

Research Article**Synthesis, characterization and biological activity of some glycolylurea and β -lactam merged heterocyclic compounds**Bhadreshkumar R. Sudani¹, Vikas A. Desai²¹Department of Chemical Engineering, Government Engineering College, Valsad, Gujarat, India-396001²Department of Chemistry, B. K. M. Science College, Tithal Road, Valsad, Gujarat, India-396001

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Abstract

Objective: The chemistry of β -lactams has established a prestigious role in organic and medicinal chemistry. The combination of these derivatives with other medicinally important class like glycolylurea might give some more applicable compounds. The objective of the present work was the synthesis and characterization of glycolylurea derivatives of some β -lactams. The synthesis involving formation of glycolylurea derivatives followed by the condensation was performed as per previously used methods. **Materials and Methods:** The synthesized compounds were characterized by various physico-chemical and analytical methods including FTIR and NMR spectroscopy. All the compounds were also investigated for their antimicrobial activity on gram negative and gram positive microbial cultures. **Results and conclusions:** It was found that from the investigated compounds one compound G5 mono-chloro derivative with one methyl group at ortho position was found active against gram negative microbes *P. aeruginosa* and G7 di-chloro derivative with one methyl group at ortho position was found active against gram positive microbes *B. subtilis*. Four out of eight compounds are moderately active against *E. coli*. Except G8 all the synthesized compounds are less or very less active against selected fungal stains.

Keywords: Glycolylurea, β -lactams, antimicrobial activity

Introduction

Glycolylurea is also known as Hydantoin and its derivatives are widely applicable heterocyclic compounds for many diseases like anticunvalsant (Singh et al., 2005; Mistry and Desai, 2012; Sudani and Desai, 2015), antiepilepsy (Anger et al., 2001; Rogawski and Loscher, 2004), antihypertensive (Menendez et al., 1992; Dylag et al., 2004) and many more. It is now well known that the β -lactam ring is part of the core structure of many antibiotic families and due that some of them are also called β -lactam antibiotics (Donowitz and Mandell, 1988). Aruna and Indra, (2018) showed the importance of the β -lactam compounds in various antibiotics including urinary tract infection (UTI). This class of compounds has played an important role in medicinal chemistry as broad spectrum antibiotic compound maker. Both of these classes had

performed well in synthetic pharmacy.

There are many derivatives synthesized with these moieties in order to get better activities. In present work some derivatives of glycolylurea were synthesized as per the known route and than they were condensed with cyclization to form β -lactam merged compounds with the prediction of better antibacterial activities

Materials and Methods

All the chemicals and reagents were of analytical reagent (AR) grade, they were used without further purification. IR spectra were recorded on Bruker ALPHA FTIR spectrophotometer in KBr pellets. The H-NMR spectra were recorded on Bruker Avance II spectrometer in d-DMSO. Chemical shifts relative to TMS used as internal standard were obtained in δ unit. The melting points were determined in open capillary tubes on SUNBIM apparatus and are uncorrected.

Synthesis of different compounds

Compounds **h1** to **h4** were synthesized with the previously used method. These eight compounds were than treated with

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hydrazine hydrate at (1:1.2 mol) at 35-40 °C for 4 to 5 hours. After continuous stirring and cooling to room temperature compounds **a1** to **a4** were obtained. All these four intermediate products were allowed to react with two aromatic aldehydes. This condensation reaction was carried out at 70-80°C for 8 hours refluxing in acetonitrile. After checking the completion of reaction by TLC the each mixture was allowed to remove acetonitrile with vacuum distillation at room temperature and the products (**az1** to **az8**) further used to react with chloroacetyl chloride (0.0016 mol) at 0-5 °C during addition in 30 minutes after 2-3 hours on adjustment of pH from 6.5 to 7.5 by diluted NaHCO₃ all the products (**G1** to **G8**) were filtered and washed with chilled water. After drying for 1 to 2 hours they were recrystallized in alcohols. After further purification all the samples were used to measure their melting points, samples were sent for analytical testing. Scheme 1 indicates the complete procedure of the reaction in figure 1.

Characterization

Thin Layer Chromatography was used to detect the reaction completion at every stage of each reaction. Suitable mobile phases were prepared including polar non polar solvents for the better upliftment and separation of the reaction mass. All the prepared samples were recrystallized from alcohol and dried samples were sent for the elemental analysis where percentages of carbon, hydrogen and nitrogen were determined. Results were compared and found resemble with calculated data as shown in table-1. In order to know the combination and groups of atoms in the synthesized compounds IR spectra of each

compound was recorded on FTIR spectrophotometer with the help of KBr pellets. The frequencies were recorded in cm⁻¹ and compared with the corresponding standard data. To know the positions of different types of hydrogen atoms in the carbon chain and particular groups H¹ NMR was also recorded on Bruker Avance II spectrometer in d-DMSO as solvent for each of the prepared compound where TMS was used as internal standard.

Antimicrobial activity

The newly synthesized compounds, as shown in table 1 were tested for their antimicrobial activity against the following microorganisms: two gram positive stains *B. subtilis* and *S. aureus*, two gram negative stains *P. aeruginosa* and *E. coli.*, three fungal stains viz. *P. piricola*, *A. niger* and *F. oxysporum*. The preliminary screening of the investigated compounds was performed using Broth dilution method. The minimum inhibitory concentrations were recorded accordingly. Secondary screening was carried out as earlier but with lower concentration in microgram/mL. The highest dilution showing at least 99 % inhibition zone is taken as MIC. The test mixture was containing 10⁸ organisms per mL. The result of this is much affected by the size of the inoculum. The results of the testing are given in the table 2.

Results and discussion

Physicochemical analytical data given in the table indicates R₂ and R₃ as per the reaction scheme shown in figure 1. Yield is calculated for the final step of the reaction.

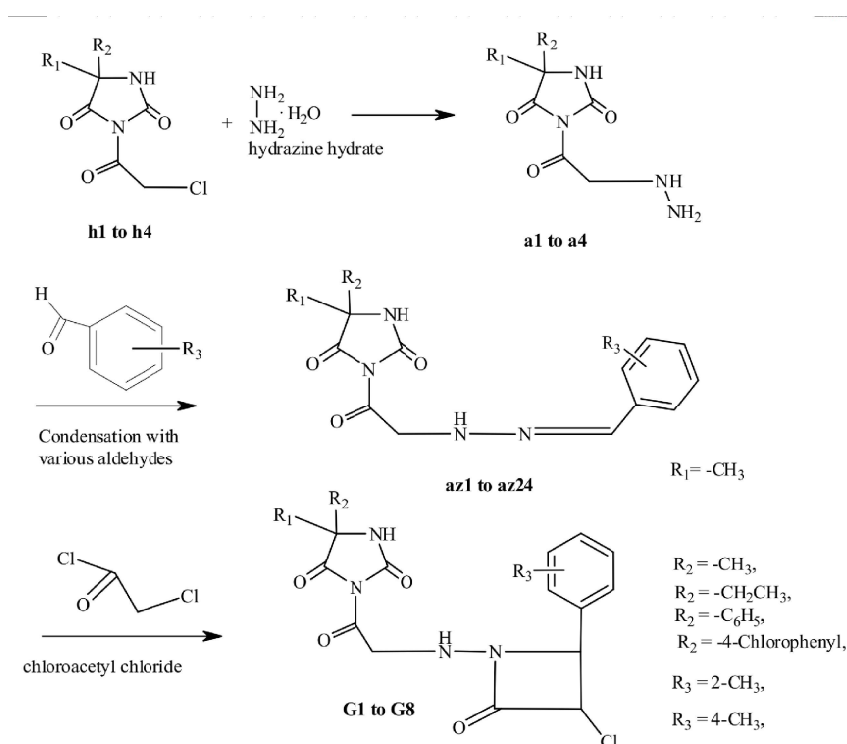


Figure 1. Scheme-1 for the reaction procedure to synthesize G1 to G8

Spectral analysis of different compounds

G1: 3-(2-((3-chloro-2-oxo-4-(o-tolyl)azetidino-1-yl)amino)acetyl)-5,5-dimethylimidazolidine-2,4-dione: **IR** (KBr, cm^{-1}): 3256(NH), 1748, 1765 (β lactam)(C=O), 1535(C=C Ar), 1428, 1408(-CH₃); **¹H NMR** (400 MHz, DMSO-d₆): δ ppm = 1.47(s, 6H), 2.33(s, 3H), 3.53(d, 2H) 5.08(d, 1H), 5.48(d, 1H), 6.80-7.40(m, 4H Ar), 9.38(s, br, 1H), 10.08(t, 1H).

G2: 3-(2-((3-chloro-2-oxo-4-(p-tolyl)azetidino-1-yl)amino)acetyl)-5,5-dimethylimidazolidine-2,4-dione: **IR** (KBr, cm^{-1}): 3260(NH), 1751, 1771 (β lactam)(C=O), 1538(C=C Ar), 1431, 1412(-CH₃); **¹H NMR** (400 MHz, DMSO-d₆): δ ppm = 1.48(s, 6H), 2.35(s, 3H), 3.55(d, 2H) 5.11(d, 1H), 5.51(d, 1H), 7.19-7.20(m, 4H Ar), 9.87(s, br, 1H), 10.21(t, 1H).

G3: 3-(2-((3-chloro-2-oxo-4-(o-tolyl)azetidino-1-yl)amino)acetyl)-5-ethyl-5-methylimidazolidine-2,4-dione: **IR** (KBr, cm^{-1}): 3272(NH), 1745, 1776 (β lactam)(C=O), 1548(C=C Ar), 1432, 1417, 1402 (-CH₂, -CH₃); **¹H NMR** (400 MHz, DMSO-d₆): δ ppm = 1.01(t, 3H), 1.65(q, 2H), 1.81(s, 3H), 2.55(s, 3H), 3.58(d, 2H) 5.15(d, 1H), 5.58(d, 1H), 6.79-7.38(m, 4H Ar), 10.02(s, br, 1H), 10.51(t, 1H).

G4: 3-(2-((3-chloro-2-oxo-4-(p-tolyl)azetidino-1-yl)amino)acetyl)-5-ethyl-5-methylimidazolidine-2,4-dione: **IR** (KBr,

cm^{-1}): 3253(NH), 1741, 1767 (β lactam)(C=O), 1551(C=C Ar), 1422, 1416, 1396 (-CH₂, -CH₃); **¹H NMR** (400 MHz, DMSO-d₆): δ ppm = 1.13(t, 3H), 1.71(q, 2H), 1.93(s, 3H), 2.65(s, 3H), 3.65(d, 2H) 5.19(d, 1H), 5.60(d, 1H), 7.23-7.24(m, 4H Ar), 10.12(s, br, 1H), 10.65(t, 1H).

From the above spectral data of compound **G1** and **G2** it is cleared that the similarity of the structure is also proven by the spectral data in both the graphs. In NMR spectra of compound **G2** there is a sharp peak (m) at 7.19-7.20 ppm indicates the presence of methyl group in aromatic ring at para position. While in the graph of compound **G1** it is broad at 6.80-7.40 ppm indicates the presence of methyl group in aromatic ring at ortho position. More over same similarity is also found in the comparison of NMR data of **G3** and **G4** compounds. In the comparison of G1 with G3 and G2 with G4, presence of one extra quartet peak in ¹H-NMR for -CH₂- group is also observed. Similar results are also observed for G5, G6, G7 and G8 compounds in order to establish the structure.

Results obtained from the biological screening of synthesized compound with minimal inhibition concentrations in $\mu\text{g/mL}$ are given in table 2.

The results shows that G5 has some good activity against *P.*

Table 1. Physicochemical analytical data

Compounds	R ₂	R ₃	M.F. /M.W. g/mol	M.P.	Yield	Elemental analysis Cal & Found (%)		
						$^{\circ}\text{C}^*$	%	C
G1	-CH ₃	-2-CH ₃	C ₁₇ H ₁₉ ClN ₄ O ₄	67	42	53.90, 53.90	5.06, 5.07	14.79, 14.80
G2	-CH ₃	-4-CH ₃	378.11	78	40	53.90, 53.91	5.06, 5.06	14.79, 14.79
G3	-C ₂ H ₅	-2-CH ₃	C ₁₈ H ₂₁ ClN ₄ O ₄	77	39	55.03, 55.04	5.39, 5.38	14.26, 14.28
G4	-C ₂ H ₅	-4-CH ₃	392.84	55	43	55.03, 55.03	5.39, 5.37	14.26, 14.27
G5	-C ₆ H ₅	-2-CH ₃	C ₂₂ H ₂₁ ClN ₄ O ₄	67	28	59.93, 59.92	4.80, 4.81	12.71, 12.69
G6	-C ₆ H ₅	-4-CH ₃	440.88	82	47	59.93, 59.93	4.80, 4.80	12.71, 12.70
G7	-4-Cl-C ₆ H ₅	-2-CH ₃	C ₂₂ H ₂₀ Cl ₂ N ₄ O ₄	66	45	55.59, 55.58	4.24, 4.24	11.79, 11.80
G8	-4-Cl-C ₆ H ₅	-4-CH ₃	474.09	79	29	55.59, 55.60	4.24, 4.23	11.79, 11.78

*Melting points are uncorrected

Table 2. Antimicrobial activity of different compounds

Compounds and Standards	Minimal Inhibitory Concentration in $\mu\text{g/mL}$						
	Bacterial Culture				Fungal Culture		
	<i>P. aeruginosa</i>	<i>E. coli</i>	<i>B. subtilis</i>	<i>S. aureus</i>	<i>P. piricola</i>	<i>A. niger</i>	<i>F. oxysporum</i>
G1	150	200	300	300	200	250	250
G2	150	250	250	500	500	500	500
G3	100	250	500	150	250	500	1000
G4	250	125	250	500	250	1000	125
G5	62.5	125	125	175	250	350	400
G6	400	250	175	250	200	150	1000
G7	125	125	62.5	150	250	125	1125
G8	125	175	250	200	125	250	100
Ciprofloxacin	125	125	250	250	ND	ND	ND
Chloramphenicol	50	50	50	50	ND	ND	ND
Nystatin	ND	ND	ND	ND	100	100	100

aeruginosa and G7 has activeness against *E.coli* while G8 has good to moderate activity against *P. piricola* and *F. oxysporum*. Both the compounds G5 and G7 contains one methyl group on phenyl ring attached to the lactam ring. Compound G3 is also showing some moderate activity against *P. aeruginosa* which also contain one ortho methyl group at same position. Compound G7 also moderate active against *P. aeruginosa* and *E. coli*. This activity might be due to the presence of one chloro group at R₂ position. Similar activity for similar group is also found in the case of compound G8 against *P. aeruginosa*. Moreover it, the compound G8 is found moderately active against only fungal stain *F. oxysporum*. All other compounds are found less or very less active against all three fungal stains. It clearly indicates that this series of compounds is more sensitive against microbial stain than that of fungal stains.

Conclusions

From the experimental data it is proven that the synthesis of these compounds can done with condensation and cyclization reaction with selected aldehydes. The process adopted can give well to moderate yields. Some of the compounds have biological activity against selected stains. This series is more antimicrobial active than that of antifungal activity.

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Conflicts of interest: Not declared.

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