ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 8, Issue, 11, pp.41647-41651, November, 2016

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUATION OF NOVEL FIVE AND SIX MEMBEREDCYCLIC IMIDEDERIVATIVESOF2-AMINO 5-METHYL, 2-AMINO 4-METHYL, 2-AMINO 6-METHYL PYRIDINE

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ARTICLE INFO

Article History:
Received 23rd August, 2016
Received in revised form
22nd September, 2016
Accepted 05th October, 2016
Published online 30th November, 2016

Key words:

1-(N-methylpyridin-2-yl) pyrrolidine-2, 5-dione, 1-(N-methylpyridin-2-yl) piperidine-2, 6-dione, Antimicrobial activities.

ABSTRACT

The five membered cyclic imide derivatives were synthesized by reacting succinic anhydride with different substituted aromatic amines to get 1-(N-methylpyridin-2-yl)pyrrolidine-2,5-dione.The six membered cyclic imide derivatives were synthesized by reacting glutaric anhydride with different substituted aromatic amines to get 1-(N-methylpyridin-2-yl) piperidine-2,6-dione. All these derivatives were screened for antimicrobial activities.

Citation: Shankarsing Sardarsing Rajput and Prashant Prakash Chaudhari, 2016. "Synthesis, characterization and antimicrobial evaluation of novel five and six memberedcyclic imidederivativesof2-amino 5-methyl, 2-amino 4-methyl, 2-amino 6-methyl pyridine", International Journal of Current Research, 8, (11), 41647-41651.

INTRODUCTION

Cyclic imides assume the role of importantclass of substrates for biological andchemical applications.They have been shown wide degree of biological activities such as antibacterial, antifungal.They have been also imputing them for medication and some of them are widely used as analgesic and anti-nociceptiveagents. (Zhang *et al*., 2009; Malgorzata and Katarzyna, 2009; Wang *et al*., 2004; Aibin *et al*., 2010; Abdl-Aziz, 2007) Cyclic imides like succinimides, male imides, phthalimides, glutarimides embracing the foremost part in the organic synthesis. (Dhivare and Rajput, 2015) An imide nucleus can be also constitute a structure of anticancer, anxiolytic and anti-inflammatory substances. (Dhivare and Rajput, 2015) The molecular model methods of the substituted cyclic imides were prospectively inaugurate cytotoxic agents on DNA bindings and apoptosis induction of peripheral blood neutrophils. (Alaa and Abdel-Aziz, 2007) It has been observed that few halo-substituted phenyl succinimideswere retrieve the significant role in the mechanism of NDPS nephro -toxicity NDHS formation (Hong *et al*., 1996).

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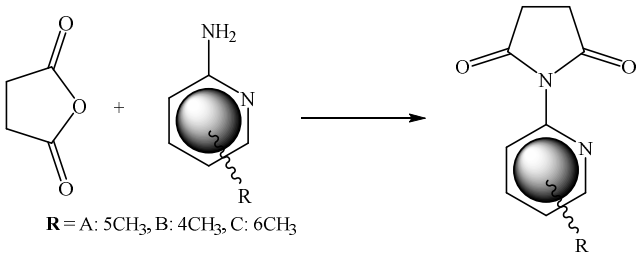
Succinimide acts as an electro-convulsions (Luszczki *et al*., 2014), anti-muscarinic and nephrotoxic. (Hudkins *et al*., 1997) Along with succinimides most of the glutarimide drugs affected the uracil transport, thymine nucleosides in the biological membranes. (Michalska *et al*., 2000) The influence of polyglutarimides PMMA thermal strengthsonorously improves the imidization (Lee *et al*., 1995) by IRTF analysis. (Legay *et al*., 2000) Natural products like glutarimide alkaloids segregated from Croton pullei species which gives outstanding antibacterial and antifungal activities. (Peixoto *et al*., 2013) The buoyant effects of glutarimides are actively found on spinal neurons (Nicholson *et al*., 1985), brain metabolism (Nicholls, 1962), mitochondrial respiration. (Prado *et al*., 2004) In spite of above discussion heterocyclic nitro (Rajput and Rajput, 2009) derivative provides the great fortune for the development of novel and compelling medicinal drugs. Heterocyclic imides such as succinimides (Rajput, 2012; Patil and Rajput, 2014), glutarimides (Rajput and Girase, 2011) and their malononitriles (Dhivare and Rajput, 2016; Lin *et al*., 2003; Dhivare and Rajput, 2015; Al-Azzawi *et al*., 2011) and chalcone (Dhivare and Rajput, 2016; AL-Azzawi *et al*., 2013; Dhivare and Rajput, 2015; Amin *et al*., 2013) centredpyrazolies (Dhivare and Rajput, 2016; Voskiene *et al*., 2007; Dhivare and Rajput, 2015), pyrimidines (Pal *et al*., 2012; Dhivare and

Rajput, 2015; Rajput and Patole, 2015; Dhivare and Rajput, 2015) derivatives plays a very important key role in the synthesis of organic compounds.

MATERIALS AND 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 obtained on Simadzu and ATR Brucker alpha FT-IR spectrophotometer. 1H NMR spectra were obtained on and 500.13 MHz by Brucker 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. All the compounds (A, B, C, D, E and F) were synthesized from the corresponding commercial available aromatic amines, succinic anhydride, glutaric anhydride and water.Anti-microbial and Anti-fungal activities were carried out by Agar diffusion assay (Disk diffusion method, Disk size 6 mm). (Jorgensen *et al*., 2007; Ingroff *et al*., 2007)



Scheme - I

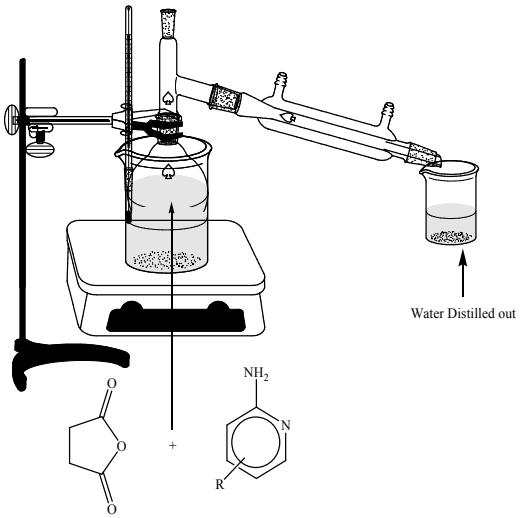


Fig.1: Experimental Demonstration of N-Succinimide Derivative (Part-I) Synthesis - Green Method

General Procedure of Synthesis

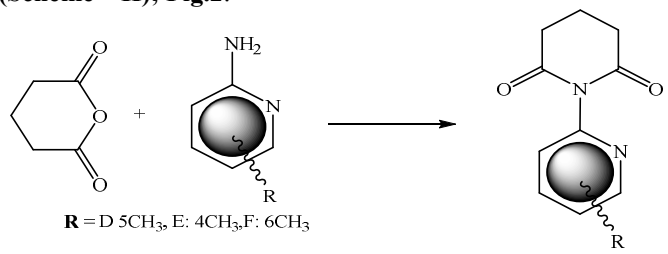
Preparation of 1-(N-methylpyridin-2-yl) pyrrolidine-2, 5-dione (A, B & C)

1.01 Mole of the appropriately substituted 2- amino pyridinewas dissolved in 20 mL of water and 0.01 mole 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 ºC and was maintained for 1.5 h. The crude products were recrystallized from isopropanol (Kami-Ski and Obniska, 2008) (Scheme – I); Fig.1 & 2.

Preparation of 1-(N-methylpyridin-2-yl) piperidine-2, 6-dione (D, E & F)

1.01 mole of the appropriately substituted 2- amino pyridine 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 ºC and was maintained for 1.5 h. The crude products were recrystallized from isopropanol

(Scheme – II); Fig.2.



Scheme - II

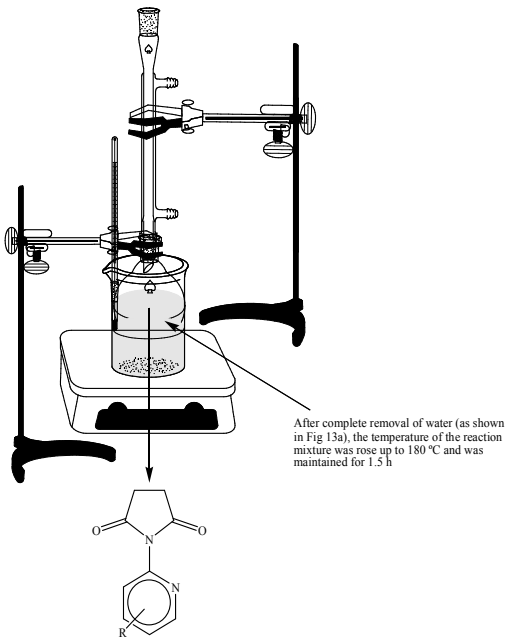


Fig.2: Experimental Demonstration of N-Succinimide(Part-II)/N-Glutarimide Derivative Synthesis - Green Method

Physicochemical and analytical data for compounds A-F:

1-(5-methylpyridin-2-yl)pyrrolidine-2,5-dione (A)

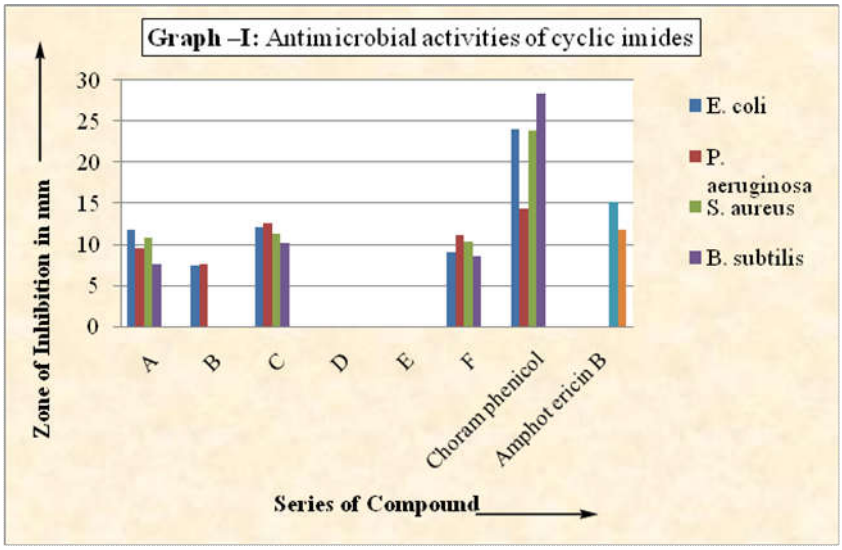
Whitish solid, Yield (66.80%), M. P. 146-148 ºC, M.F. $C_{10}H_{10}O_2N_2$,M.W.190.20, Composition: C (63.15%) H (5.30%) N (14.73%) O (16.82%); IR (KBr): 1709,2487,1334,1301, 3044,2967,2924,1393,1490,1551,1598,2759 cm^{-1}. ^1H NMR (500.13 MHz, DMSO-d_6, δ ppm): 2.35 (s, 3H, CH_3-pyridine), 2.90 (s, 4H, imide), 7.85-8.47 (m, 2H, pyridine), 8.23 (d, 1H, pyridine).

1-(4-methylpyridin-2-yl)pyrrolidine-2,5-dione (B)

Whitish solid, Yield (60.65%), M. P. 142-144 ºC, M.F. $C_{10}H_{10}O_2N_2$, M.W.190.20, Composition: C (63.15%)H (5.30%) N

Table I. Antimicrobial activities of cyclicimides

S.No.	Sample	*E.coli*	*P.aeruginosa*	*S.aureus*	*B.subtilis*	*C.albicans*	*A.niger*
		Mean±SD	*Mean±SD*	*Mean±SD*	*Mean±SD*	*Mean±SD*	*Mean±SD*
1.	A	11.77±0.31	9.47±0.08	10.87±0.33	7.64± 0.21	---	---
2.	B	07.48±0.34	7.58±0.26	---	---	---	---
3.	C	12.05±0.06	12.51± 0.18	11.31±0.05	10.2± 0.07	---	---
4.	D	---	---	---	---	---	---
5.	E	---	---	---	---	---	---
6.	F	9.02±0.16	11.19±0.40	10.35±0.12	8.48± 0.07	---	---
	Choramphenicol	24.09±0.10	14.39±0.07	23.92±0.17	28.43± 0.29	NA	NA
	AmphotericinB	NA	NA	NA	NA	15.21±0.15	11.8±0.08



(14.73%) O (16.82%); IR (KBr): 1700,2447,1353,1301,3014, 2969,2813,1444,1491,1551,1405,2764 cm^{-1}. ^1H NMR (500.13 MHz, DMSO-d_6, δ ppm): 2.41 (s, 3H, CH3-pyridine), 2.90 (s, 4H, imide), 7.16-7.19 (m, 2H, pyridine), 8.49 (d, 1H, pyridine).

1-(6-methylpyridin-2-yl)pyrrolidine-2,5-dione (C)

Whitish solid, Yield (65.47%), M. P. 148-150 ºC, M.F. $C_{10}H_{10}O_2N_2$, M.W.190.20, Composition: C (63.15%) H (5.30%) N (14.73%) O (16.82%); IR (KBr): 1689,2363,1261, 2967,2792,1640,1544,1403,1309,2559 cm^{-1}. ^1H NMR (500.13 MHz, DMSO-d_6, δ ppm): 2.59 (s, 3H, CH_3-pyridine), 2.90 (s, 4H, imide), 7.06(d, 1H, pyridine), 7.22 (d, 1H, pyridine), 7.74 (t, 1H, pyridine).

1-(5-methylpyridin-2-yl)piperidine-2,6-dione (D)

Whitish solid, Yield (71.95%), M. P. 140-142 ºC, M.F. $C_{11}H_{12}O_2N_2$, M.W. 204.225,Composition: C (64.69%) H (5.92%) N (13.72%) O (15.67%); IR (KBr): 1682,1342,1310, 3272,1583,1455,1417, 1378,3083 cm^{-1}. ^1H NMR (500.13 MHz, DMSO-d_6, δ ppm): 2.35 (s, 3H, CH_3-piperidine), 2.16 (t, 4H, imide), 1.80 (m, 2H, imide), 7.82-8.47 (m, 2H, piperidine), 8.23 (d, 1H, piperidine).

1-(4-methylpyridin-2-yl)piperidine-2,6-dione (E)

Whitish solid, Yield (68.39%), M. P. 150-152 ºC, M.F. $C_{11}H_{12}O_2N_2$, M.W. 204.225, Composition: C (64.69%) H (5.92%) N (13.72%) O (15.67%); IR (KBr): 1670, 1332,1295, 3262,1573,1445,1407,1368,3073 cm^{-1}, ^1H NMR (500.13 MHz, DMSO-d_6, δ ppm): 2.40 (s, 3H, CH_3-piperidine), 2.16 (t, 4H, imide), 1.80 (m, 2H, imide), 7.19-7.23 (m, 2H, piperidine), 8.52 (d, 1H, piperidine).

1-(6-methylpyridin-2-yl)piperidine-2,6-dione (F)

Whitish solid, Yield (69.75%), M. P. 154-156 ºC, M.F. $C_{11}H_{12}O_2N_2$, M.W. 204.225, Composition: C (64.69%) H (5.92%) N (13.72%) O (15.67%); IR (KBr): 1692,1357,1305, 2966,1663,1636,1561,1484,3025 cm^{-1}. ^1H NMR (500.13 MHz, DMSO-d_6, δ ppm): 2.35 (s, 3H, CH_3-piperidine), 2.16 (t, 4H, imide), 1.80 (m, 2H, imide), 7.09(d, 1H, piperidine), 7.25 (d, 1H, piperidine), 7.77 (t, 1H, piperidine).

RESULTS AND DISCUSSION

Chemistry

The series of cyclicimides A, B and C were prepared by the reaction of succinican hydride and primary aromaticamines by distillation and reason ableyield is obtained. The formation offivemembered cyclicimides was confirmed byI R, ^{13}CNMR and ^{1}HNMR and elemental analysis. These ries of cyclicimides D, E and F were preparedby the reaction ofglutaricanhydrideand primaryaromaticamines by distillation and reasonable yield is obtained. The formation of six membered cyclicimides was confirmed by IR, ^{13}CNMR and ^{1} HNMR and elemental analysis.

Antimicrobial Activities

All the synthesized compounds A, B, C, D, E and F were screened for their antibacterial activity against gram positive bacteria Staphylococcus aureus (NCIM 2079), Bacillus subtilis (NCIM 2250) and gram negative bacteria Escherichia coli (NCIM 2109), Pseudomonas aeruginosa (NCIM 2036) using DMSO solvent. Also, all these compounds were screened against Fungi (Yeast) Candida albicans (NCIM 3471) and Aspergillus niger (NCIM 545). The bacterial cultures were purchased from NCIM: National Collection of Industrial Microorganisms, National Chemical Laboratory (NCL), Pune 411008 (India). Someof the compound showed moderate to good activities against Bacillus Subtilis and E- colias shownin the Table–I and Graph –I;

Conclusion

In conclusion, 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-dionefrom of 2-amino 5-methyl, 2-amino 4-methyl, 2-amino 6-methyl pyridine for the first time under convenient reaction conditions.These new series of compoundspossess potent antimicrobial activities against some common pathogens like Bacillus Subtilis and E-coli. Further studies on structure activity relationships and on the scope of application of the compounds is going on.

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