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Review Article

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A Review on Glycosylation and Its Implications of Biological Interest

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Abstract Glycosylation is the process of addition of sugar moiety with the target molecule. The Glycosylated compounds have greater medicinal values. Due to their natural abundance and low toxicity, they are used to develop new therapeutic agents. These agents are subjected to many research studies because of their broad spectrum biological activity like Antiviral, Antitubercular and antimicrobial. The glycosylation have the benefits of enhanced bioavailability, absorption, drug targeting and low toxicity. This review focuses on the diverse implications and applications of biological interest of the glycosylation.

Keywords Glycosylation, N-Glycoside, Antibacterial, Antiviral and Antitubercular Activity

Introduction

The covalent attachment of carbohydrate to the target macromolecule is known as glycosylation. It involves the coupling of Glycosyl donor to an acceptor. The four major functions of glycans are the structure and modulatory role, intrinsic and extrinsic recognition and molecular mimicry of host glycans [1]. The Glycosyl linkage gives two stereo outcomes i.e., ∝ or β and cis or trans. Among these, the ∝& cis are more difficult to synthesize. A stereogenic centre is formed by the linkage [2].

The major types of glycosylation are the N-, O-, and C- glycosylation. The N-glycosylation is the common and occurs co-translationaly. The O-glycosylation gives ∝ or β and 1,2-cis or 1,2-trans form. The C-glycosylation is very rare approach; the C-mannosylation is commonly seen. The Glycans which are β-linked most commonly seen while the ∝-linked synthesis of Glycans faces two main challenges i.e., the electron deficient Sp & Sp^2 hybridized N atoms show the alpha orientation at C_1 due to anomeric effect and the generation likely to proceed through oxocarbonium intermediate [1].

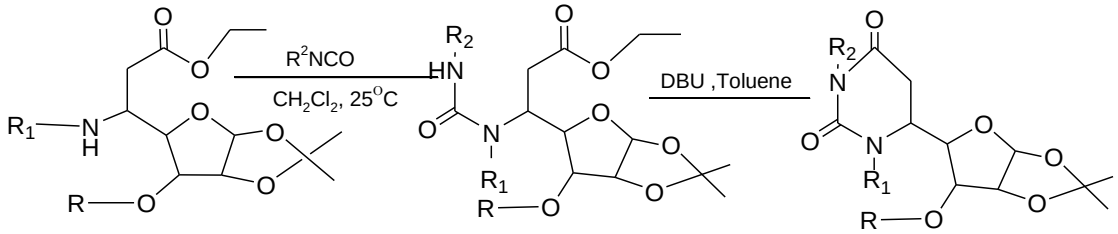
The Glycosyl proteins and amides are most widely used synthetic strategy for the drug design. Glycosyl protein occurs either by co-translationaly or post-translationaly. It involves the attachment of sugar moiety to a protein. It is necessary for the function, cell physiology and is involved in the conformation of protein and maintenance of activity. In Glycosyl amides, the therapeutic activity is enhanced by the condensation of amides with sugar moiety [3].

The Glycosylation of new chemical entities have significant role in enhancing and maintenance of their physiologically relevant therapeutic activity.

Review of Literature

Neetu Tewari *et al* (2003) [4] conducted a study on Glycosyl urea as ∝-glucosidase inhibitor and its effect on mycobacterium. In therapy of diabetes, inhibition of ∝-glucosidase is beneficial. They synthesized Glycosyl amino

ester, in rigid and flexible conformation, by the conjugate addition of sugar derived olefinic ester to different primary amines and simple addition of different isocyanate gave Glycosyl ureides. They on further cyclative amidation with DBU in refluxing toluene gave Glycosyl dihydropyrimidinone (scheme 1). The compounds with high percent of inhibition and their substitution is listed on Table 1. The N^3 phenyl with chloro or fluoro substitution resulted in better enzyme inhibition. The good enzyme inhibition was the result of combined effect of N^1, N^3& 3-O substitution of sugar.



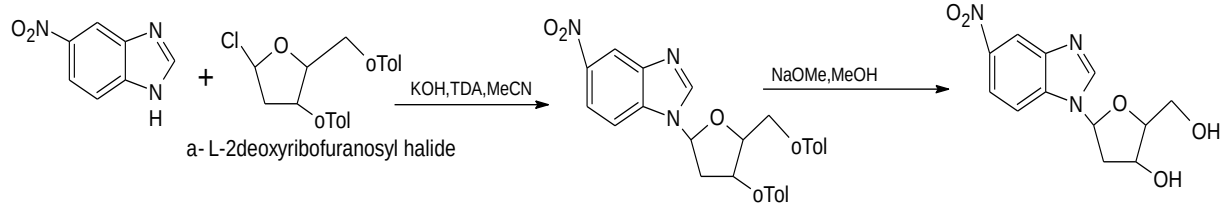
Scheme 1: Synthesis of glycosyl dihydropyrimidinone

Table 1: ∝-glucosidase inhibitor activity of flexible and rigid analogue of Glycosyl ureas [4]

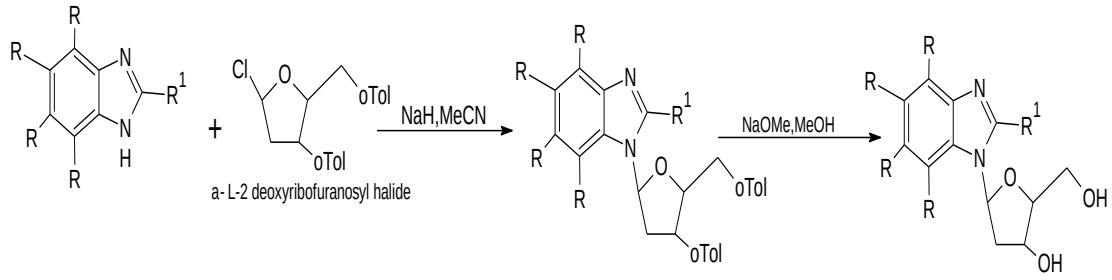
Compounds	R	R_1	R_2	% of Inhibition
1	CH_3	H	4-Cl(Phenyl)	47.0
2	CH_3	Cyclopropyl	4-Cl(phenyl)	4.3
3	CH_3	Cyclopropyl	Benzyl	81.7
4	CH_3	n-Butyl	4-F(Phenyl)	85.6
5	CH_3	Heptyl	Benzyl	13.7
6	CH_3	Dodecyl	4-Cl(phenyl)	93.5
7	CH_3	Hexadecyl	Phenyl	34.8
8	CH_3	Hexadecyl	4-Cl(phenyl)	31.5
9	CH_3	Oleyl	Benzyl	16.4
10	CH_2Ph	H	4-Cl(phenyl)	97.2
11	CH_2Ph	Cyclopropyl	3-Acetyl(phenyl)	74.7
12	CH_2PH	Cyclopropyl	4-Cl(phenyl)	15.3
13	CH_2Ph	Cyclopropyl	Benzyl	40.5
14	CH_2Ph	n-Butyl	4-F(phenyl)	49.3
15	CH_2Ph	Dodecyl	3-Acetyl(phenyl)	11.9
16	CH_2Ph	Dodecyl	4-F(phenyl)	20.9
17	CH2Ph	Dodecyl	4-Cl(phenyl)	94.3
18	CH_2Ph	Dodecyl	Benzyl	10.8
19	CH_2Ph	Oleyl	Benzyl	12.3
20	CH_2Ph	Cyclopropyl	Benzyl	61.8

Simone Budow *et al* (2009) [5] conducted a study on the antiviral activity of substituted benzimidazole β-L &β-D-2 deoxy ribonucleoside. They synthesized substituted benzimidazole and Glycosylated them. They are cytotoxic against the host cell lines. The nitro benzimidazole was Glycosylated with ∝-L-2-deoxyribofuranosyl halide (scheme 2), brominated benzimidazole with halogenase (scheme 3) and nucleobase with fluoro sugar (scheme 4).

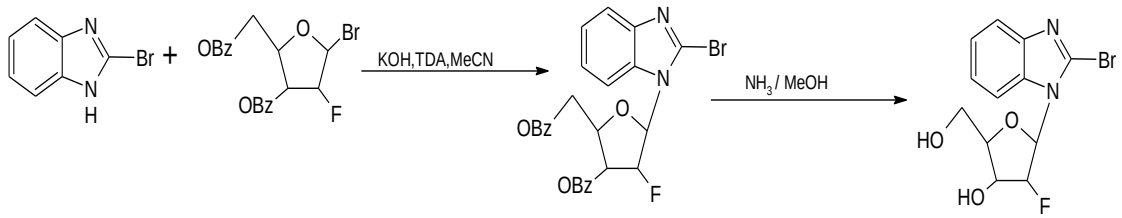
Among them, all derivatives synthesized,the 4,5,6,7-tetra brominated benzimidazole β-L-2 deoxyribonucleoside shows better antiviral activity. The nucleoside enter the cell effortlessly and release the active benzimidazole derivative.



Scheme 2: Nitro benzimidazole Glycosylated with ∝-L-2-deoxyribofuranosyl halide

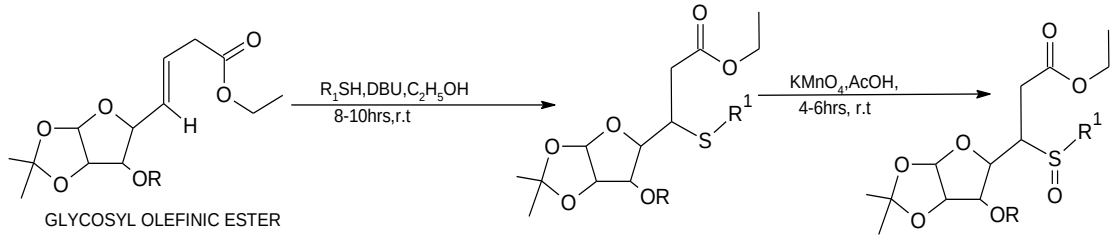


Scheme 3: Brominated benzimidazole with halogenase



Scheme 4: Nucleobase with fluoro sugar

R. P. Tripathi *et al* (2007) [6] conducted a study on antitubercular activity of S-glycosyl mercaptans. By 1,4-conjugate addition of sulphur nucleophile to Glycosyl olefinic ester, a series of s-glycosyl alkyl thiols were synthesized. Among them, some selected compounds were oxidized with $KMnO_4$ giving sulphones (Scheme 5). Two among the entire derivative, were active marginally against the virulent strain of *M. Tuberculosis* (Table 2). The significant antitubercular efficacy activity was shown by the compounds with carbethoxy group and sugar moieties having 3-O methyl substituent which is not bulky in the sugar ring.

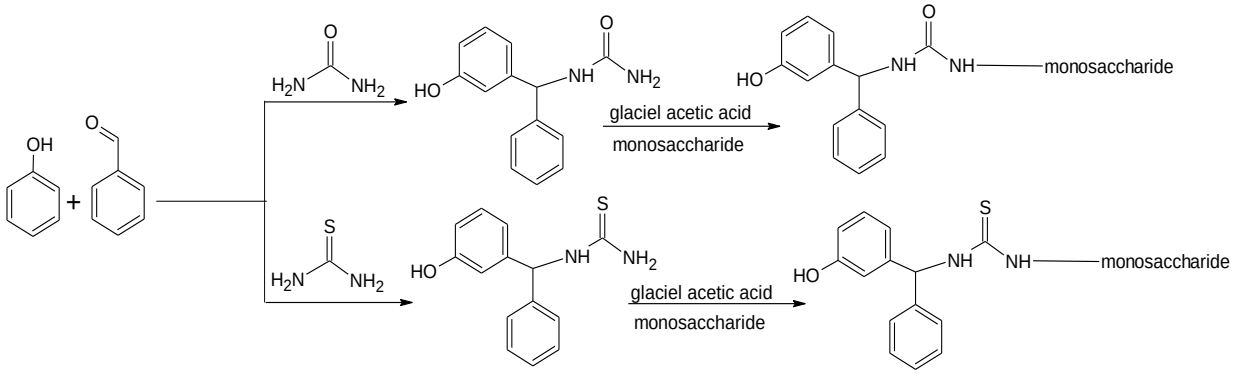


Scheme 5: Synthesis of sulphones

Table 2: Synthesis of Glycosylated mercaptoesters & its corresponding sulphanones & their antitubercular activities [6]

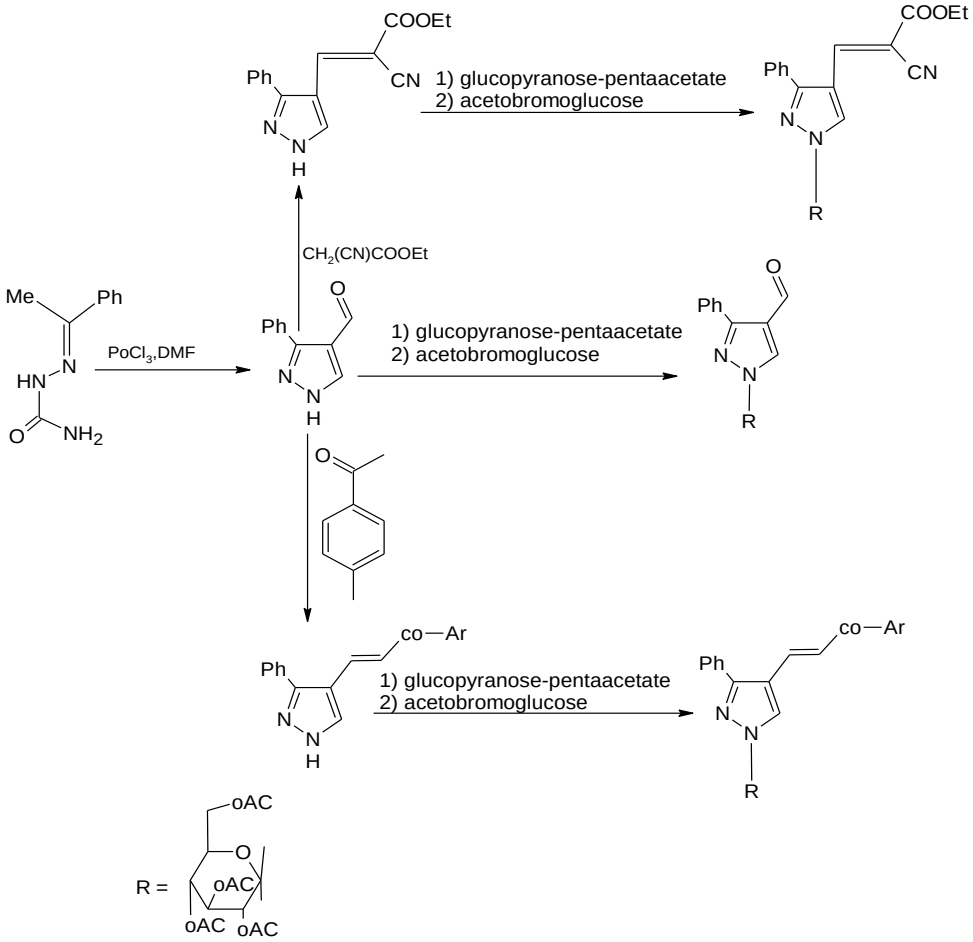
Compound	**R**	**R_1**	**Yield (%)**	**MIC (µg/ml)** ***M. Tuberculosis*** **$H_{37}Ra$**
1	CH_3	SCH_2CH_2	92	12.5
2	CH_3	SCH_2CH_2	95	25
3	CH_3	C_6H_5	90	50
4	CH_3	4-Cl-$C_6H_5CH_2$	90	>50
5	CH_3	$HOCH_2CH_2$	90	50
6	$CH_2C_6H_5$	$HOCH_2CH(OH)CH_2$	90	>25
7	$CH_2C_6H_5$	C_6H_5	90	>100
8	$CH_2C_6H_5$	4-Cl-$C_6H_4CH_2$	90	>100
9	$CH_2C_6H_5$	$HOCH_2CH_2$	90	>25
10	$CH_2C_6H_5$	$HOCH_2CH(OH)CH_2$	90	>50
11	$CH_2C_6H_5$	SCH_2CH_2	90	>25

Amira A Ghoneim *et al* (2017) [7]**:** They synthesized new heterocyclic compounds from thiourea and urea linked with some hexoses. The multicomponent reaction of phenol, benzaldehyde and urea or thiourea gave a series of urea and thiourea derivatives. The amide derivatives formed was condensed with different monosaccharide to give N-glucoside compound (Scheme 6). It was seen that the linkage with monosaccharides increased the antimicrobial activity of the derivatives.



Scheme 6: Glycosylation of urea and thiourea derivatives

Atef. M. Amer *et al* (2014) [8] synthesized new N-glycoside from phenyl pyrazole derivatives and evaluated the antimicrobial activity. The initial reactions of acetophenone semicarbazone with phosphorous oxychloride to give 3-phenyl-1H-pyrazole-4-carbaldehyde 2 and with glucose gave N-Glycoside (Scheme 7). The synthesized compounds showed strong activity against the gram negative and positive bacteria and moderate activity against fungus (*Candida albicans*).



Scheme 7: Synthesis of N-Glycoside

V. K. Tiwari *et al* (2014) [9] conducted a study on the antitubercular activity of bis-glycosylated diamino alcohols by MABA assay and agar dilution method (Figure 1). The bis-xylofuranosylated amino alcohol were synthesized from the respective xylofuranosylated amino esters, followed by reduction with lithium aluminium hydride. They used 3-O-benzyl glycofuranosylated, galactopyranosylated olefinic ester and Diamino alkanes. Many of the compounds displayed good anti tubercular activity and one among them displayed good activity against clinical isolates of resistant strain (Table.3).

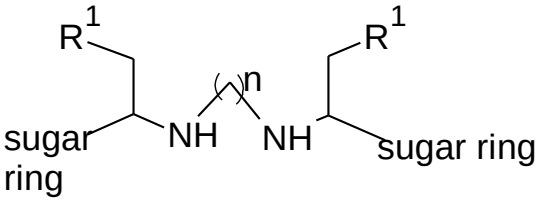


Figure 1: bis-glycosylated diamino alcohols

Table 3: Antitubercular activity of Glycosylated amino ester and corresponding alcohols

n	R_1	Sugar Ring	MABA MIC (µg/ml) against *M. Tuberculosis* $H_{37}Ra$	Agar dilution method MIC (µg/ml) against *M. Tuberculosis* $H_{37}Rv$
8	COOEt	Furanose	25	6.25
8	COOEt	Pyranose	>25	12.5
12	CH_2OH	Furanose	12.5	6.25
10	CH_2OH	Pyranose	>25	6.25

Conclusion

The review of literature points to the fact that the glycosylation plays a vital role in the biological process. The attachment of sugar moiety with the chemical entities increases their therapeutic values. From the above literatures it is evident that the Glycosylated compounds show good pharmacokinetic properties. They enter the cells more efficiently and also function as a release system for delivering the active drug. The glycosylation is an effective synthetic strategy to improve the bioavailability of compound and show beneficial effect on activity.

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