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DEVELOPMENT OF NOVEL CARBOHYDRATE BASED COMPOUNDS FOR BETTER ANTIPYRETIC ACTIVITY

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Keywords:

N- glycosides, Carbohydrate, Antipyretic activity, Glycoconjugates

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ABSTRACT: Carbohydrate-based therapeutics are extremely potent, and many carbohydrate-based drugs are in the stage of preclinical or clinical trials. There is a growing interest in developing carbohydrate analogues for novel drug discovery as most of the recently used carbohydrate drugs display significant pharmacological activities and low toxicity. Also, the search for an antipyretic drug is a never-ending challenge. This research aimed at the development and synthesis of a series of amide-linked sugars (PV1-PV20) by coupling brominated sugars with varying amino acids coupled with nicotinic acid (GP1-GP10). Characterization of the derivatives synthesized was done by Infrared and Nuclear Magnetic Resonance Spectroscopy. These congeners were tested to analyze their antipyretic potential, and eight analogs out of twenty showed significant antipyretic activity. Thus, the carbohydrate-based amide derivatives show important action in obstruction and therapy of fever. Further work on these lines may play an important role in maintaining good health at a low cost.

INTRODUCTION: Oligosaccharides, carbohydrates and glycoconjugates are demanding ingredients for being alive. They intervene many crucial biological systems by cell-based complex operations which can trigger and assist life to percept developments required for disease related to autoimmune system, inflammation, and organ exclusion. The diversity of carbohydrate structures reflects that functional diversity. Natural and synthetic derivatives of carbohydrates have a good amount of therapeutic potential using them to treat various disorders [1].

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Deep knowledge of biology of sugar chains and glycans is in demand nowadays for the effective approach for oligosaccharides and glycoconjugates [2, 3, 4]. Selective acylation of monosaccharide derivatives is of growing importance in the field of carbohydrate chemistry because of its usefulness for providing newer derivatives of biological importance. These derivatives may have further synthetic utility as versatile intermediates in the synthesis of a much important class of drugs. Carbohydrates not only involved in the storage of energy but also act as an important ingredient in the exoskeleton. Besides this action, it has vital action in cellular interactions, tumor metastasis, pathogen recognition, and signaling of fertilization. Other biological potentials of carbohydrates are antioxidants, antineoplastics, anticoagulants, anti-viral and anti-inflammatory [5].

Another class is carbopeptoids which is amide linked oligosaccharides or amide-linked sugars [6, 7]. In nature, carbohydrates establish an utmost lavish category of compounds. Carbohydrates have diversified structures and confer various properties in context with stereochemistry.

Recently, a paper described the easy and systematic preparation of new series of derivatives of carbohydrates with some modification and conjugation with berberine. The anti-diabetic and cytotoxicity measurements of all berberine derivatives were accomplished. Cytotoxicity of berberine was significantly reduced when modified with mannose. IC_{50} range of these congeners was around 1.5 more than the previous berberine. Other potential of these analogs was also seen as having increased antidiabetic effect with a broad range of doses, which can be further used as leads for drug development of new derivatives against diabetes [8].

In our study, a lipophilic molecule was taken as a lead compound. Various structural modifications were carried out in its general structure with a view to design more potent biologically active derivatives. We have tried to increase the biological activity of selected lipophilic molecule by attaching them with carbohydrates. Nicotinic acid amide is highly lipophilic in nature.

Hydrophilicity of this molecule is increased by attaching of the glycosidic moiety to it. This type of effect changes the properties that are related to pharmacokinetics (like distribution, excretion and drug concentration in body fluid) of the individual analogs. Change in hydrophilicity has a major effect on the transport of derivatives through the membranes. Solubility of the compounds in the constituents of the membrane is responsible for the entrance of them into cells [9, 10]. Although a number of derivatives have already been formed, there is still a large scope to modify its structure for enhancement of biological activity.

MATERIALS AND METHODS:

Materials:

Equipment Used: The equipment used in the study were Rota evaporator (M/S Equitron, India), Magnetic stirrer (M/S JSGW, India), Weighing balance (M/S WENSAR, India), U. V Chamber (M/S JSGW, India), Vaccum Oven (M/S MACRO Scientific works, India), Hot Air Oven (M/S Narang Scientific works, India), Deep Freezer (M/S REMI, India), Water bath (M/S JSGW, India).

Solvents and Reagents: Pre-coated TLC plates and glass plates with silica gel G were used for analytical thin-layer chromatography. Detection was done under UV lamps or by using different spray reagents. The silica gel G (160-120 mesh) utilized for thin-layer chromatography was purchased from M/S Nice chemicals, Cochin, India). Other reagents and solvents used in the study were procured from M/S Qualigens fine chemical, Mumbai, M/S Rankem, RFCL Limited, New Delhi, and M/S Nice chemicals, Cochin.

Methods:

Preparation of N-glycoside: This step consists of the following substeps: a) Acetylation of sugars b) Bromination of acetylated sugars c) Synthesis of amino acid ester d) Preparation of amide e) Synthesis of N-glycoside f) Deacetylation of N-glycoside.

Synthesis of Initial Nucleus: Sugar was refluxed with sodium acetate and acetic anhydride, forming acetylated sugar (PS1-PS2). This acetylated sugar was further subjected to bromination using a mixture of HBr and acetic anhydride. Brominated sugar derivatives (BS1-BS2) were confirmed through thin layer chromatography and spectral analysis [11, 12]. Then amino ethyl esters (AE1-AE5) were synthesized by amino acid in the presence of conc. H_2SO_4 and absolute ethanol, whereas amino methyl esters (AM1-AM5) were synthesized by amino acid in the presence of methanol and conc. H_2SO_4. These amino acid esters were coupled with nicotinic acid to formed amide (GP1-GP10) **Fig. 1**.

Synthesis of Final Compounds: The amide (GP1-GP10) was reacted with brominated sugar in equal amount in the presence of HOBT, resulting into N-glycosides (AV1-AV20). The last step in the synthetic route was the de-protection of acetylated sugar by sodium methoxide and methanol [13, 14]. The reaction was quenched with ion exchange resin IR-120H^+ to produce the title compound (PV1-PV20). All the products and intermediates were obtained in good yield except few ones. The resulting compounds were subjected to column chromatography or recrystallization for purification. Final compounds were confirmed through the TLC, IR, and NMR spectroscopy **Fig. 2**.

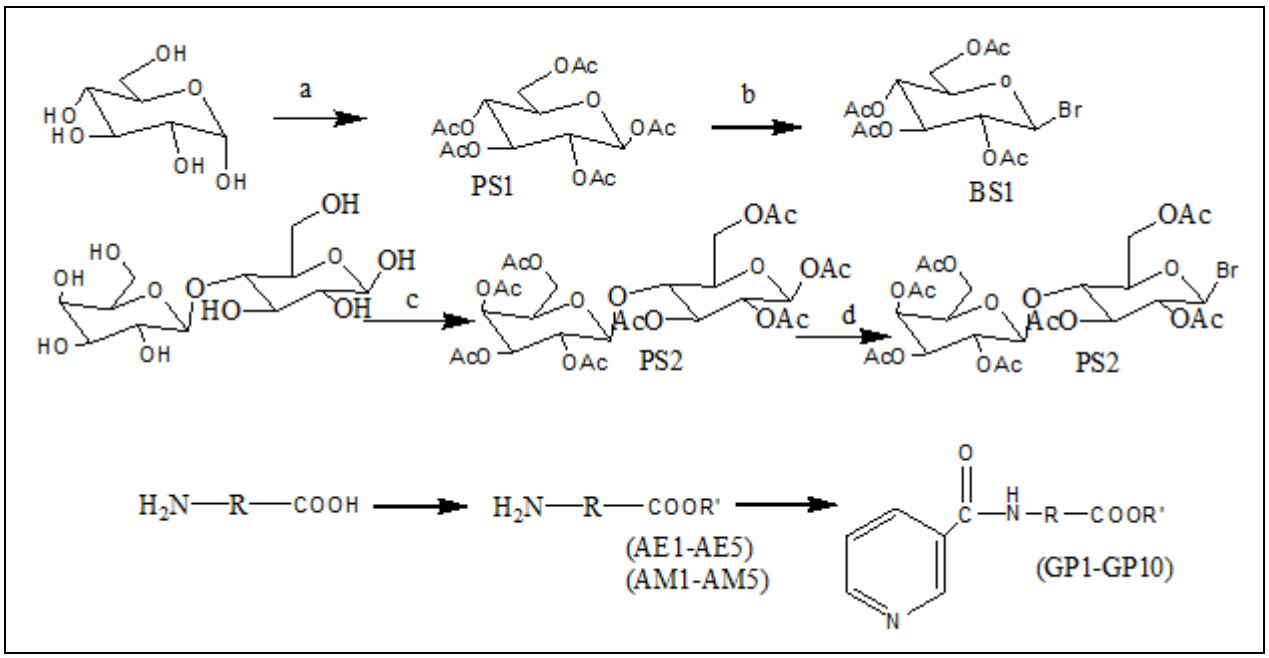


FIG. 1: SCHEME FOR SYNTHESIS OF INITIAL NUCLEUS

Reagents: (a) acetic anhydride, sodium acetate, methanol. (b) HBr-AcOH, acetic anhydride, DCM. (c) EtOH, conc. H_2SO_4, aq. ammonia solution. (d) HOBT, DCM, nicotinic acid, Et_3N.

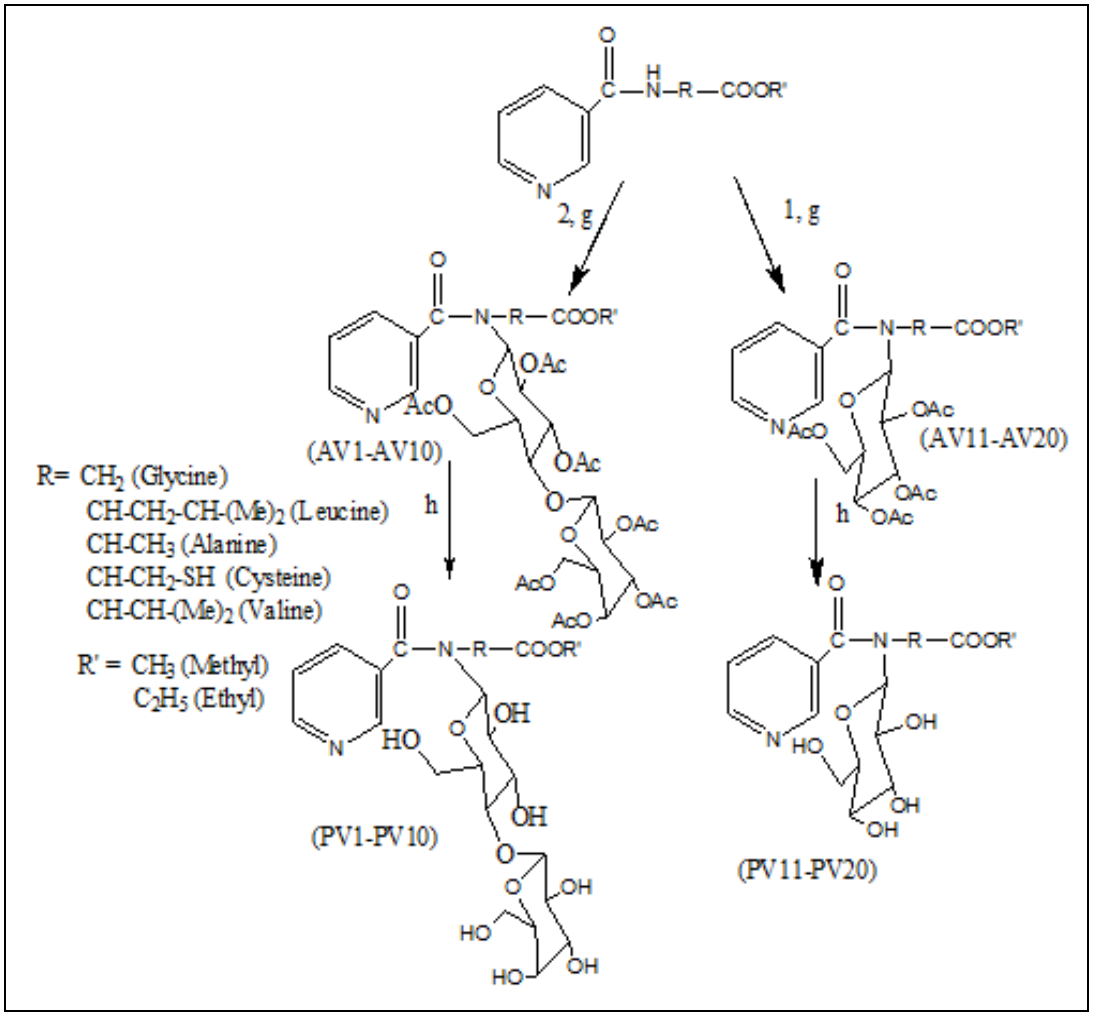


FIG. 2: SCHEME FOR SYNTHESIS OF FINAL COMPOUNDS

Reagents : (g) DMF, Et_3N, DCM (h) anhydrous MeOH, NaOMe, DCM, ion exchange resin (IR-120H^+).

Antipyretic Activity of Synthesized Compounds: In the present study wistar rats (150-200 g) of any sex was taken for the process of activity test. These rats were purchased and securely got hold of from DFSAH, CCS HAU, Hisar, India. For the procedure of the experiment, prior permission was taken from Institutional Animal Ethics Committee having No-LSCP/2018/874 dated 08-05-2018. All the animals were kept in close and healthy supervision, which is given in CPCSEA guidelines, Ministry of Forests & Environment, Govt. of India. Food and water were timely provided to the animals as per the diet mentioned in CPCSEA. Animals were given 12 h of light treatment and then 12 h of dark treatment and then were accommodated for five days in conditions required for the experiment.

The yeast-induced pyrexia model was used for evaluating the potential of synthesized compounds on fever. Experimentation was started by inducing pyrexia by giving 10mL/kg of 15 percent suspension of Brewer's yeast in 0.9% saline subcutaneously in the back underneath the backside of the neck. The area where the injection is to do is rub-down to escalate suspension under the skin.

After yeast was introduced in the body, food was instantly evacuated. After 18 h, temperature was noticed which was again done after 30 min. The animals received the test compound (200mg/kg) by oral administration [15]. In this study, paracetamol was taken as a standard drug. The protocol is:

Group 1- marked as control and given saline 1mL/100g body weight of animals.

Group 2- given paracetamol (150mg/kg) followed 18 hours later by administration of yeast (10ml/kg of 15% w/v).

Group 3- marked as test groups (PV1-PV20) and (GP1-GP10), which was seen for the effect of derivatives on yeast (10ml/kg of 15% w/v) induced pyrexia in the rat.

Rectal temperature was recorded again at 30 min, 60 min, 120 min, 180 min, and 240 min post-dosing. The rise in temperature was measured using a telethermometer [16].

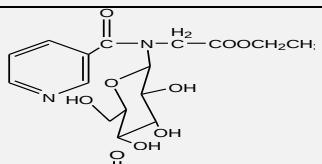
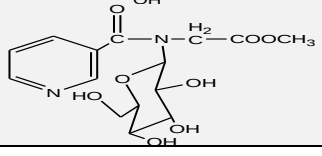
Analysis by Statistical Methods: Demonstration of values was done as mean ± SEM. Dunnett t-test was performed for all recorded values in analysis data, and statistical significance was $p < 0.05$ for tests.

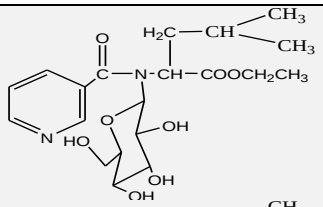
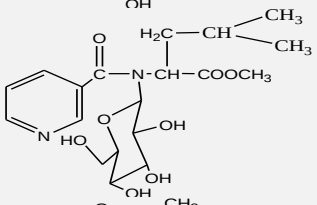
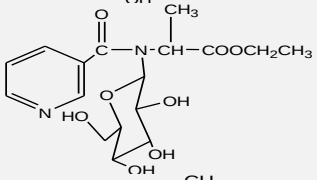
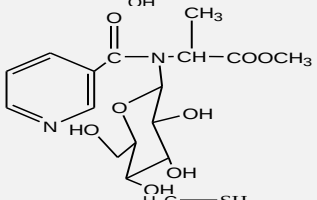
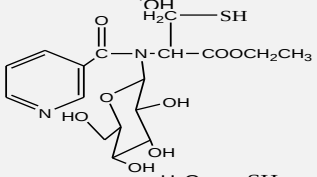
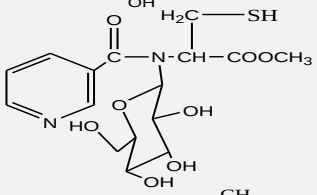
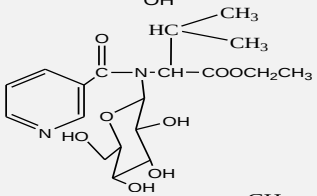
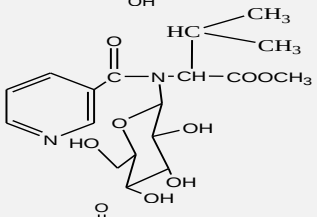
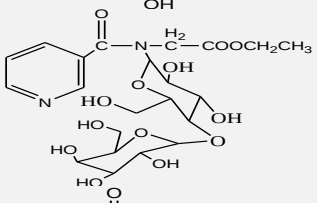
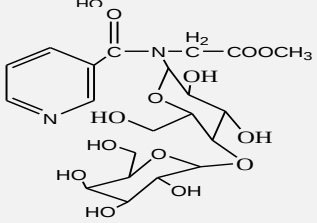
Effect on Yeast Induced Pyrexia in Rats: In this study, yeast significantly increased the temperature of rats. Pretreatment with thirty test compounds, twelve showed (GP1, GP2, GP9, GP10, PV1, PV2, PV9, PV10, PV11, PV12, PV19, PV20) significantly preventive effect on yeast induced pyrexia in rats.

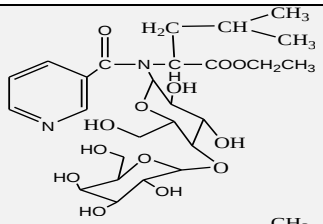
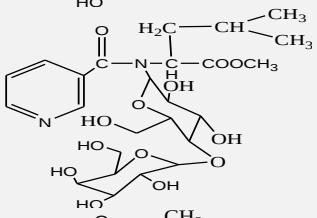
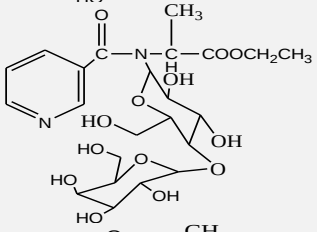
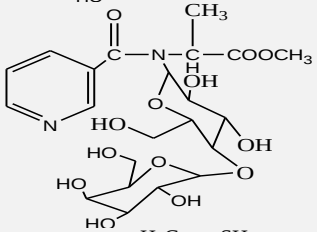
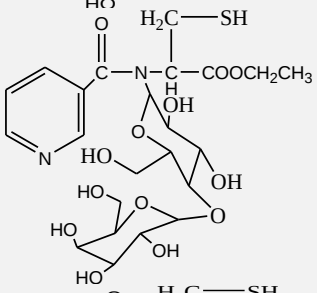
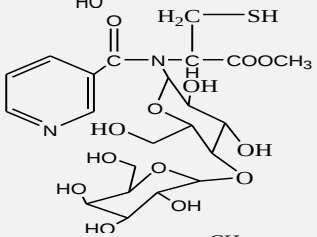
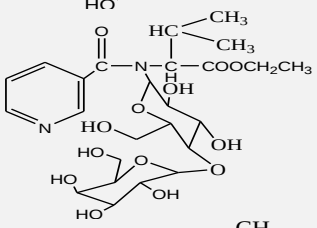
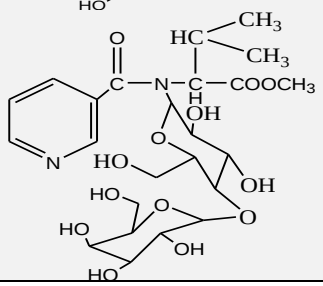
RESULTS AND DISCUSSION: All the products and intermediates were obtained in good yield except few ones. The resulting compounds were subjected to column chromatography for purification. Final compounds were confirmed through the TLC and spectral analysis. These compounds were assigned IUPAC names after analysis of IR and NMR spectroscopic data followed by their evaluation for pharmacological activity.

Chemistry: All melting points of synthesized compounds were measured on a Buchi melting point apparatus. Structure, IUPAC names, melting point range, yield, and molecular weight of the title compounds are shown in **Table 1**.

TABLE 1: STRUCTURE, IUPAC NAMES, MELTING POINT, YIELD AND MOLECULAR WEIGHT OF TITLE THE COMPOUNDS

Compound code	Structure	IUPAC Name	Melting point range	Yield	Molecular weight
PV1		Ethyl [(Pyridin-3-yl carbonyl)-β-D-gluco pyranosyl)amino]acetate	182-185°C	80%	370
PV2		Methyl [(Pyridin-3-yl carbonyl)-β-D-gluco pyranosyl)amino]acetate	175-178°C	56%	356

PV3		Ethyl 4-methyl-2-[(Pyridin-3-yl carbonyl)-β-D-glucopyranosyl) amino] pentanoate	195-198ºC	70%	426
PV4		Methyl -4-methyl-2-[(Pyridin-3-yl carbonyl)-β-D-glucopyranosyl) amino] pentanoate	187-191ºC	71%	412
PV5		Ethyl [(Pyridin-3-yl carbonyl)-β-D-gluco pyranosyl)amino] propanoate	184-187ºC	59%	384
PV6		Methyl [(Pyridin-3-ylcarbonyl)-β-D-glucopyranosyl)amino] propanoate	179-183ºC	50%	370
PV7		Ethyl 2-[(Pyridin-3-ylcarbonyl)-β-D-glucopyranosyl)amino]-3-sulfanylpentanoate	208-211ºC	29%	416
PV8		Methyl 2-[(Pyridin-3-yl carbonyl)-β-D-glucopyranosyl)amino]-3-sulfanylpentanoate	202-206ºC	61%	402
PV9		Ethyl 3-methyl-2-[(pyridin-3-yl carbonyl)-β-D-glucopyranosyl) amino]butanoate	189-192ºC	49%	412
PV10		Methyl 3-methyl-2-[(pyridine-3-ylcarbonyl)-β-D-glucopyranosyl) amino]butanoate	183-187ºC	42%	398
PV11		Ethyl [(Pyridin-3-ylcarbonyl)-(β-D-galactopyranosyl-(1,4)-D-xylosyl) amino]acetate	211-213ºC	30%	532
PV12		Methyl [(Pyridin-3-ylcarbonyl)-(β-D-galactopyranosyl-(1,4)-D-xylosyl)amino]acetate	207-211ºC	21%	518

PV13		Ethyl 4-[(Pyridin-3-ylcarbonyl)-(β-D-galactopyranosyl-(1,4)-D-xylosyl)amino] methyl-2-pentanoate	237-241ºC	29%	588
PV14		Methyl 4-[(Pyridin-3-ylcarbonyl)-(β-D-galactopyranosyl-(1,4)-D-xylosyl)amino] methyl-2-pentanoate	228-231ºC	32%	574
PV15		Ethyl [(Pyridin-3-ylcarbonyl)-(β-D-galactopyranosyl-(1,4)-D-xylosyl) amino]propanoate	224-228ºC	49%	546
PV16		Methyl [(Pyridin-3-ylcarbonyl)-(β-D-galactopyranosyl-(1,4)-D-xylosyl)amino]propanoate	213-218ºC	41%	532
PV17		Ethyl 2-[(Pyridin-3-ylcarbonyl)-(β-D-galactopyranosyl-(1,4)-D-xylosyl)amino]-3-sulfanylpentanoate	269-273ºC	29%	578
PV18		Methyl 2-[(Pyridin-3-ylcarbonyl)-(β-D-galactopyranosyl-(1,4)-D-xylosyl)amino]-3-sulfanylpentanoate	243-248ºC	23%	564
PV19		Ethyl 3-methyl-2-[(Pyridin-3-ylcarbonyl)-(β-D-galactopyranosyl-(1,4)-D-xylosyl)amino]butanoate	223-228ºC	29%	574
PV20		Methyl 3-methyl-2-[(Pyridin-3-ylcarbonyl)-(β-D-galactopyranosyl-(1,4)-D-xylosyl) amino]butanoate	219-223ºC	48%	560

The structures of the compounds were established through the interpretation of spectral data. Infrared transmissions, ν_{max} in cm^{-1}, were recorded in KBr pellet/Neat on Bruker spectrophotometer. The ^{1}H-NMR spectra were recorded in deuterated solvents with Me_4Si as the internal standard on Bruker NMR spectrometer operating at 300 MHz. The chemical shifts were recorded in ppm (δ) & coupling constants (J) in Hz. The solvent system used in the TLC was ethyl acetate: pet. ether: 6: 4. The TLC, FTIR, ^{1}H NMR data of the title compounds are shown in **Table 2**.

TABLE 2: R_f VALUE, FTIR DATA, ^{1}H NMR DATA OF THE TITLE COMPOUNDS

Compound code	R_f value	FTIR data	^{1}H NMR data
PV1	0.67	3639- 3604 (O-H str); 3120, 2941 (C-H aromatic str);1729 (C=O ester str); 1681 (C=N str); 1634 (C=O amide str);1275(C-str); 1233 (C-N str)	7.9-8.8 (4H, m; -CH);5.9 4.38(5H,m;-CH);3.9(2H,s; -CH_2);3.6(2H,d;-CH_2); 3.4 (2H, q; -CH_2); 2.1 (4H, s; -OH); 1.3(3H, t; CH_3)
PV2	0.64	3632- 3597 (O-H str); 3153, 2996 (C-H aromatic str); 1730(C=O ester str);1682(C=str);1627(C=O amide str); 1213 (C-O str); 1168(C-N str)	8-8.8 (4H, m; -CH); 6-4.37 (5H, m; -CH); 3.8 (2H, s; -CH_2); 3.7 (2H, d; -CH_2); 3.5 (3H, s; -CH_3); 2.1 (4H, s; -OH)
PV3	0.29	3604- 3576 (O-H str); 3086 (C-H aromatic str) ; 1722 (C=O ester str); 1695 (C=N str); 1636 (C=O amide str);1347(C-N str); 1051(C-O str)	8.5-7.5 (4H, m; -CH); 5.8- 4.48(5H, m; -CH); 3.9(1H, t;-CH);3.7(2H,d;-CH_2);3.5 (2H, q; -CH_2); 2.3 (4H, s; -OH); 1.9(1H, m; -CH);1.6 (2H, dd; -CH_2); 1.2 (3H, t; -CH_3); 0.7(6H, d; -CH_3)
PV4	0.26	3593-3561(O-H str);3125,3002(C-H aromatic str);732(C=O ester str); 1668 (C=N str); 1636 (C=O amide str);1415(C=C str);1363(C-N str);1095(C-O str);	8.5-7.8 (4H, m; -CH); 6.4- 4.12(5H,m;-CH);3.9(2H,d; -CH_2); 3.8(3H,s;-CH_3); 3.4 (1H,t;-CH);2.3(4H,s;-OH); 1.9(1H,m;-CH);1.7(2H,dd; -CH_2); 0.9(6H,d;CH_3)
PV5	0.69	3628-3589 (O-H str); 3167, 3049 (C-H aromatic str); 2981,2906 (C-H aliphatic str);1746(C=O ester str); 1673 (C=N str); 1629 (C=O amide str); 1442 (C=C stre); 1324 (C-N str); 1238 (C-O str);	8.3-7.2(4H,m;CH);6.2(1H, d;H-1,J 8.24Hz); 5.4-4.4(4 H, m;-CH);3.9(2H,d;-CH_2); 3.7 (1H, q; -CH); 3.3(2H, q; -CH_2); 2.2 (4H, s; -OH); 1.5 (3H, t; -CH_3); 1.2 (3H, d; -CH_3)
PV6	0.68	3648- 3612 (O-H str); 3172- 3103 (C-H aromatic str); 2927,2865 (C-H aliphatic str);1731(C=O ester str); 1668 (C=N str); 1632 (C=O amide str);1359 (C=C str);1342(C-N str);1207(C-O str);	8.4-7.2(4H,m;-CH);6.2(1H,d;H-1, J 8.24Hz); 5.3-4.31(4H, m; -CH); 3.6 (2H, d; -CH_2); 3.5(1H,q; -CH); 3.2 (3H, s; -CH_3); 2.4 (4H, s; -OH); 1.2 (3H, d; -CH_3)
PV7	0.54	3584- 352 (O-H str); 3141, 2986 (C-H aromatic str); 2899,2814(C-H aliphatic str);2512(S-H str); 1763 (C=O ester str);1668 (C=N str); 1637 (C=O amide str); 1436(C=C str);	8.3-7.2(4H,m;CH);5.8(1H, d;H-1,J 7.79Hz); 4.9-4.18(4H,m;-CH);3.8(1H,t;-CH); 3.6(2H,d;-CH_2);3.4 (2H, q; -CH_2);2.4(2H,d;-CH_2); 2.1(4H, s; -OH); 1.53 (1H, s; -SH);1.3(3H,t;-CH_3)
PV8	0.58	3589- 3546 (O-H str); 3146 (C-H aromatic str); 3057(C-H aliphatic str); 1749 (C=O ester str); 1687 (C=N str); 1626 (C=O amide str); 1431 (C=C str); 1265 (C-N str); 1216 (C-O str); 624 (C-S str)	8.6-7.9(4H,m;CH);6.1(1H, D;H-1, j8.08Hz); 5.1-4.38(4H,m;-CH);3.9(1H,t;-CH); 3.6(2H,d; -CH_2); 3.2(2H,s;-CH_2);2.5(2H,d;-CH_2); 2.1(4H,s;-OH);1.48(1H,s;SH)
PV9	0.43	3657- 3613 (O-H str); 3119, 3078 (C-H aromatic str); 2945,2896 (C-H aliphatic str); 1748(C=O ester str); 1672 (C=N str); 1634 (C=O amide str); 1445 (C=C str); 1204 (C-O str); 1103 (C-N str); 1239(C-N str)	8.1-6.9(4H,m-CH);6.2(1H, d;H-1, j8.12Hz); 5.3-4.34(4H,m;-CH); 3.9(2H,d;CH_2); 3.6 (1H,d;-CH); 3.3(2H,q; -CH_2);2.3(4H,s; -OH); 1.8(1H,m;-CH);1.1(3H,t;-CH_3); 0.8 (6H,d; -CH_3);
PV10	0.41	3663- 3518 (O-H str); 3138, 3016 (C-H aromatic str); 2886, 2827(C-H aliphatic str);1739(C=O ester str); 1648 (C=N str);1642 (C=O amide str);1309(C-N str); 1379 (C=C str);1264 (C-O str)	8.9-8.1(4H,m;CH);6.2(1H, d; H-1, j8.24Hz); 5.1-4.43(4H,m;-CH);3.9(1H,d;-CH); 3.7(2H,d;-CH_2);3.6(3H, s; -OH);1.9(1H, m;-CH); 0.8(6H,d;-CH_3)
PV11	0.45	3638- 3587 (O-H str); 3119, 2996 (C-H	8.3-7.2 (4H, m; -CH); 5.5 (1H,d; H-1,

		aromatic str); 2848, 2783(C-H aliphatic str); 1737(C=O ester str); 1686 (C=N str); 1654 (C=N amide str); 1442 (C=C str); 1126 (C-O str); 1076 (C-N str)	j8.1Hz);5 (1H, d;H-7);4.89-4.3(8H,m;-CH); 3.9(2H,s;CH_2); 3.7(4H,d; -CH_2); 3.4(3H,s;-CH_3); 2.3 (7H,s; -OH)
PV12	0.42	3615- 3571 (O-H str); 3043, 2935 (C-H aromatic str); 2883,2809(C-H aliphatic str);1739(C=O ester str); 1664 (C=N str); 1653 (C=O amide str); 1439 (C=C str); 1261(C-N str); 1094 (C-O str)	8.3-7.2 (4H, m; -CH); 5.7 (1H, d; H-1, j7.76);5.1(1H, d;H-7);4.89-4.3(8H,m;-CH); 3.9(2H,s;CH_2); 3.7(4H,d;-CH_2);3.4(3H,s;-CH_3);2.3 (7H,s;-OH)
PV13	0.39	3579- 3528 (O-H str); 3158 (C-H aromatic str); 3087 (C-H aliphatic str); 1671 (C=O amide str); 1636 (C=N str);1618(C=O ester str); 1410 (C=C str); 1363 (C-N str); 1123(C-O str)	8.6-7.9 (4H, m; -CH); 6.1(1H, d; H-1, j8.17 Hz); 5.4(1H, d; H-7); 4.81-4.2 (8H,m;-CH); 3.7(1H,t;-CH);3.5 (4H, d; -CH_2); 3.3 (2H, q;-CH_2); 2.1(7H, s; -OH); 1.9(1H, m; -CH); 1.6(2H, dd; -CH_2); 1.4(3H,t;-CH_3); 0.9 (6H,d;-CH_3)
PV14	0.36	3627- 3597 (O-H str); 3070 (C-H Aromatic str); 2925 (C-H aliphatic str); 1755 (C=O ester str); 1672 (C=N str); 1649 (C=O amide str); 1372 (C=C str); 1153 (C-N str)	7.9-6.7(4H,m;-CH);6.4(1H,d;H-1,j8.42Hz); 5.6(1H,d; H-7); 4.75-4.21 (8H, m; -CH); 4 (4H, d; -CH_2); 3.8 (1H, t; -CH); 3.5 (3H, s; -CH_3); 2.3(7H,s; -OH); 1.9 (1H, m; -CH); 1.7 (2H,dd;-CH_2); 0.8(6H,d;-CH_3)
PV15	0.56	3595- 3532 (O-H str); 3127 (C-H aromatic str); 2925 (C-H aliphatic str); 1739 (C=O ester str); 1662 (C=N str); 1589 (C=O amide str);1098 (C-N str); 1038 (C-O str)	8.6-7.2(4H,m;-CH);5.9(1H, d;H-1, j7.1Hz); 5(1H,d;H-7); 4.89 4.33(8H, m; -CH); 3.9(4H,d; -CH_2); 3.7(1H,q;-CH); 3.4(2H,q; -CH_2); 2.2(7H,s;-OH); 1.5(3H,t;-CH_3); 1.2(3H,d;-CH_3)
PV16	0.49	3658- 3622 (O-H str); 3157,2979 (C-H aromatic str); 2875, 2829(C-H aliphatic str); 1751(C=O ester str); 1663 (C=N str); 1648 (C=O amide str); 1335 (C-N str); 1329 (C=C str); 1054 (C-O str)	8.3-7.1(4H,m;-CH);6.2(1H, d;H-1,j8.23Hz); 5.7(1H,d; H-7); 4.67-4.12 (8H, m; -CH); 3.8 (1H, q; -CH); 3.5(4H, d; -CH_2); 3.4 (3H, s; CH_3); 2.4 (7H,s; -OH); 1.2 (3H,d;-CH_3)
PV17	0.47	3642- 3607 (O-H str); 3247 (N-H str); 3125(C-H aromatic str); 2875(C-H aliphatic str);2489(S-H stretching); 1712 (C=O ester str); 1626 (C=N str); 1608 (C=O amide str); 1441 (C=C str); 1209 (C-N str); 1139 (C-C str); 686 (C-S str)	8.5-7.2(4H,m;-CH);5.8(1H, d; H-1, j7.84Hz); 5(1H, d;H-7);4.8 4.32(8H,m;-CH); 3.8(4H,d; -CH_2); 3.7(1H, t;-CH); 3.2 (2H,q; -CH_2);2.7(2H, d; -CH_2); 2.3 (7H, s; -OH); 1.8 (1H, s; -SH); 1.2 (3H, t; -CH_3)
PV18	0.49	3620- 3573 (O-H str); 3095, 2972 (C-H aromatic str); 2903,2871(C-H aliphatic str); 2560 (S-H str); 1682 (C=N str); 1636 (C=O amide str); 1408(C=C str); 1209(C-N str); 1027 (C-O str); 658 (C-S str)	8.9-7.8(4H,m;-CH);6.5(1H,d;H-1,j8.54Hz); 5.7(1H,d; H-7); 4.79-4.42 (8H, m; -CH); 3.9 (1H, t; -CH); 3.8(4H, d; -CH_2); 3.4(3H, s; -CH_3); 2.4(2H,d;-CH_2);2.3 (7H, s; -OH); 1.74 (1H, s; -SH)
PV19	0.54	3636- 3602 (O-H str); 3129 (C-H aromatic str); 3059 (C-H aliphatic str); 1738 (C=O ester str); 1694 (C=N str); 1652(C=O amide str); 1449 (C=C str); 1317 (C-N str); 1042(C-O str)	8.5-7.5(4H,m;-CH);6.1(1H,d;H-1,j8.19Hz); 5.6(1H,d; H-7);4.59-4.12(8H,m;-CH); 3.9(1H,d;-CH); 3.5 (4H,d; -CH_2); 2.2 (7H,s; -OH); 1.6 (1H, m; -CH); 1.1 (3H, t; -CH_3); 0.8(6H,d;-CH_3)
PV20	0.51	3617-3567 (O-H stretching); 3123, 3068 (C-H aromatic str); 2975, 2893(C-H aliphatic str); 1672 (C=O ester str); 1654 (C=N str); 1464 (C=C str); 1286 (C-O str); 1254 (C-N str)	8.4-7.2(4H,m;-CH);5.9(1H,d;H-1,j7.95Hz); 5.1(1H,d; H-7); 4.79-4.34 (8H, m; -CH); 3.7(4H, d; -CH_2); 3.5 (3H, s; -CH_3); 2.1 (7H, s; -OH); 1.9(1H,m; -CH); 0.9 (6H,d; -CH_3)

Antipyretic Activity: The yeast-induced pyrexia model was used for evaluating antipyretic activity. In this study, yeast significantly increased the temperature of rats. Treatment with test compounds significantly prevented the increase in temperature in rats **Table 3**.

The compounds do not show any significant effect at 2 h, but the effect was significantly seen after 4 h. Experimental groups were compared with 0 h of the same group, and there was a decrease in pyrexia in rats. Pretreatment was done with thirty test compounds; twelve showed (GP1, GP2, GP9,

GP10, PV1, PV2, PV9, PV10, PV11, PV12, PV19, PV20) significantly ($p<0.05$) preventive effect **Table 3, 4**. The biological activity comparison between the amide derivatives and N-glycosides indicated that a slight increase in antipyretic activity was observed in N-glycosides when compared to amide derivatives. The graph of the effect of the test (N-glycosides) compounds on induction of yeast-induced pyrexia in rats after 2 h and4 h are shown in **Fig. 3** and **4,** respectively.

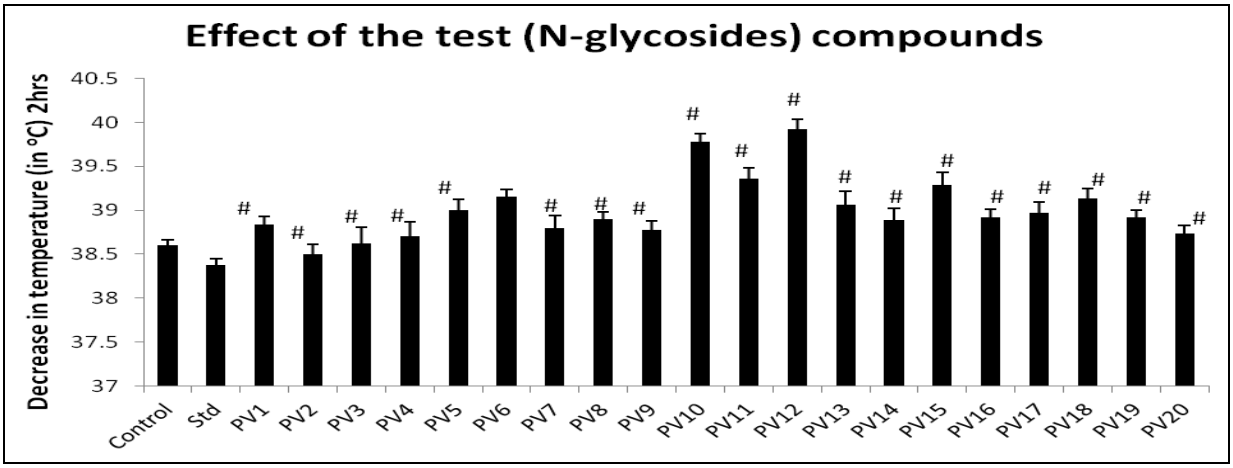


FIG. 3: EFFECT OF THE TEST (N-GLYCOSIDES) COMPOUNDS ON INDUCTION OF YEAST INDUCED PYREXIA IN RATS AFTER 2 h. Key: p**< 0.01 (highly significant); p*< 0.05 (significant); p# > 0.05 (not significant)

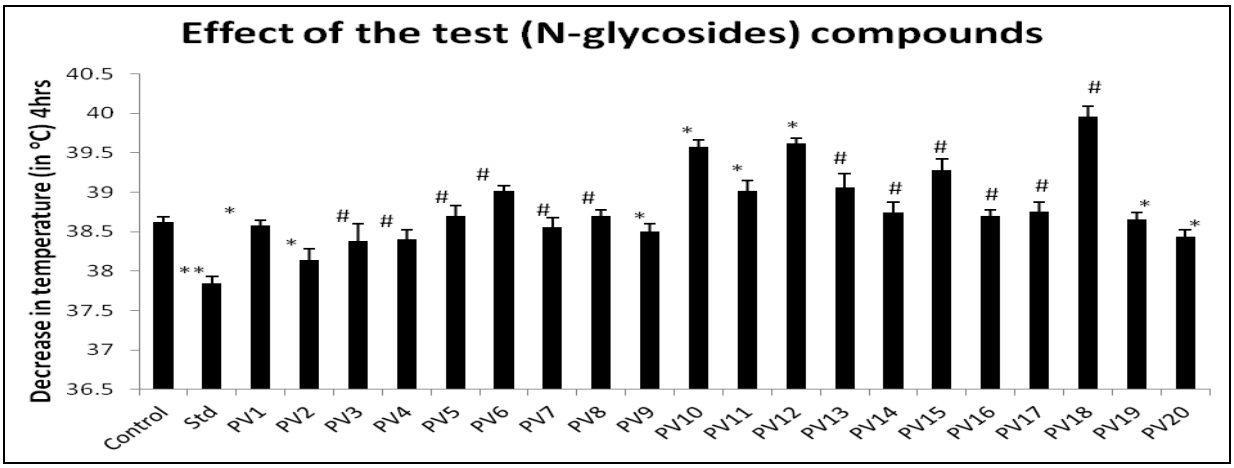


FIG. 4: EFFECT OF THE TEST (N-GLYCOSIDES) COMPOUNDS ON INDUCTION OF YEAST INDUCED PYREXIA IN RATS AFTER 4 h. Key: p**< 0.01 (highly significant); p*< 0.05 (significant); p# > 0.05 (not significant)

TABLE 3: EFFECT OF THE TEST (AMIDE DERIVATIVES) AND STANDARD COMPOUNDS ON INDUCTION OF YEAST INDUCE PYREXIA IN RATS

Group	Temp at 0h (ºC)	Decrease in temp at 2 h (ºC)	% decrease in temp (ºC)	Decrease in temp at 4 h (ºC)	% decrease in temp (ºC)
Control	38.48±0.07	38.6±0.06	_	38.62±0.07	_
Standard	38.88±0.06	38.38±0.07**	45.4	37.85±0.08**	93
GP1	39.12±0.06	39.04±0.08#	6	38.8±0.05*	24
GP2	38.98±0.07	38.9±0.08#	5.9	38.66±0.09*	23.8
GP3	39.36±0.12	39.16±0.14#	14.7	39±0.13#	26.4
GP4	38.98±0.10	38.86±0.10#	8.2	38.87±0.10#	21.2
GP5	39±0.09	38.92±0.08#	6.2	38.85±0.05#	11.7
GP6	39.02±0.05	38.92±0.08#	7.1	38.84±0.05#	12.8
GP7	39.18±0.12	39.02±0.13#	12.3	38.76±0.10#	32.3
GP8	39.06±0.09	38.88±0.08#	13.4	38.78±0.19#	20.8
GP9	38.92±0.07	38.68±0.11#	17.9	38.5±0.10*	31.3
GP10	39.3±0.07	39.16±0.08#	12	38.96±0.06*	29.3

Paracetamol was used as standard drug. Values were expressed as Mean ± SEM,*p < 0.05 in comparison to control (n=6)
Key: p**< 0.01 (highly significant); p*< 0.05 (significant); p# > 0.05 (not significant)

TABLE 4: EFFECT OF THE TEST (N-GLYCOSIDES) COMPOUNDS ON INDUCTION OF YEAST INDUCED PYREXIA IN RATS

Group	Temp at 0 h (ºC)	Decrease in temp at 2 h (ºC)	% decrease in temp (ºC)	Decrease in temp at 4 h (ºC)	% decrease in temp (ºC)
Control	38.48±0.07	38.6±0.06	_	38.62±0.07	_
Standard	38.88±0.06	38.38±0.07**	45.4	37.85±0.08**	93
PV1	38.96±0.08	38.84±0.09#	9.5	38.58±0.07*	36.5
PV2	38.64±0.14	38.5±0.11#	13.2	38.14±0.14*	47.1
PV3	38.78±0.18	38.62±0.19#	12	38.38±0.22#	31.7
PV4	38.88±0.14	38.7±0.17#	14	38.4±0.13#	37.5
PV5	39.12±0.09	39±0.12#	9	38.7±0.13#	31.8
PV6	39.3±0.07	39.16±0.08#	12	39.02±0.06#	24.1
PV7	38.92±0.12	38.8±0.14#	9.8	38.56±0.12#	29.5
PV8	39.02±0.12	38.9±0.08#	9.3	38.7±0.08#	25
PV9	38.94±0.11	38.78±0.10#	12.1	38.5±0.10*	33.3
PV10	39.02±0.10	38.78±0.09#	19.3	38.58±0.08*	57.6
PV11	39.48±0.12	39.36±0.12#	9.8	39.02±0.13*	37.7
PV12	39.06±0.10	38.92±0.12#	11.2	38.62±0.07*	35.4
PV13	39.1±0.16	39.06±0.16#	3.1	39.06±0.18#	23.3
PV14	38.86±0.12	38.89±0.13#	5.4	38.74±0.14#	17.1
PV15	39.28±0.12	39.29±0.14#	8.5	39.28±0.14#	20.3
PV16	38.96±0.06	38.92±0.09#	9.8	38.7±0.08#	19.6
PV17	38.96±0.10	38.97±0.12#	8.8	38.76±0.11#	29.8
PV18	39.24±0.12	39.13±0.12#	9.1	38.96±0.13#	23.3
PV19	38.98±0.10	38.92±0.08#	4.6	38.66±0.08*	30.6
PV20	38.84±0.08	38.74±0.09#	7.5	38.44±0.08*	30.3

Paracetamol was used as a standard drug. Values were expressed as Mean ± SEM,*p < 0.05 in comparison to control (n=6)
Key: p**< 0.01 (highly significant); p*< 0.05 (significant); p# > 0.05 (not significant)

CONCLUSION: A series of 20 amide-based carbohydrates were successfully synthesized. Among the synthesized compounds, eight out of twenty compounds *viz*., PV1, PV2, PV9, PV10, PV11, PV12, PV19, PV20 were found to be more active. These compounds can play a significant role in the treatment of fever.

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