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Synthesis, Characterization and Microbial screening of dioxolane and thiazolidinones derivatives of 2,5-dichloro-3,4-diformyl (*N*-substituted phenyl) pyrroles

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ABSTRACT

Formylation of N-substituted phenyl succinimides was carried out by using Vilsmeier-Haack reagent which formed 2,5-dichloro-3,4-diformyl (N-substituted Phenyl) pyrroles ***(III)*** *compounds. Compounds* ***(III)*** *was treated with ethylene glycol in presence of PTSA to get dioxolane derivatives* ***(IV)*** *which on further treatment with hydrazine hydrate formed compound* ***(V)*** *described in* ***(Scheme-I).*** *The synthesis of Schiff bases* ***(VI)*** *by treating 2 moles of substituted aromatic primary amines with 1 mole of compound* ***(III).*** *This compound* ***(VI)*** *on treatment with 2 moles of thioglycolic acid formed corresponding 4-thiazolidinone derivatives* ***(VII)*** *of 2,5-dichloro-3,4-diformyl (N-substituted phenyl) pyrroles.* ***(Scheme-II)***

Key words: Succinimides, Vilsmeier-Haack, dioxolane, Schiff bases, 4-thiazolidinones.

INTRODUCTION

1,3-dioxolanes[1] are widely used as protecting groups for ketones, aldehydes and 1,2 diols inorganic synthesis.[2]There are wide range of 1,3-dioxolanes with significant biological activity, for example methylene acetals are found in a wide range of natural products including carpanone,[3] the mild cytotoxic agent taiwankadsurin B4 and nigramide A (Which is isolated from the roots of piper nigrum)[5]. The fumgal metabolite (-)-(s)- guignardic acid is an example of natural product that is a 1,3-dioxolan-4-one.[6] 1,3-dioxolanes are in general resistant to basic reaction conditions and only react with nucleophiles in the presence of Lewis acids. Triazole compounds containing 1,3-dioxolaites have been shown to have remarkable preveltative and control activities for a variety of plant diseases.12 Propiconazole and difenocolnazole are two important representatives of this class, especially the latter, which has been used as the most efficient triazole fungicide in the control of some common plant diseases. In view of the useful biological activities and clinical applications[6-11] of dioxolane derivatives many researchers have synthesized these compounds as target structures. Some important methods are described[12-17] in references.

There are Numerous biologically active molecules with five membered rings, containing two heteroatoms among which is the 4-thiazolidinone ring system which is a core structure in various synthetic compounds and an important scaffold known to be associated with several biological activities such as antitumor[19-20], antidiabetic[21], Antiparkinsons,[22] antiviral,[23] anthelminitic,[24] anti-inflammatory, anti-proliferative, antihistaminic, anti-HIV,[25-27] antibacterial,[28] antifungal,[29] antithyroid,[30] local anaesthetic,[31] monoamineoxidase inhibition, [32]antihyperglycemic,[33] anticancer,[34] diuretic,[35] nematocidal,[36] anticonvulsant[37] and antitubercular

activity against M. tuberculosis H37Rv.[38] Thiazolidinone contain β-lactum ring with sulphar atom and these derivatives inhibit the biosynthesis of the peptidoglycan polymer essential for cell wall of bacteria on inactivation of MurB enzyme. MurB enzyme is a unique target for antibacterial activity of thiazolidinone.[39] Various synthetic approaches of 4-thiazolidinones have been reported.[40-57]

The starting compounds Schiff bases derived from from the condensation of aromatic primary amines with compounds having active carbonyl groups. Compounds with the structure of –C=N- (azomethine group) are known as Schiff bases. Schiff bases have a wide variety of applications in many fields, e.g. biological, inorganic and analytical chemisty.[58] They are known to exhibit potent antibacterial, anticonvulsant, anti-inflammatory activities.[59]In addition some Schiff bases show pharmacologically useful activities like anticancer,[60] anti-hypertensive and hypnotic[61] activities.

Schiff bases and other derivatives synthesized from furfural and indole-3-aldehyde possess various types of biological activities such as analgesic,[62] antitumor[63] and antimalarial[64] etc. Schiff bases are also employed as ligands for the complexation of metal ions,[65] The azomethine (C=N) linkage in Schiff bases imparts in elucidating the mechanism of transamination and resamination reactions in biological system.[66]

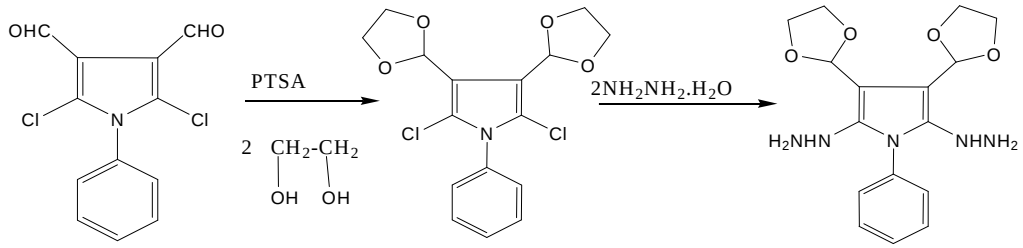
MATERIALS AND METHODS

All melting points were determined in open capillary & are uncorrected. I.R. spectra were recorded on Perkin-Elmier spectrum .H^1NMR were recorded on Bruker DRX 500 MHz.NMR spectrometer with DMSO-d_6 as a solvent using TMS as interal references.(chemical shift in δ ppm)

Experimental Work : Scheme-I

General procedure for the synthesis of 2,5-dichloro-3,4-bis-[1-3]dioxolan-2-yl-1-(*N*-substituted phenyl)-1H-pyrroles. (IVa-d)

The corresponding 2,5-dichloro-1-(*N*-substituted phenyl)-1H-3,4-dicarbaldehydes (**IIIa-d)** (1mmole) was suspended in toluene (20 ml), and ethylene glycol (0.37 gm, 6 mmole) and few crystals of P-toluene sulphonic acid were added. The reaction mixture was refluxed for 4 hrs. with the continuous removal of the formed water by using Dean-Stark trap. After completion of reaction, saturated aq. Sodium carbonate (20 ml) was added. The organic layer was separated, washed with water, dried and evaporated under vaccume which gave pale yellow solid. It was recrystalised from ethanol to afford a pure 2,5-dichloro-3,4-bis-[1,3] dixolan-2-yl-1-(*N*-substituted phenyl)-1H-pyrroles. (**IVa-d)**



III **IV** **V**

R for IV is a = H, b = 4-Cl, c = 3-Cl, d = 3-OCH_3

R for V is a = 4-Cl, b = 3-Cl

Spectral Characterization Data :

2,5-dichloro-3,4-di(1,3-dioxolan-2-yl)-1-phenyl-1H-pyrrole. (IVa)

2,5-dichloro-1-(phenyl)-1H-pyrrole-3,4-dicarbaldehyde (**IIIa)** on treatment with ethylene glycol in toluene in presence of PTSA afforded a white solid 2,5-dichloro-3,4-di(1,3-dioxolan-2-yl)-1-phenyl-1H-pyrrole. **(IVa)** in 78% yield, m.p. 210-212^{0}C. The IR spectrum of this compound reveals bands at 3018, 1423, 1216, 1016 and 771 cm-1 corresponding to the –CH str., ArC=C, C-N, C-O and C-Cl groups respectively. It was correctly analysed for $C_{16}H_{15}O_4NCl_2$ Calcd.(%) : C-53.93, H-4.21, N-3.93. Found (%) : C-53.90, H-4.19, N-3.90.

2,5-dichloro-1-(4-chlorophenyl)-3,4-di(1,3-dioxolan-2-yl)-1H-pyrrole.(IVb)
Mol. Formula: $C_{16}H_{14}O_4NCl_3$ **Mol.Wt :** 390.5; **Physical nature :** whitish **Yield (%) :** 70 % **M.P :** 340-342 ^{0}C **IR (KBr) cm^{-1} :** 3014(-CH str.), 1416 (ArC=C), 1213 (C-N), 1089 (C-O), 768 (C-Cl). **Elemental Analysis** : Calculated for $C_{16}H_{14}O_4NCl_3$: C-49.16, H-3.58, N-3.58. Found : C-49.15, H-3.56, N-3.55. **LC-MS [ESI] *m/z* (%) (Fig.M-1) :** 393 (45), 284 (45), 238 (45), 184 (90).

2,5-dichloro-1-(3-chloro phenyl)-3,4-di(1,3-dioxolan-2-yl)-1H-pyrrole.(IVc)
Mol. Formula: $C_{16}H_{14}O_4NCl_3$ **Mol.Wt :** 390.5 **Physical nature :** whitish **Yield (%) :** 72 % **M.P :** 230-232^{0}C **IR (KBr) cm^{-1} :** 3018(-CH str.), 1419 (ArC=C), 1224 (C-N), 1089 (C-O), 779 (C-Cl). **H^{1}NMR (300MHz, :** 7.74 (m, 4H, ArH), 4.08-4.15 (m, 8H, 2-OCH_2CH_2O-) **DMSO-d_6,δppm C^{13}NMR:** 143 (C=N), 119 (C-Cl), 121-129 (ArC-H). **Elemental Analysis** : Calculated for $C_{16}H_{14}O_4NCl_3$: C-49.16, H-3.58, N-3.58. Found : C-49.14, H-3.57, N-3.56.

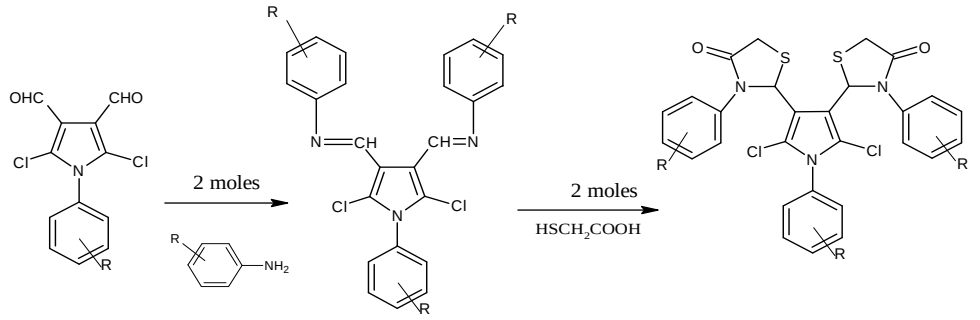
2,5-dichloro-3,4-di(1,3-dioxolan-2-yl)-1-(3-methoxy phenyl)-1H-pyrrole.(IVd)
Mol .Formula : $C_{17}H_{17}O_5NCl_2$ **Mol.Wt :** 386 **Physical nature :** whitish **Yield(%) :** 71 % **M.P :** 250-252 ^{0}C **IR(KBr)cm^{-1}:** 3010(-CH str.), 1419 (ArC=C), 1217 (C-N), 1090 (C-O), 780 (C-Cl). **H^{1}NMR(300MHz, :** 7.74 (m, 4H, ArH), 4.08-4.15 (m, 8H, 2-OCH_2CH_2O-) **DMSO-d_6,δppm) C^{13}NMR:** 143 (C=N), 119 (C-Cl), 121-129 (ArC-H). **Elemental Analysis:** Calculated for $C_{17}H_{17}O_5NCl_2$: C-52.84, H-4.40, N-3.62. Found : C-52.82, H-4.38, N-3.60.

General procedure for the synthesis of 2,5-dihydrazino-3,4-bis-[1-3]dioxolan-2-yl-1-(*N*-substituted-phenyl)-1H-pyrroles. (Va-b)
A solution of 2,5-dichloro-3,4-bis-[1,3] dixolan-2-yl-1-(*N*-substituted phenyl)-1H-pyrroles. (**IVa-d)** (1mmole) in ethanol and hydrazine hydrate (20 mmol) was heated under reflux for 3-4 hrs. Then cooled solution was evaporated and residue recrystalized from ethanol to give a pure 2,5-dihydrazino-3,4-bis-[1,3] dioxolan-2-yl-1-(*N*-substituted-phenyl)-1H-pyrroles. (**Va-b)**

Spectral Characterization Data :
1-(4-chloro phenyl)-3,4-di(1,3-dioxolan-2-yl)-1H-pyrrole-2,5-dihydrazine.(Va)
Condensation of 2,5-dichloro-1-(4-chlorophenyl)-3,4-di(1,3-dioxolan-2-yl)-1H-pyrrole.**(IVb)** with hydrazine hydrate in ethanol afforded a white solid 1-(4-chloro phenyl)-3,4-di(1,3-dioxolan-2-yl)-1H-pyrrole-2,5-dihydrazine**.(Va)** in 78% yield, m.p. 240-242^{0}C. The IR spectrum of this compound reveals bands at 3348, 3018, 1423, 1216, 1016 and 771 cm^{-1} corresponding to the –NH str., –CH str., ArC=C, C-N, C-O and C-Cl groups respectively. It was correctly analysed for $C_{16}H_{20}O_4N_5Cl$ Calcd. (%) : C-50.32, H-5.24, N-18.34. Found (%) **:** C-50.30, H-5.22, N-18.32. LC-MS [ESI] *m/z* (%) : 393 (75), 288 (50), 234 (55), 184 (90).

1-(3-chloro phenyl)-3,4-di(1,3-dioxolan-2-yl)-1H-pyrrole-2,5dihydrazine.(Vb)
Mol Formula : $C_{16}H_{20}O_4N_5Cl$ **Mol.Wt :** 381.5 **Physical nature :** whitish **Yield (%) :** 72 % **M.P :** 235-237 ^{0}C **IR (KBr) cm^{-1} :** 3330 (NH), 1260 (C-N), 1442 (ArC=C), 1078 (C-O). **H^{1}NMR (300MHz, :** 2.5 (s, 6H, 2NHNH2), 4.08-4.15 (m, 8H, 2-OCH_2CH_2O-), **DMSO-d_6,δppm)** 7.40 -6.70 (m, 4H, ArH). **C^{13}NMR :** 143 (C=N), 119 (C-Cl), 121-129 (ArC-H). **Elemental Analysis :** Calculated for $C_{16}H_{20}O_4N_5Cl$: C-50.32, H-5.24, N-18 Found **:** C-50.31, H-5.23, N-18.33.

Scheme-II Genral procedure for preparation of Schiff bases (VIa-c):-
2,5-dichloro-1-(N-substituted phenyl)-1H-pyrrole-3,4-dicarbaldehydes. **(IIIa-f)** (1mmole) was refluxed with two different aromatic primary amines (2mmole) in water bath for 4-5 hours using ethanol as solvent and few drops of glacial acetic acid. The reaction mixture was poured in to crushed ice. The product was isolated and recrystallized from ethanol to give **(VIa-c)**



III **(VIa-c)** **(VIIa-b)**

R is a = H **R is a = 2-Cl**
b = 3-Cl **b = 3-Cl**
c = 2-Cl

Characterization data of Schiff bases

(16E)-N-[(4-(E)-(3-methoxyphenylimino)methyl)-2,5-dichloro-1-(phenyl)-1H-pyrrole-3-yl)methylene]-4-chlorobenzeneamine. (VIa) Schiff bases

2,5-dichloro-1-(N-substitutedphenyl)-1H-pyrrole-3,4-dicarbaldehyde **(IIIa)** on condensation with m-anisidine in ethanol and glacial acetic acid afforded a deep yellow solid (16E)-N-[(4-(E)-(3-methoxyphenylimino)methyl)-2,5-dichloro-1-(phenyl)-1H-pyrrole-3-yl)methylene]-4-chlorobenzeneamine **(VIa)** in 77% yield, m.p. 302-304^{0}C. The IR spectrum of this compound reveals bands at 3018, 1600, 1419, 1218, 783, cm^{-1} corresponding to the aliphatic C-H str., C=N, ArC=C, C-N and C-Cl groups. The ^{1}HNMR spectrum of this compound in DMSO-d_6 reveals the singlets at 2.25, 8.10 ppm corresponding to the CH_3 ptotons and CH=N proton.The appearance of multiplets at 7.82-7.20-7.08 was due to the five aromatic protons of phenyl group and eight aromatic protons of 3-methoxy phenyl groups respectively. It was correctly analysed for $C_{26}H_{21}O_2N_3Cl_2$ Calcd (%) : C-65.27, H-4.39, N-8.78. Found (%) : C-65.25, H-4.36, N-8.76.

(16E)-N- [(4-(E)-(3-methoxy phenyl imino) methyl)2,5-dichloro-1-(3-chloro phenyl)-1H-pyrrole-3-yl) methylene]-4-chlorobenzene amine. (VIb) Schiff base

Mol.formula : $C_{26}H_{20}O_2N_3Cl_3$ **Mol. Weight :** 512.5 **Physical nature :** whitish **Yield (%) :** 72 % **M.P :** 310-312 ^{0}C **IR (KBr) cm^{-1} :** 2930 (CH_3), 1610 (C=N), 1490 (ArC=C), 1248 (C-N), 820 (C-Cl). **H^{1}NMR (300MHz,** 2.20 (s, 6H, 2CH_3O), 6.92-6.82 (m, 8H, Ar-H), **DMSO-d_6,δppm):** 7.4-7.0 (m, 5H, Ar-H), 7.88 (s, 2H, 2CH=N). **Elemental Analysis** : Calculated for $C_{26}H_{20}O_2N_3Cl_3$: C-60.87, H-3.90, N-8.19. Found : C-60.85, H-3.88, N-8.17.

(16E)-N-[(4-(E)-(4-chloro phenyl imino) methyl)2,5-dichloro-1-(2-chloro phenyl)-1H-pyrrole-3-yl) methylene]-4-chlorobenzene amine. (VIc) Schiff base

Mol.formula : $C_{24}H_{14}N_3Cl_5$ **Mol. Weight :** 521.5 **Physical nature :** whitish **Yield(%) :** 71 % **M.P :** 315-317^{0}C **IR(KBR)cm^{-1}** :1595(C=N), 1442(ArC=C), 1247(C-N), 827(C-Cl),790(C-N). **H^{1}NMR (300MHz,** 2.20 (s, 6H, 2CH_3O), 6.92-6.82 (m, 8H, Ar-H), **DMSO-d_6,δppm):** 7.4-7.0 (m, 5H, Ar-H), 7.88 (s, 2H, 2CH=N). **Elemental Analysis**: Calculated for $C_{24}H_{14}N_3Cl_5$: C-55.22, H-2.68, N-8.05 Found : C-55.20, H-2.66, N-8.03,

Genral procedure for preparation of 4-thiazolidinones

The Schiff bases (1mmole) were refluxed with thioglycolic acid (2mmole) in the presence of catalytic amount of anhydrous $ZnCl_2$ in dry 1,4-dioxane (30ml) for 7 hours. The mixture was then cooled and poured in to crushed ice and water. The product separated was filtered, dried and recrystalised from ethanol to give products. **(VIIa-b)**

Spectral characterization data of 4-thiazolidinones (VIIa-b)

2-(2,5-dichloro-1-(3-chloro-phenyl)-4-(3-(4-chlorophenyl)-4-oxothiazolidine-2-yl)-1H-pyrrole-3-yl)-3-(4-chloro phenyl)thiazolidine-4-one.(VIIa)

The Schiff base **(VIb)** on condensation with thioglycolic acid in the presence of catalytic amount of anhydrous $ZnCl_2$ in dry 1,4-dioxane afforded a white solid 2-(2,5-dichloro-1-(3-chloro-phenyl)-4-(3-(4-chlorophenyl)-4-oxothiazolidine-2-yl)-1H-pyrrole-3-yl)-3-(4-chlorophenyl)thiazolidine-4-one. **(VIIa)** In 71% yield, m.p. 320-322^{0}C. The IR spectrum of this compound reveals bands at 3018, 1708, 755, 671 cm^{-1} corresponding to the CH str., >C=O,

C-Cl and C-S-C groups. The ^{1}HNMR spectrum of this compound in DMSO-d_6 reveals the singlets at 3.60 ppm and 5.32 ppm corresponding to the CH_2S protons and N-CH proton respectively. The appearance of multiplets at 7.11-6.98 due to twelve aromatic protons of three substituted phenyl rings. It was correctly analysed for $C_{28}H_{18}O_2N_3S_2Cl_5$ Calcd.(%) : C-50.15, H-2.68, N-6.26. Found(%) **:** C-50.13, H-2.66, N-6.24

2-(2,5-dichloro-1-(2-chloro-phenyl)-5-(3-(4-chlorophenyl)-4-oxothiazolidine-2-yl)-1H-pyrrole-3-yl)-3-(4-chloro phenyl)thiazolidine-4-one.(VIIb)

Mol.formula : $C_{28}H_{18}O_2N_3S_2Cl_5$ **Mol. Weight :** 669.88 **Physical nature :** whitish **Yield(%) :** 77 % **M.P :** 265-267 ^{0}C **IR(KBR)cm^{-1} :** 3018 (CH str.), 1700 (>C=O), 760(C-Cl), 671 (C-S-C). **H^{1}NMR (300MHz** 2.98 (s, 2H, CH_2), 3.58 (s, 4H, 2CH_2-S), 5.38 (2H, 2N-CH), **DMSO-d_6,δppm**) **:** 7.15-6.50 (m, 4H, ArH), 7.35-7.18 (m, 8H, ArH). **Elemental Analysis**: Calculated for $C_{28}H_{18}O_2N_3S_2Cl$: C-50.15, H-2.68, N-6.26. Found : C-50.12, H-2.65, N-6.24.

Table-1 shows physical data of compounds

Comp	R	M.F.	M.P(^{0}C)	Yield(%)
IVa	-H	$C_{16}H_{15}O_4NCl_2$	210-212	78
IVb	4-Cl	$C_{16}H_{14}O_4NCl_3$	340-342	70
IVc	3-Cl	$C_{16}H_{14}O_4NCl_3$	230-232	72
IVd	3-OCH_3	$C_{17}H_{17}O_5NCl_2$	250-252	71
Va	4-Cl	$C_{16}H_{20}O_4N_5Cl$	240-242	78
Vb	3-Cl	$C_{16}H_{20}O_4N_5Cl$	235-237	72
VIa	-H	$C_{26}H_{21}O_2N_3Cl_2$	302-304	77
VIb	3-Cl	$C_{26}H_{20}O_2N_3Cl_3$	310-312	72
VIc	2-Cl	$C_{24}H_{14}N_3Cl_5$	315-317	71
VIIa	2-Cl	$C_{28}H_{18}O_2N_3S_2Cl_5$	320-322	71
VIIb	3-Cl	$C_{28}H_{18}O_2N_3S_2Cl_5$	265-267	77

Biological Testing of compounds

Heterocyclic dioxolane and Schiff bases compounds were evaluated for antibacterial activity against Escherichia coli (Ec), pseudomona S. aeruginosa (PA), staphylococcus aureus (SA), Bacillus subtillis (BS), And antifungal against candida albicans (CA), Asperginus niger (AN).

The result were obtained in the form of clearing zone and were noted after the period of incubation (37^{0}C for 24 hrs). The zone of inhibition was measured in mm and data is presented in table

Media used

For bacteria : Nutrient agar (Hi-media)
For yeast : MGYP
Inoculum size :
Bacteria : 1 x 10 bacteria per ml.
Yeast : 1 x 10 cells per ml

- concentration of compound

(Prepared in ethanol) 100 µ gm 1 disc

- method used

(disc method, disc size 6mm)
"__" means no zone of inhibition.

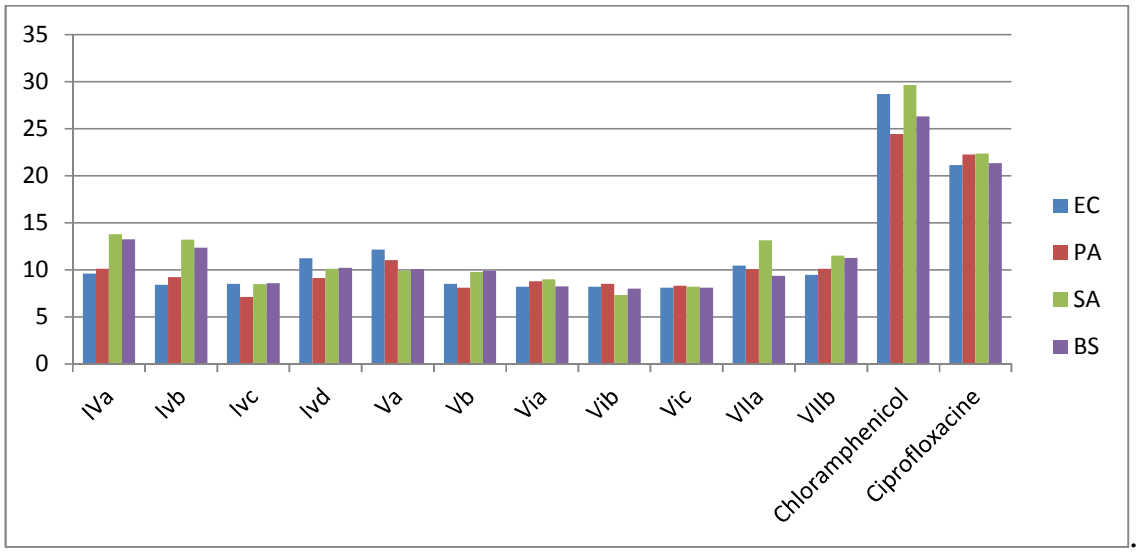
CULTURE USED:

	Culture name	Culture code
ES	*Escherichia coli*	NCIM 1209
PA	*Pseudomonas aeruginosa*	NCIM 2036
SA	*Staphylococcus aureus*	NCIM 2079
BS	*Bacillus subtilis*	NICM 2250
AN	*Aspergillus niger*	NICM 545

Table-2 shows microbial activity data of compounds

Sr	Comp	EC	PA	SA	BS	CA	AN
1	IVa	9.61	10.12	13.81	13.23	-	-
2	IVb	8.4	9.23	13.21	12.36	-	-
3	IVc	8.5	7.11	8.46	8.56	-	-
4	IVd	11.23	9.12	10.14	10.23	-	-
5	Va	12.14	11.01	9.89	10.11	-	-
6	Vb	8.5	8.12	9.75	9.89	-	-
7	VIa	8.2	8.8	9.01	8.23	-	-
8	VIb	8.2	8.5	7.33	8.01	-	-
9	VIc	8.1	8.3	8.2	8.1	-	-
10	VIIa	10.45	10.11	13.14	9.37	-	-
11	VIIb	9.45	10.12	11.52	11.24	-	-
12	chloramphenicol	28.67	24.44	29.63	26.30	NA	NA
13	Ciprofloxacin	21.11	22.23	22.33	21.34	NA	NA

Microbial activity graph of compounds :



CONCLUSION

In the present work we have developed a general method for the synthesis of dioxolane and 4-thiazolidinone derivatives of 2,5-dichloro-3,4-diformyl (N-substituted phenyl) pyrroles with good yield. Which are unknown synthones and may be used for the synthesis of various heterocyclic systems by functional group interconversion.

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