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Original Article

Synthesis and evaluation of pharmacological activities of some 3-O-benzyl-4-C-(hydroxymethyl)-1,2-O-isopropylidene-α-D-ribofuranose derivatives as potential anti-inflammatory agents and analgesics

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Abstract

Background and purpose*:* α-D-ribofuranose analogues are reported to have multifarious biological properties such as analgesic, anti-inflammatory, and antiviral activities. The present study aims to synthesize some α-D-ribofuranose derivatives and investigate their biological properties.
Experimental approach*:* Four derivatives (**2a, 2b, 3,** and **4**) were synthesized from the starting material 3-O-benzyl-4-C-(hydroxymethyl)-1,2-O-isopropylidene-α-D-ribofuranose *via* subsequent benzylation, tosylation, and acetylation reactions in good yields. The compounds were confirmed by spectroscopic methods such as Fourier-transform infrared (FTIR) and proton nuclear magnetic resonance (^{1}HNMR), and then evaluated for various pharmacological activities using standard *in vitro* and *in vivo* procedures.
Findings / Results*:* Compound **2a** (50 mg/kg) exhibited both central and peripheral analgesic activity in the tail immersion test (2.52 ± 0.14 min tail flicking reaction time after 30 min from administration, $P < 0.001$) and the acetic acid-induced writhing test (65.33 ± 2.06% reduction in abdominal writhing, $P < 0.001$) respectively. In the anti-inflammatory assay, percent paw edema inhibition of carrageenan-induced rats for compounds **2a** and **4** (100 mg/kg) after 4 h of administration were 82.6% ($P < 0.001$) and 87.6% ($P < 0.001$), respectively. The compounds were also tested for antioxidant activity in 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay, antimicrobial property in disk diffusion assay, and cytotoxicity in HeLa cell line; however, no significant results were observed in any of those tests.
Conclusion and Implications*:* Our study indicated that some of the synthesized compounds exhibited promising analgesic and anti-inflammatory effects and may serve as potential lead compounds.

Keywords: α-D-ribofuranose; Anti-inflammatory; Anti-nociception; Cytotoxicity; Modified derivatives.

INTRODUCTION

Carbohydrate is one of the most prolific classes of biomolecules with prevalent importance in various biological processes involved in the living system (1). Recently carbohydrate-based therapeutic agents are becoming more popular and a great deal of interest has been focused on the development of new derivatives as potential lead compounds (2). D-ribose is a potent carbohydrate well known for its supplemental use in myocardial dysfunction (3), fibromyalgia-related pain (4), and chronic fatigue syndrome (5). D-ribose was also successful in improving the ischemic threshold in congestive heart failure patients during clinical trials (6). It also empowers the diastolic function by aiding the recovery of ATP levels in congestive heart failure patients (7) and some have even hypothesized that D-ribose can restore cardiac energy metabolism by increasing ATP metabolism (8).
α-D-ribofuranose, which is a D-ribose sugar, is particularly known for its innate ability to be used as a sugar moiety for synthesizing nucleoside analogues, which have a wide variety of biological activities (9).

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Nucleotide and nucleoside analogues synthesized from the α-D-ribofuranose sugar moiety have previously shown potent antinociceptive activity without any side effects (10). Chemically modified small interfering RNAs (siRNAs) containing ribofuranose sugar moiety in the 3'-overhang region seemed to have increased nuclease resistance and knockdown effect generating great interest in the field of RNA interference-based therapeutics (11). Ribofuranose nucleosides also exhibited cytotoxic activity in different cell lines (12) as well as antiproliferative activity in both molecular docking study and solid tumor-derived cell lines (13,14). Chemo-enzymatically synthesized ribofuranose derived cationic surfactants and ribofuranose derivatives of 1,5-benzothiazepines have been reported to have good antimicrobial activity (15,16). Inspired by the remarkable biological activities reported, herein a number of different α-D-ribofuranose analogues were synthesized from 3-O-benzyl-4-C-(hydroxyl-methyl)-1,2-O-isopropylidene-α-D-ribofuranose and investigated for their analgesic, anti-inflammatory, antioxidant, antimicrobial, and cytotoxic activity.

MATERIALS AND METHODS

Instrumentation

Chemicals, solvents, and reagents used in this study were all purchased from either Merck (Germany) or Sigma-Aldrich (USA). For purification of crude products, column chromatography was applied using silica gel 60-120 mesh (Lobachemie, India). Fourier-transform infrared (FTIR) spectra were recorded with FTIR 8400 (Shimadzu, Japan) and proton nuclear magnetic resonance (1HNMR, 400 MHz) was recorded in deuterated chloroform ($CDCl_3$) on a Bruker 400 MHz spectrometer (Germany). The reactions were monitored using thin layer chromatography (TLC) with appropriate mobile phase and detection of TLC peak was accomplished by para-anisaldehyde/ H_2SO_4/ glacial acetic acid stain and subsequent charring over a hot plate above 120 °C for about 1-2 min.

General procedure for synthesis of compounds

The synthesis of α-D-ribofuranose derivatives was accomplished according to the synthesis procedure first described by Koshkin *et al*. with some slight modifications and are illustrated in Fig. 1 (17,18). Regioselective benzylation of two hydroxyl group-containing diol from 3-O-benzyl-4- C- (hydroxymethyl)-1,2-O-isopropylidene-α-D-ribofuranose **(1)** yielded two products, the monobenzyl derivative 3,5-di-O-benzyl-4-C -(hydroxymethyl) -1,2-O-isopropylidene-α-D-ribofuranose **(2a)** and the dibenzyl derivative 3,5-di-O-benzyl-4-C-(benzyloxymethyl)-1,2-O-isopropylidene-α-D-ribofuranose **(2b)**.

The higher yield monobenzyl derivative **(2a)** was then isolated and tosylation reaction was performed using *p*-toluenesulphonyl chloride which yielded 3,5-di-O- benzyl-4-C- (*p*-toluenesulphonyloxy- methyl)-1,2-O-isopropylidene-α-D-ribofuranose **(3)**. Finally, acetolysis of the isopropylidene ring in product **3** was performed in the presence of concentrated sulfuric acid to give1, 2-di-O-acetyl -3,5- di-O-benzyl -4- C-(p-toluenesulphonyloxy - methyl) - 1, 2-O-isopropylidene-α-D-ribofuranose **(4)** in good yield.

Synthesis of benzylated α-D-ribofuranose derivatives (2a, 2b)

Compound **1** (5 g, 16 mmol) was dissolved in dimethylformamide and benzyl bromide (2.3 mL, 19.2 mmol) was added to the solution in presence of sodium hydride. After stirring at room temperature for 6 h, TLC confirmed the completion of the reaction and the synthesis of derivatives **2a** and **2b**, which were separated using column chromatography.

3,5-di-O-benzyl-4-C-(hydroxymethyl)-1,2-O-isopropylidene-α-D-ribofuranose (2a)

Yield: 4.2 g, 65.6%; colorless oil; IR (KBr, cm^{-1}): 3567 (O-H), 3031 (C-H, aromatic), 2981 (C-H), 1452 (C=C, aromatic); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.36 (3H, s, isopropyl CH_3^c), δ 1.63 (3H, s, isopropyl CH_3^d), δ 3.56 (2H, dd, J = 10.4 Hz, J = 27.2 Hz, CH_2^g), δ 3.87 (2H, dd, J = 12 Hz, J = 42.4 Hz, CH_2^h), δ 4.27 (1H, d, J = 4.8 Hz, C-H^e), δ 4.43-4.55 (4H, m, CH_2^f, CH_2^i), δ 4.64 (1H, s, OH), δ 4.77 (1H, d, J = 12 Hz, C-H^b) , δ 5.8 (1H, s, C-H^a), δ 7.24-7.36 (10H, m, aryl C-H).

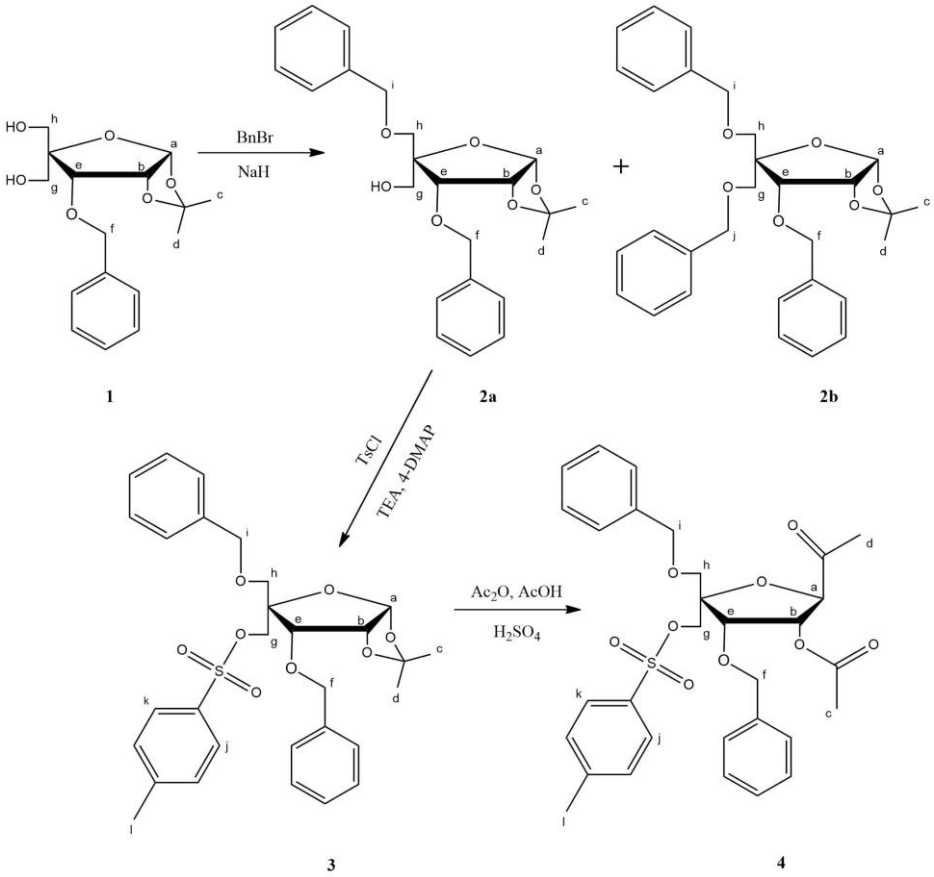

Fig. 1. General procedure for the preparation of α-D-ribofuranose derivatives.

3,5-di-O-benzyl-4-C-(benzyloxymethyl)-1,2-O-isopropylidene-α-D-ribofuranose (2b)

Yield: 1.1 g, 15.2%; yellow colored oil; IR (KBr, cm^{-1}): 3088 (C-H, aromatic), 1456 (C=C, aromatic), 2954 (C-H), 734 (C-H, aromatic); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.33 (3H, s, isopropyl CH_3^c), δ 1.51 (3H, s, isopropyl CH_3^d), δ 3.64 (2H, dd, *J* = 10.4 Hz, *J* = 62.8 Hz, CH_2^g), δ 3.88 (2H, dd, *J* = 10.8 Hz, *J* = 84.4 Hz, CH_2^h), δ 4.24 (1H, d, *J* = 5.2 Hz, C-H^e), δ 4.52-4.61 (4H, m, CH_2^f, CH_2^i), δ 4.72 (1H, d, *J* = 12 Hz, C-H^b), δ 5.77 (1H, d, *J* = 3.2 Hz, C-H^a), δ 7.24-7.32 (15H, m, aryl C-H).

Synthesis of 3,5-di-O-benzyl-4- C- (p-toluenesulphonyloxymethyl)- 1,2,- O-isopropylidene-α-D-ribofuranose (3)

p-toluenesulfonyl chloride (2.3 g, 12 mmol) was added to a solution of compound **2a** (3 g, 7.5 mmol) in dichloromethane in presence of triethylamine and 4-dimethylaminopyridine. After stirring at room temperature for 3 h, TLC confirmed the synthesis of derivative **3** as a colorless oil. Yield: 2.7 g, 64.9%; colorless oil; IR (KBr, cm^{-1}): 3031 (C-H, aromatic), 1454 (C=C, aromatic), 2870 (C-H), 737 (C-H, aromatic); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.29 (3H, s, isopropyl CH_3^c), δ 1.45 (3H, s, isopropyl CH_3^d), δ 2.41 (3H, s, tosyl CH_3^l), δ 3.82 (2H, dd, *J* = 10.8 Hz, *J* = 91.6 Hz, CH_2^g), δ 4.13 (1H, d, *J* = 4.8 Hz, C-H^e), δ 4.14 (2H, dd, *J* = 10.4 Hz, *J* = 35.2 Hz, CH_2^h), δ 4.44-4.56 (4H, m, CH_2^f, CH_2^i), δ 4.69 (1H, d, *J* = 12 Hz, C-H^b), δ 5.64 (1H, s, C-H^a), δ 7.23-7.33 (12H, m, aryl C-H), δ 7.4 (2H, d, *J* = 8 Hz, aryl C-H^{k,j}).

Synthesis of 1,2-di-O-acetyl-3,5-di-O-benzyl-4-C- (p-toluenesulphonyloxymethyl)-α-D-ribofuranose (4)

Acetic anhydride (2 mL, 21.6 mmol) was added to a solution of compound **3** (2 g, 3.6 mmol) in acetic acid with concentrated sulfuric acid acting as the catalyst. Stirring at room temperature for 4 h yielded compound **4** as a yellowish oil.

Yield: 1.73 g, 80.2%; yellow colored oil; IR (KBr, cm^{-1}): 3032 (C-H, aromatic), 1456 (C=C, aromatic), 2849 (C-H), 738 (C-H, aromatic), 1755 (C=O, ester); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.00 (3H, s, acetyl CH_3^d), δ 2.03 (3H, s, acetyl CH_3^c), δ 2.42 (3H, s, tosyl CH_3^l), δ 4.1 (2H, dd, *J* = 11.6 Hz, *J* = 22 Hz, CH_2^g), δ 4.22

(1H, d, J = 5.6 Hz, C-H^{e}), δ 4.23 (2H, dd, J = 10.4 Hz, J = 16 Hz, CH_2^{h}), δ 4.47 (4H, dd, J = 11.6 Hz, J = 48 Hz, CH_2^{f}, CH_2^{i}), δ 5.26 (1H, d, J = 4.8 Hz, C-H^{b}), δ 5.97 (1H, s, C-H^{a}), δ 7.22-7.34 (12H, m, aryl C-H), δ 7.76 (2H, d, J = 8 Hz, aryl C-H^{k,j}).

Analgesic activity

The synthesized compounds were tested for central analgesic activity using the tail immersion method described by Saldanha *et al.* with some slight modifications (19). Fifty Swiss albino mice were divided in ten equal groups- one for positive control (morphine, 2 mg/kg), one for negative control (0.9% NaCl saline solution) and the others were for testing two separate doses (25 and 50 mg/kg) of the four synthesized compounds. The mice in each group were orally fed with synthesized compounds (25 and 50 mg/kg) and after a certain interval of time (0, 30, 60, and 90 min), their tails were immersed in a water bath kept at 55 °C. The time required to withdraw the tail was recorded. A cut off time of 10 sec was imposed to prevent any injury to the tail (20).

For testing the peripheral analgesic activity, the acetic acid-induced writhing model of was employed with slight modifications (19). Fifty Swiss albino mice were grouped similarly as in the previous test and pre-treated orally with 0.9% NaCl saline solution (as negative control), diclofenac (as positive control), and synthesized compounds (25, 50 mg/kg) 30 min before intraperitoneal injection of 0.7% acetic acid (10 mL/kg, i.p.). The number of writhes induced by acetic acid was counted cumulatively for 15 min after a latency period of 5 min. Doses for both the tests (25, 50 mg/kg) were selected based on a pilot study where mice were orally fed different concentrations of test materials ranging between 5 to 400 mg/kg. The final doses selected were the ones that exhibited significant analgesic property while causing no animal mortality.

All the manipulations of animals were carried out following the rules provided by the Ethics Committee in Animal Experimentation (Ref: DU/Pharm_ETA: 05_04/2018) of the Department of Pharmacy, University of Dhaka, Bangladesh. All efforts were made to minimize animal suffering. The absolute minimum number of animals required was used and the intensity of the noxious stimuli was kept as low as possible to demonstrate consistent effects of the drug treatments.

Anti-inflammatory activity

Anti-inflammatory activities of the synthesized compounds were examined using a slightly modified procedure of carrageenan-induced hind paw edema assay in rats (21). Thirty-five male Wistar rats were divided into 7 separate groups including carrageenan group (injected with carrageenan only), negative control (injected with carrageenan, and orally fed 0.9% NaCl saline), positive control (aceclofenac, 100 mg/kg) and the four synthesized compounds (100 mg/kg) group. Each of the rats were injected with 0.1 mL of 1% carrageenan solution in the sub-plantar region of the hind paw 1 h after being orally treated with saline, aceclofenac or the synthesized compounds (100 mg/kg). Anti-inflammatory activity was measured at 0, 1, 2, 3, and 4 h intervals as the inhibition of average percent increment in the volume of hind paw compared against a control group that received neither standard nor test materials. The dose of test materials was selected based on a pilot study and on the usual dosage of aceclofenac (100 mg/kg), a commonly used non-steroidal anti-inflammatory drug (NSAID), which was used for comparing anti-inflammatory property in this test.

Cytotoxic activity

Cytotoxicity of the synthesized α-D-ribofuranose derivatives was assessed by WST-8 cell viability assay using the cell counting kit-8 (CCK-8) (22). HeLa cells (cervical cancer) were first seeded into a 96-well plate and incubated at 37 °C for 24 h to ensure cell growth. The cells were then induced with different concentrations of the sample and cell viability was examined after 48 h of incubation under a microscope using CCK-8, non-radioactive colorimetric cell proliferation and cytotoxic assay kit (Sigma-Aldrich, USA).

Antimicrobial activity

Antimicrobial activity was screened using a slightly modified version of the disk diffusion

method and compared with standard ciprofloxacin disk (23). Dry sterilized disk of about 6 mm diameter were diffused with 400 µg/disk of synthesized compounds and placed on agar Petri-dishes previously cultured with different bacterial and fungal species which include Gram (+) species such as *Bacillus cereus, Bacillus megaterium, Bacillus subtilis, Staphylococcus aureus,* and *Sarcina lutea*; Gram (-) species such as *Escherichia coli, Salmonella typhi, Shigella boydii, Shigella dysenteriae, Vibrio mimicus, Vibrio parahemolyticus, Pseudomonas aeruginosa,* and *Salmonella paratyphi*; fungal species such as *Candida albicans, Aspergillus niger,* and *Sacharomyces cerevacae*. Antimicrobial activity was qualitatively measured by observing the formation of a clear, distinct zone of inhibition area surrounding the disks and comparing it with standard ciprofloxacin (30 µg/disk).

Antioxidant activity

The antioxidant activity of the synthesized compounds was measured using a previously described method using 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay with slight modifications (24). The antioxidant potential was measured in IC_{50}, which is the concentration of compounds required to scavenge DPPH radical by 50%.

Statistical analysis

The data collected from the tests were analyzed using IBM SPSS Statistics package for Windows, Version 25.0 (Armonk, NY, USA). All experiments were repeated three times and expressed as the mean ± standard error of the mean (SEM). The results were analyzed statistically by one-way analysis of variance (ANOVA) followed by Tukey's post hoc analysis where $P < 0.05$ was considered to be statistically significant.

RESULTS

Analgesic activity of synthesized α-D-ribofuranose derivatives

The analgesic activity of the synthesized compounds at different concentrations (25 and 50 mg/kg) was tested using both central anti-nociception determining tail immersion assay and peripheral anti-nociception determining acetic acid-induced writhing assay.

In the tail immersion test compound **2a** (50 mg/kg, p.o.) exhibited highest tail flicking reaction time of 2.52 ± 0.14 min after 30 min from administration time compared to the negative control (0.78 ± 0.08 min) and positive control (3.26 ± 0.16 min) at that same time frame, $P < 0.001$. Compound **2a** (50 mg/kg, p.o.) showed statistically significant ($P < 0.001$) increase in tail flicking reaction time at 60 and 90 min after administration as well, whereas at 25 mg/kg dose compound **2a** showed increase reaction time at 30 min ($P < 0.001$) and 60 min ($P < 0.01$) after administration only. Other than that, compounds **2b** (25 and 50 mg/kg, p.o.) and **3** (50 mg/kg, p.o.) showed a significant increase in tail flicking reaction time at different time intervals which are shown in Fig. 2. The tested samples at both concentrations exhibited significantly different tail flicking reaction times when compared to the positive control group at 30, 60, and 90 min after administration (P <0.05, 0.01, and 0.001). In the acetic acid-induced writhing assay compound **2a** at both 25 mg/kg (p.o.) and 50 mg/kg (p.o.), significantly inhibited writhing by 42.22 ± 2.9% ($P < 0.001$) and 65.33 ± 2.06% ($P < 0.001$), respectively compared to the negative control group (5.33 ± 1.66%). Similarly compound **2b** at both 25 mg/kg (p.o.) and 50 mg/kg (p.o.) doses also inhibited writhing by 31.11 ± 2.22% ($P < 0.001$) and 41.33 ± 3.34% ($P < 0.001$), respectively whereas the positive control inhibited writhing by 84.44 ± 2.22 ($P < 0.001$) in comparison with the negative control. All other test compounds showed no statistically significant reduction in writhing as shown in Fig 3 compared to the negative control. The negative control group and test samples at both doses showed significantly different inhibition in writhing ($P < 0.01$ and $P < 0.001$) when compared to the positive control.

Anti-inflammatory activity of synthesized α-D-ribofuranose derivatives

The compounds were tested for anti-inflammatory activity based on their inhibition of the hind paw edema of rats induced by administration of 1% carrageenan solution on the sub-plantar surface of the right hind paw.

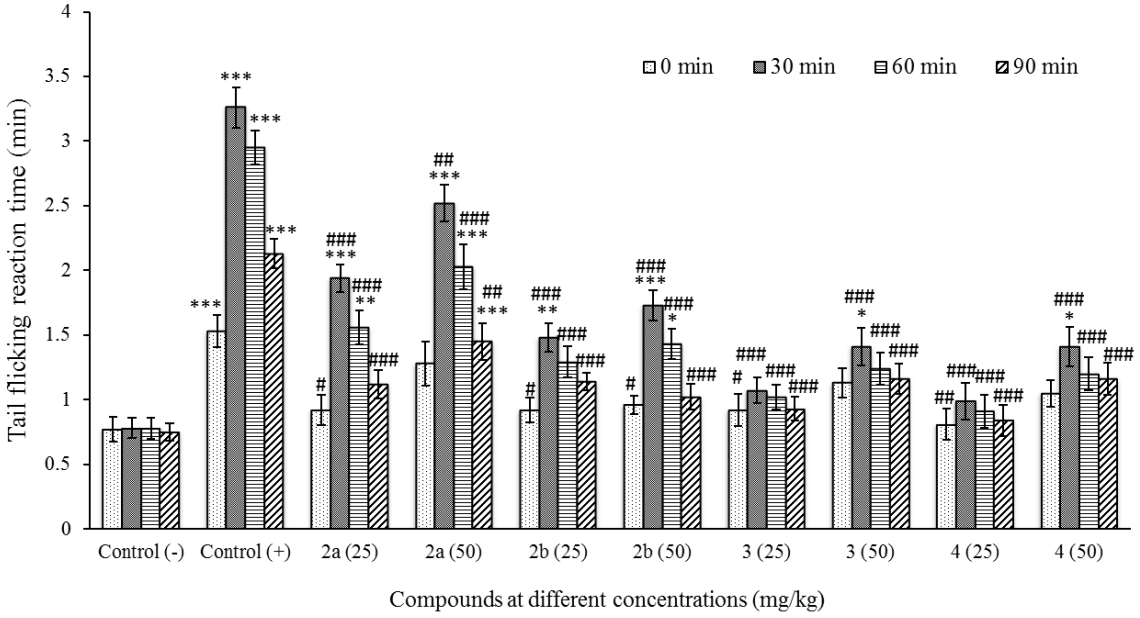

Fig. 2. Determination of central antinociception activity at different concentrations (25 and 50 mg/kg) of synthesized compounds. Data are expressed as mean ± SEM, n = 5. **P* < 0.05, ***P* < 0.01, and ****P* < 0.001 indicate significant differences in comparison with negative control group (0.9% NaCl solution). $^{\#}P$ < 0.05, $^{\#\#}P$ < 0.01, and $^{\#\#\#}P$ < 0.001 indicate significant differences compared to positive control (morphine, 2 mg/kg).

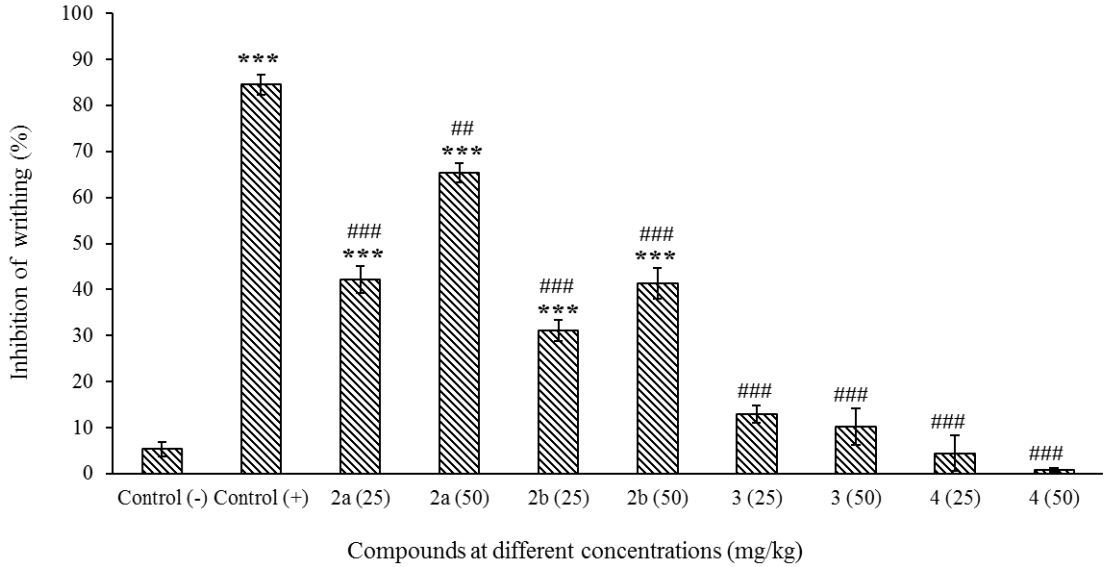

Fig. 3. Determination of peripheral antinociception activity at different concentrations (25 and 50 mg/kg) of synthesized compounds. Data are expressed as mean ± SEM, n = 5. **P* < 0.05, ***P* < 0.01, and ****P* < 0.001 indicate significant differences compared to the negative control group (0.9% NaCl solution). $^{\#}P$ < 0.05, $^{\#\#}P$ < 0.01 and $^{\#\#\#}P$ < 0.001 indicate significant differences compared to positive control (diclofenac, 25 mg/kg).

Both compounds **2a** and **4** (100 mg/kg, p.o.) showed significant anti-inflammatory effect from the first hour and onward up to four hours compared to that of standard aceclofenac (100 mg/kg p.o.). Compared to the negative control (0.9% NaCl saline) group, the % paw edema inhibition of **2a** was 21.2%, 56.3% (*P* < 0.001), 70.4% (*P* < 0.001), and 82.6% (*P* < 0.001), and for **4** was 16.7%, 59.2% (*P* < 0.001), 72.4% (*P* < 0.001), and 87.6% (*P* < 0.001) in 1st, 2nd, 3rd and 4th hour, respectively which is comparable to aceclofenac's 46.2, 78.7, 85.7, and 95.4% reduction of paw edema. The other compounds exhibited insignificant differences (compared to the negative control) in the reduction of paw edema as shown in Fig. 4.

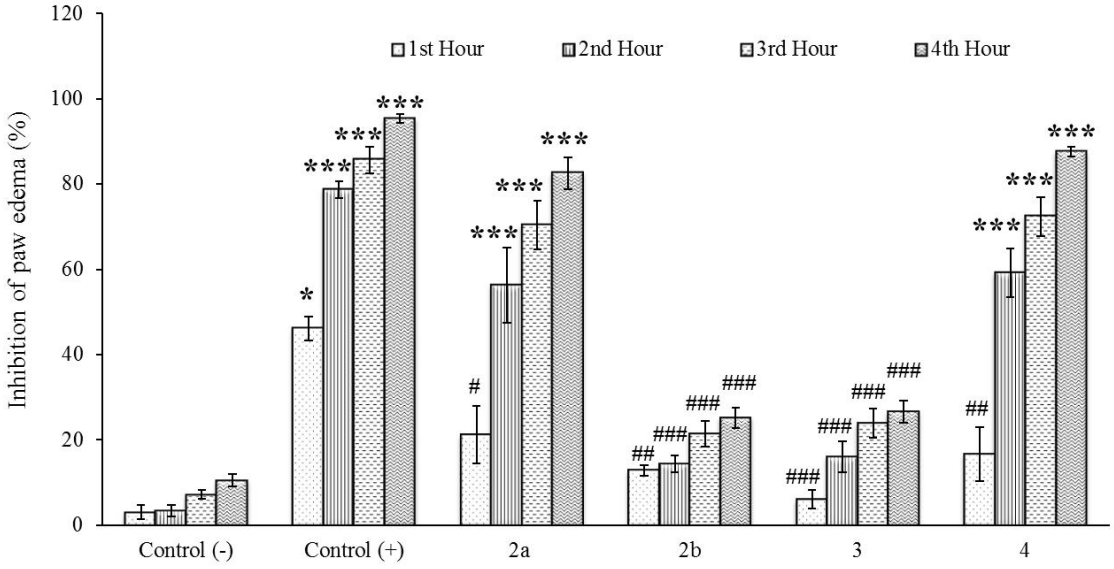

Fig. 4. Effects of the compounds (100 mg/kg) in the carrageenan induced hind paw edema test. Values are expressed as mean ± SD, n = 5. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ indicate significant differences compared to the negative control group (0.9% NaCl saline). $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, and $^{\#\#\#}P < 0.001$ indicate significant differences compared to the positive control group (aceclofenac ,100 mg/kg).

Cytotoxic, antimicrobial and antioxidant activity of synthesized α-D-ribofuranose derivatives

Different concentrations (0.1-1000 µM) of synthesized α-D-ribofuranose were assessed for cytotoxic activity on the HeLa cancer cell line, antimicrobial activity on a number of Gram (+) and Gram (-) organisms and antioxidant activity on DPPH radical scavenging assay. All the assays yielded negative results so no further sophisticated cytotoxic, antimicrobial, or antioxidant assays were performed on the compounds.

DISCUSSION

Nucleotide and nucleoside analogues synthesized from the α-D-ribofuranose sugar moiety have previously shown anti-nociceptive activity to some extent (10). Several nucleoside analogues had also demonstrated analgesic activity in a number of antinociceptive assays such as thermal nociception test (25), formalin induced paw screening assay (26) and the hot plate test (27). The present study demonstrated for the first time compound **2a** produces both central and peripheral antinociceptive effects in experimental models *in vivo*. In order to assess the central and peripheral antinociceptive activity of the synthesized compounds, we examined their effect in hot water tail immersion test, a model, which is only sensitive to centrally acting drugs and the acetic acid-induced abdominal writhing test, an important test for screening analgesic activity, respectively (28). There is a great correlation between results in the central and peripheral analgesic effects. The compound **2a** induced a significant increase of latency in reaction time of tail flicking in central analgesic screening. Similar to the central antinociceptive assay, compound **2a** again demonstrated significant activity against the visceral nociception induced by acetic acid. Based on these two assays it may be assumed that compound **2a** has potential analgesic activity and might be tested further to confirm the mechanism of its antinociceptive action. Further structural modifications of this compound might lead to the discovery of potential analgesic drugs.

In the present study, the synthesized compounds were tested for anti-inflammatory activity by administering them on the carrageenan-induced hind paw edema. The edema formed after carrageenan injection is the result of two events; an initial event characterized by the release of serotonin and histamine which begins right after administration of carrageenan and lasts up to one hour (29). The second phase begins right after, due to the release of various inflammatory mediators such as proteases, leukotrienes, and

prostaglandins thus activating cyclooxygenase enzymes (30). As demonstrated in the test both compounds **2a** and **4** showed a macroscopic anti-inflammatory effect by decreasing paw edema thickness from 2 to 4 h after the injection of carrageenan. From this, we hypothesize that the compounds exhibited anti-inflammatory action either by decreasing the release of inflammatory mediators or by a competitive antagonistic action on cyclooxygenase enzyme.

Another possible explanation of the analgesic and anti-inflammatory activities of the compound can be correlated to their structural similarities with ribofuranose analogues that are known to be adenosine kinase inhibitors. Adenosine is a purine ribonucleoside, which is a ubiquitous neuromodulator of a number of cellular activities, and when inhibited in the central and peripheral nervous systems it can produce anticonvulsant, analgesic and anti-inflammatory action (31). Ribofuranoyl adenosine kinase inhibitors structurally similar to our synthesized compound have been previously reported to exhibit anti-nociceptive and anti-inflammatory properties (25,26). However, computation models must be explored before we can hypothesize an inhibitory action of adenosine kinase receptors and we plan to explore this in the future. The synthesized compounds did not show any evidence of cytotoxic, antimicrobial and antioxidant properties in their respective assays.

CONCLUSION

Four α-D-ribofuranose derivatives were synthesized successfully and evaluated for various pharmacological activities where compound **2a** showed prominent analgesic and anti-inflammatory activity and compound **4** showed promising anti-inflammatory activity. Further investigations and structural modifications of these compounds may lead to derivatives that are more potent.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest for this study.

AUTHOR'S CONTRIBUTION

S. M. Abdur Rahman contributed to the concept, design and defining intellectual content relevant to the research, supervised the work, and is the corresponding author of this work. F. I. Rahman performed the literature search, experimental studies, data acquisition, and statistical analysis. F. Hossain and N. Saqueeb assisted in this research work and helped in the manuscript preparation, editing, and review.

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