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Synthesis of Certain Bioactive Molecules Containing N-Glucosylated s-Triazines.

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ABSTRACT

A series of 6-tetra-O-acetyl-β-D-glucopyranosylimino 2 dimethylamino-4 aryl/alkyl imino-1,4,5,6 tetrahydro-1,3,5 triazines have been synthesized by the interaction of tetra-O-acetyl α-D glucopyranosyl bromide and various 1,3,5 triazines. The latter were synthesized by following the interaction of metformin hydrochloride and N-aryl/alkyl imino isocyanodichloride in chloroform medium. The identities of these new N-glucosylated triazines have been established on the basis of elemental analysis, I.R., NMR and mass spectral studies. The newly synthesized compounds were screened for their antimicrobial and antifungal activities. Some of them showed moderate to less antimicrobial activity.

Keywords: N-glucosylated 1, 3 ,5 triazines, antimicrobial activity.

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INTRODUCTION

s-Triazine and its derivatives are one of several isomeric triazines useful in a variety of applications[1].Triazine derivatives are interesting compounds with biologically important properties[2-6] and have found a number of applications as herbicides, for catalysis or in polymer chemistry ,as reactive dyes and in medicinal chemistry as drugs[7]. The s-triazines and its derivatives have their own importance in heterocyclic compounds due to their very good activities. The s-triazines have been associated with a wide range of therapeutic activities [8-12] such as antibacterial[13], antimicrobial[14],fungicidal, antiarthritic, local anesthetic, anticonvulsant, algaecide and disinfectant, hypoglycemic, analgesic, sedative and anti-inflammatory, anthelmintic and antitubercular .

The other application is in the Gattermann reaction used to attach the formyl group to aromatic substrates. It is a common reagent, and readily forms derivatives which are used as pharmaceutical products, as well as herbicides, such as atrazine[5,15]. In view of the importance of metformin as hypoglycemic agent it was thought interesting to incorporate the skeleton of metformin in resulting heterocyclic moiety and hence this work was undertaken.

MATERIALS AND METHODS

The chemicals and reagents used in present work were of AR grade and LR grade purchased from SD fine chem. Ltd., and,Loba chem. Ltd., Amines used were aniline, o-toludine, p-toludine ,o-chloro aniline ,p-chloro aniline, o-anisidine, p-anisidine etc. The reaction progress was monitored by TLC technique by using suitable mobile phase of solvent. Purification of compounds was done by recrystalization method by using suitable solvent. Determination of melting point was done by using melting point apparatus and are uncorrected. IR spectra recorded on HAPP-GENZEL. ^{1}H NMR spectra on Bruker avance-II 400 NMR spectrometer at 400 MHz in $CDCl_3$ as solvent were recorded. The mass spectra were recorded on TOF MS ES+ 2.77e^3 mass spectrometer (at 1.24 e V).The compounds were screened for their antibacterial and antifungal activities by the agar diffusion method.

Experimental

Synthesis of 2-dimethylamino-4-phenylimino-6-imino 1,4,5,6 tetrahydro-1,3,5 triazine. (III) (where R=Phenyl)

A mixture of metformin hydrochloride (1.65 g, 0.01 M) and phenyl isocyanodichloride (II a, 1.74 g, 0.01 M) in chloroform (10 ml) was refluxed for 4 hours on water bath till the complete evolution of hydrogen chloride gas was observed. The solvent was vacuum distilled and resulting

solid (III a) recrystalized from ethanol, m.p. 227 °C.

The other compounds (III b-III h) were synthesized by extending the reaction of metformin hydrochloride with related isocyanodichlorides (II b-II h)

Synthesis of N-glucosylated 1,3,5 triazine :

6-tetra-O-acetyl-β-D glucopyranosylimino 2-dimethylamino-4-aryl/alkylimino-1,4,5,6 tetrahydro-1,3,5 triazine,(V),(Where R= phenyl)

The reaction of tetra-O-acetyl-α-D glucopyranosyl bromide (1.8g, 0.0043M) and 2-dimethylamino-4-phenylimino-6-imino 1,4,5,6 tetrahydro-1,3,5 triazine(III a, 1g, 0.0043M) was carried out in pyridine on boiling water bath for 1 hour. After completion of reaction, the reaction mixture was poured into cold water when a white solid (Va) was obtained. It was filtered, dried and crystallized from ethanol, m .p. 113 °C.

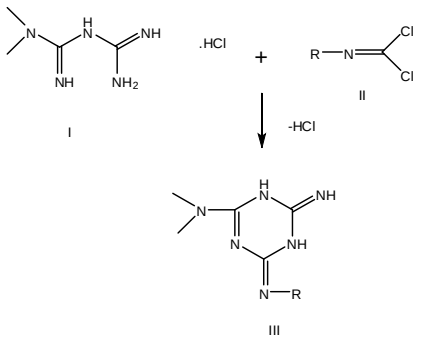
Other compounds V b-V h were synthesized by extending the above reactions with appropriate reagents, respectively.

Procedure for Antimicrobial Screening:

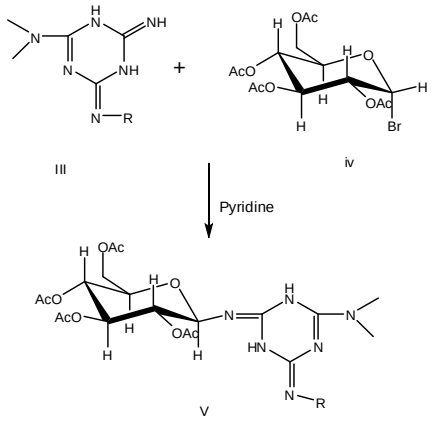
Antibacterial: Initially, the stock cultures of bacteria were revived by inoculating in broth media (peptone-10g,NaCl-10 g and Yeast extract 5g,Agar 20g in 1000ml of distilled water) and grown at 37 °C for18 hours. The agar plates of the above media were prepared and wells were made in the plate. Each plate was inoculated with 18 hour old cultures (100ul,10^{-4} cfu) and spread evenly on the plate. After 20 minutes, the wells were filled with the solution of compounds at different concentrations. The control wells with Gentamycin were also prepared. All the plates were incubated at 37 °C for 24 hours and the diameter of inhibition zone were measured. **Antifungal**: Potato dextrose agar 250g of peeled potato were boiled for 20 minutes and squeezed and filtered. To this filtrate 20 g of dextrose was added and the volume was made up to 1000 ml by distilled water. Initially, the stock cultures of fungi were prepared and wells were made in the plate. Each plate was inoculated with 48 hour old cultures (100ul,10^{-4}cfu)and spread evenly on the plate .After 20 minutes, the wells were filled with solution of compounds at different concentrations .The control plates with antibiotic Amphotericin were also prepared. All the plates were incubated at 27 °C for 48 hours and the diameter of inhibition zone were measured.

RESULTS AND DISCUSSION

1, 3, 5 Triazines (**scheme 1**) were synthesized by following the interaction of metformin hydrochloride and N-aryl/alkyl imino isocyanodichloride in chloroform medium by refluxing on water bath for 4 hours. The solvent was vacuum distilled and the resulting solid recrystalized



Scheme-1 **Synthetic route of the compounds (III)a-h**



Scheme-2 **Synthetic route of the compounds (V)a-h**

Where R in III and V are
a) Phenyl b)) o-tolyl c) p- tolyl d) o-chloro-phenyl e) p-chloro-phenyl f) o-anisyl g) p-anisyl h) t-butyl .

Table 1:-Physicochemical parameters of 1,3,5 triazine .

Sr.no	Comp. Code	R	Molecular formula	Molecular weight	Melting point(^{0}c)	Yield%
1	IIIa	C_6H_5	$C_{11}H_{14}N_6$	230	227	69.56
2	IIIb	o-$CH_3C_6H_4$	$C_{12}H_{16}N_6$	244	227	57.37
3	IIIc	p-$CH_3C_6H_4$	$C_{12}H_{16}N_6$	244	217	80.32
4	IIId	o-ClC_6H_4	$C_{11}H_{13}N_6Cl$	264.5	227	60.11
5	IIIe	p- ClC_6H_4	$C_{11}H_{13}N_6Cl$	264.5	224	55.57
6	IIIf	o- $CH_3OC_6H_4$	$C_{12}H_{16}N_6O$	260	225	46.15
7	IIIg	p-$CH_3OC_6H_4$	$C_{12}H_{16}N_6O.HCl$	296.5	226	46.15
8	IIIh	t-butyl	$C_9H_{18}N_6$	210	226	70

Table 2:- Physicochemical parameters of N-glucosylated 1,3,5 triazine

Sr.no	Compound Code	R	Molecular formula	Molecular weight	Melting point(^{0}c)	Yield%
1	Va	C_6H_5	$C_{25}H_{32}O_9N_6$	560	113	8.0
2	Vb	o-$CH_3C_6H_4$	$C_{26}H_{34}O_9N_6$	574	110	8.0
3	Vc	p-$CH_3C_6H_4$	$C_{26}H_{34}O_9N_6$	574	83	7.7
4	Vd	o-ClC_6H_4	$C_{25}H_{31}O_9N_6Cl$	594.5	113	8.5
5	Ve	p- ClC_6H_4	$C_{25}H_{31}O_9N_6Cl$	594.5	109	7.5
6	Vf	o- $CH_3OC_6H_4$	$C_{26}H_{34}O_{10}N_6$	590	102	7.5
7	Vg	p-$CH_3OC_6H_4$	$C_{26}H_{34}O_{10}N_6$	590	114	8.0
8	Vh	t-butyl	$C_{23}H_{36}O_9N_6$	540	111	24.0

from ethanol. The reaction of tetra-O-acetyl-α-D glucopyranosyl bromide and 1, 3, 5 triazine (**scheme 2**) was carried out in pyridine on boiling water bath for 1 hour. After completion of reaction, the reaction mixture was poured into cold water when a white solid was obtained. It was filtered, dried and crystallized from ethanol.

Antimicrobial Activity

The synthesized compounds were screened for their antibacterial activities against Escherichia coli (E.coli) and, Staphylococcus aureus (S.aureus) by agar diffusion method at a concentration 2 mg/l in dimethyl sulphoxide(DMSO) by using the standard drug Gentamycin for bacteria. Amongst the compounds tested for antibacterial activity, compounds V c and V f showed moderate activity and other compounds showed very less to negligible activity.

Antifungal Activity

All the compounds were also screened for their antifungal activities by the agar diffusion method at a concentration 2 mg/l in DMSO against Aspergilus niger (A.niger).and Candida albicans.(C.albicans) The standard drug Amphotericin was used for comparison. The compound V c showed moderate activity against A.niger and C.albicans.

Characterization data for 1,3,5 triazines (III)

III a: **2-dimethylamino-4-phenylimino-6-imino 1,4,5,6 tetrahydro-1,3,5 triazine.** Molecular formula (M.F) $C_{11}H_{14}N_6$,m.p. 227°C,I.R(KBr)cm^{-1} 1595(C=N),2980(C-H),3180 (Ar-H),3300 (N-H),^{1}HNMR ppm .δ value 1.25 (2 N-H), δ 1.57 (- N-$(CH_3)_2$) , δ 7.3 (Ar - H), δ 7.4 (=NH)

III b: **2-dimethylamino-4-o-tolylimino-6-imino 1,4,5,6 tetrahydro-1,3,5 triazine** M.F $C_{12}H_{16}N_6$, m.p. 227°C I.R(KBr)cm^{-1} 3390(N-H),3180(Ar-H) , 3310 , ^{1}HNMR ppm .δ value=1.3-1.6 (- N-$(CH_3)_2$), δ value0.9 (N-H), δ 2.27(Ar-CH_3), δ 7.1-7.3(Ar - H), δ 7.2-7.6(N-H), Mass spectrum: m/z 244 (M^+)

III c: **2-dimethylamino-4-p-tolylimino-6-imino 1,4,5,6 tetrahydro-1,3,5 triazine** M.F .$C_{12}H_{16}N_6$, m.p. 217°C, I.R(KBr)cm^{-1} 3380 (N-H),3180 (Ar-H), ^{1}HNMR ppm .δ value= 1.25 (- N-$(CH_3)_2$) , δ 7.8 and 7.95 (N-H), δ 2.32 (Ar-CH_3), δ 7.3-7.5 (Ar-H),Mass spectrum : m/z 244 (M^+)

III d: **2-dimethylamino-4-o-chloro-phenylimino-6-imino 1,4,5,6 tetrahydro-1,3,5 triazine** M.F $C_{11}H_{13}N_6Cl$, m.p .227°C, I.R(KBr)cm^{-1} 3460 (N-H),1637(C=N) ^{1}HNMR ppm .δ value 1.25 -1.28(- N-$(CH_3)_2$), δ 7.05-7.45 (Ar - H), δ 7.6(N-H)

III e: **2-dimethylamino-4-p-chloro-phenylimino-6-imino 1,4,5,6 tetrahydro-1,3,5 triazine** M.F $C_{11}H_{13}N_6Cl$, m.p 224°C I.R(KBr)cm^{-1} 3390 (N-H),1590(C=N),

III f: **2-dimethylamino-4-o-anisylimino-6-imino 1,4,5,6 tetrahydro-1,3,5 triazine** M.F $C_{12}H_{16}N_6O$, m.p 225°C I.R(KBr)cm^{-1},3462.6 (N-H),2999.7(Ar-H),2982.3(C-H,CH_3) 2849.2(-C-H),1741.9 (C=O), ^{1}HNMR ppm. δ value 1.2 (- N-$(CH_3)_2$), δ 3.8 (- OCH_3) δ 6.8-7.3 (Ar - H), δ 7.53(N-H)

III g: **2-dimethylamino-4-p-anisylimino-6-imino 1,4,5,6 tetrahydro-1,3,5 triazine** M.F $C_{12}H_{16}N_6O.HCl$, m.p 226°C I.R(KBr)cm-^{1} 3378(N-H),1563 (C=N),3178(Ar-H), Mass spectrum : m/z 260 (M+1)$^+$ monohydrochloride.(M + HCl^{35} =295, M+HCl^{37}=297 in 3:1 ratio were also observed.)

III h) **2-dimethylamino-4-t-butylimino-6-imino 1,4,5,6 tetrahydro-1,3,5 triazine** M.F $C_9H_{18}N_6$, m.p 226°C I.R(KBr)cm^{-1} 3390(N-H),3190 (Ar-H),1570 (C=N)

Characterization data for N-glucosylated 1,3,5 triazines.(V)

V a: **6-tetra-O-acetyl-β-D glucopyranosylimino 2-dimethylamino-4-phenylimino-1,4,5,6 tetrahydro-1,3,5 triazine.** M.F .$C_{25}H_{32}O_9N_6$, m.p 113°C, I.R(KBr)cm^{-1} 3465 (N-H),2970(C-H),1735(C=O),1269(C-N), ^{1}HNMR ppm .δ value 1.2 (2N-H) ,δ 2.0271-2.1864 (- N-$(CH_3)_2$), δ 4.1-6.3308 (glucosyl protons), δ 2.1864(-$COCH_3$), δ 7.2(5Ar - H), Mass spectrum : m/z 413 (M- (N$(CH_3)_2$ & -PhNC group.) ,m/z 331(tetra-O-acetyl- β –D-glucopyranosyl group =TAG)$^+$,m/z 271.1(TAG-CH_3COOH)$^+$

V b) **6-tetra-O-acetyl-β-D glucopyranosylimino 2-dimethylamino-4-o-tolylimino-1,4,5,6 tetrahydro-1,3,5 triazine** M.F .$C_{26}H_{34}O_9N_6$, m.p 110 °C

V c) **6-tetra-O-acetyl-β-D glucopyranosylimino 2-dimethylamino-4-p-tolylimino-1,4,5,6 tetrahydro-1,3,5 triazine** M.F .$C_{26}H_{34}O_9N_6$, m.p 83°C, I.R(KBr)cm^{-1} 3449 (N-H),2918(C-H of Ar-H),1741(C=O),1224(C-N),2849 (CH_2) ^{1}HNMR ppm . δ value 1.25 & 1.40(- N-$(CH_3)_2$), δ 1.2 (2N-H), δ 2.2 (Ar-CH_3), δ 4.1 -6.3 (glucosyl protons) ,δ 2.1864(-$COCH_3$), δ 7.1(Ar - H), Mass spectrum: m/z 559 (M – CH_3)$^+$, m/z 530 (M- N$(CH_3)_2$)$^+$, m/z 482(M –tolyl gp.)$^+$,m/z 331(TAG)$^+$, m/z 245(M - TAG)$^+$

V d) **6-tetra-O-acetyl-β-D glucopyranosylimino 2-dimethylamino-4-o-chloroimino-1,4,5,6 tetrahydro-1,3,5 triazine** M.F .$C_{25}H_{31}O_9N_6Cl$, m.p 113°C, I.R(KBr)cm^{-1} 3462 (N-H),2999(C-H of Ar-H),1741(C=O),1385-1365(C-N),2966 (C-H,CH_3) ^{1}HNMR ppm. δ value 2.0 (- N-$(CH_3)_2$), δ 1.6 (N-H), δ 4.05 -6.4 (glucosyl protons), δ 7.2 (Ar-H),

Mass spectrum: m/z 413(M -3CH_3COOH)$^+$, m/z 331(TAG)$^+$ m/z 271(TAG- CH_3COOH)$^+$, 211(TAG- 2CH_3COOH)$^+$

V e) **6-tetra-O-acetyl-β-D glucopyranosylimino 2-dimethylamino-4-p-chloro-phenylimino-1,4,5,6 tetrahydro-1,3,5 triazine** M.F .$C_{25}H_{31}O_9N_6Cl$, m.p. 109 °C

V f) **6-tetra-O-acetyl-β-D glucopyranosylimino 2-dimethylamino-4-o-anisylimino-1,4,5,6 tetrahydro-1,3,5 triazine** M.F . $C_{26}H_{34}O_{10}N_6$, m.p 102°C, I.R(KBr)cm^{-1} 3452(N-H),2926(C-H of Ar-H),1741(C=O),1222(C-N),2849 (CH_2) , Mass spectum : m/z 489(M- o-anisyl gp.)$^+$, 331 (TAG)$^+$, 271 (TAG - CH_3COOH)$^+$, m/z 211(TAG -2 CH_3COOH)$^+$

V g) **6-tetra-O-acetyl-β-D glucopyranosylimino 2-dimethylamino-4-p-anisylimino-1,4,5,6 tetrahydro-1,3,5 triazine** M.F . $C_{26}H_{34}O_{10}N_6$, m.p 114 °C

V h) **6-tetra-O-acetyl-β-D glucopyranosylimino 2-dimethylamino-4-t-butylimino-1,4,5,6 tetrahydro-1,3,5 triazine** M.F .$C_{23}H_{36}O_9N_6$, m.p 111°C, I.R(KBr)cm^{-1} 2966(C-H of Ar-H),1741(C=O),1458(C=N), Mass spectum: m/z 413 (M^+ -tert butyl-3AcOH), 331 (TAG)$^+$,m/z 211(TAG – 2CH_3COOH)$^+$

All compounds gave satisfactory C, H, N analysis.

CONCLUSION

The presented synthetic procedure is convenient and simple method for the synthesis of the various new 1,3,5 triazines and N-glucosylated triazines. Presently antibacterial and antifungal activities are reported. Further screening for some other activities in related field may prove their more utility.

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