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Synthesis, Characterization and Antimicrobial Evolution of Six Membered Cyclic Imides

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A B S T R A C T

The six membered cyclic imide derivatives were synthesized by reacting glutaric anhydride with different substituted aromatic amines to get 4-(N-phenylcarbamoyl) butanoic acid. These intermediates underwent ring closer with acetyl chloride furnished six membered cyclic imides derivatives. All these derivatives were screened for antimicrobial activities.

Keywords: Six memebered cyclic imides, 4-(N-phenylcarbamoyl) butanoic acid, N-phenyl glutarimide

A R T I C L E I N F O

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1. Introduction

Cyclic imides like succinimides, male imides, phthalimides, glutarimides embracing the foremost part in the organic synthesis. The different substituted six membered glutarimide derivatives are hydrophobic nature which reflects antibacterial and antifungal potencies. Some of the glutarimide drugs affected the thymine nucleosides, uracil transport in the biological membranes [1]. The influence of polyglutarimides PMMA thermal stability noticeably improves the imidization [2] by IRTF analysis [3]. Natural products like glutarimide alkaloids isolated from Croton pullei species which gives preeminent antibacterial and antifungal activities [4]. The optimistic effects of

glutarimides actively found on spinal neurons [5], brain metabolism [6], mitochondrial respiration [7]. The different substituted heterocyclic imides including glutarimides were prepared from cyclic anhydrides [8], by using PPA [9], Baylis Hillman adducts [10], tandem process [11], succinic and glutaric acids [12]. Thus the selective synthesis of glutarimide analogous has been highlighted in this research paper [13] [14].

2. Experimental

2.1 Material Methods

Melting points were recorded in open glass capillaries and were uncorrected. IR spectra in KBr (pallets) were recorded on Shimadzu-8400S and ATR Brucker alpha FT-IR spectrophotometer. ^{1}H NMR, ^{13}C NMR spectra were recorded on 300 MHz, 500.13 MHz and 125.77 MHz by Brucker spectrophotometers. The reaction was monitored by thin layer chromatography which was performed by using pre-coated silica gel aluminium plates with mixture of diethyl ether and ethyl acetate 7:3 proportion. All the compounds 3a-j and 4a-j were synthesized in hours from the corresponding commercial available aromatic amines, glutaric anhydride, acetyl chloride and benzene.

2.2 General procedure for Preparation of six membered cyclic imides

2.2.1 Preparation of 4-(N-phenylcarbamoyl) butanoic acid (3a-j):

To glutaric anhydride (10 mmole) benzene was added and heated under reflux with constant stirring for 15 to 20 minutes till the solution becomes clear. Into this solution the primary aromatic amine (10 mmole) in 5 ml benzene was slowly poured with constant stirring for 15 to 20 minutes till the solution becomes homogenized. Upon evaporation of benzene the whitish amorphous powder of 4-(N-phenylcarbamoyl) butanoic acid was obtained [15]. The experimental method diagrammatically shown in fig.1;

2.2.1.1 4-(phenyl carbamoyl) butanoic acid (3a):
Brownish powder, M.F. $C_{11}H_{13}NO_3$, Mol. Wt. 207.23, M.P. 110 ºC

2.2.1.2 4-(4-bromophenylcarbamoyl) butanoic acid (3b): Whitish brown powder, M. F. $C_{11}H_{12}BrNO_3$, Mol. Wt. 286.12, M.P. 139 ºC

2.2.1.3 4-(4-chlorophenylcarbamoyl) butanoic acid (3c): Brown powder, M.F.: $C_{11}H_{12}ClNO_3$, Mol. Wt. 241.67, M.P. 109 °C

2.2.1.4 4-(p-tolylcarbamoyl) butanoic acid (3d):
Cream colour powder, M.F. $C_{12}H_{15}NO_3$, Mol. Wt. 221.25, M.P. 148 ºC

2.2.1.5 4-(4-methoxyphenylcarbamoyl) butanoic acid (3e): Brownish white powder, M.F. $C_{12}H_{15}NO_4$, Mol. Wt. 237.25, M.P. 132 ºC

2.2.1.6 4-(4-fluorophenylcarbamoyl) butanoic acid (3f):
Brownish gray powder, M.F. $C_{11}H_{12}FNO_3$, M.P. 112 ºC
Mol. Wt. 225.22.

2.2.1.7 4-(4-nitrophenylcarbamoyl) butanoic acid (3g):
Greenish gray powder, M.F. $C_{11}H_{12}N_2O_5$, Mol. Wt. 252.22, M.P. 122 ºC

2.2.1.8 4-(naphthalen-4-ylcarbamoyl) butanoic acid (3h):
Brown powder, M.F. $C_{15}H_{15}NO_3$, Mol. Wt. 257.28, M.P. 143 ºC

2.2.1.9 4-(3-chloro-4-fluorophenylcarbamoyl) butanoic acid (3i):
Wheat colour powder, M.F. $C_{11}H_{11}ClFNO_3$, Mol. Wt. 259.66, M.P. 111 ºC

2.2.1.10 4-(2,4,5-trichlorophenylcarbamoyl) butanoic acid (3j): White powder, M.F. $C_{11}H_{10}Cl_3NO_3$, Mol. Wt. 310.56, 128 ºC

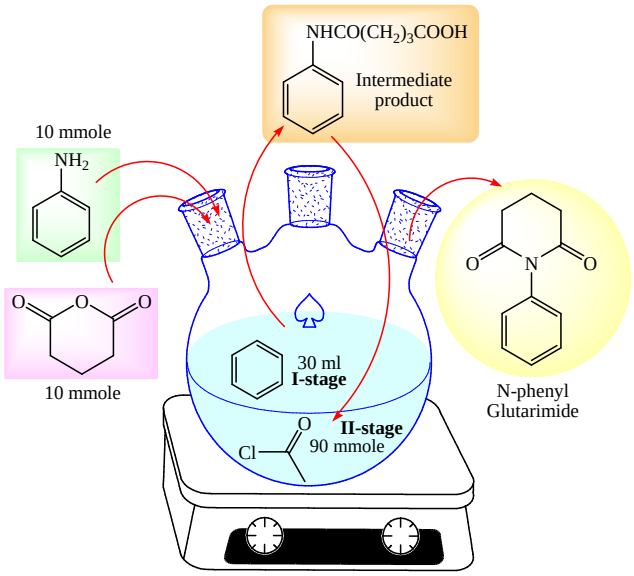
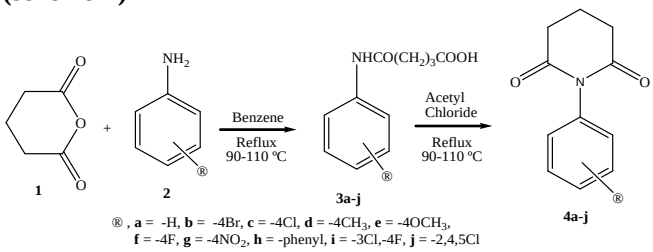


Figure1: Experimental display of the N-phenyl glutarimide synthesis

2.2.2 Preparation of N-Phenyl glutarimides:

The mixture of 4-(phenyl carbamoyl) butanoic acid and acetyl chloride (90 mmole) was reflux for 15 to 20 minutes till the complete evolution of HCl gas. The reaction mixture was cooled at room temperature the solid product was obtained and purified by recrystallization from ethanol **(scheme–I)**



Scheme - I: Preparation of N-phenyl Glutarimides

2.2.2.1 1-phenylpiperidine-2, 6-dione (4a):
Cream colour solid, yield (77.92%), m. p. 120-122 ºC, M.F. $C_{11}H_{11}NO_2$, Mol. Wt. 189.21; IR (KBr): 1674, 1770, 2971, 1314, 1499, 1535, 1598 cm^{-1};

2.2.2.2 1-(4-bromophenyl) piperidine-2, 6-dione (4b):
Whitish brown solid, yield (82.94%), m. p. 144-146 ºC, M.F. $C_{11}H_{10}BrNO_2$, Mol. Wt. 268.11; IR (KBr): 1695, 1719, 2992, 1301, 1490, 1526, 1589, 1070 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.40-7.55 (d, 4H, Ar-H), 1.87 (m, 2H, $-CH_2-CH_2-CH_2-$), 2.226 (t, 4H, imide)

2.2.2.3 1-(4-chlorophenyl) piperidine-2, 6-dione (4c):

Faded lavender solid, yield (86.70%), m. p. 123-125 ºC, M.F. $C_{11}H_{10}ClNO_2$, Mol. Wt. 223.66; IR (KBr): 1726, 1782, 2979, 1300, 1495, 1527, 1591, 1090 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 7.25-7.58 (d, 4H, Ar-H), 1.98 (m, 2H, $-CH_2-CH_2-CH_2-$), 2.23 (t, 4H, imide)

2.2.2.4 1-p-tolylpiperidine-2, 6-dione (4d):

Marble colour solid, yield (77.07%), m. p. 179-181 ºC, M.F. $C_{12}H_{13}NO_2$, Mol. Wt. 203.24; IR (KBr): 1698, 1746, 2962, 1310, 1536, 1599, 1661 cm^{-1}

2.2.2.5 1-(4-methoxyphenyl) piperidine-2, 6-dione (4e):

Brownish solid, yield (76.66%), m. p. 138-140 ºC, M.F. $C_{12}H_{13}NO_3$, Mol. Wt. 219.24; IR (KBr): 1697, 1718, 2954, 1302, 1515, 1536, 1600, 1272 cm^{-1}

2.2.2.6 1-(4-fluorophenyl) piperidine-2, 6-dione (4f):

Brownish solid, yield (76.35%), m. p. 119-121 ºC, M.F. $C_{11}H_{10}FNO_2$, Mol. Wt. 207.2; IR (KBr): 1696, 1722, 2961, 1305, 1519, 1613, 1658, 1186 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 7.6-7.55 (d, 4H, Ar-H), 1.68 (m, 2H, $-CH_2-CH_2-CH_2-$), 2.15 (t, 4H, imide)

2.2.2.7 1-(4-nitrophenyl) piperidine-2, 6-dione (4g):

Cream yellow solid, yield (84.01%), m. p. 168-170 ºC, M.F. $C_{11}H_{10}N_2O_4$, Mol. Wt. 234.21; IR (ATR): 1710, 1750, 2960, 1300, 1520, 1590, 1600, 1500 cm^{-1}

2.2.2.8 1-(naphthalen-4-yl) piperidine-2, 6-dione (4h):

Dark lavender solid, yield (83.61%), m. p. 153-155 ºC, M.F. $C_{15}H_{13}NO_2$, Mol. Wt. 239.27; IR (ATR): 1651, 1703, 2958, 1316, 1405, 1443, 1500, 1529, 1596 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 7.30-7.57 (m, 6H, Ar-H), 1.62 (m, 2H, $-CH_2-CH_2-CH_2-$), 2.22 (t, 4H, imide)

2.2.2.9 1-(3-chloro-4-fluorophenyl) piperidine-2, 6-dione (4i): Whitish brown solid, yield (91.30%), m. p. 104-106 ºC, M.F. $C_{11}H_9ClFNO_2$, Mol. Wt. 241.65; IR (ATR): 1638, 1700, 2951, 1312, 1497, 1546, 1600, 1191, 1055 cm^{-1}; ^1H NMR (500.13 MHz, DMSO-d_6, δ ppm): 7.34-7.92 (m, 3H, Ar-H), 1.80 (m, 2H, $-CH_2-CH_2-CH_2-$), 2.28 (t, 4H, imide); ^{13}C NMR (125.77 MHz, DMSO-d_6, δ ppm): 20.72, 33.35, 35.75, 39.95, 117.19, 119.70, 120.82, 136.93, 152.35, 154.29, 171.42, 174.56

2.2.2.10 1-(2,4,5-trichlorophenyl) piperidine-2,6-dione (4j):

Pure white solid, yield (85.73%), m. p. 138-140 ºC, M.F. $C_{11}H_8Cl_3NO_2$, Mol. Wt. 292.55; IR (ATR): 1665, 1697, 2968, 1306, 1457, 1513, 1570, 1076 cm^{-1}; ^1H NMR (500.13 MHz, $CDCl_3$, δ ppm): 7.28-7.49 (d, 2H, Ar-H), 2.10 (m, 2H, $-CH_2-CH_2-CH_2-$), 2.27 (t, 4H, imide)

3. Results and Discussion

3.1 Chemistry:

The intermediate 3a-j compounds were prepared by the reaction of glutaric anhydride using aromatic amines. The series of cyclic imides 4a-j were synthesized in reasonable yields by condensation of intermediate 3a-j with acetyl chloride formation of six membered cyclic imides was confirmed by IR, ^{13}C NMR and ^1H NMR and elemental analysis.

3.2 Antibacterial activities:

All the synthesized compounds 4a-j were Screened for their antibacterial activity against gram positive bacteria *Bacillus Subtilis* (MCMB-310) and gram negative bacteria *E. Coli* (MCMB-301) using DMF solvent. The bacterial cultures were purchased from ARI, Pune. Some of the compound illustrated moderate to good activities against *Bacillus Subtilis* and *E. coli* as shown in the table –1.

Table 1: Antibacterial activities of N-Phenyl Glutarimides

Compound Code	Gram +ve bacteria			Gram -ve bacteria		
	Bacillus Subtilis			E. Coli		
	100µg/ml	200µg/ml	300µg/ml	100µg/ml	200µg/ml	300µg/ml
4a	--	8.33±0.33	11±0.57	7.33±0.33	10.33±0.33	12.33±0.33
4b	--	8.66±0.33	11±0.57	--	11.33±0.33	12.33±0.33
4c	6.66±0.33	9±0.57	12.33±0.33	8.33±0.33	12.33±0.33	14.66±0.33
4d	--	6±0.00	11.33±0.33	7±0.57	9±0.57	12±0.00
4e	--	6±0.00	11±0.57	--	11.33±0.33	13.33±0.33
4f	--	7.33±0.33	11.33±0.33	8±0.57	12.66±0.33	15.66±0.33
4g	--	--	--	7.33±0.33	10.66±0.33	13±0.57
4h	--	6±0.00	6.66±0.33	7.33±0.33	11±0.00	12±0.00
4i	6±0.00	7.33±0.33	9.33±0.33	--	9.66±0.33	12.66±0.33
4j		7.33±0.33	11±0.57	--	9.33±0.33	13.66±0.33
Control	0	0	0	0	0	0
Ampicillin	18.66±0.33	22.33±0.33	24±0.57	18.66±0.33	21±0.57	24±0.57

Keynote: *Zone of inhibition measured in mm (Mean±S.E.M.) (N=3) '--' means no zone*

4. Conclusion

A method for synthesis of glutarimide **(4a-j)** has been developed in good yield. All these compounds were characterized by their spectral analysis. Most of the compound exhibited moderate to good activity against *Bacillus Subtilis* and *E. coli.* The synthesized compounds may be used for preparation of various heterocyclic systems.

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