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One Pot Synthesis and antibacterial activity of 4-phenyl-2-thioxo-1, 2, 3, 4-Tetrahydropyrimidine-5-Carboxylate analogous catalysed by Mg $(NO_3)_2$ as Catalyst

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ABSTRACT:

In the present study, the main focus for synthesis of to find a molecule bearing containing drug treatment means the drug which resists the antimicrobial activities scaffold due to microbial infection and study of the exploration of chemistry and medicinal diversity of pyrimidine-2-thiones. An efficient three component one pot synthesis of Methyl-6-methyl-4-phenyl -2-thioxo-1, 2, 3, 4-tetrahydro pyrimidineidin-5-yl) ethanone based on the reaction of readily available of starting molecules aromatic aldehyde, acetyl acetone and thiourea in presence followed by Mg $(NO_3)_2$ as a catalysed dehydration as well as solvent The products were prepared in good excellent yield under mild, solvent as well as catalysed conditions. The structure of these derivatives has been calculated on the basis of their advanced spectroscopic data ^{1}HNMR, ^{13}CNMR and LCMS spectral data and also structural determination was estimated by elemental analysis.

KEY WORDS:

Aacetyl acetone, aromatic aldehyde, thiourea, Mg $(NO_3)_2$, tetrahydropyrimidine-5-carboxylate, antimicrobial activities

1. INTRODUCTION:

Heterocyclic compounds with six members that contain nitrogen have been used extensively in medical chemistry. The most prevalent atoms in heterocyclic compounds are nitrogen, oxygen, and sculpture. Heterocyclic compounds are cyclic compounds that contain at least two different or the same elements as ring members. Numerous naturally occurring heterocyclic compounds, such as hormones, antibiotics, caffeine, and others, are abundant in nature and play a vital role in our daily live

One of the most important medical advancements in history is the antibacterial. Around the world, they are used to treat a variety of serious bacterial illnesses. Unfortunately, bacterial resistance has emerged as a result of the overuse and abuse of these drugs. The effectiveness of antibiotics, which for many decades

saved millions of lives, is under jeopardy due to these dangerous phenomena. Additionally, during the past three decades, the pharmaceutical industry has significantly reduced the number of new antibiotics it develops. As a result, the demand for novel, potent antibiotics to combat resistant bacteria keeps rising. Targeting the resistant microbe with a novel drug that has many mechanisms of action is one way to accomplish it

Pyrimidines and fused Pyrimidines represent a wide range class of compounds .which have received considerable attention because of their biological activities [11-14] in addition .the chemistry and the synthesis of 1, 2, 3, 4-tetrahydropyrimidine-2-thione have attracting wide spread attention in recent years. The present popularity of these tetrahydropyrimidine is mainly because of their close structural relationship to the clinically important dihydropyridines calcium-channel blockers and related compounds [15-16].1,2,3,4-tetrahydropyrimidine-2-thione is known as versatile heterocyclic compound that has been subjected to a large variety of structural modification in order to synthesized derivatives with different biological properties. Pyrimidines derivatives possessing anti-inflammatory and analgesic activities have been reported in the literature [17, 18]. In addition to the aforementioned activities and pyrimidine derivatives was possessing antitumor [19], antimicrobial [20]. Antibacterial [21], antifungal [22] and anti-infective [23] activities have also been reported in the literature.

This protocol was followed by the alkali metal nitrates catalysed three component reaction between a substituted aromatic aldehyde, 1, 3-dicorbanyal components and Thiourea. The Pyrimidine's skeleton available in a broadly of natural occurring compounds and also in clinically useful molecules having diverse biological activities and here it is great importance to Chemistry and Biology. Organic reactions under ethanol solvent conditions are of interest from both industrial and academic viewpoints.

MATERIALS AND METHOD

The entire chemicals were supplied by Finar and Sigma Aldrich Chemie Pvt. Ltd. Melting points were determined by open tube capillary method and were uncorrected. The 1H-NMR was recorded on Bruker advanced^{1}NMR-400MHz instruments using $CDCl_3$ as solvent and TMS (Tetra methylsilane) as internal standard, chemical shifts were expressed as δ values (ppm). Purity of compounds was checked by thin layer chromatography (TLC) on silica gel-G in solvent system hexane-ethyl acetate (1:1) and the spots were located under iodine vapours and UV light.

2.1. GENERAL PROCEDURE:

Methyl 6-methyl-4-phenyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate-2-thiones analogue was synthesised by heating a mixture of methyl acetate, substituted aromatic aldehyde, and thiourea in ethanol as a

solvent with I2 present for three hours while stirring. Thin layer chromatography was used to monitor the reaction mixture (4:6 ethyl acetate: n-hexane). Following the completion of the reaction conditions, thiourea was used to consume the reactants. The reaction mixture was rinsed with a saturated sodium bicarbonate solution after being placed into a beaker filled with ethyl acetate. Ethylacetae were vacuum-distilled from crude, and the product was then recrystallized using ethanol.

2.2.1.Methyl6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a):

Yield: 85%, pale-yellow solid; mp-210-212ºC ;^{1}H NMR (400 MHz, $CDCl_3$): δ ppm: 9.854(1H, s, NH), 9.516 (1H, s, NH), 7.754-7.321 (5H, m, Ar-H), 5.031(1H, d, J = 7.2Hz, CH), 3.660 (s,3H, OCH_3), 2.245 (s,3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm:173.81, 164.55, 145.72, 143.08, 128.18, 127.72, 126.65,102.73, 54.22, 49.49, 16.71; LCMS(m/z) :262.45. Molecular formulae: $C_{13}H_{14}N_2O_2S$.Elemental Analysis: calculated: C- 59.52, H-5.38 .N-10.68, Obtained: C-59.45, H-5.36, N-10.77.

2.2.2.Methyl4-(4-hydroxy-3,5-dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate(4b).

Yield: 89%, pale-yellow solid; mp -219-221ºC;^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.854 (1H, s, NH),9.450(1H, s, NH), 8.980 (1H, s, OH), 6.984 (2H, s, Ar-H), 5.204 (1H, d, J = 7.6Hz, CH), 3.774 (s,3H, OCH_3), 3.774 (s,3H,OCH_3), 2.128 (s,3H, CH_3); ^{13}C NMR (100 MHz,$CDCl_3$)δppm:174.58,165.86,147.06,144.66,136.28,132.87,103.98,101.10,55.77,54.54, 49.78,17.26;LC-MS(m/z):338.38.Molecularformule:$C_{15}H_{18}N_2O_5S$.ElementalAnalysis : Calculated:C-53.24, H-5.36.N-8.28,Obtained:C-53.20,H-5.34,N-8.34.

2.2.3.Methyl4-(3,5-dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate(4c):

Yield: 94%, pale-yellow solid; mp-231-233ºC; ^{1}H NMR (400 MHz,$CDCl_3$)δ ppm: 9.737 (s,1H, NH),9.598 (s,1H, NH), 7.194 (d, J =7.8Hz,2H, Ar-H), 7.125 (t, J = 8.0Hz, Ar-H), 5.044 (s,1H, -CH-), 3.754 (s,3H, OCH_3), 3.594 (3H, s, OCH_3), 2.530 (s,3H, CH_3); ^{13}C NMR(100MHz,$CDCl_3$)δppm:174.71,164.84,159.94,146.47,145.05,103.06,102.81,98.02,54. 76, 52.49, 50.26,16.79;LC-MS(m/z)-322.38.Molecularformule: $C_{15}H_{18}N_2O_2S$ .Elemental Analysis: calculated:C-55.88,H-5.63.N-8.69,Obtained:C-55.83,H-5.62,N-8.75.

2.2.4. Methyl 4-(3, 4, 5-trimethoxyphenyl)-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydro pyrimidine -5-carboxylate (4d):

Yield: 94%, pale-yellow solid; m.p -236-238ºC; ^{1}H NMR (400 MHz,$CDCl_3$)δppm : 9.820(s,1H, NH), 8.990 (s,1H, NH), 7.074 (s,2H, Ar-H), 5.052 (d, J = 8.8Hz,1H, -CH), 3.757 (s,9H,OCH_3), 2.378(s,3H,-CH_3);^{13}CNMR(100MHz,$CDCl_3$)δppm;175.86,164.78,153.78,146. 86,136.75,134.46,103.09,101.72,61.584,56.44,54.67,49.73,16.85;LCMS(m/z)-352.74 .Moleculaformule:$C_{16}H_{20}N_2O_5S$.ElementalAnalysis:calculated:C-54.53,H-5.72.N-7.95, Obtained:C-54.47,H-5.70,N-8.04.

2.2.5.Methyl4-(4-acetamidophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate(4e).

Yield: 87%, pale-yellow solid; mp-225-227ºC;^{1}H NMR(400 MHz, $CDCl_3$)δppm: 9.812 (s,1H, NH), 9.514 (s,1H, NH), 9.325 (s,1H,$NHCOCH_3$),7.870 (d, J = 7.4Hz,2H,Ar-H),7.518 (d,J =7.6Hz,2H,Ar-H), 5.047 (d, J =7.2Hz, -CH), 3.701 (s,3H,- OCH_3), 2.512 (s,3H, CH_3),2.020(s,3H,CH_3);^{13}CNMR(100MHz,$CDCl_3$)δppm:177.08,166.84,163.14,144.40,138. 72,136.90,126.80,118.22,99.57,53.71,51.85,23.16,17.40;LCMS:(m/z)-319.56.Molecular formule:$C_{15}H_{17}N_2O_2S$.ElementalAnalysis:calculated: C-56.41, H-5.37.N-13.16,Obtained:C-56.35,H-5.36,N-13.22.

2.2.6.Methyl4-(4-fluorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbo xylate(4f):

Yield: 89%, Yellow solid; mp-236-238ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:9.740 (s,1H, NH), 9.542 (s,1H NH), 7.746 (d, J = 8.4Hz,2H, Ar-H), 7.415 (t, J = 9.8, 2H,Ar-H), 5.087(d, J = 7.8Hz,1H,-CH),3.742(s,3H,-OCH_3),2.221(s,3H,-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$)δppm :176.09,166.52,162.58,145.16,138.04,128.59,114.28,100.78,53.26,50.45,17.37;LCMS(m/z): 280.87.Moleculaformule:$C_{13}H_{13}FN_2O_2S$.ElementalAnalysis: Calculated: C-55.70,H-4.67.N-9.99,Obtained:C-55.65,H-4.65,N-10.06

2.2.7.Methyl4-(2,4-dichlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate(4g):

Yield: 93%, Dark yellow solid; m.p 243-245ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 9.927 (s,1H, NH), 9.504 (s,1H, NH), 7.840 (s,1H, Ar-H), 7.714-7.428 (m,2m, Ar-H), 5.045 (d, J=7.8Hz,1H,- CH), 3.748(s,3H,-OCH_3), 2.015 (s,3H,- CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:176.05,165.58,146.25,139.28,133.74,130.15,128.94,128.08,127.05,99.12,52.57,49.45,16.48; LCMS(m/z); 331.22.Moleculaformule: $C_{13}H_{12}Cl_2N_2O_2S$.ElementalAnalysis: Calculated : C-47.14, H-3.65.N-8.46,Obtained : C-47.08,H-3.63,N-8.52

2.2.8.4-(5-(methoxycarbonyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-yl) benzoic acid (4h):

Yield: 89%, Yellow solid; m.p (ºC): 241-243^{0}C; ^{1}HNMR (400 MHz, $CDCl_3$) δ ppm: 9.614(s,1H, NH), 9.324 (s,1H, NH),7.884 (d, J = 8.0 Hz,2H,Ar-H), 7.595 (d, J = 8.8Hz, Ar-H), 5.227(d,J=5.8Hz,1H,-CH),3.743(3H,s,-OCH_3),2.245(s,3H,-CH_3);^{13}CNMR (100MHz, $CDCl_3$) δppm:175.28,167.55,164.84,146.25,145.09,132.41,128.58,126.07,102.48,54.68,50.27,18.74;LCMS(m/z)=306.34.Molecularformule:$C_{14}H_{14}N_2O_2S$.ElementalAnalysis:Calculated:C-54.89, H-4.61.N-9.14,Obtained:C-54.84,H-4.60,N-9.21

3. BIOLOGICAL ACTIVITY:

3.1. ANTI BACTERIAL ACTIVITY:

The anti-bacterial activities of newly synthesized analogous are evaluated against 4 pathogenic bacteria strains. The result of antibiotic activity studies for the compounds as shown in table-I. The gram negative bacteria screened were E. Coli ,P. aeruginosa. The gram positive bacteria screened were S-aureas and Bacillus .The target compounds were used at the concentration of 250 µglml and 500 µglml using DMSO as a solvent the streptomycin 10 µglml disc were used as a standard. The rest of the compounds were found to be moderate active against the tested microorganism.

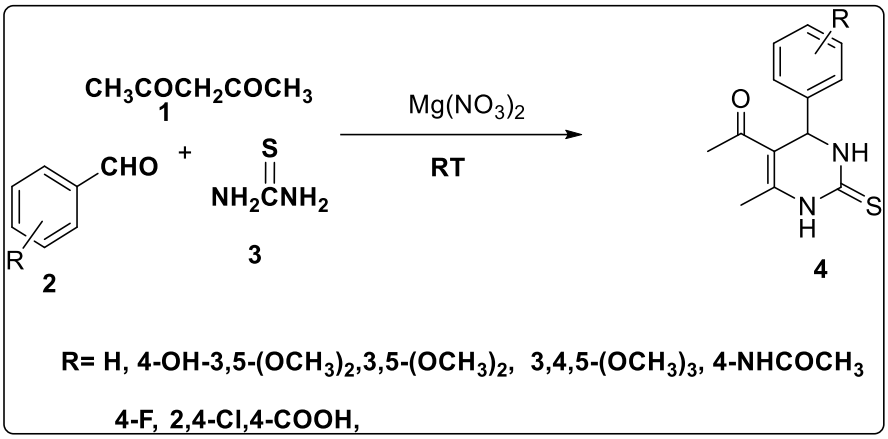
Table-I Antimicrobial activity screening activity synthesized scaffold:

Entry	Anti-Bacteria Activity			
	P.aeruginosa	E.coli	S.aureus	B.Substill
4a	07	08	09	07
4b	19	17	14	18
4c	18	16	14	19
4d	20	21	18	18
4e	15	12	14	11
4f	17	18	15	18
4g	21	22	19	18
4h	08	11	13	11
Streptomycin	25	25	22	22
Fluconazole	NA	NA	NA	NA
DMSO	---	----	---	---

4. RESULTS AND DISCUSSION:

The present work deals with Biginelli-type reactions to be found in the scientific literature, The fast approach for the synthesis of this Methyl- 6-methyl-4-phenyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate derivate were on the application of $Mg(NO_3)_2$ and a one pot three component of starting from equimolar amounts of aromatic aldehyde and 3 molar equivalent of thiourea. However 75^oC followed by cooling room temperature, pouring the crude product mixture over crushed, filtration of the yellow solid the precipitated and recrystallization from ethanol.

. Aromatic aldehydes having both electron-withdrawing and electron-donating group of substituent moieties, were employed as reactants, the synthesis of titled compounds being in short reaction times, using a small amount of Mg $(NO_3)_2$ and acetyl acetone as solvent and Lews acid catalyst under reflux (**Scheme -1).** The isolated yields were generally excellent yield, ranging from (4a-4h) of 1,2,3,4-tetrahydropyrimidine-2(1H)-thiones.Methyl-6-methyl -4- phenyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate and its analogues can be prepared by the $Mg(NO_3)_2$ as a promoter of Biginelli cyclocondensation reaction of acetyl acetone , aromatic aldehyde and thiourea at 75^oC.The role of this I_2 acts as catalyst. The yields of the products as good to excellent yield. In this synthesis, the product of the synthesized compound can be obtained 85-92% of the yield. ^{1}HNMR signals of N-H protons showed at 9.72-8.8.91.This values indicate that two different protons is the Pyrimidines ring. ^{1}HNMR values of –OH protons of 4b compounds exhibited 7.80.The proton values of ^{1}HNMR values of $–OCH_3$ group 4b,4c and 4d compounds exhibited different values at 3.71,3.58,3.69,3.65,3.68. The proton value of amide is 9.59.



The bacterial activity of titled derivatives were showed various values active potent and among the titled derivatives , electron releasing group of moieties such as **4b, 4c, 4d** and halogen substituent **4f,4g** exhibited good active potent value whereas electron withdrawing substituent **4h** exhibited poor potent activity . Anti-fungal activity of 4g was exhibited excellent active potent as shown **Table-I.**

5. CONCLUSIONS:

An appropriate procedure for the synthesis of pyrimidine-2-thione analogous under mild and clean conditions was studied. The scope and advantages of catalyst in these chemical reactions is short reaction times, excellent yields and milder conditions could be of use in industrial applications in the pharmaceutical or fine chemical industries and low cost available chemical. The compounds are exhibited well to excellent anti-microbial activity

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