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Research Article

Synthesis and Characterization of Glucopyranosyloxyphenylacetamide: ADMET and PASS Evaluation as a Prodrug Analog

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Abstract

This study investigates the manufacturing of glycoside-based derivatives of drugs, and their applications to produce injectable medications for colds and flu that alleviate problems with low solubility in water. Regarding these perspectives, this research was designed to prepare 4-o-β-D-glucopyranosyloxyphenylacetamide (**7**) through multistep synthesis, which was characterized through FT-IR spectra, ^{1}H NMR, ^{13}C NMR, and melting point analysis, comparing it with the reported compound (**8**). ADMET and PASS of the synthesized compound were performed to assess the compounds' pharmacokinetics, toxicological profiles, and biological activities, i.e., low carcinogenicity, AOT category III, and antiviral potentiality etc.

Keywords: Prodrugs, Glucopyranosyloxyphenylacetamide, ADMET and PASS.

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1 Introduction

A chemically modified or inert version of an active drug that, once administered within the body, is activated by an enzymatic or chemical process to generate an active molecule that is accountable for its therapeutic effects is referred to as a "prodrug" [1] are also considered chemical or bio-reversible derivatives of drug molecules [2]. For the improvement of drugs and finding new drugs, prodrugs have been adopted extensively since 1960. It is estimated that up to 10% of all drugs that are marketed are prodrugs [3]. Indeed, working with a novel chemical entity is crucial to develop a prodrug. However, prodrugs are not as costly to produce as new drugs. Faster drug development may result in savings on time, money, and effort because the drug performs better in comparison to its original drug [4–6]. The molecular renaissance in the fields of biology and medicine has enabled a current strategy for the design of prodrugs, which considers molecular/cellular variables and is directed toward specific target proteins in the body [5, 7–9]. To target specific enzymes or transporters, the drug carrier is covalently bonded to the parent medication. The parent distribution of drug control used in the present prodrug strategy has benefits and drawbacks that affect precise targeting.

Computer simulations can be used to optimize this process [5, 7, 8]. The prodrug method is very beneficial and effective for minimizing issues related to the formulation, toxicity, site specificity, absorption, distribution, solubility, instability, and bioavailability [10–12]. Prodrugs enter the body through the parent drug and pair moiety, causing problems with ovulation and bioavailability. Prodrugs are often used to cover up a drug's polar and ionizable groups to increase oral absorption and membrane permeability [13]. The method of the prodrug is used generally for developing absorption of the drug after oral delivery. The traditional prodrug technique can be used by using different carboxylic acid esters, which liberate the active carboxylic acid upon hydrolysis, to mask charged moieties and improve drug lipophilicity as well as passive diffusion [14]. More recently, the study of transporters along with enzymes has led to the development of a novel "targeted-prodrug" technique utilizing transport through carriers to improve drug absorption [3, 14]. The oligopeptide transporter (PEPT1), which is predominantly revealed in the interior tract, is a low-capacity, high-affinity transporter that absorbs dipeptides, tripeptides, as well as peptidomimetic drugs like β-lactam antibiotics and ACE inhibitors [15-16]. Therefore, PEPT1-targeted prodrugs could offer an appropriate strategy for enhancing drug administration.

Paracetamol is an important nonsteroidal anti-inflammatory drug (NSAID) that impacts several inflammatory mediators. It is a potent anti-inflammatory and analgesic medication with a decent tolerance profile. Unfortunately, it has certain side effects, including GI system disruption, dyspepsia, and restricted absorption, just like other NSAIDs [17]. A possible remedy to this issue is to develop prodrugs by transforming the free functional group of paracetamols. Prodrugs of acids and amines have been developed using an amide-based, amidase-sensitive method [18]. Very little irritation of the stomach mucosa was caused by the chlorzoxazone ester prodrugs of several acidic NSAIDs [17]. A prodrug called nebumetone causes GI ulcers more rarely than traditional NSAIDs [19]. Prodrugs offer higher bioavailability and strong chemical stability against hydrolysis, according to the results of the literature review. Prodrugs have utilized glycosylation to enhance the stability, solubility, and selective activation of small compounds. Studies show that adding glucopyranoside groups to drugs improves pharmacokinetics and minimizes gastrointestinal side effects, exemplified by ibuprofen prodrugs with glucopyranoside esters that reduce gastric ulceration [20-21]. Other glucopyranoside-linked prodrugs, like naproxen conjugated with glucosyl thiamine, enhance central nervous system uptake. Additionally, phenylacetamide glycosides exhibit mild anti-hyperglycemic effects, while synthetic derivatives have been explored for various biological activities without glucopyranosyl modifications [22-23]. The prodrug strategy is a versatile approach in medicinal chemistry aimed at overcoming issues like poor solubility, low permeability, and rapid metabolism of primary drugs [24]. Glycosylation is particularly effective in designing prodrugs, as it enhances solubility and enzyme activation. Glucose-linked derivatives are noted for their ability to utilize glucose transporters for cellular entry and be activated by β-glycosidase,

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releasing the active drug in targeted tissues. Additionally, phenylacetamide scaffolds and glycosylated derivatives are considered promising due to their favorable safety profiles [25-26].

Considering the extensive biological and pharmacological significance of prodrugs, it is deemed worthwhile to create a novel conjugate amide prodrug having biological and pharmacological importance that contains glucose and paracetamol. In the present research work, we synthesized a novel conjugate amide prodrug containing glucose and paracetamol. The synthesis compounds were characterized by using FT-IR, ^{1}H NMR, ^{13}C NMR, and melting points. The recorded ^{1}H NMR, ^{13}C NMR and FT-IR spectra were interpreted and compared with the reported compound [27] and also the melting points of the synthesized compound was compared. In this study, the amide derivatives were chosen to mask the free hydroxyl group of paracetamols because it is a condition for prodrug that the pre-moiety should be nontoxic and prodrugs formed could show varying degrees of lipophilicity and fewer side effects. This prodrug is not harmful to a living system. For chemical as well as toxicological prediction, *in silico* methods are commonly used in order to conserve money and time [28]. The ADMET and PASS prediction techniques are used in this work to investigate the pharmacological and toxicological effects of GPPA. Current research focuses on synthesizing and characterizing glucopyranosyloxyphenylacetamide, including its in silico evaluation to assess its potential as a prodrug.

2 Experimental

2.1 Materials and Methods

2.1.1. Materials

Solvents were purified before using, such as chloroform was washed with water to remove ethanol, then dried for several hours over anhydrous $CaCl_2$ and fractionally distilled. Acetone was distilled (~ 56°C) after drying with $CaCl_2$, dichloromethane (DCM) was purified by treatment with basic alumina and distilled then stored over molecular sieves under nitrogen atmosphere. Acetyl chloride was refluxed with PCl_5 about a couple of hours and distilled for purification. Methanol was dried over anhydrous CaO then distilled, and molecular sieves also was used in it for higher purity but analytical grade of pyridine (99%, Sigma-Aldrich) was used as received. Coated TLC with silica gel 60 and Kieselguhr F_{254} (thinness 0.02 cm F. MARACK) were used on aluminum plates. A small iodine tank was used to develop chromatograms. For column chromatography, a cylindrical glass column (50 cm in length and 1 cm in diameter), a cotton plug, silica gel 60 (70–230 mesh), and a mixture of dichloromethane and methanol were also used. UV light (Narva UV tube light) was used to detect the presence of a compound or mixture.

2.1.2 Characterization

The IR spectra were recorded on Shimadzu FTIR 8101 as KBr disc at ambient temperature within the range of 4000-400 cm^{-1}. The melting points of all synthesis compounds were recorded by a thin-disc Fischer-Jones electro-thermal melting point apparatus in the Department of Chemistry at Jahangirnagar University. ^{1}H NMR and ^{13}C NMR were recorded on a spectrophotometer (Bruker Avence III HD spectrometer, 400 MHz) from chloroform-D solution, while TMS was an internal standard. The progress of the reactions and purity of the products were monitored by TLC, and a rotatory vacuum evaporator was used under reduced pressure at normal temperature to remove the solvent from the reaction mixture.

2.2 Synthesis

2.2.1. Synthesis of *4-o-β-D-glucopyranosyloxyphenylacetamide (GPPA)* (7)

The compound 4-o-β-D-glucopyranosyloxyphenylacetamide (GPPA) (7) (Yields: 86% and Melting point: 120-125 °C) was synthesized by following **Scheme 1.** Firstly, a mixture of 7.56 mL of dry pyridine and 6.3 mL of dry chloroform was cooled in an ice-salt bath and previously cooled mixture of 6.3 mL of acetyl chloride at 6.3 mL of dry chloroform was added in the mixture of ice-salt bath. Then 3 gm (0.01 mol) of dry β-D-glucose was added to the vigorously stirred acetylating reagent at a rate which maintains the temperature below 10°C. The pink colored reaction mixture was allowed to stand at 0°C for 24

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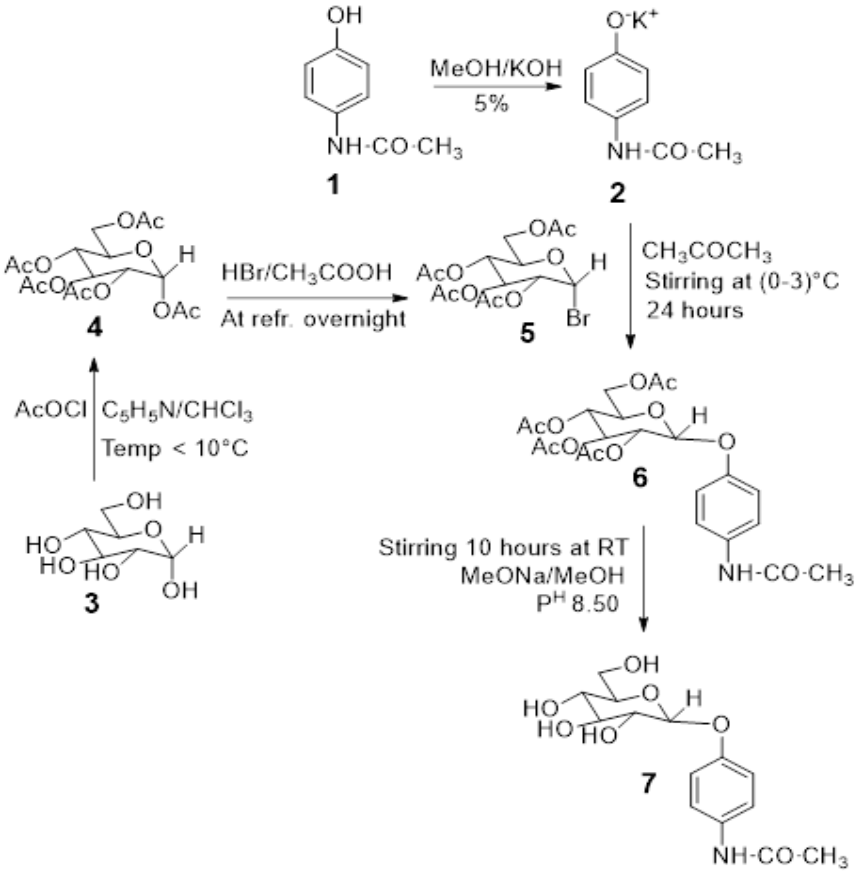
hours, diluted with DCM; then washed the solutions successively with dilute aqueous sulfuric acid (2M), water, saturated aqueous sodium hydrogen carbonate and dried over anhydrous sodium sulphate. After removing DCM using rotary evaporator to give a yellow solid which was ground up with industrial spirit, filtered and washed well with spirit and after recrystallization. Pure product 1,2,3,4,6-penta-o-actyl--β-D-glucopyranose (4) was obtained.

Secondly, the product (4) was dissolved in DCM. A solution of HBr in glacial acetic acid was added to compound (4) and stoppered in the flask and allowed to keep the reaction mixture in the refrigerator overnight, poured the mixture into ice water and washed the organic layer of mixture with water. It was then dried over magnesium sulphate and filtered the mixture; a radish brown color semisolid product 2,3,4,6-tetra-o-acetyl-β-D-glucopyranosyl bromide (5) was obtained after removing DCM using rotatory evaporator.

Thirdly, the product (5) was dissolved in dry acetone and cooled to (0-3) °C. The solution of potassium salt of paracetamol (2) in 5% methanolic KOH was added dropwise to the solution of compound (5) under a nitrogen atmosphere. The resulting mixture was stirred at (0–3) °C for 24 hours, and the reaction was monitored by TLC (ethanol and chloroform 1:1). After completing the reaction, the solvent was removed. The resulting syrup was dissolved in methanol and chromatographed on 60-120 mesh silica gel eluted with 10% ethanol in DCM to obtain the product 2,3,4,6-tetra-o-acetyl-β-D-glucopyranosyloxyphenylacetamide (6) as a brown syrup.

Fourthly, the compound (6) was dissolved in dry methanol (P^H = 8.50), and a freshly prepared solution MeONa-MeOH was added to that solution. The mixture was kept at room temperature with continuous stirring an inert atmosphere. After 10 hours, the reaction mixture was neutralized by acetic acid, and the reaction mixture was filtered and evaporated to get brown semi-solid final compound 4-o-β-D-glucopyranosyloxyphenylacetamide (GPPA) (7). The formation of GPPA (7) was characterized by FTIR, ^{1}HNMR, ^{13}CNMR, melting point and compared with the reported compound (8) [29] (**Scheme 2; Figure S5 and S6.**).



Scheme 1 Synthesis of GPPA (7)

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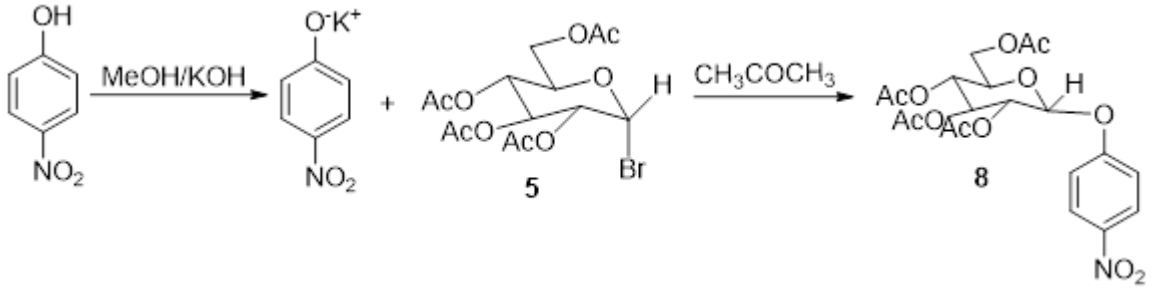

Scheme 2 Synthesis of 4-o-β-D-glucopyranosyloxyphenylnitride (8) [29]

3 Spectral Characterization and Analysis

3.1 Spectral Characterization

IR of 1,2,3,4,6-penta-o-acetyl-β-D-glucopyranose (4).
IR (KBr): 2964 cm^{-1} (-CH_3), 1754 cm^{-1} (=CO ester), 1373 cm^{-1} (C-O ester), Yields: 65% **(Figure S2).**

IR of 2,3,4,6-tetra-o-acetyl-β-D-glucopyranosyl bromide (5).
IR (KBr): 2925 cm^{-1} (-CH_3), 1734 cm^{-1} (=CO ester), 1236 cm^{-1} (C-O ester), 1038 cm^{-1} (C-Br), Yields: 80% **(Figure S3)**.

IR of 2,3,4,6-tetra-o-acetyl-β-D-glucopyranosyloxyphenylacetamide (6).
IR (KBr): 3423 cm^{-1} (-NH-, secondary amide), 2921 cm^{-1} (-CH_3 stretching), 1651 cm^{-1} (=CO amide), 1509 cm^{-1} (C=C aromatic), Yields: 73% **(Figure S4).**

IR of 4-o-β-D-glucopyranosyloxyphenylacetamide (GPPA) (7).
IR (KBr): 3423 cm^{-1} (-OH-, alcohol), 2928 cm^{-1}(-CH_3 stretching) and 2993 cm^{-1} (C-H, aromatic) 1654 cm^{-1} (=CO amide), 1575 cm^{-1} (C=C aromatic), **(Figure 1).**

^{1}H NMR of 4-o-β-D-glucopyranosyloxyphenylacetamide (GPPA) (7)
^{1}HNMR (400 MHz, CD_3OD): δ 1.9 (s, 3H), 4.89 (d, 1H), 7.06 (d, 2H), 7.47 (d, 2H), the pyranosyl ring protons located at δ 3.00-4.50 **(Figure 2).**

^{13}C NMR of 4-o-β-D-glucopyranosyloxyphenylacetamide (GPPA) (7)
C-1 resonated at δ 100.76 of the ^{13}C NMR spectrum **(Figure 3)**. Yields: 86%, Melting point: (120-125) °C

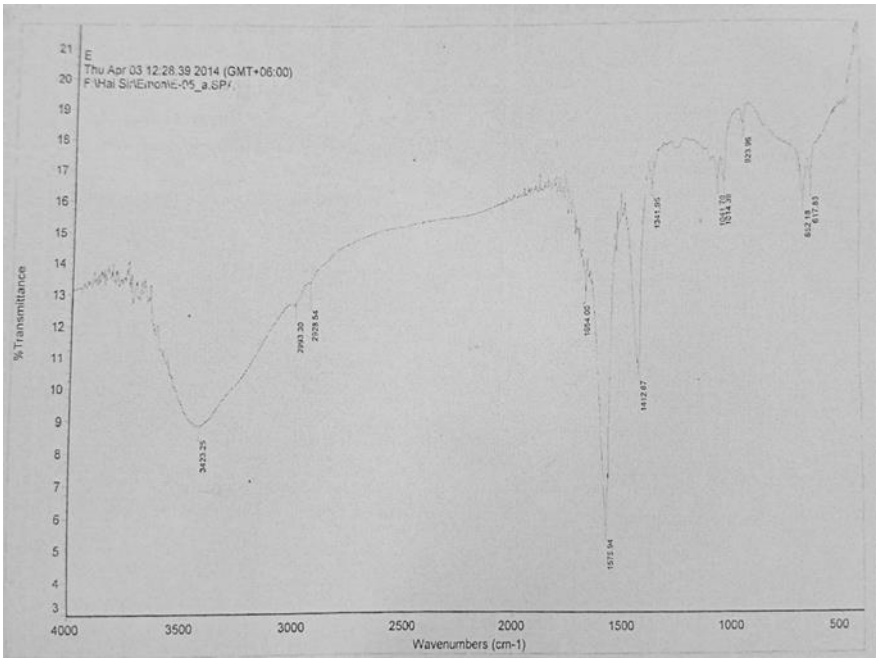

Figure 1 IR spectra of 4-o-β-D-glucopyranosyloxyphenylacetamide (GPPA) (**7**)

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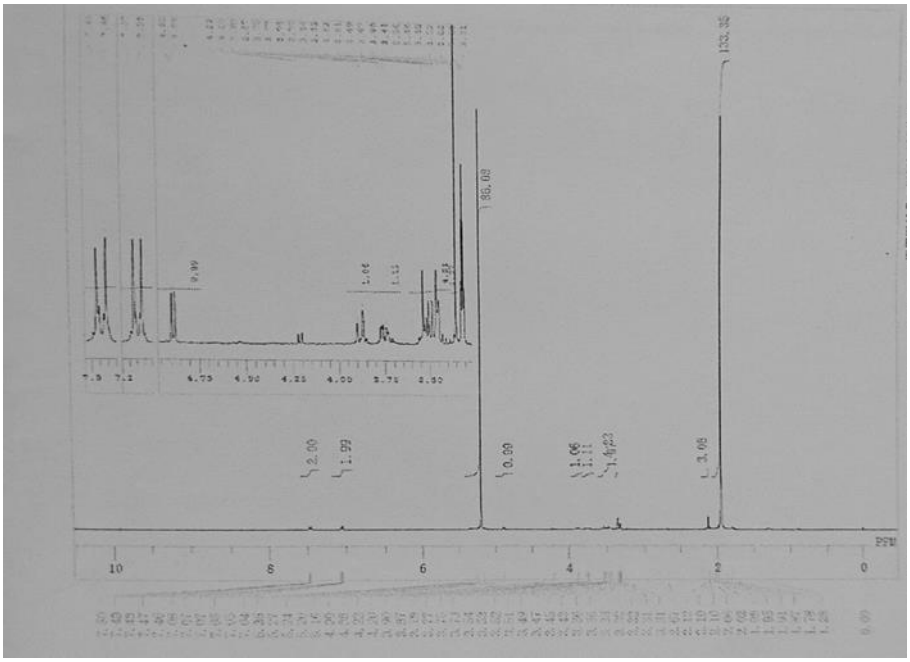

Figure 2 [1]H-NMR of 4-o-β-D-glucopyranosyloxyphenylacetamide (GPPA) (**7**).

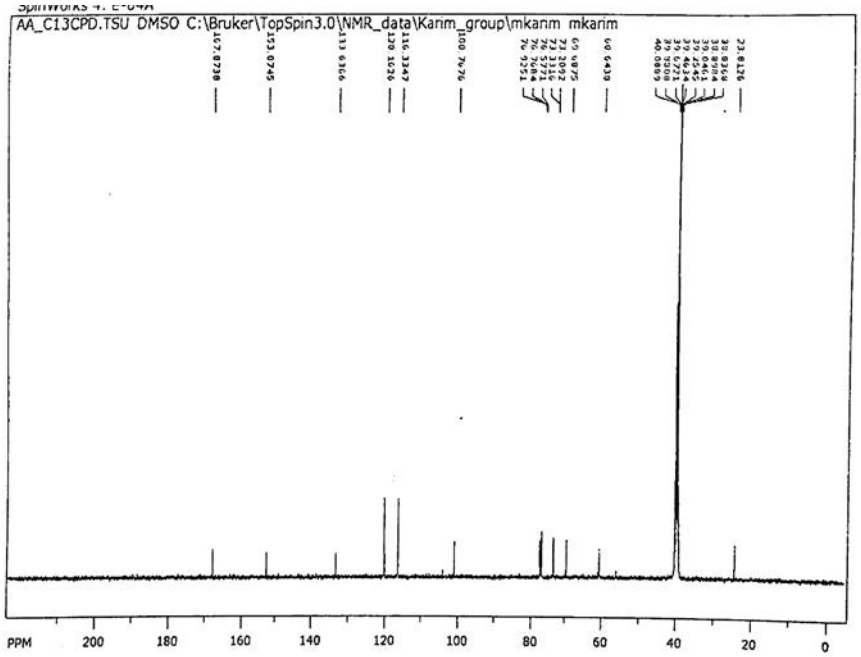

Figure 3 [13]C-NMR of 4-o-β-D-glucopyranosyloxyphenylacetamide (GPPA) (**7**).

3.2 Spectral Analysis

3.2.1 ***Spectral analysis of 4-o-β-D-glucopyranosyloxyphenylacetamide (GPPA)* (7).**

^{1}H NMR (400 MHz, CD_3OD): The synthesized compound (**7**) exhibited δ values at 1.9 (s, 3H) for the acetamide methyl proton (CH_3-CO-NH-), 4.89 (d, 1H) for the anomeric proton with coupling constant J (H-1 and H-2) of 7.4 Hz. This relatively large coupling constant is characteristic for β-D-glucopyranosylanomer with a diaxially H-1 and H-2 interaction. It showed signals in the form of doublet. Ultimately, it confirms β-anomer. Again, it also displayed δ 7.06 (d, 2H) and 7.47 (d, 2H) for substituted benzene ring protons and δ 3.00-4.50 (m, 6H) for the pyranosyl ring protons. **(Figure 5).**

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^{13}C NMR: The synthesized compound (**7**) also showed the δ values at 100.76 indicating anomeric carbon (C-1) of β-D-glucopyranosylanomer. δ 69.68 (C-6) for CH_2 of primary alcohol on sugar; δ value at (73.20-76.92) for ring carbon (C2-C5) of pyranose, δ value at 116.33-133.69 carbon of aromatic ring and δ at 153.07 for iso carbon of aromatic ring. Again, δ 167.87 displayed for carbon of amide group. **(Figure 6)**.

3.2.2 ***Spectral analysis of 2,3,4,6-tera-o-acetyl- β-D-glucosepyranosoyloxyparanitobenzene*** (8)

FT-IR: IR (KBr): 2923 cm^{-1}(-CH_3 stretching) and 2964.20 cm^{-1} (C-H, aromatic) 1734.77 cm^{-1} (=CO ester), 1577.06 cm^{-1} (C=C aromatic), 1262 cm^{-1} (-NO_2), 3473.79 cm^{-1} (-OH, for KBr containing moisture), 1093 cm^{-1} (C-O) **(Figure 7)**.

^{1}HNMR (400 MHz, CD_3OD): Anomeric proton gives the doublet at 4.56 ppm **(Figure 8)**. Yields: 85% and melting point: (120 -125) ^{0}C (Decomposed).

4 Prediction of ADMET and Biological Activities

The "*ADMET* (absorption, distribution, metabolism, excretion, and toxicity)" parameters are essential in pharmacological studies. Here, the *ADMET* profile was predicted using the *admetSAR* (http://lmmd.ecust.edu.cn/admetsar1/predict/) server [30]. The "prediction of activity spectra for substances (PASS)" web application was used to forecast the biological activities of the tested compounds [21]. **Tables 1** and **2** show the ADMET and PASS of all substances under investigation. In each case, all results were predicted with a "simplified molecular input line entry system (SMILES)" and structural data files.

4.1 ADMET Analysis

All of the characteristics of the possible drug are studied using ADMET forecasting [31]. The *ADMET* features of the tested compounds (**1, 3** and **7**) were obtained from the *admetSAR* online database. According to **Table 1**, "Human intestinal absorption (HIA)" reacts with all substances positively, nothing can escape from the body through the urine or rectal systems more quickly [32]. Here, compound 7 showed the lowest HIA (e.g., +0.552), indicating the substance was removed safely from the body through renal and rectal systems. Again, the "human oral bioavailability (HOB)" of each analog was (i.e., +0.552), indicating human health issues may result from positive HOB [33]. The permeability coefficient of the Caco-2 colon carcinoma cell line, grown on permeable scaffolds, is frequently utilized to predict the distribution of xenobiotics and other oral medications [34]. All of the compounds, tested in our study had positive C2P responses in the range of +0.553 to +0.829, suggesting that the human body consumes these drugs rapidly. The "blood-brain barrier (BBB)" regulates cell, ion, and molecule flow between the brain and body, protecting the central nervous system from pathogens, illness, inflammation, injury, and disease. Concerningly, a positive BBB response indicates that they do not pass BBB inspections rapidly [32]. Here, compound 7 exhibited a safe BBB response (e.g., +0.516) (**Table 1**). Negative *p*-Gp inhibition values were seen in all of the substances evaluated, suggesting that *p*-Gp is not inhibited and cannot influence permeability, absorption, or retention [35]. No substance in this investigation showed negative inhibitions against the significant cytochrome P450 enzyme CYP2C9.

The possibility of long QT syndromes and other serious cardiac outcomes, such as sudden death, is increased because none of the drugs now being studied significantly reduce the human "ether-α-go-go-related gene (hERG)" [36]. All tested compounds exhibited "acute oral toxicity (AOT)" category III, which implies relatively low carcinogenicity. The anticipated LD_{50} varied between 1.859 to 2.065 mol/Kg, indicating a significant range [37]. Overall, Compound **3** exhibits promise in CNS-related illnesses, while the robust ADME profile of Compound **1** makes it the most attractive option for development. Because of its possible antiviral potential, compound **7** is best suited for alteration [38]. Compound **7** is best suited for prodrug modification since it may be able to unlock its antiviral potential by boosting its metabolism and overcoming *p*-Gp efflux.

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However, *p*-Gp interaction and hERG danger require early experimental validation; therefore, prodrugs based on peptides or esters are sensible choices [39].

Table 1. Absorption, distribution, metabolism, and toxicological properties of compounds 1, 3 and 7.

Serial no.	Absorption			Distribution		Metabolism	Toxicity			
	HIA	HOB	C2P	BBB	*p*-GpI	CYP4502C9	hERG	Carcinogen	AOT	RAT
1	+0.992	+0.550	+0.829	+0.954	NI (0.982)	NI (0.907)	WI (0.972)	NC (0.765)	III	1.859
3	+0.775	+0.550	+0.553	+0.940	NI (0.874)	NI (0.979)	WI (0.977)	NC (0.917)	III	2.018
7	+0.552	+0.550	+0.692	+0.516	NI (0.572)	NI (0.901)	WI (0.967)	NC (0.955)	III	2.065

HIA = Human intestinal absorption, HOB = Human oral bioavailability, C2P = CACO-2 permeability, BBB = Blood-brain barrier, *p*-GpI = *p*-glyco protein inhibitor, hERG = Human ether-α-go-go related gene, NI = Non-inhibition, NC = Non-carcinogen, AOT = Acute oral toxicity, RAT = Rat acute toxicity (LD_{50}, mol/kg).

4.2 Biological activities

"Prediction of activity spectra for substances (PASS)" is a revolutionary computer-aided approach that has been used to predict the outcomes of 1000 toxicological and biological experiments [37]. Furthermore, the characteristics of the drugs, the biological entity, and the way it is dosed all affect biological behaviour [30]. Here, Table 2, interprets that newly synthesized compound 7 exhibited analgesic (0.213), gastrin inhibition (0.430), antifungal (0.280), and antiviral (0.734) efficacy. It concludes that **7** has more significant antiviral activities than other tested compounds. In order to evaluate both activity as well as metabolic release patterns, successful prodrug development frequently involves PASS prediction with activated enzyme experiments and ADME profiling, according to the literature [40]. Overall, Compound **7**, showed a promising antiviral candidate with potent influenza action, requires enzyme-mediated conversion and metabolic activation to be effective [40]. Again, chemical **1** exhibited NSAID-like properties, and also determines its toxicity. The antiviral and antifungal properties of compound **3** are mild.

Table 2. Predicted biological activities of compounds **1, 3** and **7**

Serial no.	Antipyretic	Analgesic	Anti-inflammation	Gastrin inhibitor	Antifungal	Antiviral	
						Activity	Virus
1	0.675	0.278	0.319	0.494	0.221	0.185	Hepatitis B
3	0.175	-	0.266	0.269	0.427	0.355	Influenza
7	-	0.213	-	0.430	0.280	0.734	Influenza

4. Conclusion

The goal of the study is to develop a novel conjugated amide prodrug GPPA (**7**) that contains paracetamol and glucose and has excellent chemical resistance against hydrolysis as well as improved bioavailability. FT-IR, ^{1}H NMR, ^{13}C NMR, and melting points were used to explain the synthesized compound. The amide derivative, i.e., GPPA (**7**) was selected to conceal the paracetamol's free hydroxyl group, guaranteeing a harmless pre-moiety, varied levels of lipophilicity, and fewer adverse effects.

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5. Declarations

5.1 Acknowledgements

We appreciate the cooperation and insightful suggestions provided by the Organic Laboratory of the Department of Chemistry at Jahangirnagar University in Savar, Dhaka, Bangladesh.

5.2 Ethics

Ethical approval was not required.

5.3 Conflict of Interest

The authors state that none of their known competing financial interests or personal connections could have appeared to have an impact on the work that is being published in this paper.

5.4 Funding Statement

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