbivudine (**5**) group showed greater reductions in serum HBV DNA compared with the lamivudine (**63**) group; in another one-year switching trial, the serum HBV DNA of telbivudine (**5**) group decreased more than that of the Adefovir group even at 24 weeks[92,93]. In addition, the adverse events of telbivudine (**5**) were mild and well tolerated by patients, thus it was approved by FDA in 2006 for the treatment of chronic HBV infection.

Clevudine (CLV, **6**) is another ʟ-enantiomeric analogue of natural ᴅ-thymidine (**65**) with an ʟ-2-deoxy-2-fluoro-β-arabino-furanosyl moiety developed by Bukwang Pharma in South Korea (Fig. 5)[94]. The triphosphate form (clevudine-TP) inhibits the second strand (DNA-dependent) synthesis by HBV DNA polymerase with an EC$_{50}$ of 16.3 ± 2.4 nmol/L and has the interaction with human DNA polymerases[95]. Clevudine (**6**) was tested in a 48-week follow-on phase III clinical trial in Korean for the treatment of HBV infection. After clevudine (**6**) treatment for 24 weeks, HBV DNA was still under the detectable line in 92% of HBeAg$^-$ patients and 59% of HBeAg$^+$ patients[96]. Based on these meaningful results, clevudine (**6**) received the first approval in South Korea in 2006.

HCV is a bloodborne and hepatotropic RNA virus, which causes acute and chronic liver inflammation and leads to severe liver diseases such as cirrhosis, liver cancer, and chronic liver failure. According to WHO, an estimated 71 million people
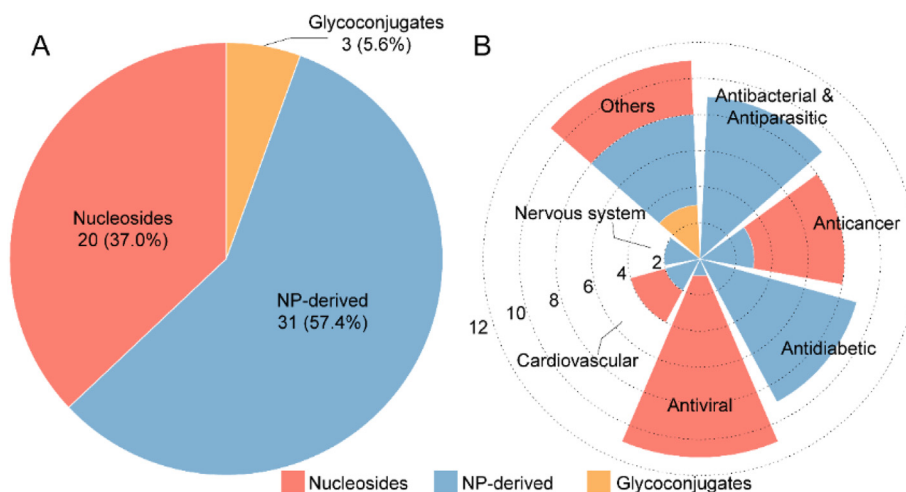

Figure 3 Statistics of the carbohydrate-based drugs according to chemical sources (A) and indications (B).
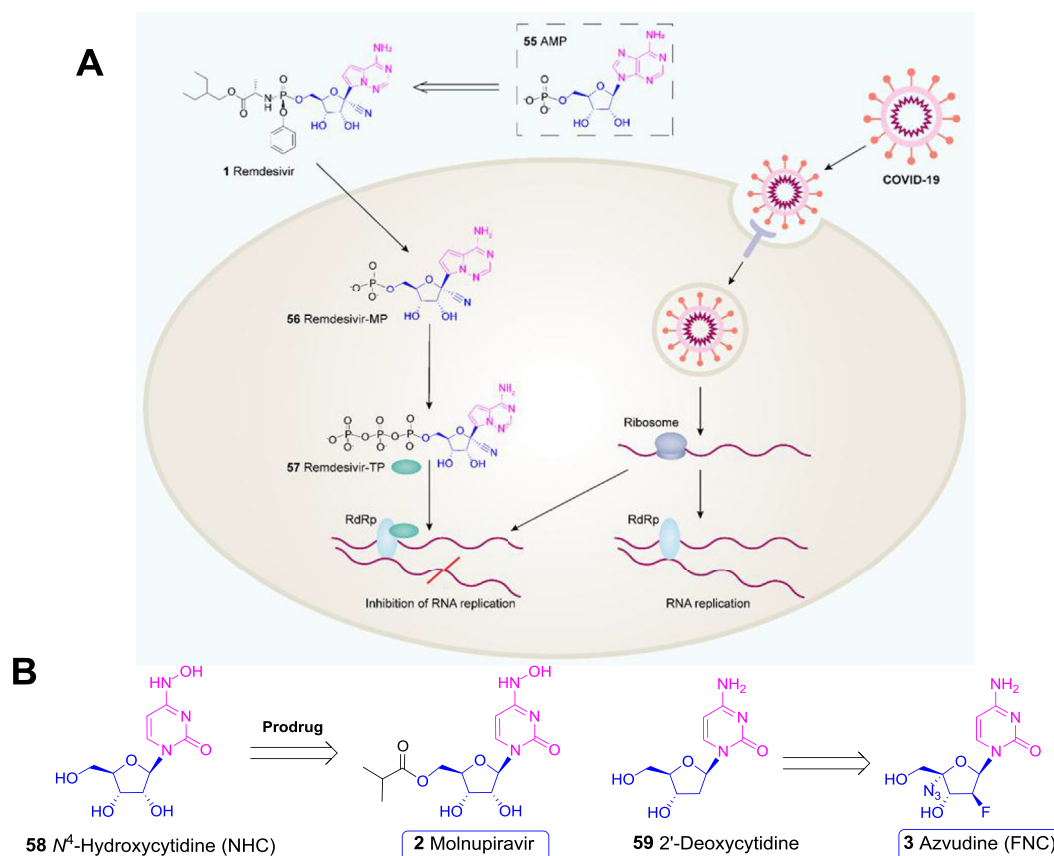
Figure 4 Carbohydrate-based drugs for COVID-19. (A) From AMP (**55**) to remdesivir (**1**) and its mode of action. RdRp, RNA-dependent RNA polymerase. (B) The potential antiviral nucleosides (**2** and **3**) for COVID-19 therapy and their parent compounds (**58** and **59**).

worldwide are chronically infected with HCV[97]. Until the recent discovery of sofosbuvir (**7**), HCV treatments require complicated long-term medications with limited efficacy and severe side effects[98,99]. Sofosbuvir (**7**), developed by Gilead, contains a β-D-2′-deoxy-2′-α-fluoro-2′-β-C-methyluridine-5′-monophosphate skeleton which mimics UMP (**66**, Fig. 5)[100]. After oral administration, sofosbuvir (**7**) is efficiently absorbed by liver cells and phosphorylated to its metabolite forms sofosbuvir-MP and sofosbuvir-TP. Sofosbuvir-TP inhibits the NS5B RNA-dependent RNA polymerase of HCV during the viral RNA replication with an EC_{50} of 92 nmol/L and an EC_{90} of 0.29 µmol/L, respectively[101]. Moreover, sofosbuvir (**7**) demonstrates low activity to

human RNA polymerases and DNA polymerases, resulting in an overall safety profile. In a phase I clinic trial, sofosbuvir (**7**) showed favorable pharmacokinetic profile and was well tolerated at the tested doses[102]. Then a series of randomized, multicenter phase II and phase III clinical trials were carried out. The sustained virologic response rates at 12 weeks (SVR12) were 97%− 99% in all administrated groups, including the combination of ledipasvir and sofosbuvir (**7**) for 12 weeks, the combination of ledipasvir, sofosbuvir (**7**), and ribavirin (**62**) for 12 weeks, the combination of ledipasvir and sofosbuvir (**7**) for 24 weeks, and the combination of ledipasvir, sofosbuvir (**7**), and ribavirin (**62**) for 24 weeks[103]. These data showed that the stubborn HCV disease could
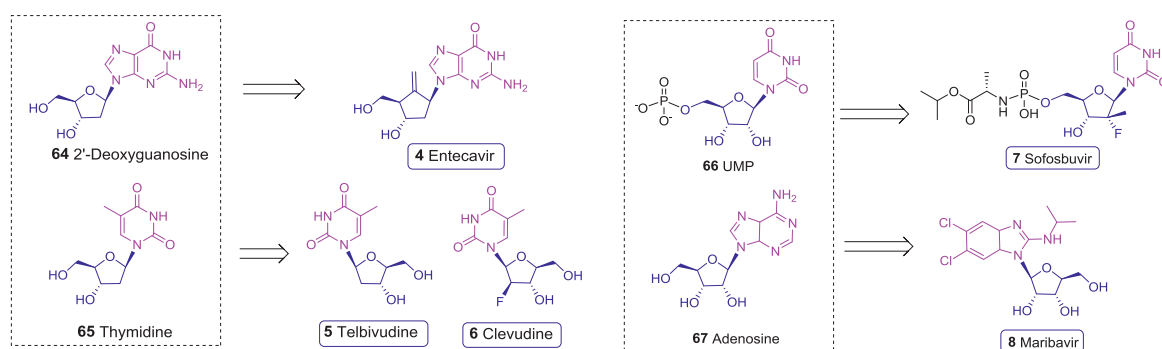
Figure 5 The antivires drugs (**4**−**8**) are derived from natural nucleoside and nucleotide **64**−**67**.

be cured by sofosbuvir (**7**) in combination with several synergetic drugs[104]. Therefore, sofosbuvir (**7**) was approved by FDA in December 2013 for the treatment of chronic HCV infection in all sub-genotypes, including those with liver cancer meeting Milan criteria and those with HIV-1 coinfections. Recently, WHO proposed a new global vision to eliminate hepatitis C infection by 2030, with the benefit of Sofosbuvir (**7**)[97].

Maribavir (**8**), which has been developed in Takeda since 2000, is a dicholoro-benzimidazole L-riboside (Fig. 5). This substituted benzimidazole neucleoside mimics adenosine (**67**) and acts as an ATP competitive inhibitor with an IC_{50} of 3 nmol/L against the cytomegalovirus (CMV) UL97 kinase, which is involved in viral DNA assembly and capsids movement from virus to infected cells[105]. DNA hybridization assay showed that the IC_{50} of maribavir (**8**) against CMV viral replication was 0.12 ± 0.01 µmol/L[107]. An early preventive clinical trial revealed that maribavir (**8**) reduced the incidence of CMV infection after allogeneic stem-cell transplantation compared with placebo, without myelosuppression[106]. Accordingly, maribavir (**8**) was granted Orphan Drug Designation for the prevention of cytomegalovirus viremia and disease in high-risk populations by the FDA in 2007. Afterwards, more trials had focused on the efficacy of maribavir (**8**) in the treatment of drug-resistant or refractory CMV infection. According to the phase II/III trials of hematopoietic-cell or solid-organ transplants with CMV reactivation, 79% of patients in maribavir (**8**) arm had a response to the treatment, not inferior to valganciclovir (67%)[107]. Recently, FDA approved it as the first drug for treating adults and pediatric patients with post-transplant CMV infection/disease that does not respond to available antiviral treatment for CMV.

3.3. Neuraminidase inhibitors

Influenza A and B are the most common influenza virus types, causing seasonal influenza and a large number of deaths every year. While influenza A can infect humans and other animals, such as birds and pigs, influenza B appears to be found only in humans. Influenza A includes various subtypes based on different expression levels of hemagglutinin (H) and neuraminidase (N) on the viral surfaces[108]. The neuraminidase is a viral enzyme that recognizes the specific α-2,3-linked sialic acid moiety to invade host cells and cleaves the sialic acid moiety to release newly formed virus[109]. Targeting this specific enzyme, sialic acid analogues were developed to block influenza A and B with unprecedented success[110].

Sialic acid (N-acetylneuraminic acid or Neu5Ac, **68**) is a high-carbon sugar with a complex nine-carbon skeleton. Based on that the neuraminidase cleaves Neu5Ac with a six-membered planar oxonium transition state, zanamivir (**69**), with a 2,3-didehydro-2-deoxy-N-acetylneuraminic acid (Neu5Ac2en) moiety, is developed as a mimic of the transitions state. It efficiently inhibits the influenza viruses with IC_{50} of 0.95 and 2.7 nmol/L for influenza A and B, respectively[111]. Since the 4-guanidinium group increases the polarity of zanamivir (**69**) and affects the oral bioavailability, zanamivir is delivered by intranasal or dry powder inhalation. It was launched in 1999. In the same year, Roche launched a blockbuster neuraminidase inhibitor, oseltamivir (**70**). This drug contains a cyclohexene core instead of the 2,3-glycal of Neu5Ac (**68**), a 4-amine instead of the 4-guanidinium group, and a pentan-3'-O-ester instead of the 6-glycerol group[112]. Oseltamivir (**70**) inhibits influenza A-H3N2, A-H1N1, and influenza B viruses with the IC_{50} values of 0.67, 0.9, 1.34, and 13 nmol/L, respectively[113]. Since the polarity has been greatly optimized by the structural modifications, both the oral bioavailability and therapeutic efficiency of oseltamivir (**70**) are improved compared to zanamivir (**69**).

Afterwards, peramivir (**9**) and laninamivir octanoate (**10**) were approved as new anti-influenza drugs around 2010. Peramivir (**9**) is a new neuraminidase inhibitor developed by BioCryst, with a cyclopentane core instead of the cyclohexene core of oseltamivir (**70**, Fig. 6A)[114]. The IC_{50} values of peramivir (**9**) in inhibiting influenza A-H1N1 virus, influenza A-H3N2 virus, and influenza B virus are 0.16, 0.13, and 0.99 nmol/L, respectively; and peramivir (**9**) also effectively prevents the release of influenza virus particles from infected cells[115]. Because the oral bioavailability of Peramivir (**9**) was low in a phase I clinical trial, further clinical trials used the intravenous administration. After more than ten years' complicated multicenter, open-label, uncontrolled clinical evaluations, and the 2009 H1N1 influenza pandemic emergency use authorization, peramivir (**9**) has proven to be effective in the treatment of human influenza A and B, including high-risk patients who have difficulties with oral drugs. It was firstly approved in Japan in 2010 for use in children's influenza treatment.

Based on the success of zanamivir (**69**), a long-acting prodrug named laninamivir octanoate (**10**) was launched in Japan in 2010. Due to the long chain ester tail (Fig. 6A), the drug converts to its active form laninamivir (**71**) slowly in lungs, which allows a single inhaled administration to maintain an effective concentration for about 5 days[116]. Laninamivir octanoate (**10**) showed a significant clinical efficacy, which is comparable to oseltamivir (**70**) and
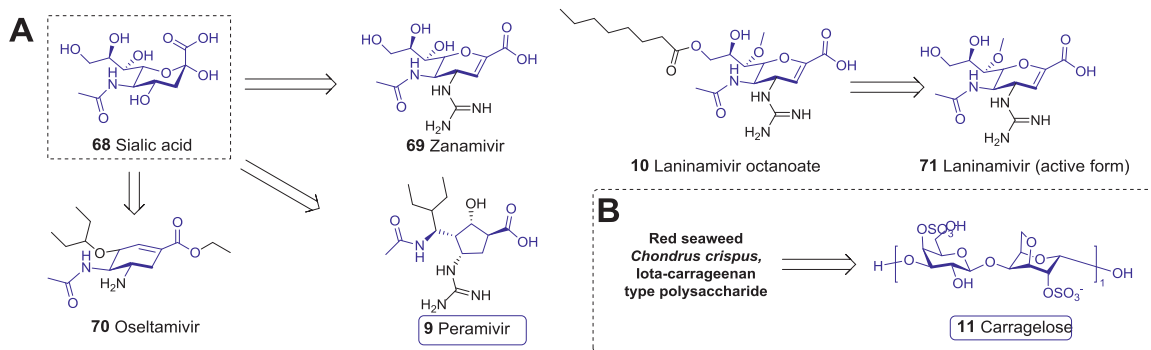
Figure 6 The structure of other carbohydrate-based antiviral drugs. (A) From sialic acid (**68**) to the anti-influenza drugs launched before and after 2000−2021. (B) The red seaweed (*Chondrus crispus*) sourced carragelose (**11**).

zanamivir (**69**) for the treatment of the 2009 H1N1 pandemic influenza strain.

3.4. Antiviral polysaccharide

Carragelose (**11**), which developed by Marinomed, is a natural algae sourced linear Iota-carrageenan type polysaccharide drug from red seaweed (*Chondrus crispus*) (Fig. 6B). Generally, carrageenans are polygalactans (molecular weight higher than 100 kDa) with various sulfated galactose and 3,6-anhydrogalactose (3,6-AG) repeating units joined by alternative α-(1,3) and β-(1,4)-glycosidic linkages[117]. Among various subcategories, iota-carrageenan demonstrates considerable and wide-spectrum antivirus activities. As demonstrated, the antivirus IC_{50} values of iota-carrageenan against influenza A H3N2 and H1N1 reach 0.04 and 0.20 µg/mL, respectively. Mechanism research reveals that Iota-carrageenan directly binds to virus and prevent its attachment to host cells, and thereby achieves effectiveness against several viruses[117,118]. Based on such bio-active characters, carragelose (**11**) was developed from iota-carrageenan polysaccharide.

Since carragelose (**11**) cannot penetrate nasal mucosa, it is safe in topically medical applications. A randomized, placebo-controlled, double-blind clinical trial enrolled 211 patients with common cold and showed that alleviation of symptoms was 2.1 days faster in the Iota-carrageenan nasal spray group than in placebo group ($P = 0.037$). Viral titers in nasal fluids also had a significantly decrease in iota-carrageenan group in the ITT population ($P = 0.024$) as well as in the per protocol population ($P = 0.018$)[119]. Consequently, carragelose (**11**) was approved as an over-the-counter (OTC) drug by EMA for cold treatment in 2013. It is worth noting that carragelose (**11**) inhibits COVID-19 virus with an IC_{50} of 2.6 µg/mL *in vitro*[120]. To date, several clinical studies (NCT04793984, NCT04681001 and NCT04590365) are on the way.

4. Carbohydrate-based antibacterial and antiparasitic drugs

Bacteria are closely associated with human health down the ages. There have been many bacteria incurred pandemics throughout history, including the bubonic plague caused by *Yersinia pestis*, tuberculosis caused by *Tubercle bacilli*, cholera caused by *Vibrio cholera*, and anthrax caused by *Bacillus anthracis*. Even today, bacterial infections remain severe threatens to human health and life[121]. Penicillin, discovered in 1928, became the first modern drug against bacteria, ushering in the "antibiotic era". Thereafter, a large number of antibiotics, including many carbohydrate-conjugated compounds have been discovered for clinical use. Most of these antibiotics, produced by microbes over long periods of evolution, possess structures beyond chemists imagination.

The protein synthesis machines are important targets of carbohydrate-based antibiotics. One important factor is that the 70S ribosome of bacteria is made up of a 30S small subunit and a 50S large subunit, which is significantly different from the 80S ribosome of eukaryotic cells[122]. Thus, carbohydrate-conjugated macrolide antibiotics and aminoglycoside antibiotics (AGs) can selectively disrupt the ribosomal functions required for the bacterial protein synthesis without affecting protein synthesis in eukaryotic cells[123]. Another unique structural feature of bacteria is their cell wall, which are mainly composed of peptidoglycans and glycolipids[124]. In order to produce these glycans, bacteria maintain sophisticated and distinctive biosynthesis systems, which are absent in eukaryotes[125]. This vital biosynthesis process of bacteria could be exploited by antibiotics to suppress bacterial infections[125,126]. However, with the widespread use of antibiotics, antimicrobial resistance (AMR) has become a global health threat[121,127]. Discovery of new antibiotic drugs is important to this global challenge[127]. During 2000 and 2021, nine new carbohydrate-based antibacterial drugs launched, including four glycomacrolide antibiotics telithromycin (**12**), cethromycin (**13**), carrimycin (**14**), and fidaxomicin (**15**), three glycopeptide antibiotics telavancin (**16**), oritavancin (**17**), and dalbavancin (**18**), and two aminoglycoside antibiotics plazomicin (**19**) and paromomycin (**20**).

4.1. Antibacterial drugs

Macrolide glycoside, consisting of macrocyclic lactones with one or more deoxysugar residues, are secondary metabolites of *Streptomyces*. They have broad spectrum antibacterial activities against aerobic Gram-positive and Gram-negative bacteria, some anaerobic bacteria, and atypical pathogens, and have been used to treat respiratory tract infections in patients allergic to penicillin[124]. All the macrolide antibiotics can interact with the nucleotides 2058−2062 in domain V of 23S rRNA, resulting in the premature release of peptidyl tRNA from the ribosomes, which inhibits protein synthesis and further kills bacteria[128]. Some glycomacrolide antibiotics can also block peptidyl-transferase activity and suppress bacterial ribosome assembly[124,128].

Hitherto, there have been three generations of macrolide antibiotics in clinical practices. The first-generation glycomacrolide antibiotics, including 14-membered-ring erythromycin (**72**) and 16-membered-ring spiramycin I (**73**, Fig. 7), are effective and well tolerated. However, their clinical efficacies are restricted by short half-life and poor oral bioavailability[124]. The second-generation macrolide antibiotics, such as clarithromycin (**74**) and azithromycin (**75**, Fig. 7), are modified at the 9-ketone, 6-hydroxy, or 12-hydroxy groups of the original macrocyclic lactones[129,130]. These modifications do not affect the antibacterial activity, but inhibit the isomerization of macrolides in acidic environments, thus improving their stability in gaster. Therefore, the second-generation macrolide antibiotics have more indications. For instance, clarithromycin (**74**) is also used to treat *Helicobacter pylori* infection and AIDS-related respiratory infections caused by *Mycobacterium avium* complex[131,132].

However, the application of the first- and second-generation macrolide antibiotics is gradually limited by antibiotic resistance, mainly mediated by erythromycin (**72**) resistance methylase (MLS_B resistance phenotype, including constitutive and inducible MLS_B resistance) and efflux of antibiotic from the bacteria[133]. Further optimization and structure−activity relationship (SAR) studies indicated that the 3-*O*-cladinose of erythromycin (**72**) was not an essential group, while the 5-*O*-desosamine dominated the antibacterial activity[133]. Thus, replacing the 3-*O*-cladinose with a ketone group improved the bacteriostatic sensitivity and resulted in the third-generation macrolide antibiotics, also known as ketolide antibiotics[133]. In 2001, FDA approved Aventis' first third-generation ketolide antibiotic telithromycin (**12**), which was derived from erythromycin A. telithromycin (**12**) contains 3-ketone, 5-*O*-desosamine, 11,12-cyclocarbamate, and a butyl-imidazole-pyridine extension moiety attached to the lactone ring (Fig. 7)[134]. The alkylaryl extension enables the new drug to bind to a specific adenine (A752) in domain II of 23S subunit, which
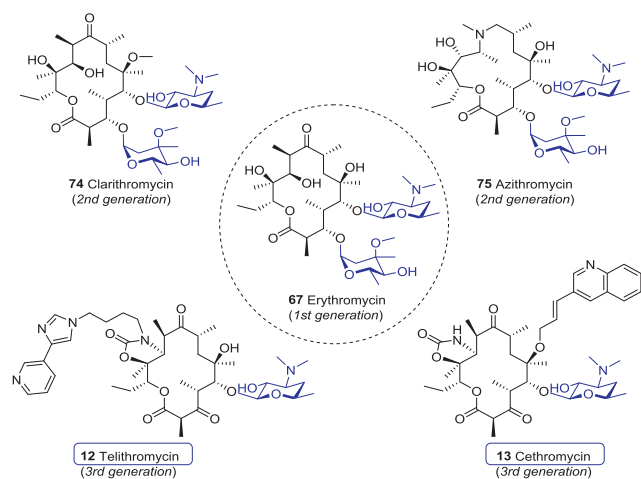
Figure 7 The representative first-, second- and third-generation macrolide glycoside antibiotics.

differs from the previous macrolide antibiotics and thus increases sensitivity against the erythromycin-resistant bacteria[135]. For erythromycin-sensitive *Streptococcus pneumoniae*, the 50% minimum inhibitory concentration (MIC_{50}) and 90% minimum inhibitory concentration (MIC_{90}) of telithromycin (**12**) are 0.016 and 0.03 µg/mL, respectively, which are about 10-fold lower than that of erythromycin (**72**)[136]. Besides, telithromycin (**12**) remains sensitive to these strains harboring inducible MLS_B resistance[137−139], as well as Gram-negative bacteria, and atypical bacteria. The MIC_{90} values of telithromycin (**12**) for *Haemophilus influenza*, *Moraxella catarrhalis*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and *Legionella pneumophila* are 4, 0.12, 0.125, 0.004, and 0.03 µg/mL, respectively[140−143].

Community-acquired pneumonia (CAP) is a common disease in outpatients. Annually, approximately 600,000 patients are hospitalized for CAP in the United States, resulting in $10.6 billion in health care expenditures[144]. The pooled analysis of several III/IV phase studies indicated that the clinical cure rate and bacteriologic eradication rate of oral telithromycin (**12**) treatment (800 mg/day) for 5 or 7−10 days reached 88.1% and 89.0%, respectively[140,145]. Thus, CAP became the first approved indication for telithromycin (**12**) in 2001[146]. After that, more clinical studies have proved that telithromycin (**12**) was also effective in treating tonsillopharyngitis, scrub typhus, and acute exacerbations of asthma[147−149]. However, it should be mentioned that side effects such as severe hepatotoxicity and visual impairment were reported and warned, limiting the use of terithromycin (**12**) for further indications[146,150].

Abbott developed another third-generation ketolide antibiotic cethromycin (**13**), which also carries 3-ketone, 5-*O*-desosamine, and 11,12-cyclocarbamate moiety (Fig. 7). In cethromycin (**13**), the aryl-alkyl side chain is attached to the 6-hydroxyl group *via* an ether linkage. Cethromycin (**13**) binds to the domain II and V of 23S rRNA, sharing similar working mechanisms of telithromycin (**12**). The *in vitro* antibacterial activity against 1223 clinical isolated species showed that cethromycin (**13**) was effective in inhibiting *S. pneumoniae* and other *Streptococci*[151]. Cethromycin (**13**) inhibits macrolide-susceptible *Streptococci* and *Staphylococci* with the MIC_{90} ranging from 0.002 to 0.03 µg/mL, and inhibits macrolide-resistant *S. pneumoniae* and *S. pyogenes* with the MIC_{90} ranging from 0.015 to 0.12 µg/mL and from 0.12 to

0.5 µg/mL, respectively[137]. Cethromycin (**13**) is active for Gram-negative bacteria and atypical bacteria with the MIC_{90} values for *H. influenzae*, *M. catarrhalis*, *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila* being 4, 0.12, 0.016, 0.06, and ≤0.001 µg/mL, respectively[151−153]. It also inhibits methicillin-resistant *Staphylococcus aureus* (MRSA) with the MIC_{90} ≤ 0.002 µg/mL[154]. Further phase II/III studies for cethromycin (**13**) against CAP indicated that 10-day course treatment (150 mg/day) and 7-day course treatment (300 mg/day) achieved clinical cure rate of 83% and 84%, bacteriologic eradication rate of 83% and 85%, respectively[155]. Importantly, cethromycin (**13**) displayed outstanding antibacterial activity for *B. anthracis*, *Y. pestis*, and *Francisella tularensis*[156−158]. In 2009, FDA accelerated approval of cethromycin (**13**) as an orphan drug for prophylactic treatment of anthrax inhalation, tularemia, and plague.

Carrimycin (**14**) is a 16-membered macrolide glycoside antibiotic developed by Tonglian Pharmaceutical. It is produced from a genetically engineered bacteria strain of *S. spiramyceticus* (Fig. 8A). Compared with the 1st generation spiramycin I (**73**), carrimycin (**14**) contains an additional 4′-*O*-isovaleryl group at the terminal sugar residue, which makes it more lipophilic and more active. The *in vitro* activities of carrimycin (**14**) against *Chlamydia trachomatis*, *C. pneumoniae*, *Ureaplasma urealyticum,* and *M. pneumoniae* are similar to azithromycin (**75**) with MICs in the range of 0.03−0.5 µg/mL, while it is more potent than acetyl-spiramycin[159]. A Phase III clinical trial showed that the efficacy and safety of carrimycin (**14**) was superior to azithromycin (**75**)[160]. Thus, carrimycin (**14**) was approved by NMPA for pneumonia treatment in 2019. Of note, carrimycin (**14**) displays a broad-spectrum antiviral activity against human coronaviruses, including COVID-19, and is preferentially distributed in the lungs by oral administration[161]. As a result, several clinical trials are currently under way to investigate the efficacy of carrimycin (**14**) against COVID-19.

Fidaxomicin (**15**), derived from the secondary metabolite of *Dactylosporangium aurantiacum*, is developed by Optimer as a novel member of macrolide glycoside antibiotics[162]. Structurally, fidaxomicin (**15**) is comprised of a 18-membered-ring with a 7-carbon sugar at 12-OH and a 4′-*O*-benzoyl-6′-deoxysugar at 21-
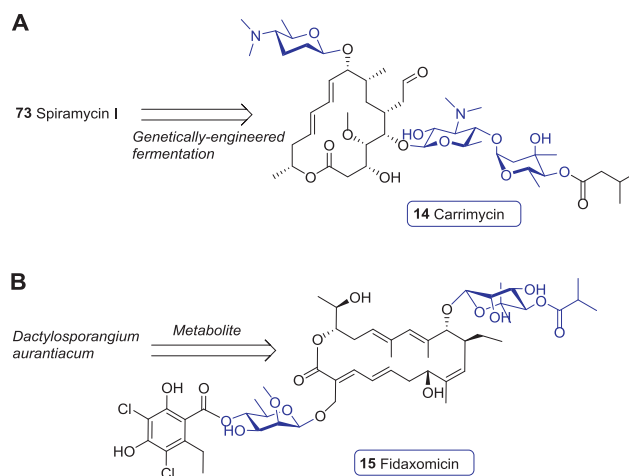
Figure 8 Launched 16- and 18-membered macrolide glycoside antibiotic. (A) The macrolide glycoside antibiotic carrimycin (**14**) derived from spiramycin I (**73**). (B) Macrolide glycoside fidaxomicin (**15**).

OH (Fig. 8B). Unlike the macrolide antibiotic drugs mentioned above, fidaxomicin (15) shows a different mode of action by binding to the bacterial DNA template-RNA polymerase (RNAP) complex, which leads to the disruption of RNA transcription. However, the exact molecular mechanism of action still needs to be fully elucidated[162,163].

Fidaxomicin (15) shows good inhibition activity against *Clostridium difficile* with the MIC_{90} values ranging from 0.008 to 0.25 μg/mL, but its activity against intestinal Gram-negative bacteria is relatively poor[163,164]. *C. difficile* infection (CDI) can cause severe infectious complications and death, especially in the elderly, and is the leading cause of healthcare-associated diarrhoea in the developed countries[165]. Previously, vancomycin (76) was the only agent approved by FDA for CDI treatment, while metronidazole was also used off-label as a treatment of mild-to-moderate CDI[166]. A multicenter, double-blind, randomized clinical trial, involving 629 patients with primary CDI or first recurrence, compared the safety and efficacy of fidaxomicin (15) and vancomycin (76). The results showed that the cure rate of fidaxomicin (15) was noninferior to that of vancomycin (76), and the recurrence rate was significantly lower than that of Vancomycin (76) with a similar adverse-event profile[167]. Thus, fidaxomicin (15) was endorsed by FDA for CDI treatment in 2011.

Glycopeptide antibiotcs (GPAs), including vancomycin (76), teicoplanins A2 (77), and chloroeremomycin (78), are secondary metabolites from *Actinomycetes* and *Streptomyces*. These molecules contain an intricate heptapeptide core modified by various glycosylation, acylation, chlorination, methylation, and/or sulfation modificaitons (Supporting Information Fig. S2)[168]. Sophisticated chemical structures endow GPAs with special antibiotic activity and mode of action. The heptapeptide core of GPAs binds to the *C*-terminal D-Ala-D-Ala of peptidoglycan precursors, which sequesters the substrate necessary for the enzyme-catalyzed bacterial cell wall cross-linking reaction and affects the *trans*-glycosylase catalyzed insertion of lipid intermediate II into the polysaccharide cell wall skeleton. Thus, GPAs hamper the bacterial cell wall construction to kill bacteria.

The emergence of drug-resistant Gram-positive bacteria, as represented by MRSA, motivated the development of GPAs. Among them, vancomycin (76) and teicoplanin A2 (77) are often described as the last defense, for their activity against a variety of Gram-positive bacteria. However, vancomycin-resistant bacteria has emerged, including vancomycin-resistant *enterococcus* (VRE) with the remodeling of D-Ala-D-Ala to D-Ala-D-Lac (this phenotype could be divided into VanA, VanB, VanC, VanD, VanE, and VanG types), vancomycin-intermediate *S. aureus* (VISA) induced by the thickening of cell wall, and vancomycin-resistant *S. aureus* (VRSA) resulted from an *in vivo* transfer of the *vanA* transposon from *Enterococcus faecalis* to MRSA[168]. Thus, there is an urgent need to develop new GPAs, and various chemical modifications on vancomycin (76) in the late 1990s paved ways[169]. Since 2000, three GPAs, also named lipoglycopeptides, for the common feature of the presence of lipid side chains, have been authorized by FDA.

Telavancin (16) is a semi-synthetic derivative of vancomycin (76) developed by Theravance. It has a lipophilic decylaminoethyl group on the vancosamine moiety and a hydrophilic aminomethyl group attached to the 4′-position of ring 7 (Fig. 9)[170]. Besides the shared action modes of GPAs, telavancin (16) also disrupts membrane barrier function *via* the interaction of the hydrophobic decylaminoethyl group with lipid II precursor[171]. As a result, though telavancin (16) has the same resistant mechanism of

vancomycin (76), it demonstrates more potent activity against MRSA, methicillin-susceptible *S. aureus* (MSSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE), methicillin-susceptible *S. epidermidis* (MSSE), VISA, and VanB-type VRE with the MIC_{90} values of 0.5, 0.5, 1.0, 1.0, 1.0, and 2.0 μg/mL[172]. A pooled analysis of two identically designed, randomized, double-blind, active control, phase III studies compared the efficacy of telavancin (16) and vancomycin (76) among 1867 patients with complicated skin and skin-structure infections (cSSSI) bred by suspected or confirmed Gram-positive bacteria. The clinical cure rates were 88.3% and 87.1% in telavancin (16) and vancomycin (76) treatment arms, respectively[173]. Among MRSA infected patients ($n = 579$), the achieved clinical cure rates were 88.3% and 87.1% in telavancin (16) and vancomycin (76) treatment arms, respectively[173]. Therefore, telavancin (16) was approved by FDA for the treatment of cSSSI in 2009.

Oritavancin (17) is a semisynthetic lipoglycopeptide drug developed by Eli Lilly from chloroeremomycin (78). It has excellent bactericidal activity against both glycopeptide-sensitive and glycopeptide-resistant Gram-positive bacteria[174]. The significant structural difference between oritavancin (17) and vancomycin (76) is that oritavancin (17) has an additional 4-*epi*-vancosamine in ring 6 and the replacement of vancosamine by 4-*epi*-vancosamine with a lipophilicity 4′-chlorobiphenylmethyl side chain (Fig. 9)[168]. Oritavancin (17) inhibits bacterial cell wall synthesis through impeding *trans*-glycosylation *via* binding to D-Ala-D-Ala/D-Ala-D-Lac and *trans*-peptidation *via* targeting a
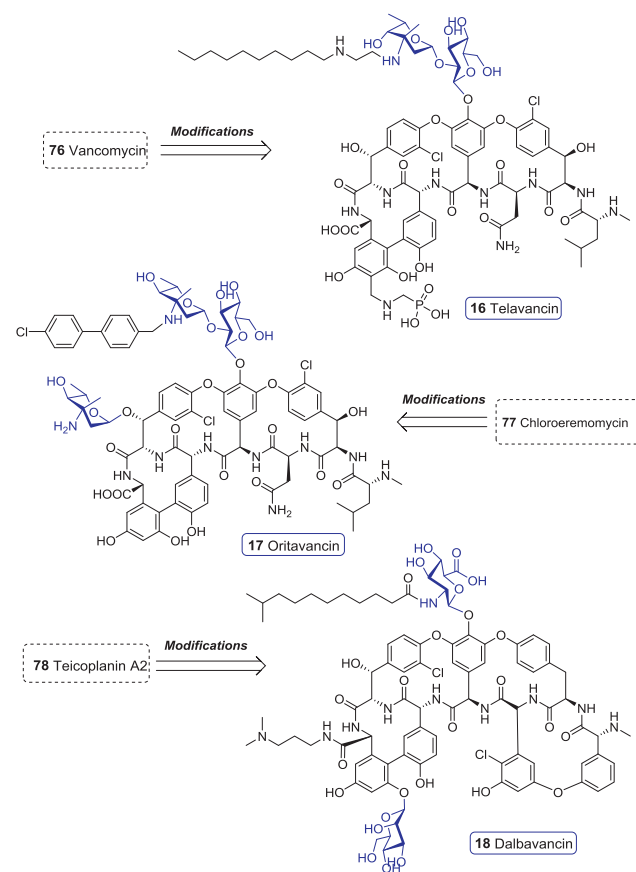
Figure 9 The lipopeptide glycoside antibiotics developed during 2000−2021.

pentaglycine bridge. On the other hand, it also develops cell membrane anchoring and self-association into dimers, which results in perturbation of cell membrane integrity and ultrastructural changes in Gram-positive bacteria. Moreover, some researches indicated that oritavancin (**17**) might also inhibit the RNA synthesis of bacteria[175]. The antibacterial activity investigation showed that oritavancin (**17**) exhibited potent activity against MRSA, MSSA, MRSE, MSSE, VISA, VRSA, VanA-type, and VanB-type VRE with the MIC$_{90}$ of 0.25, 0.12, 0.5, 0.5, 1.0, 0.5 (modal MIC), 0.25, and 0.03 μg/mL, respectively[168]. A randomized, double-blind clinical trial conducted for adults with acute bacterial skin and skin-structure infections (ABSSSI), revealed that the efficacy of oritavancin (**17**) was noninferior to vancomycin (**76**). The primary end point data of oritavancin (**17**) and vancomycin (**76**) were 82.3% and 78.9%, respectively[176]. These results impelled the approval of oritavancin (**17**) for ABSSSI by FDA in 2014.

Dalbavancin (**18**) is a semisynthetic lipoglycopeptide developed by Durata from the teicoplanin-like antibiotic A-40926, which was found from the actinomycete *Nonomuria* spp[177]. Dalbavancin (**18**) differs from teicoplanin A2 (**77**) in that it lacks the *N*-acetylglucosamine (GlcNAc) residue and a chlorine atom, but has an extra terminal methylamino group (Fig. 9). The lipophilic side chain of dalbavancin (**18**) enhances the binding affinity to the D-Ala-D-Ala site through dimer formation and membrane anchoring, leading to the destabilization of cell membranes[168]. Dalbavancin (**18**) exhibits potent antibacterial activity against MRSA, MSSA, MRSE, MSSE, VISA-type, and VanB-type VRE with the MIC$_{90}$ of 0.06, 0.06, 0.06, 0.06, 2.0, and 0.03 μg/mL, but poor inhibition activity against VRSA and VanA VRE. According to three phase III studies carried out for comparing the efficacy of dalbavancin (**18**) to linezolid, cefazolin, and vancomycin (**76**) in cSSSI treatment, dalbavancin (**18**) displayed an activity noninferior to the other three antibiotics[168]. Intention-to-treat (ITT) analysis revealed that dalbavancin (**18**) achieved a higher response rate than vancomycin (86% *vs.* 65.3%). A pooled analysis of DISCOVER 1 and DISCOVER 2 trials suggested that onceweekly intravenous dalbavancin (**18**) was not inferior to twicedaily intravenous vancomycin (**76**) followed by oral linezolid

for ABSSSI treatment[178]. Accordingly, dalbavancin (**18**) was approved for treating ABSSSI by FDA in 2014.

4.2. Aminoglycoside antibiotics antiparasitic drugs

Aminoglycosides (AGs) are a class of broad-spectrum antibacterial antibiotics used mainly for the treatment of Gram-negative bacteria infections. AGs binds to the decoding A-site in helix 44 of 16S RNA, and converts bacterial ribosome 30S subunit into a special conformation that can bind to unpaired tRNA which resulting in protein mistranslation[179]. The clinical use of AGs has been limited by two considerations. In one aspect, the side effects of AGs, including neuromuscular block, ototoxicity, and nephrotoxicity are intolerable; in another aspect, the aminoglycoside-modifying enzymes (AMEs) induced resistance to extended-spectrum β-lactamase (ESBL)-producing enterobacteriaceae and carbapenemresistant enterobacteriaceae (CRE). Thus, AGs are mainly used in treating severe Gram-negative bacteria infection during genetic disorders, Ménière's disease, and HIV treatments[180–182].

Plazomicin (**19**), a novel semisynthetic aminoglycoside derived from sisomicin (**79**), was approved recently (Fig. 10A)[183]. Compared with the traditional AGs, plazomicin (**19**) contains three key structural modifications, including 1-N amide substitution with 4-amino-2-hydroxybutanoic acid, dehydroxylation at the 3′- and 4′-positions, and 6′-N modificaiton of the hydroxyethyl group (Fig. 10A). These chemical modifications successfully provent the antibiotic from inactivation by such AMEs as *O*-nucleotidyltransferase ANT (reaction at 4′), *O*-phosphotransferase APH (reaction at 3′), and *N*-acetyltransferase AAC[184]. Therefore, plazomicin (**19**) possesses higher activity against CRE, ESBL-producing enterobacteriaceae, and AMEs mediated resistant bacteria compared to the traditional AGs[184].

A multicenter, randomized, double-blind, phase II study in adults with complicated urinary tract infection (cUTI) indicated that in the groups receiving plazomicin (**19**) at 10 or 15 mg/kg, and levofloxacin at 750 mg, the microbiological eradication rates were 50.0%, 60.8%, and 58.6%, respectively, in modified ITT populations, and 85.7%, 88.6% and 81.0%, respectively, in the microbiologically evaluable population. In the modified ITT
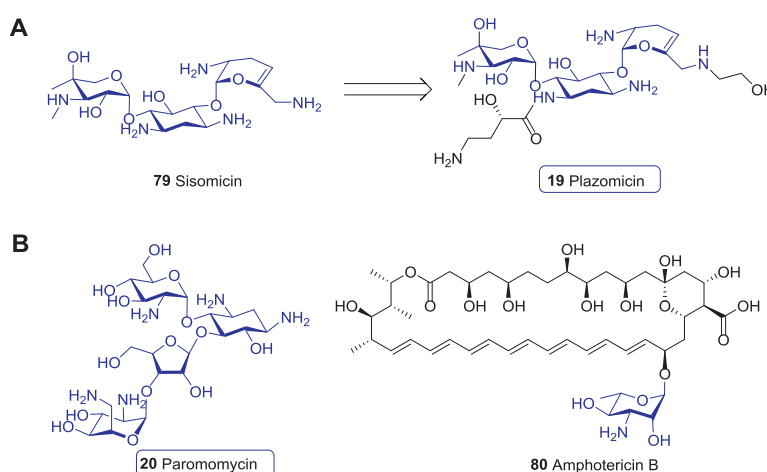
Figure 10 Aminoglycoside antibiotics antiparasitic drugs. (A) Antibacterial aminoglycoside plazomicin (**19**) derived from sisomicin (**79**). (B) The antileishmanicidal drug paromomycin (**20**) and amphotericin B (**80**).

population, the clinically cured rates were 66.7%, 70.6%, and 65.5% in three groups, respectively[185]. Another phase III study in cUTI, which compared the efficacy and safety of plazomicin (**19**) to meropenem, suggested that plazomicin (**19**) was noninferior to meropenem with respect to the primary efficacy end points[186]. Given these advantages, FDA legalized the application of plazomicin (**19**) for the treatment of cUTI in 2018.

Paromomycin (**20**) is an old AG drug derived from the filtrates of *Streptomyces krestomuceticus* in the 1950s, and has a wide antibacterial spectra against most Gram-negative and many Gram-positive bacteria (Fig. 10B)[187]. Moreover, paromomycin (**20**) acts as an effective oral drug for treating the infections caused by intestinal protozoa, such as *Entamoeba histolytica, Giardia lamblia*, and *Dientamoeba fragilis*, leading to its FDA approval for amoebiasis treatment[188]. Paromomycin (**20**) is also found effective in the treatment of leishmaniasis, a fatal infectious disease that threatens 350 million people in 98 countries worldwide. Obligate intracellular protozoa of the genus Leishmania causes a range of diseases, broadly manifested as cutaneous (CL), mucosal (MCL), and visceral leishmaniasis (VL)[189]. The antileishmanicidal activity of paromomycin (**20**) may be through inhibition of parasite metabolism and mitochondrial respiration[190]. A phase III clinical trial conducted in India indicated that paromomycin (**20**) showed a reasonable safety profile and efficacy for Leishmania treatment, which was noninferior to amphotericin B (**80**, Fig. 10B). The final cure rates of paromomycin (**20**) and amphotericin B (**80**) were 94.6% and 98.8%, respectively[191]. Consequently, paromomycin (**20**) was legitimated in India in 2006.

5. Carbohydrate-based anticancer drugs

Cancer cells aberrantly express various glycans, which regulate different aspects of cancer progression, including proliferation, invasion, angiogenesis, and metastasis[192−198]. Based on the carbohydrates-related cancer hallmarks, various treatments for cancer have been developed over the past 20 years, including diagnosis, chemotherapy, radiotherapy, targeted therapy, and immunotherapy[199−203].

Abnormally expressed glycans and glycoproteins are special markers of various cancers and provide valuable information for cancer diagnosis and prognosis[195]. Indeed, serum glycoproteins, including carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), CA19-9, and prostate-specific antigen (PSA), have been widely employed for early warning of colorectal, ovarian, pancreatic, and prostate cancers, respectively[204−206]. Cancer cells consume large amounts of glucose through aerobic glycolysis to support the biosynthetic requirements of uncontrolled proliferation, known as the Warburg effect[198]. Based on this phenomenon, positron emission tomography (PET) with *in vivo* 2-^{18}F-2-deoxyglucose distribution monitor has become an important indicator of cancer diagnosis[207].

Since 2000, there have eight carbohydrate-based anticancer drugs been approved for clinical cancer treatments, including five antineoplastic nucleosides or nucleotides azacitidine (**21**), decitabine (**22**), clofarabine (**23**), nelarabine (**24**), and forodesine (**25**), two carbohydrate conjugated chemotherapy drugs amrubicin (**26**) and midostaurin (**27**), and an immunomodulator drug mifamurtide (**28**).

5.1. Antineoplastic nucleosides and nucleotides

Although targeted therapy and immunotherapy have made breakthroughs, nucleosides and nucleotides mediated chemotherapy remains as the first-line therapy for various cancers[199]. Most antineoplastic nucleosides and nucleotides are pro-drugs that are transformed to active forms during metabolism[199]. The concentrative nucleoside transporters (CNT) and/or equilibrative nucleoside transporters (ENT) primarily mediate the diffusion of these pro-drugs into cells[202,208]. These pseudo nucleosides act as the substrates of DNA/RNA polymerases during DNA replication or RNA transcription[202,208]. These events result in stalled replication forks and chain termination, and trigger DNA damage response to arrest cell cycle progress and induce apoptosis[199]. Since DNA replication occurs more frequently in cancer cells than in normal cells, nucleoside and nucleotide therapies are selective for cancer cells[202,208].

Azacitidine (**21**), developed by Pharmion, is a 5-N analogue of cytidine (**81**, Fig. 11), which can be converted to the 5'-O-triphosphate active form in cancer cells[209]. The antitumor activity of azacitidine (**21**) is mediated by multiple mechanisms, including inducing the cytotoxic effects by incorporating into DNA (10%−20%) and RNA (80%−90%), inhibiting proteins synthesis, and inducing apoptosis[210]. Decitabine (**22**), developed by MGI Pharma, is a 5-N analogue of 2'-deoxycytidine (**59**, Fig. 11). It can be converted to the 5'-O-triphosphate decitabine (**82**) active form and incorporated into DNA[210].

In addition to the cytotoxic activities, azocytidine (**21**) and decitabine (**22**) also affect epigenetic gene regulation in various cancer cells[210]. Specifically, the incorporation of these nucleosides into DNA leads to the inactivation of DNA methyl transferases (DNMTs) and subsequent hypomethylation of DNA, most likely restoring the expression of some tumor suppressor genes that are frequently silenced by aberrant DNA methylation in malignant tumors[199]. Active DNA replication and aberrant methylation could be frequently observed in myelodysplastic syndrome (MDS), a hematopoetic cell disease that could elicit cytopenias and acute myeloid leukemia (AML) progression[211]. Hence, azacitidine (**21**) and decitabine (**22**) are potential therapeutic agents for MDS. In a multicenter, randomized, open-label, phase III clinical trial, MDS patients (*n* = 191) were randomized to azacitidine (**21**) or supportive therapy group. The trial indicated that the response rates in azacitidine (**21**) and supportive therapy arms were 23% (7% complete response or CR, and 16% partial response or PR) and 0%, and the median time to leukemic transformation and death
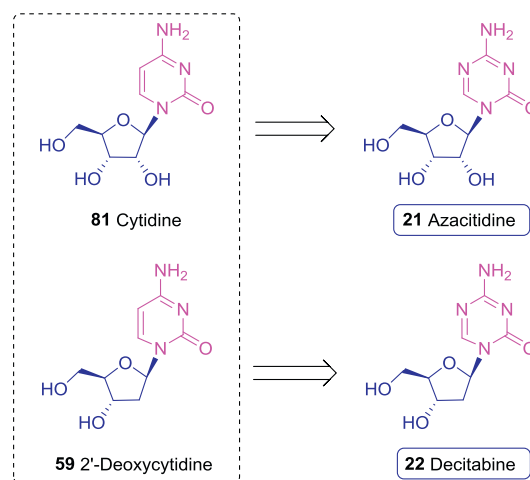
Figure 11 The anticancer nucleosides azacitidine (**21**) and decitabine (**22**) derived from cytidines (**81**) and 2'-deoxycytidine (**59**).

was 21 and 13 months, respectively[211,212]. Another phase III study carried out by International Working Group MDS criteria compared decitabine (**22**) group and supportive therapy group, showed that the response rate in supportive therapy group was significantly lower than that in the former group (0% *vs.* 17%), and the AML transfer rate in supportive therapy group was 1.68 folds higher than in the decitabine (**22**) group[213–215]. Accordingly, FDA approved azacitidine (**21**) and decitabine (**22**) for the treatment of MDS in 2004 and 2006, respectively. Recently, the clinical trials of azacitidine (**21**) and decitabine (**22**) for the treatment of more hematological malignancies as well as solid tumors, such as AML, lung cancer, colorectal cancer, and ovarian cancer, are under evaluations[216–221].

Fludarabine (**83**) and cladribine (**87**) are adenosine derived anticancer drugs developed in the 1980s; however, their clinical applications are hampered by *in vivo* cleavage of the glycosidic bonds[222]. Thus, 2-fluoroadenine (**84**) is produced by the cleavage of fludarabine (**83**). 2-Fluoroadenine (**84**) can be further transformed to 2-fluoroadenosine (**85**) triphosphate, which is highly toxic (Fig. 12A)[222]. Thus, structural modifications to enhance the stability of these nucleosides and decrease the toxicity are required.

Clofarabine (**23**), developed by Genzyme, is a 2′-deoxyadenosine (**86**) analogue with a C2′-fluorine substitution of cladribine (**87**), which significantly improves the stability of the glycosidic bond in acidic conditions (Fig. 12B)[222,223]. Clofarabine (**23**) is converted to the corresponding triphosphate active form, which was then incorporated into DNA by DNA polymerase[224]. The damaged DNA results in the release of cytochrome *c* from the mitochondria and induces cell apoptosis[225]. As expected, clofarabine (**23**) displays potent antitumor activity against various leukaemia and solid tumor cell lines with the IC$_{50}$ values ranging from 28 to 290 nmol/L[226].

Clofarabine (**23**) was further investigated in a series of clinical trials for hematological malignancies[227–229]. The clinical trial data from pediatric patients with acute lymphoblastic leukaemia (ALL) showed that 12% (6/49) patients achieved CR, 8% (4/49)

achieved CR but without platelet recovery, and 10% (5/49) achieved PR. Combined with these data, clofarabine (**23**) was approved by FDA in 2004 for ALL treatment[228,230].

Nelarabine (**24**), developed by GSK, is an purine arabinoside bearing a 2-amino-6-methoxy substitution in the adenine moiety (Fig. 12C)[231]. It acts as a prodrug, which can be demethoxylated to arabinosylguanine (ara-G, **88**) in serum and cells[231]. Once in plasma, ara-G (**88**) acts as a guanine nucleoside (**89**) analogue and is phosphorylated by cellular kinases to form ara-G 5′-triphosphate[199,232]. The active ara-G 5′-triphosphate can be incorporated into DNA to result in cell death[233,234]. The cytotoxicity of nelarabine (**24**) towards human bone marrow progenitor cell lines is around micromolar concentrations *in vitro*[235]. Nelarabine (**24**) were evaluated for hematologic malignancy, especially T-cell relating diseases[236–238]. According to several phase II/III clinical trials on T-cell acute lymphoblastic leukemia (T-ALL)/lymphoblastic lymphoma (T-LBL), the CR rate and objective response rate (ORR) of nelarabine (**24**) were 26%−47% and 33%−60%, respectively[239–242]. Base on these data, nelarabine (**24**) was approved by FDA in 2005 for the treatment of patients with recurrent or refractory T-cell lymphoblastic leukemia or lymphoma[235].

Forodesine (**25**), developed by Mundi Pharma, is a *C*-glycoside analogue of purine nucleoside[242,243]. Being different from most antineoplastic nucleosides and nucleotides, forodesine (**25**) could not be phosphorylated as forodesine phosphate (**90**) and incorporated into DNA or RNA (Fig. 12D). Instead, forodesine (**25**) can increase plasma 2′-deoxyguanosine (dGuo, **91**) *via* suppressing purine nucleoside phosphorylase (PNP) (Fig. 12D), whose deficiency facilitates a relatively selective depletion of T cells in humans[242,243]. The increased dGuo (**91**) is further converted to dGTP and leads to increased intercellular dGTP levels, resulting in the cell apoptosis[243]. *In vitro* assay indicated that under the treatment of forodesine (**25**), T-ALL cell lines were more sensitive to dGuo (**91**) than B-cell precursor-ALL (B-ALL) cell lines with the IC$_{50}$ being 1.6 and 8.8 μmol/L, respectively[244]. A series of clinical studies
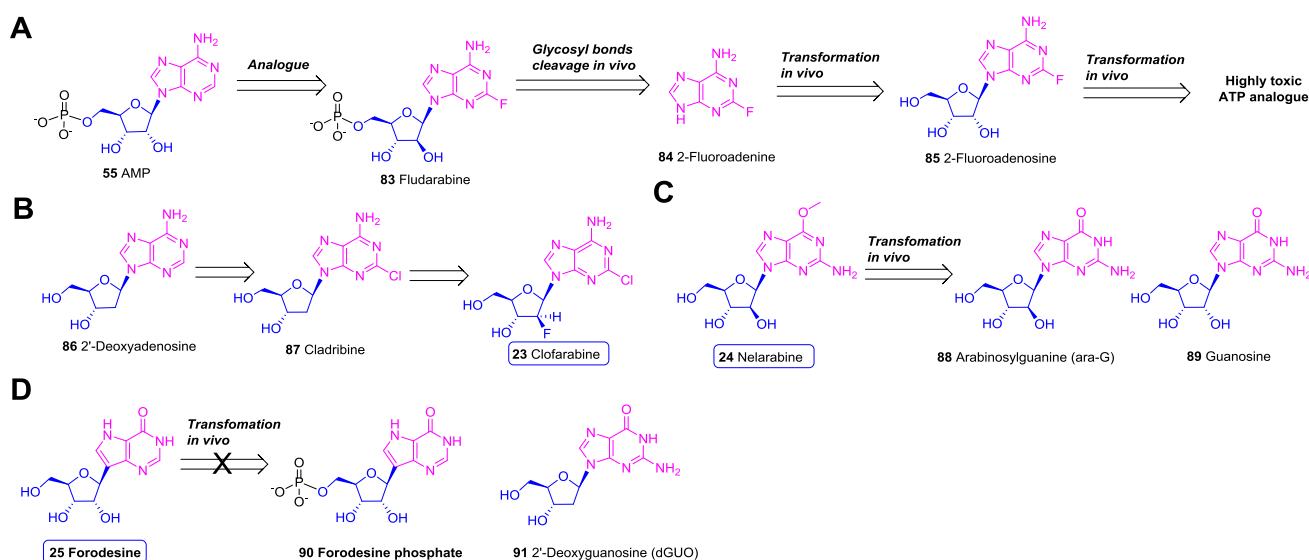
Figure 12 Carbohydrate-based antineoplastic nucleosides and nucleotides. (A) The metabolism and resultant toxicity of fludarabine (**83**). (B) The anticancer nucleoside clofarabine (**23**) derived from 2′-deoxyadenosine (**86**). (C) The *in vivo* metabolism of nelarabine (**24**). (D) The anticancer nucleoside forodesine (**25**) which increase the plasma 2′-deoxyguanosine (**91**).

were carried out to evaluate the efficacy of forodesine (25) in B-ALL and T-ALL, in which the CR rate was 16.7% (2/12) and 20.6% (7/34), respectively[245,246]. Afterwards, 37 patients with refractory cutaneous T-cell lymphoma (CTCL) were evaluated in a phase II study of oral forodesine (25), in which the ORR was 54% (7% CR, 46% PR)[247]. Therefore, forodesine (25) was approved for recurrent or refractory peripheral T-cell lymphoma treatment in 2017 in Japan.
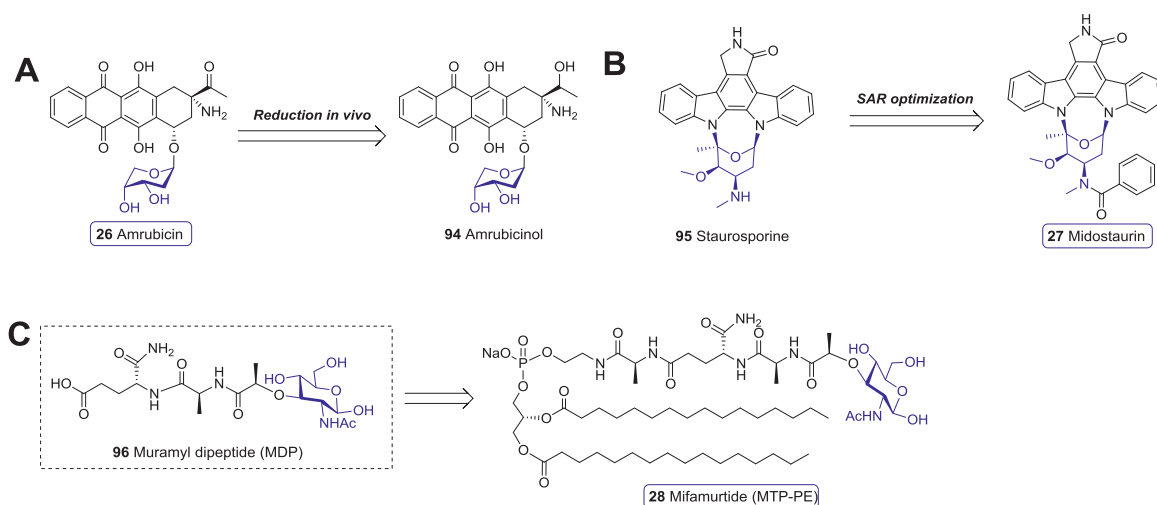
5.2. Chemotherapy drugs

Anthracyclines, containing planar aromatic quinone rings decorated with a rare sugar moiety, constitute an important class of chemotherapy drugs[248]. Daunorubicin (92), epirubicin, and doxorubicin (93) are among the most prescribed drugs for the treatment of hematological malignancies and solid tumors (Supporting Information Fig. S3)[248,249].

Amrubicin (26), developed by Sumitomo Pharma, is a third-generation synthetic anthracycline bearing 9-α-amino and 2-deoxypentose moieties (Fig. 13A)[250]. It can be converted to the more active metabolite amrubicinol (94), which inhibits the proliferation of various cancer cell lines, with IC_{50} values against lung cancer cells range from 0.16 to 0.64 μmol/L[251−253]. Both amrubicin (26) and amrubicinol (94) showed decreased DNA intercalation activity compared to the previous anthracyclines. Inhibition of topoisomerase II turns out to be their primary mechanism of action[252]. An important merit of amrubicin (26) is its low cardiotoxicity compared to doxorubicin (93)[254]. The safety and efficacy of amrubicin (26) as a chemotherapy agent have been studied extensively in clinical trials. A phase II study indicated that the response rates to amrubicin (26) in chemotherapy-naive patients with stage III or IV non-small cell lung cancer (NSCLC) and extensive-stage small cell lung cancer (SCLC) were 25% and 79%, respectively[255,256]. Accordingly, amrubicin (26) was approved in 2002 in Japan[257].

Staurosporine (95), a indolocarbazole glycoside isolated from Streptomyces staurosporus, is a pan-inhibitor of a series of serine/threonine protein kinases. However, the high toxicity of staurosporine (95) hinders its potential clinical application[258]. Thus, various modifications were explored to reduce the toxicity of staurosporine (95). Midostaurin (27), developed by Novartis, is a N-benzoate of staurosporine (95) (Fig. 13B)[259−262]. It can inhibit a variety of kinases, including protein kinase C (PKC), protein kinase B (Akt), protein kinase A (PKA), and FMS-like tyrosine kinase 3 (FLT3) at nanomolar concentrations[260]. Midostaurin (27) selectively induced G1 arrest and apoptosis of AML cell lines with oncogenic FLT3 mutation (IC_{50} < 10 nmol/L) in vitro[264]. The multi-target ability of midostaurin (27) results in strong anti-proliferative activity against a variety of cancer cells[258,260,263].

According to a phase II study, midostroin (27) achieved >50% (BR) reduction in peripheral blood or bone marrow blast-cells in more than half of the patients with mutated FLT3 AML and 42% of the patients with wild-type FLT3 AML, while no patients achieved CR[265,266]. Afterwards, a multi-institutional, multinational, randomized, double-blind, placebo-controlled phase III trial was carried out across 17 countries to evaluate the combinatory effects of midostaurin (27) with standard chemotherapy in AML patients with FLT3 mutant. In this trial, the addition of mitotolin (27) to standard chemotherapy in AML patients with FLT3-mutant showed significant clinical efficacy[267]. Thus, midostaurin (27) was approved by FDA for the treatment of FLT3-mutant AML in 2017. It is worth noting that midostaurin (27) is the first clinical agent approved for AML since 2000, as well as the first multi-kinase inhibitor for the FLT3-mutant subtype disease[263]. Another important progress for midostaurin (27) is its application for advanced systemic mastocytosis (SM). SM is a rare amyeloid neoplasm that results from the accumulation of abnormal mast cells in the bone marrow, liver, spleen, and skin[268]. 90% of the SM patients harbor a gain-of-function mutation (D816V) of KIT[268]. An open-label study of midostaurin (27) in 116 patients with SM demonstrated that the overall response rate of midostaurin (27) was 60%; the median overall survival (mOS) of midostaurin (27) reached 28.7 months, and the median progression-free survival (mPFS) was 14.1 months[269]. These data

Figure 13 Other carbohydrate-based chemotherapy drugs. (A) The representative anthracycline anticancer drugs (92 and 93) and a active metabolit (94) of amrubicin (26). (B) The anticancer drug midostaurin (27) derived from staurosporine (95). (C) The immunomodulator anticancer drug mifamurtide (28) derived from MDP (96).

confirmed the efficacy of midostaurin (**27**) in SM treatment. Therefore, FDA also approved midostaurin (**27**) for treatment of SM in 2017.

5.3. Immunomodulator anticancer drug

Mifamurtide (MTP-PE, **28**), developed by Ciba-Geigy AG, is a synthetic immunomodulator for cancer therapy[270]. It is derived from the covalent addition of alanine and dipalmitoyl phosphatidylethanolamine to muramyl dipeptide (MDP, **96**), a common immune-stimulatory glycopeptide in the bacterial cell walls (Fig. 13C)[270−272]. These modifications make MTP-PE (**28**) possess the superior ability to activate human monocytes and macrophages, as well as a longer half-life in the plasma and lower toxicity[273]. Immunoassays indicated that MTP-PE (**28**) displayed enhanced stimulating activity for murine macrophages and human monocytes by 100-folds compared with MDP (**96**)[274]. Activation of these immune cells increased anti-tumor activities accordingly[275]. A phase III clinical trial in the patients with metastatic osteosarcoma showed that the addition of MTP-PE (**28**) to chemotherapy trended to improve 5-year event-free survival (EFS) and OS (42% *vs.* 26%, $P = 0.23$; 53% *vs.* 40%, $P = 0.27$)[276]. Therefore, MTP-PE (**28**) was approved for the treatment of non-metastatic osteosarcoma in European Union in 2009.

6. Carbohydrate-based antidiabetics

The incidence of diabetes mellitus (DM) is increasing rapidly. More than 90% of these cases are T2DM, and the remaining types include type 1 diabetes (T1DM) and hybrid forms of diabetes[277,278]. Effective control of blood glucose is the basis of treatment for all patients with diabetes. While T1DM patients need the lifelong insulin replacement therapy, for some T2DM patients, especially whose β-cells remain certain insulin secreting function, oral hypoglycemic agents (OADs) can be used. Since the blood glucose is a major driving factor of diabetes, glucose-based molecules have been extensively studied for the diabetes treatment. Two types of glucose-based OADs, namely the α-glucosidase inhibitors and SGLT2 inhibitors, have been on the market leading to significantly improved glycemic control in the majority of T2DM patients[279−282]. The approved α-glucosidase inhibitors, including acarbose, voglibose, and miglitol, are a class of sugar mimics. They reversibly suppress the activity of α-glucosidase, block exogenous sugar uptakes from food digestion in small intestine, and are particularly suitable for the control of postprandial plasma glucose (PPG).

Based on the novel hypoglycemic concept, the SGLT2 inhibitors were discovered to have good hypoglycemic activity by enhancing urinary glucose excretion (UGE) and thereby decreasing the renal glucose reabsorption[280]. Since 2013, nine new SGLT1/2 inhibitors, including dapagliflozin (**29**), canagliflozin (**30**), empagliflozin (**31**), ipragliflozin (**32**), luseogliflozin (**33**), Tofogliflozin (**34**), ertugliflozin (**35**), sotagliflozin (**36**), and remogliflozin etabonate (**37**) have been approved worldwide.

6.1. α-Glucosidase and α-amylase inhibitors

Acarbose (**97**), a α-amylase inhibitor developed by Bayer in 1980s, is a pseudo-tetrasaccharide from the metabolites of *Actinomycetes*. Clinical data showed that acarbose (**97**) effectively reduced the fasting plasma glucose (FPG), PPG, postload insulin and glycosylated hemoglobin[283−285]. Voglibose (**99**), a potent α-glucosidase inhibitor developed by Taketa Pharma in 1990s, is a *N*-glycerol derivative of valiolamine (**98**, Supporting Information Fig. S4)[286]. Clinical trials indicated that voglibose (**99**) significantly reduced PPG, triglyceride, and increased the high-density lipoprotein cholesterol (HDL-C)[286].

Nojirimycin (**100**) and 1-deoxynojirimycin (DNJ, **102**), two natural iminosugars with the nitrogen atom substitution of the sugar ring oxygen, are inhibitors of α/β-glucosidase[287]. A series of N-substituted derivatives were developed as the second-generation α-glucosidase inhibitors[288]. Among them, miglitol (**101**) and emiglitate (**103**) were proved to be effective in controlling post-sucrose glycaemia (Fig. S5); while miglitol (**101**) was approved in Germany for the treatment of T2DM in 1998[289−293]. Up to now, acarbose (**97**), voglibose (**99**), and miglitol (**101**) have been widely used in the treatment of T2DM. However, no new α-glucosidase inhibitors have been launched ever since.

6.2. SGLT1/2 inhibitors

In the intestine and kidney, glucose is transported into the epithelial cells by sodium-glucose cotransporters (SGLTs) and glucose transporters (GLUTs)[294]. There are six members of the SGLT family (SGLT1−6), among which SGLT1 and SGLT2 have attracted the most attention[295]. SGLT1 is a low-capacity, high-affinity transporter, which primarily exists in the small intestine, responsible for the intestinal glucose and galactose absorption[295]. SGLT2 is a high-capacity, low-affinity transporter, which mainly expresses in the segment1 (S1) of the proximal convoluted tubule (PCT) in kidney, accounting for about 90% of the glucose reabsorption in kidney (Fig. 14A)[296,297]. The remaining reabsorption in kidney is *via* SGLT1 in the segment2 (S2) of PCT and segment3 (S3) of proximal straight tubule (PST)[296,297]. Significantly elevated SGLT2 and GLUT2 levels in PCT cells are found in T2DM patients, implying the increased capacity of renal glucose reuptake in T2DM patients[298].

Phlorizin (**104**, Fig. 14B), a naturally occurring glucoside of dihydrochalcone, was found to be able to increase urinary glucose of rats in the 1980s. Subsequent studies showed that the non-selective inhibition of SGLT1 and SGLT2 by phlorizin (**104**) was responsible for the glycosuria effect[299], indicating a new approach to lower the glucose level. However, phlorizin (**104**) has a low bioavailability and is rapidly degraded by β-glucosidase *in vivo*. Modifications of phlorizin (**104**) are thus conducted to enhance the SGLT2 selectivity and to improve the stability and safety profile[297]. In order to improve the metabolic stability of the phenol *O*-glucoside, shielding of the 6-OH of the glucose moiety with an etabonic acid is a promising strategy. Thus T-1095 (**105**) turned out to be the first reported orally effective phlorizin analogue (Fig. 14B), whose active form T-1095A (**106**) can effectively reduce blood sugar and HbA1c, and improve hyperinsulinemia, hypertriglyceridemia, and microalbuminuria[300]. However, it demonstrated weak selectivity against SGLT1 and SGLT2, with the IC$_{50}$ values being 0.20 and 0.05 μmol/L, respectively.[300]

Dapagliflozin (**29**), developed by AstraZeneca and BMS, is the first approved SGLT2 inhibitor[301]. SAR studies showed that the *meta*-substituted diarylmethanes had a stronger SGLT2 inhibitory activity than the other *C*-glucoside derivatives, leading to the final discovery of dapagliflozin (**29**, Fig. 15A)[301]. *In vitro* studies revealed that dapagliflozin (**29**) was highly selective for human SGLT2, with EC$_{50}$ values for SGLT2 and SGLT1 being 1.12 and 1391 nmol/L, respectively (∼1200 fold)[302]. Meanwhile, dapagliflozin (**29**) displayed an extremely
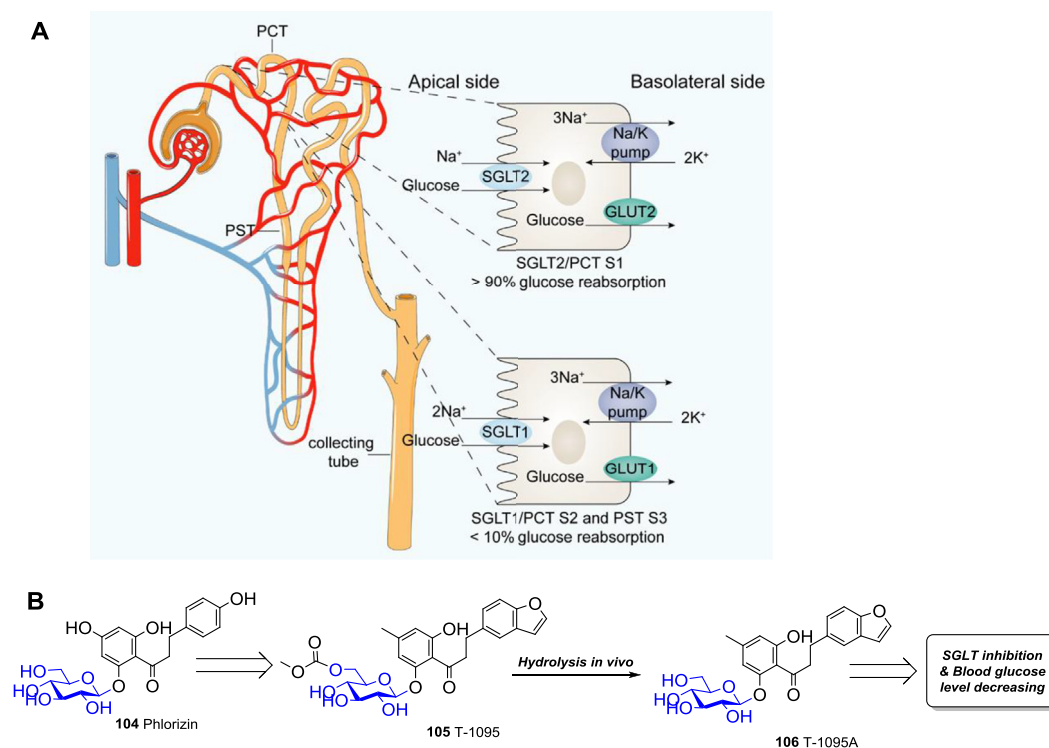
Figure 14 The action mechanism of SGLT1/2 inhibitors. (A) The glucose reabsorption mechanism of SGLT1/2 in renal tubule. (B) The SGLT2 inhibitory natural glycoside phlorizin (**104**), an active derivative T-1095 (**105**), and its metabolite T-1095A (**106**).
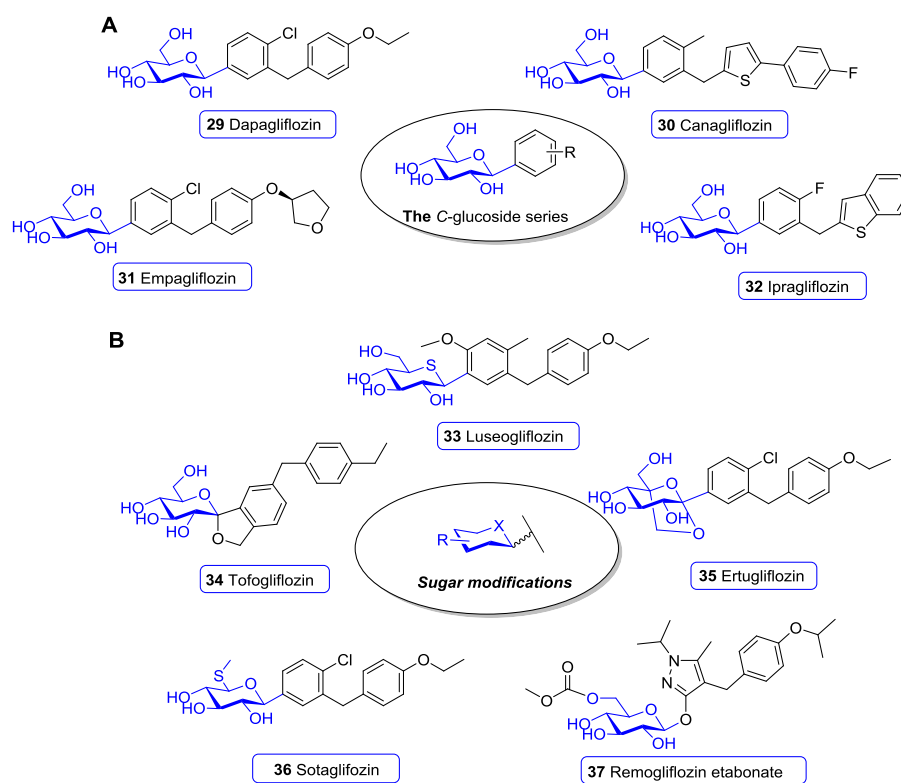
Figure 15 Chemical structure of SGLT1/2 inhibitors. (A) *C*-Glucoside SGLT2 inhibitors (**29**−**32**) launched during 2000−2021. (B) SGLT1/2 inhibitors bearing modified glucose units (**33**−**37**) launched during 2000−2021.

weak activity against GLUTs, showing 8%−9% inhibition in protein-free buffer at 20 µmol/L[302]. In a rat model, oral administration of dapagliflozin (**29**) effectively lowered FPG and improved the animals' metabolic status[302]. A 24-week phase III trial with T2DM patients indicated that the mean HbA1c reduction in the placebo group and 10 mg dapagliflozin (**29**) group was 0.23% *vs.* 0.89% ($P < 0.0001$), mean FPG reduction was 4.1 mg/dL *vs.* 28.8 mg/dL ($P < 0.0001$), and mean body weight reduction was 2.2 kg *vs.* 3.2 kg, respectively[303]. The portion of patients who achieved glycemic control (HbA1c < 7%) at 24 weeks was 51% in the dapagliflozin (**29**) arm and 32% in the placebo arm[303]. Moreover, the addition of dapagliflozin (**29**) to nmol/letformin, pioglitazone, or insulin effectively improved disease control in patients with T2DM who had inadequate glycemic control with monotherapy[304−306]. Based on these data, dapagliflozin (**29**) was approved for T2DM therapy by EMA in 2012.

Canagliflozin (**30**), developed by Mitsubishi Tanabe and marketed by Johnson & Johnson, is a *C*-glucoside derivative with a thiophene ring linked to a flourophenyl ring (Fig. 15A)[307]. The SAR studies revealed that the thiophene derivative markedly improved inhibitory potency against SGLT2[307]. Canagliflozin (**30**) showed good selectivity for SGLT2 and SGLT1 with IC$_{50}$ of 2.2 and 910 nmol/L (410 times), respectively, and >10 µmol/L for GLUT1[307,308]. The phase I clinical trial indicated that this molecule effectively increased UEG and was well tolerated with no or rare hypoglycemia[309]. A phase III study showed that oral administration of 300 mg canagliflozin (**30**) strongly ameliorated the glycemic control. After 26 weeks of treatment, the least squares mean (LSM) changes of oral administration of 300 mg canagliflozin (**30**) and placebo in HbA1c were −1.03% *vs.* 0.14% ($P < 0.001$), in FPG were −34.2 *vs.* 9.0 mg/dL ($P < 0.001$), and in body weight were −3.4 *vs.* −0.5 kg ($P < 0.001$), respectively[310]. In addition, canagliflozin (**30**) significantly decreased the level of PPG, blood pressure, postprandial insulin, and increased HDL-C[310,311]. Canagliflozin (**30**), combined with other antidiabetic drugs or add-on therapy, showed excellent therapeutic efficacy and enhanced glycemic control for patients who cannot achieve sufficient glycemic control with monotherapy[311−314]. Consequently, canagliflozin (**30**) was approved for T2DM therapy by FDA in 2013[314].

Empagliflozin (**31**), developed by Boehringer Ingelheim and Eli Lilly, is a analogue of dapagliflozin (Fig. 15A)[315]. The replacement of the ethoxy group in the distal phenyl unit in dapagliflozin (**29**) with 3-tetrahydrofuran greatly improves its selectivity against SGLT2. The IC$_{50}$ values against SGLT2 and SGLT1/4/5/6 are 3.0 nmol/L, and 8.3, 11, 1.1 and 2.0 µmol/L, respectively[315]. A multi-center, randomized, placebo-controlled, phase III trial demonstrated that compared with placebo, oral administration of 25 mg empagliflozin (**31**) for 24 weeks caused a significant reduction of HbA1c (0.85%, $P < 0.0001$), FPG (36.2 mg/dL, $P < 0.0001$), and body weight (2.15 kg, $P < 0.0001$)[316]. Empagliflozin (**31**) elicited more portion of patients with HbA1c < 7.0% than that in the placebo arm at 24 weeks (43.6% *vs.* 12.0%, $P < 0.0001$)[316]. Empagliflozin (**31**) was also effective in reducing PPG, blood pressure, and postprandial insulin levels, and improved disease control in patients who cannot benefit from monotherapy[317−322]. As a result, empagliflozin (**31**) was approved by the EMA and FDA in 2014 as the third SGLT2 inhibitor for clinical use.

Ipragliflozin (**32**), developed by Astellas, Kotobuki, and Merck Sharp & Dohme, is a *p*-fluorophenyl *C*-glucoside bearing a distal benzothiophene moiety (Fig. 15A)[323]. The *in vitro* assay indicated that ipragliflozin (**32**) demonstrated 254-fold selectivity for SGLT2 over SGLT1, with the IC$_{50}$ values of 7.4 and 1876 nmol/L, respectively[323,324]. It showed no significant effects on human SGLT4 or SGLT5 isoforms (IC$_{50}$ > 1.0 µmol/L) or GLUT at concentrations up to 3.0 µmol/L[325]. In a phase III study, patients in the ipragliflozin (**32**) arm had a reduction in mean HbA1c of 1.23% compared with placebo ($P < 0.001$), and in mean body-weight of 1.47 kg[326]. 43.5% of the patients achieved HbA1c < 7.4% in the ipragliflozin (**32**) arm, while only 4.5% in the placebo arm[326]. More clinical trials in patients with T2DM, including monotherapy and combination therapy, showed that ipragliflozin (**32**) significantly reduced HbA1c, body weight, FPG, and blood pressure[327]. Based on these studies, ipragliflozin (**32**) received its first approval for the treatment of T2DM in 2014 by the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan.

Luseogliflozin (**33**), developed by Novartis and Taisho, contains a similar phenyl aglycon as dapagliflozin (**29**) but a rare D-1-thioglucitol moiety in place of the glucose unit in dapagliflozin (Fig. 15B)[328]. It exhibited potent SGLT2 inhibition activity (IC$_{50}$ = 2.26 nmol/L), with more than 1700-folds selectivity over SGLT1 (IC$_{50}$ = 3.99 µmol/L) and 50,000-folds selectivity over GLUTs[328−330]. The randomized, double-blind, placebo-controlled, comparative phase III study with T2DM patients suggested that oral administration of 2.5 mg luseogliflozin (**33**) caused a significant decrease of HbA1c, FPG, and body weight compared to placebo, with the values of 0.75% ($P < 0.001$), 27.5 mg/dL ($P < 0.001$) and 1.77 kg ($P < 0.001$), respectively[331]. At the end of the trial, glycemic control with HbA1c < 7.0% was achieved by more patients in the luseogliflozin (**33**) arm than the placebo arm (24.1% *vs.* 3.8%)[331]. Further monotherapy or combination therapy trials further demonstrated that luseogliflozin (**33**) effectively ameliorated the glycemic control, including decreasing HbA1c, FPG, PPG, postprandial insulin and body weight[330,331]. Accordingly, luseogliflozin (**33**) was approved for the treatment of T2DM in 2014 by PMDA in Japan.

Tofogliflozin (**34**, Fig. 15B), developed by Chugai, Kowa, and Sanofi, is a *O*-spiroketal-*C*-aryl glucoside. This structure was identified through a structural database search according to the 3D pharmacophore model derived from reported inhibitors[332]. SAR studies showed that the *para*-substitution of small alkyl groups on the distal phenyl ring was conductive to increase both SGLT2 inhibitory potency and SGLT2 selectivity over SGLT1[332]. As observed, the *para*-ethyl group on the distal phenyl ring enhanced SGLT2 inhibition (IC$_{50}$ = 2.9 nmol/L) with 2900 folds selectivity over SGLT1 (IC$_{50}$ = 8.4 µmol/L)[332]. A multicenter, placebo-controlled, randomized, double-blind parallel-group, phase II/III study indicated that T2DM patients got significant benefits from tofogliflozin (**34**) arm (20 mg oral administration) compared to the placebo arm, with the mean reduction of HbA1c, FPG, 2-h PPG, and body weight being 0.99% ($P < 0.001$), 27.34 mg/dL ($P < 0.001$), 67.67 mg/dL ($P < 0.001$), and 2.50 kg ($P < 0.001$), respectively[333]. Tofogliflozin (**34**) also significantly improved blood pressure, HDL-C and triglyceride, and displayed well combination effects[333,334]. Accordingly, tofogliflozin (**34**) was authorized for T2DM treatment in 2014 by PMDA in Japan.

Ertugliflozin (**35**, Fig. 15B), developed by Merck Sharp & Dohme and Pfizer, is a *C*-aryl glucoside containing a dioxa-bicyclo[3.2.1]octane carbohydrate unit[335]. SAR studies revealed that the 4-Cl substitution on the central phenyl ring and the *para*-ethoxy group on the distal phenyl ring achieved a well-balanced profile for selective SGLT2 inhibition[335]. Ertugliflozin (**35**)

showed an impressive SGLT2 inhibitory potency (IC_{50} = 0.92 nmol/L) and 2200-folds selectivity against SGLT1 (IC_{50} = 2.05 μmol/L)[335]. A set of phase III randomized double-blind trials indicated that oral administration of ertugliflozin (35) effectively improved glycaemic control and body weight[336,337]. At Week 26, 15 mg ertugliflozin (35) caused a reduction of LSM HbA1c (1.16%, $P < 0.001$), mean FPG (43.92 mg/dL, $P < 0.001$), mean 2-h PPG (67.32 mg/dL, $P < 0.001$), and mean body weight (2.16 kg, $P < 0.001$)[336]. The percentage of patients with HbA1c < 7.0% was 35.8% in the ertugliflozin (35) arm compared to 13.1% in the placebo group ($P < 0.001$)[336]. Moreover, ertugliflozin (35) improved blood pressure and displayed well combination effect with other anti-diabetic therapy, such as metformin[338–342]. These series of trials supported the FDA's approval of ertugliflozin (35) for the adult T2DM treatment in 2017[343].

Sotaglifozin (36, Fig. 15B), which was developed by Lexicon Pharma and Sanofi, is a C-aryl glucoside with a special D-6-thioglucose moiety and the same aglycon with ertugliflozin (35). As reported, sotaglifozin (36) is the first dual inhibitor of SGLT1 and SGLT2 with the IC_{50} values of 36 and 1.8 nmol/L respectively, thus blunting and delaying absorption of glucose from the gastrointestinal tract and reabsorption of glucose by kidney[344,345]. In the tandem clinical trial program, three double-blind placebo-controlled phase III clinical trials which enrolled more than 3000 T1DM patients showed that as an adjunct to optimized insulin therapy, sotaglifozin (36) demonstrated a significant reduction in HbA1c, FPG, weight as well as total daily insulin dose[344,335]. Compared with placebo group, more episodes of DKA and fewer episodes of severe hypoglycemia were observed in sotaglifozin group. Accordingly, sotaglifozin (36) achieved EMA's approval for treating T1DM patients with BMI ≥27 kg/m² in 2019.

Remogliflozin etabonate (37, Fig. 15B), which was discovered by Kissei Pharmaceutical and marketed by Glenmark, is the only approved O-aryl glucoside SGLT2 inhibitor to date[346]. Following the stability improvent logic of T-1095 (105), an etabonic acid ester was introduced into the molecule. The etabonate quickly transformed into its active form remogliflozin in vivo[346]. Compared with T-1095 (105), remogliflozin demonstrated much potent and selective profile with the inhibition constant K_i values for SGLT2 and SGLT1 being 12.5 nmol/L and 4.52 μmol/L, respectively[346]. A double blind, double dummy phase III study conducted in India with T2DM patients indicated that 100 mg or 250 mg oral administration of remogliflozin etabonate (37) (twice daily) caused a significantly reduction of HbA1c by 0.72% and 0.77%, respectively, which was superior to dapagliflozin (29) ($P < 0.001$)[347,348]. Remogliflozin etabonate (37) also effectively decreased FPG and PPG, although noninferior to dapagliflozin (29)[347,348]. And no significant difference between these two drugs was observed when compared the percentage of patients who achieved glycemic control at 24 weeks[347,348]. Supported by these data, remogliflozin etabonate (37) was approved for T2DM therapy in 2019 in India[348].

Insulin deficiency caused by pancreatic β-cell loss accounts for the major pathophysiological defect in T1DM. This determines the pivotal role of insulin for the treatment of T1DM[349]. As mentioned above, SGLT2 inhibitors can lower blood sugar level via an insulin-independent manner and improve β-cell function indirectly[279,280,297,350,351]. Hence, SGLT2 inhibitors were studied as potential adjunctive drugs for T1DM therapy. In a large long-term phase III study of dapagliflozin (29) for T1DM treatment, diabetic ketoacidosis (DKA) events occurred more frequently in

the dapagliflozin (29) arms than that in the placebo arm, although the hypoglycemia events were comparable[352,353]. Similar results were observed from clinical trials for canagliflozin (30) and empagliflozin (31)[354–357]. However, according to a related clinical trial for ipragliflozin (32) add-on therapy to insulin T1DM patients, at 24 weeks, oral administration of 50 mg ipragliflozin (32) acquired marked reductions in HbA1c (0.36%, $P = 0.001$), body weight (2.87 kg, $P < 0.001$), and insulin daily dose (7.35 IU, $P < 0.001$) compared to the placebo arm[338]. Of note, no DKA occurred in this study[358]. To date, only sotaglifozin has been recommended for T1DM, and the risk to benefit profile of other SGLT2 inhibitors deserves further studies[359].

Besides the blood sugar control effects, SGLT2 inhibitors also have organ protective effects, especially the cardiorenal protective effects[280,360–363]. Five large clinical trials have provided extensive clinical evidence of the cardiorenal benefits from SGLT2 inhibitors recently[364–371]. Importantly, the cardiorenal benefits of SGLT2 inhibitors occurred rapidly after therapy initiation and maintained throughout the treatment, while the glycemic control took more time to show measurable effects[360]. Of note, cardiorenal benefits can also be achieved in patients without DM[368]. It was suggested that SGLT2 inhibitors induced aestivation-like hypometabolic patterns in kidney and heart, which economized their function and supported their longevity[361]. This explains, at least in part, the mechanisms behind the clinically observed cardiorenal benefits. Based on these results, SGLT2 inhibitors may find more applications in the future.

7. Carbohydrate-based cardiovascular drugs

Cardiovascular diseases (CVD) represent one of the most frequent causes of death globally, with cases of CVD nearly doubled from 271 million in 1990 to 523 million in 2019[372]. Thrombotic events are considered as the primary pathology underlying a board range of CVD. Physiologically, the process of thrombosis, also known as hemostasis or coagulation, plays an important role in maintaining the integrity of the circulatory system and normal cardiovascular functions[373]. Under pathologic conditions, thrombosis or thromboembolism blocks the natural blood flow, leading to the related organ dysfunction[374], including ischemic stroke, peripheral artery disease, and ischemic heart disease (IHD) consisting of chronic coronary artery disease (CAD) and acute coronary syndrome (ACS)[375–381]. Therefore, antithrombotic therapy, including anticoagulant therapy, antiplatelet therapy, and thrombolytic therapy, is widely applied in these scenarios and regarded as the cornerstone of CVD therapy.

Carbohydrate-based drugs occupy an unshakable position in the field of antithrombotic therapy. The earliest natural anticoagulant heparin (107) was discovered from dog liver in 1916, and belongs to the glycosaminoglycan (GAG) polysaccharide family[382]. With a highly complex and heterogeneous polysaccharide structure, heparin (107) can bind a large variety of proteins and thus exhibit a wide range of biological functions. Importantly, a rare pentasaccharide unit of heparin binds strongly to antithrombin III to mediate the robust anticoagulant effects[384]. In addition, the purinergic receptor P2Y$_{12}$, which is stimulated by ADP (108) but inhibited by ATP (109), plays an important role in platelet hemostasis[387–389]. Therefore, some adenine nucleotide analogs own antiplatelet effects[389]. From 2000 to 2021, there were two anticoagulation drugs tinzaparin sodium (38) and fondaparinux sodium (39), and two antiplatelet drugs, ticagrelor (40) and cangrelor (41), approved for CVD treatments.

7.1. Anticoagulation drugs

Heparin sulfate (**107**) is a negatively charged highly sulphated linear polysaccharide, consisting of 1,4-glycosidic bonds between D-glucosamine (GlcN) and D-glucuronic acid (GlcA) or L-iduronic acid (IdoA) units (Supporting Information Fig. S6)[383−386,390]. In unfractionated heparin (UFH), a unique and uncommon pentasaccharide sequence, namely NS6SGlcNα→GlcAβ→NS3S6SGlcNα→2SIdoAα→NS6SGlcN, included in about one third of the chains, was proved to be the binding site for serine protease inhibitor AT-III[391−393]. This pentasaccharide motif can bind and change the conformation of AT-III, leading to inhibition of the serine proteases involved in the coagulation cascade[385,393]. In fact, UFH has been widely use as an anticoagulant drug in treating cardiopulmonary bypass, extracorporeal membrane oxygenation, hemodialysis, deep venous thrombosis (DVT), pulmonary embolism (PE), and other coagulation abnormalities[384]. However, the heparin materials are prepared from animal tissues, thus bringing a series of safety issues because of various contamination[390].

The second generation heparin product is low-molecular-weight heparin (LMWH), being produced by chemical or enzymatic depolymerization of heparin[384]. Tinzaparin (Logiparin) sodium (**38**) developed by DuPont, is a representative LMWH drug with an average molecular weight of 5500−7500 Da. It is derived from the controlled enzymatic degradation of porcine heparin by the *Flavobacterium heparinum* heparinase (Fig. 16A)[394,395]. Tinzaparin binds to AT-III and induces its inhibitory function against multiple activated coagulation factors, particularly factor Xa, and the release of tissue factor pathway inhibitor (TFPI)[394,395]. Compared with heparin (**107**), Tinzaparin displayed a decreased binding affinity with platelets and plasma proteins[396,397], but significantly prolonged the whole blood activated coagulation time (WBACT)[398−400]. In addition, the activated partial thromboplastin time (APTT) is only limitedly prolonged in the tinzaparinsodium (**38**) treatment, but is more pronounced than in enoxaparin sodium or bemiparin sodium treatments[400−403].

A series of clinical studies showed that tinzaparin sodium (**38**) was as effective and safe as enoxaparin sodium in the prophylaxis of DVT after total hip replacement (21.7% *vs.* 20.1%), and nonfatal PE were observed in both arms[404]. In patients after spinal cord injury, tinzaparin sodium (**38**) displayed a superior prophylaxis effect against thromboembolism to heparin (0% *vs.* 23.8%,

$P = 0.006$)[405]. Further studies indicated that subcutaneous treatment of tinzaparin sodium (**38**) appeared to be as effective and safe as intravenous UFH in patients with acute PE and proximal DVT[406,407]. Therefore, tinzaparin sodium (**38**) was approved by FDA for the application in DVT in 2000.

The third generation heparin drug is the chemically synthesized ultra LMWH (ULMWH)[384]. Fondaparinux (**39**), developed by Sanofi and Organon, was the first launched ULMWH drug consisting of the mentioned active heparin pentasaccharide motif (Fig. 16B)[408]. Fondaparinux sodium (**39**) shows a high binding affinity to AT-III with the K_d value of 41−58 nmol/L[409−411]. This binding results in an irreversible conformational change of AT-III, triggering a robust inhibition of factor Xa and formation of thrombin and fibrin[412]. *In vivo* evaluation indicated that fondaparinux sodium (**39**) had no significant effect on APTT, PT, bleeding time, and plasma AT-III levels[413,414]. In addition, fondaparinux sodium (**39**) does not cause platelet aggregation and activation, but inhibits heparin-induced thrombocytopenia (HIT) antibody-induced platelet activation[412].

One clinical study enrolled 1049 patients after elective major knee surgery showed that fondaparinux sodium achieved a superior prophylaxis effect against thrombotic events to enoxaparin sodium, including less venous thromboembolism (VTE) (12.5% *vs.* 27.8%, $P < 0.001$), DVT (12.5% *vs.* 27.1%, $P < 0.001$), and distal DVT (9.4% *vs.* 21.3%, $P < 0.001$)[415]. Another study involved 1711 patients after hip-fracture surgery revealed that fondaparinux sodium treatment caused a reduction of the incidence in VTE (8.3% *vs.* 19.1%, $P < 0.001$), DVT (7.9% *vs.* 18.8%, $P < 0.001$), proximal DVT (0.9% *vs.* 4.3%, $P < 0.001$), and distal DVT (6.7% *vs.* 15.0%, $P < 0.001$) compared with enoxaparin sodium[416]. Consequently, fondaparinux sodium (**39**) was approved by the FDA in 2001 for the prevention of DVT.

7.2. Antiplatelet drugs

Purinergic G-protein-coupled receptors (GPCR) P2Y$_1$ and P2Y$_{12}$ of platelet play fundamental roles in cardiovascular thrombosis[387−389]. When endothelium is injured, the activated platelets secrete prothrombotic signal molecule ADP (**108**), and initiate the platelet aggregation by activating P2Y$_1$ receptor as well as the downstream processes, including granule release, platelet pro-inflammatory, and procoagulant activition[387−389]. Intriguingly, ATP (**109**) can act as an endogenous blocker against
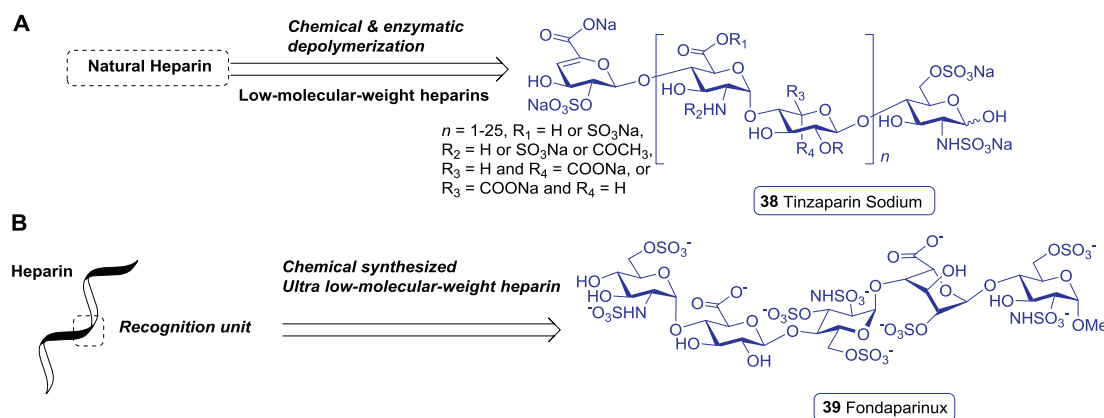
Figure 16 Launched second and third generation heparin products. (A) The low-molecular-weight heparin tinzaparin sodium (**38**) derived from natural heparin. (B) The synthetic heparin pentasaccharide fondaparinux (**39**).

P2Y$_{12}$ receptor[389]. Thus, it could be an effective way to mimic such process in blocking platelet function for IHD as well as stroke prevention[389,417,418]. Following this rationale, a series of reversible and competitive P2Y$_{12}$ receptor antagonists were developed based on the scaffold of adenine nucleotide, among which ticagrelor (**40**) and cangrelor (**41**) have been approved (Fig. 17).

Ticagrelor (**40**), a pseudo adenine nucleotide developed by AstraZeneca, is a selective and reversible P2Y$_{12}$ receptor antagonist[419]. Compared with AMP (**55**), the D-ribose was replaced with a cyclopentane moiety, and the 5′-O-phosphate was replaced by 2-hydroxyethoxy group, both of which improved the lability of the drug. The 5-propylthio side chain and the 7-phenylcyclopropylamino group on the purine base increased its binding affinity to P2Y$_{12}$ receptor[419]. The *in vitro* assay indicated that the IC$_{50}$ of ticagrelor (**40**) to inhibit platelets aggregate was 5 nmol/L[420]. It is worth noting that the metabolite AR-C124910XX in absence of the ethylene glycol moiety remained active[421].

Clinical studies indicated that ticagrelor (**40**) had a more rapid onset action against platelet aggregation than clopidogrel[422]. Other two trials on patients with ACS revealed that ticagrelor (**40**) had a stronger and more stable antiplatelet effect compared with clopidogrel and prasugrel[423,424]. In addition to the antiplatelet effect, ticagrelor (**40**) also increased local endogenous adenosine by suppressing equilibrative nucleoside transporter-1 mediated adenosine uptake, leading to the sensation of dyspnea[425,426]. Data from the PLATO trial demonstrated that dyspnea occurred in the ticagrelor (**40**) group was frequently mild or moderate in intensity[427]. Taken these results together, ticagrelor (**40**) was approved for ACS treatment in Europe in 2010 and subsequently obtained FDA's approval in 2011.

Cangrelor (**41**), developed by Medicines Company, is an ATP analogue with reversible inhibition against P2Y$_{12}$ receptor. Compared with ATP (**109**), the purine base was modified with 2-trifluoropropylthio and N-(2-(methylthio) ethyl) side chains, which enhanced its affinity with P2Y$_{12}$ receptor (Fig. 17). Intriguingly, the β,γ-diphosphate of ATP (**109**) was reconnected by a dichloromethylene linkage, which increases cangrelor's resistance to ectonucleotidases mediated degradation[428]. The *in vitro* assays suggested the IC$_{50}$ of cangrelor (**41**) against platelets aggregate was about 0.4 nmol/L[428]. Due to its rapid hydrolysis by nucleotide pyrophosphatases and metabolically unstable characters, cangrelor (**41**) was developed as an intravenously administered antiplatelet drug. Since its half-life was only 3−6 min, cangrelor (**41**) mediated a rapid offset of action[389]. These characteristics make it particularly useful when a rapid onset and offset antiplatelet effect is required.

A clinical trial was conducted in 11,145 patients receiving either urgent or elective treatments, and the primary efficacy endpoint was set as a composite of death, myocardial infarction (MI), ischemia-driven revascularization or stent thrombosis at 48 h after randomization[429]. These data showed that cangrelor (**41**) arm resulted in a significant reduction in the rate of primary efficacy endpoint compared with clopidogrel arm (4.7% *vs.* 5.9%, OR = 0.78, *P* = 0.005), with no significant increase in severe bleeding events (0.16% *vs.* 0.11%, OR = 1.50, *P* = 0.44)[429]. A frame-by-frame angiographic analysis revealed that cangrelor (**41**) caused a lower incidence of intraprocedural stent thrombosis (IPST) than clopidogrel (0.6% *vs.* 1.0%, OR = 0.65, *P* = 0.04)[430]. Accordingly, cangrelor (**41**) was approved by FDA in 2015 for reducing the risk of periprocedural MI, repeat coronary revascularization, and stent thrombosis in patients undergoing PCI[431].

8. Carbohydrate-based nervous system drugs

In the past two decades, two carbohydrate-based drugs for the nervous system dieases have been approved, sodium oligomannate (**42**) for Alzheimer's disease (AD) and sugammadex (**43**) for reversing neuromuscular block (NMB).

8.1. Sodium oligomannate for Alzheimer's disease (AD)

AD, a severe neurodegenerative disease of the central nervous system, is a leading cause of dementia, affecting more than 40 million people around the world[432,433]. The neuropathology of AD is characterized by an extensive deposition of amyloid-β (Aβ) plaques in the neocortex and a hyper phosphorylated tau protein in neurofibrillary tangles located at limbic and cortical junction areas[434]. However, the pathogenesis of AD is complicated and has not been completely understood, which involves Aβ-tau synergy, oxidative stress, reactive glial, and microglial changes, while bacterial infections in brains as well as gut microbiota regulated central nervous system could also impact the course[435,436]. The present AD drugs could only relieve some clinical symptoms[437,438]. Despite enormous efforts have been made in the past two decades, including the exploration of various Aβ antibodies and tau centric therapy strategies, few success has been obtained in late-stage clinical trials[439−441].

Sodium oligomannate (GV-971, **42**), developed by Green Valley, is derived from marine brown algae β-D-(1,4)-poly-mannuranate (PM, **110**) with 2−10 sugar units (Fig. 18A)[436,443]. Ethological experiments indicated that sodium oligomannate (**42**) had a significant ameliorative effect on the animal models of cognitive impairment[436], with multiple targeting mechanisms. It was reported that sodium oligomannate (**42**) could penetrate the blood−brain barrier (BBB) in its original form *via* GLUT1. It can directly bind to Aβ, inhibit the formation of Aβ fibril, destabilize the existed fibrils into non-toxic monomers, and promote microglia-mediated Aβ phagocytosis[436]. Moreover, sodium oligomannate (**42**) has a specific impact on gut microbiota,
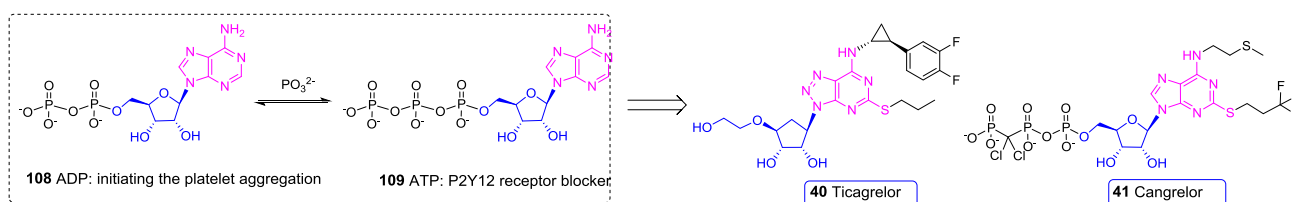
Figure 17 The antiplatelet drugs ticagrelor (**40**) and cangrelor (**41**) derived from ADP (**108**) and ATP (**109**).
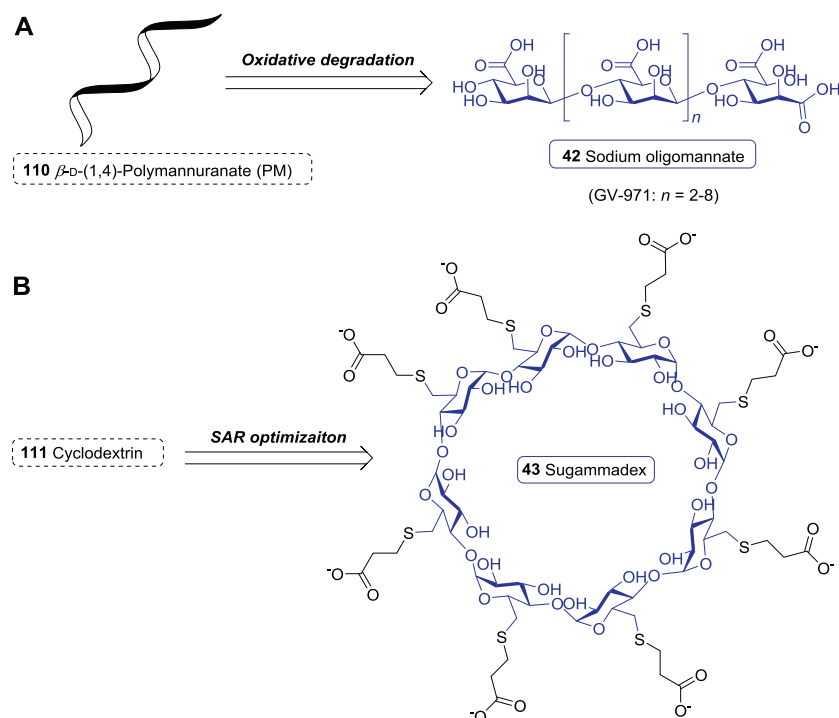
Figure 18   Carbohydrate-based nervous system drugs. (A) The AD drug sodium oligomannate (**42**) derived from brown algae β-D-(1,4)-polymannuranate (**110**). (B) Sugammadex (**43**) developed from cyclodextrin (**111**).

suppressing accumulation of phenylalanine and isoleucine to reduce the Th1 cells' infiltration to the brain. The cross talk with M1 microglia could be responsible for reducing AD-associated neuroinflammation and reversing the cognition impairment[436].

A recently reported 36-week randomized, double-blind, placebo-controlled phase III trial of mild-to-moderate AD participants ($n = 818$) showed remarkable drug-placebo differences at all measurement time points for the AD Assessment Scale-cognitive subscale 12-item (ADAScog12). The sodium oligomannate (**42**) oral administration group (900 mg/day) demonstrated noticeable efficacy in improving cognition, with sustained improvement in all observation periods of the trial ($P < 0.0001$), as well as great safety and tolerability[444]. Accordingly, sodium oligomannate (**42**) was approved by NMPA in 2019 for the treatment of mild to moderate AD[443]. Afterwards, an amplified phase III clinical trial named Green Memory was started in US for further evaluation of the safety, tolerability, and treatment efficacy of sodium oligomannate (**42**) in mild to moderate AD patients.

8.2.   The selective reversal agent for nuromuscular block: Sugammadex

Neuromuscular blocking agents (NMBAs) are important drugs for general anesthesia. However, the residual neuromuscular block (NMB) effects after surgery are undesired and often cause side effects like hypoxia[444]. Acetylcholinesterase (AChE) inhibitors, for example neostigmine and pyridostigmine, are employed to reverse NMB through increasing the level of AChE[445]. However, increased AChE could stimulate nicotinic and muscarinic receptors, yielding a group of other side effects[445].

Sugammadex (**43**), developed by Merck Sharp & Dohme, is a selective relaxant binding agent with novel and distinct mechanism for reversing NMB. It is a modified γ-cyclodextrin that consists of eight D-glucose units linked *via* β-1,4-glycosidic bonds (Fig. 18B)[446]. Due to the special cyclic structure and the hydroxyl group distribution, cyclodextrin (**111**) has a well-defined lipophilic cavity and a hydrophilic exterior[447]. Depending on the van der Waals and the hydrophobic interactions, cyclodextrin (**111**) could trap various drugs in the cavity and form a water-soluble guest-host complex[446]. Thus, it has been widely used as solubilizing agents in drug formulations[447]. It was found that the addition of negatively charged side chains at the 6-OH positions of the glucose residues in cyclodextrin could enhance its capture capacity towards the rigid rocuronium. Based on extensive SAR studies, sugammadex (**43**) was discovered as a unique drug for reversing NMB[446].

The *in vitro* studies indicated that the EC$_{50}$ of sugammadex's reversal activity against rocuronium mediated NMB was 1.2 ± 0.8 μmol/L[446]. Animal model studies showed that sugammadex (**43**) could effectively capture steroidal NMB agents *in vivo*, resulting in excretion of the rocuronium-sugammadex complex in urine[445].

A number of clinical trials were conducted for sugammadex (**43**) to estimate its reversal effect of rocuronium or vecuronium induced NMB[448]. Its mediated recovery mean time from rocuronium induced NMB was shorter than that of neostigmine (1.5 *vs.* 18.6 min, $P < 0.0001$). Similar results were obtained in vecuronium induced NMB (2.7 *vs.* 17.9 min, $P < 0.0001$)[449,450]. A phase III trial enrolled surgical patients with American Society of Anesthesiologists (ASA) physical status I−IV suggested that sugammadex (**43**) treatment had a superior reversal effect against rocuronium induced NMB to neostigmine treatment, with the mean time to recovery to a train-of-four (TOF) ratio of 0.9 being 2.9 min *versus* 50.4 min ($P < 0.0001$)[451]. Consequently, sugammadex (**43**) was approved by EMA in 2008 as the first selective NMB reversal drug.

9. Other carbohydrate-based drugs

In addition to the above mentioned indications, carbohydrate-based drugs have been used in the treatment of dry eye disease, chronic idiopathic constipation (CIC), and liver injury. Besides, carbohydrate-based medicines have also found applications in orphan diseases, such as Gaucher's disease, hereditary lacto-bacteriuria (HOA), Fabry's disease, and acute hepatic porphyria (AHP), as well as diagnostic agents, including vasodilators and contrast agents. Besides, some other carbohydrate conjugate drugs, for example the carbohydrate-enhanced siRNA and carbohydrate-based vaccines are also discussed in this chapter. In 2000−2021, eleven carbohydrate-based molecules as well as glycoconjugate drugs are approved in the mentioned areas.

9.1. Drugs for other diseases and orphan diseases

Diquafosol tetrasodium (44), developed by Inspire, Allergan, and Santen, is a second-generation uridine nucleotide, containing a symmetrical structure of two UDP (112) units, namely Up4U, for the treatment of dry eye disease. This molecule belongs to the dinucleoside 5′,5′-polyphosphates (DNP) class, which is commonly present in tears, aqueous humour, and retina, and works for ocular functions (Fig. 19A)[452,453]. Diquafosol tetrasodium (44) is an agonist of P2Y$_2$ purinergic receptor which is a G protein-coupled receptor, and can stimulate secretion of mucins from the conjunctiva into tears[442−445]. SAR studies revealed that the length of the phosphate chains determined its selectivity against P2Y$_2$, P2Y$_4$, and P2Y$_6$ receptors, in which four phosphates achieved favorable selectivity to P2Y$_2$ (EC$_{50}$ = 0.1 μmol/L)[453−455]. In animal experiments, diquafosol tetrasodium (44) significantly enhanced the corneal barrier function, including increase of tear fluid secretion and corneal epithelial resistance[456−458].

A phase II trial showed that the diquafosol tetrasodium (44) treated arms (1% or 3% concentrations) resulted in a significant amelioration in fluorescein (FL) corneal staining scores compared with the placebo arm (1% concentration arm, $P = 0.037$; 3% concentration arm, $P = 0.002$), with a dose-dependent manner[459,460]. Rose bengal (RB) corneal and conjunctival staining scores revealed a significant improvement of diquafosol tetrasodium (44) compared with placebo (1% concentration arm, $P = 0.007$; 3% concentration arm, $P = 0.004$), and both diquafosol tetrasodium (44) groups achieved a favorable subjective dry eye symptom scores ($P = 0.033$)[460]. A phase III study indicated that no significant different in FL staining scores was observed between 3% diquafosol tetrasodium (44) and 0.1% sodium hyaluronate in the treatment of dry eye patients, whereas diquafosol tetrasodium (44) displayed a superior efficacy in improving RB staining scores[461]. According to these data, diquafosol tetrasodium (44) was approved for dry eye disease treatment in 2010 in Japan[459,462].

Lactitol (45), the reduced form of disaccharide lactose (113, Fig. 19B), is a widely used sweetener in food industry. Since lactitol (45) is hard to be absorbed in small intestine, oral intake of lactitol (45) displays almost no influence on blood sugar level and insulin excretion. In consequence, it is a suitable sweetener for diabetes mellitus patients[463]. Besides, as an osmotic laxative, lactitol (45) can enhance osmotic pressure in the intestinal lumen, increase the fecal volume and moisture content, and stimulate peristalsis[464−466].

A large phase III study (NCT02819297) enrolled 1020 CIC patients, with the primary efficacy analysis being based on the first 12 weeks of the 6 months treatment period for 594 patients. As a result, lactitol (45) showed a greater response than the placebo
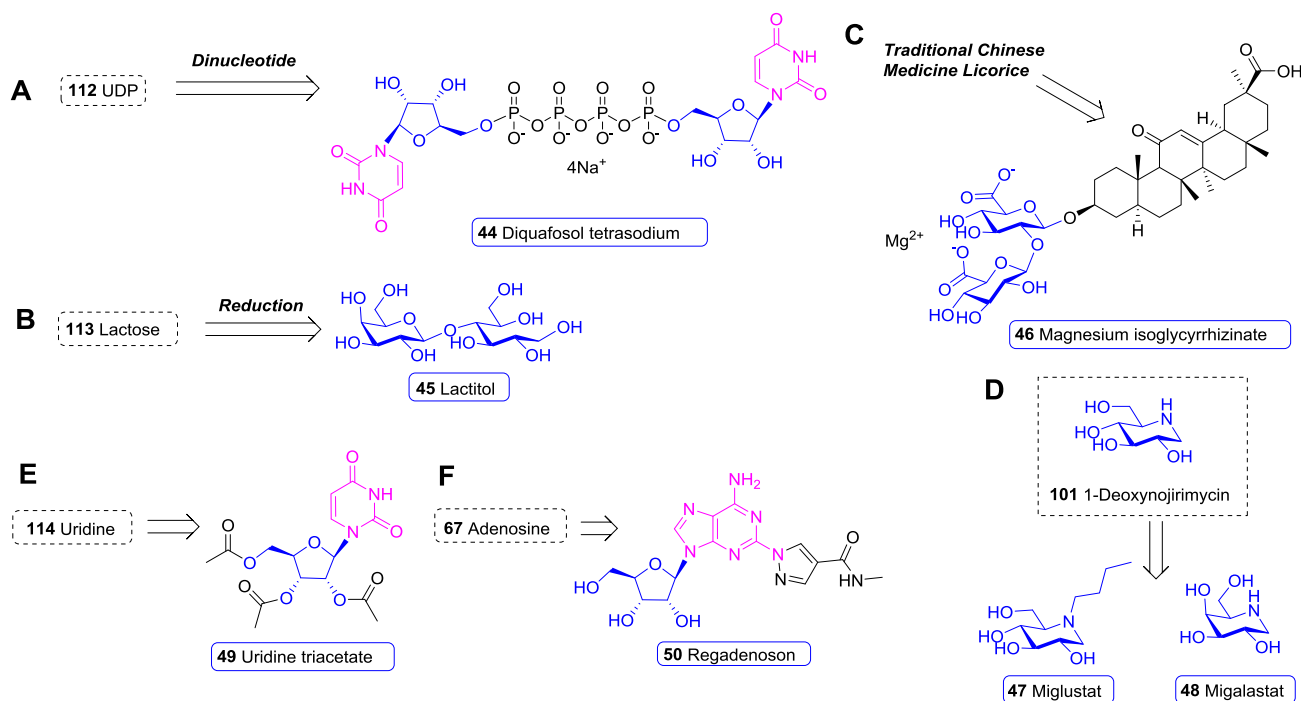
Figure 19 Carbohydrate-based drugs for other diseases. (A) Diquafosol tetrasodium (44) derived from UDP (112). (B) Lactitol (45) derived from lactose (113). (C) Magnesium isoglycyrrhizinate (46) prepared from licorice. (D) Miglustat (47) and migalastat (48) derived from 1-deoxynojirimycin (101). (E) Uridine triacetate (49) derived from uridine (114). (F) Regadenson (50) derived from adenosine (67).

group (25% *vs.* 13%, *P* < 0.05). Another phase III study (NCT02481947) provided a similar result, further confirming the efficacy and safety of lactitol (**45**). Therefore, lactitol (**45**) was approved by FDA for treating CIC in 2020[467].

Magnesium isoglycyrrhizinate (MgIG, **46**), developed by Chia Tai Tianqing Pharm for anti-inflammatory and hepatoprotective treatment, is a magnesium salt of 18α-glycyrrhizic acid (Fig. 19C)[468,469]. Glycyrrhizic acid, containing 18α and 18β glycyrrhizic acid stereoisomers, is a natural triterpene glycoside extracted from *Licorice*, which has been used to improve liver function in traditional Chinese medicine (TCM). Clinical evaluations demonstrated that the 18α stereoisomer possessed better liver protection efficacy and fewer side effects[470−473]. Though the exact mechanism of action was not clear, MgIG (**46**) was approved for anti-inflammatory and hepatoprotective treatment by NMPA in 2005.

Orphan diseases, also known as rare diseases, are a group of disorders associated with the infrequent and unusual qualities, and 80 percent of the reported cases have a genetic basis[474,475]. Although hard to estimate, the burden of orphan diseases is tremendous, both in terms of loss of human life and economic burden[474]. Since 2000, an increasing number of orphan drugs have been approved, including three carbohydrate-based drugs, namely miglustat, uridine triacetate, and migalastat.

Miglustat (**47**, Fig. 19D), developed by Actelion, is a iminosugar for the treatment of Gaucher's disease (glycosphingolipid lysosomal storage disorder). Derived from the structure of deoxynojirimycin (**102**), SAR studies revealed that the presence of *N*-butyl residue led to the inhibition of glucosyltransferase inhibition[476]. Using ceramide as an acceptor, the K_i value of miglustat (**47**) against ceramide-specific glucosyltransferase, a pivotal enzyme for the glycosphingolipid biosynthesis, reached 7.4 μmol/L[476]. Data from *in vitro* Gaucher's disease model revealed that miglustat (**47**) effectively offset the cell storage of glucosylceramide (GlcCer)[477]. In a Sandhoff disease (another glycosphingolipid lysosomal storage disorder) mouse model, miglustat (**47**) caused a significant reduction of glycosphingolipids storage in brain and liver by 35%−86% (*P* < 0.05−0.001), delayed the onset time of symptoms (136 days *vs.* 40 days, *P* < 0.001), and prolonged life expectancy (170 days *vs.* 125 days, *P* < 0.001) compared with the untreated group[478].

An open-labeled, phase II study that assigned 36 patients with type I Gaucher's disease indicated that in the patients clinically stable on enzyme replacement therapy, monotherapy with miglustat (**47**) could be an effective maintenance therapy and miglustat (**47**) plus imiglucerase could not achieve better benefits[479]. In addition, studies on patients with type III Gaucher's disease showed that miglustat (**47**) did not appear to achieve significant benefits on the neurological manifestations[480]. Though the incidence of diarrhea in patients who received miglustat (**47**) treatment was up to 80%, the severity of diarrhea was mild to moderate and often self-limiting[481]. For these reasons, miglustat (**47**) was approved as an orphan drug for treating type I Gaucher's disease by EMA and FDA in 2002 and 2003, respectively[481].

Of note, several clinical trials also assessed the efficacy and safety of miglustat (**47**) for treating Niemann-Pick Disease Type C (NPC)[482]. A randomized controlled trial (RCT) about miglustat (**47**) in juveniles and adults with NPC indicated that miglustat (**47**) treatment for 12 months achieved an improved horizontal saccadic eye movement velocity (HSEM-α) compared with the standard care (excluding patients taking benzodiazepines, *P* = 0.028), as well several other clinically relevant symptoms, with a well safety profile[483]. A further study allowed these patients to continue treatment in a 12-month, non-controlled extension, and revealed that long-term miglustat (**47**) therapy could stabilize neurological symptoms caused by NPC, including its effect on HSEM-α, swallowing, ambulation, and cognition[484]. Accordingly, miglustat (**47**) was further authorized for NPC treatment by EMA in 2013[482].

Migalastat (**48**), developed by Amicus Therapeutics, is a synthetic iminosugar for Fabry disease treatment (Fig. 19D)[485]. As 1-deoxygalactonojirimycin, migalastat (**48**) owns a galactose mimic structure and could selectively and reversibly bind to mutated α-galactosidase A, thereby to stabilize the enzyme in the endoplasmic reticulum and ensure its proper transportation to lysosome[486]. In the Fabry disease cell lines, migalastat (**48**) increased the level of 49 different missense mutant α-galactosidase A by 1.5−28 folds, with an EC_{50} ranging from 820 nmol/L to > 1 mmol/L[486]. Data from transgenic mice model suggested that oral administration of migalastat (**48**) resulted in a significant and dose-dependent increase of α-galactosidase A activity, which might account for globotriaosylceramid reduction in skin, heart, kidney, brain, and plasma[487].

According to a phase III study, migalastat (**48**) caused a significant change in the mean globotriaosylceramid inclusions per kidney interstitial capillary (−0.25 *vs.* 0.07, *P* = 0.008), as well in the mean plasma globotriaosylsphingosine (−11.2 *vs.* 0.6, *P* = 0.003)[488]. In addition, for patients with suitable mutant α-galactosidase, migalastat (**48**) treatment was extended to 24 months and the data showed that migalastat (**48**) treatment caused a significant decrease of the left-ventricular-mass index from baseline[488]. Based on these results, migalastat (**48**) was approved for the treatment of Fabry disease by EMA and FDA in 2016 and 2018, respectively[489].

Uridine triacetate (**49**), developed by Wellstar, is an acetylated prodrug of uridine for HOA treatment (Fig. 19E)[490,491]. It displayed 4- to 6-fold enhanced ability to enter the systemic circulation compared to uridine (**114**)[491]. As an orphan disease, a single arm phase III study suggested that all enrolled patients (*n* = 4) achieved stable predetermined principal hematologic parameters in 6 weeks treatment of Uridine Triacetate (NCT02110147). Moreover, uridine triacetate (**49**) could be well tolerated according to the trial data. Afterwards, uridine triacetate (**49**) was approved by FDA in 2015. Of note, it also obtained FDA's approval for another indication, the emergency treatment of adult and pediatric patients following a fluorouracil or capecitabine overdose, in the same year[492].

9.2. Diagnostic agents

The coronary problem caused ischemic heart disease (IHD) is responsible for approximately 50% of CVD related deaths. Among clinical diagnosis of IHD, myocardial perfusion imaging (MPI) or stress MPI, is considered as a pivotal evaluation method[372,493]. Since the exercise stress MPI is only available for patients who could adequately perform exercise, the pharmacologic stress MPI serves more application. Adenosine (**67**), the nonselective inhibitor of A_1, A_{2A}, A_{2B}, and A_3 receptor, can vasodilate the coronary and peripheral arterial beds, enhance myocardial blood flow (MBF), and cause sympathoexcitation *via* A_{2A} and A_{2B} receptors activation, which results in pharmacologic stress MPI[494]. However, adenosine's activation activity against other receptors can yield undesirable side effects, and the short half-life necessitates a continuous intravenous infusion[474]. Hence, selective A_{2A} receptor inhibitors are required.

Regadenoson (**50**) is a 2-[*N*-1-(4-*N*-methylcarboxamidopyr-azolyl)] adenosine analogue developed by CV Therapeutics (Fig. 19F)[495]. The SAR studies revealed that the 4-substituted pyrazole derivative confered highly selective affinity with A_{2A} receptor over A_1, A_{2B}, and A_3 receptor[495,496]. The high A_{2A} receptor binding affinity results in a long duration of action, while the low affinity leads to short actuation duration, and the latter is more suitable for stress MPI[496]. Therefore, the low-affinity agonist regadenoson (**50**) produces an equivalent response and becomes an ideal drug for pharmacologic stress MPI[494,496].

A phase II study enrolled 36 patients suggested that regadenoson (**50**) stress MPI was well-tolerated and achieved 86% agreement with the results from adenosine stress MPI[497]. According to the results of phase III, the average agreement in adenosine-adenosine and adenosine-regadenoson were 0.62 ± 0.03 and 0.63 ± 0.02, respectively[498]. In addition, regadenoson (**50**) can be safely administered as a fixed unit bolus regardless of age, gender, or body mass index[498]. Afterwards, regadenoson (**50**) was approved as a pharmacological stress agent for myocardial perfusion imaging by FDA in 2008.

Lymph node metastasis is the hallmark of malignant tumors, which could be treated by lymph node dissection. However, how to trace the sentinel lymph node (SLN) in cancers, especially in melanoma and breast cancer, is considered as a fundamental issue for performing effective sentinel lymph node biopsy (SLNB) and lymph node dissection[499−501]. Technetium-99m ([99mTc]) is a radioisotope commonly used in nuclear medicine[502]. Based on its wide range of diagnostic uses, Navidea Biopharmaceuticals developed [99mTc]tilmanocept (Lymphoseek, **51**; Supporting Information Fig. S7A), a CD206 mannose receptor targeted radio agent, for SLN detection[496]. [99mTc]tilmanocept (35.8 kDa) is a synthetic nanomolecule composed of a dextran backbone (9.5 kDa) attaching with multiple units, including diethylene triamine penta-acetic acid (DTPA) and mannose moieties. The DTPA group serves as the binding site for labeling the macromolecule with [99mTc][503,504], and the mannose moieties in the macromolecule are responsible for binding to CD206, the mannose receptor with high level in tumor-associated macrophages (TAMs), conferring its tracing ability against SLN[505]. Animal model studies suggested that [99mTc]-labeled-tilmanocept possessed several advantages of an ideal SLN imaging, which include the rapid clearance from the injection site, the rapid accumulation with prolonged retention in the SLN, as well a low uptake in distal lymph nodes[503,506,507].

Clinical trials set the proportion of nodes detected by vital blue dye (VBD) and [99mTc]tilmanocept (**51**) as the primary endpoint, and assessed the lymphatic mapping performance of [99mTc]tilmanocept (**51**)[508,509]. Two phase III trials conducted in breast cancer showed that 207 of 209 lymph nodes detected by VBD were also detected by [99mTc]tilmanocept (**51**) with a concordance rate of 99.04% ($P < 0.0001$), and of 33 pathology-positive lymph nodes, [99mTc]tilmanocept (**51**) detected more than VBD did (93.9% *vs.* 75.8%, $P < 0.05$)[508]. In addition, [99mTc]-labeled-tilmanocept detected at least 1 SLN in more patients than VBD (146 *vs.* 131, $P < 0.0001$)[508]. Another combined analysis of phase III trials in melanoma showed that [99mTc]tilmanocept (**51**) detected 232 of 235 lymph nodes detected by VBD (concordance rate $=$ 99.04%, $P < 0.001$), and identified more pathology-positive lymph nodes than VBD (100% *vs.* 80%, $P = 0.004$) as well more patients with at least 1 SLN (150 *vs.* 138, $P = 0.002$)[509]. Moreover, no serious adverse events were observed in these trials[508,509]. Afterwards, [99mTc]tilmanocept

(**51**) was approved as the first lymphatic mapping agent for patients with breast cancer or melanoma by FDA in 2013.

9.3. Carbohydrate-enhanced siRNA drug

Small interfering RNA (siRNA) is a general genetic therapy method for treating various diseases. However, the durability and therapeutic effect of siRNA were highly limited for its *in vivo* instable characters. To solve such problems, chemical modified nucleotides, enhanced stabilization chemistry (ESC) and delivery of molecularly targeted therapy technologies were developed for siRNA drug R & D. Among which, the chemical modified nucleotides efficiently increase the durability of the RNA strands, and the tri-GalNAc-conjugate technology enables subcutaneous dosing with increased potency, and therapeutic index, and demonstrates great potential for liver targeted siRNA drugs[510].

Givosiran (**52**), an aminolevulinate synthase 1 (ALAS1)-directed small interfering RNA (siRNA) drug developed by Alnylam Pharma, is selected as an example for demonstrating the fast developed siRNA drug field recently. For structural detail, givosiran (**52**) consists of a 21-base sense strand and a 23-base antisense strand, which is modified with 16 nucleotides containing a $2'$-F or $2'$-OMe substituted nucleotides (Fig. S7B). Besides, six of its backbone linkages distributed at the ends of the strands are covalently conjugated to the tri-GalNAc moiety, which allows for high-uptake into the liver, the major site of ALAS1 synthesis, through subcutaneous administration[511]. Afterwards, the siRNA conjugate is efficiently and specifically delivered to hepatocytes[511]. In hepatocytes, this siRNA inhibits both the translation and expression of the ALAS1 protein, thus decreases systemic levels of neurotoxic precursors δ-aminolevulinic acid (ALA) and porphobilinogen (PBG), the main factors for causing acute porphyria attacks in AHP. A double-blind, placebo-controlled, phase III clinical trial enrolled 94 AHP patients and found that the mean annualized attack rate was significantly decreased in Givosiran group than in placebo group (3.2 *vs.* 12.5, $P < 0.01$)[512]. Givosiran (**52**) resulted lower levels of urinary ALA and PBG, fewer days of hemin use, as well as better daily scores for pain than placebo. Hence, Givosiran received its first approval from FDA in 2019 for the treatment of adults with AHP.

9.4. Carbohydrate-based vaccines

Vaccination is a highly effective and cost-efficient interventions for infectious disease and even cancer preventions[513]. Since it was well recognized that some specific glycan units (*e.g.*, capsular polysaccharide) are essential components for growth and virulence of pathogenic microorganism, carbohydrate-based vaccines have turn to be important vaccine categories that protected humans against diseases associated with severe bacterial pathogens, such as *Haemophilus influenzae*, *S. pneumoniae*, and *Neisseria meningitides* since the 1970s[513].

In recent years, the developed conjugate vaccines that constructed by carrier proteins and antigen polysaccharides *via* covalent linkages induce long-lasting and stable immune responses for immune barrier establishment[514]. During 2000 and 2021, two categories of carbohydrate-based vaccines launched for preventing *S. pneumoniae* infection and typhoid[515].

S. pneumoniae is an important pathogen that cause several diseases ranging from sinusitis and otitis media to life-threatening diseases such as pneumonia, bacteremia and meningitis[516]. In order to control pneumococcal disease, several pneumococcal

conjugated vaccines (PCVs, **53**) have been approved for *S. pneumoniae* infection prevention since 2000. PCV7 (including serotypes 1, 4, 6B, 9V, 14, 18C, 19F, and 23F) developed by Wyeth Pharma was introduced into children's immunization in USA in 2000. Afterwards, PCV13 (PCV7 plus serotypes 1, 3, 5, 6A, 7F, and 19A) developed by Pfizer was approved by FDA in 2010, and WHO comprehensively assessed the situation of serotype replacement since PCV7 introduction and decided to use PCV13 instead of PCV7 in the same year. Recently, PCV15 (PCV13 plus serotypes 22F and 33F) developed by Merck and PCV20 (PCV13 plus 8, 10A, 11A, 12F, 15B, 22F, and 33F) developed by Pfizer were approved by FDA in 2021. The promotion and application of these vaccines remarkably declined the disease burden of *S. pneumoniae* (Supporting Information Fig. S8)[516].

Typhoid fever is an acute systemic infectious disease responsible for an estimated 12−20 million cases and over 150,000 casualties annually[517]. A typhoid Vi polysaccharide vaccine (Typhim Vi, **54**) developed by Sanofi is composed of purified Vi polysaccharide from *S. enterica* subsp. enterica Typhi (*S. Typhi*; Fig. S8)[7]. A single vaccination dose of Typhim Vi (**54**) is sufficient to induce a 3-year cumulative protection from typhoid infection in 55% of the vaccinated population[518]. Accordingly, Typhim Vi (**54**) was approved by FDA in 2014 for preventing typhoid fever.

In addition to the carbohydrate enhanced pathogen-targeting vaccines, the tumor-associated carbohydrate antigens (TACAs), including glycoproteins (*e.g.*, mucin *O*-antigens) and glycolipid antigens (*e.g.*, gangliosides, globosides and Lewis determinants), based cancer vaccines have made great progress in the past decades for cancer prophylaxis, diagnosis and therapy[514]. Though there is still no TACA based cancer vaccine launched for some efficacy and safety problems, it has turn to be one of the most attractive fields for future carbohydrate drugs[514].

10. Conclusions

Small molecular carbohydrates and carbohydrate-conjugated macromolecules are fundamental materials of life. Some of them are involved in energy metabolism; some take part in various signal transductions; and some others are weapons against viruses, bacteria, or parasites. Following the rationale of "learn from nature", the carbohydrate-based drugs were developed with a variety of biological activities in the field of disease treatment and diagnosis. Since 2000, drug discovery and development processes are accelerating, along with the great progresses of basic chemistry and biology researches. The development of carbohydrate-based drugs has also made great achievements in the past 20 years, with 54 carbohydrate-based chemical entities approved worldwide for antiviral, antibacterial, antiparasitic, anticancer, antidiabetic, cardiovascular, neurological, and orphan diseases, siRNA, vaccines, as well as for diagnostic purposes. These drugs have brought enormous benefits to the world.

In many ways, there is huge scope for future sugar-based drugs. For example, the fourth generation heparin products, namely chemoenzymatically and bioengineered heparins have been proposed[384]. However, due to the huge difficulty in synthesis and purifications of the complex oligosaccharide, these works are still in progress. Besides, sugars play an important role in immunity, and most of the key molecules involved in innate and adaptive immune responses are glycoproteins[519]. The aberrant glycosylation or glyco-codes allows tumour to evade the perception of immune system and can also induce immunosuppressive signals[200]. The TACAs, including mucin-related TACAs, blood group Lewis-related TACAs, Globo class, and gangliosides, are uniquely or excessively expressed on the surface of tumor cells. They could be personalized cancer targets involved in tumor metastasis, development, and prognosis[520]. TACAs-based vaccines, including conjugated vaccines, nonconjugated vaccines based on self-assembly strategy, and vaccines based on modifications of TACAs, are expected to benefit in tumor treatments or recurrence prevention through immunity stimulation and activation[520]. Taken together, there is great potential for developing carbohydrate-based cancer diagnostics, vaccines, and treatments[197,201−203]. Continuous learning from nature, not only in the traditional glycochemistry and glycobiology areas, but also in broad glycosciences[521,522], including glycomics, glycoproteomics, and glycogenomics, will inspire the creation of more innovative carbohydrate-based drugs, and bring more benefits to human health.

Author contributions

Xin Cao and Biao Yu conceived the concept of the review. Xin Cao, Xiaojing Du, Heng Jiao, Quanlin An and Ruoxue Chen performed the literature review, organized and prepared the manuscript. Xin Cao, Biao Yu, Xiaojing Du, Pengfei Fang and Jing Wang revised the manuscript. All authors approved the submission of this manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

Appendix A. Supporting information

Supporting data to this article can be found online at https://doi.org/10.1016/j.apsb.2022.05.020.

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