

PGR Evaluation of Novel Synthesized Five and Six Membered Cyclic Imides

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Abstract: A huge number of cyclic imides have been designed, developed due to their various effective properties. By considering all elevated applications, it was scheduled to design and synthesize the novel class of N-phenyl succinimides and N-phenyl glutarimides. In this article some of the appealing and significant schemes for the making of cyclic imides are epitomized. The five/six membered cyclic imides were synthesized by reacting succinic / glutaric anhydride with different substituted aromatic amines to get 1-(N-methylpyridin-2-yl) pyrrolidine-2, 5/6-dione. During this synthetic route acetyl chloride and water are used as solvent in traditional and green pathways respectively. The beauty of greener exercise helps to replace hazardous solvent acetyl chloride by water. All synthesized compounds were tested as plant growth regulator against maize (Rajeshwar), moong (PKVM-8802).

Keywords: Glutaric anhydride, Green pathway, PGR, Succinic anhydride, Traditional pathway

I. INTRODUCTION

As the Green Chemistry movement has gained momentum [1], definitions of Green Chemistry [2-5] have been dominated predominantly. Green Chemistry concepts, however, apply to an incredible diversity of scientific endeavour, which has invariably led to differences between academia and industry. Speaking primarily about the pharmaceutical industry, they have been achieved lot of advances because of Green Chemistry[6].

Cyclic imides have been attracted much more attention of organic and medicinal chemists due to their biological activities. Most of them are extensively used as analgesic[7], anti-nociceptive agents[8] or as reactants for polymer synthesis[9]. An imide nucleus can also be found in a structure of anxiolytic, antimicrobial, anticancer and anti-inflammatory substances[10-12]. 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[13]. The substituted cyclic imides coumarins and atacoumarins confer significant antimicrobial and antifungal activities and pthalimide proven α -amylase enzymes inhibitory actions[14]. It has been observed that certain aromatic derivatives of succinimide enhance the growth of root of germinating seeds[15]. The different substituted six membered glutarimide derivatives are hydrophobic in nature which exhibits remarkable antibacterial and antifungal efficacy[16]. The anti-proliferative activity of NCI-DIP glutarimide derivatives and 3D QSAR study gives useful guidelines to design and synthesis of novel compounds. They can express significant potency towards differentiated human cells [17]. In this regard different substituted glutarimides were prepared from cyclic anhydrides[18], PPA[19], Baylis Hillman adducts[20], tandem process[21], succinic and glutaric acids[22] etc.

In spite of above discussion, heterocyclic nitro derivative provides the great fortune for the development of novel and compelling medicinal drugs. Heterocyclic imides such as succinimides[23], glutarimides[24] and their malononitriles[25-30] and chalcone[31-35] centered pyrazolies[36-38], pyrimidines[39-41] plays a very important key role in the synthesis of organic compounds.

II. MATERIAL METHODS

Melting points were recorded in open glass capillaries and were uncorrected. The chemical structures of the obtained compounds were confirmed by spectral analyses. IR spectra (in KBr pallets) were recorded on Simadzu and ATR Bruker alpha FTIR spectrophotometer. ¹H NMR spectra were recorded on and 500 MHz by Bruker spectrophotometer. The chemical shifts were reported as parts per million (ppm) with (CH₃)₄Si (TMS) as an internal standard. Signal multiplicities are represented by: s (singlet), d (doublet), t (triplet), m (multiplet). The purity of compound was checked 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.

In conventional method, all the compounds (i-vi) were synthesized from the corresponding commercial available aromatic amines, succinic/Glutaric anhydride, acetyl chloride and benzene.

In green method, all the compounds (i-vi) were synthesized from the corresponding commercial available aromatic amines, succinic/Glutaric anhydride and water.

A. General Procedure for the Synthesis

1) Preparation of 1-(N-methylpyridin-2-yl) pyrrolidine-2, 5-dione (i-iii)

B. Conventional Method

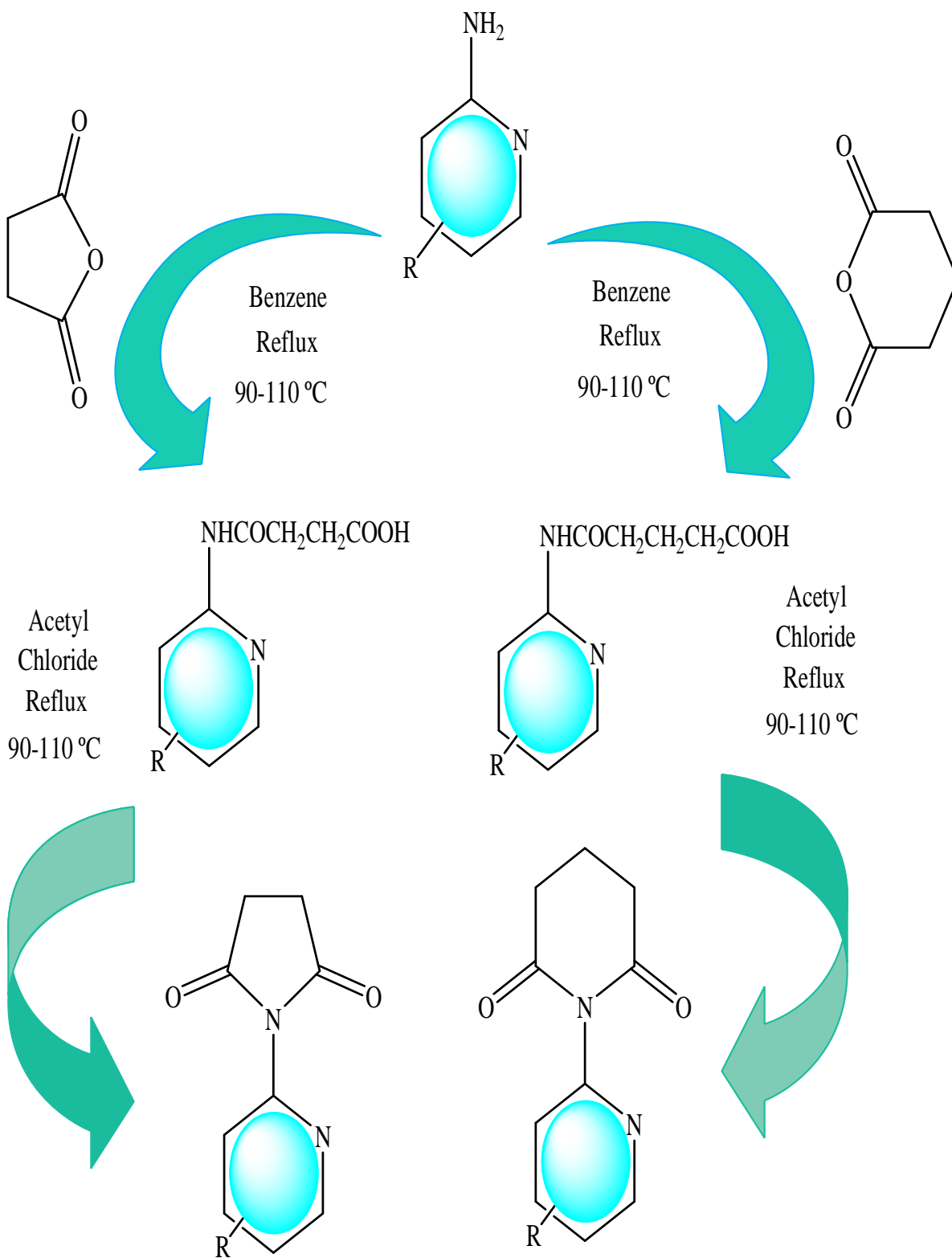
To succinic anhydride (0.01 mole) benzene was added and heated under reflux with constant stirring for 15 to 20 minutes till the solution becomes clear. Into this solution the substituted 2- aminopyridine (0.01 mole) in 5 ml benzene was slowly poured with constant stirring for 15 to 20 minutes till the solution becomes homogenized. Upon evaporation of benzene the whitish amorphous powder of 3-(N-methylpyridin-2-ylcarbamoyl)propanoic acid was obtained. Then the mixture of 3-(N-methylpyridin-2-ylcarbamoyl)propanoic acid and acetyl chloride (0.09 mole) 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 (Scheme-I) was obtained and purified by recrystallization from isopropanol and percent yield of all the compounds are graphically shown in the chart.

C. Green Method

0.01 mol of the appropriately substituted 2- aminopyridine was dissolved in 20 mL of water and 0.01 mol of succinic anhydride was gradually added. The mixture was heated in an oil bath with simultaneous distillation of water. After the water was completely removed, the temperature of the reaction mixture was rose up to 180 °C and was maintained for 1.5 h. The crude products (Scheme-II) were recrystallized from isopropanol.

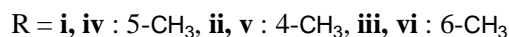
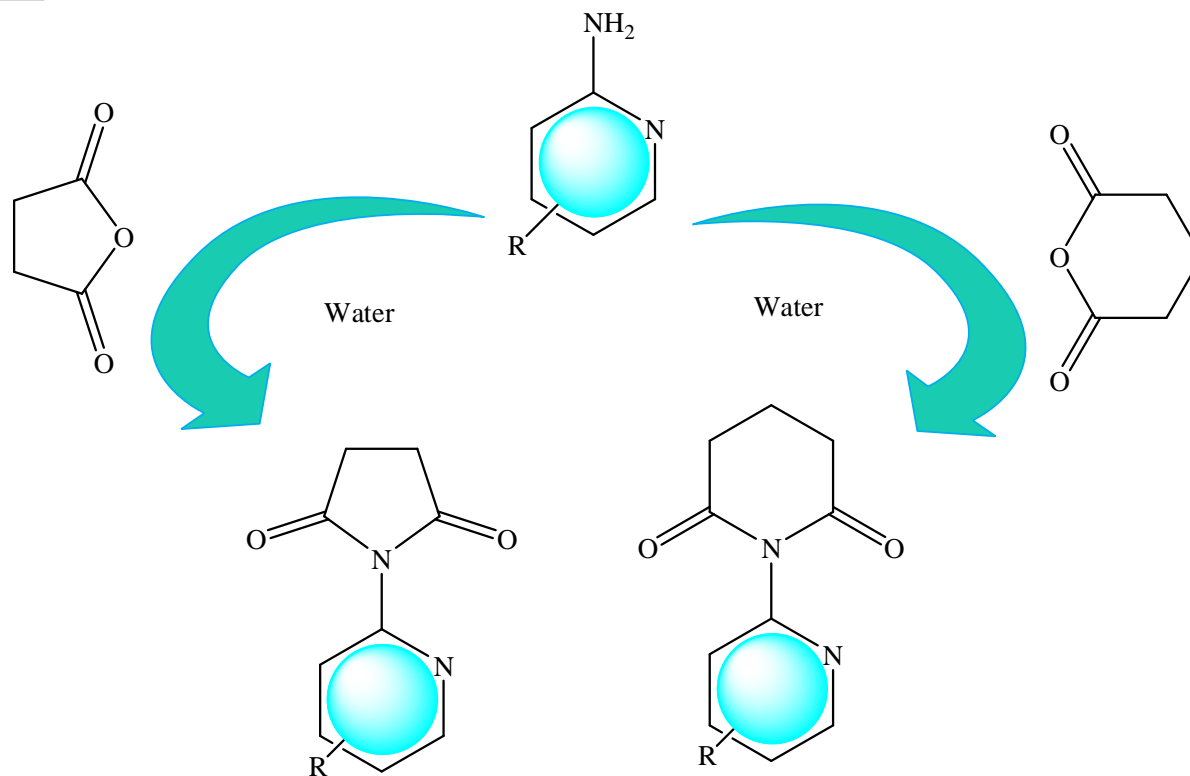
D. Preparation of 1-(N-methylpyridin-2-yl) piperidine-2, 6-dione (iv-vi)

- 1) *Conventional Method:* To glutaric anhydride (0.01 mole) benzene was added and heated under reflux with constant stirring for 15 to 20 minutes till the solution becomes clear. Into this solution the substituted 2- aminopyridine (0.01 mole) 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-methylpyridin-2-ylcarbamoyl)butanoic acid was obtained. Then the mixture of 4-(N-methylpyridin-2-ylcarbamoyl)butanoic acid and acetyl chloride (0.09 mole) 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 (Scheme-I) was obtained and purified by recrystallization from isopropanol and percentage yield of all the compounds are graphically shown in the chart.
- 2) *Green Method:* 0.01 mole of the appropriately substituted 2- aminopyridine was dissolved in 20 mL of water and 0.01 mole of glutaric anhydride was gradually added. The mixture was heated in an oil bath at 180 °C and was maintained for 1.5 hr. The crude products (Scheme-II) were recrystallized from isopropanol.



R = **i, iv** : 5-CH₃, **ii, v** : 4-CH₃, **iii, vi** : 6-CH₃

Scheme - I :Preparation of N-phenyl Succinimide/Glutarimide - Conventional Pathway



Scheme - II :Preparation of N-phenyl Succinimide/Glutarimide - Green Pathway

E. Physicochemical and Analytical Data For Compounds i-vi

- 1) *1-(5-methylpyridin-2-yl) pyrrolidine-2,5-dione (i)*: Whitish Solid, C₁₀H₁₀O₂N₂, MW: 190.20, Product %: Conventional: 64.24% Green: 66.80%, MP: 146-148 °C, Cal: C (63.15) H (5.30) N (14.73); Obs: C (63.32) H (5.51) N (14.87), FTIR (KBr): >C=O (2-Peaks): 1709.98, 1675.78; cyclic CH₂-CH₂ (2-Peaks): 2967.90, 2924.54; C-N Aromatic (2-Peaks): 1334.43, 1301.00; aromatic ring (3-Peaks): 1490.30, 1551.06, 1598.26; -CH₃ (1-Peak): 2759.09; -CH₃ bend (2-Peaks): 1490.30, 1357.61 cm⁻¹, 1H NMR (500.13 MHz, DMSO-d₆, δ ppm): 2.42 (s, 3H, CH₃ - pyridine), 2.81 (s, 4H, imide), 7.85-8.47 (m, 2H, pyridine), 8.23 (d, 1H, pyridine).
- 2) *1-(4-methylpyridin-2-yl) pyrrolidine-2,5-dione (ii)*: Whitish Powder, C₁₀H₁₀O₂N₂, MW: 190.20, Product %: Conventional: 65.45% Green: 63.78%, MP: 142-144 °C, Cal: C (63.15) H (5.30) N (14.73); Obs: C (63.32) H (5.51) N (14.87), FTIR (KBr): >C=O (2-Peaks): 1700.00, 1670.62; cyclic CH₂-CH₂ (2-Peaks): 2969.77, 2813.35; C-N Aromatic (2-Peaks): 1301.57, 1221.14; aromatic ring (3-Peaks): 1491.75, 1551.49, 1405.84; -CH₃ (1-Peak): 2764.62; -CH₃ bend (2-Peaks): 1444.63, 1353.90 cm⁻¹, 1H NMR (500.13 MHz, DMSO-d₆, δ ppm): 2.42 (s, 3H, CH₃ - pyridine), 2.92 (s, 4H, imide), 6.91-8.56 (m, 3H, pyridine).
- 3) *1-(6-methylpyridin-2-yl) pyrrolidine-2,5-dione (iii)*: Whitish Solid, C₁₀H₁₀O₂N₂, MW: 190.20, Product %: Conventional: 66.37% Green: 70.67%, MP: 148-50 °C, Cal: C (63.15) H (5.30) N (14.73); Obs: C (63.32) H (5.51) N (14.87), FTIR (KBr): >C=O (2-Peaks): 1689.97, 1640.97; cyclic CH₂-CH₂ (2-Peaks): 2967.90, 2924.35; C-N Aromatic (2-Peaks): 1309.75, 1261.44; aromatic ring (1-Peak): 1544.23; -CH₃ (1-Peak): 2792.79; -CH₃ bend (2-Peaks): 1403.95, 1309.75 cm⁻¹, 1H NMR (500.13 MHz, DMSO-d₆, δ ppm): 2.42 (s, 3H, CH₃-pyridine), 3.05 (s, 4H, imide), 7.09-7.65(d, 1H, pyridine).
- 4) *1-(5-methylpyridin-2-yl) piperidine-2,6-dione (iv)*: Whitish Solid, C₁₁H₁₂O₂N₂, MW: 204.225, Product %: Conventional: 68.83% Green: 71.95%, MP: 140-142 °C, Cal: C (64.69) H (5.92) N (13.72); Obs: C (64.37) H (5.58) N (13.83), FTIR (KBr): >C=O (2-Peaks): 1708.22, 1676.25; cyclic CH₂-CH₂ (2-Peaks): 2965.07, 2922.27; C-N Aromatic (2-Peaks): 1330.81, 1297.05; aromatic ring (2-Peaks): 1523.90, 1407.27; -CH₃ (1-Peak) 3085.91; -CH₃ bend (2-Peaks): 1445.25, 1360.12; -CH₂

- bend (1-Peak): 1470.55 cm⁻¹, ¹H NMR (500.13 MHz, DMSO-d₆, δ ppm): 2.40 (s, 3H, CH₃-piperidine), 2.24 (t, 4H, imide), 1.79 (m, 2H, imide), 7.88-8.30 (m, 3H, piperidine)
- 5) *1-(4-methylpyridin-2-yl) piperidine-2,6-dione (v)*: Whitish Solid, C₁₁H₁₂O₂N₂, MW: 204.225, Product %: Conventional: 67.15% Green: 68.39%, MP: 150-152 °C, Cal: C (64.69) H (5.92) N (13.72); Obs: C (64.35) H (5.56) N (13.80), FTIR (KBr): >C=O (2-Peaks): 1670.86, 1622.35; cyclic CH₂-CH₂ (2-Peaks): 2960.32, 2918.51; C-N Aromatic (2-Peaks): 1332.49, 1295.39; aromatic ring (1-Peak): 1573.22; -CH₃ (1-Peak) 3073.79; -CH₃ bend (2-Peaks): 1407.82, 1368.35; -CH₂ bend (1-Peak): 1445.60 cm⁻¹, ¹H NMR (500.13 MHz, DMSO-d₆, δ ppm): 2.41 (s, 3H, CH₃-piperidine), 2.30 (t, 4H, imide), 1.81 (m, 2H, imide), 7.75-8.32 (m, 3H, piperidine).
- 6) *1-(6-methylpyridin-2-yl) piperidine-2,6-dione (vi)*: Whitish Solid, C₁₁H₁₂O₂N₂, MW: 204.225, Product %: Conventional: 64.27% Green: 69.75%, MP: 154-56 °C, Cal: C (64.69) H (5.92) N (13.72); Obs: C (64.34) H (5.59) N (13.85), FTIR (KBr): >C=O (2-Peaks): 1735.26, 1692.69; cyclic CH₂-CH₂ (2-Peaks): 2966.06, 2785.35; C-N Aromatic (2-Peaks): 1305.34, 1236.60; aromatic ring (3-Peaks): 1663.82, 1636.28, 1561.33; -CH₃ (1-Peak) 3025.26; -CH₃ bend (2-Peaks): 1404.05, 1357.13; -CH₂ bend (1-Peak): 1484.82 cm⁻¹, ¹H NMR (500.13 MHz, DMSO-d₆, δ ppm): 2.39 (s, 3H, CH₃-piperidine), 2.21 (t, 4H, imide), 1.70 (m, 2H, imide), 7.08-7.88(m, 3H, piperidine).

III. RESULTS AND DISCUSSION

A. Chemistry

The series of cyclic imides i-vi were prepared by the reaction of succinic/glutaric anhydride and primary aromatic amines by using conventional and green pathway. It has been observed that reasonable yield is obtained for both synthesis techniques but more or less better yield is obtained in case of green pathway than conventional except 1-(4-methylpyridin-2-yl) pyrrolidine-2,5-dione. The formation of five/six membered cyclic imides was confirmed by IR, ¹³C NMR and ¹H NMR and elemental analysis.

TABLE-I
% OF YIELD BY TRADITIONAL AND GREEN PATHWAY

Sample	% of Yield-Traditional Pathway	% of Yield-Green Pathway
i	64.24	66.8
ii	65.45	60.65
iii	70.67	65.47
iv	68.83	71.95
v	67.15	68.39
vi	64.27	69.75

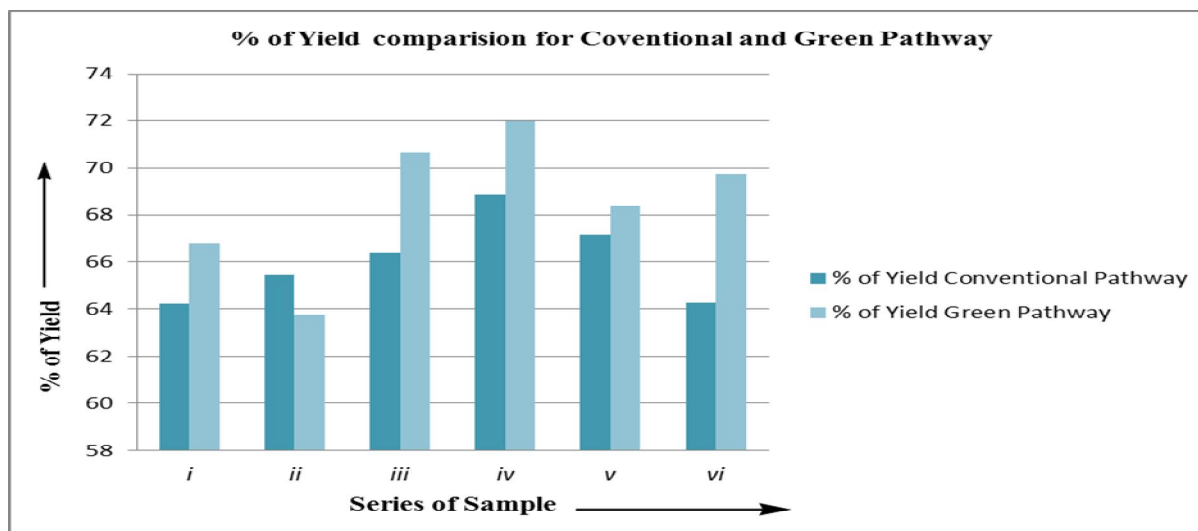


Fig. 1 Comparison: % of Yield by Traditional and Green Pathway

B. Plant Growth Activities of Cyclic Imides

All the novel class of cyclic imides and Standard I, II, III were tested for their plant growth activity versus maize (Rajeshwar) and moong (PKVM-8802) by using DMSO as solvent. They were tested for root length, shoot length and weight of root before and after heating (at 50 °C).

After 3 days: Compound No v is found effective for the shoot of maize.

After 6 days: Compound No v and Compound No ii were traced efficient for the root and shoot of maize and moong respectively.

After 9 days: Compound No v and Compound No ii has been recognized outstanding for the root of maize and moong respectively.

Also, Compound No v and Compound No iii-v are revealed most prestigious activities for the shoot of maize and moong respectively. Weight of root (before heating) for maize as well as moong has been observed admirable because of Compound No i, v.

Weight of root (after heating) for maize has been displayed excellent because of Compound No i, ii.

TABLE II
ROOT/SHOOT LENGTH (in mm) AFTER 3 DAYS FOR i-vi

Sample	Root Length (in mm)		Shoot Length (in mm)	
	Maize	Moong	Maize	Moong
i	3	2	3	5
ii	0	4	4	8
iii	3	0	2	3
iv	2	3	3	6
v	4	0	15	2
vi	0	2	5	5
Standard-I	10	3	14	11
Standard-II	11	2	15	16
Standard-III	9	4	12	10

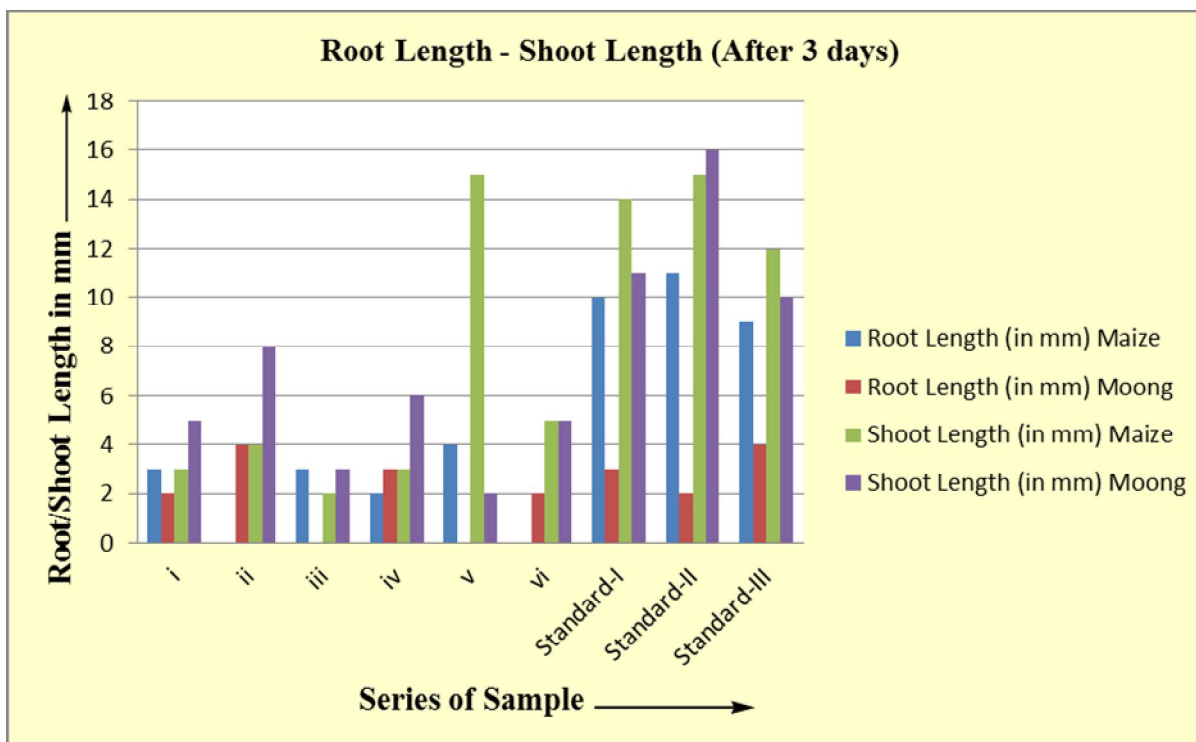


Fig. 2 Root/Shoot Length (in mm) after 3 days for i-vi

TABLE III
ROOT/SHOOT LENGTH (in mm) AFTER 6 DAYS FOR i-vi

Sample	Root Length (in mm)		Shoot Length (in mm)	
	Maize	Moong	Maize	Moong
i	7	3	7	9
ii	3	7	9	14
iii	8	2	10	10
iv	5	4	8	8
v	10	3	31	11
vi	4	4	21	9
Standard-I	12	6	34	20
Standard-II	15	8	39	29
Standard-III	11	12	30	22

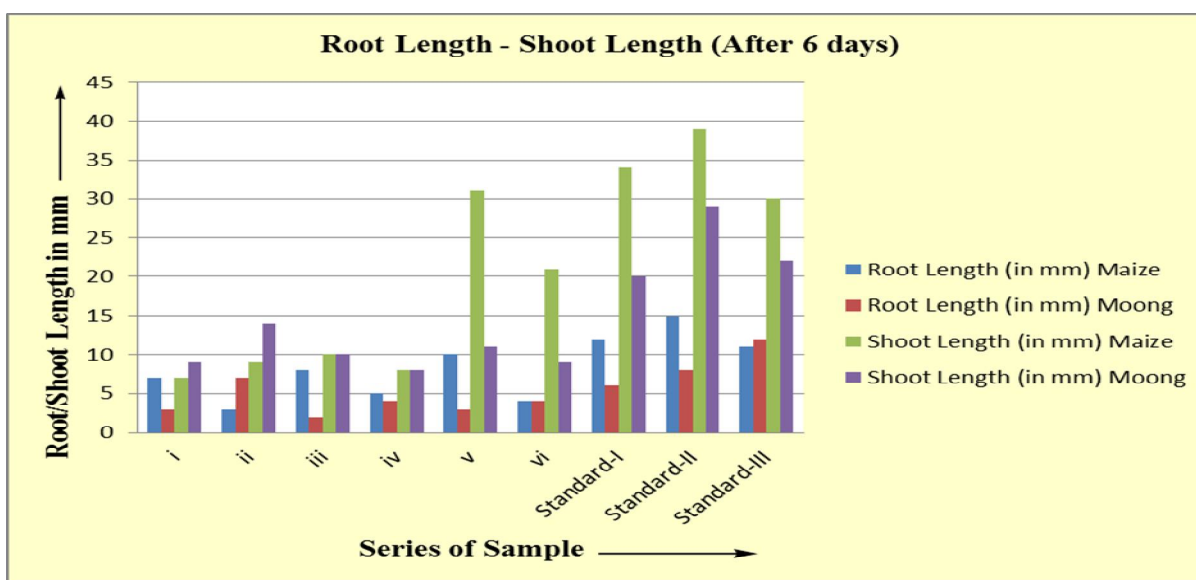


Fig. 3 Root/Shoot Length (in mm) after 6 days for i-vi

TABLE IV
ROOT/SHOOT LENGTH (in mm) AFTER 9 DAYS FOR i-vi

Sample	Root Length (in mm)		Shoot Length (in mm)	
	Maize	Moong	Maize	Moong
i	13	6	21	23
ii	8	10	23	20
iii	13	5	22	28
iv	10	7	20	26
v	22	6	57	25
vi	9	6	38	24
Standard-I	34	10	58	31
Standard-II	36	11	57	45
Standard-III	30	19	46	40

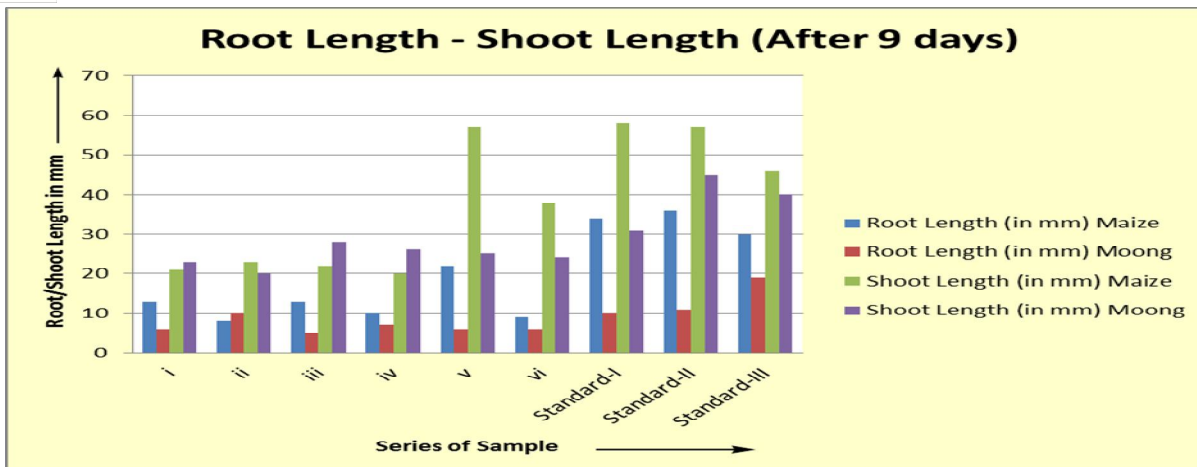


Fig. 4 Root/Shoot Length (in mm) after 9 days for i-vi

TABLE V

WEIGHT OF ROOT (in gm) BEFORE AND AFTER HEATING (AFTER 9 DAYS) FOR i-vi

Sample	Before Heating		After Heating	
	Maize	Moong	Maize	Moong
i	0.028	0.071	0.021	0.048
ii	0.023	0.08	0.018	0.053
iii	0.021	0.091	0.015	0.058
iv	0.025	0.063	0.018	0.044
v	0.057	0.079	0.042	0.052
vi	0.019	0.058	0.014	0.040
Standard-I	0.03	0.089	0.023	0.057
Standard-II	0.028	0.087	0.021	0.056
Standard-III	0.025	0.068	0.019	0.048

#Observations are made after 6 hrs during 24 hrs for 9 days

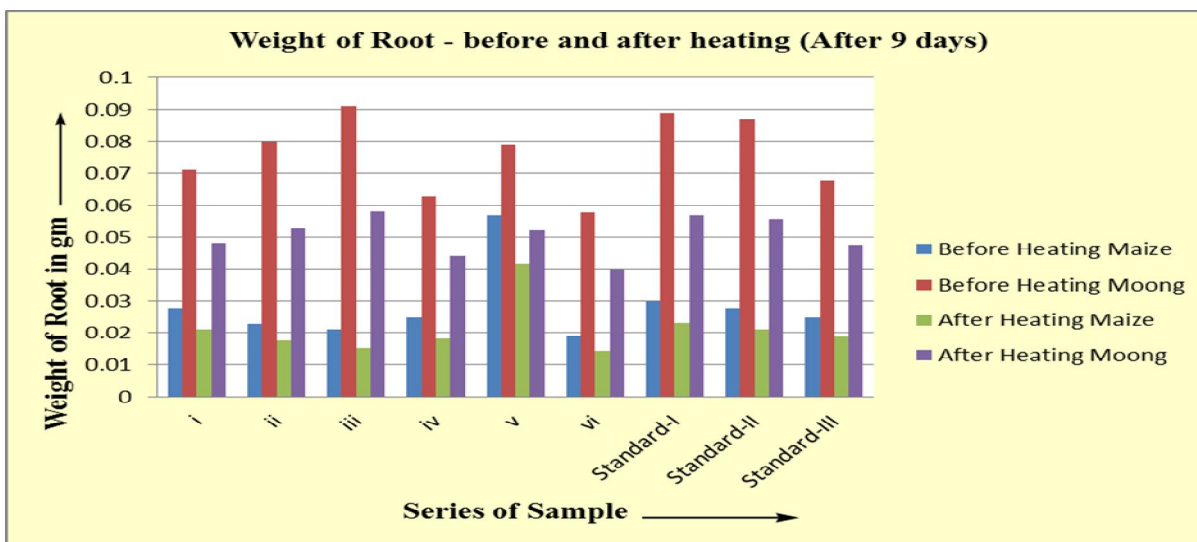


Fig. 5 Weight of Root (in gm) before and after heating (after 9 days) for i-vi

TABLE VI
WEIGHT OF SHOOT (in gm) BEFORE AND AFTER HEATING (AFTER 9 DAYS) FOR i-vi

Sample	Before Heating		After Heating	
	Maize	Moong	Maize	Moong
i	0.58	0.134	0.400	0.035
ii	0.523	0.096	0.366	0.032
iii	0.378	0.163	0.291	0.058
iv	0.382	0.152	0.294	0.055
v	0.38	0.143	0.293	0.053
vi	0.443	0.135	0.323	0.041
Standard-I	0.49	0.281	0.358	0.097
Standard-II	0.552	0.269	0.381	0.095
Standard-III	0.44	0.215	0.326	0.084

#Observations are made after 6 hrs during 24 hrs for 9 days

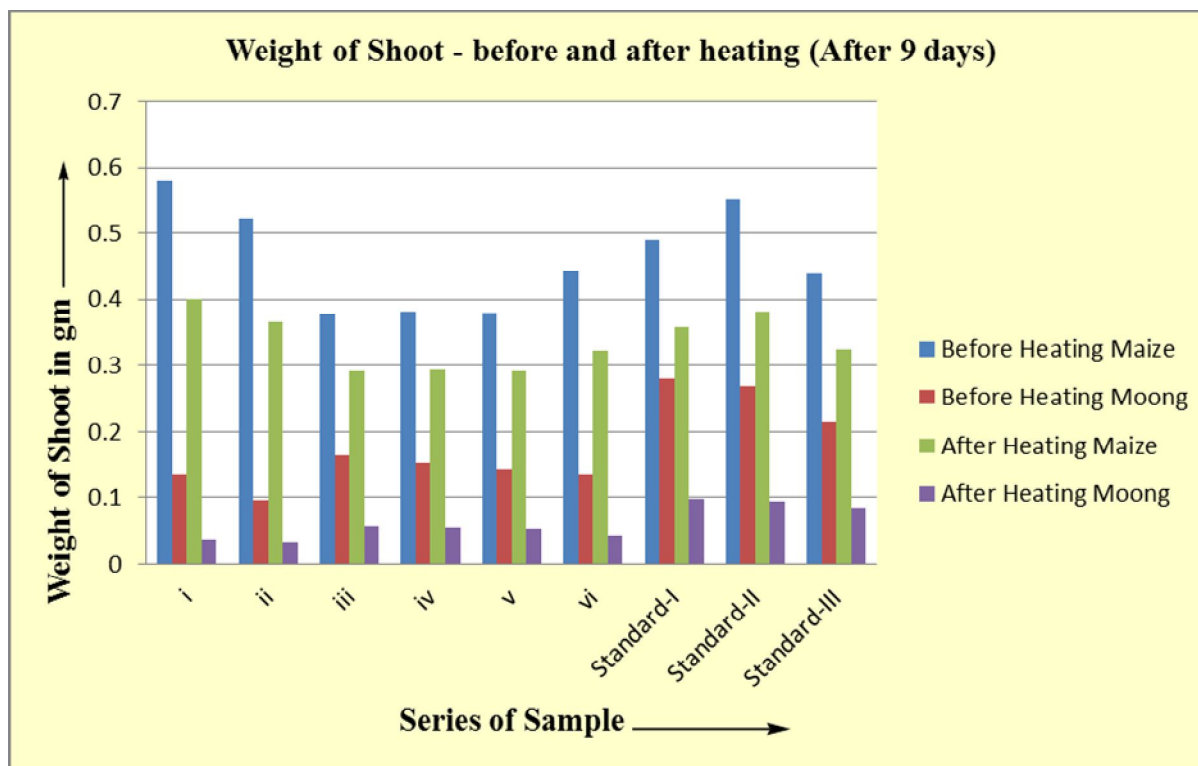


Fig. 6 Weight of Shoot (in gm) before and after heating (after 9 days) for i-vi

IV. CONCLUSIONS

To put it briefly, we have synthesized a series of five membered cyclic imides 1-(N-methylpyridin-2-yl) pyrrolidine-2,5-dione and a novel series of six membered cyclic imides 1-(N-methylpyridin-2-yl) piperidine-2, 6-dione from of 2-amino 5-methyl, 2-amino 4-methyl, 2-amino 6-methyl pyridine for the first time under convenient reaction conditions. The beauty of greener exercise helps to replace hazardous solvent acetyl chloride is by using water and use of non-renewable benzene is avoided with the help of greener approach. All novel class of synthesized compounds have shown better activities as plant growth regulator for maize (Rajeshwar) and moong (PKVM-8802) seeds. Compound No ii, v have been exhibited most excellent PGR activities for maize and moong respectively.

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