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Review Article

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A Review on Glycosylation: An Effective Synthetic Strategy for Glucosides with Therapeutic Potential

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Abstract This review highlights various methods for the synthesis of glycoconjugates and recent progress in the development of glycosylated derivative therapeutics. Review lies in the discussion of recent mechanistic theories and supporting experimental evidences on chemical glycosylation on compounds. The impact of glycosylation is noteworthy in overcoming the existing barriers that restrict oral and brain delivery of drugs.

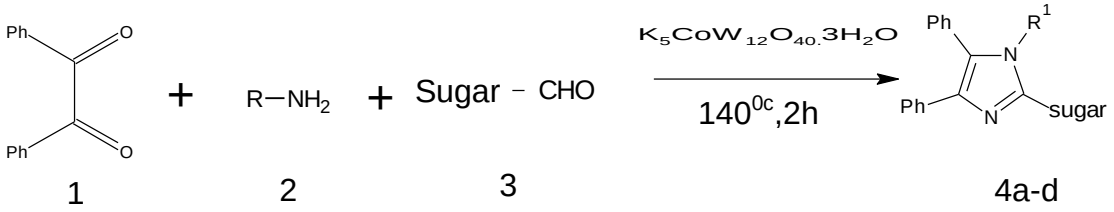
Keywords Glycosylation, Glycoconjugates, Antibacterial activity, Antiviral activity, Antimalarial activity, Antitumor activity

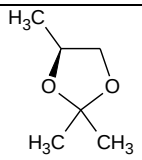
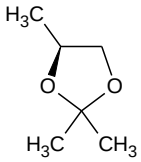
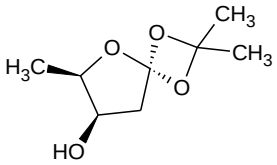
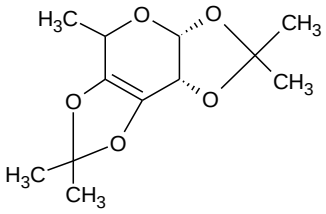
Introduction

Glycosylation is an enzymatic process in which sugars are added to other molecules to produce a glycosylated product. A chemical glycosylation reaction is a coupling reaction involves the coupling of a glycosyl donor to a glycosyl acceptor forming a glucoside [1]. Carbohydrate can be linked to an aromatic aglycone through O-, N- and C- aryl glycosides respectively [2]. Glycosylation may affect solubility, stability or molecular recognition associated with the biological target. This review elaborates the impact of glycosylation as an effective strategy for drug delivery and its application in the development of therapeutics [3]. The formation of a glycosydic linkage allows for the synthesis of complex glucosides which may plays important roles in biological processes and pathogenesis and therefore allows for further studies with respect to their biological importance [4].

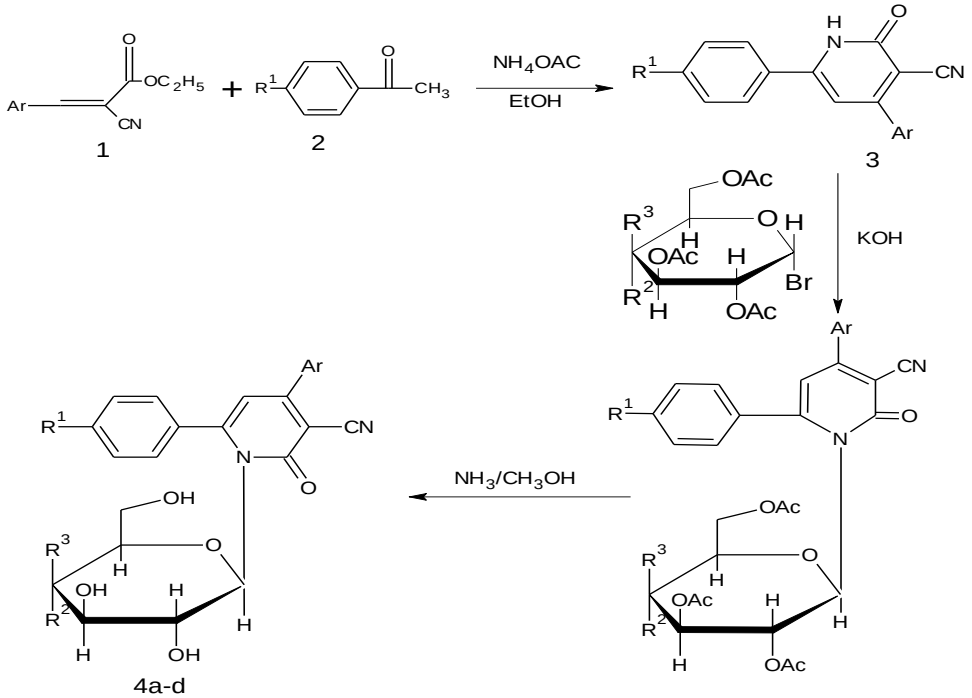
Literature Review

Lingaiah Nagarapu *et al* synthesized novel C-linked imidazole derivative in good to excellent yields and characterized by analytical and spectral analysis. They Synthesized tetra substituted novel imidazolyl sugars (4a-d) using benzyl, various sugar aldehydes, amines, ammonium acetate and $K_5CoW_{12}O_{40}.3H_2O$. All the derivatives were screened for antibacterial activity. All the compounds 4a-d showed activity against Gram-negative and Gram-positive bacteria [5].



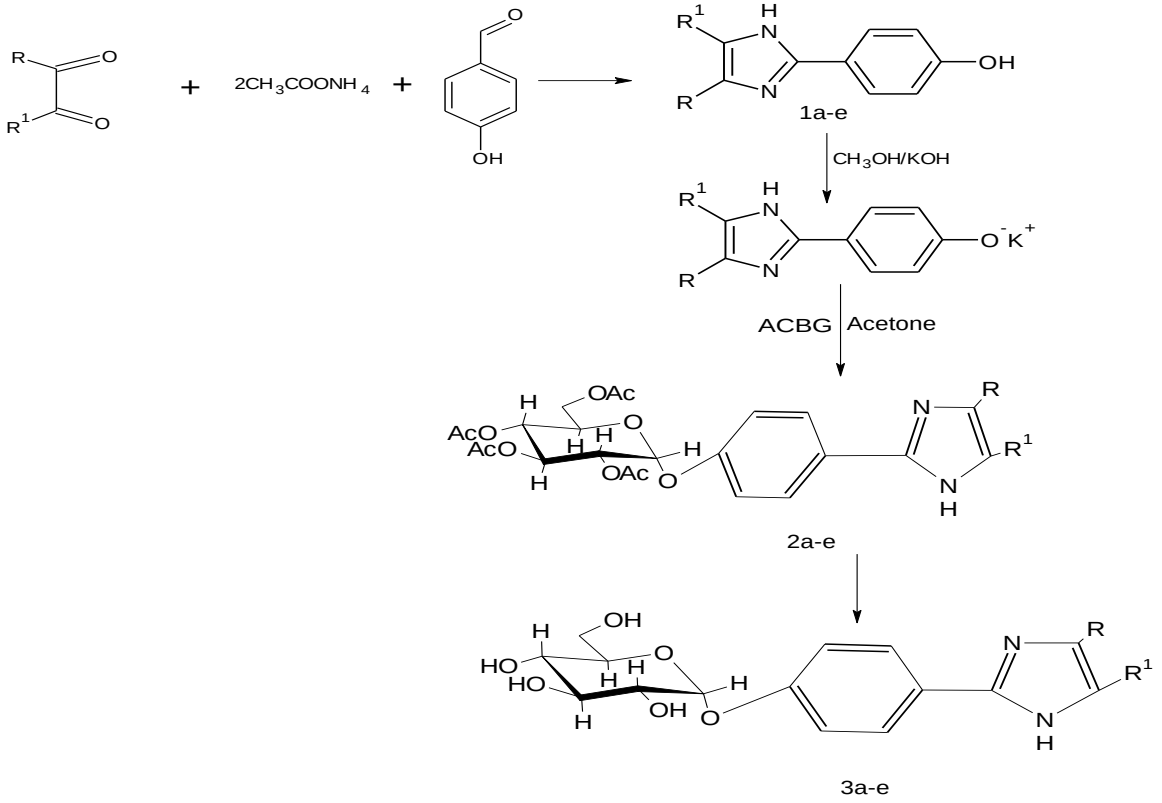
Entry	R-NH_2	Sugar
a	4-F-phenyl	
b	4-Methyl-phenyl	
c	Benzyl	
d	4-Methyl-Phenyl	

E.S. Ibrahim *et al* synthesized a series of 3-cyanopyridine glycosides. α,β-unsaturated nitriles (1) with acetophenones (2) in boiling ethanol containing ammonium acetate forms an intermediate (3) which on reaction with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide in presence of aqueous potassium hydroxide to give corresponding N-glucosides (4). The synthesized derivatives were evaluated for their inhibitory activity against Human immunodeficiency virus replication in MT-4 cells. Among them 6-(p-methyl phenyl) and 6-(p-amino phenyl) were the most selective inhibitors of HIV replication [6].



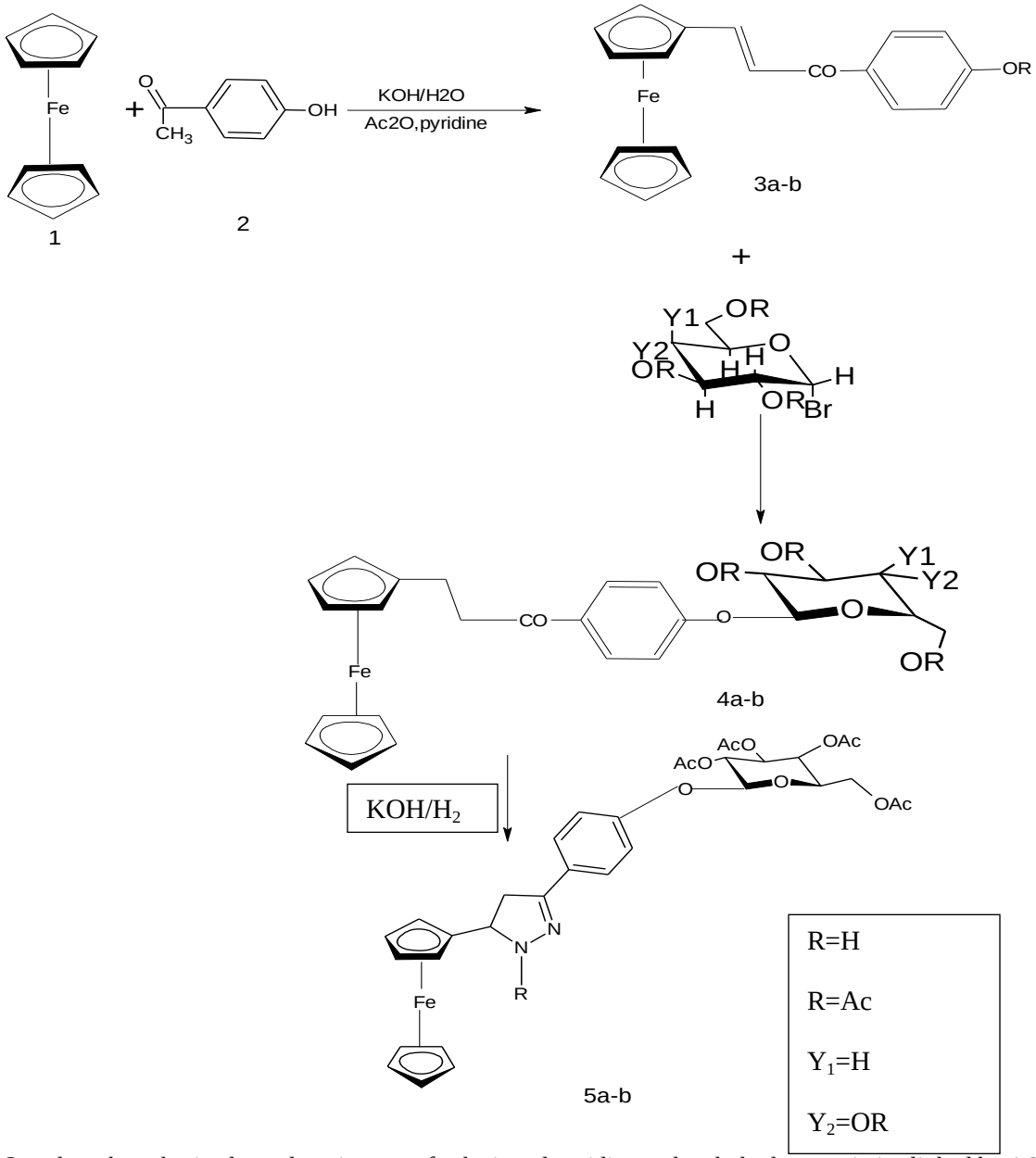
Compounds	Ar	R^1	R^2	R^3
4a	Phenyl	H	H	OH
4b	Phenyl	CH_3	H	OH
4c	Phenyl	OCH_3	H	OH
4d	phenyl	NH_2	H	OH

V.S. Taile *et al* synthesized a series of 2-(4-hydroxyphenyl)-4,5-disubstituted imidazoles (1a-e) from α-diketones, ammonium acetate and parahydroxybenzaldehyde. These derivatives were glucosylated by using α-acetobromoglucose and on catalytic deacetylation to form 2-(4-o-β-D-glucosidoxyphenyl)-4,5-disubstitutedimidazoles (3a-e). Compounds were characterized by elemental analysis and by instrumental technique. These compounds were investigated for antimicrobial and antifungal activity [7].

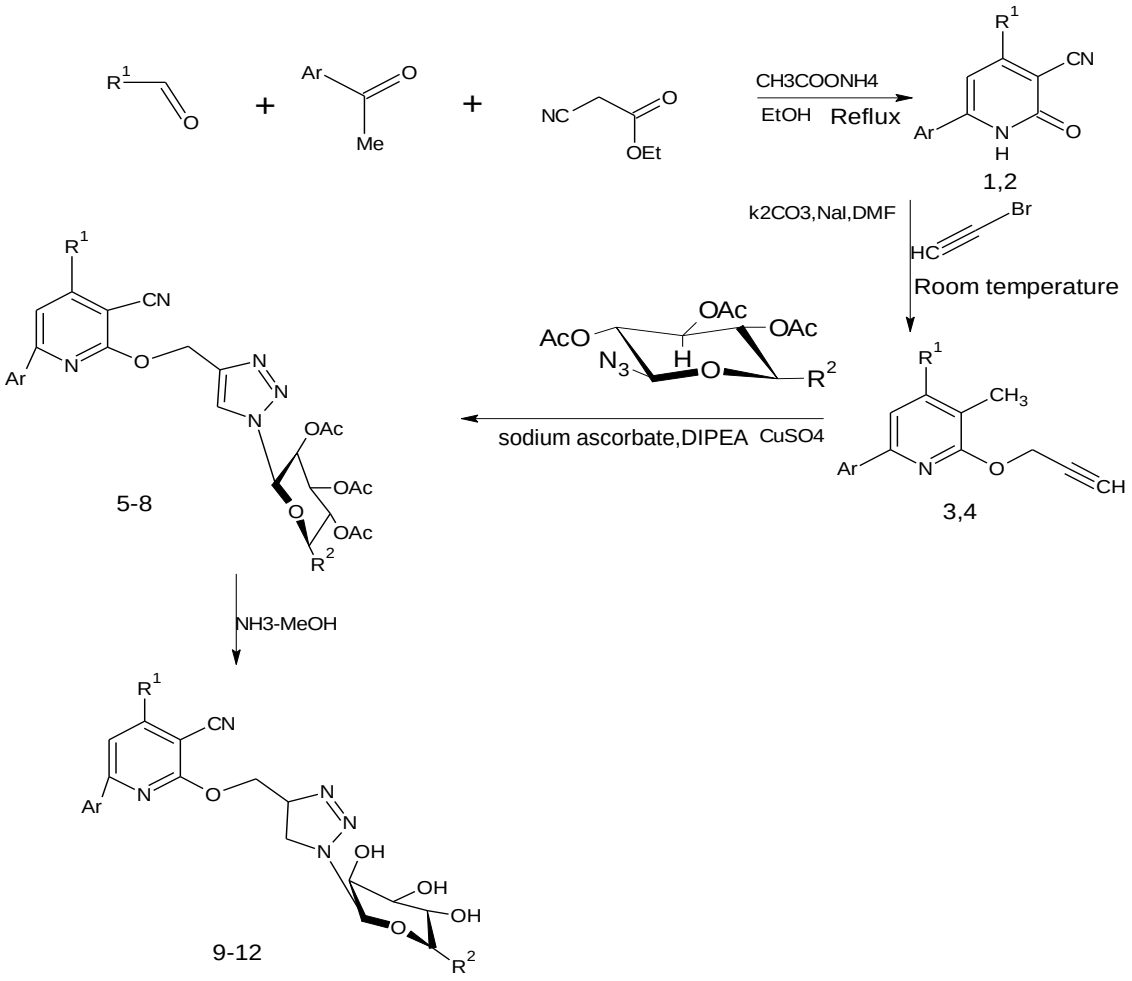


Derivatives	R	R^1
a	C_6H_5	C_6H_5
b	H	C_6H_5
c	H	H
d	CH_3	CH_3
e	4-ClC_6H_5	4-ClC_6H_5

Virag Zsoldos-Mady *et al* synthesized derivatives of some new glycosides of 3-ferrocenyl-1-(4'-hydroxyphenyl)-prop-2-en-1-one by transforming into corresponding pyrazoline and pyrazole derivatives. The structures of compound were proved by IR and NMR spectroscopy. The in vitro antitumor activity was investigated against human leukemia (HL-60) cells by the MTT method. Among these new compounds, some chalcone derivatives 4a, 4b showed attractive in vitro antitumour effects on human leukemia cells [8].



W.A. EI-Sayed *et al* synthesized novel conjugates of substituted pyridine and carbohydrate moieties linked by 1,2,3-triazoles were synthesized. Attachment of carbohydrate molecules to the substituted pyridine core was performed by Cu-catalyzed cycloaddition of propargyl sugars with azidoethoxypyridine derivative with substituted oxypyridines which afforded the corresponding 1,2,3-triazoles in high yields. Synthesized derivative were studied for antiviral activity against H_5N_1 influenza virus and triazolyl glycoside demonstrated high activity in addition to its low toxicity. The effect of attachment of glycosyltriazole derivatives to pyridinyl ring was studied in SAR correlation, which has been found to enhance antiviral activity [9].



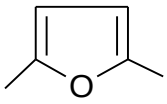
1,3 - R'=thiophene-2-yl
2,4 - R'=5-methylfuran-2-yl

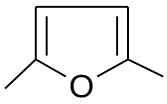
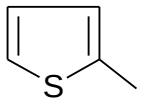
Ar= CH_3 R^1= CH_3 R^2= CH_2OAc

(5);R^1= ;R^2=H (6);R^1= R^2= CH_2OAc

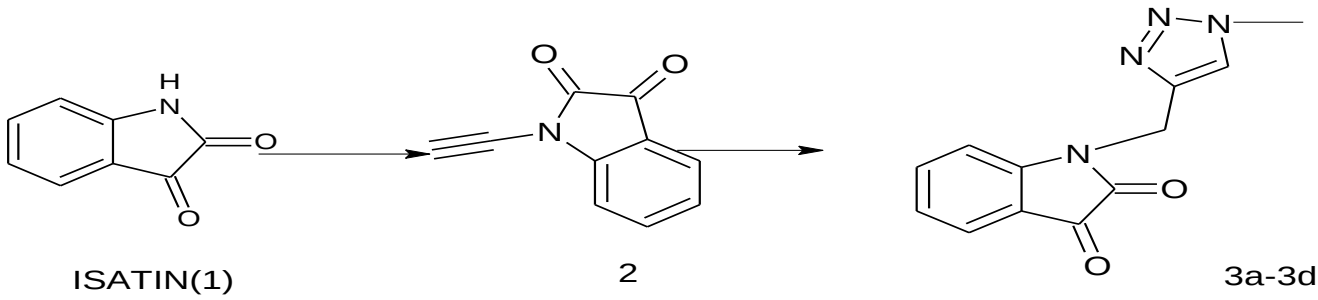
(7);R^1= R^2= H (8);R^1= ;R^2= CH_2OH

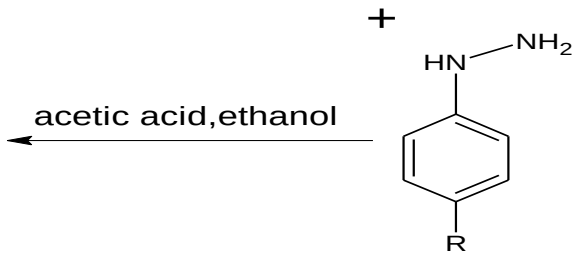
(9);R^1= ;R^2= H

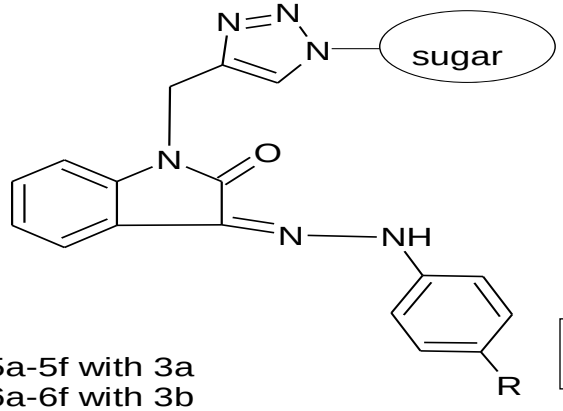
(10);R^1=  R^2= CH_2OH

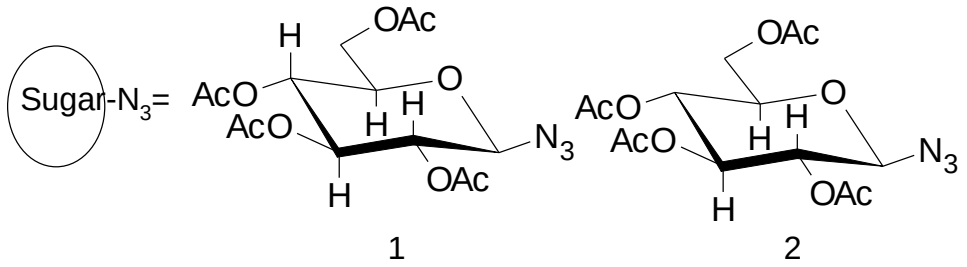
(11);R^1=  R^2= H (12);R^1=  ;R^2= H

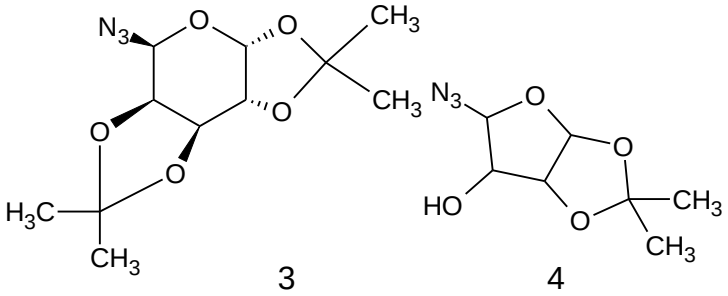
Ravi Kumar Thakur *et al*, synthesized glycohybrids of phenylhydrazono-indolines employing glycosylated 1,2,3-triazolyl-methyl-indoline-2,3-diones and different phenylhydrazines via acid catalyzed reaction. All the compounds were screened for their antiplasmodial activity in vitro. Compounds 6c, 7c and 7b showed significant activity with the IC_{50} values 1.27,1.6 and 1.96µM, respectively against CQ sensitive pf3D7 strain [10].











Conclusion

Design of therapeutics with optimized in vivo efficacy can be achieved through the simultaneous optimization of drug molecular stability, pharmacokinetics, pharmacodynamics and targeting by engineered glycosylation. The incorporation of carbohydrate moieties into the compounds can change their physiochemical properties, leading to increased membrane permeability across biological membranes and improved proteolytic stability against digestive enzymes. These analogues resulted in improvement of biological selectivity along with improvement in solubility. Progress in the area of chemical glycosylation has significantly improved the ability to synthesize various glycosidic linkages with impressive yields and stereo selectivity.

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