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PharmTech

International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.4, No.2, pp 523-531, April-June 2012

Synthesis of 2, 5-dichloro 3, 4-diformyl (N-substituted phenyl) pyrroles and their synthetic utility.

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Abstract: A series of N-substituted phenyl succinimides and their formylation has been carried out by using Vilsmeier-Haack reaction. From these compounds various heterocyclic compounds have been synthesized. All compounds were screened for antibacterial and antifungal activity.
Key words: Vilsmeier-Haack reaction, formylation, Antimicrobial activity.

INTRODUCTION:

Formylation is a key process in organic synthesis in which the resulting aldehyde group acts as a 'crossroads' intermediate. Hence, Variety of methods have been developed for the formylation.

Succnimide is a part of many active molecules possessing activities such as CNS depressant[1], analgesic[2], antitumor[3], cytostastic[4], anorectic[5], nerve conduction blocking[6], antipasmodic[7], bactrieostatic[8], muscle relaxant[9], hypotensive[10], antibactrial[11], antifungal[12], anti-convulsant[13] and anti-tubercular activity[14].

In view of above and in continuation of our work in the synthesis of various heterocyclic compounds[15-36], we are reporting a new series of succinimides (2a-d). Then these succinimides are formylated (3a-d). The diformyl intermediates are then used to synthesize various heterocyclic ring compounds (4a-d & 5a-d), Scheme-I.

MATERIALS AND METHODS:

All melting points were determined in open capillary and are uncorrected.IR spectra were recorded on Perkin-Elmer spectrum.[1]HNMR were recorded on Bruker DRX 500MHz NMR spectrometer with DMSO- d6 as a solvent using TMS as internal reference(chemical shift in δ ppm). The starting compounds were synthesized according to **scheme-I**. Succinic acid 1 was converted in to N- substituted phenyl succinimides 2a-d which were then diformylated using Vilsmeier-Haack reaction to form 3a-d. The synthones 3a-d were characterised and used to synthesize compounds 4a-d and 5a-d.

1-(3, 4-dichlorophenyl)-pyrrolidine-3, 4-dione (2a).

A mixture of succinic acid (11.8gm, 0.1m) and thionyl chloride (26.18gm, 2.2m) was refluxed for 30 minutes. In 5ml benzene, different aromatic amines (0.1m) were dissolved. This solution of aromatic amines was added slowly in above reaction mixture. Then the reaction mixture was refluxed till complete HCl gas is evolved. The product obtained was cooled and recrystllized from ethanol.

Yield 82%, m.p.194-196^{0}C.

IR (KBR) cm^{-1}: 2927.52(CH_2), 1699.91(>C=O), 1476.01(ArC=C),1204.87(C-N), 820.35(Cl).

^{1}HNMR (300 MHz, DMSO-d-6, δppm**) :** 3.5 to 2.9δ (s,4H), 8.1 to 6.9δ(m,3H,Ar-H).

Compounds 2b-d were prepared by using above method.

1-(3, 5-dichlorophenyl)-pyrrolidine-3, 4-dione (2b).

Yield 88%, m.p.132-135^{0}C.
IR (KBR) cm^{-1}**:** 2930.85(CH_2), 1696.37(>C=O), 1417.28(ArC=C),1202.09(C-N), 805.71(Cl).
^{1}HNMR (300 MHz, DMSO-d-6, δppm) **:** 2.9 to 2.7δ (s,4H), 7.9 to 6.8δ(m,3H,Ar-H)

1-(4-methoxyphenyl)-pyrrolidine-3, 4-dione (2c).

Yield 63%, m.p.110-112^{0}C.
IR (KBR) cm^{-1}**:** 2924.55(CH_2), 1702.32(>C=O), 1419.73(ArC=C),1202.25(C-N).
^{1}HNMR (300 MHz, DMSO-d-6, δppm**):**2.8- 2.7δ (s,4H),3.16δ(s,3H,CH_3),3.64δ(s,3H,CH_3), 7.5- 6.9δ (m, 3H, Ar-H).

1-(3, 4-dichlorophenyl)-pyrrolidine-3, 4-dione (2d).

Yield 74%, m.p.156-158^{0}C
IR (KBR) cm^{-1}**:** 2933.94(CH_2), 1706.47(>C=O), 1511.42(ArC=C),1252.19(C-N), 1175.59(-OCH_3).
^{1}HNMR (300 MHz, DMSO-d-6, δppm**):**2.3δ(s,4H,2CH_2)2.8δ(s,3H,-OCH_3), 7.5-7.1δ (m, 4H, Ar-H),

2, 5-dichloro-1-(3, 4-dichlorophenyl)-1H-pyrrole-3, 4-dicarbaldehyde (3a):

To a cooled dimethylformamide (0.24 moles) freshly distilled $POCl_3$ (0.12 moles) was slowly added in a drop wise fashion with constant stirring at 5-10 ^{0}C. Then the succinimides 2(a-d) (0.02moles) were slowly added to a cooled Vilsmeier-Haack reagent in small aliquots at a time with constant stirring using magnetic stirrer. This reaction mixture was heated at 60-70 ^{0}C for 6hrs. This mixture was kept overnight and was then slowly added to crushed ice with stirring and stirred for another 30 minutes. Then the resulting clear coloured solution was reacted with 40% NaOH (50ml) maintaining the temperature below 50^{0}C. The reaction mixture was then heated at 50-60^{0}C for half an hour. After cooling in an ice bath coloured compounds were obtained. These compounds were recrystllized with aqueous methanol as solvent.

Yield 86%, m.p.110-112^{0}C
IR (KBR) cm^{-1}**:**2820(CHO), 1700.40(>C=O), 1475.11(Ar=C), 1311.14(C-N), 812.81(C-Cl).
^{1}HNMR (300 MHz, DMSO-d-6, δppm)**:** 8.3-7.2δ (m, 3H, Ar), 10.9δ (br. s, 2H, 2-CHO)
Mass Analysis**:** 301.19 (76), 267.09 (78).
Elemental Analysis: Calculated for $C_{12}H_5O_2NCl_4$: C-42.75, H-1.48, Found **-** C-42.69, H- 1.42, N- 4.10.

Compounds 3b-d were prepared by using same method.

2, 5-dichloro-1-(3, 5-dichlorophenyl)-1H-pyrrole-3, 4-dicarbaldehyde (3b):

Yield 82%, m.p.123-125^{0}C
IR (KBR) cm^{-1}: 2830(CHO), 1640(>C=O), 1448.1271.54(C-N), 789.44(C-Cl).
^{1}HNMR (300 MHz, DMSO-d-6, δppm) : 8.3-7.3δ(m,3H,Ar), 10.6δ (br. s, 2H, 2-CHO).
Mass Analysis: 301 (60)
Elemental Analysis: Calculated for $C_{12}H_5O_2NCl_4$: C-42.75, H-1.48, N- 4.15. Found - C-42.63, H- 1.39, N-4.08.

2, 5-dichloro-1-(3, 4-dimethylphenyl)-1H-pyrrole-3, 4-dicarbaldehyde (3c):

Yield 76%, m.p.121-123^{0}C
IR (KBR) cm^{-1}:2835(CHO), 1705.93(>C=O), 1507.61(ArC=C), 1187(C-N),
^{1}HNMR (300 MHz, DMSO-d-6, δppm): 3.3δ(s, 3H), 4.2δ9(s, 3H). 6.9-7.6δ (m, 3H, Ar), 10.1δ (br.s, 2H, 2-CHO).
Mass Analysis: 318.045 (65). 226.112 (100).
Elemental Analysis: Calculated for $C_{14}H_{11}O_2NCl_2$: C-56.78, H-3.71, N- 4.73. Found - C-56.73, H- 3.69, N-4.68.

2,5-dichloro-1-(4-methoxylphenyl)-1H-pyrrole-3, 4-dicarbaldehyde (3d):

Yield 88%, m.p.140-142^{0}C.
IR (KBR) cm^{-1}:2860(CHO), 1705.93(>C=O), 1507.61(ArC=C), 1187(C-N),
^{1}HNMR (300 MHz, DMSO-d-6, δppm): 3.5δ(s, 3H –OCH_3)7.8-7.2δ (s, 4H, Ar-H), 10.3δ (br.s, 2H, 2-CHO).
Mass Analysis: 259 (53), 294 (100).
Elemental Analysis: Calculated for $C_{13}H_9O_3NCl_2$: C-52.37, H-3.02, N- 4.69. Found - C-52.33, H- 2.98, N-4.64.

2, 5-diazo-1-(3, 4-dichlorophenyl)-1H-pyrrole-3, 4-dicarbaldehyde (4a):

To a solution of 3a-d (1m moles) in absolute ethanol (10ml), P-toluenesulphonic acid (2m moles) and sodium azide (3m moles) were added and reaction mixture heated under reflux for time ranging between10-12hrs.The refluxed mixture was added to ice cold water which precipitated compounds 4a-d.These were filtered and recrystllized from ethanol.

Yield 92%, m.p.114-116^{0}C.
IR (KBR) cm^{-1}:2854.51(CHO), 1624.58(>C=O), 2102.51(N_3), 1130.99(C-N), 692.29(C-Cl).

^{1}HNMR (300 MHz, DMSO-d-6, δppm): 7.9to 7δ (m, 3H, Ar-H), 10.6δ (br.s, 2H, 2-CHO).
Mass Analysis: 349.166 (23), 314.12 (37).
Elemental Analysis: Calculated for $C_{12}H_5O_2N_7Cl_2$: C-44.58, H-1.42, N- 28.00.Found - C-44.52, H- 1.36, N-28.10.
Compounds 4b-d were prepared by using similar method.

2, 5-diazo-1-(3, 5-dichlorophenyl)-1H-pyrrole-3, 4-dicarbaldehyde (4b):
Yield 87%, m.p.132-135^{0}C.
IR (KBR) cm^{-1} : 2854.40(CHO), 1591.34(>C=O), 2104.39(N_3),1443.82 (C-N), 693.15(C-Cl).
^{1}HNMR (300 MHz, DMSO-d-6, δppm): 7.8to7δ (m, 3H, Ar-H), 10.9δ (br.s, 2H, 2-CHO).
Mass Analysis: 314.12 (31).
Elemental Analysis: Calculated for $C_{12}H_5O_2N_7Cl_2$: C-44.58, H-1.42, N- 28.00, Found - C-44.54, H- 1.39, N- 28.08.

2, 5-diazo-1-(3, 4-dimethylphenyl)-1H-pyrrole-3, 4-dicarbaldehyde (4c):
Yield 81%, m.p.144-146^{0}C
IR (KBR) cm^{-1}: 2851.64(CHO), 1730(>C=O), 2109.89(N_3), 1385.48(C-N), 690.75(C-Cl).
^{1}HNMR (300 MHz, DMSO-d-6, δppm): 2.2δ(s, -CH_3), 2.5δ(s, -CH_3), 7.5-6.9δ (m, 3H, Ar-H),
9.9δ (br.s, 2H, 2-CHO).Mass Analysis: 308.15 (35), 272.214 (100).
Elemental Analysis: Calculated for $C_{14}H_{11}O_2N_7$: C-54.36, H-3.5, N- 31.71.Found - C-54.32, H- 3.3, N-31.65.

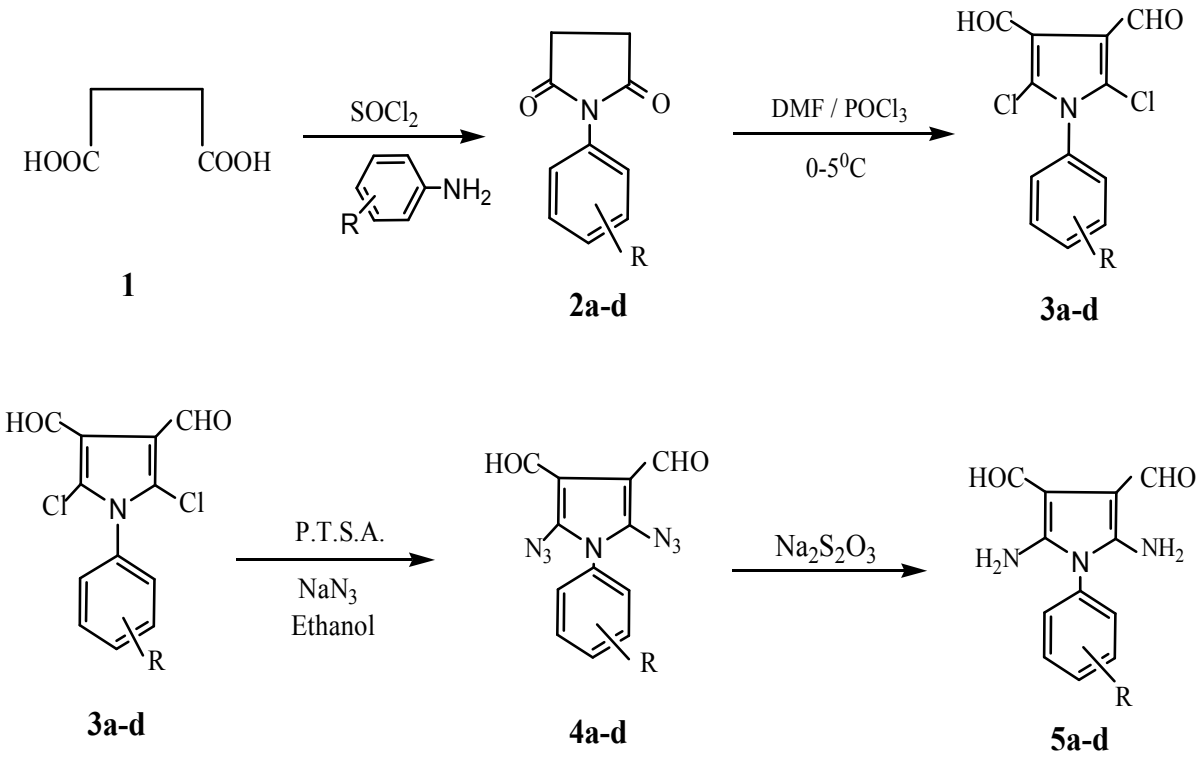
2,5-diazo-1-(4-methoxyphenyl)-1H-pyrrole-3,4-dicarbaldehyde (4d):
Yield 83%, m.p.165-167^{0}C
IR (KBR) cm^{-1}: 2857.14(CHO), 1630.96(>C=O), 2214.28(N_3), 1513.55(C-N), 692.71(C-Cl).
^{1}HNMR (300 MHz, DMSO-d-6, δppm): 2.6δ(s, 3H,-OCH_3), 7.6to7δ (m, 4H, Ar-H),9.8δ (br.s, 2H,2-CHO).
Elemental Analysis: Calculated for $C_{13}H_9O_3N_7$: C-50.16, H-2.89, N- 31.51.Found - C- 50.12, H- 2.86, N-31.48.

2, 5-amino-1-(3, 4-dichlorophenyl)-1H-pyrrole-3, 4-dicarbaldehyde (5a):
The mixture of compound 4a-d (2.6 mmoles), sodium dithionate (5.4mmoles) and methanol (12ml) was refluxed for 5 hrs. The reaction mixture was filtered; the inorganic residues were washed with methanol. The combined methanolic solution was distilled and poured over crushed ice. The resultant solid was filtered, washed with water, dried and recrystllized using benzene as a solvent.
Yield 82%, m.p.138-140^{0}C
IR (KBR) cm^{-1}:3401.82(NH_2), 2853.18(CHO), 1592.11(>C=O), 1475.34(Ar-C=C), 1131.15(C-N), 775.13(C-Cl).
^{1}HNMR (300 MHz, DMSO-d-6, δppm): 10.4δ(s, 2H, 2CHO), 7.8to7.2δ (m, 3H, Ar-4.1δ (s, 4H, 2NH_2).
Elemental Analysis: Calculated for $C_{12}H_9O_2N_3Cl_2$: C-48.33, H-3.02, N- 14.10.Found- C- 48.24, H- 2.08, N-14.08.
Compounds 5b-d were prepared by using similar method.

2, 5-amino-1-(3, 5-dichlorophenyl)-1H-pyrrole-3, 4-dicarbaldehyde (5b):
Yield 84%, m.p.122-125^{0}C
IR (KBR) cm^{-1}: 3392.08(NH_2), 2852.95(CHO), 1588.05(>C=O), 1449.12(Ar-C=C), 1112.86(C-N), 718.84(C-Cl).
^{1}HNMR (300 MHz, DMSO-d-6, δppm): 10.4δ(s, 2H, 2CHO), 7.6to7δ (m, 3H, Ar-H), 3.9δ (s, 4H, 2NH_2).
Elemental Analysis: Calculated for $C_{12}H_9O_2N_3Cl_2$: C-48.33, H-3.02, N- 14.10.Found - C- 48.24, H- 2.08, N-14.08.
Mass Analysis: 322.05 (07), 272.25 (13).

2, 5-amino-1-(3, 4-dimethylphenyl)-1H-pyrrole-3, 4-dicarbaldehyde (5c):
Yield 79%, m.p.117-119^{0}C
IR (KBR) cm^{-1}: 3422.30(NH_2), 2851.64(CHO), 1625.05(>C=O), 1506.19(Ar-C=C), 1017.87(C-N), 756.50(C-Cl).
^{1}HNMR (300 MHz, DMSO-d-6, δpp m):2.8 δ(s,-CH_3), 3.2δ(s,-CH_3), 4.1δ (s, 4H, 2NH_2), 7.6to7δ (m, 3H, Ar-H), 9.8δ(s, 2H, 2CHO).
Elemental Analysis: Calculated for $C_{14}H_{15}O_2N_3$: C-65.36, H-5.83, N- 16.34.Found- C- 65.32, H- 5.79, N-16.31.
Mass Analysis: 258.20 (95), 239.5 (92).

2, 5-amino-1-(4-methoxyphenyl)-1H-pyrrole-3, 4-dicarbaldehyde (5d):
Yield %, m.p.117-119^{0}C
IR (KBR) cm^{-1}: 3405.98(NH_2), 2853.07(CHO), 1628.27(>C=O), 1459.55(Ar-C=C), 1250.62(C-N), 832.29(C-Cl).
^{1}HNMR (300 MHz, DMSO-d-6, δppm): 2.5δ(s,-OCH_3), 3.8δ (s, 4H, 2NH 9.8δ(s, 2H, 2CHO), 7.2to6.6δ (s, 4H, Ar-H),
Elemental Analysis: Calculated for $C_{13}H_{13}O_3N_3$: C-60.33, H-5.01, N- 16.21.Found- C- 60.28, H- 4.08, N-16.19.



1 **2a-d** **3a-d**

3a-d **4a-d** **5a-d**

R, a = 3, 4 -Cl, c = 3 ,4 -CH_3,

b = 3 ,5 -Cl, d = 4 -OCH_3

(Scheme- I)

Table-1: Shows physical data of compounds.

Compounds	R	M.F.	M.P.(^{0}C)	Yield(%)
2a	-3,4 Cl	$C_{10}H_7O_2NCl_2$	194- 196	82
2b	-3,5 Cl	$C_{10}H_7O_2NCl_2$	132-135	88
2c	-3,4CH_3	$C_{12}H_{13}O_2N$	110-112	63
2d	-4OCH_3	$C_{11}H_{11}O_3N$	156-158	74
3a	-3,4 Cl	$C_{12}H_5O_2NCl_4$	110-112	86
3b	-3,5 Cl	$C_{12}H_5O_2NCl_4$	123-125	82
3c	-3,4CH_3	$C_{14}H_{11}O_2NCl_2$	121-123	76
3d	-4OCH_3	$C_{13}H_9O_3NCl_2$	140-142	88
4a	-3,4 Cl	$C_{12}H_5O_2N_7Cl_2$	114-116	92
4b	-3,5 Cl	$C_{12}H_5O_2N_7Cl_2$	132-135	87
4c	-3,4CH_3	$C_{14}H_{11}O_2N_7$	144-146	81
4d	-4OCH_3	$C_{13}H_9O_3N_7$	165-167	83
5a	-3,4 Cl	$C_{12}H_9O_2N_3Cl_2$	138-140	82
5b	-3,5 Cl	$C_{12}H_9O_2N_3Cl_2$	122-125	84
5c	-3,4CH_3	$C_{14}H_{15}O_2N_3$	117-119	79
5d	-4OCH_3	$C_{13}H_{13}O_3N_3$	146-148	86

BIOLOGICAL TESTING OF COMPOUNDS:-

All the synthesized compounds 2a-d, 3a-d, 4a-d, 5a-d were evaluated in-vitro for antifungal and antibacterial activity against fungi Trichoderma varied(TV), Neurospora crassa(NC), Curvularia lunata(CL), Candida albicans(CA) and bacteria Staphylococcous aureus(SA), Escherichia coli (EC).The results were obtained in the form of clearing zone and were noted after the period of incubation (37^0C for 24 hrs.). The zone of inhibition was measured in mm and data is presented in Table-2.

CULTURE USED:

Culture abbreviation	Culture Name	Culture code
TV	Trichoderma viride	NMC 1221
NC	Neurospora crassa	NCIM 1284
CL	Curvularia lunata	NCIM 716
CA	Candida albicans	NICM 3471
SA	Staphylococcus aureus	NICM 2079
EC	Escherichia coli	NICM 2109

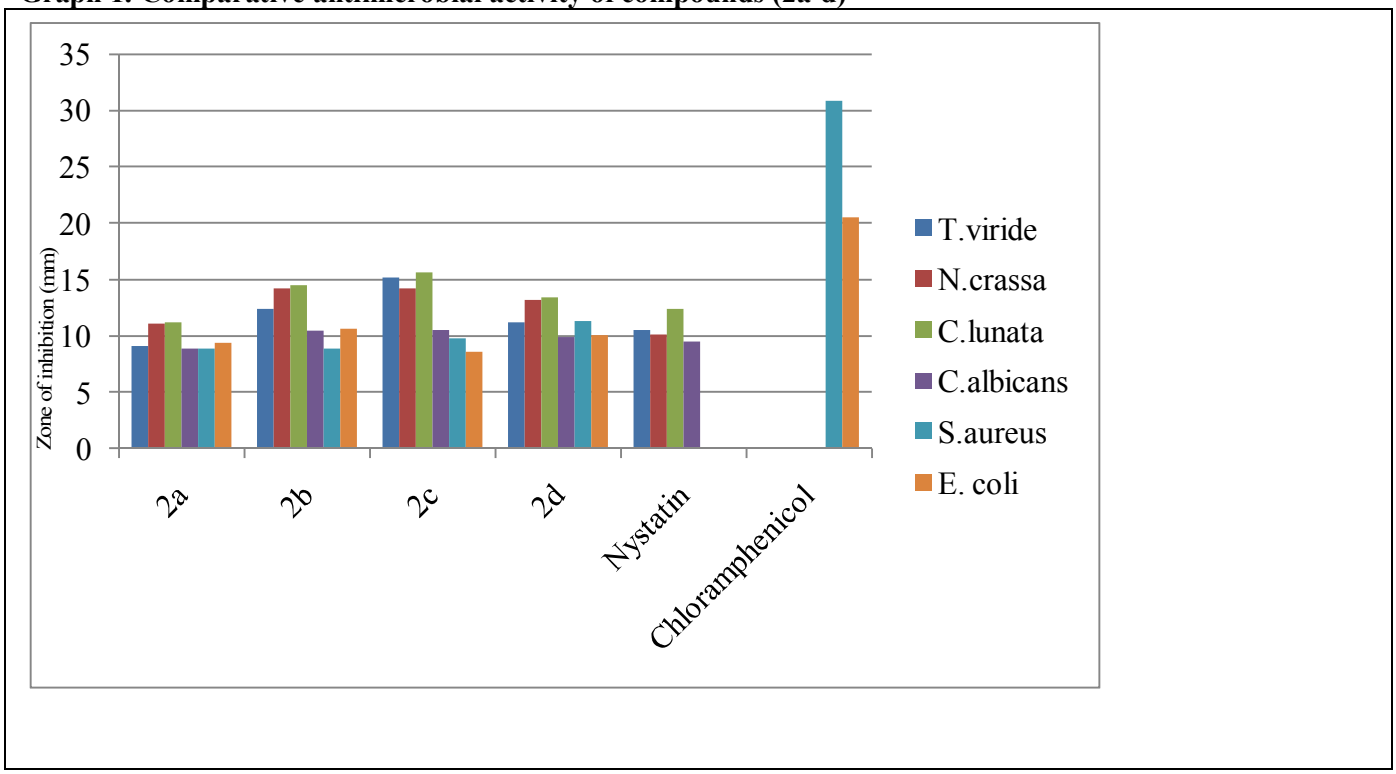
MEDIA USED:

For Bacteria : Nutrient agar (Hi-media)
For Yeast : MGYP
•Inoculum size
Bacteria : 1x10 bacteria per ml.
Yeast : 1x10 cells per ml.
•Concentration of compound : 100µgm/disc (prepared in Ethanol)
•Method used : Agar diffusion assay (Disc method, Disc size 6 mm)
"_" means no zone of inhibition.

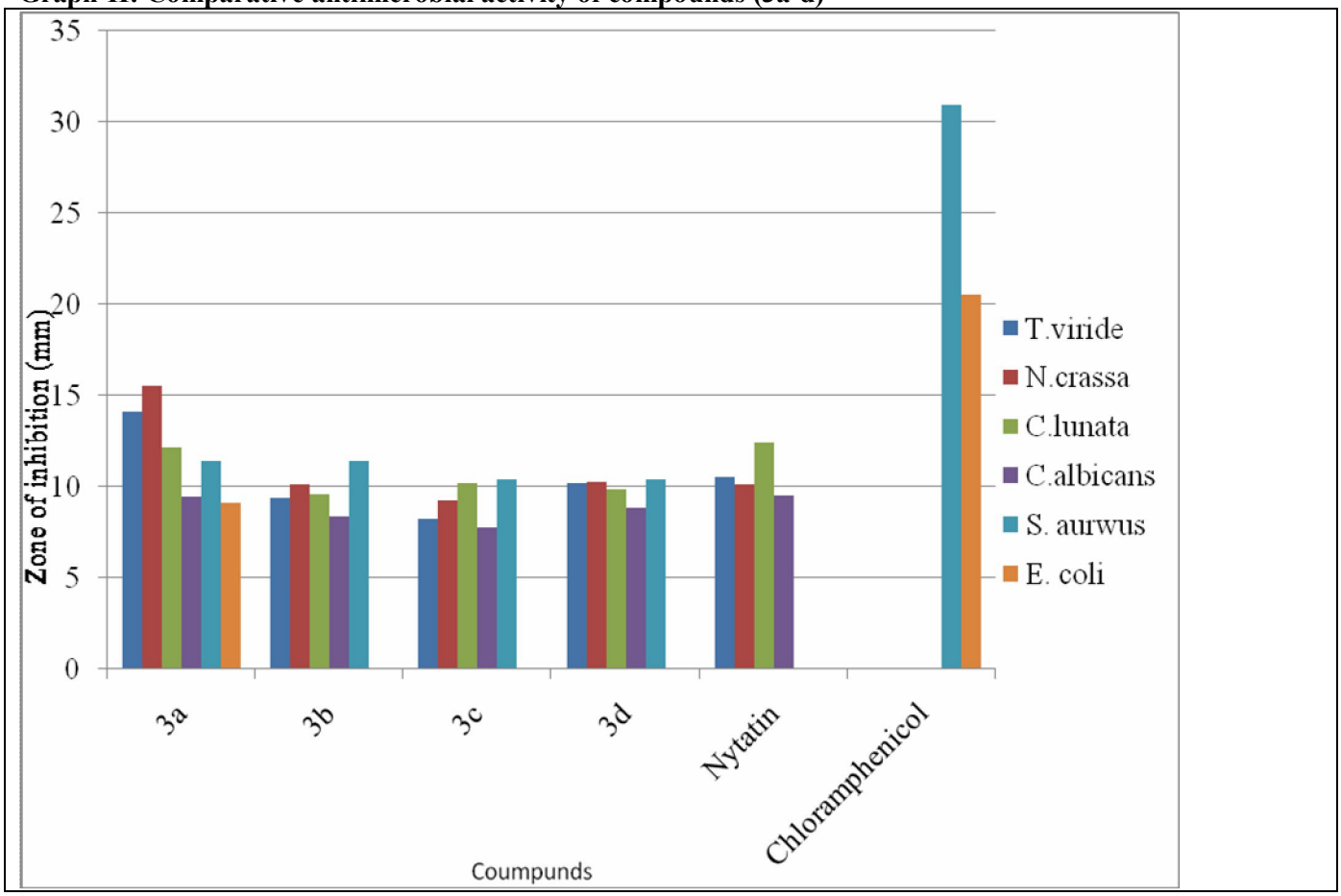
Table-2: Antimicrobial activity of compounds. (Zone of inhibition in mm.)

Sr.	Compound	TV	NC	CL	CA	SA	EC
1	2a	9.13	11.12	11.23	8.88	8.89	9.43
2	2b	12.43	14.23	14.52	10.51	8.91	10.68
3	2c	15.23	14.23	15.63	10.56	9.84	8.65
4	2d	11.23	13.20	13.45	9.91	11.34	10.12
5	3a	14.13	15.52	12.13	9.49	11.39	9.10
6	3b	9.40	10.12	9.58	8.39	11.44	-
7	3c	8.23	9.25	10.23	7.75	10.41	-
8	3d	10.22	10.25	9.88	8.85	10.42	-
9	4a	7.00	-	9.63	6.64	8.02	-
10	4b	9.13	10.11	11.20	7.76	9.85	12.58
11	4c	10.12	9.63	12.22	7.63	-	-
12	4d	11.23	10.56	10.25	7.65	-	-
13	5a	-	-	-	-	9.85	9.61
14	5b	-	-	-	-	7.55	10.32
15	5c	-	-	-	-	6.55	9.34
16	5d	-	-	-	-	7.54	9.35
17	Nystatin[100 U/ml]	10.53	10.14	12.44	9.53	-	-
18	Standard Chloramphenicol [10meg/dise	-	-	-	-	30.94	20.52

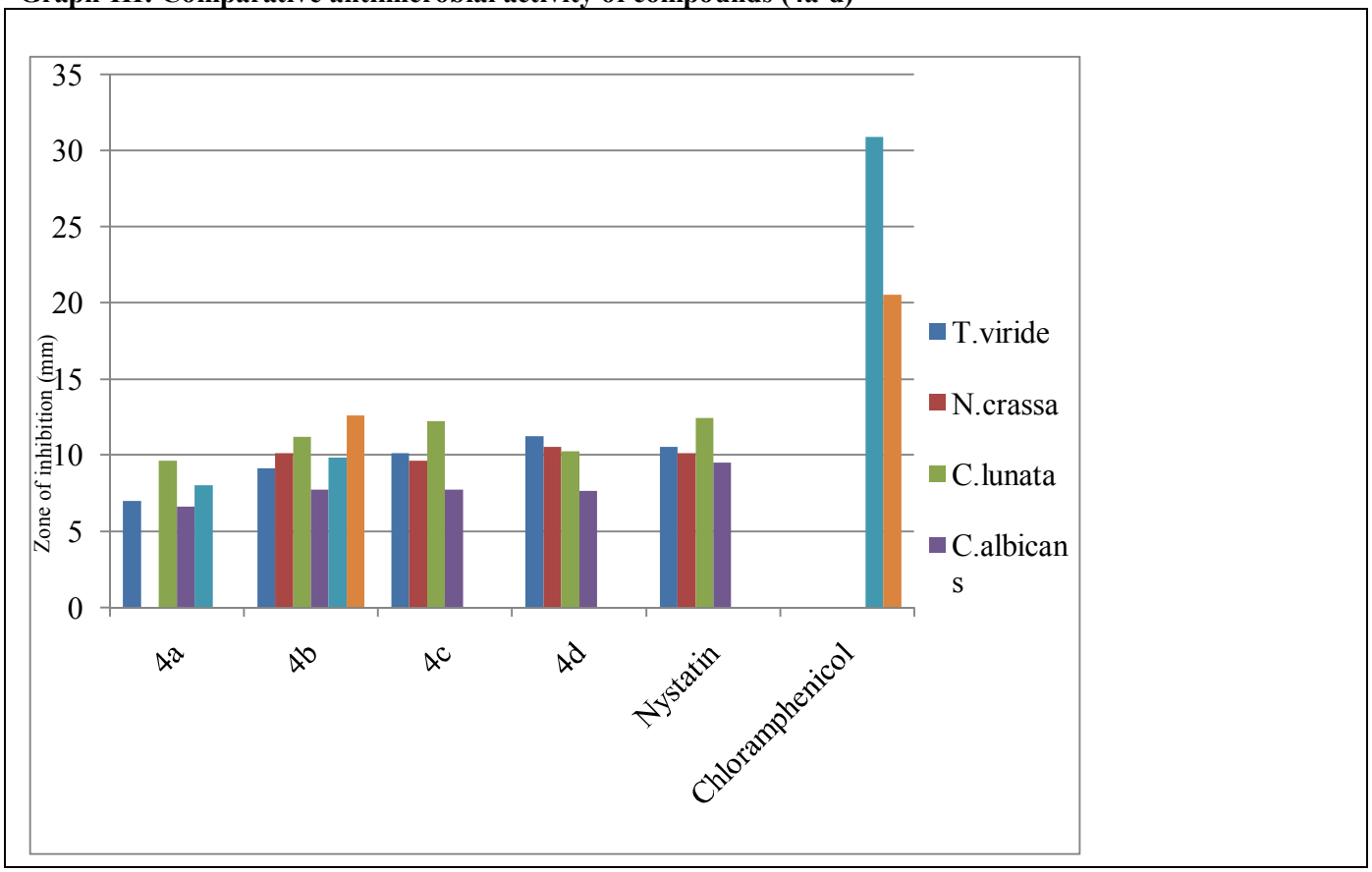
Graph-I: Comparative antimicrobial activity of compounds (2a-d)



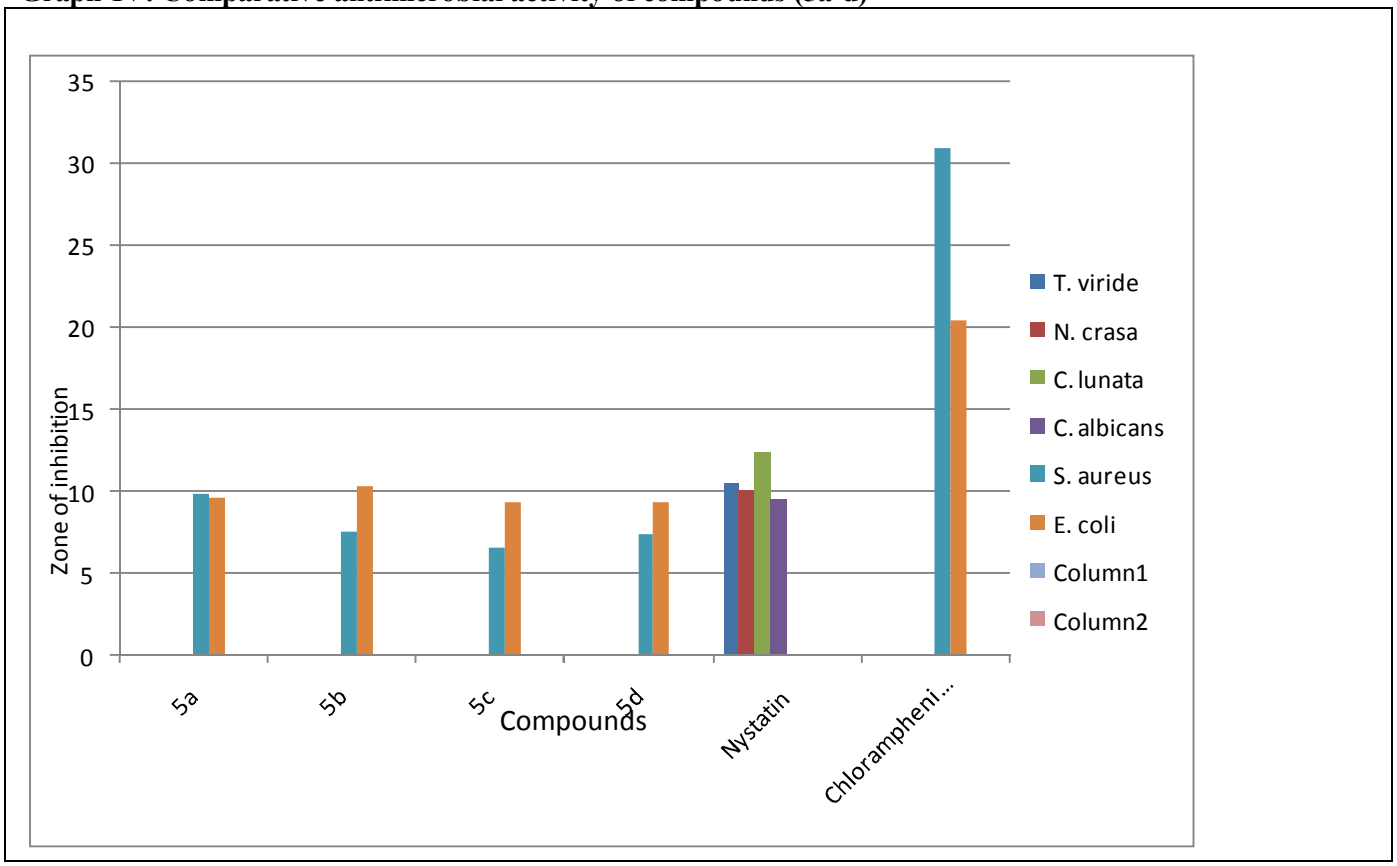
Graph-II: Comparative antimicrobial activity of compounds (3a-d)



Graph-III: Comparative antimicrobial activity of compounds (4a-d)



Graph-IV: Comparative antimicrobial activity of compounds (5a-d)



RESULTS:

The compounds **2b**, **2c** and **2d** were found more potent than standard Naystatin against TV, NC, CL and CA respectively. The compound **3a** was found more potent than standard Naystatin against TV, NC and CA. The compound **3d** was also found potent than standard. The compound **4d** was found more potent than standard Naystatin against TV and NC. The compounds **4b** and **4c** showed good antimicrobial activity against TV and NC. The compound **4a** did not show zone of inhibition against NC and EC. The compounds **5a-d** did not show zone of inhibition against fungi TV, NC, CL, and CA. The antibacterial activity of all the compounds was not found so promising.

CONCLUSION:

In present work we have developed a general method for the synthesis of succinimides with good yield which can be used for the synthesis of various heterocyclic systems. The dicarboaldehydes formed **3a-d** are unknown synthones and may be used for the synthesis of various heterocyclic systems.

The method was developed to transform synthones **3a-d** in to 2, 5-diazo **4a-d** compounds which can use as dyes, plastics, pharmaceuticals and pesticides. The synthones **3a-d** also transformed in to 2, 5-diamino compounds posses herbicidal properties.

ACKNOWLEDGMENT:

This work was supported by The principal, Z.B. Patil College Dhule,The principal, Uttamrao Patil arts & Science College Dahivel. Spectroscopic data were obtained from IIT Mumbai, Arti Drugs Boisar.

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