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SYNTHESIS, CHARACTERISATION AND BIOLOGICAL EVALUATION OF ETHYL-4-(4-ALKYLPHENYL)-6-METHYLSULFANYLDIENE-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXYLATE

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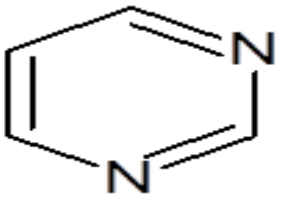
ABSTRACT

The work include the synthesis of four Derivatives of Ethyl-4-(4-alkylphenyl)-6-methylsulfanyldiene-1,2,3,4-tetrahydropyrimidine-5-carboxylate by one pot multicomponent reaction, involving reaction of Aromatic aldehyde, β keto ester, Thiourea in presence of concHCl and ethanol. The structure of synthesised compound was confirmed by IR spectroscopic analysis. The synthesised compounds were screened for their antibacterial activity against Gram positive bacteria (Enterococcus faecalis and Staphylococcus aureus) and gram negative bacteria (Escherichia coli and Pseudomonas aeruginosa) using Ciprofloxacin 5mg/ml as standard.

KEYWORDS: Pyrimidine, substituted aldehydes, antibacterial.

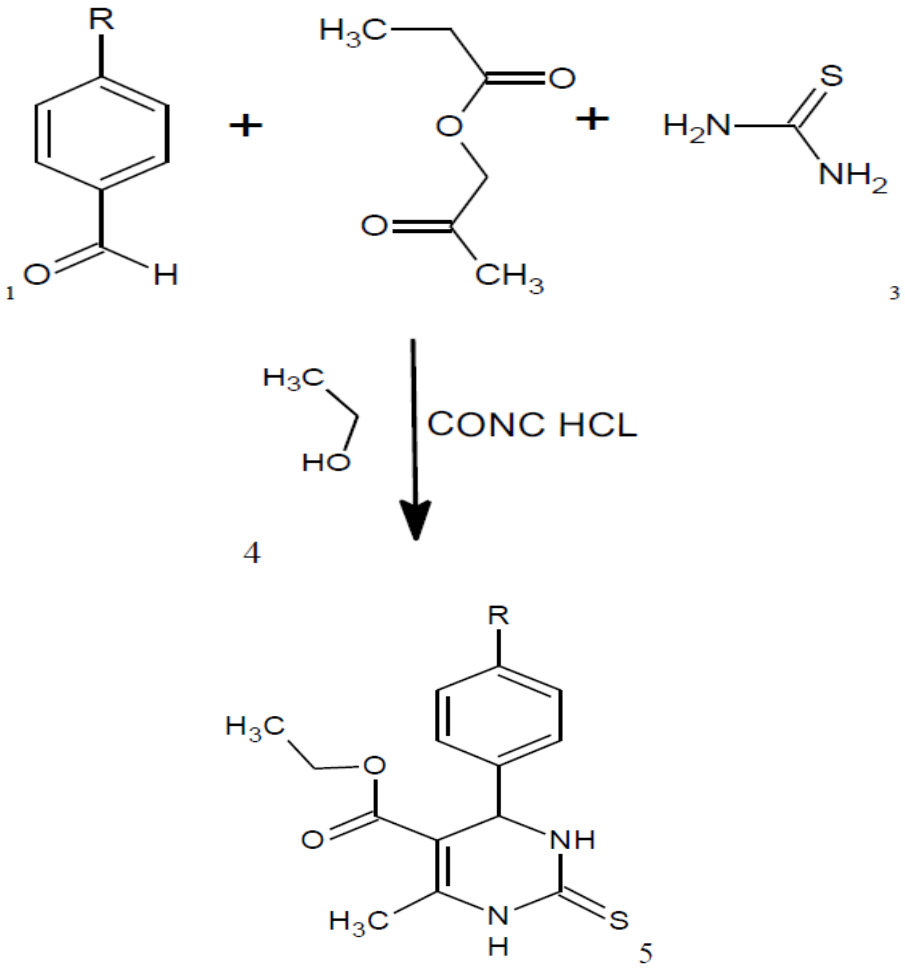
INTRODUCTION

Microbes are organisms that adapt to varying environment and have resistance in adverse conditions. Antimicrobial agents are used to cure most of the infections. Pyrimidine derivatives constitute important classes of various natural & synthetic products which possess antimicrobial, antifungal, antiviral, antioxidant activities. Pyrimidine is a heterocyclic ring with nitrogen at 1,3 position. The work include the synthesis of Ethyl-4-(4-alkylphenyl)-6-methylsulfanyldiene-1,2,3,4-tetrahydropyrimidine-5-carboxylate by aromatic aldehyde, Thiourea, beta ketoesterin presence of ethanol and concHcl as catalyst and to screen antibacterial activity.



Pyrimidine

Scheme of work



Compound 1a	R=cl
Compound 2a	R=OH
Compound 3a	R=CH3
Compound 4a	R=OCH3

*(1)-Aromatic aldehyde,(2)-ethylacetoacetate,(3)-thiourea,(4)-ethanol,(5)-Product

General procedure for synthesis of ethyl-4-(4-alkylphenyl)-6-methylsulfanyldiene-1,2,3,4-tetrahydropyrimidine-5-carboxylate

A mixture of aromatic aldehyde (0.01M),β-Ketoester (0.01M) & Thiourea (0.012M) was stirred overnight in absolute alcohol (20ml) using 3-5drops of concHCl as catalyst. The solid product formed, the reaction mixture was filtered, wash with water, recrystallized from absolute alcohol to obtain pure product and the derivatives were synthesised through bignelli condensation reaction.

Screening of anti bacterial activity

Antibacterial activity of synthesized compounds

Micro organisms

Gram positive bacteria (*Enterococcusfaecalis* and *Staphylococcus aureus*) and gram negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) were used to evaluate antibacterial activity in vitro. The microorganisms were collected from the laboratories of different locations of Kerala. *Enterococcus faecalis*,*Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Escherichia coli*.

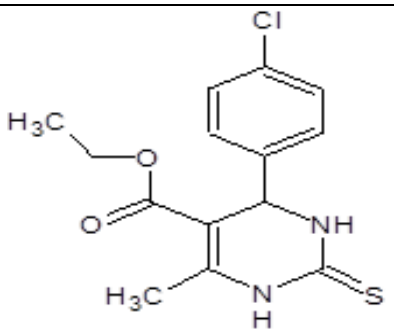
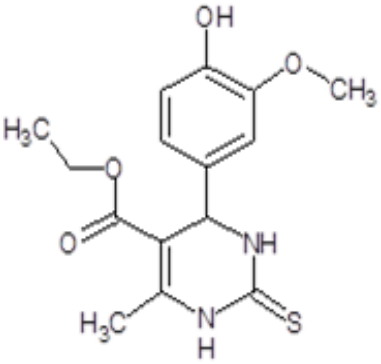
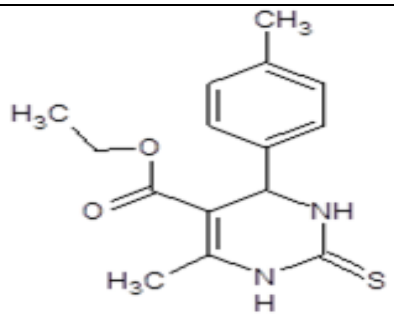
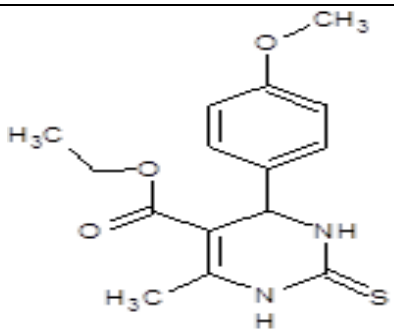
Cup plate method

Ciprofloxacin was used during the experimental protocol. Test samples were prepared at different concentration in DMSO. Ciprofloxacin (5 mg/ml) was used as reference standard and DMSO as control. In this method nutrient agar is melted, cooled at 45°C and poured into a sterile petriplate. After solidification, the microorganisms were swabbed on the surface of the nutrient agar. After this holes about 9 mm in diameter are cut in the medium with a sterile cork borer. The standard, control and test were poured into the holes using micro pipette. Incubated for 24 hours at 37± 2°C. The zone of inhibition gives an indication of the relative antibacterial activities of the different compounds

RESULT AND DISCUSSION

The synthesized compounds are crystalline solid, the structure of derived compounds are given the table 1.

Table 1: Chemical structure and name of synthesized compounds.

Compound Code	R	R^1	Structure	Name
1a	**Cl**	**H**		ethyl 4-(4-chlorophenyl)-6-methyl-2-sulfanylidene-1,2,3,4-tetrahydropyrimidine-5-carboxylate
2a	**OH**	**OCH_3**		ethyl 4-(4-hydroxy-3-methoxyphenyl)-6-methyl-2-sulfanylidene-1,2,3,4-tetrahydropyrimidine-5-carboxylate
3a	**CH_3**	**H**		ethyl 6-methyl-4-(4-methylphenyl)-2-sulfanylidene-1,2,3,4-tetrahydropyrimidine-5-carboxylate
4a	**OCH_3**	**H**		ethyl 4-(4-methoxyphenyl)-6-methyl-2-sulfanylidene-1,2,3,4-tetrahydropyrimidine-5-carboxylate

Chemical features of derivatives and Spectral data are given in table 2 and 3respectively.

Table 2: Chemical features of synthesized compound.

Compound Code	R	Molecular Weight	Molecular formula	% yield	Melting Point (^{0}C)	Rf Value
1a	Cl	3.105	$C_{14}H_{15}N_2O_2SCl$	25.1%	144-146	0.595
2a	OH	3.22	$C_{14}H_{18}N_2O_4S$	8.071%	190-195	0.560
3a	CH_3	2.99	$C_{15}H_{18}N_2O_2S$	34.11%	154-158	0.558
4a	OCH_3	3.06	$C_{15}H_{18}N_2O_3S$	51.30%	140-144	0.534

Table 2: Spectral data of derived compounds.

Compound code	IR cm^{-1}
1a	1572(C=C),1572(N-H),1251(Ø-O-R),643.43(C-Cl),1012(C-N),746(C-H),3176(NH_2-2^0 and 3^0),1174(C=S)
2a	1683(C=O),1579(N-H),1195(C=S),722(C-H)
3a	1282(Ø-O-R),1250(CN-Vibration),755(C-H),3323(NH_2-2^0and3^0),1671(C=CO),1174(C=S)
4a	3176(NH_2-2^0and3^0),1659(C=C),1573(N-H),1453(C=C),1174(C=S),1114(OH bending

Antimicrobial screening

The synthesized derivatives were screened for anti-microbial activity. The result were shown in the table 3, 4 and fig1,2,3 and 4.

Table 3: Quantitative screening of the test compounds for antibacterial activity against gram positive organisms.

Sl. No.	Drug used	Concentration	Diameter of zone of inhibition	
			S. aureus	E. faecalis
1	Standard	5 mg/ml	30 mm	27 mm
2	Control	-	-	-
3	1a	Min: 10 mg/ml	14 mm	12 mm
		Max: 25 mg/ml	20 mm	16 mm
4	2a	Min: 10 mg/ml	16 mm	16 mm
		Max: 25mg/ml	22 mm	22 mm
5	3a	Min: 10 mg/ml	10 mm	10 mm
		Max: 25 mg/ml	18 mm	16 mm
6	4a	Min: 10 mg/ml	12 mm	12 mm
		Max: 25mg/ml	17 mm	14 mm

(-) indicates no zone of inhibition

Concentration used: Minimum 10mg

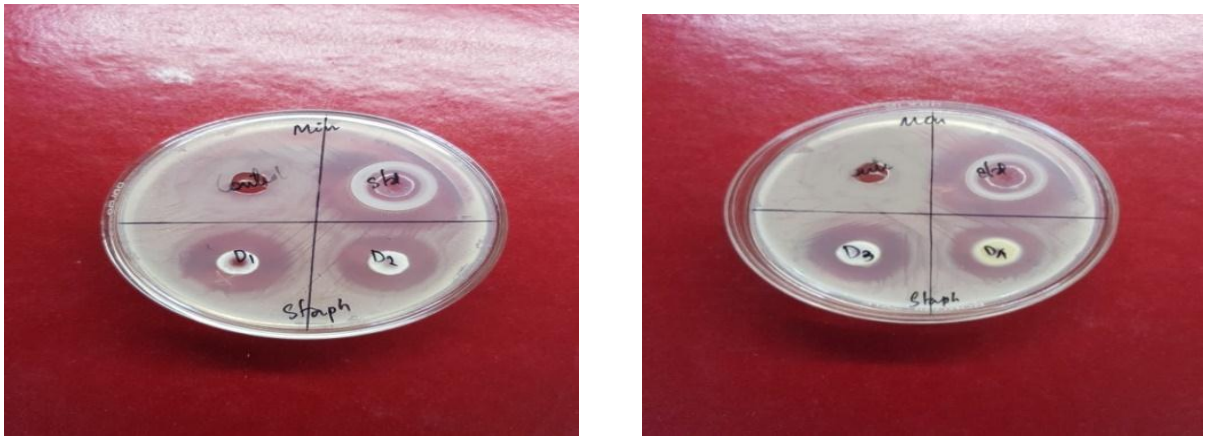
Maximum 25mg

Standard disc : Ciprofloxacin 5mg/ml

Solvent used : DMSO (Dimethyl sulfoxide)

Zone of inhibition of sensitive compounds against *Staphylococcus aureus*

Min: 10mg/ml



Max: 25mg/ml

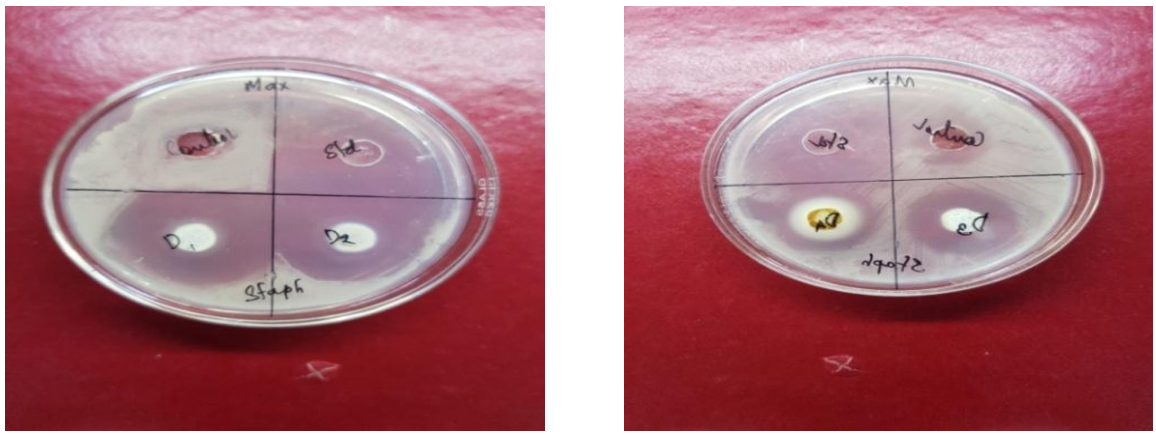
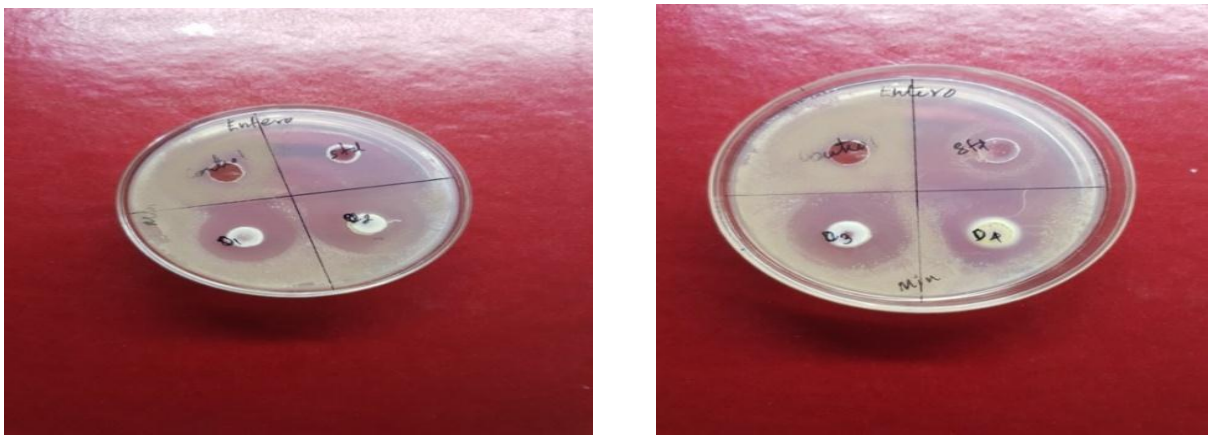


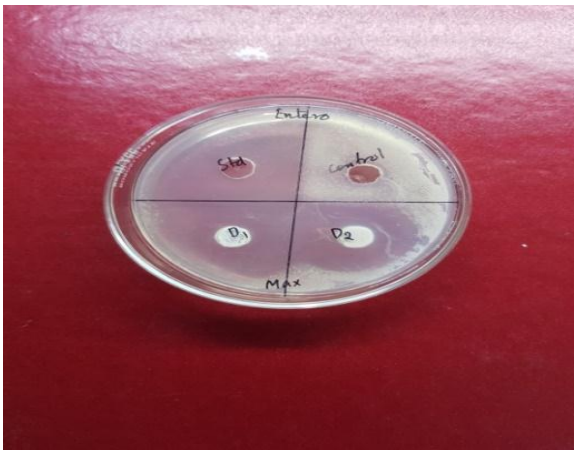
Figure no. 1.

Zone of inhibition of the sensitive compounds against *Enterococcus faecalis*

Min:10mg/ml



Max: 25mg./ml



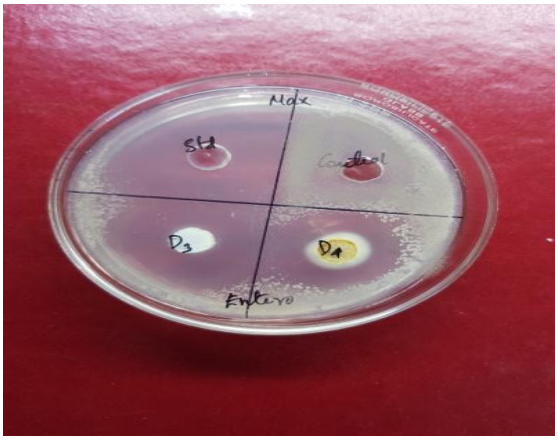


Figure no. 2.

Table 4: quantitative screening of the test compounds for antibacterial activity against gram negative organisms.

Sl. no.	Drug used	Concentration	Diameter of zone of inhibition	
			E. coli	P. aeruginosa
1	Standard	5 mg/ml	32 mm	29 mm
2	Control	-	-	-
3	1a	Min: 10 mg/ml	15 mm	13 mm
		Max: 25 mg/ml	18 mm	18 mm
4	2a	Min: 10 mg/ml	16 mm	14 mm
		Max: 25mg/ml	22 mm	22 mm
5	3a	Min: 10 mg/ml	14 mm	12 mm
		Max: 25 mg/ml	15 mm	18 mm
6	4a	Min: 10 mg/ml	10 mm	10 mm
		Max: 25mg/ml	14 mm	16 mm

(-) indicates no zone of inhibition

Concentration use: Minimum 10mg

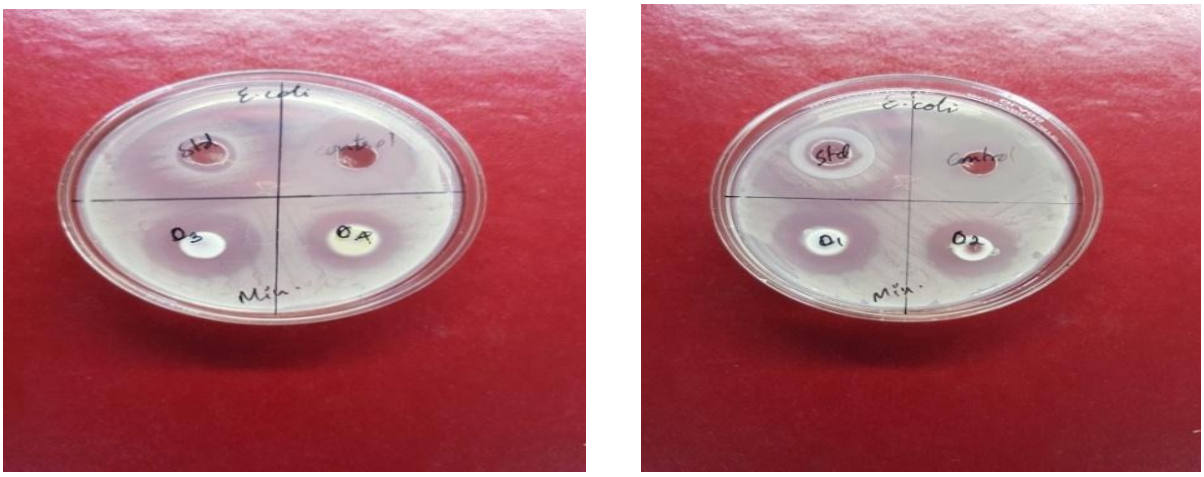
Maximum 25mg

Standard disc : Ciprofloxacin 5mg/ml

Solvent used : DMSO (Dimethyl sulfoxide)

Zone of inhibition of the sensitive compounds against*Escherichia coli*

Min:10 mg/ml



Max: 25mg./ml

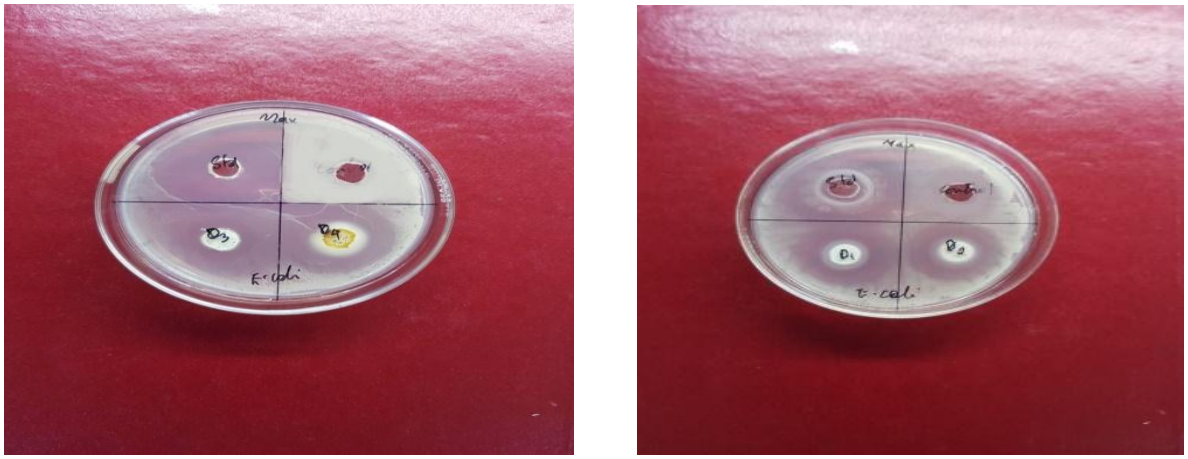


Figure no. 3.

Zone of inhibition of the sensitive compounds against *Pseudomonas aeruginosa*

Min:10 mg/ml

Max: 25mg/ml

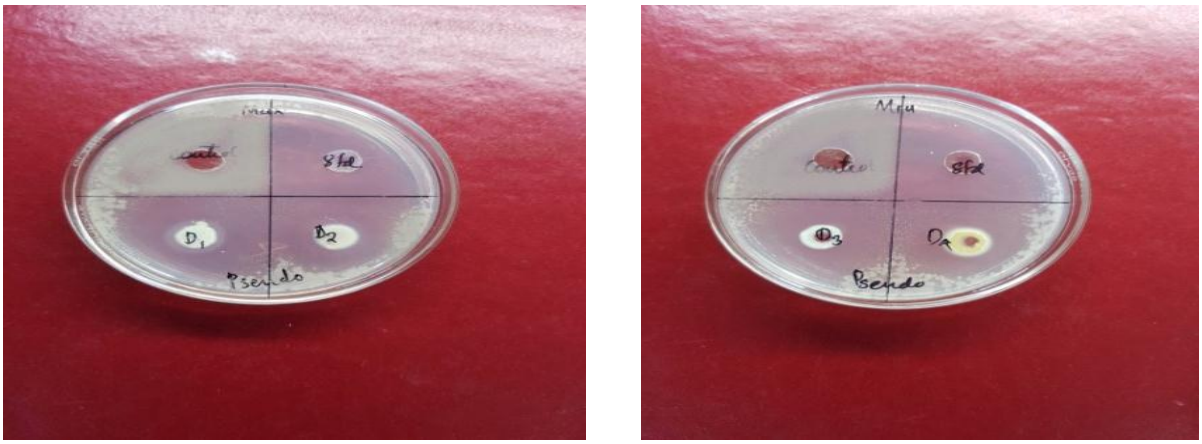


Figure no. 4.

The compound 2a was highly sensitive at 10mg/ml & 25mg/ml against both Gram positive & Gram negative bacteria. The compound 3a & 1a was Moderately sensitive at 10 mg/ml& 25 mg/ml against both Gram positive & Gram negative bacteria. The compound 4a was less sensitive at 10mg/ml & 25mg/ml against both Gram positive & Gram negative bacteria

CONCLUSION

The four derivative of Ethyl-4-(4-Alkylphenyl)-6-methylsulfanyldine-1,2,3,4-tetrahydropyrimidine-5-carboxylate are synthesised via bignelli condensation reaction and the newly synthesised compounds are evaluated for antibacterial activity. The purity of the compound were confirmed by single spot on TLC the structure of the compound were assigned based upon the spectral data. The IR data showed that the compounds were found to have the expected peak signal. The antimicrobial study shows that the parahyrdoxy derivative of pyrimidine have the significant antibacterial activity.

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