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Dihydropyrimidine Derivatives as an Antimicrobial agent.

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ABSTRACT:
Three2-oxo-6-methyl-4-(substituted-benzaldehyde)-5N-(1-pyrroline-2,5-dione)-carboxamide-1,3-dihydropyrimidine (Ia-Ic) have been synthesized in a three step reaction. In first step2-oxo-4-(substituted-benzaldehyde)-5-ethylcarboxylate-6-methyl-1,3dihydropyrimidine(Ia-Ic)and in second step 2-oxo-6-methyl-4-(substituted-benzaldehyde)-1,3-dihydropyrimidine-5-carbonyl- hydrazine (IIa-IIc). Third step involves synthesis of2-oxo-6-methyl-4-(substituted-benzaldehyde)-5N-(1-pyrroline-2,5-dione)-carboxamide-1,3-dihydropyrimidine (IIIa-IIIc). Their structures are confirmed by IR, 1H-NMR, C13NMR and Mass. The compounds were tested for antimicrobial, antifungal activity by Muller-Hinton agar (Hi-Media) medium for antibacterial activity and Sabouraud's dextrose agar (Hi-Media) medium for antifungal activity. The activity of synthesized compounds was reported by cup plate method measuring the diameter of inhibition zone (in mm). The results showed that synthesized compounds IIIa, and IIIb exhibited good antibacterial activity against S. aureus and compound IIIa shows good antibacterial activity against E. coli at the concentration of 500 µg/ml when compared with the ciprofloxacin. The result of antifungal activity showed that compound IIIa is effective as compared with the standard miconazole. All compounds were found to be ineffective at concentration of 50 µg /ml against all tested strains of fungi.

KEYWORDS- Beta-dicarbonyl, Quinolinodihydropyrimidines; MW assisted synthesis; Sabouraud's dextrose agar (Hi-Media) medium for antifungal activity. Three component reaction; Antibacterial activity; Antifungal activity.

I. INTRODUCTION:-

Pyrimidine was first isolated by Gabriel and Columan in 1899 [01:] Pyrimidine is an aromatic heterocyclic organic compound one of the three diazines (six-member heterocyclic with two nitrogen atoms in the ring), it has the nitrogens at positions 1 and 3 in the ring In nucleic acids, three types of nucleobases are pyrimidine derivatives: cytosine (C), thymine (T), and uracil (U).

The pyrimidine ring system has wide occurrence in nature substituted and ring fused compounds and derivatives, including the nucleotides, thiamine (vitaminB1) and alloxan found in barbiturates and the HIV drug, zidovudine. Although pyrimidine derivatives such as uric acid and alloxan were known in the early 19th century, a laboratory synthesis of a pyrimidine was not carried out until 1879, when Grimaux reported the preparation of barbituric acid from Ivy urea and malonic acid in the presence of phosphorus oxychloride. The systematic study of pyrimidines began in 1884 with Pinner, who synthesized derivatives by condensing ethyl acetoacetate with amidines. Pinner first proposed the name "pyrimidin" in 1885[02].

Microbial Infection: Infection is the invasion of a host organism's bodily tissues by disease-causing organisms, their multiplication and the reaction of host tissues to these organisms and the toxins they produce. Infectious diseases, also known as transmissible diseases or communicable diseases, comprise clinically evident illness (i.e., characteristic medical signs and/or symptoms of disease) resulting from the infection, presence and growth of pathogenic biological agents in an individual host organism[03].

Antimicrobial agents : Chemical compounds biosynthetically or synthetically produced which either destroy or usefully suppress the growth of metabolism of a variety of microscopic or submicroscopic forms of life. An antimicrobial is a substance that kills or inhibits the growth of microorganisms such as bacteria, fungi, protozoa[04]

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II. EXPERIMENTAL

2.1. General reaction: Scheme for synthesis of substituted 1, 3-dihydropyrimidine derivatives

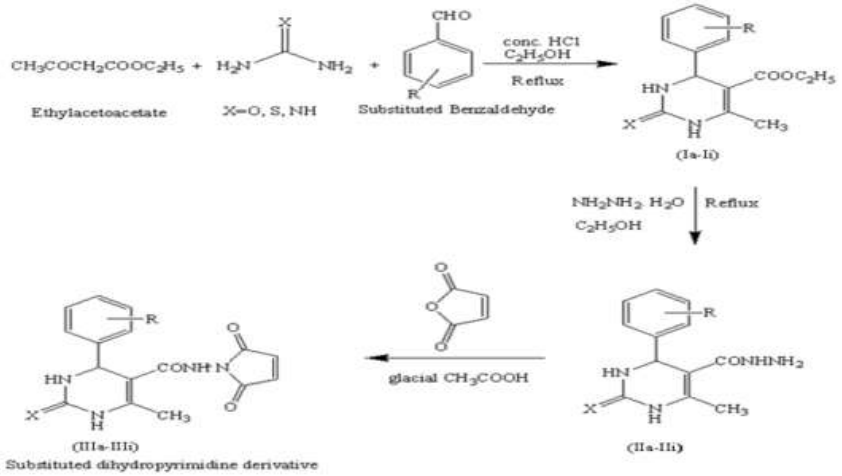

Fig 1 : Scheme for synthesis of substituted 1, 3-dihydropyrimidine derivatives

2.2. Various substitutions of synthesized compounds (IIIa-IIIc).

compound	X	R
IIIa	-O	-4-NO_2
IIIb	-S	4-$N(CH_3)_2$
IIIc	-NH	-4-NO_2

Table 1. Various substitutions of synthesized compounds

General Procedure for Synthesis of Compound (IIIa-IIIb)

Step-1 :2-oxo-4-(substituted-benzaldehyde)-5-ethylcarboxylate-6-methyl-1,3dihydropyrimidine (IIIa-IIIc) [05].

A mixture of 0.15mole of thiourea /urea/guanidine, 0.1mole of ethylacetoacetate and 0.1mole of benzaldehyde were dissolved in 25ml of ethanol along with 3 drops of concentrated HCl and refluxed for three and half an hours. The reaction mixture was then poured into 100 ml ice cold water with stirring and left over night at room temperature, filtered and the product was dried and recrystallized using ethanol.

Step-2:2-oxo-6-methyl-4-(substituted-benzaldehyde)-1,3-dihydropyrimidine-5-carbonyl-hydrazine (IIIa-IIIc)[06].

A mixture of 0.1 mole of above biginelli compound and 0.1 mole of hydrazine hydrate were dissolved in 20 ml of ethanol along with 4 drops of concentrated H_2SO_4 and refluxed for 3 hours. Reaction mixture was evaporated to obtain the residue of hydrazido product.

Step-3:2-oxo-6-methyl-4-(substituted-benzaldehyde)-5N-(1-pyrroline-2,5-dione)-carboxamide-1,3-dihydropyrimidine (IIIa-IIIc) [06].

About 0.5 gm of hydrazido product and 0.5 gm of maleic anhydride, 5 ml glacial acetic acid was refluxed for one and half hour. The reaction mixture was then poured in ice cold water in a beaker, filtered and dried. The precipitate was then recrystallized from using ethanol.

Mechanism of reactions involved in synthesis [07]:

Step- 1.The first step involves cyclization of beta-dicarbonyl compounds with N-C-N compounds. Reaction of the former with amidine to give 2-substituted pyrimidine, with urea to give 2-pyrimidiones, and guanidine to give 2-aminopyrimidines are typical .The first stage involves a nucleophilic attack on the fairly +ve C-atom by lone pair of on the N-atom. In second

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stage, the C-O double bond reforms and at last stage, removal of hydrogen ion from the nitrogen.

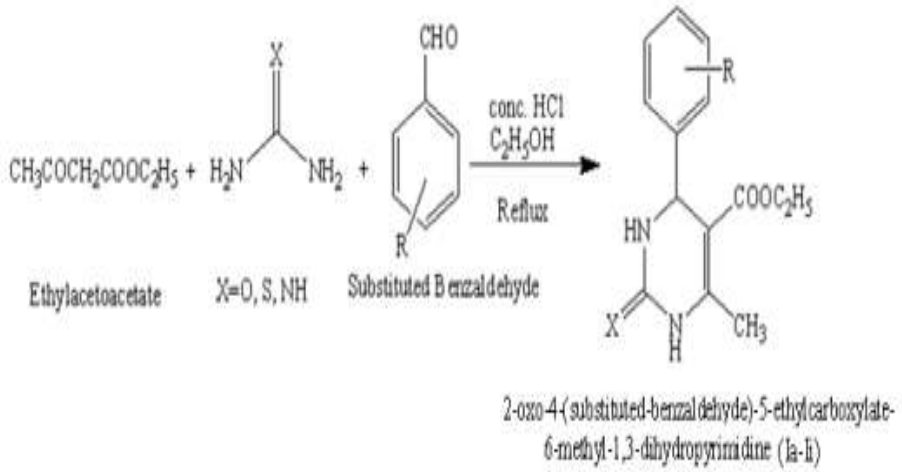

Fig 2 : mechanism of reaction for synthesis of substituted 1, 3-dihydropyrimidine derivatives

Step-2- Nucleophilic substitution reaction

In this step the primary amines i.e. hydrazine hydrate acts as nucleophile which attacks on carbonyl carbon atom of compound (Ia-Ib).The resulting compound (IIa-IIb**)** is obtained with liberation of water molecule. The reaction begins by 1,2-addition of the nitrogen on the carbonyl carbon. This is followed by transfer of a proton from the nitrogen to the oxygen and then 1,2-elimination of hydroxide. Finally the hydrogen is removed from the nitrogen.

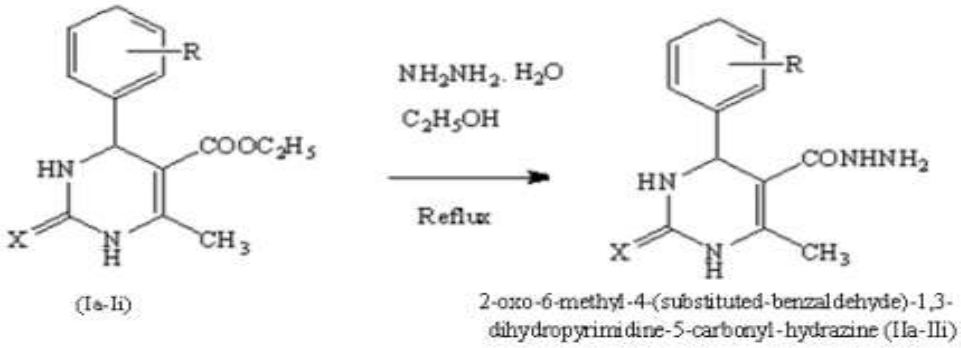

Fig.3: Mechanism of reaction for synthesis of 1, 3- dihydropyrimidine derivative.

Step-3-Nucleophilic substitution reaction

In this step the primary amines i.e. compound (IIa-IIc) acts as nucleophile which attacks on maleic anhydride. The resulting compound (IIIa-IIIc) is obtained with liberation of water molecule.

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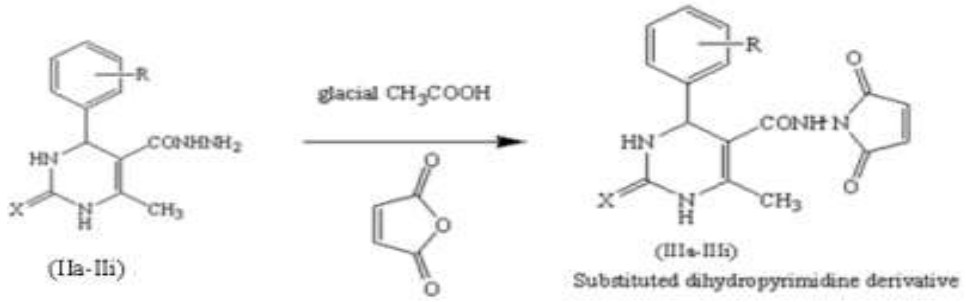


Fig 4: Nucleophilic substitution reaction for synthesis of substituted 1, 3-dihydropyrimidine derivatives

Physicochemical data of synthesized compounds (IIIa-IIIc)

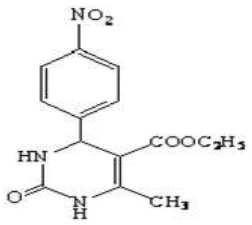
Compounds	**Colour**	**Melting point* (^{0}C)**	**Yield (%)**	**Molecular Formula (Mol. Wt.)**	**Rf value****
IIIa	White	148-150	75.66	$C_{16}H_{12}N_5O_6$ (370)	0 0.62#
IIIb	Orange	200-210	60.32	$C_{18}H_{18}N_5O_3$ S (384)	0.58#
IIIc	Red	276-280	71.46	$C_{16}H_{13}N_6O_5$ (369)	0.59##

Table 2: Physicochemical data of synthesized compounds (IIIa-IIIc)

***Uncorrected , Mobile Phase Cyclohexane:Water (8:2)**
Cyclohexane:Water (9:1)
Methanol:Ethyl acetate (8:2)

Spectral Data of Synthesized Compounds.

1) 2-oxo-4-(4–nitrophenyl)-5-ethylcarboxylate-6-methyl-1,3-dihydropyrimidine (IIIa).



(compound IIIa)

Characterization

I) Infrared absorption spectrum of compound IIIa

The potassium bromide pellets containing compound Ia was prepared to record the spectrum in the range of 4000-500 cm^{-1} by using FT-IR spectrophotometer as shown in Fig. 5 and spectral analysis is shown in Table 3.

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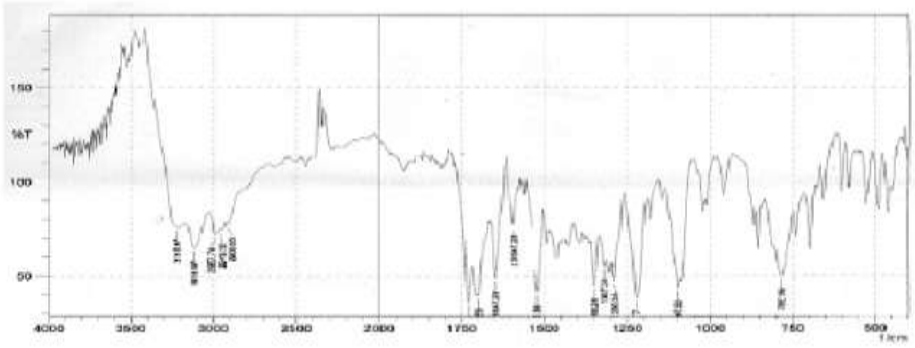

Fig.5: FT-IR spectrum of compound IIIa

Frequency (cm^{-1})	Assignment
3418.52	Sec. N-H stretching
3120.32	Aromatic C-H stretching
2987.74,2817.14	Aliphatic C-H stretching
1547.21	N=O stretching
1730.20	C= O stretching in ester

Table 3. FT-IR spectral analysis of compound IIIa

Mass spectrum of compound IIIa

Mass spectrum of compound IIIa is shown in Fig. 6 and spectral analysis is shown in Table 4

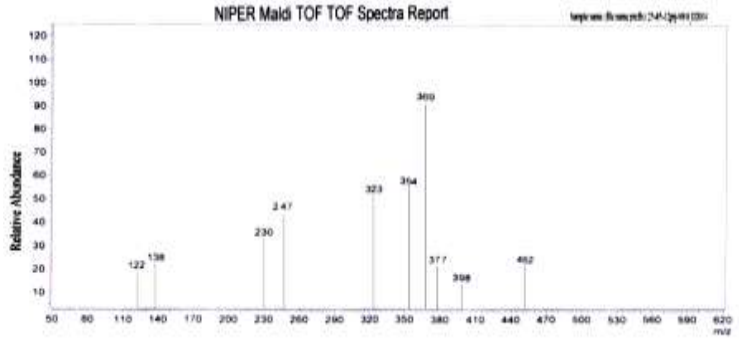

Fig 6 : Mass spectrum of compound IIIa

(m/z)	(m/z)
122	323
138	354
230	369
247	

Table 4: Mass spectral analysis of compound IIIa

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c) NMR spectrum of compound IIIa

NMR spectrum of compound **IIIa** is shown in **Fig. 7**and spectral analysis is shown in **Table 5.**

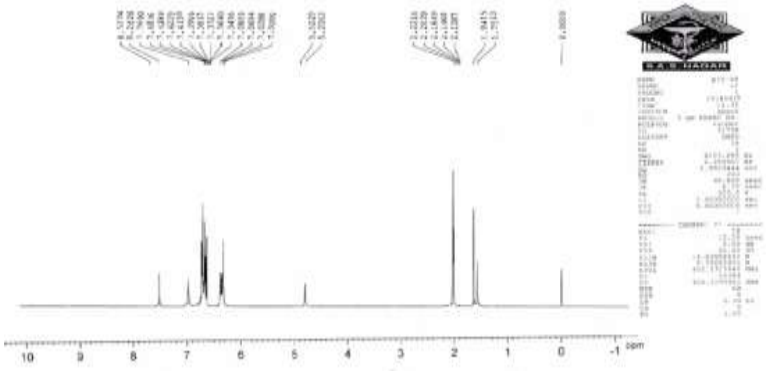
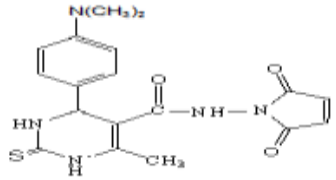


Fig. 7: NMR Spectrum of compound IIIa

(δppm)	Assignment
7.4133	dArH
5.2163	s CH
8.2076	s NO_2
1.7413	s1H- NH
8.5294	S3H- NH
7.7692	SNH
2.2345	s CH_3

Table 5. NMR spectral analysis of compound IIIa

2)2-thio-6-methyl-4-(4-dimethylamino-phenyl)-5N-(1-pyrolline-2,5-dione)-carboxamide-1,3-dihydropyrimidine (IIIb).



(compound IIIb)

Characterization

a) Infrared absorption spectrum of compound IIIb

The potassium bromide pellets containing compound IIIg was prepared to record the spectrum in the range of 4000-500 cm^{-1} by using FT-IR spectrophotometer as shown in Fig.08 and spectral analysis is shown in Table 6.

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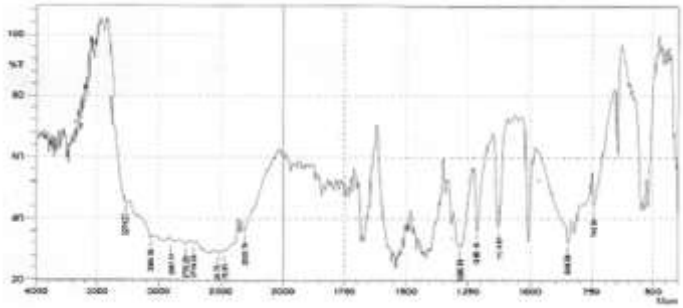


Fig. 8: IR Spectrum (KBr, cm^{-1}) of compound IIIb

Frequency (cm^{-1})	Assignment
3274.20	Sec. N-H stretching
3044.27	Aromatic C-H stretching
2987.74, 2892.24	Aliphatic C-H stretching
1108.51	C= Sstretching

Table 6. FT-IR spectral analysis of IIIb

b) Mass spectrum of compound IIIb

Mass spectrum of compound IIIb was shown in Fig.11 and spectral analysis was shown in Table 7.

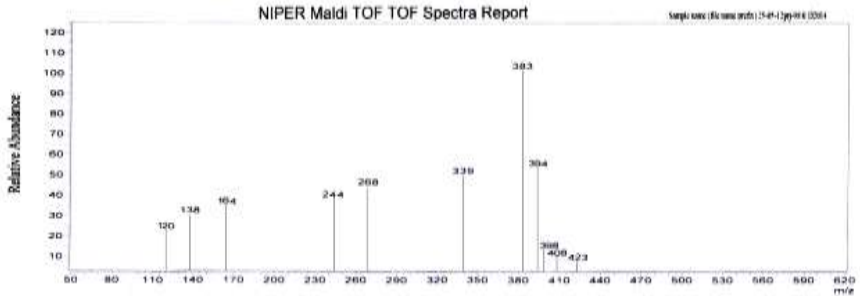
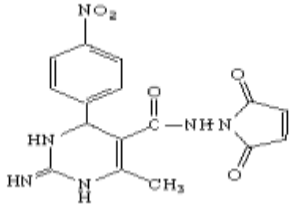


Fig.9: Mass spectrum of compound IIIb

(m/z)	(m/z)
120	268
138	339
164	383
244	

Table 7. Mass spectral analysis of compound IIIb

3)2-imino-6-methyl-4-(4-nitrophenyl)-5N-(1-pyrroline-2,5-dione)-carboxamid 1dihydropyrimidine (IIIc)



(compound IIIc)

Characterization

a) Infrared absorption spectrum of compound IIIc

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The potassium bromide pellets containing compound IIIi was prepared to record the spectrum in the range of 4000-500 cm^{-1} by using FT-IR spectrophotometer as shown in Fig. 12 and spectral analysis is shown in Table 8.

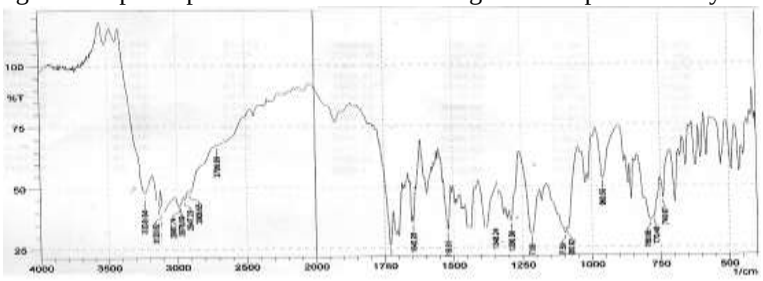

Fig. 10. IR Spectrum (KBr, cm^{-1}) of compound IIIc

Frequency (cm^{-1})	Assignment
3320.44	Sec. N-H stretching
3120.82	Aromatic C-H stretching
2978.00, 2836.85	Aliphatic C-H stretching
1510.81	N=O stretching
1625.29	C=O stretching
1670.24	C=N stretching

Table 8. FT-IR spectral analysis of IIIc

b) Mass spectrum of compound IIIc

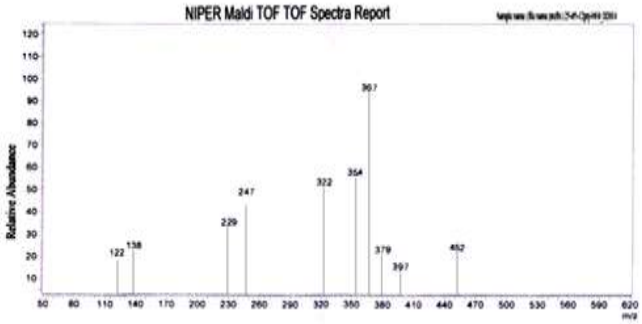

Fig.11 : Mass spectrum of compound IIIc

(m/z)	(m/z)
122	322
138	354
229	367
247	

Table 9: Mass spectral analysis of compound IIIc

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Antibacterial and antifungal screening [08].

The preliminary antibacterial activity of synthesized compounds was studied against E. coli, S. aureus and antifungal activity of compounds were studied against A. niger Ciprofloxacin and Miconazole were used as standard for antibacterial and antifungal activity respectively. The agar dilution method was performed using Muller-Hinton agar (Hi-Media) medium for antibacterial activity and Sabouraud's dextrose agar (Hi-Media) medium for antifungal activity. This method depends on the diffusion of drug from bore through the solidified agar layer of a petri dish to an extent such that growth of the inoculated micro-organism is prevented entirely in a circular area "zone" around the cup containing the solution of a compound under test. The medium was sterilized by autoclaving at 12-15 lb pressure for 30 minutes. One loopful of the stock culture was inoculated at 10 ml of agar slant previously in sterilized test tubes, and incubated at 37^0 C for 24 hrs and 7 days respectively for bacteria and fungi. About 3 ml of distilled water was added to the test tube and suspension of the culture was obtained by shaking for few minutes.

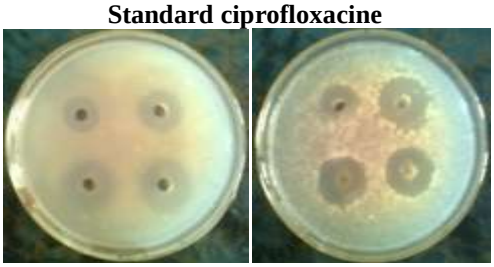
Procedure for antimicrobial activity [09].

All the operations were carried out under aseptic conditions. Sterile medium was melted on water bath and kept at 45 ^{0}C in constant temperature water bath. In each sterile petri dish molten medium was added so that thickness was approximately 4-5 mm and sub cultured organism under study was inoculated. The inoculated dishes were allowed to set for 30 min at room temperature. Cups of 6 mm diameter were then made with the help of sterile stainless steel bore; 1ml of test solution was added to each cup. Petri dishes were kept in refrigerator for 30 minutes so as to allow diffusion of the solutions in the medium, and then incubated at 37 ^{0}C for 24 hrs for antibacterial activity and 72 hrs for antifungal activity. Zone of inhibition produced by test compounds were measured in mm. The results are shown in tables and figures.

Table 10: Result of Bacteria/Fungi along with zone of inhibition (mm) zone of inhibition

Compound	Bacteria/Fungi along with zone of inhibition (mm)											
	S. aureus				*E. coli*				*A. niger*			
	50 µg/ml	100 µg/ml	200 µg/ml	500 µg/ml	50 µg/ml	100 µg/ml	200 µg/ml	500 µg/ml	50 µg/ml	100 µg/ml	200 µg/ml	500 µg/ml
IIIa	09	12	15	17	8	11	16	19	-	13	16	20
IIIb	9	15	17	20	-	-	9	15	-	-	10	14
IIIc	-	-	12	14	-	06	10	16	-	7	15	16
Ciprofloxacin	16	18	21	24	14	19	22	25	-	-	-	-
Miconazole									15	19	24	30

Standard ciprofloxacine



E. coli S.Aureus

Standard miconazole

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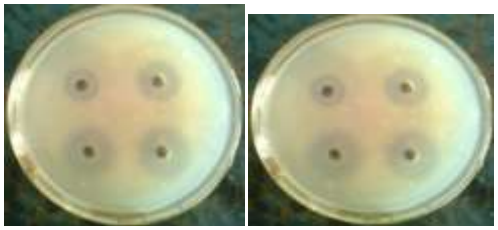
Fig. 12: Photograph showing zone of inhibition by standard ciprofloxacin against S. aureus, ciprofloxacin against E. coli and miconazole against fungi A. niger



Compound IIIa Compound IIIb

Compound IIIc

Fig. 13: Photograph showing zone of inhibition by compound IIIa-IIIc against S.aureus.

Compound IIIa Compound IIIb

Compound IIIc

Fig. 14: Photograph showing zone of inhibition by compound IIIa-IIIi against E. coli.

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Compound IIIa Compound IIIb

Compound IIIc

Fig. 15: Photographs showing zone of inhibition by compound IIIa-IIIc against fungi A. niger.

III. DISCUSSION AND CONCLUSION

Substituted1,3-dihydropyrimidine derivatives have been reported to possess different biological activities like anticancer, anthelmintic, anti-diabetic, anti-inflammatory, anticonvulsant, antimicrobial etc. So the present work was done to synthesize some substituted 1,3-dihydropyrimidine derivatives and evaluated for antimicrobial activity (antibacterial and antifungal).

Synthesis : In present investigation, cyclization of beta-dicarbonyl compounds with N-C-N gave the compound 2-substituted pyrimidine. With urea gave 2-oxo-6-methyl-4- (substituted phenyl)-1,3-dihydropyrimidine-5-carboxylate Ia, With thiourea gave 2-thio-6-methyl-4-(substituted phenyl)-1,3-dihydropyrimidine-5-carboxylate Ib with guanidine gave 2-imino-6-methyl-4-(substituted phenyl)-1,3-dihydropyrimidine-5-carboxylate The compound I was treated with hydrazine hydrates (NH_2NH_2) and ethanol (C_2H_5OH). Compound Ia gave 2-oxo-6-methyl-4-(substituted phenyl)-1,3-dihydropyrimidine-5-carbonyl-hydrazine (IIa)compound (Ib) gave 2-thio-6-methyl-4-(substituted phenyl)-1,3-dihydropyrimidine-5-carbonyl-hydrazine (IIb).The compound (II) was treated with maleic anhydride in glacial acetic acid, compound (IIa) gave 2-oxo-6-methyl-4-(substituted-phenyl)-5N-(1-pyrroline-2,5-dione)-carboxamide-1,3-dihydropyrimidine (IIIa), compound (IIb) gave 2-thio-6-methyl-4-(4-substituted-phenyl)-5N-(1-pyrroline-2,5-dione)-carboxamide-1,3-dihydropyrimidine (IIIb), The synthesis procedure is given in scheme. The spectral data of synthesized compound (IIIa-IIIc) are listed in Table 5 to Table 09. The compound Ia display characteristic absorption bands in IR spectrum at 3418.52 cm^{-1} due to N-H stretching and at 1730.20 cm^{-1} due to C-O stretching in ester. The compound IIa display characteristic absorption bands at 3470.91 cm^{-1} and 3106.91 cm^{-1} due to -NH_2 functional group and 3176.01 cm^{-1} due to -NH functional group and at 1643.70 cm^{-1} due to C-O stretching in amide. The compound IIIa display characteristic absorption bands at 3320.48 cm^{-1} due to -NH functional group and there is disappearance of bands of -NH_2functional group .

A) 2-oxo-6-methyl-4-(4–nitrophenyl)-5N-(1-pyrroline-2,5-dione)-carboxamide-1,3-dihydropyrimidine (IIIa)

Yield 75.66%, colour-yellow, molecular weight 370, melting point 148-150ºc, IR (kbr) 3320.48 cm^{-1} (N-H stretching), 3110.83 cm^{-1} (Aromatic C-H stretching), 2915.30 cm^{-1}, 2812.20 cm^{-1} (Aliphatic C-H stretching), 1521.84 cm^{-1} (N=O stretching), 1647.21 cm^{-1} (C=O). Rf value 0.62 (cyclohexane: water, 8:2).

B) 2-thio-6-methyl-4-(4-dimethylaminophenyl)-5N-(1-pyrolline-2,5-dione)-carboxamide-1,3-dihydropyrimidine (IIIb)

Yield 60.32 %, colour-orange, molecular weight 384, melting point 200-202ºC, IR (KBr) 3274.20 cm^{-1} (N-H stretching), 3044.27 cm^{-1} (Aromatic C-H stretching), 2987.74 cm^{-1} , 2892.24 cm^{-1} (Aliphatic C-H stretching), 1108.51 cm^{-1} (C=S stretching). Rf value 0.58 (cyclohexane: water, 8:2).

C) 2-imino-6-methyl-4-(4-nitrophenyl)-5N-(1-pyrroline-2,5-dione)-carboxamide-1,3-dihydropyrimidine (IIIc)

Yield 71.46 %, colour- red, molecular weight 369, melting point 276-278ºC, IR (KBr) 3320.44 cm^{-1} (N-H stretching), 3120.82 cm^{-1} (Aromatic C-H stretching), 2978.00 cm^{-1}, 2836.85 cm^{-1} (Aliphatic C-H stretching), 1510.81 cm^{-1} (N=O stretching),

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1625.29 cm^{-1} (C=O stretching), 1670.24 cm^{-1} (C=N stretching). Rf value 0.59 (methanol: ethyl acetate, 8:2).

Antimicrobial activity

In vitro antimicrobial activities of synthesized compounds were studied by cup plate method using Ciprofloxacin and Miconazole as standard for antibacterial and antifungal activity respectively. The synthesized compounds were evaluated for their anti-bacterial activity against S. aureus and E. coli and antifungal activity against A. niger.The activity of synthesized compounds was reported by measuring the diameter of inhibition zone (in mm)[10]. The results showed that synthesized compounds IIIa, and IIIb exhibited good antibacterial activity against S. aureus and compound **IIIa** shows good antibacterial activity against E. coli at the concentration of 500 µg/ml when compared with the ciprofloxacin.

The result of antifungal activity showed that compound **IIIa** is effective as compared with the standard miconazole. All compounds were found to be ineffective at concentration of 50 µg /ml against all tested strains of fungi.

IV. CONCLUSION

In the present study, an attempt has been made to synthesize and characterize some 1,3-dihydropyrimidine derivatives and to evaluate them for their antimicrobial activity.

The compounds were prepared as per reported procedure in literature with a good yield. The physicochemical characteristic like melting point, % yield, Rf value was noted and data is given in Table 2. The infrared spectral analysis of each derivative has been carried out and data is given in Table 5,8 and 10. The in-vitro antimicrobial activity was also carried out by using Ciprofloxacin and Miconazole as standard for antibacterial and antifungal activity respectively. Compound **IIIa** and **IIIb** are effective against Gram-positive bacteria and compound **IIIa** effective against Gram-negative bacteria. Only compound **IIIa** effective against A. niger as compared with standard. This states that substitution with 4-nitrophenyl, 3-chlorophenyl, 4-hydroxyphenyl and 4-dimethylaminophenyl i.e. electron withdrawing groups at position 3 or 4 of the phenyl ring system favours the more antibacterial activity. Maximum concentration of derivative is required to produce effect, low concentration is not effective. Compound **IIIa** is effective against bacteria and fungi. 4-nitro substitution on phenyl ring is important to produce both antibacterial and antifungal activity.

V. SUMMARY

Antimicrobial agents are widely used in the management of infectious disease but the increase in drug-resistant bacterial strain isolate during recent years presents a therapeutic challenge to physicians selecting anti-microbial agents. The 1,3-dihydropyrimidine derivatives (IIIa-IIIc) has been synthesized as reported in general scheme.

Thiourea /urea/guanidine, as starting material, has been used for the preparation of different derivatives of 1,3-dihydropyrimidine. Thiourea /urea/guanidine was reacted with ethylacetoacetate and substituted benzaldehyde were dissolved in ethanol along with drops of concentrated HCl. The reaction mixture was then poured into ice cold water with stirring and left over night at room temperature, filtered and the product was dried and recrystallised using ethanol. It was reacted with hydrazine hydrate and ethanol along with drops of concentrated H_2SO_4 and last reaction with maleic anhydride . The prepared 1,3-dihydropyrimidine derivatives were subjected to physicochemical studies like melting point determination, TLC and % yield. The structures of 1,3-dihydropyrimidine derivatives were characterized by spectroscopy, FT-IR spectroscopy, Mass spectroscopy and NMR spectroscopy.

Antibacterial screening of newly synthesized compounds (IIIa-IIc) was carried out against E. coli, S. aureus and antifungal activity against A. niger according to cup-plate method.

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