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One-pot three component ($LaCl_3 \cdot 7H_2O$) catalysed biginelli reaction for the synthesis of 1,2,3,4-tetrahydropyrimidine

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ABSTRACT

A Series of tetrahydropyrimidine has been derived by $LaCl_3 \cdot 7H_2O$ catalysed one pot three component biginelli reaction. The compounds have synthesised from an aldehyde, ethyl acetoacetate and urea or thiourea in an ethanolic medium using a catalytic amount of ($LaCl_3 \cdot 7H_2O$). This method provides quantitative yield and the catalysis can be easily recovered from the reaction medium and be re-used.

***Keywords*:** Multicomponent reaction; Biginelli reaction; 1,2,3,4-tetrahydropyrimidine; one pot synthesis

1. INTRODUCTION

In recent years the growing interest on exploitation of Multicomponent reaction (MCR)[1-4] for the fast development of library of biologically active compounds. The promising greener route in terms of higher atom economy as compared to Multicomponent reaction one such MCR is the classical Biginelli[5] three component reaction which involves ($LaCl_3 \cdot 7H_2O$), catalysed. This work focuses on the synthesis of Biginellicompounds using lanthanide

trichlorideas acatalyst under solvent conditions at 80-70 °C. To the best of knowledgelanthanide trichloridehave been explored as a catalyst for Biginellicondensation reaction. There are few reports[6-8] the synthesis of 1,2,3,4-tetrahydropyrimidineusing of ($LaCl_3 \cdot 7H_2O$), in the presences of solvent but there is no report for the Biginellireaction[10-12] here in we wish to report first time a novel simple and efficient methodology for the synthesis of 1,2,3,4-tetrahydropyrimidinein moderate to good yields (65-90%) by reaction of aldehyde, ketoester and urea, thioureausing catalytic amount of ($LaCl_3 \cdot 7H_2O$), one pot strategy of a solvent condition.

2. EXPERIMENTAL MATERIALS AND METHODS

All reagents purchased were of analytical grade from the Alfa aesar chemical companies and used without further purification. Melting points were determined in open capillary tubes and uncorrected. Formation of the compounds was routinely checked by TLC on silica gel - Gplates of 0.5 mm thickness and spots were located by iodine vapours. The IR spectra were recorded on a shimadu FT-IR250 instrument using KBr pellet. The mass spectra were instrument respectively recorded on shimazdu LC-MS QP - 2010 modal using direct injection probe technique ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO (d_6) on a Bruker 300 MHz and 100 MHz spectrometer.

2. 1. General procedure

A mixture of methylacetoacetate (0.002 mol), urea (0.004 mol) or thiourea (0.004 mol), aldehyde (002 mol), $LaCl_3 \cdot 7H_2O$ (0.002 mol, in 25%) and 12 M HCl (1 drop) in an absolute ethanol 10 ml were refluxed in 25 ml RB flack for 5h. The contents were then poured in to ice, and solid precipitated was filtered and recrystallized with ethyl acetate (Scheme 1). The product formed 1,2,3,4-tetrahydropyrimidinewas checked with the literal melting point of Biginelli product. The above procedure was employed to prepare the entire compound.

4b. 1-4-(4-ethoxyphenyl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl)ethanone
IR (KBr, cm^{-1}); 3378, 3312 NH, 2943 ArH, 1661 (CO), ^{1}H NMR (400 MHz, DMSO - d_6); δ 9.62 (s, 1H), 7.0-7.1 (d, 3H), 5.11-5.10 (d, 1H, NH), 3.9-4.0 (m, 2H), 3.5 (s, 3H), 3.3 (s, 3H), 2.2 (s, 2H), 1.0-1.3 (t,5H), ^{13}C NMR (400 MHz, DMSO); δ 174, 158, 157, 135, 127, 114, 104, 78, 62, 59, 40, 39, 38, 17, 14. Mass: m/e 289 (M^+).

4c.Ethyl4-(5-bromothipen-2-yl)-6-methyl-2-oxo1,2,3,4tetrahydropyrimidine-5-carboxylate
IR (KBr, cm^{-1}); 3237, 3112(NH), 2973, 1708, 1648(CO), NMR (400 MHz, DMSO - d_6); δ7.9 (s, 2H), 7.04-7.06 (d, 2H), 6.71-6.72 (s, 1H), 5.32-5.33 (d, 2H, NH), 4.0-4.1 (t, 5H), 3.34 (s, 3H), 1.1-1.2 (m, 5H), ^{13}C NM (400 MHz, DMSO); δ 164, 152, 150, 149, 131, 129, 124, 109, 78, 59, 39, 17, 14. Mass: m/e 345 (M^+).

4d.1-(4-(5bromothiphen-2-yl)-6-methyl-2-thioxo-1,2,3,4tetrahydropyrimidine-5-yl) ethanone
IR (KBr, cm^{-1}); 3305, 3165 (NH), 2983, 1668, 1571 (CO), NMR (400 MHz, DMSO-d_6); 9.82 (s, 1H, NH), 7.0 (d, 2H), 6.72-6.73 (d, 2H), 3.6-4.1 (q, 2H, NH), 3.3 (s, 3H), 2.5 (s, 3H), 2.2

(s, 1H, NH), ^{13}C NMR (400 MHz, DMSO); 174, 165, 164, 148, 145, 130, 124, 110, 100, 59, 39, 17. Mass: m/e 331(M^+).

4e.ethyl6-methyl-2-oxo-4-(3,4,5-trimethoxyphenl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate

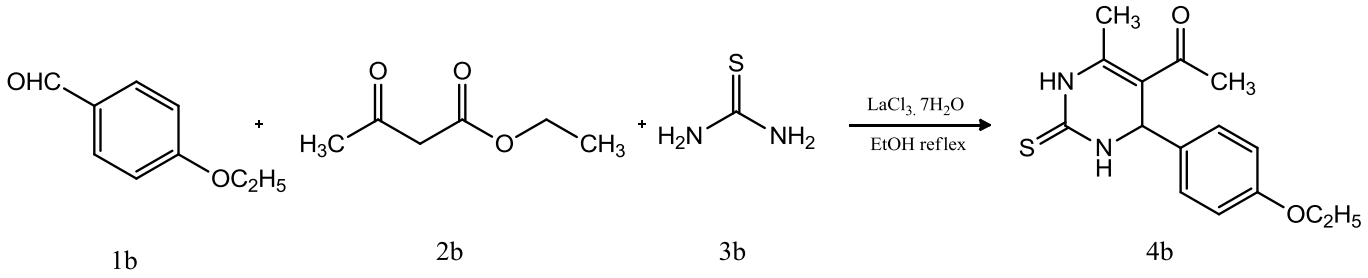
IR(KBr, cm^{-1}); 3232, 3015 (NH), 2938, 1717, 1653 (CO): NMR (400 MHz, DMSO-d_6); δ7.72 (s, 1H), 6.5 (s, 1H, NH), 5.1 (d, 2H, NH), 3.9-4.0 (q, 5H), 3.62 (s, 9H), 2.0-2.5 (m, 3H), 1.1-1.15 (m, 5H), ^{13}C NMR (400 MHz, DMSO); 165, 152, 148, 140, 136, 103, 99, 77, 59, 55, 40, 17, 14. Mass: m/e 351 (M^+)

3. RESULT AND DISCUSSION

The evaluation of the feasibility of using $LaCl_3 \cdot 7H_2O$ as a catalyst in the Biginelli reaction, (Scheme 1) utilizing building blocks such as 4-ethoxybenzaldehyde (1b) Methyl acetoacetate (2b) and thiourea (3b) to get 1-(4-(4-ethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethanone (4b), the reactions were performed under various reaction conditions and the results are summarized in Table 1.

The reaction of 1b, 2b and 3bin EtOH was first tested in the presence of 0.002 mol % of $LaCl_3 \cdot 7H_2O$ the desired product 4bwas obtained in 62% yield after 2 h (Table 1, entry 1). Next, optimization of reaction conditions was undertaken to increase the yield of the product using same amounts of $LaCl_3 \cdot 7H_2O$ and time version. Interestingly, the yield of 4bwas significantly increased to 65% by employing 0.002 mol % of the catalyst (Table 1, entry 2). Further improvement was not observed in terms of either reaction time increasing the same amount of catalyst (Table 1, entry 3).

Furthermore, the catalytic efficiency of $LaCl_3 \cdot 7H_2O$was examined using different solvents, which showed prominent influence on reaction time and yields to obtain desired products (Table 1, entries 4, 5). Water, THF and toluene were not found to be suitable solvents for the reaction; however excellent yield of the desired product was obtained using EtOH, although longer reaction time was required for the completion of reaction (Table 1, entry 6).



1b 2b 3b 4b

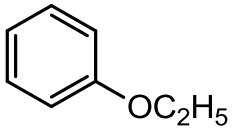
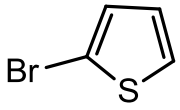
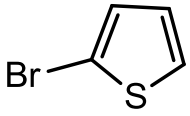
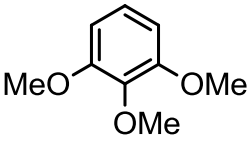
Scheme 1. $LaCl_3 \cdot 7H_2O$ catalysed synthesis of 4b.1-(4-(4-ethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethanone *Biginelli reaction.*

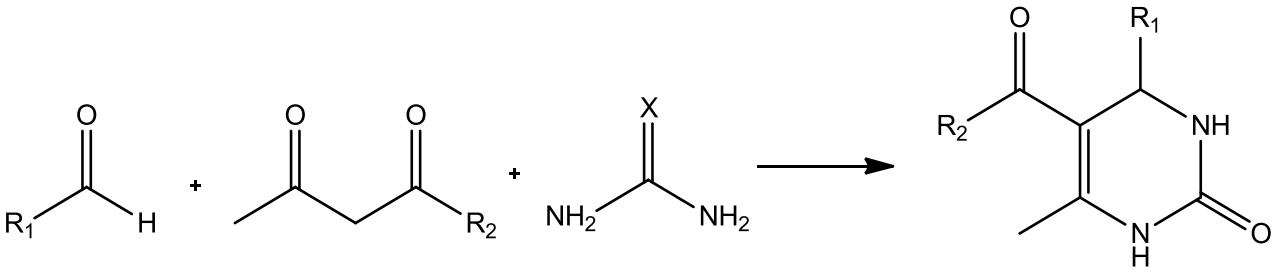
Reaction conditions: 4-ethoxybenzaldehyde (1b, 0.002 mol), Ethyl acetoacetate (2b, 0.005 mol), Urea (3b, 0.004 mol), $LaCl_3 \cdot 7H_2O$ (0.002 mol) reflux Isolated yield. Reaction was performed under solvent free Conditions.

Table 1. Optimization of reaction conditions for the synthesis of 1,2,3,4-tetrahydropyrimidine 4b

Entry	$LaCl_3 \cdot 7H_2O$ (Mol in 25 %)	Solvent	Time h	Yield %
1	0.002	EtoH	2	62
2	0.002	EtoH	3	65
3	0.002	EtoH	4	77
4	0.002	Water	2	58
5	0.002	THF	2	68
6	0.002	EtoH	5	94 This work

Table 2. $LaCl_3 \cdot 7H_2O$ catalyzed synthesis of 1,2,3,4-tetrahydropyrimidine.

Entry	R_1	R_2	X	Time	product	yield %	Ref
1		OMe	S	5	4b	94	13
2		OEt	O	5	4c	96	14
3		OMe	S	5.5	4d	95	15
4		OEt	O	5	4e	92	16



Reaction conditions: Aldehyde (0.002 mol), Dicarbonyl compound (0.002 mol), urea/thiourea (0.004 mol), EtOH (10 mL), $LaCl_3 \cdot 7H_2O$ (0.002 mol %), reflux. R_2 = OEt, R_2 = OMe, X = O, X = S,4 b. Isolated yield. Novel compound

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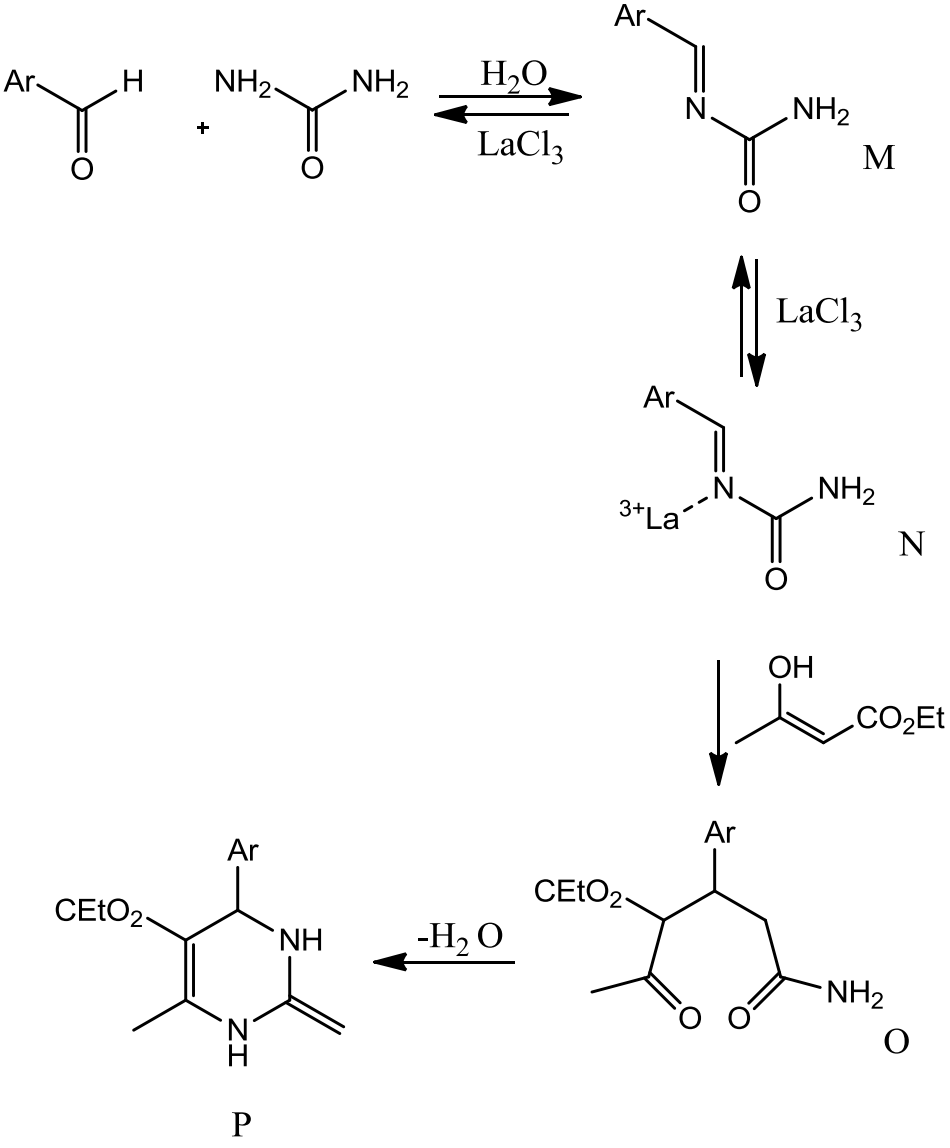


Scheme 2. Assumed mechanism for $LaCl_3 \cdot 7H_2O$ - catalyzed biginelli reaction.

The present study deals with the synthesis of newer tetrahydropyrimidine derivatives through Biginelli reaction. The structures of the titled compounds were confirmed by melting point, thin layer chromatography, infra-red analysis and NMR analysis.

To establish the generality and scope of present methodology, various aromatic and heteroaromatic aldehydes were treated with urea or thiourea and 1,3-dicarbonyl compounds under optimized reaction conditions to afford corresponding 1,2,3,4-tetrahydropyrimidineand the results are summarized in Table 2.

It was observed that the compounds containing both electron-withdrawing and electron-donating substituent's on aromatic ring reacted efficiently under the present reaction conditions to obtain corresponding 1,2,3,4-tetrahydropyrimidine (4a, 4e) in excellent yields and high purity.

The novel aspect of the present methodology was successfully extended to various heterocyclic, which proceeded smoothly to afford the corresponding 1,2,3,4-tetrahydropyrimidine (4c) in good to excellent yields. To generalize the catalytic efficiency of $LaCl_3 \cdot 7H_2O$ for the Biginelli reaction, we employed thiourea instead of urea under similar reaction conditions and obtained corresponding 1,2,3,4-tetrahydropyrimidine (4d) inhigh yields, which are also of much interest with regard to biological activity.

Comparatively, thiourea was found to be more reactive than urea (Table 2, entry 2). The mechanism of the Biginelli reaction has recently beenrevised by Kappe.[17] Based on this work we suggest the following mechanism for the $LaCl_3 \cdot 7H_2O$-catalyzed Biginelli reaction (Scheme 2).

The first step is the acid-catalyzed condensation of aldehydeand urea (or thiourea). The formation of *N*-acyl imineintermediate Mis the rate-limiting step of the reaction. The intermediate Mis complexed by lanthanide chlorides, giving N, which acts as an electrophile for the nucleophilicaddition of the ketoesterenol. The resulting adduct Oundergoes condensation with the urea-NH_2 to give the cyclized product P.

4. ANTIMICROBIAL ACTIVITY

All the synthesized compounds 4b – 4e were tested for their antibacterial and antifungal activity in vitro by agar disc diffusion methods[18-20] with the gram positive bacteria, three gram negative bacteria and three fungal activities. Stock cultures' were maintained at 5 °C on Nutrient agar slant active culture from the stock cultures in the test tube containing nutrient broth that were incubated for 24 h 37 °C.

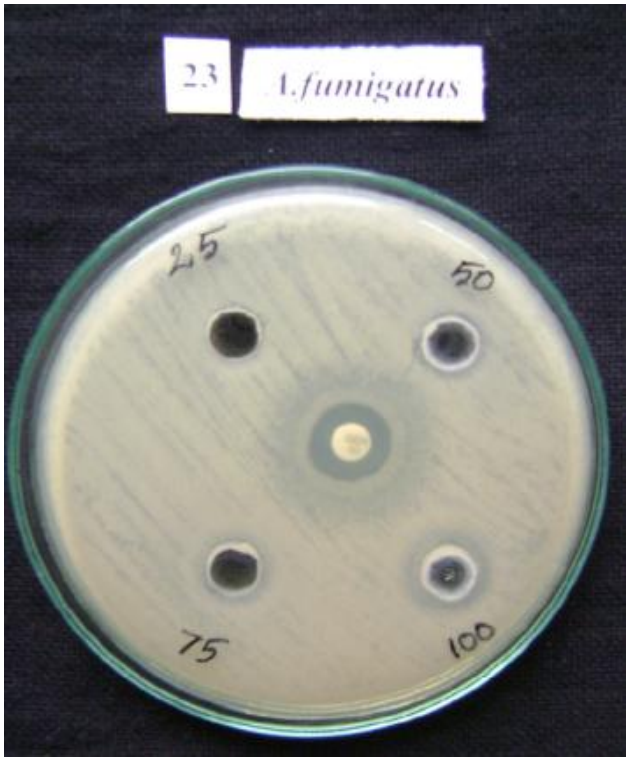
The assay was performed by agar disc diffusion method on Muller Hinton agar (MHA) medium. MullerHinton agar medium is poured into the petriplates, after themedium was solidified. The inoculums were spread on the solid plates with sterile swab moistened with the bacterial suspension. (*Staphylococcus aureus, Enterobacter, Bacillus subtillis, E. coli, Pseudomonas aeruginosa, Klebsiellapneumonia, Candida albicans, A. niger, A. fumicatus)* Table 3.

The disc was placed in MHA plate's and100µlof the sample concentration (25, 50, 75, and 100) were placed in the disc. The plates were incubated at 37 °C for 24 hrs then the antimicrobial activity was determined by measuring the diameter of zone of inhibition. (Figure 1).

Table 3. Data of in vitro antimicrobial activity of Compounds (4b-e).

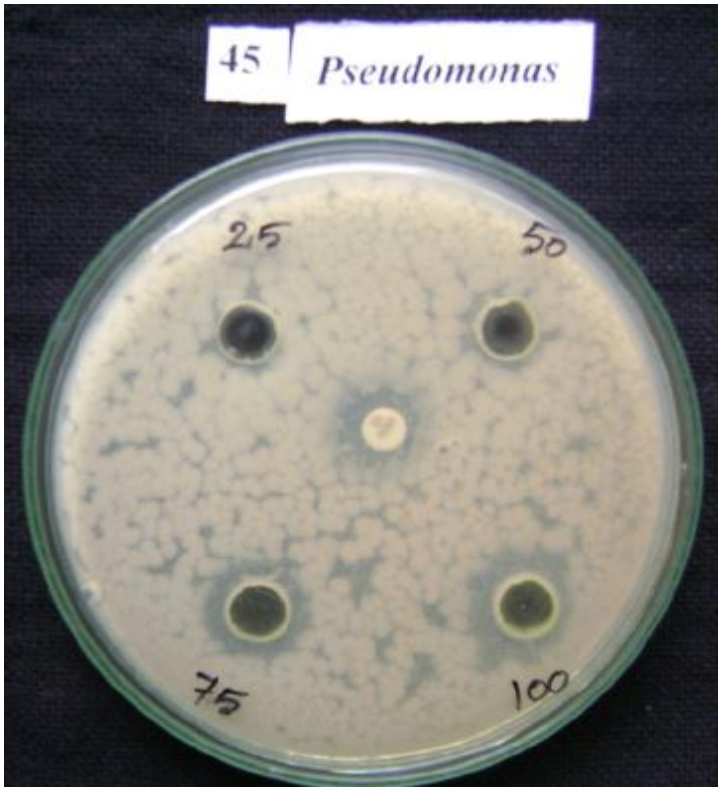
Compds	Zone of inhibition (mm)						Fungi		
	Gream positive bactria			Gream negative bactria					
	Staphylococcus aureus	*Enterobacter*	*Bacillus subtillis*	*E. coli*	*Pseudomonas aeruginosa*	*Klebsiellapneumoniae*	*Candida albicans*	*A. niger*	*A. fumicatus*
4b	14	15	29	20	18	14	14	18	17
4c	15	12	16	17	12	12	13	16	16
4d	18	16	20	22	20	24	18	25	21
4e	12	16	13	25	12	14	22	14	22
Gentamicin 100 µl	20	20	22	22	15	18	15	25	28

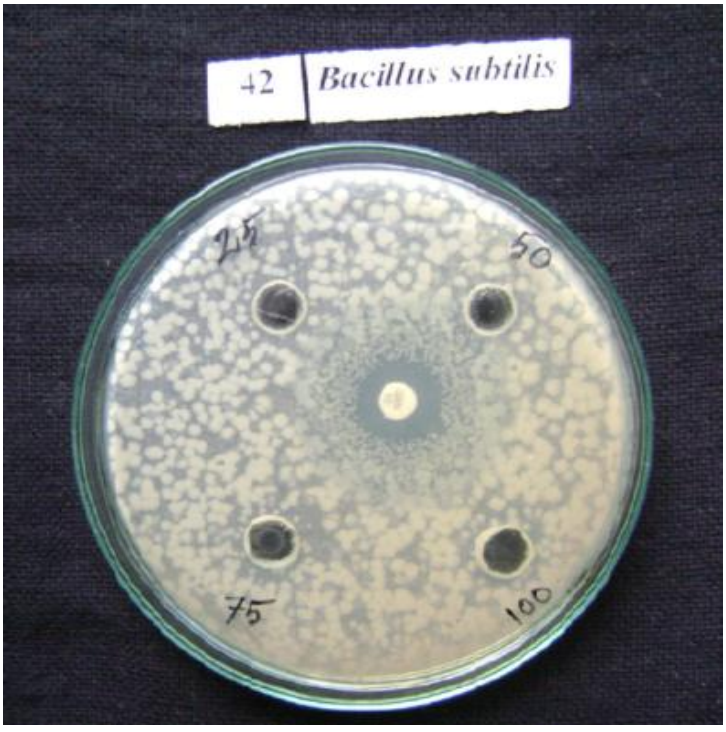

23
Candida albicans
25
50
75
100


23
A.fumigatus
25
50
75
100


42
A.niger
25
50
75
100


42
Entrobacter
25
50
75
100


45
Pseudomonas
25
50
75
100


42
Bacillus subtilis
25
50
75
100

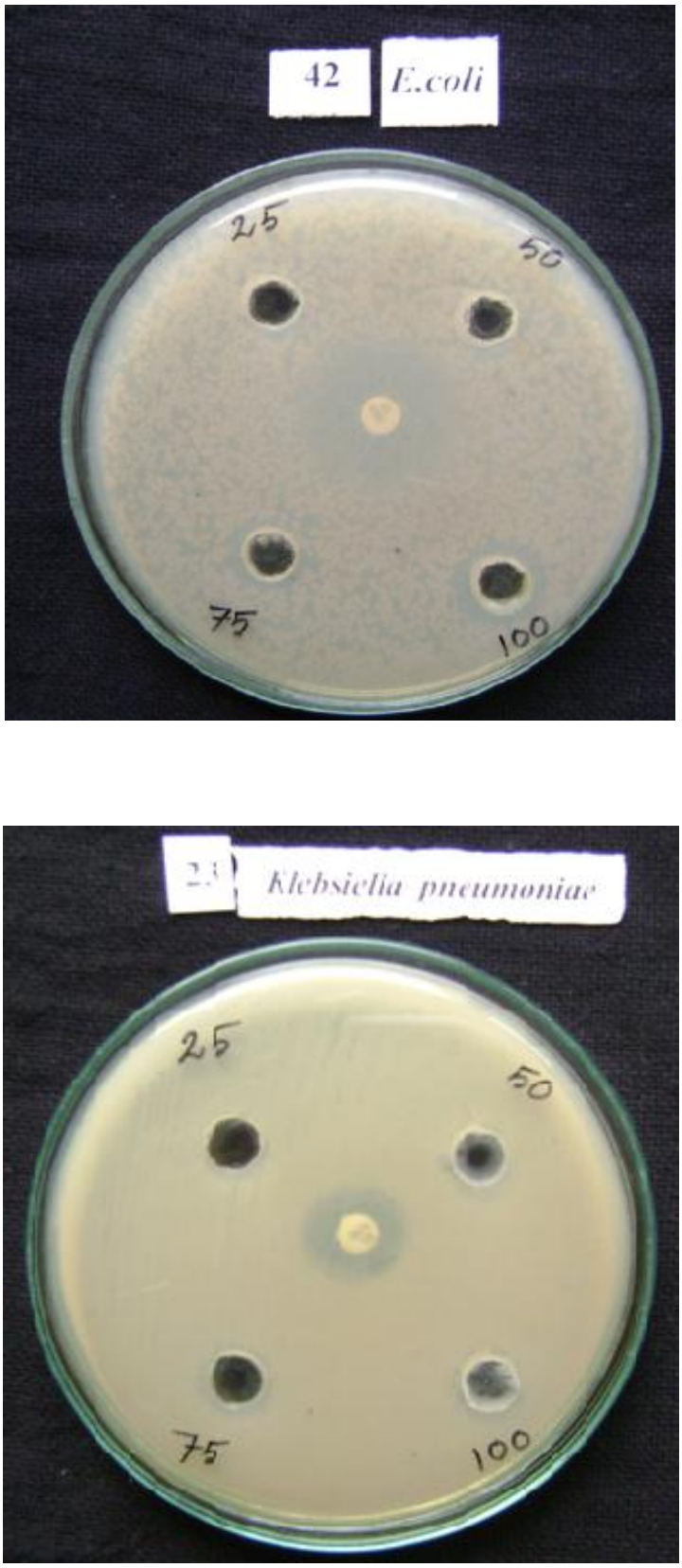


Figure 1. In vitro antibacterial and anti fungal activity.

5. CONCLUSION

A novel method for the synthesis of 1,2,3,4-tetrahydropyrimidineby threecomponent Biginelli condensations of aldehydes with dicarbonyl compounds and urea using reflex conduction ($LaCl_3 \cdot 7H_2O$) as catalyst under solvent-free and neutral conditions was developed on high yield for the first time. The main advantages of this methodology are: (1) relatively simple catalyst system; (2) long reaction times; (3) higher yields; (4) free of organic solvent, and (5) easy synthetic procedure. Further investigations of the scope and Mechanism of this reaction is under way.

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