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Research Article

Synthesis and Evaluation of Antimicrobial activity of Gamma Butyrolactone

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Abstract

Series of gamma Butyrolactones were synthesized and their antimicrobial activity was evaluated by agar plate diffusion assay. The scheme used in present study for synthesis of gamma Butyrolactone nucleus by an efficient route and very simple procedure. The scheme overcomes the problems associated with previous methods**.** Antibacterial activity was tested against gram positive strain of *B. subtilus, S. aureus* and gram negative strains of *P. Aeurigenosa, E. coli, and S.Typhi* microorganism and compound synthesized found to be active when compared with Ciprofloxacin.

1.0 Introduction

The increasing incidence of infection caused by the rapid development of bacterial resistance to most of the known antibiotics is a serious health problem[1-4]. While many factors may be responsible for mutations in microbial genomes, it has been widely demonstrated that the incorrect use of antibiotics can greatly increase the development of resistant genotypes[5-9]. As multidrug-resistant bacterial strains proliferate, the necessity for effective therapy has stimulated research into the design and synthesis of novel antimicrobial molecules.

The present work relates to a lactone derivative, its synthetic method and evaluation of its antimicrobial activity. In Chemistry, a lactone is a cyclic ester which can be seen as the condensation product of an alcohol group -OH and a carboxylic acid group -COOH in the same molecule. It is characterized by a closed ring consisting of two or more carbon atoms and a single oxygen atom, with a ketone group in one of the carbons adjacent to the other oxygen[10, 11].

Literature survey clearly indicates that gamma Butyrolactone scaffold is not only synthetically important but also possesses a wide range of promising biological activity including antimicrobial, antitumor and cytoxic activity, which make them interesting lead structures for new drugs[12-16]. Given their widespread occurrence in nature and their broad range of biological activity, a great deal of attention has been paid to the synthesis of this ring. Although there has been tremendous development for obtaining several gamma Butyrolactone derivatives, different synthetic routes have been highlighted to suffer from various problems such as prolonged reaction times, harsh reaction conditions, unsatisfactorily yields, difficulty in product isolation, use of polar, volatile and hazardous organic products and often use of expensive catalyst[17,18]. So it is required to find out new economical methods for synthesis of gamma Butyrolactone. Thus, the drive is continues to find a better and improved strategies for synthesis of gamma Butyrolactone core. The scheme used in present study for synthesis of gamma Butyrolactone nucleus by an efficient route and very simple procedure. The scheme overcomes the problems associated with previous methods and it is improved and environmentally benign approach for their preparation in great demand.

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2.0 Materials and Methods

Starting materials used for each reaction and the products obtained were assessed for purity by physical constant determination, and Thin Layer Chromatography (TLC). For thin layer chromatography pre- coated TLC plates (Silica gel 60-120#) were used with Ethyl acetate: n-Hexane in the proportion (4:1) solvent systems. TLC plates were observed in Iodine chamber. Melting points were taken in open capillary tubes on DBK programmable melting point apparatus and were uncorrected. The structures of the synthesized compounds were characterized by IR and NMR. Infrared spectroscopy was carried out using potassium bromide (KBr) pellet method on the JASCO FTIR 4100. The nuclear magnetic resonance is a very important technique for structural elucidation of the compounds. The (^{1}H NMR) spectra of synthesized compounds were recorded at Department of Chemistry, University of Pune, Varian-NMR-Mercury300 MHz spectrophotometer using TMS as an internal standard and chloroform and DMSO as a solvent.

2.1 Experiment

2.1.1 Synthesis of methyl phenyl acetate (2a)

Phenyl acetic acid (1a) (0.01M) was dissolved in methanol and added 1-2 drops of Concentrated Sulphuric acid and the solution was heated under reflux for 5-6 hrs. at temperature between 65^{0}C-70^{0}C .Methanol was removed, and the residue redissolved in ethyl acetate. The solution was washed with (5×10ml) aqueous Na_2CO_3, dried over Na_2SO_4, and the solvent evaporated to give the methyl esters in quantitative yields; the compounds were used without further characterization.

2.1.2 Synthesis of methyl 2-phenylpent-4-enoate (3a)

Quantities of (2a), potassium carbonate and allyl bromide and DMSO were taken in 1:2:10 proportion respectively, in 250ml conical flask. 2a was added with potassium carbonate in dimethyl sulfoxide containing conical flask was covered with aluminum foil and the resulting mixture was stirred on magnetic stirrer for 30 minutes. Meanwhile dissolved quantity of allyl bromide in 1ml Dimethyl Sulfoxide in a small beaker. Added the solution of allyl bromide drop by drop after 30 minutes in the above solution and again stirred for 30 minutes. Observed color changes in the solution. Completion of reaction was checked on TLC plates. The solution was then diluted with ethyl acetate, washed with water. The extracted product was used for final step.

2.1.3 Synthesis of 5-methyl-3-phenyldihydrofuran-2(3*H*)-one (4a)

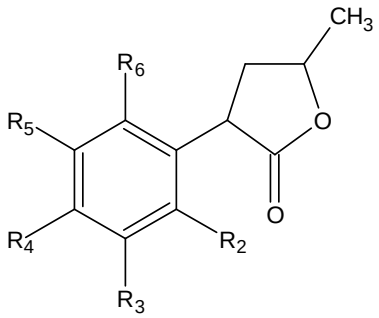
To a solution of (3a) in dimethyl sulfoxide (10 ml) was added a catalytic amount of iodine. The reddish reaction mixture was heated in an oil bath at 130^{0}C for 30 min. After cooling, the reaction mixture was diluted with ice-cold water and the iodine was removed by the addition of a saturated solution of sodium thiosulfate and washing with water and brine. The product was extracted with ethyl acetate (10ml × 3) and washed with water (10ml × 2). The ethyl acetate was removed by evaporation. The γ-butyrolactone (4a) was precipitate out in the form of solidified product and purified by recrystallization from a suitable solvent.

2.1.4 Synthesis of (4b-4g)

Similar method of synthesis was followed for all steps involved, except in step 1(1b-1g) was used instead of (1a) respectively.

2.2 Characterization of Data

4a - Yield: 80%, M.P.: 131-137 ^{0}C, R_f: 0.25, IR (cm^{-1}): 3036, 2304, 1730, 1600, 1284, ^{1}HNMR: 7.2-7.8(m, 5H), 4.25 (septed 1H), 3.65 (d, 1H), 2.6-2.85 (dd, 1H)
4b - Yield: 83.71 %, M.P.: 120-122 ^{0}C, R_f: 0.56, IR (cm^{-1}): 3090, 2374, 1714, 1559, 1100, 765,709, ^{1}HNMR: 7.2 (d,1H) 7.4 (d,1H) 7.5(s,1H) 3.65(d,1H) 2.6-2.85 (dd, 1H) 4.25 (septet, 1H) 1.3 (d, 3H)
4c - Yield: 63.95 %, M.P.: 209-211 ^{0}C, R_f: 0.36, IR (cm^{-1}): 3055, 2377, 1774, 1559, 1134, 730
4d - Yield: 71.46 %, M.P.: 89-90 ^{0}C, R_f: 0.61, IR (cm^{-1}): 3050, 2374, 1660, 1597, 1170, 660
4e - Yield: 57.17 %, M.P.: 104-106 ^{0}C, R_f: 0.65, IR (cm^{-1}): 2932, 2373, 1734, 1623, 1253, 748, ^{1}HNMR: 7.0-7.8 (m, 4H) 3.65 (d, 1H) 2.6-2.8 (dd, 1H) 4.2 (septet, 1H)
4f - Yield: 88.26 %, M.P.: 68-70 ^{0}C, R_f: 0.63, IR (cm^{-1}): 3009, 2300, 2338, 1712, 1509, 1253
4g - Yield: 56.21 %, B.P.: 108-110 ^{0}C, R_f: 0.56, IR (cm^{-1}): 3009, 2301, 2338, 1739, 1535, 1253
4h - Yield: 58.33 %, M.P.: 105-110 ^{0}C, R_f: 0.48, IR (cm^{-1}): 3079, 2453, 2353, 1693, 1503, 1250
4i - Yield: 62.23 %, M.P.: 90-92 ^{0}C, R_f: 0.58, IR (cm^{-1}): 3102, 2371, 1243, 1179, 1718, 1583
4j - Yield: 70.25 %, M.P.: 145-148 ^{0}C, R_f: 0.58, IR (cm^{-1}): 3009, 2494, 1161, 1122, 1718, 1587
4k -Yield: 85.51%, M.P.: 135-140 ^{0}C, R_f: 0.53, IR (cm^{-1}): 3079, 2453, 1734, 1522, 1346, 1167
4l - Yield: 60.26 %, M.P.: 154-158 ^{0}C, R_f: 0.64, IR (cm^{-1}): 2927, 2364, 1712, 1550, 1490, 1011
4m - Yield: 44.02 %, M.P.: 84-87 ^{0}C, R_f: 0.59, IR (cm^{-1}): 2963, 2363, 1700, 1508, 1241, 1097, ^{1}HNMR: 6.82 (dd, 2H) 7.4 (dd, 2H) 3.68 (d, 1H) 2.6-2.8 (dd, 1H) 4.4 (septet, 1H)

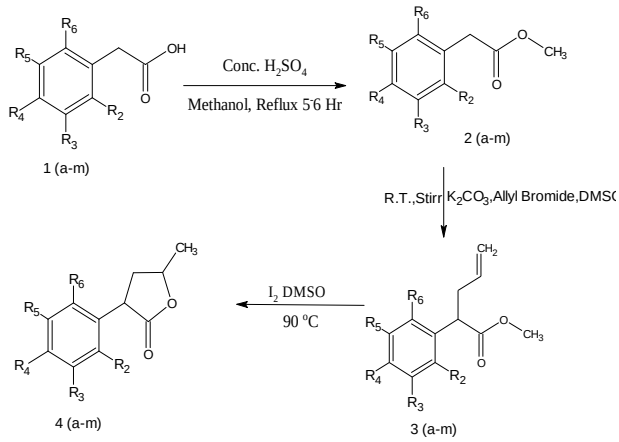


5-methyl-3-(substituted) phenyldihydrofuran-2(3*H*)-one

Table 1: Series of synthesized compound

S. No	Compound	R_2	R_3	R_4	R_5	R_6
1	4a	H	H	H	H	H
2	4b	Cl	H	Cl	H	H
3	4c	H	Cl	Cl	H	H
4	4d	H	H	Cl	H	H
5	4e	Cl	H	H	H	H
6	4f	CH_3	H	H	H	H
7	4g	H	H	CH_3	H	H
8	4h	CH_3	H	H	CH_3	H
9	4i	H	H	H	OCH_3	H
10	4j	H	OCH_3	H	OCH_3	H
11	4k	H	H	H	NO_2	H
12	4l	H	OH	H	H	H
13	4m	H	H	H	F	H

2.3 Scheme for Synthesis



2.4 Antibacterial Activity

The inhibition of microbial growth under standardized conditions was utilized for demonstrating the therapeutic efficacy of antibacterial agents. All the compounds were subjected to antibacterial activity by agar plate diffusion assay. Nutrient Agar was used as media. The antibacterial activity was tested against two gram positive strain of *B. subtilus, S. aureus* and three gram negative strains of *P. Aeurigenosa, E. coli, and S.Typhi* microorganism. Comparison was done with the standard ciprofloxacin and DMSO as control sample. The results of the antibacterial activity against all species tested are given in table below.

Table 2: Zone of inhibition for Gamma Butyrolactone Derivatives for gram negative bacteria

Compound Number	Zone of inhibition (mm) for 500µg		
	P. aeurigenosa	*E. coli*	*S. typhi*
4a	13	12	13
4b	10	10	09
4c	10	11	10
4d	11	13	10
4e	12	11	10
4f	07	04	07
4g	07	06	10
4h	05	08	09
4i	08	07	10
4j	11	05	08
4k	05	03	04
4l	08	09	10
4m	11	12	11
Ciprofloxacin	15	16	18

Table 3: Zone of inhibition for Gamma Butyrolactone Derivatives for gram positive bacteria.

Compound Number	Zone of inhibition (mm) for 500µg	
	B. subtilus	*S. aureus*
4a	07	10
4b	12	13
4c	10	12
4d	12	11
4e	12	13
4f	08	09
4g	06	09
4h	10	07
4i	08	09
4j	08	07
4k	04	03
4l	10	09
4m	11	12
Ciprofloxacin	18	17

3.0 Results and Discussion

All the compounds gave the characteristic IR peak which proved the presence of particular functional group. Elemental analysis (C, H, N and O) was carried out to find out the exact composition of the compounds synthesized. H^1NMR confirmed the anticipated structures.

Amongst all the synthesized compounds, compounds 4b, 4d, 4e and 4m showed better activity against *Bacillus subtilis*, compounds 4b, 4c, 4e, and 4m showed better activity against *Staphylococcus aureus*. Compounds 4f, 4h and 4l were also found to possess good activity against *Bacillus subtilis*, compounds 4f, 4g and 4i was found to possess good activity against *Staphylococcus aureus.* Amongst all the synthesized compounds, compounds 4a, 4b, and 4e showed better activity against *P. aeurigenosa,* compounds 4a, 4e and 4l showed better activity against *E. coli,* compound 4a and 4m showed better activity against *Salmonella typhi.* Amongst all the synthesized compounds, compounds 4c, 4j, 4k, 4j and 4m showed good activity against *P. aeurigenosa,* compound 4c, 4d, and 4e showed good activity against *E. coli,* compounds 4d, 4e, 4g, 4i, and 4l showed good activity against *Salmonella typhi.*

4.0 Conclusion

Gamma Butyrolactone molecules can be better candidate in coming future, in treatment of infection. Keeping this in mind a we synthesized series of compounds and compounds were evaluated for antimicrobial activity. The compounds were found to be quite active when compared to ciprofloxacin.

The present study has added an informative data to the area of antimicrobial research which may help to develop newer antimicrobial drugs and drug combinations acting as an alternative for current drugs. Although it is premature to conclude at this stage that studied compounds can be used as effective antimicrobials, this finding provides a foundation for further exploration of a new potent drug.

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