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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF FIVE MEMBERED CYCLIC IMIDE DERIVATIVES OF MONO, DI AND TRI SUBSTITUTED AROMATIC AMINES AND NAPTHYL AMINE

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ABSTRACT

The five membered cyclic imide derivatives were prepared by reacting succinic anhydride with substituted aromatic amines and napthyl amine to get 3-(N-phenylcarbamoyl) propanoic acid and 3-(N-napthylcarbamoyl) propanoic acid. These intermediates underwent ring closer with acetyl chloride furnished five membered cyclic imides derivatives. All these derivatives were screened for antimicrobial activities.

KEYWORDS: Heterocycles, 3-(N-phenylcarbamoyl) propanoic acid, 3-(N-napthylcarbamoyl) propanoic acid, cyclic imides, antimicrobial activity.

INTRODUCTION

Heterocyclic compounds are the world's largest and varied kinfolk of organic and synthetic routes. Cyclic imides comprising the most common heterocyclic elements like nitrogen, oxygen and sulphur plays a vital role in the development of pharmaceutical, medicinal, chemical and agricultural fields. Cyclic imides revealed the CNS anxiolytic and anti-depressive activities on rats by open field test and porsolt test.[1] Their biotransformation of racemic and chiral forms was also susceptible on fungi.[2] They are also remarkable regio-selective and stereo-selective agents by $NaBH_4$ reduction.[3] The molecular model methods of the substituted cyclic imides were prospectively found cytotoxic agents on DNA bindings and apoptosis induction of peripheral blood neutrophils.[4] The substituted cyclic imides coumarins and atacoumarins confer significant antimicrobial and antifungal activities and pthalimide proven α-amylase enzymes inhibitory actions.[5] Some halo-substituted phenyl

succinimides obtained the significant role in the mechanism of NDPS nephro-toxicity NDHS formation.[6] Succinimide acts as an electro-convulsions[7], anti-muscarinic and nephrotoxic[8], anticonvulsant against maximum electroshocks[9][10][11], anti-mutagenic with anti-epileptic[12], analgesic[13] agents. Some optically active succinimide derivatives found good antagonistic activity towards acetylcholine on the ileum of the guinea-pigs.[14] Cyclic imides like succinimides, maleimides, itaconimide and oxazolidinediones showed the preventive and curative antifungal potency against rice blast and kidney bean stem rots[15] in the green house test. They also inhibit a selective mono-glyceride lipase and psychiatric disorders like anxiety and depression.[16] Instead of these, the molecular polarizability ellipsoids of the heterocyclic five membered cyclic imides are strongly interacted with other molecular fragments which found reasonable electric properties.[17] The numbers of succinimide derivatives have proved the seedling growth stimulator activities against Henry wheat and Scarlet globe radish [18]. Therefore the synthesis and selective functionalization of cyclic imides has been focus of active research area over the years.[19] [20] [21]

MATERIAL METHODS

Melting points were recorded in open glass capillaries and were uncorrected. IR spectra in KBr pallets) were recorded on Simadzu and ATR Brucker alpha FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on 400 MHz and 500 MHz by Brucker spectrophotometer. 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, succinic anhydride, acetyl chloride and benzene.

GENERAL PROCEDURE FOR CYCLIC IMIDES

Preparation of 3-(N-phenyl/napthylcarbamoyl) propanoic acid (3a-j)

To succinic 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 amines / napthyl 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 3-(N-phenyl/napthylcarbamoyl) propanoic acid was obtained. The experimental method diagrammatically shown in **fig.1**;

3-(phenylcarbamoyl) propanoic acid (3a): White powder, M.F.: $C_{10}H_{11}NO_3$, Mol. Wt.: 193.2, M.P. 118 ºC

3-(4-bromophenylcarbamoyl) propanoic acid (3b):Shiny white powder,M. F.: $C_{10}H_{10}BrNO_3$, Mol. Wt.: 272.1, M.P. 149 ºC

3-(4-chlorophenylcarbamoyl) propanoic acid (3c):White powder, M.F.: $C_{10}H_{10}ClNO_3$, Mol. Wt.: 227.64, M.P. **136 °C**

3-(p-tolylcarbamoyl) propanoic acid (3d): White powder, M.F.: $C_{11}H_{13}NO_3$, Mol. Wt.: 207.23, M.P. 146 ºC

3-(4-methoxyphenylcarbamoyl) propanoic acid (3e): White powder, M.F.: $C_{11}H_{13}NO_4$, Mol. Wt.: 223.23, M.P. 151ºC

3-(4-fluorophenylcarbamoyl) propanoic acid (3f):White powder, M.F.: $C_{10}H_{10}FNO_3$, Mol. Wt.: 211.19, M.P. 135 °C

3-(4-nitrophenylcarbamoyl) propanoic acid (3g):Pale yellow powder, M.F.: $C_{10}H_{10}N_2O_5$, Mol. Wt.: 238.2, M.P. 172 ºC

3-(naphthalen-4-ylcarbamoyl) propanoic acid (3h):Faded lavender coloured powder, M.F.: $C_{14}H_{13}NO_3$, Mol. Wt.: 243.26, M.P. 111 ºC

3-(3-chloro-4-fluorophenylcarbamoyl) propanoic acid (3i):White powder, M.F.: $C_{10}H_9ClFNO_3$, Mol. Wt.: 245.63, M.P. 124 °C

3-(2,4,5-trichlorophenylcarbamoyl) propanoic acid (3j):White powder, M.F.: $C_{10}H_8Cl_3NO_3$, Mol. Wt.: 296.53, 169 °C

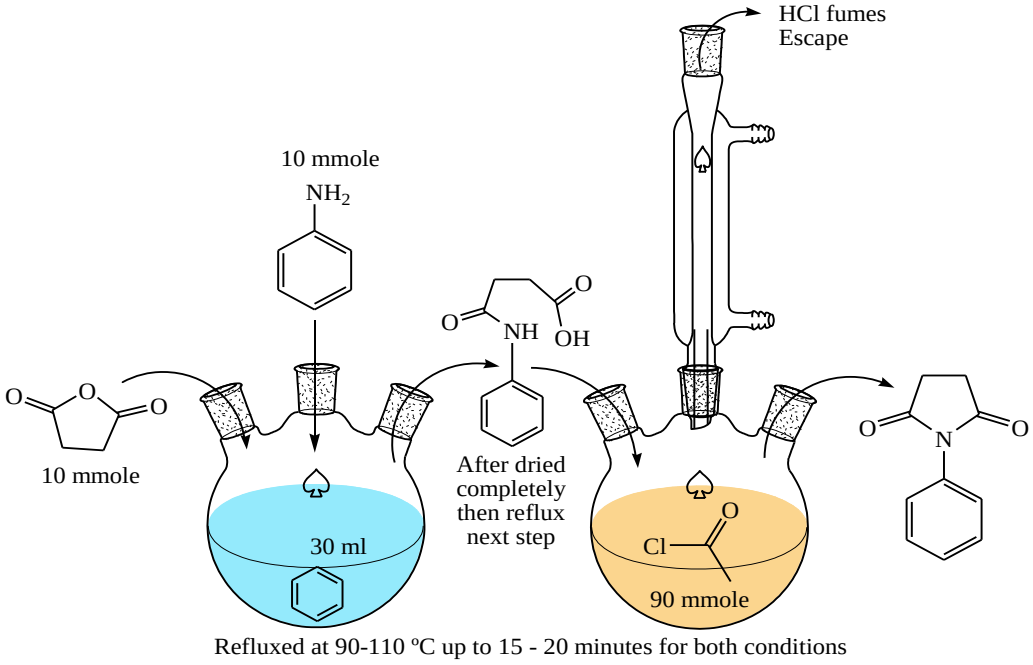


Fig. 1: Experimental demonstration of cyclic imides synthesis

Preparation of N-phenyl/napthyl-pyrrolidine-2,5-dione or cyclic imides:

The mixture of 3-(N-phenyl/napthylcarbamoyl) propanoic 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 methanol or ethanol **(scheme–I)** and percent yield of all the compounds are graphically shown in the chart. 1.

Phenylpyrrolidine-2, 5-dione (4a)

Cream white solid, yield (79.91%), m. p. 154-156 ºC[22],M.F.$C_{10}H_9NO_2$,M.W. 175.06;IR (KBr): 1708, 1774, 2937, 1291, 1457, 1502, 1595 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 7.1-7.42 (m, 5H, Ar-H), 2.93 (s, 4H, imide)

(4-bromophenyl) pyrrolidine-2, 5-dione (4b)

Whitish brown solid, yield (89.78%), m. p. 174-176 ºC, M.F. $C_{10}H_8BrNO_2$,M.W.254.08; IR (KBr): 1707,1766, 2998, 1295, 1455, 1488, 1588, 1070 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 7.16-7.40 (m, 4H, Ar-H), 2.95 (s, 4H, imide)

1-(4-chlorophenyl) pyrrolidine-2, 5-dione (4c)

Whitish lavender solid, yield (76.60%), m. p. 159-161 ºC, M.F. $C_{10}H_8ClNO_2$,M.W. 209.63; IR (KBr): 1711,1773,2985,1302, 1495, 1527, 1589, 1093 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 7.12-7.46 (m, 4H, Ar-H), 2.89 (s, 4H, imide)

1-p-tolylpyrrolidine-2, 5-dione (4d)

Cream white solid, yield (62.73%), m. p.150-152 ºC, M.F.$C_{11}H_{11}NO_2$,M.W. 189.21; IR (KBr): 1710,1774,2995, 1288, 1450, 1519, 1589 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 7.01-7.48 (m, 4H, Ar-H), 2.89 (s, 4H, imide), 2.31 (s, 3H, CH_3)

4-methoxyphenyl) pyrrolidine-2, 5-dione (4e)

Brownish solid, yield (78.91%), m. p.160-162 ºC, M.F. $C_{11}H_{11}NO_3$,M.W. 205.21; IR (KBr): 1708, 1770, 2963, 1302, 1476, 1512, 1606, 1178 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 6.28-7.20 (m, 4H, Ar-H), 2.91 (s, 4H, imide), 3.84 (s,3H, OCH_3)

1-(4-fluorophenyl) pyrrolidine-2, 5-dione (4f)

Brownish solid, yield (62.90%), m. p. 176-178 ºC, M.F. $C_{10}H_8FNO_2$,M.W. 193.17; IR (KBr): 1712, 1767, 3000, 1290, 1456, 1513, 1604, 1178 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 7.16-7.36 (m, 4H, Ar-H), 2.94 (s, 4H, imide)

1-(4-nitrophenyl) pyrrolidine-2, 5-dione (4g)

Cream yellow solid, yield (88.86%), m. p. 219-221 ºC, M.F.$C_{10}H_8N_2O_4$,M.W. 220.18; IR (ATR): 1617, 1679, 2883, 1300, 1501, 1564, 1596, 1501 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 7.84-8.22 (m, 4H, Ar-H), 2.91 (s, 4H, imide)

1-(naphthalen-4-yl) pyrrolidine-2, 5-dione (4h)

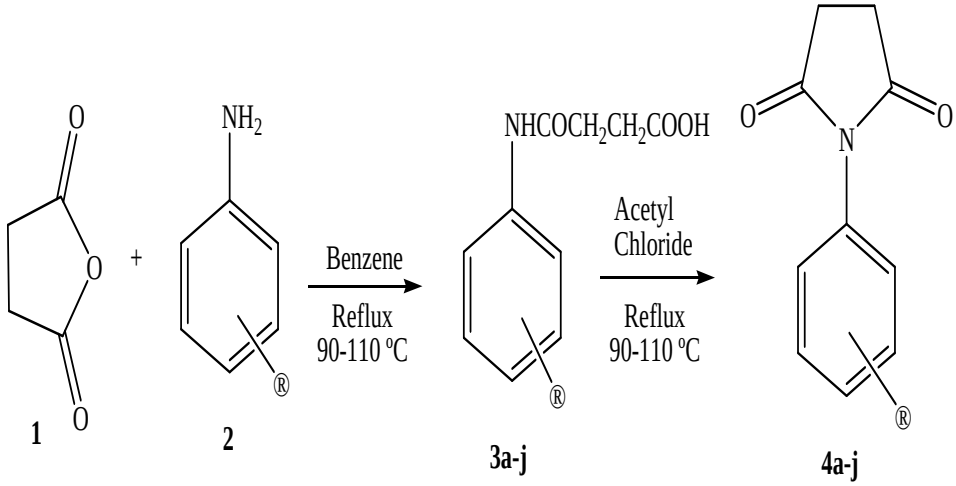
Dark lavender solid, yield (99.11%), m. p. 148-150 ºC, M.F. $C_{14}H_{11}NO_2$,M.W. 225.24; IR (ATR): 1700, 1776, 2939, 1291, 1440, 1463, 1509, 1570, 1595 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 7.30-8.03 (m, 7H, napthyl), 3.06 (s, 4H, imide)

1-(3-chloro-4-fluorophenyl) pyrrolidine-2, 5-dione (4i)

Pinkish white solid, yield (84.60%), m. p. 158-160 ºC, M.F.$C_{10}H_7ClFNO_2$,M.W. 227.62; IR (ATR): 1698, 1776, 2800, 1294, 1490, 1502, 1595, 1173, 1059 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 7.25-7.44 (m, 3H, Ar-H), 2.92 (s, 4H, imide)

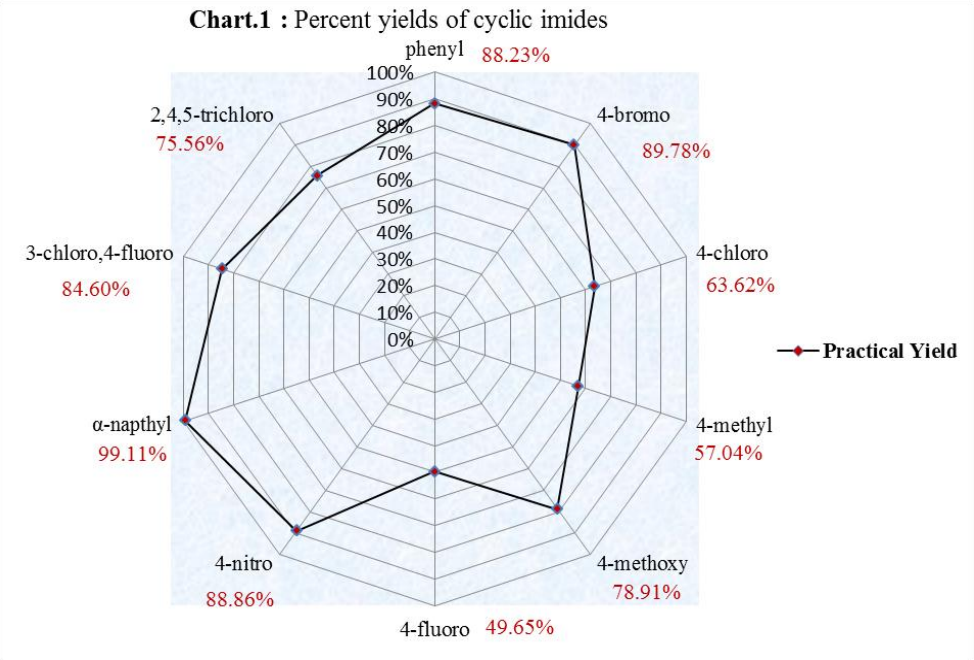
1-(2, 4, 5-trichlorophenyl) pyrrolidine-2, 5-dione (4j)

Purewhite solid, yield (75.56%), m. p. 196-198 ºC, $C_{10}H_6Cl_3NO_2$, M.W. 278.52; IR (ATR): 1660, 1700, 2993, 1356, 1454, 1508, 1570, 1072 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 7.28-7.49 (m, 2H, Ar-H), 2.27 (s, 4H, imide)



® , **a** = -H, **b** = -4Br, **c** = -4Cl, **d** = -4CH_3, **e** = -4OCH_3,
f = -4F, **g** = -4NO_2, **h** = -phenyl, **i** = -3Cl,-4F, **j** = -2,4,5Cl

Scheme -1: Preparation of N-phenyl Succinimides



RESULTS AND DISCUSSION

Chemistry:

The intermediate 3a-j compounds were prepared by the reaction of succinic anhydride using primary aromatic amines and napthyl amine. The series of cyclic imides 4a-j were synthesis in reasonable yields by condensation of intermediate 3a-j with acetyl chloride formation of cyclic imides was confirmed by IR and ^{1}H NMR and elemental analysis.

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 showed moderate to good activities against Bacillus Subtilis and E-coli as shown in the table –I;

Table-I: Antibacterial activities of cyclic imides

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	--	8.66±0.33	11±1.15
4b	--	6.33±0.33	6.33±0.33	--	8.66±0.33	11.33±0.33
4c	--	-	8.33±0.33	7.33±0.33	9.66±0.33	12.66±0.33
4d	6.33±0.33	7.33±0.33	10.66±0.33	7±0.00	9.66±0.33	11.66±0.33
4e	--	--	--	--	10±0.00	13±0.57
4f	6.33±0.33	9±0.57	11±0.57	7.33±0.33	9.66±0.33	12.66±0.33

4g	--	--	17±0.57	7±0.00	9.33±0.33	11.66±0.33
4h	--	--	--	--	10.66±0.33	13±0.57
4i	--	7±0.00	14.33±0.33	--	9.66±0.33	12.33±0.33
4j	7±0.57	10±0.57	17±0.57	--	9.66±0.33	12±0.57
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).*

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