Final Report of the work done
on UGC Sponsored
Minor Research Project

"SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF N-ARYL CYCLIC IMIDES USING SOLID-PHASE SYNTHESIS"

Principal Investigator

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Affiliated to

North Maharashtra University, Jalgaon, Maharashtra

Submitted to

University Grants Commission,

Western Regional Office (WRO),

Pune University Campus, Ganeshkhind, Pune-411007

Annexure –VII

UNIVERSITY GRANTS COMMISSION
BAHADUR SHAH ZAFAR MARG
NEW DELHI – 110 002

Final Report of the work done on the Minor Research Project.

1. Title of research project: **"SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF N-ARYL CYCLIC IMIDES USING SOLID-PHASE SYNTHESIS"**
2. Name and address of Principal Investigator : **Milind Maharu Patil**
   Flat No. 303, NRI Villas, Maloni, Shahada
   Dist-Nandurbar, Maharashtra 425409
3. Name and address of the institution : **PSGVP Mandal's, ASC College, Shahada,**
   Dist-Nandurbar, Maharashtra 425409
4. UGC approval letter no. and date : **File No: 47-608/13(WRO) dated**
5. Date of implementation : **June 01st, 2014**
6. Tenure of the project : **Two year**
7. Total Grant allocated : **Rs.359400/-**
8. Total grant received : **Rs. 234400/-**
9. Final Expenditure : **Rs. 361128/-**
10. Title of the project: **"Synthesis, Characterization and Biological activity of N-aryl cyclic imides using Solod-phase synthesis"**
11. Objective of the project:

On the basis of literature survey it was observed that very less work has been done on the synthesis of bis-1,2,3 triazine, bis-azidoformyl pyrrole, bis pyridinone and diazo compounds. In view of this finding I have proposed this work for the synthesis of new heterocyclic compounds.

1. It is planned to synthesize the N-aryl cyclic imides by using SBBC as a green cyclodehydrating reagent.
2. The N-aryl cyclic imides converted into halovinyl derivative using DMF/$POCl_3$ with expectation to furnished dichloro diformyl derivatives.

3. The dichloro diformyl derivatives derivative using sodium azide with expectation to furnish diazido diformyl derivatives.
4. The diazido diformyl derivatives of succinimides and glutarimides using hydrazine hydrate with expectation to furnish bis-1,2,3-trizine derivatives.
5. The versatile diazido diformyl derivative with different primary amines will furnish Schiff bases.
6. The evaluation of biological activity in vitro of compound synthesize will be discussed.

12. Whether objective were achieved: Yes. As per the planning the synthesis were successfully done using Silica Bound Benzoyl Chloride (SBBC) as a green cyclodehydrating agent. The Product obtain in series of reaction were subjected to the biological screening. Most of the compounds shows good to moderate activity against fungi and bacteria. The Schiff bases were screen for their plant growth regulator (PGR) activity. It was observe that the compound also shows good activity.

13. Achievements from the project: Develop new green method for cyclic imide synthesis
14. Summary of the finding: Separate Sheet Attached (in 500 words)
15. Contribution to society: Greener methodology will reduce the environmental damage.
16. Whether any Ph.D. enrolled/produced out of the project: No
17. No. of publication out of the project: 03 (publications attached)

(Milind M. Patil)
Principal Investigator

(Prof. Dr. R. S. Patil)
Principal

PRINCIPAL
P.S.G.V.P. M'S, Arts, Science & Commerce Sr. College, SHAHADA
Dist.Nandurbar (Pin-425409)

Final Report of the work done

Year-I

i. Brief objective of the project

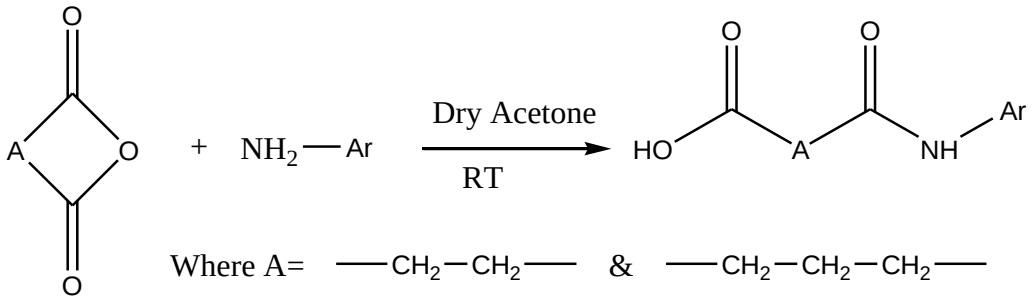
On the basis of literature survey it was observed that very less work has been done on the synthesis of bis-1,2,3 triazine, bis-azidoformyl pyrrole, bispyridinone and diazo compounds. In view of this finding I have proposed this work for the synthesis of new heterocyclic compounds.

7. It is planned to synthesize the succinimides and glutarimides by using literature procedures. The succinimide and glutarimides derivatives using DMF/$POCl_3$ with expectation to furnished dichlorodiformyl derivatives.
8. The N-aryl cyclic imides derivatives using DMF/$POCl_3$ with expectation to furnished dichlorodiformyl derivatives.
9. The dichlorodiformyl derivatives derivative using sodium azide with expectation to furnish diazidodiformyl derivatives.
10. The diazidodiformyl derivatives of succinimides and glutarimides using hydrazine hydrate with expectation to furnish bis-1,2,3-trizine derivatives.
11. The versatile diazidodiformyl derivative with different primary amines will furnish Schiff bases.
12. The evaluation of biological activity in vitro of compound synthesize will be discussed.

(i) Work done so far and results achieved and publications, if any, resulting from the work (Give details of the papers and names of the journals in which it has been published or accepted for publication): Attached at the end of report.

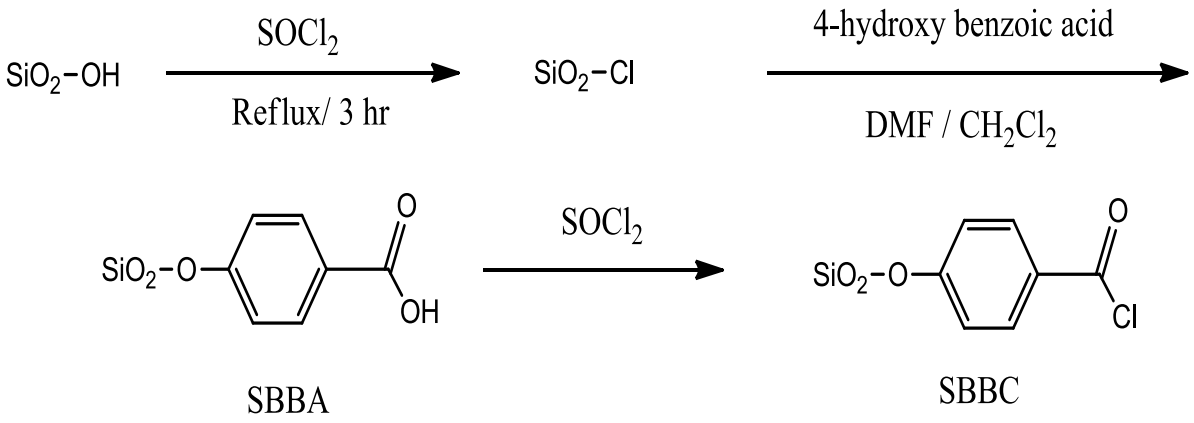
ii. Work done so far and results achieved and publications, if any, resulting from the work:

In this proposed work initially aniline, 4-chlorobenzenamine, 4-aminophenol, p-toluidine, 4-bromobenzenamine, 4-nitrobenzenamine, 3-clorobenzenamine, 4-methoxy benzenamine (p-anicidine), naphthalen-1-amine etc. will be used to synthesize the succinimide and glutarimide by the condensation of succinic anhydride and glutaric anhydride with different aromatic amine gives acid amide intermediate as 3(substitutedphenylcarboxyl) propionic acid and 4(substitutedphenylcarboxyl) butanoic acid respectively (Scheme-I).

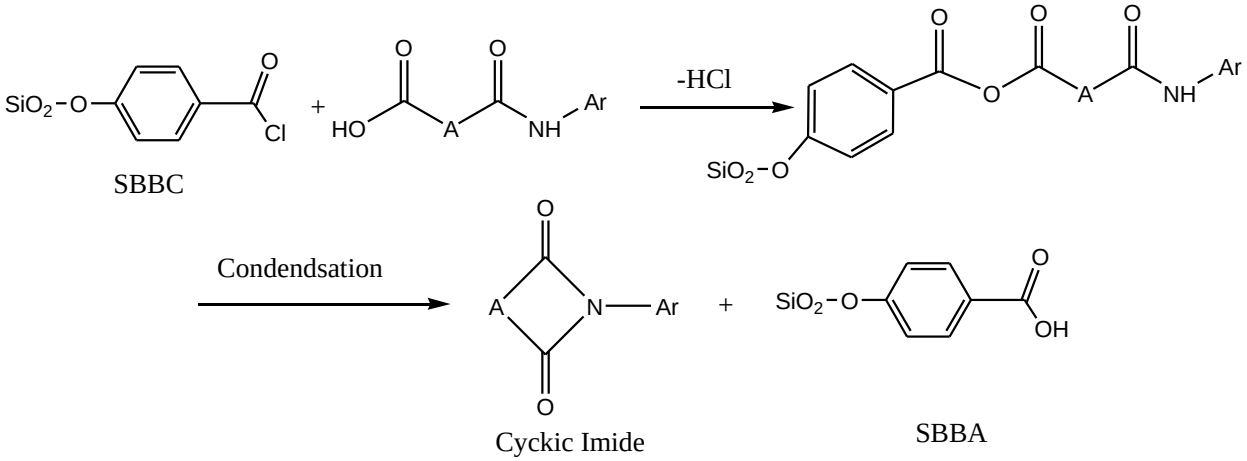


Scheme I

SBBC separately synthesized by In presence of benzoyl chloride bonded with silica (dehydrating agent) (Scheme-II) gives 1-substitutedphenylpyrrolidine-2,5-dione and 1-substitutedphenylpiperidine-2,6-dione respectively (Scheme-III).



Scheme II

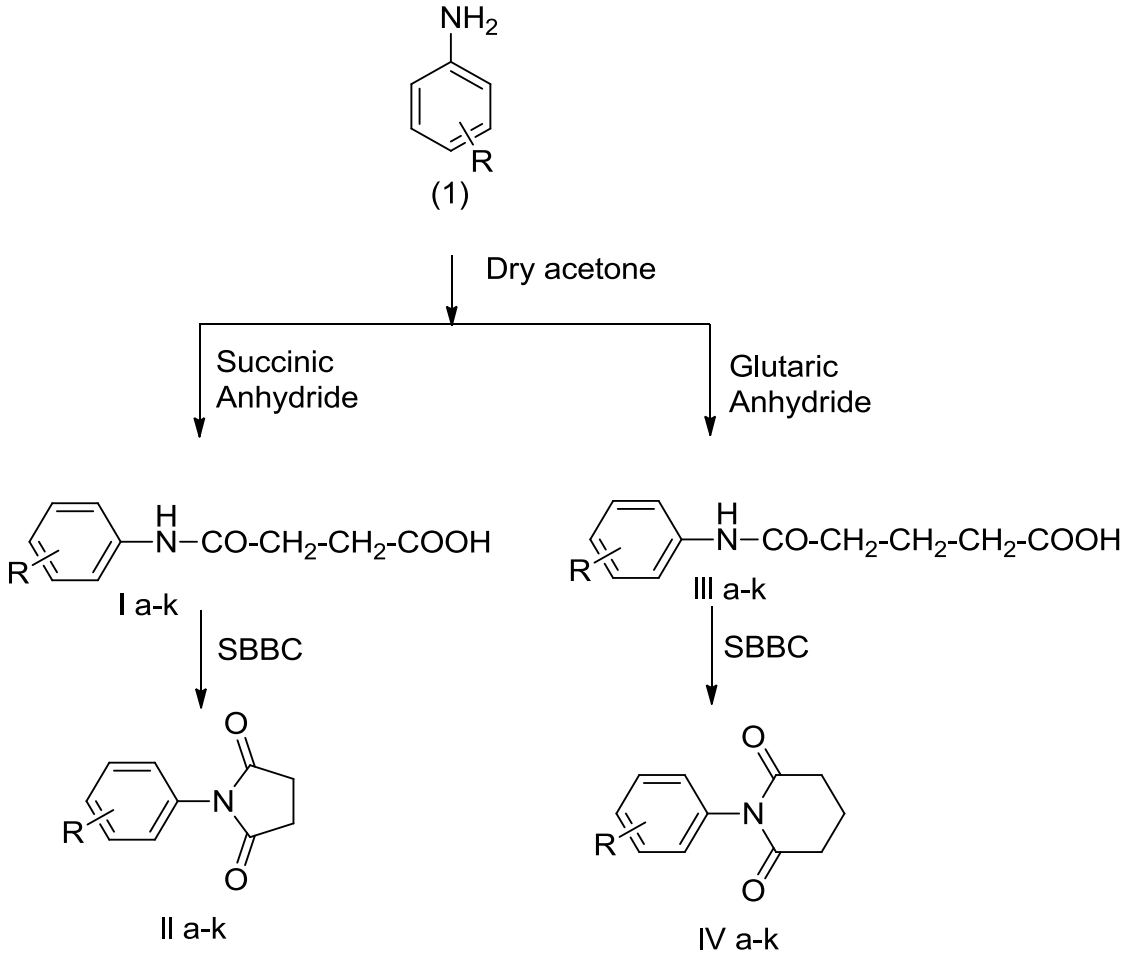


Where A= —CH_2—CH_2— & —CH_2—CH_2—CH_2—

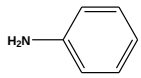
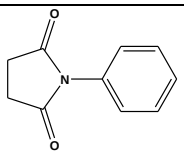
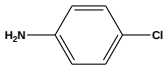
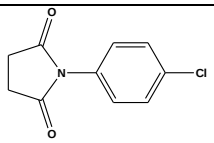
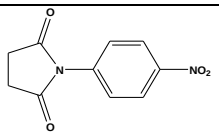
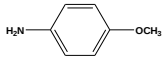
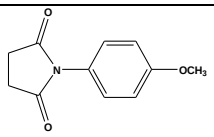
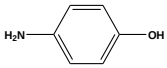
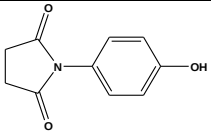
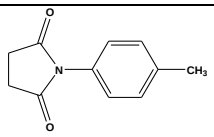
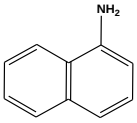
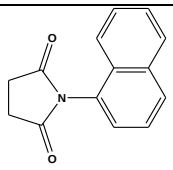
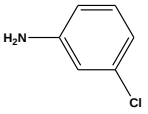
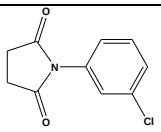
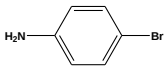
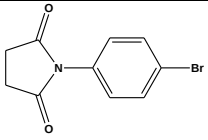
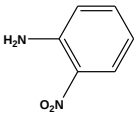
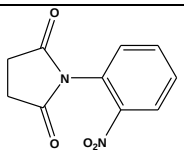
Scheme III

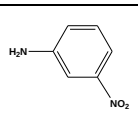
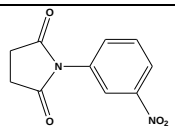
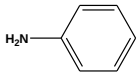
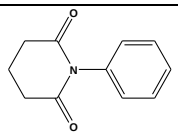
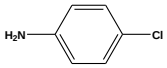
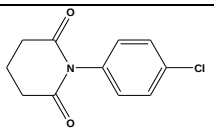
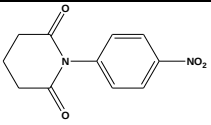
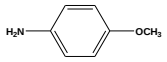
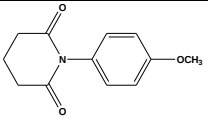
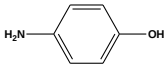
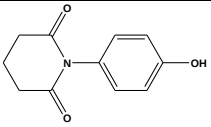
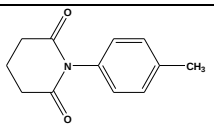
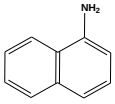
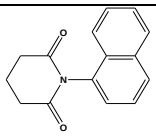
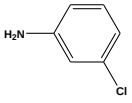
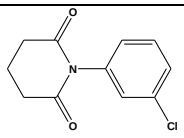
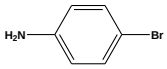
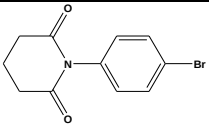
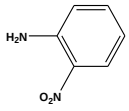
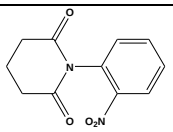
Synthesis of N-aryl succinimides and glutarimides from cyclic:

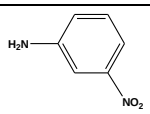
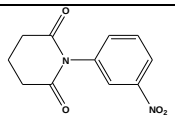
Synthesis of N-aryl succinimide and glutarimides from succinic anhydride and glutaric anhydride using substituted aniline using greener approach (SBBC Mediated reaction) and their characterization.



Different substituted aniline were use in synthesis and the cyclic imides. Melting points were determined by open capillary method and uncorrected. IR spectra (cm^{-1}) were recorded on Perkin Elmer spectrophotometer in KBr pellets. Reaction was monitored by TLC on silica gel plates.

Entry	Anhydride	Amine	Product	Code	Yield(%)	M.P.(^{0}C)
1	A			II a	87.5	154
2	A			II b	92.3	160
3	A			II c	83.2	209
4	A			II d	94.0	157
5	A			II e	91.7	139
6	A			II f	93.0	155
7	A			II g	80.3	148
8	A			II h	87.0	120
9	A			II i	89.5	145
10	A			II j	72.9	134

11	A			II k	79.5	167
12	B			IV a	83.0	144
13	B			IV b	84.5	123
14	B			IV c	76.7	156
15	B			IV d	84.5	145
16	B			IV e	82.3	173
17	B			IV f	83.8	149
18	B			IV g	76.2	137
19	B			IV h	79.3	165
20	B			IV i	79.0	156
21	B			IV j	70.1	143

22	B			IV k	78.6	152

Where A= Succinic anhydride B= Glutaric anhydride

CHARACTERISATION:

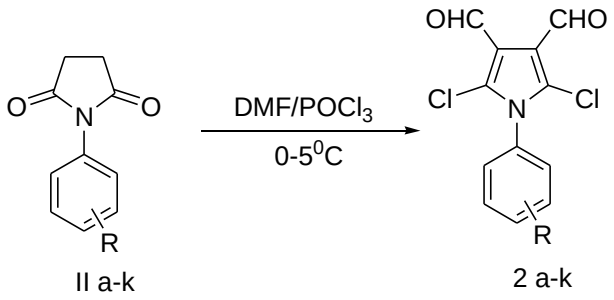
Infrared spectral analysis shows the characteristic frequencies(cm^{-1})[#] of the Imides in the spectra of cyclic imides (Succinimides and Glutarimides).

Succinimides	Glutarimides	Assignment of IR Spectra
3180-3190 s, br	3200-3210 s, br	N-C(Ar) Stretching
3070-3080 s, br	3060-3070 s, br	Fermi resonance N-CO-
1770 m	1770	C=O Stretching (free)
1710 vs, br	1710, vs, b	C=O Stretching (H-bonded)
1428 m	1377 m	C-N-C bending
948 m	987 s	Ring vibration
663 m	656 m	C=O in plane bending
548 w	556 w	C=O out of plane deformation

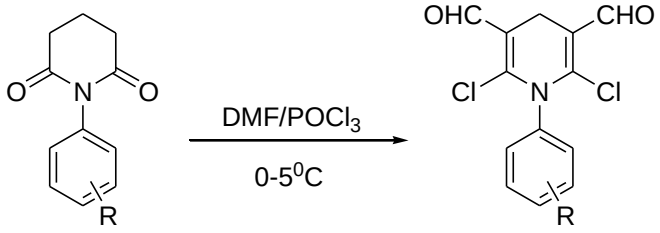
[#] s=strong, m=medium, w= weak, v= very, br=broad

Synthesis of dicarbaldehyde compounds from N-aryl succinimides and glutarimides using Vilsmeier-Haack reaction:

Synthesis of 2,5-Dichloro-1-phenyl(substituted)-1H-pyrrole-3,4-dicarbaldehyde and 2,6-Dickloro-1-phenyl(substituted)-1,4-dichloro-pyridine-3,5-dicarbaldehyde derivative using Vilsmeire-Haack ($DMF/POCl_3$) at 0-5^{0}C.



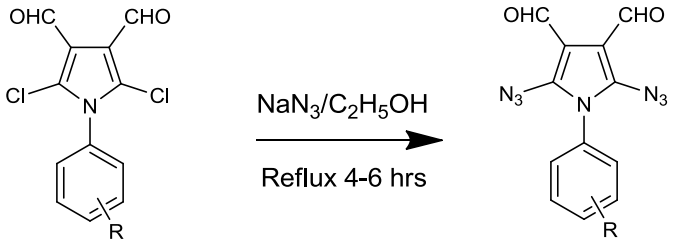
II a-k 2 a-k

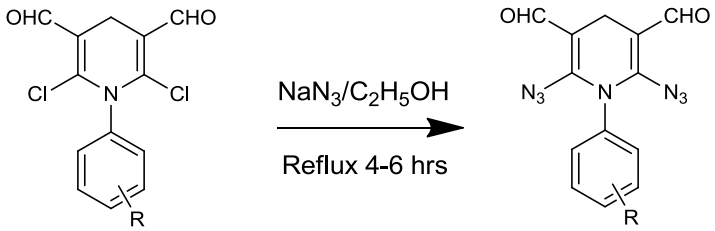


IV a-k 3 a-k

Synthesis of azide derivatives from N-aryl succinamide and N-aryl glutarimides:

In continuation of our previous work a solution of 2,5-diazido-1-substitutedphenyl-1H-pyrrole-3,4-dicarbaldehyde 1a-j (0.01 moles) in absolute ethanol (10 mL), P-toluene sulphonic acid (0.02 moles) and sodium azide (0.03 moles) were added and reaction mixture heated under reflux for time ranging between 4-6 hrs. The refluxed mixture was added to ice cold water which precipitated compounds 2a-j. These were filtered and recrystallized from ethanol.





2,5-bis((E)-(2-hydroxynaphthalen-1-yl)diazenyl)-1-phenyl-1H-pyrrole-3,4-dicarbaldehyde:

Light brown; M. F.: $C_{32}H_{21}N_5O_4$; Mol. Wt.: 539.54; Percent yield: 77; Melting point (^{0}C): 247-249; FTIR (cm^{-1}) : 1695 (>C=O stretch, aldehyde), 2730 (H-C=O; C-H stretch), 3202 (C-H stretch, aromatics), 1660 (-C=C- stretch), 2902 (C-H stretch, aromatics), 1523 (C-C stretch, in ring aromatics), 3444 (O-H stretch, aromatic phenol), 1500 (-N=N- stretch); ^{1}HNMR (δ ppm): 9.7 (s, 2H, CHO), 5.2 (s, 2H, Ar-OH), 7.4 (s, 5H, Ar-H), 7.1 (m, 4H, Ar-H), 7.2-7.3 (m,8H, Ar-H).

2,5-bis((E)-(2-hydroxynaphthalen-1-yl)diazenyl)-1-(3-chlorophenyl)-1H-pyrrole-3,4-dicarbaldehyde:

Yellowish brown; M. F.: $C_{32}H_{20}ClN_5O_4$; Mol. Wt.: 573.99; Percent yield: 66; Melting point (^{0}C): 236-238; FTIR (cm^{-1}): 1705 (>C=O stretch, aldehyde), 2827 (H-C=O; C-H stretch), 3367 (C-H stretch, aromatics), 1640 (-C=C- stretch), 3055 (C-H stretch, aromatics), 1570 (C-C stretch, in ring aromatics), 3505 (O-H stretch, aromatic phenol), 1485 (-N=N- stretch), 739 (C-Cl stretch); ^{1}HNMR (δ ppm): 9.3 (s, 2H, CHO), 5.3 (s, 2H, Ar-OH), 7.0 (d, 2H, Ar-H), 7.5 (d, 4H, Ar-H), 7.3 (s, 1H, Ar-H), 7.1-7.5 (m, 9H, Ar-H).

2,5-bis((E)-(2-hydroxynaphthalen-1-yl)diazenyl)-1-(4-chlorophenyl)-1H-pyrrole-3,4-dicarbaldehyde:

Gray; M. F.: $C_{32}H_{20}ClN_5O_4$; Mol. Wt.: 573.99; Percent yield: 75; Melting point (^{0}C): 257-259; FTIR (cm^{-1}): 1678 (>C=O stretch, aldehyde), 2717 (H-C=O; C-H stretch), 3280 (C-H stretch, aromatics), 1604 (-C=C- stretch), 3081 (C-H stretch, aromatics), 1585 (C-C stretch, in ring aromatics), 3445 (O-H stretch, aromatic phenol), 1455 (-N=N- stretch), 739 (C-Cl stretch); ^{1}HNMR (δ ppm): 9.9 (s, 2H, CHO), 4.9 (s, 2H, Ar-OH), 7.2 (d, 2H, Ar-H), 7.3 (d, 2H,Ar-H), 7.0 (d, 2H, Ar-H), 7.6 (m, 4H, Ar-H), 7.4 -7.5 (m, 6H, Ar-H).

2,5-bis((E)-(2-hydroxynaphthalen-1-yl)diazenyl)-1-(4-bromophenyl)-1H-pyrrole-3,4-dicarbaldehyde:

Light gray; M. F.: $C_{32}H_{20}BrN_5O_4$; Mol. Wt.: 618.44 ; Percent yield: 69; Melting point (^{0}C): 216-218; FTIR (cm^{-1}): 1690 (>C=O stretch, aldehyde), 2712 (H-C=O; C-H stretch), 3240 (C-H stretch, aromatics), 1644 (-C=C- stretch), 3076 (C-H stretch, aromatics), 1479 (C-C stretch, in ring aromatics), 3595 (O-H stretch, aromatic phenol), 1480 (-N=N- stretch), 610 (C-Br stretch); ^{1}HNMR (δ ppm): 9.5 (s, 2H, CHO), 5.1 (s, 2H, Ar-OH), 7.2 (d, 2H, Ar-H), 7.4 (d,2H, Ar-H), 7.0 (d, 2H, Ar-H), 7.6 (m, 4H, Ar-H), 7.3 -7.5 (m, 6H, Ar-H).

2,5-bis((E)-(2-hydroxynaphthalen-1-yl)diazenyl)-1-(2-nitrophenyl)-1H-pyrrole-3,4-dicarbaldehyde:

Dark brown; M. F.: $C_{32}H_{20}N_6O_6$; Mol. Wt.: 584.54; Percent yield: 60; Melting point (^{0}C): 171-173; FTIR (cm^{-1}): 1713 (>C=O stretch, aldehyde), 2802 (H-C=O; C-H stretch), 3338 (C-H stretch, aromatics), 1685 (-C=C- stretch), 2990 (C-H stretch, aromatics), 1540 (C-C stretch, in ring aromatics), 3512 (O-H stretch, aromatic phenol), 1510 (-N=N-stretch), 1280 (N-O symmetric stretch), 1525 (N-O asymmetric stretch); ^{1}HNMR (δ ppm): 9.5 (s, 2H, CHO), 5.1 (s,2H, Ar-OH), 7.0 (d,2H,Ar-H), 7.2-7.3 (m,4H,Ar-H), 7.5-7.7 (m,9H,Ar-H), 8.2 (m,1H,Ar-H).

2,5-bis((E)-(2-hydroxynaphthalen-1-yl)diazenyl)-1-(3-nitrophenyl)-1H-pyrrole-3,4-dicarbaldehyde:

Brown; M. F.: $C_{32}H_{20}N_6O_6$; Mol. Wt.: 584.54; Percent yield: 66; Melting point (^{0}C): 210-212; FTIR (cm^{-1}): 1680 (>C=O stretch, aldehyde), 2770 (H-C=O; C-H stretch), 3308 (C-H stretch, aromatics), 1670 (-C=C- stretch), 3110 (C-H stretch, aromatics), 1464 (C-C stretch, in ring aromatics), 3235 (O-H stretch, aromatic phenol), 1455 (-N=N- stretch), 1298 (N-O symmetric stretch), 1545 (N-O asymmetric stretch); ^{1}HNMR (δ ppm): 9.8 (s, 2H, CHO), 5.4 (s, 2H, Ar-OH), 7.1 (d, 2H, Ar-H), 7.2-7.3 (m, 4H, Ar-H), 7.5-7.6 (m, 8H, Ar-H), 8.2 (d, 2H, Ar-H).

2,5-bis((E)-(2-hydroxynaphthalen-1-yl)diazenyl)-1-(4-nitrophenyl)-1H-pyrrole-3,4-dicarbaldehyde:

Dark brown; M. F.: $C_{32}H_{20}N_6O_6$; Mol. Wt.: 584.54; Percent yield: 76; Melting point (^{0}C): 224-226; FTIR (cm^{-1}): 1682 (>C=O stretch, aldehyde), 2810 (H-C=O; C-H stretch), 3290 (C-H stretch, aromatics), 1700 (-C=C- stretch), 3072 (C-H stretch, aromatics), 1502 (C-C stretch, in ring aromatics), 3279 (O-H stretch, aromatic phenol), 1440 (-N=N- stretch), 1318 (N-O symmetric stretch), 1550 (N-O asymmetric stretch); ^{1}HNMR (δ ppm): 10.0 (s, 2H, CHO), 5.2 (s, 2H, Ar-OH), 6.9 (d, 2H, Ar-H), 7.2-7.3 (m, 4H, Ar-H), 7.5-7.6 (m, 8H, Ar-H), 8.3 (d, 2H, Ar-H).

2,5-bis((E)-(2-hydroxynaphthalen-1-yl)diazenyl)-1-(4-hydroxyphenyl)-1H-pyrrole-3,4-dicarbaldehyde:

Bright Red; M. F.: $C_{32}H_{21}N_5O_5$; Mol. Wt.: 555.54; Percent yield: 71; Melting point (^{0}C): 261-263; FTIR (cm^{-1}): 1708 (>C=O stretch, aldehyde), 2790 (H-C=O; C-H stretch), 3346 (C-H stretch, aromatics), 1637 (-C=C- stretch), 2995 (C-H stretch, aromatics), 1603 (C-C stretch, in ring aromatics), 3500, 3600 (O-H stretch, aromatic phenol), 1475 (-N=N- stretch); ^{1}HNMR (δ ppm): 9.8 (s, 2H, CHO), 5.0 (s, 1H, Ar-H), 5.3 (s, 2H, Ar-OH), 6.7 (d, 2H, Ar-H), 7.0 (d, 2H, Ar-H), 7.1 (d, 2H, Ar-H), 7.2-7.3 (m, 4H, Ar-H), 7.5-7.6 (m, 6H, Ar-H).

2,5-bis((E)-(2-hydroxynaphthalen-1-yl)diazenyl)-1-(p-tolyl)-1H-pyrrole-3,4-dicarbaldehyde:

Reddish brown; M. F.: $C_{33}H_{23}N_5O_4$; Mol. Wt.: 553.57; Percent yield: 70; Melting point (^{0}C): 266-268; FTIR (cm^{-1}): 1692 (>C=O stretch, aldehyde), 2823 (H-C=O; C-H stretch), 3261 (C-H stretch, aromatics), 1672 (-C=C- stretch), 3040 (C-H stretch, aromatics), 1490 (C-C

stretch, in ring aromatics), 3550 (O-H stretch, aromatic phenol), 1500 (-N=N- stretch), 1450, 1355 (C-H bend and rock, aromatic alkyl); ^{1}HNMR (δ ppm): 9.7 (s, 2H, CHO), 5.0 (s, 2H, Ar-OH), 7.5 (d, 2H, Ar-H), 7.6 (d, 4H, Ar-H), 7.0-7.3 (m, 10H, Ar-H), 2.4 (s, 3H, Ar-CH_3).

2,5-bis((E)-(2-hydroxynaphthalen-1-yl)diazenyl)-1-(4-methoxyphenyl)-1H-pyrrole-3,4-dicarbaldehyde:

Violet; M. F.: $C_{33}H_{23}N_5O_5$; Mol. Wt.: 569.57; Percent yield: 66; Melting point (^{0}C): 230-232; FTIR (cm^{-1}): 1720 (>C=O stretch, aldehyde), 2698 (H-C=O; C-H stretch), 3390 (C-H stretch, aromatics), 1690 (-C=C- stretch), 3121 (C-H stretch, aromatics), 1585 (C-C stretch, in ring aromatics), 3400 (O-H stretch, aromatic phenol), 1482 (-N=N- stretch), 1469, 1370 (C-H bend and rock, alkyl); ^{1}HNMR (δ ppm): 9.8 (s, 2H, CHO), 4.9 (s, 2H, Ar-OH), 6.8 (d, 2H, Ar-H), 7.0 (d, 2H, Ar-H), 7.2-7.3 (m, 6H, Ar-H), 7.5 (d, 2H, Ar-H), 7.6 (d, 4H, Ar-H), 3.8 (s, 3H, Ar-OCH_3).

Result and Discussion:

Chemistry:

The starting compounds of azo vinyl aldehyde were prepared by the reaction of 2,5-diazido-1-substitutedphenyl-1H-pyrrole-3,4-dicarbaldehyde using sodium dithionite. Diazo coupling reaction were carried out over 2,5-diamino-1-substitutedphenyl-1H-pyrrole-3,4-dicarbaldehyde gives the diazonium salt, followed by the coupling reaction using 2-napthol. The series of 2,5-bis((E)-(2-hydroxynaphthalen-1-yl)diazenyl)-1-(substituted phenyl)-1H-pyrrole-3,4-dicarbaldehyde 5a-j were synthesized in reasonable yields. The structure of azo vinyl was confirmed by FT-IR and ^{1}HNMR analysis.

Antimicrobial susceptibility test :

The disc diffusion method was used to screen the antimicrobial activity. In vitro antimicrobial activity was screened by using Mueller Hinton Agar (MHA) obtained from Hi-media. The MHA plates were prepared by pouring 15 mL of molten media into sterile Petri plates. The plates were allowed to solidify for 5 minutes and 0.1 % inoculum suspension was swabbed uniformly and the inoculum was allowed to dry for 5 minutes. The fix concentrations were loaded on 6 mm sterile disc. The loaded disc was placed on the surface of the medium and the compound was allowed to diffuse for 5 minutes and the plates were kept for incubation at 37^{0}C for 24 hrs. At the end of incubation, inhibition zones formed around the disc were measured with the transparent ruler in millimeter. All the synthesized compounds were screened for their

antibacterial activity against gram- positive bacteria *Bacillus subtilis* (MCMB-310) and gram negative bacteria *Escherichia coli* (MCMB-301) using DMF solvent. Ampicillin was used as standard and results were shown in the **graph 1**. The same procedure was followed for the fungus using Potato Dextrose Agar (PDA) as a nutrient medium. The antifungal activities against *Candida albicans* (NCIM-3471) and *Aspergillus niger* (NCIM- 545) strains using DMSO solvent in using Amphotericin-B as a standard revealed in the graph 2. All the results of the synthesized compounds were carried out by the triplicate format N=3 with Mean ± SD. The calculated data were tabulated in **Table 1**;

Table 1 Antimicrobial activity of synthesized diazo compound

Entry	Zone diameter in mm (Mean±S.D.)			
	Bacillus subtilis	Escherichia coli	Candida albicans	Aspergillus niger
3a	9.38±0.24	8.55±0.28	--	--
3b	17.76±1.25	14.84±0.61	18.57 ± 0.27	14.27 ± 0.49
3c	9.33±1.22	8.43±0.57	13.83 ± 0.22	12.56 ± 0.78
3d	11.33±0.13	7.26±1.15	--	--
3e	12.66±0.33	10.32±0.52	8.69 ± 0.39	13.63 ± 0.39
3f	18.66±0.5	14.33±0.53	12.34 ± 0.34	13.15 ± 3.76
3g	18.33±0.55	12.66±0.23	16.77 ± 0.40	15.45 ± 0.39
3h	18.33±0.54	14.66±1.04	10.68 ± 0.22	11.65 ± 1.13
3i	17.33±0.37	17.11±0.03	11.30 ± 0.32	14.95 ± 3.20
3j	16.33±0.57	14.33±0.57	8.40 ± 0.04	12.37 ± 0.64
Ampicillin	19.36 ±0.04	17.63 ±0.06	--	--
Amphotericin-B	--	--	12.98 ± 0.44	11.38 ± 0.54

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

Conclusions

An entire new series of 2,5-bis((E)-(2-hydroxynaphthalen-1-yl)diazenyl)-1-(substituted phenyl)-1H-pyrrole-3,4-dicarbaldehyde 5a-j have been synthesized in facile manner from 2,5-diazido-1-substitutedphenyl-1H-pyrrole-3,4-dicarbaldehyde **1a-j** in good yield. Based on our experimental findings, the new substituted azovinyl aldehyde derivatives containing cyclic imide moiety **5a-j** exhibiting excellent bactericidal and fungicidal potentials could be proposed for dyeing and antimicrobial finishing for silk, wool, cotton, and polyester fabrics.

Year-II

i. Brief objective of the project

On the basis of literature survey it was observed that very less work has been done on the synthesis of bis-1,2,3 triazine, bis-azidoformyl pyrrole, bispyridinone and diazo compounds. In view of this finding I have proposed this work for the synthesis of new heterocyclic compounds.

13. It is planned to synthesize the succinimides and glutarimides by using literature procedures. The succinimide and glutarimides derivatives using DMF/$POCl_3$ with expectation to furnished dichlorodiformyl derivatives.
14. The N-aryl cyclic imides derivatives using DMF/$POCl_3$ with expectation to furnished dichlorodiformyl derivatives.
15. The dichlorodiformyl derivatives derivative using sodium azide with expectation to furnish diazidodiformyl derivatives.
16. The diazidodiformyl derivatives of succinimides and glutarimides using hydrazine hydrate with expectation to furnish bis-1,2,3-trizine derivatives.
17. The versatile diazidodiformyl derivative with different primary amines will furnish Schiff bases.
18. The evaluation of biological activity in vitro of compound synthesize will be discussed.

ii. Work done so far and results achieved and publications, if any, resulting from the work:

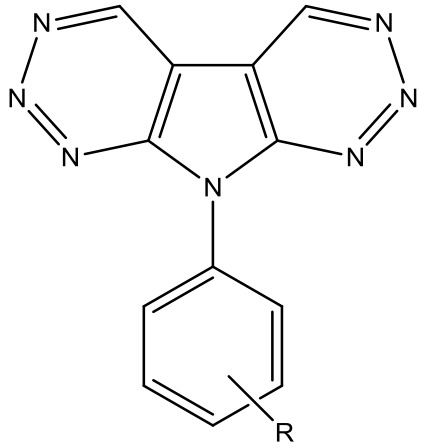
- **Synthesis of bis-1, 2, 3-triazine -**

As per the literature review done so far the research work on 1,2,3-Triazine is very limited. It generally very few reports on synthesis and application of 1,2,3-Triazine in scientific journals. The 1,2,3-Triazines are a class of biologically active compounds that exhibit a broad spectrum of biological activities, including antibacterial, antifungal, antiviral, antiproliferative, analgesic and anti-inflammatory properties. The 1,2,3-triazine and related benzo- and hetero-fused derivatives possessing antitumor activity. Their efficacy, combined with a simple synthesis

confers to these molecules a great potential as scaffold for the development of antitumor compounds.

1. **Synthesis of 1,2,3-triazine derivative of succinamide from azo vinyl aldehyde of succinamide:**

General Structure:

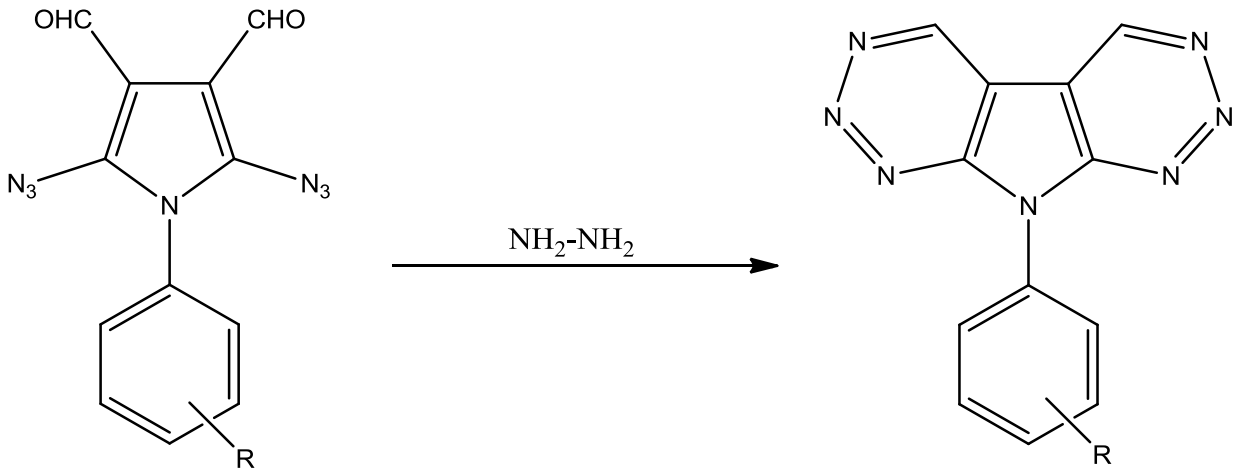


9-substituted phenyl-9*H*-pyrrolo[2,3-*d*:5,4-*d'*]bis([1,2,3]triazine)

Material and Method: All the reagents were purchased in the highest quality available and were used without further purification. All the solvents used in synthesis were obtained from commercial suppliers and used without further purification and distillation. Infrared spectra (FTIR) were recorded on a Lambda FT-IR 7600 spectrophotometer. Nuclear magnetic resonance 1H-NMR spectra (at 500 MHz) were recorded on a Bruker (AVANCE III HD) (Liquid State 500 MHz) spectrometer in $CDCl_3$ with TMS as internal standard. Melting points were obtained by open capillary method and remain uncorrected.

General Procedure: To a solution of 2,5-diazido-1-phenyl-1H-pyrrole-3,4-dicarbaldehyde (1) (1 equivalent) in ethanol, a solution of hydrazine hydrate (3 equivalent) in ethanol was added. The reaction mixture was refluxed for 30 min. The reaction was monitored and confirmed its completion by TLC in hexane-ethyl acetate system (20 % ethyl acetate). The reaction mixture was poured into beaker of 50 g crushed ice and stirred for 10 min. The product was extracted in CH_2Cl_2. The organic solution was washed with water, dried over anhydrous Na_2SO_4, and

faltered, and the solvent was evaporated under reduced pressure to give a product 9-phenyl-9H-pyrrolo[2,3-d:5,4-d']bis([1,2,3]triazine) (2).



1a-j **2a-j**

Where R a=4H, b=3Cl, c=4Cl, d=4Br, e=2NO_2, f= 3NO_2, g=4NO_2, h=4OH, i=4CH_3, j=4OCH_3

Scheme-I

Entry	R in 1a-j	Yield(%)	M.P.(^{0}C)	Bruker (AVANCE III HD) (Liquid State 500 MHz) NMR in δ
2 a	4H	63.1	184	7.37 (m, 1H), 7.53 (m, 2H), 7.77 (m, 2H), 9.49 (d, 2H)
2 b	3Cl	68.4	192	7.23 (m, 1H), 7.46 (m, 1H), 7.81 (m, 1H), 7.92 (m, 1H), 9.22 (d, 2H)
2 c	4Cl	73.2	118	7.80 (m, 2H), 7.95 (m, 2H), 9.21 (d, 2H)
2 d	4Br	75.7	138	7.79 (m, 2H), 7.92 (m, 2H), 9.22 (d, 2H)
2 e	2NO_2	58.4	148	7.66 (m, 1H), 7.80 (m, 1H), 7.97 (m, 1H), 8.25 (m, 1H), 9.25 (d, 2H)
2 f	3 NO_2	66.3	152	7.68 (m, 1H), 7.84 (m, 1H), 8.18 (m, 1H), 8.45 (m, 1H), 9.26 (d, 2H)
2 g	4 NO_2	59.3	190	7.93 (m, 2H), 8.30 (m, 2H), 9.25 (d, 2H)
2 h	4OH	75.8	208	7.30 (m, 2H), 7.89 (m, 2H), 9.19 (d, 2H)
2 i	4CH_3	74.9	156	2.18 (s, 3H), 7.56 (m, 2H), 7.91 (m, 2H), 9.20 (d, 2H)
2 j	4OCH_3	78.5	168	3.73 (s, 3H), 7.30 (m, 2H), 7.89 (m, 2H), 9.22 (d, 2H)

- **DPPH Free Radical Scavenging Activity of 1,2,3-triazine derivative of succinamide:**

- **Results:**

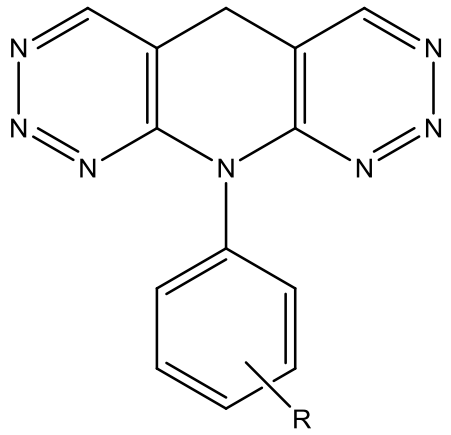
Concentration (µg/mL)	50	100	150	200	250
Ascorbic Acid	78.63±.05	90.22±.16	93.44±.03	95.12±.10	99.53±.10
2a	84.82±.16	87.43± .15	89.13± .05	90.43± .05	91.14± .16
2b	68.89± .28	69.97± .23	71.37± .35	73.97± .46	77.23±.46
2c	41.72± .16	48.42± .16	58.94± .21	60.48± .16	63.84± .16
2d	68.66±.13	70.62±.06	72.32±.24	75.09±.29	83.49±.4.5
2e	75.93±.23	77.72±.15	78.74±.09	80.13±.08	81.45±.15
2f	77.15± .23	79.04± .08	81.14± .15	82.28±.05	83.25±.15
2g	90.68±.08	92.95±.07	95.07±.89	96.84±.65	97.81±.07
2e	69.47±.24	73.22±.34	75.04±.92	77.55±.63	79.25±.24
2f	73.25±.21	76.29±.21	78.33±.15	81.19±.16	83.76±.16
2j	79.79±.23	82.75±.06	85.09±.11	87.02±.13	88.21±.11

Value represent means± SD, n=3

Table-1: DPPH Scavenging activity of 9-phenyl-9H-pyrrolo[2,3-d:5,4-d']bis([1,2,3]triazine) in ethanol

2. Synthesis of 1,2,3-triazine derivative of glutarimide from azo vinyl aldehyde of glutarimide:

General Structure:

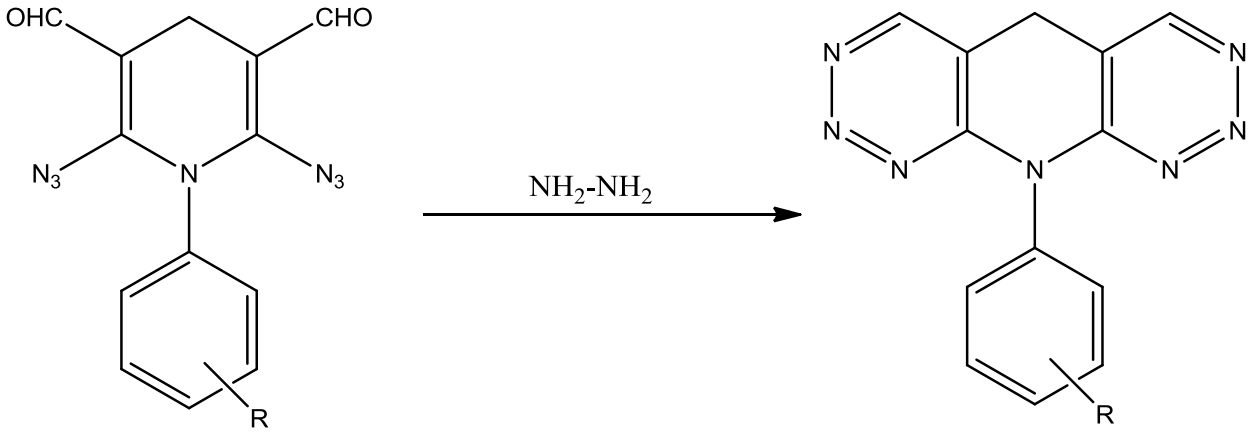


10-substituted phenyl-5,10-dihydropyrido[2,3-*d*:6,5-*d'*]bis([1,2,3]triazine)

Material and Method: All the reagents were purchased in the highest quality available and were used without further purification. All the solvents used in synthesis were obtained from commercial suppliers and used without further purification and distillation. Infrared spectra (FTIR) were recorded on a Lambda FT-IR 7600 spectrophotometer. Nuclear magnetic resonance 1H-NMR spectra (at 500 MHz) were recorded on a Bruker (AVANCE III HD) (Liquid State 500

MHz) spectrometer in $CDCl_3$ with TMS as internal standard. Melting points were obtained by open capillary method and remain uncorrected.

General Procedure: To a solution of 2,6-diazido-1-phenyl-1,4-dihydropyridine-3,5-dicarbaldehyde (3) (1 equivalent) in ethanol, a solution of hydrazine hydrate (3 equivalent) in ethanol was added. The reaction mixture was refluxed for 30 min. The reaction was monitored and confirmed its completion by TLC in hexane-ethyl acetate system (20 % ethyl acetate). The reaction mixture was poured into beaker of 50 g crushed ice and stirred for 10 min. The product was extracted in CH_2Cl_2. The organic solution was washed with water, dried over anhydrous Na_2SO_4, and faltered, and the solvent was evaporated under reduced pressure to give a product 10-phenyl-5,10-dihydropyrido[2,3-d:6,5-d']bis([1,2,3]triazine) (4).



3a-j **4a-j**

Where R a=4H, b=3Cl, c=4Cl, d=4Br, e=2NO_2, f= 3NO_2, g=4NO_2, h=4OH, i=4CH_3, j=4OCH_3

Scheme-II

Entry	R in 3a-j	Yield(%)	M.P.(^{0}C)	Bruker (AVANCE III HD) (Liquid State 500 MHz) NMR in δ
4 a	4H	54.3	212	4.0 (d, 2H), 7.34 (m, 1H), 7.46 (m, 2H), 7.60 (m, 2H), 8.36 (s, 2H)
4 b	3Cl	59.5	182	4.31 (d, 2H), 7.20 (m, 1H), 7.39 (m, 1H), 7.45 (m, 1H), 7.67 (m, 1H), 8.36 (s, 2H)
4 c	4Cl	62.7	178	4.31 (d, 2H), 7.47 (m, 2H), 7.48 (m, 2H), 8.38 (s, 2H)
4 d	4Br	68.9	156	4.34 (d, 2H), 7.46 (m, 2H), 7.51 (m, 2H), 8.36 (s, 2H)
4 e	2NO_2	52.4	192	4.34 (d, 2H), 7.43 (m, 1H), 7.64 (m, 1H), 7.74 (m, 1H), 8.08 (m, 1H), 8.36 (s, 2H)
4 f	3 NO_2	58.1	188	4.31 (d, 2H), 7.48 (m, 1H), 7.55 (m, 1H), 7.60 (m, 1H), 8.20 (m, 1H), 8.36 (s, 2H)
4 g	4 NO_2	54.5	202	4.35 (d, 2H), 7.72 (m, 2H), 8.08 (m, 2H), 8.38 (s, 2H)

4 h	4OH	75.3	156	4.31 (d, 2H), 6.68 (m, 2H), 7.65 (m, 2H), 8.36 (s, 2H)
4 i	$4CH_3$	74.2	178	2.22 (s, 3H), 4.31 (d, 2H), 7.14 (m, 2H), 7.36 (m, 2H), 8.36 (s, 2H)
4 j	$4OCH_3$	69.7	184	3.77 (s, 3H), 4.31 (d, 2H), 6.64 (m, 2H), 7.89 (m, 2H), 8.36 (s, 2H)

- **DPPH Free Radical Scavenging Activity of 1,2,3-triazine derivative of glutarimide:**

- **Results:**

Concentration (µg/mL)	50	100	150	200	250
Ascorbic Acid	78.63±.05	90.22±.16	93.44±.03	95.12±.12	99.53±.10
4a	73.36±.31	74.56±.08	76.11±.12	80.22±.21	86.34±.15
4b	85.61±.10	88.93±.06	91.56±.11	93.65±.12	96.23±.96
4c	72.12±.24	73.52±.46	75.05±.41	76.05±.17	77.42±.36
4d	66.31±.35	67.47±.24	69.35±.35	70.93±.35	71.97±.24
4e	56.36±.15	57.35±.11	59.53±.40	62.78±.12	76.82±.11
4f	53.65±.06	54.96±.12	57.07±.17	59.04±.06	61.92±.06
4g	70.18±.11	72.28±.06	73.83±.06	77.35±.13	78.62±.12
4h	60.8± .16	65.07±.12	70.68±.17	74.74±.44	76.18±.45
4i	72.12±.13	78.44±.09	80.99±.71	84.13±.33	89.88±.08
4j	44.21± .12	49.23± .12	55.54± .11	62.23± .14	65.14± .12

Value represent means± SD, n=3

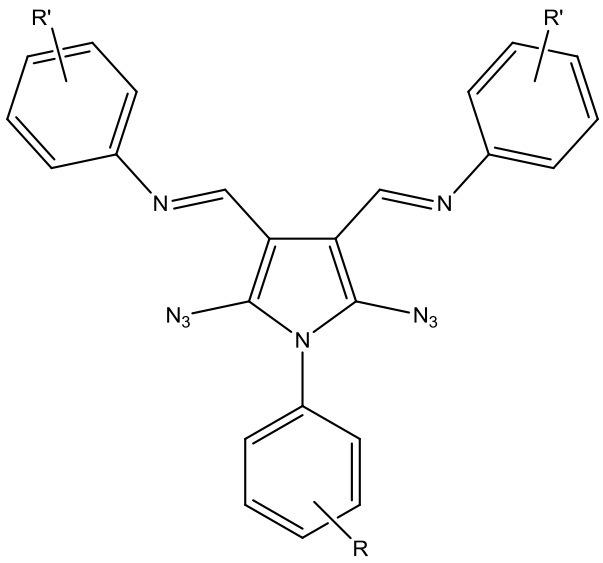
Table-1: DPPH scavenging activity of 10-phenyl-5,10-dihydropyrido[2,3-d:6,5-d']bis([1,2,3]triazine) in ethanol

Synthesis of Schiff base derivative-

A efficient procedure for the synthesis of a series of schiff bases under ethanol reflux. is described here. The present work involves condensation of azo vinyl aldehyde of succinamide and glutarimide with various aromatic amines in ethanol under reflux xondition. A one step reaction gives a good yield of product. The structures of synthesized compounds were confirmed by IR and ^{1}HNMR.

1. **Synthesis of Schiff base derivative of succinamide from azo vinyl aldehyde of succinamide:**

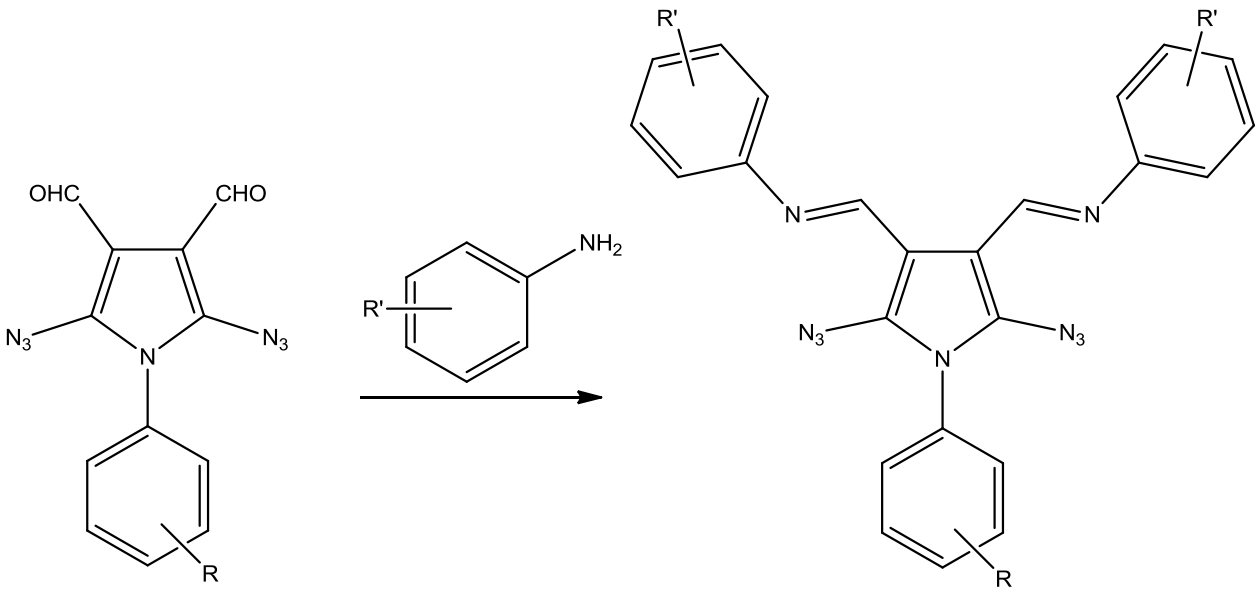
General Structure:



(*N*,*N'E*,*N*,*N'E*)-*N*,*N*'-((2,5-diazido-1-substituted phenyl-1*H*-pyrrole-3,4-diyl)bis(methanylylidene))dianiline

Material and Method: All the reagents were purchased in the highest quality available and were used without further purification. All the solvents used in synthesis were obtained from commercial suppliers and used without further purification and distillation. Infrared spectra (FTIR) were recorded on a Lambda FT-IR 7600 spectrophotometer. Nuclear magnetic resonance 1H-NMR spectra (at 500 MHz) were recorded on a Bruker (AVANCE III HD) (Liquid State 500 MHz) spectrometer in $CDCl_3$ with TMS as internal standard. Melting points were obtained by open capillary method and remain uncorrected.

General Procedure: To a solution of 2,5-diazido-1-phenyl-1H-pyrrole-3,4-dicarbaldehyde (1) (1 equivalent) added to a solution of aniline (2.2 equivalent) in ethanol. The reaction mixture was refluxed for 20 min. The reaction was monitored and confirmed its completion by TLC in hexane-ethyl acetate system (30 % ethyl acetate). The reaction mixture was poured into beaker of 50 g crushed ice and stirred for 10 min. The product was extracted in CH_2Cl_2. The organic solution was washed with water, dried over anhydrous Na_2SO_4, and faltered, and the solvent was evaporated under reduced pressure to give a product (N,N'E,N,N'E) -N,N'-((2,5-diazido-1-phenyl-1H-pyrrole-3,4-diyl)bis(methanylylidene)) dianiline (5).



1a-j **5aa-5jc**

Where R a=4H, b=3Cl, c=4Cl, d=4Br, e=2NO_2, f= 3NO_2, g=4NO_2, h=4OH, i=4CH_3, j=4OCH_3

Where R' a=4H, b=4Cl, c=4NO_2

Scheme-III

Entry	R in 3a-j	Yield(%)	M.P.(^{0}C)
5 aa	4H	58.7	132
5 ba	3Cl	59.5	154
5 ca	4Cl	61.8	174
5 da	4Br	67.5	188
5 ea	2NO_2	52.7	136
5 fa	3 NO_2	58.9	196
5 ga	4 NO_2	54.6	212
5 ha	4OH	68.7	148
5 ia	4CH_3	69.3	194
5 ja	4OCH_3	68.2	178
5 ab	4H	64.2	138
5 bb	3Cl	69.7	218
5 cb	4Cl	72.8	192
5 db	4Br	69.4	146
5 eb	2NO_2	62.9	174
5 fb	3 NO_2	68.3	206
5 gb	4 NO_2	64.9	110

5 hb	4OH	72.4	140
5 ib	$4CH_3$	75.3	218
5 jb	$4OCH_3$	73.7	184
5 ac	4H	48.3	198
5 bc	3Cl	49.1	218
5 cc	4Cl	52.1	194
5 dc	4Br	58.3	210
5 ec	$2NO_2$	44.7	190
5 fc	3 NO_2	52.2	208
5 gc	4 NO_2	46.3	242
5 hc	4OH	59.2	188
5 ic	$4CH_3$	57.1	210
5 jc	$4OCH_3$	59.2	198

NMR Data on Bruker (AVANCE III HD) (Liquid State 500 MHz) in δ of 5aa, 5ca and 5ia:

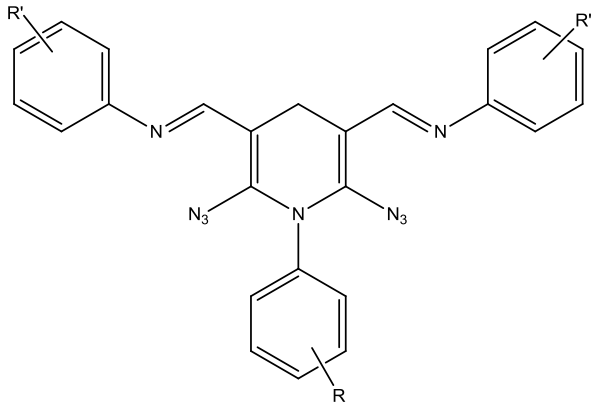
5aa: 7.55-7.97 (m, 15H), 9.26 (s, 2H)

5ca: 7.53-7-99 (m, 14H), 9.25 (s, 2H)

5ia: 2.33 (s, 3H), 7.54-7.98 (m, 14H), 9.26 (s, 2H)

Synthesis of Schiff base derivative of glutarimide from azo vinyl aldehyde of glutarimide:

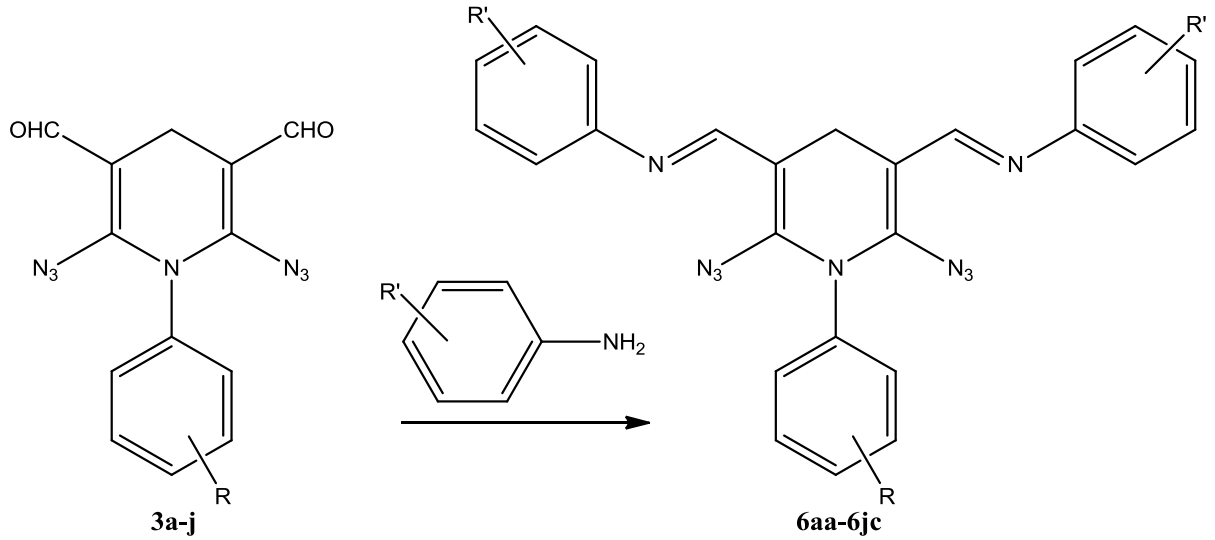
General Structure:



(*N*,*N*'*E*,*N*,*N*'*E*)-*N*,*N*'-((2,6-diazido-1-substituted phenyl-1,4-dihydropyridine-3,5-diyl)bis(methanylylidene))dianiline

Material and Method: All the reagents were purchased in the highest quality available and were used without further purification. All the solvents used in synthesis were obtained from commercial suppliers and used without further purification and distillation. Infrared spectra (FTIR) were recorded on a Lambda FT-IR 7600 spectrophotometer. Nuclear magnetic resonance 1H-NMR spectra (at 500 MHz) were recorded on a Bruker (AVANCE III HD) (Liquid State 500 MHz) spectrometer in $CDCl_3$ with TMS as internal standard. Melting points were obtained by open capillary method and remain uncorrected.

General Procedure: To a solution of 2,6-diazido-1-phenyl-1,4-dihydropyridine-3,5-dicarbaldehyde (3) (1 equivalent) added to a solution of aniline (2.2 equivalent) in ethanol. The reaction mixture was refluxed for 20 min. The reaction was monitored and confirmed its completion by TLC in hexane-ethyl acetate system (30 % ethyl acetate). The reaction mixture was poured into beaker of 50 g crushed ice and stirred for 10 min. The product was extracted in CH_2Cl_2. The organic solution was washed with water, dried over anhydrous Na_2SO_4, and faltered, and the solvent was evaporated under reduced pressure to give a product (N,N'E,N,N'E) -N,N'-((2,6-diazido-1-phenyl-1,4-dihydropyridine-3,5-diyl)bis(methanylylidene)) dianiline (6).



Where R a=4H, b=3Cl, c=4Cl, d=4Br, e=2NO_2, f= 3NO_2, g=4NO_2, h=4OH, i=4CH_3, j=4OCH_3

Where R' a=4H, b=4Cl, c=4NO_2

Scheme-IV

Entry	R in 3a-j	Yield(%)	M.P.(^{0}C)
6 aa	4H	54.4	188
6 ba	3Cl	56.3	204
6 ca	4Cl	58.5	170
6 da	4Br	59.3	130
6 ea	2NO_2	48.2	190
6 fa	3 NO_2	52.2	210
6 ga	4 NO_2	49.1	192
6 ha	4OH	58.3	198
6 ia	4CH_3	59.9	188
6 ja	4OCH_3	62.3	210
6 ab	4H	64.4	190
6 bb	3Cl	68.3	212
6 cb	4Cl	72.1	158
6 db	4Br	73.2	178
6 eb	2NO_2	54.2	164
6 fb	3 NO_2	58.4	218
6 gb	4 NO_2	56.1	170
6 hb	4OH	71.3	210
6 ib	4CH_3	69.0	144
6 jb	4OCH_3	73.1	212
6 ac	4H	47.4	156
6 bc	3Cl	48.0	198
6 cc	4Cl	51.3	144
6 dc	4Br	54.8	230
6 ec	2NO_2	42.7	138
6 fc	3 NO_2	48.2	160
6 gc	4 NO_2	44.7	158
6 hc	4OH	52.4	168
6 ic	4CH_3	59.1	182
6 jc	4OCH_3	56.3	174

NMR Data on Bruker (AVANCE III HD) (Liquid State 500 MHz) in δ of 6aa, 6ca and 6ia:

6aa: 3.30 (d, 2H), 7.17-7.88 (m, 15H), 9.47 (s, 2H)

6ca: 3.29 (d, 2H), 7.22-7-87 (m, 14H), 9.43 (s, 2H)

6ia: 2.23 (s, 3H), 3.29 (d, 2H), 7.16-7.87 (m, 14H), 9.49 (s, 2H)

Conclusions:

An entire new series of 9-phenyl-9H-pyrrolo[2,3-d:5,4-d']bis([1,2,3]triazine) **2a-j** and 10-phenyl-5,10-dihydropyrido[2,3-d:6,5-d']bis([1,2,3]triazine) **4a-j** have been synthesized from 2,5-diazido-1-substitutedphenyl-1H-pyrrole-3,4-dicarbaldehyde **1a-j** and 2,6-diazido-1-phenyl-1,4-dihydropyridine-3,5-dicarbaldehyde **3a-j** in good yield. Based on our experimental findings, the new substituted 1,2,3-triazine derivatives containing cyclic imide moiety **5a-j** exhibiting **good antioxidant** properties.

A series of compound were synthesized as (N,N'E,N,N'E) -N,N'-((2,5-diazido-1-phenyl-1H-pyrrole-3,4-diyl)bis(methanylylidene)) dianiline **5aa-jc** and (N,N'E,N,N'E) -N,N'-((2,6-diazido-1-phenyl-1,4-dihydropyridine-3,5-diyl)bis(methanylylidene)) dianiline **6aa-jc** from condensation of aldehyde group of 2,5-diazido-1-substitutedphenyl-1H-pyrrole-3,4-dicarbaldehyde **1a-j** and 2,6-diazido-1-phenyl-1,4-dihydropyridine-3,5-dicarbaldehyde **3a-j** with aniline and substituted aniline under ethanol reflux.

Publication:

1. Review article: **Succinamide: Synthesis, Reaction and Biological Activity**, International Journal of Pharmacy and Pharmaceutical Sciences (ISSN 0975-1491), IJPPS, 2014, 6(11), 8-14
2. **Synthesis and antimicrobial evaluation of some Novel Diazo derivative of cyclic imides using diazotization coupling reaction**, Chemical Science Review and Letters (ISSN 2278-6783), 2016, 5(17), 46-52 (UGC recognized Journal).
3. **Green synthesis and antimicrobial evaluation of N-aryl cyclic imides using silica bound benzyl chloride mediated solid phase synthesis**, International Journal of Green and Herbal Chemistry Section A: Green Chemistry (E-ISSN: 2278-3229), 2017, 7 (1), 35-46 (UGC recognized Journal).

Presentation:

Poster entitled by *"Synthesis and antimicrobial evaluation of biologically active dihydrazinyl-pyrrolo bis oxadiazepine and dihydrazinyl-dihydropyrido bis oxadiazepine compounds from halo vinyl aldehyde of substituted cyclic imides"* presented in 23rd CRSI National Symposium in Chemistry (CRSI-NSC-23) at IISER Bhopal, Madhyapradesh, india (13 to 15th Julyl-2018).

Patents:

1) Title processed for the registration in Indian national patent 'NOVEL PYRROLO DIPYRIDINE DIOL COMPOUNDS AND PROCESS FOR PREPATATION THEREOF' accepted **Application Number – 201821028492**.

2) Title processed for the registration in Indian national patent 'NOVEL DIHYDROPYRIDO NAPHTHYRIDINE DIOL COMPOUNDS AND PROCESS FOR PREPARATION THEREOF' accepted **Application Number – 201821028501**.

3) Title processed for the registration in Indian national patent 'NOVEL DIHYDRAZINYL-PYRROLO BIS OXADIAZEPINE AND DIHYDRAZINYL-DIHYDROPYRIDO BIS OXADIAZEPINE COMP' accepted **Application Number – 201821028535**.

Summary of Work done

1. In this work initially aniline, 4-chlorobenenamine, 4-aminophenol, p-toludine, 4-bromobenzenamine, 4-nitrobenzenamine, 3-chlorobenzamine, 4-methoxybenzenamine (p-anicidine) napthalen-1-amine etc. will be used to synthesize the succinamide and glutarimides by the condensation of succinic anhydride and glutaric anhydride with different aromatic amine gives acid imides intermediate as 3 (substituted phenyl carboxyl) propionic acid and 4 (substituted phenyl carboxyl) butanoic acid respectively.
2. **SBBC** separately synthesized by in presence of benzoyl chloride bonded with silica (**greener dehydrating agent**).
3. **SBBC** was used to gives 1-substituted phenyl pyrrolidine-2, 5-dione and 1-substituted phenyl piperidine-2, 5-dione respectively.
4. Synthesis of 2, 5-dichloro-1-phenyl (substituted)-1*H*-pyrrole-3, 4-dicarbaldehyde and 2, 6-dichloro-1-phenyl (substituted)-1, 4-dicloro-pyridine-3, 5-dicarbaldehyde derivative using Vilsmeier-Haack ($DMF/POCl_3$) at 0-5 ^0C.
5. Synthesis of azide derivative compounds from N-aryl succinimides and N-aryl glutarimides and successfully characterize for their biological susceptibility.
6. The entire synthesized compound was dispatched for the elemental analysis, ^{1}H-NMR, ^{13}C-NMR and mass analysis.
7. The 1,2,3-triazine and related benzo- and hetero-fused derivatives possessing antitumor activity. Their efficacy, combined with a simple synthesis confers to these molecules a great potential as scaffold for the development of antitumor compounds.
8. The series of 1,2,3-triazine are screen for DPPH scavenging (antioxidant) activity in ethanol shows good results.
9. The molecular library of Schiff base derivative of succinamide and glutarimide were successfully created and characterized using FTIR and ^{1}H-NMR.

(Milind M. Patil)

Principal Investigator

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Review Article

SUCCINIMIDES: SYNTHESIS, REACTION AND BIOLOGICAL ACTIVITY

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ABSTRACT

This review summarizes the synthetic methods, reactions and biological application of important pharmacological succinimides and summarizes recent developments in their derivatives such as dichlorodiformyl, Schiff base, chalcone, Barbier type allylation etc. Over the last years. The biological activity of the cyclic imides is also briefly discussed. Formation of succinimidyl radicals and Single crystal studies on this type of compounds are beyond the scope of this review and will not be discussed. Nor referenced.

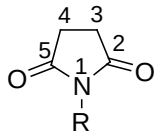
Keywords: Succinimides, Biological activity, Dichlorodiformyl, Cyclic imides.

INTRODUCTION

Substituted succinimides are important compounds of many drugs and drug candidates. One of the most fundamental objectives of organic and medicinal chemistry is the design and synthesis of molecules having value as human therapeutic agents. Cyclic imides and their derivatives contain an imide ring and the general structure –CO–N(R)–CO–, so they are cross biological membranes in vivo [1].

A diversity of biological activities and pharmaceutical uses have been attributed to them, such as succinimide is a part of many active molecules possessing activities such as CNS depressant [2], analgesic [3], antitumor [4], cytostatic [5], anorectic [6], nerve conduction blocking [7], antispasmodic [8], bacteriostatic [9], muscle relaxant [10], hypotensive [11], antibacterial [l2], antifungal [13], anti-convulsant [14] and anti-tubercular [15].

Substituted succinimide moiety **1** appears as an interesting precursor of many biologically active of the above class compounds.



1

where R= aliphatic or aromatic

This review provides an overview of the synthesis and reactivity of succinimides and derivatives. In the first part we intend to outline the general methods by which substituted succinimides are prepared. The second and third parts are devoted to the chemical reactivity of substituted succinimides.

Synthetic methods

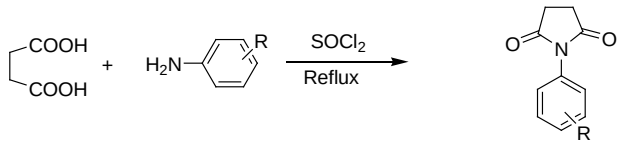
There have been a number of practically important routes to synthesize succinimides.

From succinic acid using $SOCl_2$

A well-established route for the synthesis of 1-substituted phenyl pyrrolidine-2,5-dione **4** was reported by condensation of succinic acid **2** and primary aromatic amine **3** using $SOCl_2$ under reflux condition (Scheme 1) [16].

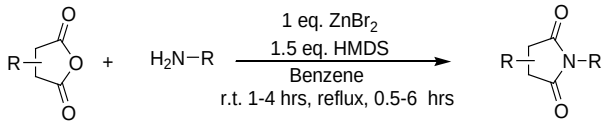
From cyclic anhydride using Lewis Acid

The convenient method was reported for the direct synthesis of substituted succinimides in which succinic anhydride **5** treated with amine **6** using Lewis acid catalyst in the presence of Hexamethyl disilazane (HMDS) in benzene afforded the substituted succinimides **7** (Scheme 2) [17].



2 **3** **4**

Scheme 1

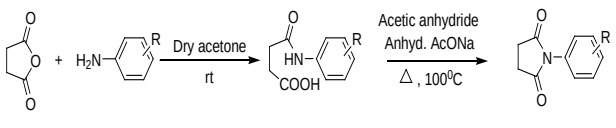


5 **6** **7**

Scheme 2

In dry acetone with acetic anhydride in anhydrous CH_3COONa

Reactions were studied and reported the synthesis in mild condition in which succinic anhydride **8** condensed with substituted aromatic amines **9** gives imic acid intermediate **10,** which on cyclization with the help of acetic anhydride in anhydrous sodium acetate at 100^{0}C gives N-phenyl succinimides **11** (Scheme 3) [18].

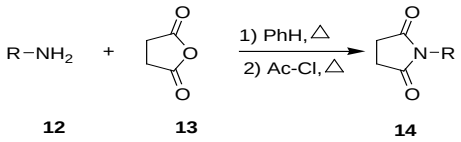


8 **9** **10** **11**

Scheme 3

From cyclic anhydride and amine in the presence of acetyl chloride

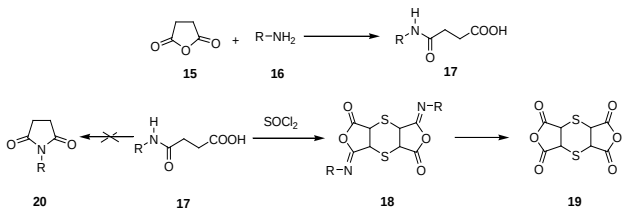
Treatment of amines **12** with succinic anhydride in the presence of benzene using acetyl chloride as dehydrating agent furnished succinimides **14** (Scheme 4) [19].



Scheme 4

Cyclic anhydride and $SOCl_2$

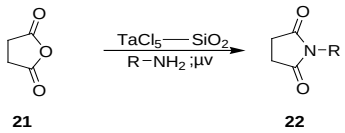
When imic acid **17** undergoes cyclization in the presence of $SOCl_2$, it gives product dithiin diisoimides **18** and diimides **19** instead of formation of N-substituted cyclic imides **20** (Scheme 5) [20].



Scheme 5

Solvent free synthesis in $TaCl_5$-Silica gel

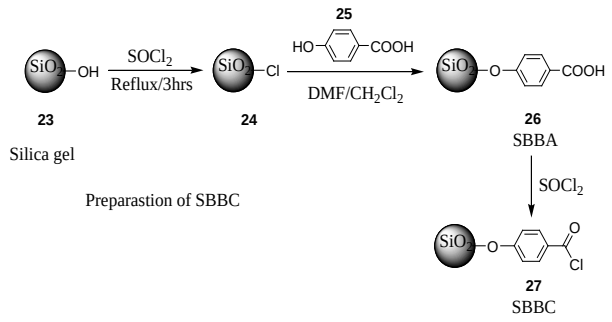
The new protocol developed for the synthesis of succinimide **22** from succinic anhydride **21** in solvent free condition using silica gel. The reaction is catalyzed by Lewis acid- $TaCl_5$. (Scheme 6) [21].



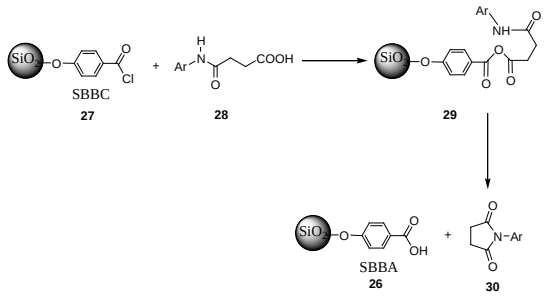
Scheme 6

Solid phase synthesis using SBBC

A new method upon adopting a solid-phase strategy for the synthesis of N-aryl succinimides **30** was described using the silica-bound benzoyl chloride (SBBC) **27** (Scheme 7) as dehydrating agent in reaction with N-arylsuccinamic acids **28** (Scheme 8) [22]. The main advantage of this method is the recyclability of SBBC.



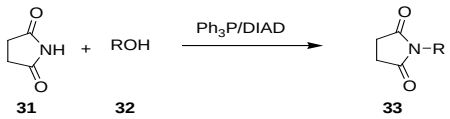
Scheme 7



Scheme 8

High Yield synthesis using a modification of Mitsunobu reaction

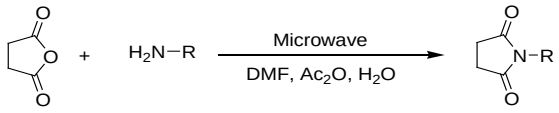
Modified Mitsunobu reaction used for the synthesis of N-substituted succinimide **33** using reaction between succinimide **31** and alcohol **32** in the presence of triphenyl phosphine and diisopropyl azodicarboxylate (DIAD) as a reagent. (Scheme 9) [23].



Scheme 9

Microwave assisted preparation of cyclic imides

Microwave-assisted preparation of substituted succinimide **36** was performed by reacting succinic anhydrides **34** and amine **35**. The reaction was carried out in solvent DMF, acetic anhydride or water. The yield reported by microwave assisted reaction was excellent as compared to conventional method. (Scheme 10) [24].

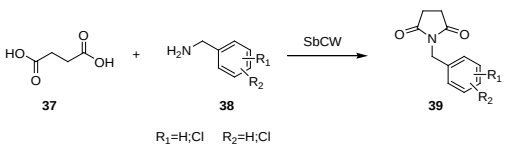


R=benzyl; R=$(CH_2)_6$; R=4-methyl phenyl; R=4,4'-methanediphenyl; R=1-naphthyl

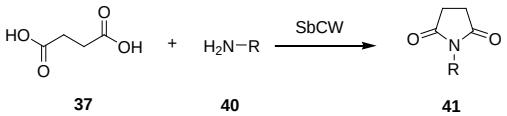
Scheme 10

Clean and efficient synthesis in sub critical water

An alternative, fast and clean method was reported using sub-critical water for the synthesis of substituted succinimide **41** by reaction of succinic acid **37** with aniline **40** in water at 280ºC in 30 min with high yield (Scheme 11 and 12) [25].



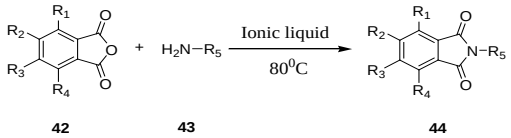
Scheme 11



Scheme 12

Synthesis using Ionic liquid

N-alkyl and N-arylimides **44** were synthesized from cyclic imides **42** and alkyl or aryl amine **43** efficiently under mild reaction conditions in the presence of ionic liquids. The use of ionic liquids offer improvements for the synthesis of cyclic imides with regard to the yield of products, simplicity in operation, short reaction times and green aspects by avoiding toxic catalyst and organic solvents (Scheme 13) [26].

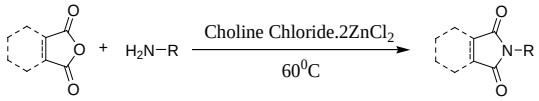


42 **43** **44**

Scheme 13

Synthesis using Lewis acid Choline Chloride.2ZnCl$_2$

The reaction of succinic anhydride **45** with aniline **46** using Lewis acidic ionic liquid Choline Cloride.2ZnCl$_2$ gave N-phenylsuccinimide **47** in good yield under mild condition (Scheme 14) [27].

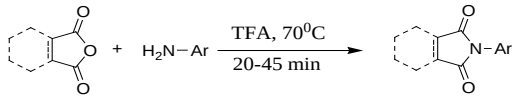


45 **46** **47**

Scheme 14

Facile synthesis using Trifluroacetic acid

A mixture of anhydride **48** and aromatic amine **49** in trifluoroacetic acid as reaction medium and promoter was refluxed at 70^{0}C for appropriate time to obtain succinimides **50** (Scheme 15) [28].

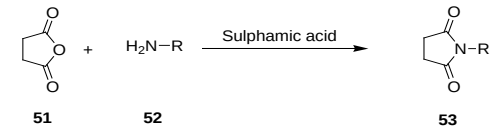


48 **49** **50**

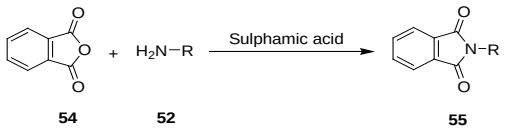
Scheme 15

One Pot Synthesis of N-alkyl and N-arylimides using Sulphamic Acid

One pot method was reported for the synthesis of succinimides **53** by reacting succinic anhydride **51** in situ with aromatic or aliphatic amines **52** using 10 % sulphamic acid as a catalyst (Scheme 16) [29].



51 **52** **53**

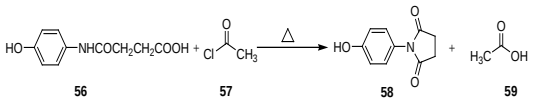


54 **52** **55**

Scheme 16

Synthesis using substituted succinamic acid and acetyl chloride

The synthesis of N(4-hydroxyphenyl)-succinimide **58** was prepared from N(4-hydroxyphenyl)- succinamic acid **56** using acetyl chloride **57** as dehydrating agent (Scheme 17) [30].



56 **57** **58** **59**

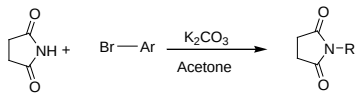
Scheme 17

Synthesis using aromatic halide and succinimide

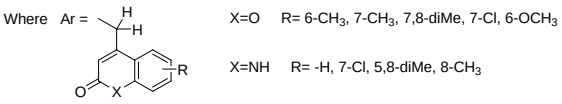
Marulashiddaiah et. al. reported the direct synthesis of N-substituted succinimides **62** from succinimide **60** and halide of coumarins and azocoumarins **61** under K_2CO_3 in acetone (Scheme 18) [31].

From succinic acid using EDC

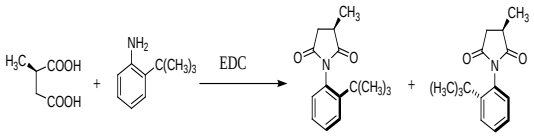
A novel approach of asymmetric deprotonation strategy to the synthesis of chiral succinimides results atroposomeric imides **65** and **66** was reported, starting from (R)-2-methyl succinic acid **63** and orthoisobutylaniline using 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) (Scheme 19) [32].



60 **61** **62**



Scheme 18

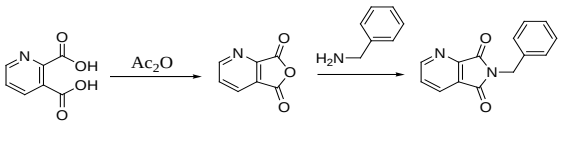


63 **64** **65** **66**

Scheme 19

Using aromatic dicarboxylic acid

The synthesis of C7 side chain began with the formation of anhydride **68** from pyridine-2,3-dicarboxylic acid **67** and acetic anhydride (Scheme 20) [33].

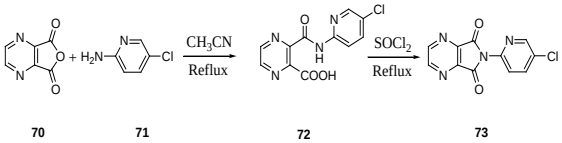


67 **68** **69**

Scheme 20

Using pyrazine anhydride and 2-amino-5-chloropyridine

The treatment of pyrazine anhydride **70** with 2-amino-5-chloropyridine **71** gave amide **73** in good yield (Scheme 21) [34].



70 **71** **72** **73**

Scheme 21

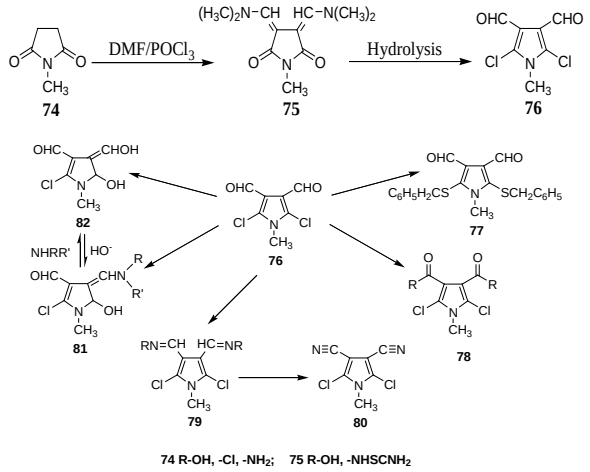
Chemical reactions

Chloroformylation

N-substituted succinimide on dichloro diformylation give halovinyl derivatives. in the presence of dimethylformamide and phosphorus oxycloride.

Chloroformylation of N-substituted succinimide

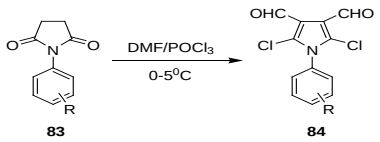
N-alkyl substituted succinimide **74** underwent dichloro diformylation in the presence of dimethylformamide and phosphorus oxycloride leads to aromatization of ring and formation of N-substituted dichlorodiformylpyrroles **76** via intermediate **75**, which was used as synthone for the preparation of derivatives **77-82** (Scheme 22) [35].



Scheme 22

Chloroformylation of N-phenyl succinimide

Halovinyl aldehyde derivative, N-phenyl-2,5-dichloro-3,4-diformyl succinimide **84** was obtained by successive reaction of **83** with Vilsmeier-Haack reagent ($DMF/POCl_3$) at 0-5^{0}C (Scheme 23) [36].



Scheme 23

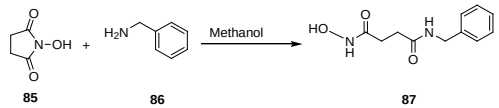
Ring opening reactions

The nucleophilic ring opening reaction of succinimides shows inter and intra molecular reaction. Each reaction is classified according to nucleophile: Nitrogen, Oxygen, Carbon linked and hybrid.

Intermolecular reactions

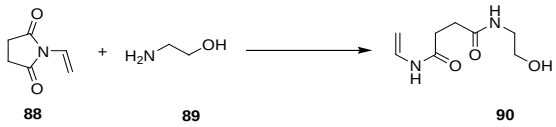
Nitrogen linked nucleophile

The activating effects of the carbonyl groups enable a succinimide to react easily with amine. The reactions have been recently reported using simple amines, diamines and hydrazine as nucleophiles. Benzylamine **86** react easily with N-hydroxy succinimides **85** to gives diamide **87** in high yield (Scheme 24) [37].



Scheme 24

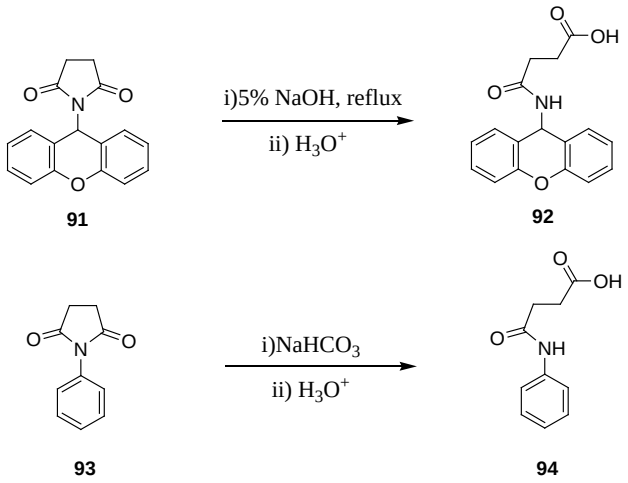
When both amino and hydroxyl groups are present in the same nucleophile, the amino group reacts selectively with succinimide. Thus N-vinyl succinimide **88** and ethanolamine **89** produce diamide **90** in almost quantitative yield at room temperature (Scheme 25) [38].



Scheme 25

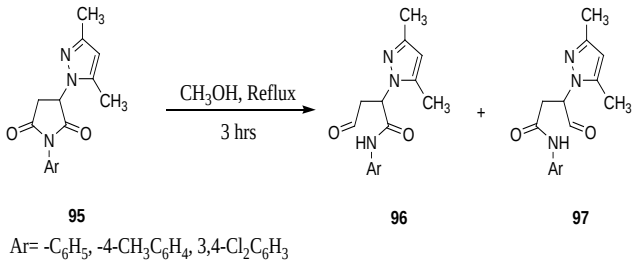
Oxygen linked nucleophile

In contrast to ordinary amides, succinimides **91** and **93** were hydrolyzed to carboxylic acids **92** and **94** under weakly basic condition (Scheme 26) [39].



Scheme 26

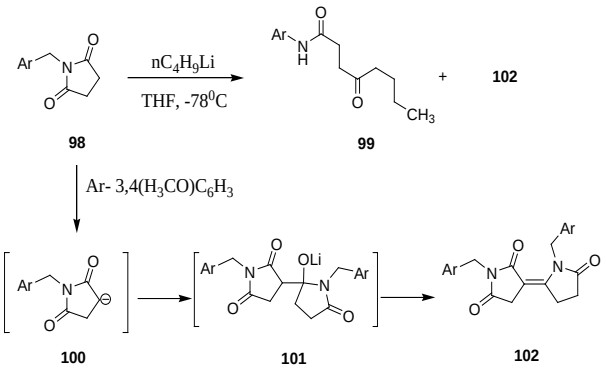
Succinimide **95** underwent ring opening reaction by methanolysis under mild condition into methyl ester **96** and **97** (Scheme 27) [40].



Scheme 27

Carbon linked nucleophile

Reaction between succinimide and lithium reagent produce low yield of ketones (e. g. **98→99**, Scheme 28). Since lithium reagents act as strong base, abstract one proton from the succinimide to formimic enolate **100**, which then undergoes intermolecular nucleophilic addition to another molecule of succinimide to produce dimeric product (Scheme 28) [41].



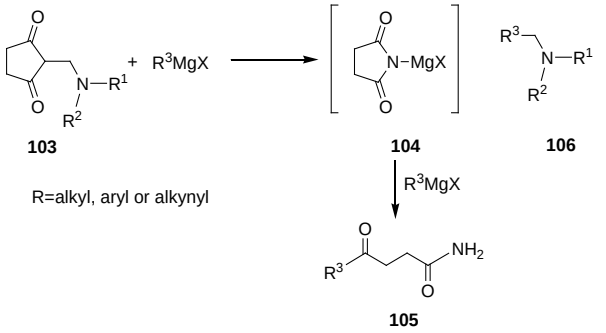
Scheme 28

Reaction of N-(aminomethylene) succinimide **103** with two equivalents of Grignard reagents afforded ring opening product γ-keto amines **105** and tertiary amines **106**. The reaction involves a salt like succinimidomagnesium halide intermediate **104**, which reacts further with various Grignard reagents to give γ-keto amines **105** (Scheme 29) [42].

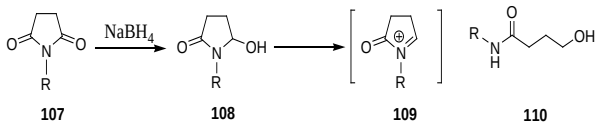
Reduction

Generally, succinimide can be reduce to give hydroxyl lactums (e. g. **107→108**, Scheme 30), which are precursors to α-acyliminium salt **109** and other functional groups.

Under certain conditions hydroxyl lactams **108** can be reduced further to give ω-hydroxy amide **110** as a product (Scheme 30) [43].



Scheme 29



Scheme 30

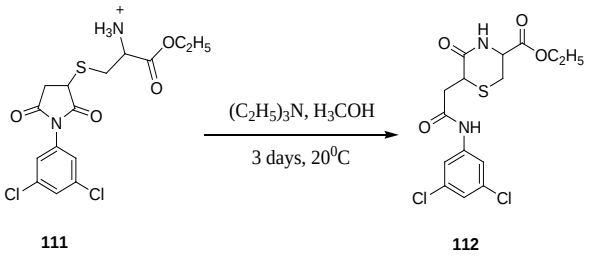
Intermolecular reactions

Nucleophilic substitution

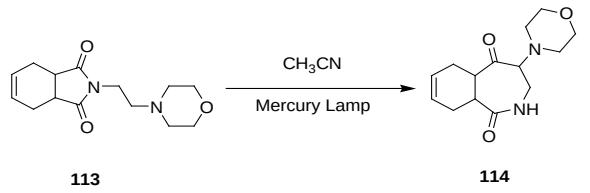
When succinimide **111** is reacting with the amino group, it forms preferentially a six member ring product **112** (Scheme 31) [44].

Photochemical ring opening

Succinimide can undergo ring opening and intramolecular cyclization under photochemical conditions. When compound **113** was irradiated in the presence of methyl Nitrile, a product **114** was obtained (Scheme 32) [45].



Scheme 31

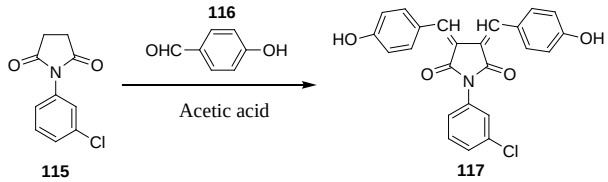


Scheme 32

Bis-heterocyclic derivatives

Bis-chalcones

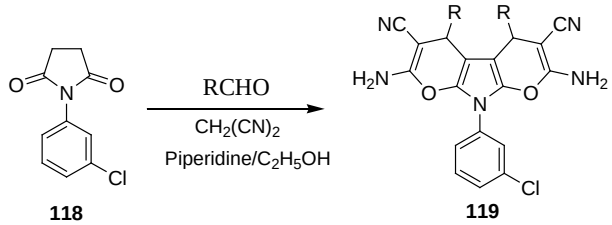
Bis chalcone **117** was obtained by reaction of N-(3-chlorophenyl) succinimide **115** and 4-hydroxy benzaldehyde **116** using glacial acetic acid. The bis chalcone separate as colored crystals (Scheme 33) [46].



Scheme 33

Azo flurorene

A mixture of N-(3-chlorophenyl) succinimide **118** refluxed with aldehyde in the presence of malononitrile in piperidine/ethanol for 4-5 hrs give azo flurorene **119** (Scheme 34) [47].



Scheme 34

CONCLUSION

Succinimides are easily available and have high chemical reactivity due to the presence of both carbonyl and methylene groups. Substituted succinimides are important compounds of many drugs and drug candidates. This survey was attempted to summarize the synthetic methods and reactions of succinimides.

ACKNOWLEDGEMENT

Financial assistance from UGC WRO, Pune under MRP.

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Research Article

Synthesis and Antimicrobial Evaluation of Some Novel Diazo Derivative of Cyclic Imides Using Diazotization Coupling Reaction

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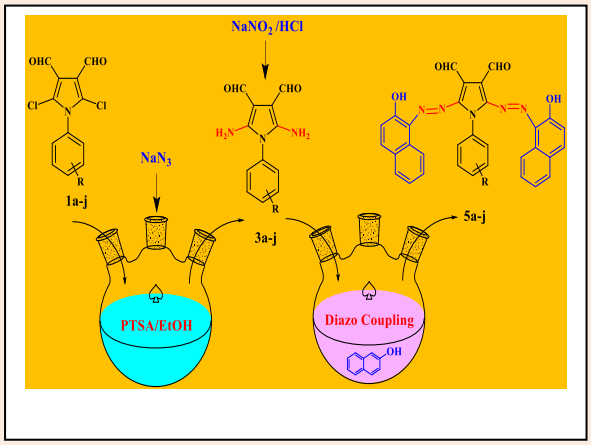
Abstract

A series of new azo coupled derivative of N-substituted cyclic imides were prepared by diazotization-coupling reaction. All the compounds were screen for their antimicrobial and antifungal activities. Most of the synthesized compounds have shown significant antimicrobial activity. Based on our experimental findings, the new substituted azovinyl aldehyde derivatives containing cyclic imide moiety exhibiting excellent bactericidal and fungicidal potentials could be proposed for dyeing and antimicrobial finishing for silk, wool, cotton, and polyester fabrics. The structures of these compounds were confirmed by various analytical tools.

Keywords: azo coupling, diazotization, coupling reaction, cyclic imides, antimicrobial activity



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Introduction

The structural diversity and industrial as well as biological importance of nitrogen and oxygen-containing heterocycles have made them attractive targeted for synthesis over many and justify continuing efforts in the development of new synthetic strategies [1]-[3]. From last few decades, the study of the chemistry of diazo compound has been given particular impacts because of their application in pigments [4]-[9], lacks [10] and dyes [11]. It has been explored and being developed as a dying [12] and coloring agent [13] for the textile industries [14]. Now a day chemistry of diazo derivative synthesized using heterocyclic ring [15] exhibit a new aspect of coupling reaction [16]. Therefore, some novel diazo cyclic imides were synthesized from halo vinyl aldehyde derivative of cyclic imides. The series of reaction were carried out over halo vinyl aldehyde to synthesized diazo coupled product.

After the extensive literature search [17]-[25], it was observed that cyclic imides [26], halo vinyl aldehyde[27] and azo compounds [28] are the important pharmacophores, but till date enough efforts have not made to combine these three moieties as a single molecular scaffold. So, our objective was to synthesize and biological screening of a series of new compound incorporates these moieties.

Experimental

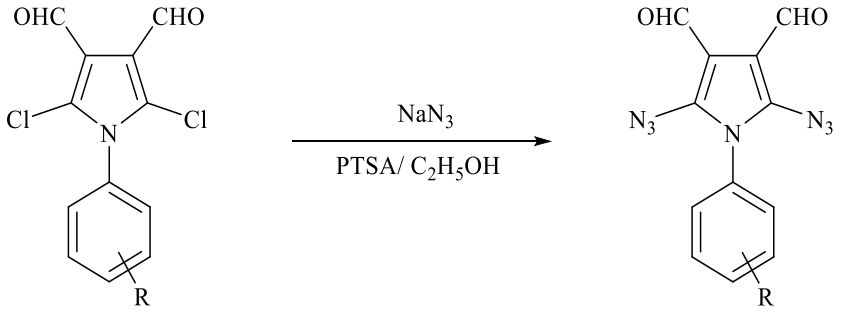
Materials and Reagents

The Melting points of all the synthesized compounds were recorded in open glass capillaries and were uncorrected. IR spectra were recorded on Lambda 7600 FTIR spectrophotometer. 1H NMR spectra were recorded on Bruker 400 MHz in DMSO-d6 using TMS as an internal standard. The reaction was monitored by TLC which was accomplished by using pre-coated silica gel aluminum plates with the mixture of hexane: ethyl acetate as a solvent phase. Chemical purchased were used as received.

General procedure for synthesis

2,5-diazido-1-substitutedphenyl-1*H*-pyrrole-3,4-dicarbaldehyde (2a-j)

In continuation of our previous work [29]-[33] a solution of 2,5-diazido-1-substitutedphenyl-1*H*-pyrrole-3,4-dicarbaldehyde **1a-j** (0.01 moles) in absolute ethanol (10 mL), P-toluene sulphonic acid (0.02 moles) and sodium azide (0.03 moles) were added and reaction mixture heated under reflux for time ranging between 4-6 hrs (**Scheme 1**). The refluxed mixture was added to ice cold water which precipitated compounds **2a-j**. These were filtered and recrystallized from ethanol.

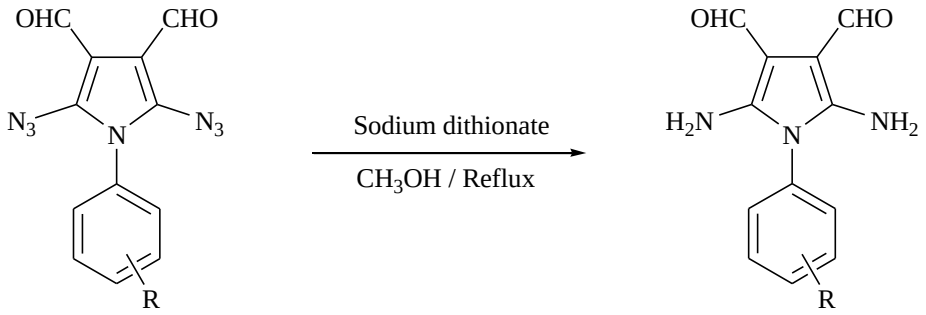


Where R a = 4H, b = 3Cl, c = 4Cl, d = 4Br, e = $2NO_2$, f = $3NO_2$, g = $4NO_2$, h = 4OH, i = $4CH_3$, j = $4OCH_3$

Scheme 1 Synthesis of 2,5-diazido-1-substitutedphenyl-1H-pyrrole-3,4-dicarbaldehyde

2,5-diamino-1-substitutedphenyl-1*H*-pyrrole-3,4-dicarbaldehyde (3a-j)

The mixture of compounds **2a-j** (0.026 moles), sodium dithionite (0.054 moles) and methanol (12mL) was refluxed for 5 hrs (**Scheme 2**). The reaction mixture was filtered and the inorganic residues were washed with methanol. The combined methanolic solution was distilled and poured over crushed ice. The resultant solids **3a-j** was filtered washed with water dried and recrystallized using ethanol as a solvent.



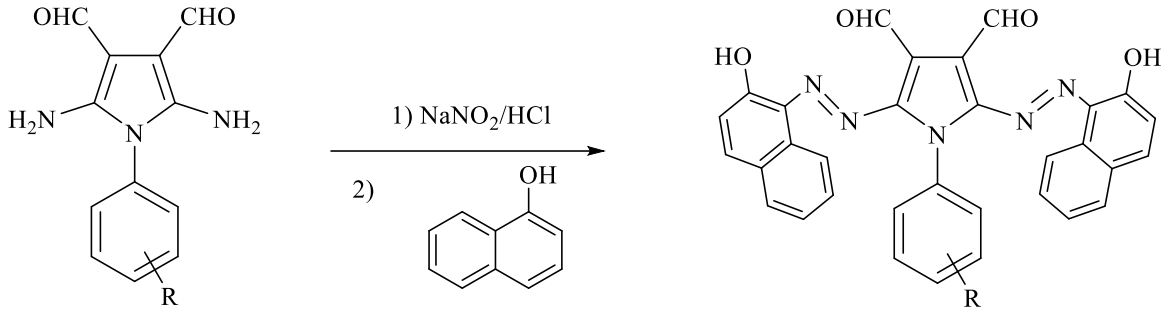
Where R a = 4H, b = 3Cl, c = 4Cl, d = 4Br, e = $2NO_2$, f = $3NO_2$, g = $4NO_2$, h = 4OH, i = $4CH_3$, j = $4OCH_3$

Scheme 2 2,5-diamino-1-substitutedphenyl-1H-pyrrole-3,4-dicarbaldehyde

2,5-bis((E)-(2-hydroxynaphthalen-1-yl)diazenyl)-1-substitutedphenyl-1*H*-pyrrole-3,4-dicarbaldehyde (5a-j)

Solution A was prepared by mixing **3a-j** (0.01 mol) with concentrated HCl (6 mL) and water (6 mL) and cooling at a temperature below 5 °C in an ice bath. $NaNO_2$ (0.02 mol) was dissolved in water (20 mL) at 5 °C to obtain solution B. Then solution A was added dropwise to solution B at 5 °C with stirring. The mixture was then slowly added into the solution of 2-napthol **4** (0.02 mol), which was dissolved in 10% NaOH (40 mL) at 5 °C. The mixture was kept chilled

in the ice bath and stirred continuously for 10 min (**Scheme 3**). The precipitate **5a-j** formed was filtered and recrystallized from glacial acetic acid, and washed with methanol and finally dried in a vacuum oven at 70 °C for 12 hours.



Where R a = 4H, b = 3Cl, c = 4Cl, d = 4Br, e = $2NO_2$, f = $3NO_2$, g = $4NO_2$, h = 4OH, i = $4CH_3$, j = $4OCH_3$

Scheme 3 (2E,5E)-2,5-di(2-(naphtha-2-olen-1-yl)diazenyl)-1-substitutedphenyl-1H-pyrrole-3,4-dicarbaldehyde

2,5-bis((E)-(2-hydroxynaphthalen-1-yl)diazenyl)-1-phenyl-1H-pyrrole-3,4-dicarbaldehyde 5a:
Light brown; M. F.: $C_{32}H_{21}N_5O_4$; Mol. Wt.: 539.54; Percent yield: 77; Melting point (^{0}C): 247-249; FTIR (cm^{-1}): 1695 (>C=O stretch, aldehyde), 2730 (H-C=O; C-H stretch), 3202 (C-H stretch, aromatics), 1660 (-C=C- stretch), 2902 (C-H stretch, aromatics), 1523 (C-C stretch, in ring aromatics), 3444 (O-H stretch, aromatic phenol), 1500 (-N=N- stretch); ^{1}HNMR (δ ppm): 9.7 (s, 2H, CHO), 5.2 (s, 2H, Ar-OH), 7.4 (s, 5H, Ar-H), 7.1 (m, 4H, Ar-H), 7.2-7.3 (m, 8H, Ar-H).

2,5-bis((E)-(2-hydroxynaphthalen-1-yl)diazenyl)-1-(3-chlorophenyl)-1H-pyrrole-3,4-dicarbaldehyde 5b:
Yellowish brown; M. F.: $C_{32}H_{20}ClN_5O_4$; Mol. Wt.: 573.99; Percent yield: 66; Melting point (^{0}C): 236-238; FTIR (cm^{-1}): 1705 (>C=O stretch, aldehyde), 2827 (H-C=O; C-H stretch), 3367 (C-H stretch, aromatics), 1640 (-C=C- stretch), 3055 (C-H stretch, aromatics), 1570 (C-C stretch, in ring aromatics), 3505 (O-H stretch, aromatic phenol), 1485 (-N=N- stretch), 739 (C-Cl stretch); ^{1}HNMR (δ ppm): 9.3 (s, 2H, CHO), 5.3 (s, 2H, Ar-OH), 7.0 (d, 2H, Ar-H), 7.5 (d, 4H, Ar-H), 7.3 (s, 1H, Ar-H), 7.1-7.5 (m, 9H, Ar-H).

2,5-bis((E)-(2-hydroxynaphthalen-1-yl)diazenyl)-1-(4-chlorophenyl)-1H-pyrrole-3,4-dicarbaldehyde 5c:
Gray; M. F.: $C_{32}H_{20}ClN_5O_4$; Mol. Wt.: 573.99; Percent yield: 75; Melting point (^{0}C): 257-259; FTIR (cm^{-1}): 1678 (>C=O stretch, aldehyde), 2717 (H-C=O; C-H stretch), 3280 (C-H stretch, aromatics), 1604 (-C=C- stretch), 3081 (C-H stretch, aromatics), 1585 (C-C stretch, in ring aromatics), 3445 (O-H stretch, aromatic phenol), 1455 (-N=N- stretch), 739 (C-Cl stretch); ^{1}HNMR (δ ppm): 9.9 (s, 2H, CHO), 4.9 (s, 2H, Ar-OH), 7.2 (d, 2H, Ar-H), 7.3 (d, 2H, Ar-H), 7.0 (d, 2H, Ar-H), 7.6 (m, 4H, Ar-H), 7.4 -7.5 (m, 6H, Ar-H).

2,5-bis((E)-(2-hydroxynaphthalen-1-yl)diazenyl)-1-(4-bromophenyl)-1H-pyrrole-3,4-dicarbaldehyde 5d:
Light gray; M. F.: $C_{32}H_{20}BrN_5O_4$; Mol. Wt.: 618.44 ; Percent yield: 69; Melting point (^{0}C): 216-218; FTIR (cm^{-1}): 1690 (>C=O stretch, aldehyde), 2712 (H-C=O; C-H stretch), 3240 (C-H stretch, aromatics), 1644 (-C=C- stretch), 3076 (C-H stretch, aromatics), 1479 (C-C stretch, in ring aromatics), 3595 (O-H stretch, aromatic phenol), 1480 (-N=N- stretch), 610 (C-Br stretch); ^{1}HNMR (δ ppm): 9.5 (s, 2H, CHO), 5.1 (s, 2H, Ar-OH), 7.2 (d, 2H, Ar-H), 7.4 (d, 2H, Ar-H), 7.0 (d, 2H, Ar-H), 7.6 (m, 4H, Ar-H), 7.3 -7.5 (m, 6H, Ar-H).

2,5-bis((E)-(2-hydroxynaphthalen-1-yl)diazenyl)-1-(2-nitrophenyl)-1H-pyrrole-3,4-dicarbaldehyde 5e:
Dark brown; M. F.: $C_{32}H_{20}N_6O_6$; Mol. Wt.: 584.54; Percent yield: 60; Melting point (^{0}C): 171-173; FTIR (cm^{-1}): 1713 (>C=O stretch, aldehyde), 2802 (H-C=O; C-H stretch), 3338 (C-H stretch, aromatics), 1685 (-C=C- stretch), 2990 (C-H stretch, aromatics), 1540 (C-C stretch, in ring aromatics), 3512 (O-H stretch, aromatic phenol), 1510 (-N=N- stretch), 1280 (N-O symmetric stretch), 1525 (N-O asymmetric stretch); ^{1}HNMR (δ ppm): 9.5 (s, 2H, CHO), 5.1 (s, 2H, Ar-OH), 7.0 (d, 2H, Ar-H), 7.2-7.3 (m, 4H, Ar-H), 7.5-7.7 (m, 9H, Ar-H), 8.2 (m, 1H, Ar-H).

2,5-bis((E)-(2-hydroxynaphthalen-1-yl)diazenyl)-1-(3-nitrophenyl)-1H-pyrrole-3,4-dicarbaldehyde 5f:
Brown; M. F.: $C_{32}H_{20}N_6O_6$; Mol. Wt.: 584.54; Percent yield: 66; Melting point (^{0}C): 210-212; FTIR (cm^{-1}): 1680 (>C=O stretch, aldehyde), 2770 (H-C=O; C-H stretch), 3308 (C-H stretch, aromatics), 1670 (-C=C- stretch), 3110 (C-H stretch, aromatics), 1464 (C-C stretch, in ring aromatics), 3235 (O-H stretch, aromatic phenol), 1455 (-N=N- stretch), 1298 (N-O symmetric stretch), 1545 (N-O asymmetric stretch); ^{1}HNMR (δ ppm): 9.8 (s, 2H, CHO), 5.4 (s, 2H, Ar-OH), 7.1 (d, 2H, Ar-H), 7.2-7.3 (m, 4H, Ar-H), 7.5-7.6 (m, 8H, Ar-H), 8.2 (d, 2H, Ar-H).

2,5-bis((E)-(2-hydroxynaphthalen-1-yl)diazenyl)-1-(4-nitrophenyl)-1H-pyrrole-3,4-dicarbaldehyde 5g:
Dark brown; M. F.: $C_{32}H_{20}N_6O_6$; Mol. Wt.: 584.54; Percent yield: 76; Melting point (^{0}C): 224-226; FTIR (cm^{-1}): 1682 (>C=O stretch, aldehyde), 2810 (H-C=O; C-H stretch), 3290 (C-H stretch, aromatics), 1700 (-C=C- stretch), 3072 (C-H stretch, aromatics), 1502 (C-C stretch, in ring aromatics), 3279 (O-H stretch, aromatic phenol), 1440 (-N=N- stretch), 1318 (N-O symmetric stretch), 1550 (N-O asymmetric stretch); ^{1}HNMR (δ ppm): 10.0 (s, 2H, CHO), 5.2 (s, 2H, Ar-OH), 6.9 (d, 2H, Ar-H), 7.2-7.3 (m, 4H, Ar-H), 7.5-7.6 (m, 8H, Ar-H), 8.3 (d, 2H, Ar-H).

2,5-bis((E)-(2-hydroxynaphthalen-1-yl)diazenyl)-1-(4-hydroxyphenyl)-1H-pyrrole-3,4-dicarbaldehyde 5h:
Bright Red; M. F.: $C_{32}H_{21}N_5O_5$; Mol. Wt.: 555.54; Percent yield: 71; Melting point (^{0}C): 261-263; FTIR (cm^{-1}): 1708 (>C=O stretch, aldehyde), 2790 (H-C=O; C-H stretch), 3346 (C-H stretch, aromatics), 1637 (-C=C- stretch), 2995 (C-H stretch, aromatics), 1603 (C-C stretch, in ring aromatics), 3500, 3600 (O-H stretch, aromatic phenol), 1475 (-N=N- stretch); ^{1}HNMR (δ ppm): 9.8 (s, 2H, CHO), 5.0 (s, 1H, Ar-H), 5.3 (s, 2H, Ar-OH), 6.7 (d, 2H, Ar-H), 7.0 (d, 2H, Ar-H), 7.1 (d, 2H, Ar-H), 7.2-7.3 (m, 4H, Ar-H), 7.5-7.6 (m, 6H, Ar-H).

2,5-bis((E)-(2-hydroxynaphthalen-1-yl)diazenyl)-1-(p-tolyl)-1H-pyrrole-3,4-dicarbaldehyde 5i:
Reddish brown; M. F.: $C_{33}H_{23}N_5O_4$; Mol. Wt.: 553.57; Percent yield: 70; Melting point (^{0}C): 266-268; FTIR (cm^{-1}): 1692 (>C=O stretch, aldehyde), 2823 (H-C=O; C-H stretch), 3261 (C-H stretch, aromatics), 1672 (-C=C- stretch), 3040 (C-H stretch, aromatics), 1490 (C-C stretch, in ring aromatics), 3550 (O-H stretch, aromatic phenol), 1500 (-N=N- stretch), 1450, 1355 (C-H bend and rock, aromatic alkyl); ^{1}HNMR (δ ppm): 9.7 (s, 2H, CHO), 5.0 (s, 2H, Ar-OH), 7.5 (d, 2H, Ar-H), 7.6 (d, 4H, Ar-H), 7.0-7.3 (m, 10H, Ar-H), 2.4 (s, 3H, Ar-CH_3).

2,5-bis((E)-(2-hydroxynaphthalen-1-yl)diazenyl)-1-(4-methoxyphenyl)-1H-pyrrole-3,4-dicarbaldehyde 5j:
Violet; M. F.: $C_{33}H_{23}N_5O_5$; Mol. Wt.: 569.57; Percent yield: 66; Melting point (^{0}C): 230-232; FTIR (cm^{-1}): 1720 (>C=O stretch, aldehyde), 2698 (H-C=O; C-H stretch), 3390 (C-H stretch, aromatics), 1690 (-C=C- stretch), 3121 (C-H stretch, aromatics), 1585 (C-C stretch, in ring aromatics), 3400 (O-H stretch, aromatic phenol), 1482 (-N=N- stretch), 1469, 1370 (C-H bend and rock, alkyl); ^{1}HNMR (δ ppm): 9.8 (s, 2H, CHO), 4.9 (s, 2H, Ar-OH), 6.8 (d, 2H, Ar-H), 7.0 (d, 2H, Ar-H), 7.2-7.3 (m, 6H, Ar-H), 7.5 (d, 2H, Ar-H), 7.6 (d, 4H, Ar-H), 3.8 (s, 3H, Ar-OCH_3).

Results and Discussion

Chemistry:

The starting compounds of azo vinyl aldehyde 5**a-j** were prepared by the reaction of 2,5-diazido-1-substitutedphenyl-1H-pyrrole-3,4-dicarbaldehyde **2a-j** using sodium dithionite. Diazo coupling reaction were carried out over 2,5-diamino-1-substitutedphenyl-1H-pyrrole-3,4-dicarbaldehyde **3a-j** gives the diazonium salt, followed by the coupling reaction using 2-napthol. The series of 2,5-bis((E)-(2-hydroxynaphthalen-1-yl)diazenyl)-1-(substituted phenyl)-1H-pyrrole-3,4-dicarbaldehyde **5a-j** were synthesized in reasonable yields. The structure of azo vinyl was confirmed by FT-IR and ^{1}HNMR analysis.

Antimicrobial susceptibility test (5a-j):

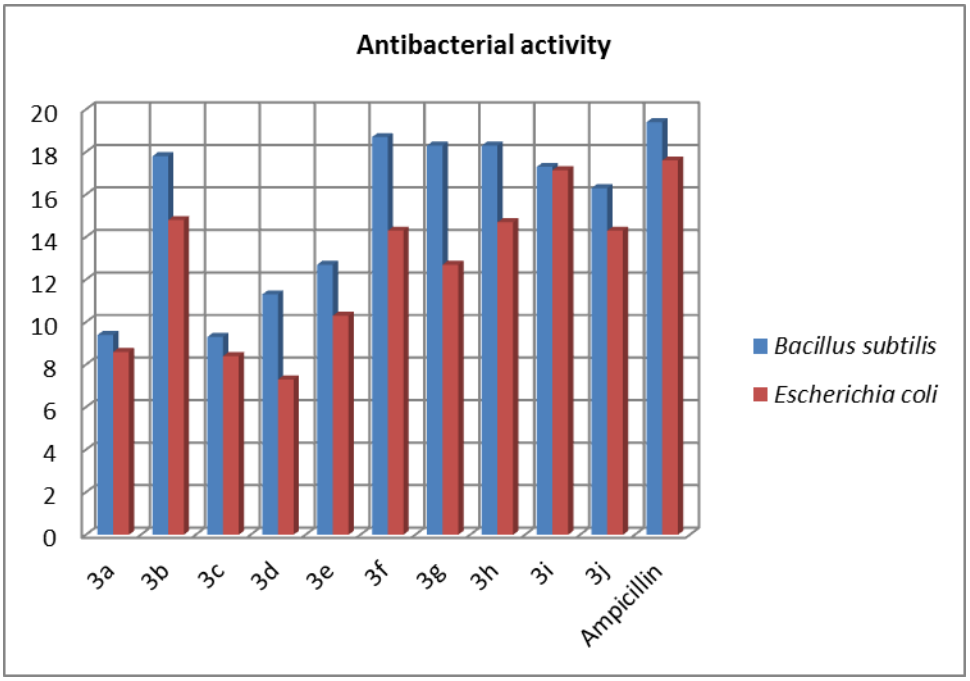
The disc diffusion method was used to screen the antimicrobial activity. In vitro antimicrobial activity was screened by using Mueller Hinton Agar (MHA) obtained from Hi-media. The MHA plates were prepared by pouring 15 mL of molten media into sterile Petri plates. The plates were allowed to solidify for 5 minutes and 0.1 % inoculum suspension was swabbed uniformly and the inoculum was allowed to dry for 5 minutes. The fix concentrations were loaded on 6 mm sterile disc. The loaded disc was placed on the surface of the medium and the compound was allowed to diffuse for 5 minutes and the plates were kept for incubation at 37°C for 24 hrs. At the end of incubation, inhibition

zones formed around the disc were measured with the transparent ruler in millimeter. All the synthesized compounds **5a-j** were screened for their antibacterial activity against gram- positive bacteria *Bacillus subtilis* (MCMB-310) and gram negative bacteria *Escherichia coli* (MCMB-301) using DMF solvent. Ampicillin was used as standard and results were shown in the **graph 1**. The same procedure was followed for the fungus using Potato Dextrose Agar (PDA) as a nutrient medium. The antifungal activities against *Candida albicans* (NCIM-3471) and *Aspergillus niger* (NCIM- 545) strains using DMSO solvent in using Amphotericin-B as a standard revealed in the **graph 2**. All the results of the synthesized compounds were carried out by the triplicate format N=3 with Mean ± SD.
The calculated data were tabulated in **Table 1**;

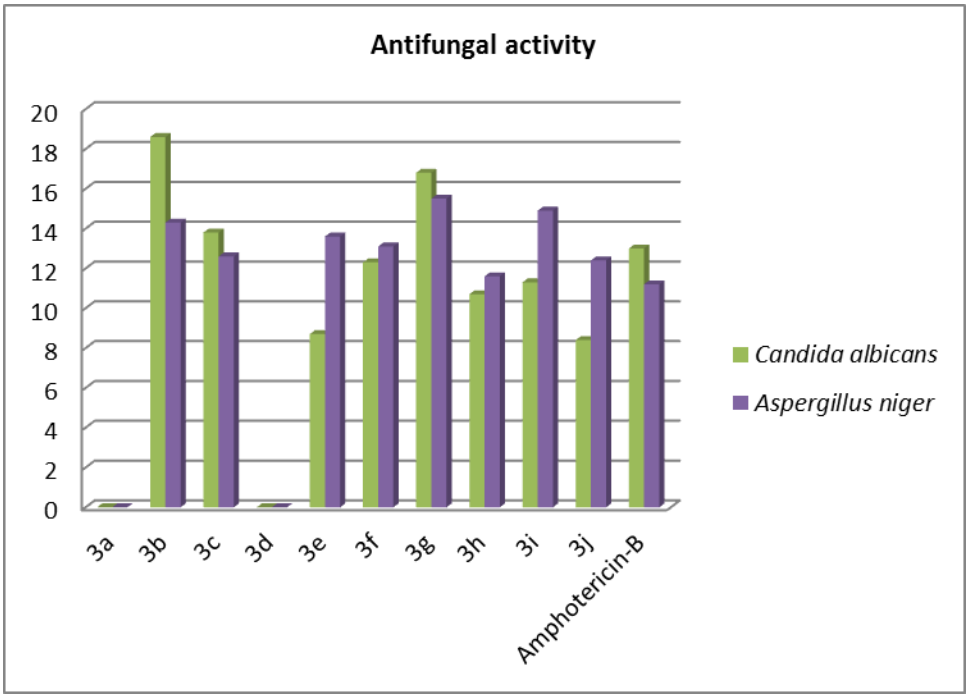
Table 1 Antimicrobial activity of synthesized diazo compound

Entry	Zone diameter in mm (Mean±S.D.)			
	Bacillus subtilis	***Escherichia coli***	***Candida albicans***	***Aspergillus niger***
3a	9.38±0.24	8.55±0.28	--	--
3b	17.76±1.25	14.84±0.61	18.57 ± 0.27	14.27 ± 0.49
3c	9.33±1.22	8.43±0.57	13.83 ± 0.22	12.56 ± 0.78
3d	11.33±0.13	7.26±1.15	--	--
3e	12.66±0.33	10.32±0.52	8.69 ± 0.39	13.63 ± 0.39
3f	18.66±0.5	14.33±0.53	12.34 ± 0.34	13.15 ± 3.76
3g	18.33±0.55	12.66±0.23	16.77 ± 0.40	15.45 ± 0.39
3h	18.33±0.54	14.66±1.04	10.68 ± 0.22	11.65 ± 1.13
3i	17.33±0.37	17.11±0.03	11.30 ± 0.32	14.95 ± 3.20
3j	16.33±0.57	14.33±0.57	8.40 ± 0.04	12.37 ± 0.64
Ampicillin	19.36 ±0.04	17.63 ±0.06	--	--
Amphotericin-B	--	--	12.98 ± 0.44	11.38 ± 0.54

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



Graph 1 Antibacterial activities of 5a-j



Graph 2: Antifungal activities of 5a-j

Conclusions

An entire new series of 2,5-bis((E)-(2-hydroxynaphthalen-1-yl)diazenyl)-1-(substituted phenyl)-1H-pyrrole-3,4-dicarbaldehyde **5a-j** have been synthesized in facile manner from 2,5-diazido-1-substitutedphenyl-1H-pyrrole-3,4-dicarbaldehyde **1a-j** in good yield. Based on our experimental findings, the new substituted azovinyl aldehyde derivatives containing cyclic imide moiety **5a-j** exhibiting excellent bactericidal and fungicidal potentials could be proposed for dyeing and antimicrobial finishing for silk, wool, cotton, and polyester fabrics.

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Research Article

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Green synthesis and antimicrobial evaluation of N-aryl cyclic imides using silica bound benzyl chloride mediated solid phase synthesis

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Abstract: A method for adopting a solid-phase strategy for the synthesis of N-substituted succinimides and glutarimides is described here; using the silica-bound benzoyl chloride mediated solid phase synthesis. We have optimized and used a simple silica bound benzyl chloride as a dehydrating agent in cyclisation reaction with N-aryl immic acids by cyclodehydration. The main advantage of this method is the silica-grafted reagent was simply recovered after the reaction and reused several times made this method as the environmental benign chemical method of synthesis of N-aryl cyclic imides.

Keywords: solid phase synthesis, cyclodehydration, immic acids, cyclic imides.

INTRODUCTION

The succinimides and glutarimides are the structural feature of many alkaloids and starting material for many drug synthesis[1-4]. Many compounds of succinamide and glutarimide are mentioned in clinical and preclinical analysis[5-13]. The substituted pyrrolidine is one of the structural subunits in

natural compounds[14-15]. Several substituted pyrrolidine display important biological properties like anticancer[16], inhibitors of alpha-glucosidase[17], antimicrobial[18] and other applications[19-25]. The structural diversity and industrial and biological importance of cyclic imides have made them an attractive target for synthesis over many and justify continuing efforts in the development of new synthetic strategy[26-44].

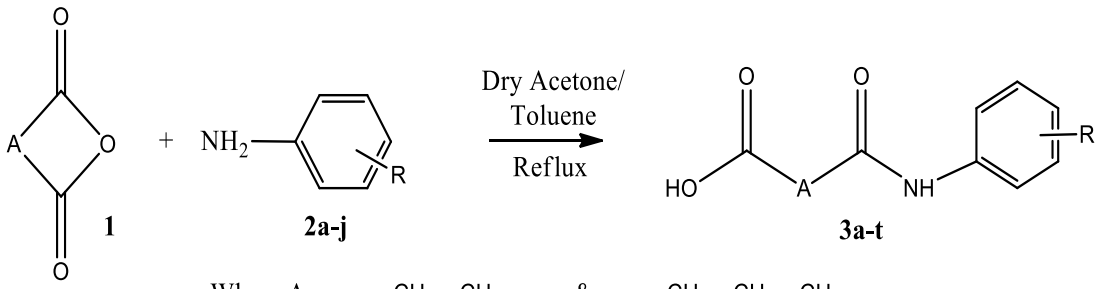
There are several procedures for synthesis of cyclic imide available in the literature. Low to a moderate yield of cyclic imide where directly obtained from the condensation reaction of primary aromatic amines with succinic or glutaric anhydride at an elevated temperature where reported in literature[45-47]. The most convenient route of synthesis of cyclic its involves the partial condensation of the aromatic amine with succinic or glutaric anhydride at an affordable low temperature (60 to 80^{0}C) followed with succinic or glutaric anhydride at affordable low temperature followed by dehydration-cyclization to form cyclic imides. There are several dehydrating agents like DCC[48], benzyl chloride[49], acetyl chloride[50-51], cyanuric chloride[52], acetic anhydride[53-56], sulphonic acid[57] etc. where utilize so far having the difficulties of handling, separation, and recovery after the reaction and may lead to environmental pollution. To overcome these disadvantages we intended to use the synthesis based on solid support. In general, the solid phase synthesis refers to the method in which the substrates are bonded into the solid support or bead and synthesized step by step in reactant solution compared with the conventional synthesis in the liquid state. The solid support is easier to remove excess reactant or byproduct from the product. The silica bound benzyl chloride as a silica grafted reagent is used for cyclo-dehydration of immic acids. Therefore we use it as an effective and reusable environmentally benign cyclo-dehydrating agent for green synthesis of N-aryl cyclic imides.

In this method use of 4-hydroxy benzoic acid the molecule having to functional group is used the phenolic proton has participated in the formation of the linkage between the silica and the benzoic acid moiety. The overall reaction of development for silica bonded benzyl chloride is illustrated in experimental section. This reaction proceeds into three steps in the first type the reaction takes place in between Silica Gel powder and thionyl chloride which gives silica chloride[58-59]. The silica chloride was then allowed to react with 4-hydroxy benzoic acid to form the silica bound benzoic acid (SBBA). The SBBA then wash with dichloromethane to remove excess of 4-hydroxy benzoic acid. In the last step, the silica bound benzoyl chloride was obtained from the reaction of SBBA with thionyl chloride.

EXPERIMENTAL

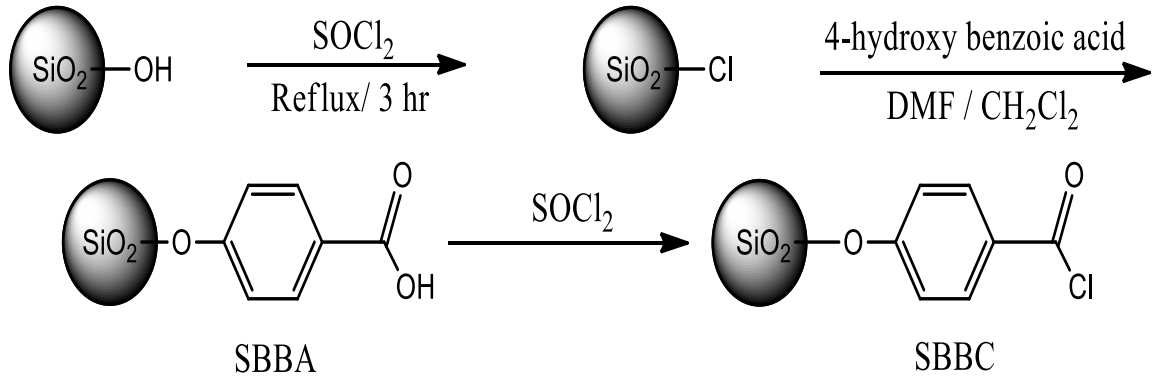
Materials and Reagents: The Melting points of all the synthesized compounds were recorded in open glass capillaries and were uncorrected. IR spectra were recorded on Lambda 7600 FTIR spectrophotometer. ^{1}H NMR spectra were recorded on Bruker 500 MHz in DMSO-d6 using TMS as an internal standard. The required N-aryl immic acids were prepared quantitatively from condensation between succinic and glutaric anhydride and an equivalent amount of an aromatic amine in refluxing toluene. The reaction was monitored by TLC which was accomplished by using pre-coated silica gel aluminum plates with the mixture of hexane: ethyl acetate as a solvent phase. Chemical purchased were used as received.

General procedure for preparation of immic acids: In this proposed work we initially use aniline and substituted anilines will be used to synthesize the succinimide and glutarimide by the condensation of succinic anhydride and glutaric anhydride in dry acetone or toluene under reflux gives acid amide intermediate as 3(substitutedphenylcarboxyl) propionic acid **3a-j** and 4(substitutedphenylcarboxyl) butanoic acid **3k-t** respectively (**Scheme 1**).



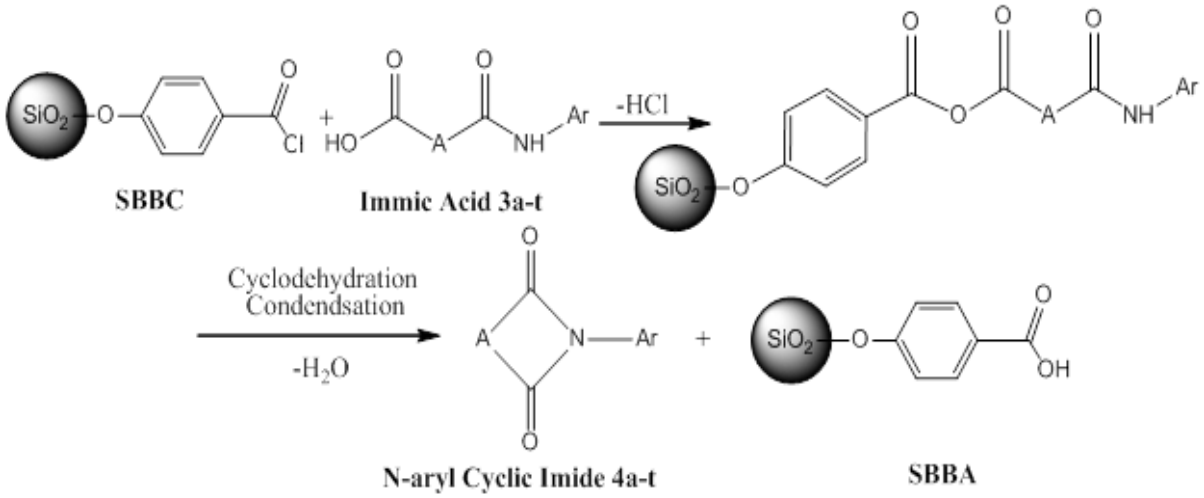
Scheme 1 **Synthesis of immic acid**

General procedure for preparation of solid support Silica bound benzoyl chloride (SBBC): The thionyl chloride (50 ml) was added into 10 g of well-dried fine powders of silica gel 60 in a round bottom flask. The mixture was refluxed for about 3 hrs and then distilled to remove the excess thionyl chloride. To 8 g of obtained white powders of silica chloride, a solution of 4-hydroxybenzoic acid (4 g) in dichloromethane (60 ml) and DMF (8 ml) was added and then refluxed for about 6 hrs. The suspension was filtered to separate the SBBA powders, and the precipitate was washed with 40 ml of 1:9 mixture of DMF-CH_2Cl_2 and dried at around 100^0C to give 11.24 g of SBBA. Thionyl chloride (50 ml) was added to 10 g of SBBA and refluxed for about 3 hrs (**Scheme 2**). The excess thionyl chloride was removed at reduced pressure, and the obtained white powder of SBBC (11.07 g) was stored in a dry bottle.



Scheme 2 **Preparation of Solid Support (cyclodehydrating agent-SBBC) for synthesis**

General procedure for preparation of cyclic imides: In to the mixture of N-aryl immic acid **3a-t** (1mmol) in dichloromethane, 1 g of solid support SBBC was added. The mixture was refluxed according to the time mentioned in **Table 1** and then was hot filtered. The filtered solids were washed with additional dichloromethane (20 ml). The combined solutions of dichloromethane were evaporated, and the residue was further purified by recrystallization using ethanol gives the N-aryl cyclic imides **4a-t** (**Scheme 3**). The residue of SBBC was renewed by washing it with 5 ml of dichloromethane, drying it and then refluxing it (3 hrs) in 8 ml of $SOCl_2$. The excess $SOCl_2$ was removed under reduced pressure.



Scheme 3 Synthesis of cyclic imides using solid support-SBBC

Table 1: Results of reaction between 3a–t and SBBC

Product	Anhydride	R	Reaction Time (min)	M.P. (^{0}C)	Yield (%)
4a	SA	4H	25	154-156	75
4b	SA	3Cl	25	116-118	78
4c	SA	4Cl	20	162-164	82
4d	SA	4Br	25	174-176	84
4e	SA	2NO_2	40	148-150	66
4f	SA	3NO_2	30	158-160	72
4g	SA	4NO_2	35	210-212	68
4h	SA	4OH	20	163-165	86
4i	SA	4CH_3	15	142-144	88
4j	SA	4OCH_3	20	157-159	85
4k	GA	4H	30	120-122	70
4l	GA	3Cl	30	130-132	68
4m	GA	4Cl	25	123-125	78
4n	GA	4Br	35	145-147	79
4o	GA	2NO_2	50	160-162	60
4p	GA	3NO_2	35	134-136	67
4q	GA	4NO_2	45	204-206	61
4r	GA	4OH	25	124-126	78
4s	GA	4CH_3	20	179-181	80
4t	GA	4OCH_3	30	138-140	78

Where SA=Succinic anhydride and GA=Glutaric anhydride

1-phenylpyrrolidine-2,5-dione 4a: M. F.: $C_{10}H_9NO_2$; Mol. Wt.: 175.18; FTIR (cm^{-1}): 1710 and 1778 (>C=O 2-Peaks), 2932 (cyclic CH_2-CH_2), 1295 (cyclic imines), 1459, 1512 and 1598 (aromatic -C=C- stretch); ^{1}H NMR: δ 2.87 (4H, m, *J* = 15.0, 8.1, 4.3 Hz), 7.31 (1H, tt, *J* = 7.5, 1.3 Hz), 7.42 (2H, m, *J* = 8.2, 1.6, 1.3, 0.5 Hz), 7.63 (2H, m, *J* = 8.2, 7.5, 1.4, 0.5 Hz).

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1-(3-chlorophenyl) pyrrolidine-2,5-dione 4b: M. F.: $C_{10}H_8ClNO_2$; Mol. Wt.: 209.62; FTIR (cm^{-1}):

1713 and 1775 (>C=O 2-Peaks), 2982 (cyclic CH_2-CH_2), 1308 (cyclic imines), 1492, 1530 and 1584 (aromatic -C=C- stretch), 1095 (Ar-Cl); ^{1}H NMR: δ 2.88 (4H, m, *J* = 15.1, 8.1, 4.3 Hz), 7.23 (1H, m, *J* = 8.1, 1.8, 1.7 Hz), 7.37-7.53 (2H, 7.42 (m, *J* = 8.2, 8.1, 0.6 Hz), 7.49 (dt, *J* = 8.2, 1.7 Hz)), 7.72 (1H, m, *J* = 1.8, 1.7, 0.6 Hz).

1-(4-chlorophenyl)pyrrolidine-2,5-dione 4c: M. F.: $C_{10}H_8ClNO_2$; Mol. Wt.: 209.62; FTIR (cm^{-1}): 1703 and 1768 (>C=O 2-Peaks), 2982 (cyclic CH_2-CH_2), 1305 (cyclic imines), 1498, 1523 and 1582 (aromatic -C=C- stretch), 1098 (Ar-Cl); ^{1}H NMR: δ 2.87 (4H, m, *J* = 15.0, 8.1, 4.3 Hz), 7.48-7.55 (4H, 7.52 (m, *J* = 8.2, 1.5, 0.5 Hz), 7.51 (m, *J* = 8.2, 1.7, 0.5 Hz).

1-(4-bromophenyl)pyrrolidine-2,5-dione 4d: M. F.: $C_{10}H_8BrNO_2$; Mol. Wt.: 254.08 FTIR (cm^{-1}): 1696 and 1778 (>C=O 2-Peaks), 2942 (cyclic CH_2-CH_2), 1298 (cyclic imines), 1492, 1513 and 1592 (aromatic -C=C- stretch), 1072 (Ar-Br); ^{1}H NMR: δ 2.92 (4H, m, *J* = 15.0, 8.1, 4.3 Hz), 7.44-7.54 (4H, 7.47 (m, *J* = 8.2, 1.4, 0.5 Hz), 7.51 (m, *J* = 8.2, 1.7, 0.5 Hz).

1-(2-nitrophenyl)pyrrolidine-2,5-dione 4e: M. F.: $C_{10}H_8N_2O_4$; Mol. Wt.: 220.18; FTIR (cm^{-1}): 1616 and 1678 (>C=O 2-Peaks), 2892 (cyclic CH_2-CH_2), 1302 (cyclic imines), 1510, 1563 and 1598 (aromatic -C=C- stretch), 1503 (Ar-NO_2); ^{1}H NMR: δ 2.90 (4H, m, *J* = 14.9, 8.1, 4.3 Hz), 7.40-7.50 (2H, 7.47 (m, *J* = 8.3, 2.0, 0.5 Hz), 7.45 (m, *J* = 8.2, 7.5, 2.0 Hz)), 7.58 (1H, m, *J* = 8.3, 7.5, 1.8 Hz), 8.09 (1H,m, *J* = 8.2, 1.8, 0.5 Hz).

1-(3-nitrophenyl)pyrrolidine-2,5-dione 4f: M. F.: $C_{10}H_8N_2O_4$; Mol. Wt.: 220.18; FTIR (cm^{-1}): 1614 and 1668 (>C=O 2-Peaks), 2896 (cyclic CH_2-CH_2), 1312 (cyclic imines), 1518, 1573 and 1592 (aromatic -C=C- stretch), 1513 (Ar-NO_2); ^{1}H NMR: δ 2.88 (4H, m, *J* = 15.1, 8.1, 4.3 Hz), 7.55 (1H, m, *J* = 8.2, 8.2, 0.4 Hz), 7.65 (1H, dt, *J* = 8.2, 1.8 Hz), 8.04 (1H, m, *J* = 8.2, 1.8, 1.7 Hz), 8.11 (1H, m, *J* = 1.8, 1.7, 0.4 Hz).

1-(4-nitrophenyl)pyrrolidine-2,5-dione 4g: M. F.: $C_{10}H_8N_2O_4$; Mol. Wt.: 220.18; FTIR (cm^{-1}): 1622 and 1683 (>C=O 2-Peaks), 2899 (cyclic CH_2-CH_2), 1318 (cyclic imines), 1512, 1570 and 1591 (aromatic -C=C- stretch), 1511 (Ar-NO_2); ^{1}H NMR: δ 2.88 (4H, m, *J* = 15.1, 8.1, 4.3 Hz), 7.55 (1H, m, *J* = 8.2, 8.2, 0.4 Hz), 7.65 (1H, dt, *J* = 8.2, 1.8 Hz), 8.04 (1H, m, *J* = 8.2, 1.8, 1.7 Hz), 8.11 (1H, m, *J* = 1.8, 1.7, 0.4 Hz).

1-(4-hydroxyphenyl)pyrrolidine-2,5-dione 4h: M. F.: $C_{10}H_9NO_3$; Mol. Wt.: 191.18; FTIR (cm^{-1}): 1708 and 1760 (>C=O 2-Peaks), 2995 (cyclic CH_2-CH_2), 1290 (cyclic imines), 1489, 1532 and 1608 (aromatic -C=C- stretch); 3522, 3610 (O-H stretch, aromatic phenol); ^{1}H NMR: δ 2.87 (4H, m, *J* = 15.0, 8.1, 4.3 Hz), 6.73 (2H, m, *J* = 8.8, 2.3, 0.5 Hz), 7.67 (2H, m, *J* = 8.8, 1.9, 0.5 Hz).

1-(p-tolyl)pyrrolidine-2,5-dione 4i: M. F.: $C_{11}H_{11}NO_2$; Mol. Wt.: 189.21; FTIR (cm^{-1}): 1712 and 1764 (>C=O 2-Peaks), 2990 (cyclic CH_2-CH_2), 1289 (cyclic imines), 3261 (C-H stretch, aromatics), 1490, 1523 and 1581 (aromatic -C=C- stretch); 1448, 1352 (C-H bend and rock, aromatic alkyl); ^{1}H NMR: δ 2.22 (3H, s), 2.87 (4H, m, *J* = 15.0, 8.1, 4.3 Hz), 7.33 (2H, m, *J* = 8.1, 1.3, 0.5 Hz), 7.47 (2H, m, *J* = 8.1, 1.5, 0.5 Hz).

1-(4-methoxyphenyl)pyrrolidine-2,5-dione 4j: M. F.: $C_{11}H_{11}NO_3$; Mol. Wt.: 205.20; FTIR (cm^{-1}): 1710 and 1769 (>C=O 2-Peaks), 2969 (cyclic CH_2-CH_2), 1309 (cyclic imines), 3261 (C-H stretch, aromatics), 1469, 1513 and 1601 (aromatic -C=C- stretch), 1180 (Ar-OCH_3); ^{1}H NMR: δ 2.87 (4H, m, *J* = 15.0, 8.1, 4.3 Hz), 3.77 (3H, s), 6.66 (2H, m, *J* = 8.8, 1.7, 0.5 Hz), 7.66 (2H, m, *J* = 8.8, 1.9, 0.5 Hz).

1-phenylpiperidine-2,6-dione 4k: M. F.: $C_{11}H_{11}NO_2$; Mol. Wt.: 189.21; FTIR (cm^{-1}): 1691 and 1778 (>C=O 2-Peaks), 2972 (cyclic CH_2-CH_2), 1312 (cyclic imines), 1489, 1532 and 1588 (aromatic -C=C- stretch); ^{1}H NMR: δ 2.87 (4H, m, *J* = 15.0, 8.1, 4.3 Hz), 3.77 (3H, s), 6.66 (2H, m, *J* = 8.8, 1.7, 0.5 Hz), 7.66 (2H, m, *J* = 8.8, 1.9, 0.5 Hz).

1-(3-chlorophenyl)piperidine-2,6-dione 4l: M. F.: $C_{11}H_{10}ClNO_2$; Mol. Wt.: 223.65; FTIR (cm^{-1}): 1721 and 1784 (>C=O 2-Peaks), 2978 (cyclic CH_2-CH_2), 1302 (cyclic imines), 1498, 1530 and 1591 (aromatic -C=C- stretch), 1092 (Ar-Cl); ^{1}H NMR: δ 1.92 (2H, m, *J* = 13.4, 3.3, 2.3 Hz), 2.40 (4H, m, *J* = 14.2, 10.2, 3.3 Hz), 7.23 (1H, m, *J* = 8.1, 1.8, 1.7 Hz), 7.37-7.53 (2H, 7.42 (m, *J* = 8.2, 8.1, 0.6 Hz), 7.50 (dt, *J* = 8.2, 1.7 Hz)), 7.72 (1H, m, *J* = 1.8, 1.7, 0.6 Hz).

1-(4-chlorophenyl)piperidine-2,6-dione 4m: M. F.: $C_{11}H_{10}ClNO_2$; Mol. Wt.: 223.65; FTIR (cm^{-1}): 1705 and 1788 (>C=O 2-Peaks), 2982 (cyclic CH_2-CH_2), 1299 (cyclic imines), 1500, 1527 and 1595 (aromatic -C=C- stretch), 1093 (Ar-Cl); ^{1}H NMR: δ 1.92 (2H, m, *J* = 13.4, 3.3, 2.3 Hz), 2.40 (4H, m, *J* = 14.2, 10.2, 3.3 Hz), 7.23 (1H, m, *J* = 8.1, 1.8, 1.7 Hz), 7.37-7.53 (2H, 7.42 (m, *J* = 8.2, 8.1, 0.6 Hz), 7.50 (dt, *J* = 8.2, 1.7 Hz)), 7.72 (1H, m, *J* = 1.8, 1.7, 0.6 Hz).

1-(4-bromophenyl)piperidine-2,6-dione 4n: M. F.: $C_{11}H_{10}BrNO_2$; Mol. Wt.: 268.10; FTIR (cm^{-1}): 1691 and 1768 (>C=O 2-Peaks), 2982 (cyclic CH_2-CH_2), 1296 (cyclic imines), 1493, 1522 and 1594 (aromatic -C=C- stretch), 1078 (Ar-Br); ^{1}H NMR: δ 1.92 (2H, m, *J* = 13.4, 3.3, 2.3 Hz), 2.40 (4H, m, *J* = 14.2, 10.2, 3.3 Hz), 7.44-7.54 (4H, 7.47 (m, *J* = 8.2, 1.5, 0.5 Hz), 7.51 (m, *J* = 8.2, 1.7, 0.5 Hz)).

1-(2-nitrophenyl)piperidine-2,6-dione 4o: M. F.: $C_{11}H_{10}N_2O_4$; Mol. Wt.: 234.20; FTIR (cm^{-1}): 1711 and 1754 (>C=O 2-Peaks), 2965 (cyclic CH_2-CH_2), 1312 (cyclic imines), 1510, 1592 and 1601 (aromatic -C=C- stretch), 1496 (Ar-NO_2); ^{1}H NMR: δ 1.93 (2H, m, *J* = 13.4, 3.3, 2.3 Hz), 2.42 (4H, m, *J* = 14.2, 10.2, 3.3 Hz), 7.41-7.51 (2H, 7.47 (m, *J* = 8.3, 2.0, 0.5 Hz), 7.46 (m, *J* = 8.2, 7.5, 2.0 Hz)), 7.58 (1H, m, *J* = 8.3, 7.5, 1.8 Hz), 8.09 (1H, m, *J* = 8.2, 1.8, 0.5 Hz).

1-(3-nitrophenyl)piperidine-2,6-dione 4p: M. F.: $C_{11}H_{10}N_2O_4$; Mol. Wt.: 234.20; FTIR (cm^{-1}): 1714 and 1764 (>C=O 2-Peaks), 2956 (cyclic CH_2-CH_2), 1318 (cyclic imines), 1512, 1594 and 1604 (aromatic -C=C- stretch), 1498 (Ar-NO_2); ^{1}H NMR: δ 1.92 (2H, m, *J* = 13.4, 3.3, 2.3 Hz), 2.40 (4H, m, *J* = 14.2, 10.2, 3.3 Hz), 7.55 (1H, m, *J* = 8.2, 8.2, 0.4 Hz), 7.65 (1H, dt, *J* = 8.2, 1.8 Hz), 8.04 (1H, m, *J* = 8.2, 1.8, 1.7 Hz), 8.25 (1H, m, *J* = 1.8, 1.7, 0.4 Hz).

1-(4-nitrophenyl)piperidine-2,6-dione 4q: M. F.: $C_{11}H_{10}N_2O_4$; Mol. Wt.: 234.20; FTIR (cm^{-1}): 1721 and 1745 (>C=O 2-Peaks), 2972 (cyclic CH_2-CH_2), 1302 (cyclic imines), 1518, 1596 and 1612 (aromatic -C=C- stretch), 1502 (Ar-NO_2); ^{1}H NMR: δ 1.92 (2H, m, *J* = 13.4, 3.3, 2.3 Hz), 2.42 (4H, m, *J* = 14.2, 10.2, 3.3 Hz), 7.58 (2H, m, *J* = 8.6, 2.7, 0.4 Hz), 8.09 (2H, m, *J* = 8.6, 1.9, 0.4 Hz).

1-(4-hydroxyphenyl)piperidine-2,6-dione 4r: M. F.: $C_{11}H_{11}NO_3$; Mol. Wt.: 205.20; FTIR (cm^{-1}): 1711 and 1744 (>C=O 2-Peaks), 2962 (cyclic CH_2-CH_2), 1309 (cyclic imines), 1512, 1594 and 1604 (aromatic -C=C- stretch), 3502, 3618 (O-H stretch, aromatic phenol); ^{1}H NMR: δ 1.92 (2H, m, *J* = 13.4, 3.3, 2.3 Hz), 2.39 (4H, m, *J* = 14.2, 10.2, 3.3 Hz), 6.73 (2H, m, *J* = 8.8, 2.3, 0.5 Hz), 7.68 (2H, m, *J* = 8.8, 1.9, 0.5 Hz).

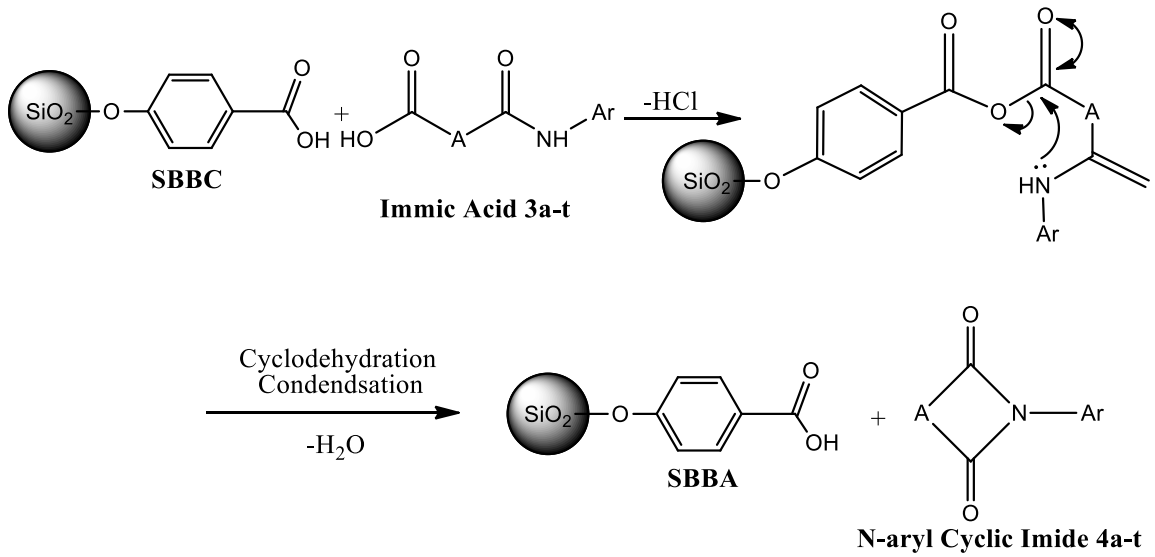
1-(p-tolyl)piperidine-2,6-dione 4s: M. F.: $C_{12}H_{13}NO_2$; Mol. Wt.: 203.23; FTIR (cm^{-1}): 1696 and 1748 (>C=O 2-Peaks), 2965 (cyclic CH_2-CH_2), 1289 (cyclic imines), 3212 (C-H stretch, aromatics), 1532, 1592 and 1662 (aromatic -C=C- stretch); 1352, 1448 (C-H bend and rock, aromatic alkyl); ^{1}H NMR: δ 1.92 (2H, m, *J* = 13.4, 10.2, 3.2 Hz), 2.22 (3H, s), 2.40 (4H, m, *J* = 14.2, 10.2, 3.3 Hz), 7.33 (2H, m, *J* = 8.1, 1.3, 0.5 Hz), 7.47 (2H, m, *J* = 8.1, 1.5, 0.5 Hz).

1-(4-methoxyphenyl)piperidine-2,6-dione 4t: M. F.: $C_{12}H_{13}NO_3$; Mol. Wt.: 219.23; FTIR (cm^{-1}): 1698 and 1749 (>C=O 2-Peaks), 2961 (cyclic CH_2-CH_2), 1311 (cyclic imines), 3256 (C-H stretch, aromatics), 1533, 1598 and 1660 (aromatic -C=C- stretch), 1184 (Ar-OCH_3); ^{1}H NMR: δ 1.92 (2H, m, *J* = 13.4, 10.2, 3.2 Hz), 2.39 (4H, m, *J* = 14.2, 10.2, 3.3 Hz), 3.76 (3H, s), 6.66 (2H, m, *J* = 8.8, 2.0, 0.5 Hz), 7.66 (2H, m, *J* = 8.8, 1.9, 0.5 Hz).

RESULTS AND DISCUSSION

Chemistry: The starting compounds N-aryl immic acids were prepared by the reaction of succinic anhydride and glutaric anhydride with aniline and substituted aniline by reflux in toluene as a solvent. Solid support was prepared by series of reaction between silica gel 60 with thionyl chloride and then reaction with 4-hydroxy bezoic acid. In final step silica bound benzoyl chloride were prepared by reaction of silica bound benzoic acid with thionyl chloride. The solid support finally use for cyclo-dehydration reaction of N-aryl immic acid gives N-aryl cyclic imide 4a-t in reasonable yields. The structure of N-aryl cyclic imides was confirmed by various analytical tools like FT-IR, 1H-NMR and elemental analysis. The infrared (IR), 1H-NMR, and MS data of all the products are in good agreement with their structures. In addition, the melting points correspond to those of the literature [32] as well as the authentic samples prepared from the previously conventional reported methods.

The possible mechanism of cyclo-dehydration reaction for the formation of cyclic imides is indicated in **Scheme 4**. This mechanism involves the formation of linkage betwwen immic acid and SBBC, which undergo thermal cyclo-elimination through intramolecular nucleophilic substitution of the nitrogen atom in favor of producing cyclic imidess with detaching SBBA. As we already mention the yield of product form in **Table 1** indicate that the substrates having electron-donating inductive or resonance effect at ortho and para position to the nitrogen substituent gave higher yields under the reaction conditions. This result clearly shows a direct dependence of reaction kinetics on electron density at the nitrogen atom and therefore we can concluded its nucleophilic character. To this end, it is reasonable to consider the thermal cyclo-elimination reaction as the rate-limiting step. Meanwhile, the starting materials, N-aryl immic acids, appear to be loaded more easily onto the solid-supported reagent.



Scheme 4 **Possible mechanism of cyclodehydration reaction**

Antimicrobial susceptibility test (4a-t): The disc diffusion method was used to screen the antimicrobial activity. In vitro antimicrobial activity was screened by using Mueller Hinton Agar (MHA) obtained from Hi-media. The MHA plates were prepared by pouring 15 ml of molten media into sterile Petri plates. The plates were allowed to solidify for 5 minutes and 0.1 % inoculum suspension was swabbed uniformly and the inoculum was allowed to dry for 5 minutes. The fix concentrations were loaded on 6 mm sterile disc. The loaded disc was placed on the surface of the medium and the compound was allowed to diffuse for 5 minutes and the plates were kept for incubation at 37°C for 24 hrs. At the end of incubation, inhibition zones formed around the disc were measured with the transparent ruler in millimeter. All the synthesized compounds **4a-t** were screened for their antibacterial activity against gram- positive bacteria *Bacillus subtilis* (MCMB-310) and gram negative bacteria *Escherichia coli* (MCMB-301) using DMF solvent. Ampicillin was used as standard and results were shown in the **Table 2**. The same procedure was followed for the fungus using Potato Dextrose Agar (PDA) as a nutrient medium. The antifungal activities against *Candida albicans* (NCIM-3471) and *Aspergillus niger* (NCIM- 545) strains using DMSO solvent in using Amphotericin-B as a standard revealed in the **Table 2**. All the results of the synthesized compounds were carried out by the triplicate format N=3 with Mean.

Table 2: Antimicrobial activity of synthesized diazo compound

Entry	Zone diameter in mm (Mean)			
	Bacillus subtilis	***Escherichia coli***	***Candida albicans***	***Aspergillus niger***
4a	8.74	9.12	10.12	11.34
4b	9.45	9.93	-	-
4c	10.12	12.24	-	-
4d	9.82	9.75	-	-
4e	10.42	8.38	-	-
4f	10.12	8.92	12.92	17.18
4g	8.22	8.94	-	-
4h	12.22	11.28	-	-
4i	10.10	10.66	10.26	12.24
4j	10.30	11.24	8.66	7.22
4k	9.88	10.22	8.12	10.34
4l	11.36	12.22	-	-
4m	12.66	12.22	-	-
4n	10.66	10.28	-	-
4o	11.34	12.24	-	-
4p	12.96	13.66	11.92	12.18
4q	10.22	12.24	-	-
4r	12.36	13.32	-	-
4s	10.52	10.22	8.26	10.24
4t	8.44	9.46	8.66	7.22
Ampicillin	14.22	12.22	-	-
Amphotericin-B	-	-	7.76	8.20

Keynote: Zone of inhibition measured in mm (Mean) (N=3) ('--' means no zone of inhibition)

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CONCLUSION

In this experiment, we utilize the greener approach for the synthesis of N-aryl cyclic imides using solid support chemistry. The main advantage of this synthesis is that the solid support can be reusable for several times. As compared to the conventional cyclo-dehydrating agents, the SBBC seems to be safer as well as can be stored and handle easily. We have used a new solid-phase synthesis protocol for the synthesis of N-aryl cyclic imides. The main advantages of this process are the recyclability of the solid support and easy release of products from the solid support. An entire series of N-aryl cyclic imides **4a-t** have been synthesized in greener manner from the condensation of substituted aniline with succinamide and glutarimide in good yield. Based on our experimental findings, most the N-substituted aryl cyclic imides exhibited moderate to good activity against bacteria and fungi. The synthesized N-aryl cyclic imides may be used for the synthesis of various heterocyclic derivatives.

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