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Synthesis, Characterization and Screening of Novel Glycoside Derivatives of Urea for Anticonvulsant Activity

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ABSTRACT:The present study consist of synthesis of 5 new novel Glycosyl derivatives of Aryl urea, prepared by the reaction of P- Aminophenol with different Aromatic Aldehydes and the condensation of these derivatives with D-Fructose. The chemical structures of synthesized compounds were confirmed by 1H-NMR, IR and Elemental analysis. The purity of compound was confirmed by the TLC. The compounds were screened for Anticonvulsant activity by Pentylenetetrazole and MES induced convulsion method. It is an effective strategy to improve the bioavailability of the compounds and show beneficial effect on activity.

KEYWORDS: Aryl urea, Glycosylation, Aromatic Aldehyde, P-Amino phenol, Anticonvulsant activity.

I. INTRODUCTION

Drug a discovery involves the identification of a lead molecule and modification of their structure by various chemical reactions or by the structural mimicking of natural products to get the desired activity[1]. Along with the enhancement of desired activity, it is possible to reduce the other undesirable properties such as high toxicity, insolubility and metabolism problems. The influence of many possible manipulations with regard to the chemical structure in variation of the biological activity is the prime focus medicinal chemistry[2]. Aryl urea forms an important construction motif for the development of new drugs that could be better in terms of efficacy and lesser toxicity[3]. The covalent attachment of carbohydrate to the target macro molecule is known as glycosylation[4].

II. MATERIALS AND METHODS

Melting points of the compounds were recorded on 'Veego' VMP-D apparatus. TLC Silica gel G plates of 3×8 cm (Sigma-Aldrich) were used and as Mobile phase - Ethyl acetate : chloroform (1:1) were used and spots located by UV chamber. The IR spectra recorded in the 4000-400cm-1 range and 1H-NMR spectra recorded in DMSO (TMS as internal standard). Elemental analysis was performed for C, H & N

III. METHODOLOGY[5]:

To the mixture of P-Amino phenol (0.05 mol), and Aromatic aldehydes (0.05 mol) added Urea in Ethanol (0.05 mol) drop wise and reaction mixture was stirred in hot water bath at 80^0 C with constant stirring for specific period according to the derivative. The solid separated on cooling was recrystallized from ethanol. The recrystallized product (1 mmol) with D-Fructose (1 mmol) was heated with absolute ethanol (10 ml) in the presence of drops of glacial acetic acid for specific period according to the derivative. After cooling the solid was filtered off and recrystallized from ethanol.

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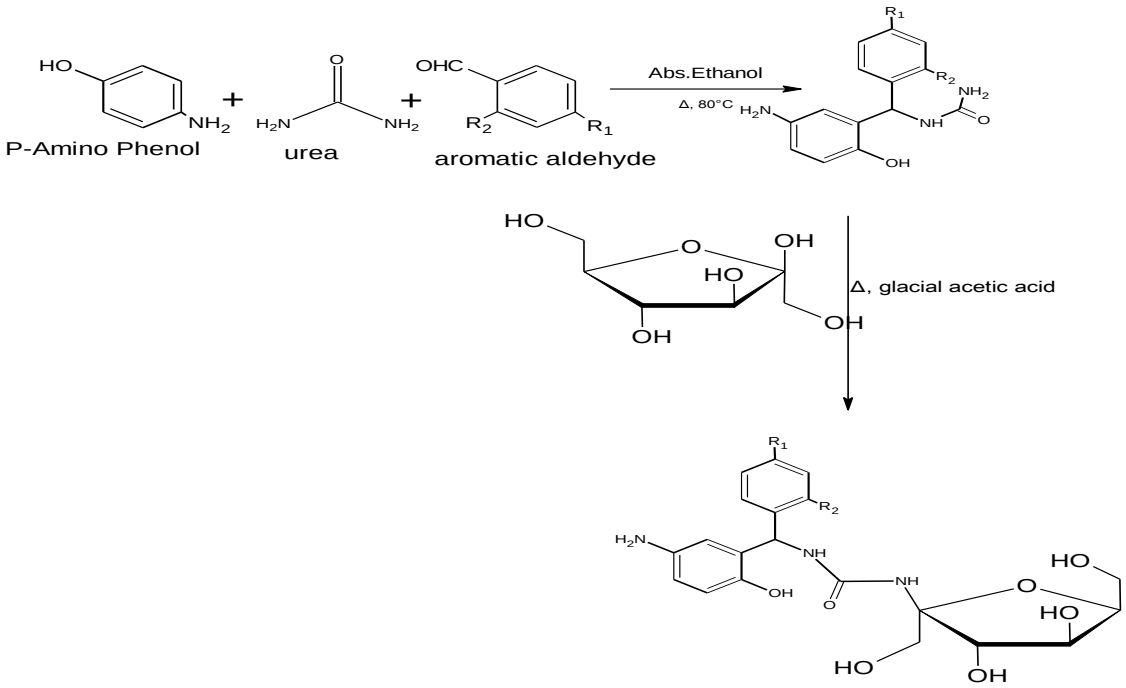

Figure 1: Synthesis of Glycosyl Urea derivatives

IV. EXPERIMENTATION

IV.i. SCREENING OF ANTICONVULSANT ACTIVITY :

IV.i.a) ANIMALS USED FOR THE STUDY

Albino rats (Wister strain) were used to carry out the studies on activities. The experiment were carried out as per the guidelines of CPCSEA, New Delhi, India and approved by the Institutional Animal Ethical Committee (IAEC). Reg. No : PCP/IAEC/2018-2/7. The synthesized compounds were screened for their Anticonvulsant activity by MES and Pentylenetetrazole induced convulsion method.

IV.i.b) Maximal electroshock seizure method[6]

Rats were divided into seven groups each containing 6 animals. Group 1 is considered as control and treated with CMC (0.5%,i.p). The second group is standard, treated with phenytoin (25mg/kg i.p). The groups 3-7 were given test substance orally. After 1 hour an electric current of 150mA for 0.2 sec was given through ear electrodes to induce convulsions. The Suppression of tonic hind limb extension is taken as the measure of anticonvulsant activity.

IV.i.c) Pentylenetetrazole induced convulsion method[6]

Rats were divided into seven groups each containing 6 animals. Control group is treated with CMC (0.5%, i.p). Diazepam (10mg/kg i.p) is administered as standard. The test substance (60mg/kg) is given orally for group 3-7. After 60 min administered Pentylenetetrazole (50mg/kg) subcutaneously and note down the latency in onset of convulsion.

V. RESULTS AND DISCUSSION

V.i. PHYSICOCHEMICAL PROPERTIES

Table 1 : Physicochemical properties

SAMPLE CODE	R1	R2	MOLECULAR WEIGHT	MELTING POINT (^{0} C)	Rf VALUE
J1	Cl	Cl	488.32	139	0.78
J2	Cl	H	453.88	165	0.53
J3	OCH2C6H5	H	463.72	173	0.57
J4	NO2	H	464.43	155	0.69

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J5	H	H	419.43	169	0.73

V.ii. SPECTRAL INTERPRETATION

1-(2-hydroxy, 4-aminophenyl) (2,4-dichlorophenyl) methyl-3- (1-deoxy-β-D-fructopyranosyl) urea (J1) : Yield 49%, IR(KBr): 3385(Ar-OH),1616(C=O), 1579(Ar C=C Streching), 1235(CN)732(C-Cl). 1H-NMR (DMSO): 7.2-7.5(m,6H,Ar-H), 8.3(d,2H,CH-NH), 9.3(s,H,Ar-C-OH). Elemental analysis calculated- C: 47.5, H:4.3, N: 7.6.

1-(2-hydroxy, 4-aminophenyl)(4-chlorophenyl) methyl-3- (1-deoxy-β-D-fructopyranosyl) urea (J2): Yield 57%, IR(KBr): 3304(Ar-OH), 3045(CH-streching), 1624(C=O), 1238(CN),750.3(C-Cl). 1H-NMR (DMSO): δ7.5-7.6(m,7H,Ar-H), δ8.07(d,2H,CH-NH), δ9.06(s,Ar-C-OH). Elemental analysis calculated- C: 51.5, H:5.1, N: 8.9.

1-2-hydroxy, 4-aminophenyl)(4-benyloxyphenyl) methyl-3- (1-deoxy-β-D-fructopyranosyl) urea (J3) : Yield 65%, IR(KBr): 3400(Ar-OH), 3037(CH Streching), 1597(NH Bending), 1240(CN). 1H-NMR (DMSO): δ8.6 (m,7H,Ar-H), δ7.9(d,2H,CH-NH), δ5.2(d,2H,CH-NH), δ6.8(d,H,NH). Elemental analysis calculated- C: 60.5, H:4.7, N: 7.6.

1-(2-hydroxy, 4-aminophenyl) (3-nitrophenyl) methyl-3- (1-deoxy-β-D-fructopyranosyl) urea (J4) : Yield 50%, IR(KBr): 3371(Ar-OH), 1616(C=O), 1514(NO2), 1226(CN). 1H-NMR (DMSO): δ9.2(s,Ar-C-OH), δ7.8 (d,2H,CH-NH), δ6.9(s,H,NH). Elemental analysis calculated- C: 50.25, H:4.34, N: 11.81.

1-(2-hydroxy, 4-aminophenyl) (phenyl) methyl-3-(1-deoxy-β-D-fructopyranosyl) urea (J5): Yield 68%, IR(KBr): 3325(Ar-OH),1624(C=O), 175(Ar C=C streching), 1235(CN). 1H-NMR (DMSO): δ5.2(Ar-CH-NH), δ9.02 (s,Ar-C-OH), δ6.3(s,H,NH). Elemental analysis calculated- C: 56.72, H:5.32, N: 9.71.

V.iii. ANTICONVULSANT ACTIVITY

In vivo anticonvulsant activity study was carried out for all the newly synthesized Glycosyl urea derivatives by the Pentylenetetrazole and MES induced convulsion method using Diazepam and phenytoin as standard .

Table 2: Anticonvulsant activity by Pentylenetetrazole induced convulsion method

GROUP	LATENCY IN ONSET OF CONVULSION (in min)
Control	0.27 ± 0.01
Standard	0
J1	1.57 ± 0.11
J2	4.22 ± 0.14
J3	6.69 ± 0.14
J4	7.90 ± 0.19
J5	2.51 ± 0.14

Figure 2: graphical representation of anticonvulsant activity of J1-J5 by Pentylenetetrazole induced convulsion method

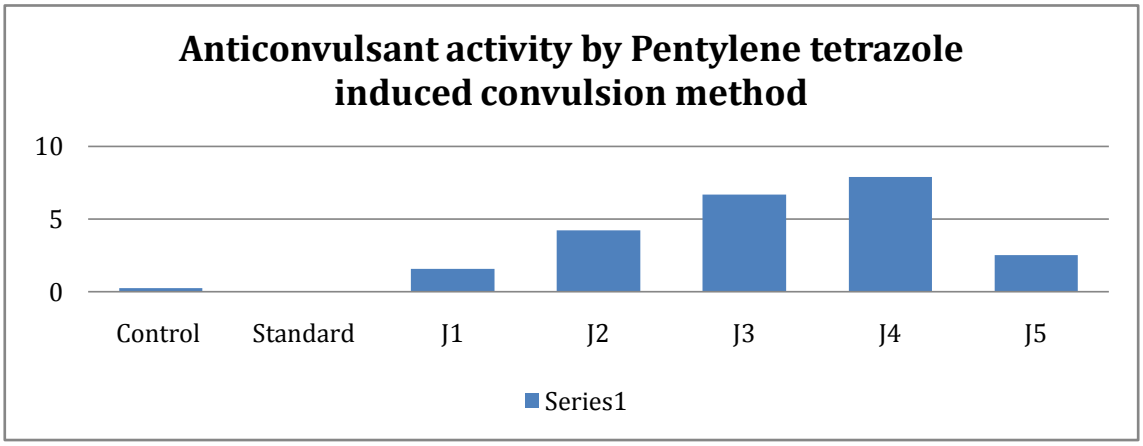

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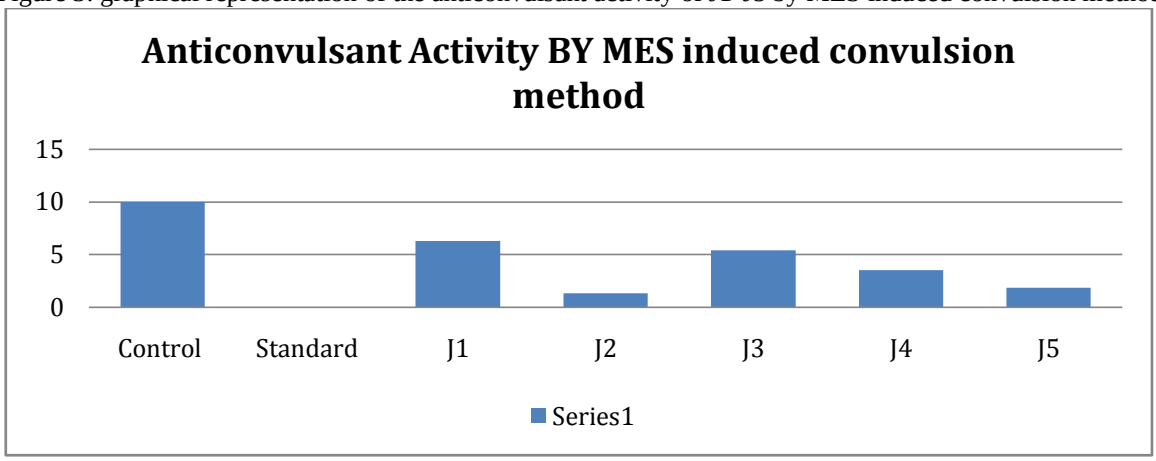
Table 3: Anticonvulsant activity by MES induced convulsion method[Maximal Electroshock induced convulsion method]

GROUP	TONIC EXTENSOR PHASE (in min)
Control	10.02 ± 0.56
Standard	0
J1	6.32
J2	1.34
J3	5.4
J4	3.56
J5	1.85

Figure 3: graphical representation of the anticonvulsant activity of J1-J5 by MES induced convulsion method



Out of 5 newly synthesized compounds, most of them showed protection against convulsion. J4 (1- (2-hydroxy, 4-aminophenyl) (3-nitrophenyl) methyl-3- (1-deoxy-β-D-fructopyranosyl) urea) with Nitro group and J3 (1-(2-hydroxy, 4-aminophenyl)(4-benyloxyphenyl) methyl-3- (1-deoxy-β-D-fructopyranosyl) urea) with p-bezyloxy group showed protective effect in Pentylenetetrazole induced convulsion method. J2 (1- (2-hydroxy, 4-aminophenyl)(4-chlorophenyl) methyl-3- (1-deoxy-β-D-fructopyranosyl) urea) with chloro group and J5 (1- (2-hydroxy, 4-aminophenyl) (phenyl) methyl-3- (1-deoxy-β-D-fructopyranosyl) urea) with unsubstitued phenyl ring showed good activity in MES induced convulsion method

CONCLUSION

Most of the synthesized compounds possess appreciable activity. The linkage with Monosaccharide can enhance the drug targeting and therapeutic effect. Among the synthesized compounds J2 & J5 were found protective against MES induced convulsion and J3&J4 were found effective against Pentylenetetrazole induced convulsion. These compounds later could be beneficial not only as new active chemical entities but also can be precursors for the synthesis of pharmacologically active compounds.

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