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Supporting Information for

Oligosaccharide Synthesis and Translational Innovation

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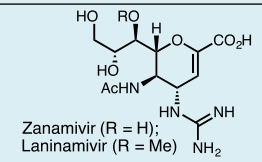
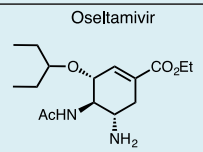
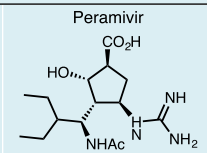
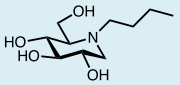
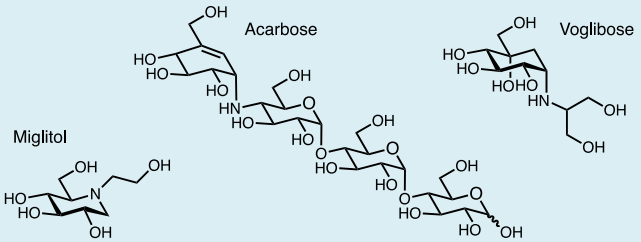
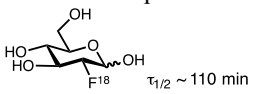
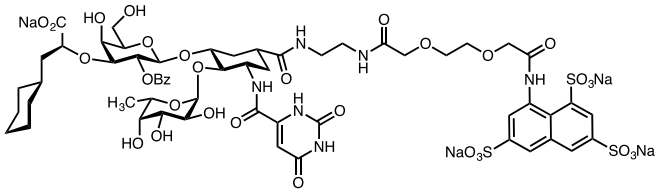
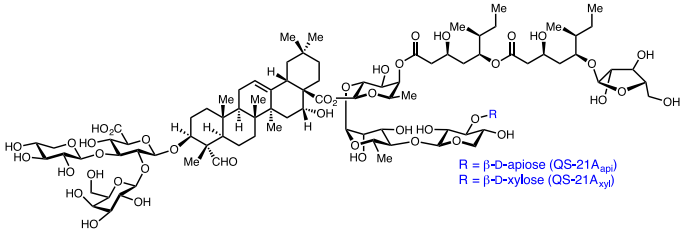
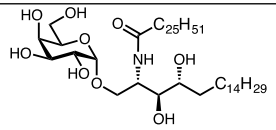
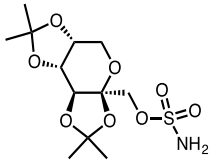
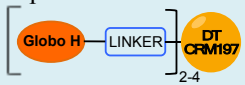
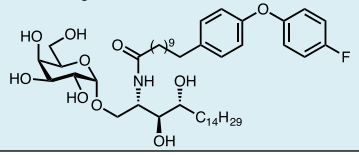
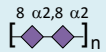
Table of Content

Table S1. Selected examples of glycotherapeutics in the clinic that contain essential glycans or target the disease-associated glycosylation, glycans, their receptors or biosynthesis.

Drug and target	**Function of target**	**Mode of action related to glycosylation[a]**	**Clinical use[b]**	**Ref.[c]**
		Enzyme inhibitors:		
Transition-state analog inhibitors of influenza neuraminidase: Zanamivir (Relenza®), Oseltamivir (Tamiflu®), Peramivir (Peramiflu®)	Neuraminidase catalyzes the cleavage of sialoside receptor on host cells during viral infection and replication.	 Zanamivir (R = H); Laninamivir (R = Me)  Oseltamivir  Peramivir	For the treatment of influenza infection.	1
Substrate reduction therapy for lysosomal storage disease: Miglustat (Zavesca®)	Glycosylceramide synthase catalyzes the formation of GlcCer.	 The type 1 Gaucher disease is associated with deficient glucocerebrosidase, which catalyzes the degradation of GlcCer. By inhibiting glycosylceramide synthase, miglustat reduces accumulation of GlcCer due to deficient glucocerebrosidase.	For the treatment of type 1 Gaucher's disease in adults not suitable for enzyme replacement therapy; and Niemann Pick (type C) disease (some countries).	2
Transition-state analog inhibitors of α-glucosidase: Miglitol (Glyset®); Acarbose (Precose®, Glucobay®); Voglibose (Glustat®)	In the intestine, α-glucosidase catalyzes the hydrolysis of oligosaccharides to glucose.	Inhibition of α-glucosidase decreases absorption of glucose.  Acarbose Voglibose Miglitol	For the treatment of type 2 diabetes mellitus.	3
Glycopeptide antibiotics: Vancomycin, Teicoplanin, Telavancin (Vibativ®), Oritavancin (Oractiv®), Dalbavancin (Dalvance®, Xydalba™)	Binding to D-Ala-D-Ala of Lipid II and Lipid IV disturbs peptidoglycan assembly and bacterial cell wall biosynthesis.	The glycan part on these inhibitors is important for the antibiotic activity *in vivo*.	For the treatment of infections caused by Gram-positive bacteria, including drug-resistant strains.	4

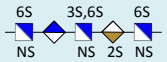
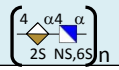
Glycosylated products or glycomimetics:				
PET radiopharmaceutical: 2-[^{18}F]Fluoro-2-deoxyglucose (^{18}F-FDG)	Indicator of glucose uptake and metablism.	FDG is transported into cells, where it accumulates as FDG-6-phosphate acting as an indicator of glucose uptake, metabolism, and cell viability.  	For oncology PET imaging.	5
A pan-selectin antagonist of E-, P-, and L-selectins: Rivipansel (GMI-1070)	E-, P-, and L-selectins mediate the adhesion and rolling of leukocytes via binding to carbohydrate epitopes (*e.g.*, sLe^x). Uncontrolled recruitment of leukocytes is associated with acute inflammation.	 Inhibitor of E-, P-, and L-selectins that cause leukocyte-mediated inflammation. Mimics the bioactive conformation of sLe^x in the binding site of E-selectin. The sulfate-binding domain is important for inhibition of P- and L-selectins.	In clinical trials (Phase III, fast track, orphan drug status) for the treatment of vaso-occlusive crisis in patients with sickle cell anemia.	6
Saponins acting as adjuvants to stimulate immune cells: QS-21	Targets immune cells as an immunostimulatory adjuvant to elicit Th1- and Th2-type cytokines; amplifies T-cell- and B-cell-mediated immune responses.	 QS-21 is the most active fraction of the bark extract from *Quillaja Saponaria* that contains predominantly saponins QS-21A$_{api}$ and QS-21A$_{xyl}$ which act as adjuvants for vaccines.	Used as vaccine adjuvant. Some QS-21 formulations (Quil A, ISCOMs, ISCOMATRIX, AS01, AS02) are currently tested in human clinical trials. Adjuvant in feline vaccine against feline leukemia virus (FeLV).	7
An adjuvant and immune stimulator KRN7000	Recognizes CD1d on dendritic cell and natural killer T cell receptor to form CD1d-KRN7000-iNKTR complex.	 αGalCer glycolipid; a synthetic analog of agelasphins from the marine sponge *Agelas mauritianus*. The lipid part binds to CD1d	KRN7000 and KRN7000-loaded dendritic cells are being tested as anticancer agents (phase 1).	8

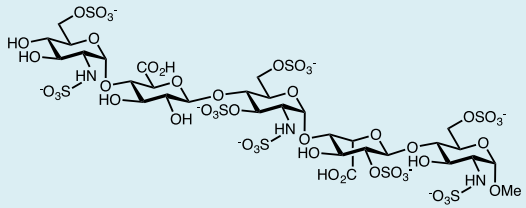
		on dendritic cell and the sugar part binds to the iNKT-cell receptor to stimulate Th1 activation.		
A neurotransmitter agonist: Topiramate (Topomax®)	Gamma-aminobutyrate receptor for neurotransmission.	 Augments the activity of the neurotransmitter gamma-aminobutyrate (GABA); blocks voltage-dependent sodium and calcium channels; inhibits carbonic anhydrase.	For the treatment of epileptic seizures and prevention of migraines.	9
Anticancer vaccines:				
Globo H-KLH vaccine with QS21 adjuvant: Adagloxad simolenin (OPT822)	Globo H is a tumor-associated carbohydrate antigen (TACA).	The vaccine containing Globo H epitope linked to the carrier protein keyhole limpet hemocyanin (KLH) and combined with QS21 adjuvant stimulates an antibody response against Globo H-expressing tumor cells, inhibiting tumor cell proliferation. Globo H-CRM197 vaccine: stimulates immune response to Globo H positive cancer cells.  C34 adjuvant:  	Under clinical investigation (Phase III) for the treatment of triple negative and Globo H positive breast cancer.	10
Globo H-CRM197 vaccine with C34 adjuvant: OBI-833	A Globo H vaccine contains Globo H antigen conjugated to a carrier protein (diphtheria toxin mutant CRM197) and C34 adjuvant, designed to target Globo H positive cancer cells.		Under clinical investigation (Phase I) as a vaccine for the treatment of breast and ovarian cancers.	
Supplements: Human milk oligosaccharides (HMOs)	Prebiotics; prevent infections; modulate epithelial and immune responses.	Substrates for beneficial bacteria; decoys for pathogens; source of sialic acid nutrient for brain development.	2'-O-Fucosyllactose (2'-FL) is an approved (EU) supplement for the infant milk formula.  	11

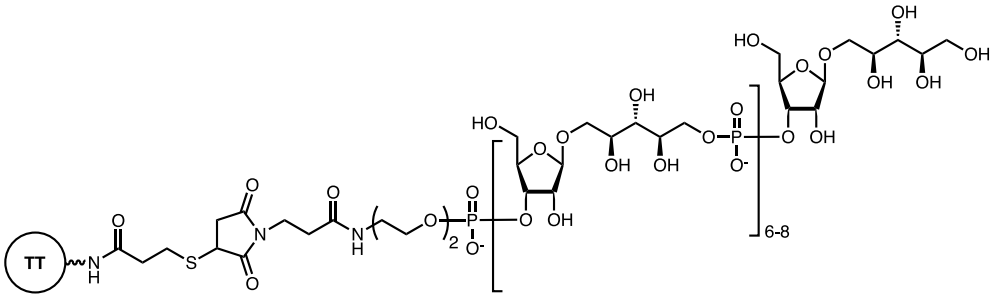
Polysialic acid (PSA) for drug formulation *(Neu5Ac-α2,8- Neu5Ac)n*	Biodegradable human polysaccharide; non-  immunogenic.	Improves pharmacokinetics of conjugated proteins. Protein modification with PSA reduces clearance; prolongs half-life. Unlike PEG, PSA does not form viscous solutions, or interfere with protein activity.		
PSA-modified rFVIII	Human factor VIII (FVIII) is an essential plasma glycoprotein, which participates in a blood coagulation cascade (i.e., serves as a cofactor for FIXa in the FX->FXa process).	PolyXen™ technology is based on the chemical conjugation of PSA to proteins. Deglycosylation of FVIII leads to reduced stability and activity.	Clinical trials in humans demonstrated enhanced half-life for the PSA-modified rFVIII, which is the first-line therapy for Hemophilia A.	12
PSA-modified alpha 1-antitrypsin (α1AT) Prolastin®, Glassia®, Zemaira®.	α1AT is a protease inhibitor; protects tissues from proteases of inflammatory cells (e.g., lung tissues from neutrophil elastase).	The enzymatic extension of *N*-glycans with PSA was shown to improve α1AT serum half-life in mice. Glycosites: N46, N83, and N247.	α1AT is used for the treatment of congenital α1AT deficiency with emphysema.	13
Therapeutic glycoproteins:				
Monoclonal antibodies (mAbs):	Immunoglobulin (IgG) with high binding affinity to a specific cell-surface antigen and to an Fc receptor on the immune cell to induce the immune response.	Glycosite: N297 (Fc domain). Apart from improving stability and preventing aggregation, the Fc-linked glycans could influence the interaction of Fc with the Fc receptors to activate the immune response and tune the effector functions of mAbs. Core fucosylation reduces Fc-FcγRIIIa interaction and the associated ADCC. Galactosylation and α2,6-sialylation promote Fc-FcγRIIb interaction to modulate the anti-inflammatory responses. Agalactosylated glycoforms are pro-inflammatory, as they can only interact with the activating FcγRs, not the inhibitory FcγRIIb. Homogeneous glycoforms of rituximab and trastuzumab for functional and structural studies have been prepared by chemoenzymatic glycan remodeling.		14
Anti-CD20 antibody Rituximab (Rituxan®)	Destroys normal and malignant B cells with expressed CD20.		Treatment of B-cell lymphoma and certain autoimmune disorder.	15
Anti-HER2 antibody Trastuzumab (Herceptin®)	Targets epidermal growth factor receptor 2 (HER2) on the cancer cell.		Treatment of HER2+ breast cancer.	*15*[a-c], 16

Anti-CD20 antibody Obinutuzumab (Gazyva®)	Targets CD20 on B cells.	Manufactured by CHO cells with overexpressed GnT-III and Golgi β-mannosidase-II to produce glycoforms without core fucose and with bisecting GlcNAc (GlycoMAb Technology, Roche) to enhance ADCC against B-cell lymphoma.	Treatment of chronic lymphocytic leukemia (with chlorambucil); follicular lymphoma (with bendamustine).	17
Anti CCR4 antibody Mogamulizumab (Poteligeo®)	Targets CC chemokine receptor type 4 (CCR4).	Non-fucosylated glycoforms of mAb are produced in the FUT8 knockout CHO cell lines (Potelligent® Technology, Kyowa Hakko Kirin, BioWa).	Treatment of some types of skin lymphoma.	18
Anti-IL5 antibody Benralizumab (Fasenra™)	Targets α-chain of the interleukin 5 (IL-5) receptor on eosinophils.	Non-fucosylated glycoforms of mAb are produced using Potelligent™ technology.	Treatment of severe eosinophilic asthma.	*18*,19
Anti-EGFR/Lgr5 antibody MCLA-158	Bispecific mAb targeting EGFR and Lgr5 (Leucine-rich repeat-containing G protein-coupled Receptor).	Non-fucosylated antibodies with enhanced ADCC are produced in fucose-starving CHO cells with overexpressed bacterial GDP-6-deoxy-n-lyxo-4-hexulose reductase (RMD), which interferes with the *de novo* biosynthesis of GDP-fucose (GlymaxX® Technology, ProBioGen).	In clinical studies (Phase I) for the treatment of solid tumor of metastatic colorectal cancer.	20
CD40 agonists Dacetuzumab (SEA-CD40)	Targets CD40 of macrophages and dendritic cells.	SEA-CD40 targets Fc receptors on neighboring cells causing cross-linking and clustering of CD40's ligand, and boosting CD40 signaling and antitumor immunity; kills CD-40 expressing tumor cells by ADCC. The non-fucosylated mAb is produced in CHO cells treated with a global metabolic inhibitor, 2-flurofucose (SEA Technology, Seattle Genetics).	In clinical trials (Phase I) for the treatment of advanced solid tumors and lymphoma.	21
Anti-EGFR antibody Cetuximab (Erbitux®)	Targets the epidermal growth factor receptor (EGFR) on the cancer cell.	Glycosites: N88 (Fab) and N297 (Fc). When compared to the commercial cetuximab, the homogeneous glycoform of mAb with sialylated bi-antennary N-glycan at N88 and galactosylated bi-antennary N-glycan without core fucose at N297 showed the enhanced NK cell activation and CD107a up-regulation.	Treatment of the metastatic colorectal cancer; squamous cell cancer and the head and neck cancer; non-small cell lung cancer; squamous cell skin cancer.	22
Anti-GD2 antibodies: Dinutuximab (Unituxin™), Dinutuximab β (Isquette™)	Binds to the ganglioside GD2 and induces ADCC and CDC against GD2-	Dinutuximab is produced in SP2/0 cell lines, whereas Dinutuximab β is produced in CHO cells resulting in a more favorable glycosylation profile and enhanced ADCC. De-	Dinutuximab is used for the treatment of pediatric neuroblastoma.	23

	expressing tumor cells (malignant melanoma, neuroblastoma, osteosarcoma, small cell carcinoma of the lungs).	fucosylation of dinutuximab was shown to further improve ADCC.		
An agonist of erythropoietin (EPO) receptor Epogen® (epoetin-α); Aranesp® (darbepoetin-α*)*	Interaction of the glycoprotein EPO with its receptor in the bone marrow stimulates the kinase signaling for the production of the red blood cells.	Sialylation of EPO improves solubility, stability, and half-life. Glycosylation was shown to protect against oxidation; thermal, chemical and pH denaturation; kinetic inactivation and degradation. Darbepoetin-α was designed to contain 7 glycosites, including the native glycosites at N24, N38, N83 and S126, and additional at N30, N88.	Treatment of anemia associated with chronic renal failure.	24
Human glycoprotein hormones (hGPH):	Consist of a common α-subunit (α-hGPH) and hormone-specific β-subunit.	Glycosylation affects bioactivity, half-life, stability, and aggregation.		25
α-hGPH	α-Subunit of hFSH, hLH, hCG, hTSH.	Glycosylation improves activity. Glycosites: N52, N78		*25*[b]
β-Follicle stimulating hormone (β-hFSH): Follitropin-α (Gonal-F®); Follitropin-β (Follistim AQ®)	hFSH stimulates maturation of primordial germ cells; regulates gametogenesis, follicular development, and ovulation.	Glycosylation improves activity. Glycosites: N7, N24	Infertility therapy for ovarian hyperstimulation; reversal of anovulation.	*25*[c]
β-Luteinizing hormone (β-hLH): Lutropin-α (Luveris®)	hLSH triggers ovulation, development of corpus luteum and secretion of progesterone; stimulates secretion of testosterone in males.	Glycosylation improves activity. Native glycosite: N30	Treatment of female infertility.	*25*[d]
β-Chorionic gonadotropin hormone (β-hCG): Choriogonadotropin-α (Ovidrel®)	hCG is produced during pregnancy; overlapping functions with hLSH.	Glycosylation improves activity. Glycosites: N13, N30, S121, S127, S132, S138	Treatment of female infertility.	*25*[d]

β-Thyroid stimulating hormone (hTSH): Thyrotropin-α (Thyrogen®)	hTSH stimulates secretion of thyroxine (T_4).	Glycosylation improves activity. Glycosite: N23	Treatment of hypothyroidism, thyroid cancer.	*25*[e]
Granulocyte-macrophage colony-stimulating factor (GM-CSF): *Sargramostim (Leukine®); Regramostim.*	GM-CSF is a cytokine; immunostimulant; white blood cell growth factor.	Glycosylation improves activity. Native glycosites: N27, N37, S5, S7, S9, T10	For cancer patients after treatment of chemotherapy.	26
Granulocyte colony-stimulating factor (G-CSF3) Lenograstim (Granocyte®); Filgrastim (Neupogen®)	G-CSF3 is a cytokine, hormone; regulates neutrophil granulocyte proliferation and maturation.	Glycosylation prevents aggregation, improves proteolytic stability. Native glycosite: T133	Treatment of chemotherapy-induced neutropenia.	27
Human interferon-β-1a (hINF-β-1a) INF-β-1a (Avonex®, Rebif®, CinnoVex®)	hINF-β-1a is a cytokine with immunomodulating, antiviral, and cytostatic activities.	Sialylation affects pharmacokinetics. Glycosite: N80	Treatment of multiple sclerosis.	28
Glycosaminoglycans:				
Hyaluronic acid (HA): Hyaluronan, sodium hyaluronate (Hyalgan®, Monovisc®, Sinovial®).	Hyaluronic acids provide lubrication, retains water, influences regulation of proliferation, cellular migration, and inflammation, etc.	The high molecular weight of HA polysaccharide influences the residence time in the joint and rheological properties.	Treatment of osteoarthritis; moisturizer (eye drops, skin humectant); dermal filler in cosmetic surgery, etc.	29
Antithrombin inhibitors: Heparin:	Antithrombin (AT) inactivates several enzymes of the coagulation system. Thrombin (factor IIa) is a serine protease, which	Heparin inhibits coagulation via binding to AT, thus leading to inactivation of factor Xa. The global anticoagulant activity of HP is associated with the formation of the HP-AT-thrombin complex. AT-binding sequence:  Thrombin binding sequence: 	Treatment of arterial and venous thrombosis, and related disorders.	30

	converts fibrinogen into fibrin in blood coagulation.			
Unfractionated heparin (UFH) *Mw_{avg} ~17,000*	AT, thrombin.	UFH is a heterogeneous mixture of HP oligosaccharides, which contain both the AT and thrombin binding sites. UFH is administrated intravenously; suitable for the treatment of renal-impaired patients. Although UFH can cause heparin-induced thrombocytopenia (HIT) and requires monitoring of bleeding parameters, the UFH could be effectively inactivated by protamine sulfate antidote. Hence, UFH could be used during surgeries with extracorporeal circulation.	Additional uses of UFH include hemodialysis, organ transplantation.	
Low molecular weight heparin (Mw_{avg} ~8,000): *LMWH: Bemiparin®, Enoxaparin®, Tinzaparin®, etc.*	AT	A heterogeneous mixture of HP oligosaccharides with variable compositions depending on the manufacturing process. Advantages LMWH includes high potency, selectivity, improved bioavailability (i.e., subcutaneous administration), prolonged half-life, reduced risk of osteoporosis and hemorrhagic conditions during prolonged treatments. LMWH could be used in renal-impaired patients only at reduced doses; inefficient deactivation by protamine antidote; does not completely eliminate the risk of HIT.	For the outpatient treatment of arterial and venous thrombosis, and related disorders.	
Ultra-low molecular weight heparin (Mw_{avg} <2,000): ULMWH: Fondaparinux (Arixtra®)		ULMWH are synthetic molecules, designed to bind AT site. ULMWH has similar advantages as LMWH, however, ULMWH cannot be inactivated by protamine antidote; cannot be used in patients with kidney failure; eliminates the risk of HIT. Fondaparinux: 		
Antimicrobial vaccines: Antimicrobial vaccines are based on immunogenic bacterial capsular oligosaccharides, which are used to prime the immune system against the associated bacterial infections.				

Capsular oligosaccharides from Streptococcus pneumonia as vaccines: Pneumovax®23	Pneumovax®23 is a mixture of 23 purified capsular oligosaccharides from *Streptococcus pneumonia*. New vaccines (semisynthetic and fully synthetic) based on the conjugation to the immunogenic carrier protein are being developed. Examples of conjugate vaccines include Prevnar®13 (capsular oligosaccharides of 13 serotypes conjugated to CRM197) and Synflorix® (capsular oligosaccharides of 10 serotypes and multiple carrier proteins).	Vaccination of high-risk populations for the prevention of pneumonia and related infections.	31
Capsular oligosaccharides from Haemophilus influenza (Hib) as vaccines: QuimiHib (synthetic);	The QuimiHib vaccine is composed of the synthetic capsular oligosaccharide from Hib conjugated to tetanus toxoid (TT). Vaccination with sPRP-TT elicited titers of anti-PRP IgG sufficient for the long-lived protection against Hib.  Vaccines based on the purified or synthetic polyribosylribitol phosphate polysaccharides conjugated to CRM 197, TT, or the meningococcal membrane protein: Monovalent vaccines: PedvaxHIB®, ActHIB®, Hiberix®. Vaccines against multiple infectious agents: Infanrix-Hib®, Infarix hexa®, Pentacel®, Hexacima®, INFANRIX-IPV/Hib®.	Vaccination of children (under the age of 5) for the prevention of pneumonia and meningitis.	32
Neisseria meningitidis vaccines: polysaccharides from serogroups A, C, and W of meningococcal meningitis.	The quadrivalent vaccines contain polysaccharides from serogroups A, C, and W (Mencevax®, Menomune®). This class of vaccines generates a short-lived, T-cell independent immune response. Conjugate vaccines (polysaccharides linked to the immunogenic protein) elicit a longer-lasting immune response. Examples of conjugate vaccines include: Meningtec® and Menjugate® (serogroup C polysaccharides conjugated to CRM197); NeisVac-C® (serogroup C polysaccharides conjugated to TT); MenAfriVac (serogroup A polysaccharides conjugated to TT);	Vaccination to prevent meningococcal meningitis associated with corresponding serotypes.	33

	Menactra® (serogroups A, C, Y, W-135 conjugates to the diphtheria toxoid); Menveo® (serogroups A, C, Y, W-135 conjugates to CRM197); Nimenrix® (serogroups A, C, Y, W-135 conjugates to the tetanus toxoid).			
Aminoglycosides, macrolides, polyketides:				
Aminoglycosides: Kasugamycin, Neomycin, Streptomycin, tobramycin, etc. *Macrolides:* Erythromycin, Azithromycin, Telithromycin, etc.	Aminoglycosides and macrolides interact with ribosomal RNA (rRNA) and inhibit the translational process	Majority of aminoglycosides bind to either the A-site of the 16S subunit of bacterial ribosome or h69 of the 23S. Macrolides target the P-site of 50S subunit of the bacterial ribosome.	Anti-infective agents; treatment of infections caused by Gram-negative bacteria.	34
Polyketides: Doxorubicin, daunorubicin, idarubicin, etc.	Polyketides bind to nucleic acids, presumably via intercalation.		Antibacterial and anticancer agent.	35

[a] For many glycoproteins, the role of glycosylation was estimated using glycoform-enriched samples. [b] Many glycoproteins and GAG pharmaceuticals contain mixtures of glycoforms. Glycosites are given for the native states. Glycosylation may vary from the native state depending on the expression host and the manufacturing process. [c] Selected references to the synthetic studies towards homogeneous samples, or samples with a controlled degree of polymerization (i.e., PSA-modified proteins and HA polymers).

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