

Multicomponent Synthesis of 1, 2, 3, 4-Tetrahydro pyrimidine-5-Carboxylate analogous catalysed by Zr (NO₃)₂ as Catalyst

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ABSTRACT:

Finding a molecule with multidrug treatment that is, a medication that resists the antimicrobial actions produced by microbial infection and investigating the chemistry and medicinal variety of pyrimidine-2-thiones are the goals of the current study. Methyl-6-methyl-4-phenyl -2-thioxo-1, 2, 3, 4-tetrahydro pyrimidineidin-5-yl) ethanone in an effective three-component one-pot synthesis based on the reaction of easily accessible aromatic aldehyde, acetyl acetone, and thiourea in ethanol as a solvent, followed by Zr(NO₃)₂ as a catalyzed dehydration. Under mild solvent and catalyzed conditions, the products were produced in moderate to fair yield. These compounds' advanced spectroscopic data¹HNMR, ¹³CNMR, and LCMS spectrum data have been used to assess their structure, and elemental analysis has also been used to estimate structural determination. In addition of study of antimicrobial activity

KEY WORDS:

Acetyl acetone, aromatic aldehyde, thiourea, Zr(NO₃)₂, Tetrahydropyrimidine-5-carboxylate, antimicrobial activities

1. INTRODUCTION:

Six-member heterocyclic molecules containing nitrogen have proved important in medical chemistry[1-5]. The most prevalent atoms in heterocyclic compounds are nitrogen, oxygen, and sculpture. Heterocyclic compounds are cyclic compounds that contain at least two separate or identical elements as ring members. Numerous naturally occurring heterocyclic compounds, such as hormones, antibiotics, caffeine, and others, are abundant in nature and play important roles in our daily lives.

The antibiotic is one of the most significant medicinal developments in history. They are used to treat a number of dangerous bacterial diseases worldwide. Unfortunately, the overuse and misuse of these medications has led to the emergence of bacterial resistance. These harmful events threaten the efficacy of antibiotics, which have saved millions of lives for decades. Furthermore, the number of new antibiotics developed by the pharmaceutical sector has drastically decreased during the last thirty years. Because of this, there is a constant need for new, powerful antibiotics to fight bacteria that are resistant. One method is to use a novel medication with multiple modes of action to target the resistant microorganism.

A review of the literature revealed that partially reduced pyridine and derivatives of pyrimidines, which have the anti-hypertensive properties of clinically used calcium channel blockers like amlodipine and nifedipine, have a 1,4-dihydropyridine ring system with a methyl carboxylate side chain at the compound's third position. A broad class of chemicals is represented by pyrimidines and fused pyrimidines. Which have also drawn a lot of attention due to their biological activity. In recent years, there has been a lot of interest in the chemistry and synthesis of 1,2,3,4-tetrahydropyrimidine-2-thione. Due to their structural similarity to the therapeutically significant dihydropyridines calcium-channel blockers and related drugs, these tetrahydropyrimidine are currently quite popular. Antibacterial Activity [6-9], Cytotoxic activity [10], Antidepressant [11], Calcium antagonistic activities [12,13], Antitumor activity [14], Antitubercular activity [15], inflammatory activity [16, 17], Analgesic activity [18], Antioxidant Activity [19]. Thiourea, 1,3-dicarbonyl components, and a substituted aromatic aldehyde are the three components of this acid-catalyzed three-component synthesis. The skeleton of pyrimidines is found in a wide range of naturally occurring compounds as well as in therapeutically effective molecules with a diversity of biological activities, and it is crucial to both chemistry and biology. Both academic and industrial perspectives are interested in organic reactions under ethanol solvent conditions.

2. MATERIALS AND METHOD

The entire chemicals were supplied by S. D. Fine Chem and Sigma Aldrich Chemie. Pvt. Ltd. The melting points of the newly prepared compounds were determined by open tube capillary method and were uncorrected. The determination prepared derivatives by using $^1\text{H-NMR}$ was recorded on Bruker advanced $^1\text{HNMR}$ (400MHz, CDCl_3) 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:

The desired product such as Methyl 6-methyl-4-phenyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate-2-thiones analogue was obtained by conventional method of procedure followed by a mixture of methyl acetate, substituted aromatic aldehyde, and thiourea in ethanol as a solvent with $\text{Zr}(\text{NO}_3)_2$ present for three hours while stirring. Thin layer chromatography was acted to progress of the reaction mixture (5:5-EtOAc: n-hexane). Following the completion of the reaction conditions, thiourea was used to produce the product the reactants. The reaction mixture was neutralised with a saturated NaHCO_3 solution after being placed into a beaker filled with ethyl acetate. Ethylacetate were vacuum-distilled from crude, and the product was then recrystallized using ethanol.

2.2.1. Methyl-6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a):

Yield: 80%, Yellow solid; M.P-189-191°C ; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ ppm: 10.058 (1H, s, NH), 8.965 (1H, s, NH), 7.710-7.336 (5H, m, Ar-H), 5.124 (1H, d, J = 7.6Hz, CH), 2.584 (s, 3H, CH_3), 1.545 (s, 3H, CH_3); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ ppm : 175.80, 163.14,

144.72, 140.14, 128.85, 128.45, 127.65, 103.77, 54.17, 49.10, 18.71; LCMS(m/z): 263.28 (M+H); Molecular formulae: C₁₃H₁₄N₂O₂S; Elemental Analysis: calculated: C- 59.51, H-5.37, N-10.65, Obtained: C-59.46, H-5.36, N-10.72.

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

Yield: 91%, pale brown solid; M.P -208-210°C; ¹H NMR (400 MHz, CDCl₃) δ ppm: 9.956 (1H, s, NH), 9.245(1H, s, NH), 9.098 (1H, s, OH), 6.541 (2H, s, Ar-H), 5.225 (1H, d, J = 7.6Hz, CH), 3.710 (s,3H, OCH₃), 3.650 (s,3H,OCH₃), 2.128 (s,3H, CH₃), 1.321 (s,3H, CH₃); ¹³CNMR(100MHz, CDCl₃)δppm: 176.58, 164.86, 146.06, 143.66, 137.28, 131.87, 106.98, 102.10, 54.77, 52.54, 48.78, 19.26 ;LC-MS(m/z): 338.47 (M+H) . Molecular formulae: C₁₅H₁₈N₂O₅S; Elemental Analysis: Calculated: C-53.25, H-5.37. N-8.29, Obtained:C-53.18, H-5.36, N-8.35.

2.2.3.Methyl-4-(3,5-dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate(4c):

Yield: 92%, pale brown solid; M.P-219-221°C; ¹H NMR (400 MHz, CDCl₃)δ ppm : 9.957 (s,1H, NH),9.207 (s,1H, NH), 7.256 (d, J =7.8Hz, 2H, Ar-H), 7.148 (t, J = 8.0Hz, Ar-H), 5.144 (s,1H, -CH-), 3.781 (s, 3H, OCH₃), 3.558 (3H, s, OCH₃), 2.408 (s,3H, CH₃), 1.425 (s,3H,CH₃); ¹³C NMR(100MHz, CDCl₃)δppm: 170.72, 162.84, 158.94, 145.47, 144.14, 105.06, 101.81, 99.02, 54.55, 51.49, 50.18,18.79 ;LC-MS(m/z)=322.38(M+H); .Molecular formulae: C₁₅H₁₈N₂O₅S.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: 95%, pale-yellow solid; M.P -231-233°C; ¹H NMR (400 MHz,CDCl₃)δppm : 9.815(s,1H, NH), 8.824 (s,1H, NH), 7.174 (d, J= 5.8Hz, 2H, Ar-H), 5.078 (d, J = 8.0Hz, 1H, -CH), 3.718(s,6H,(OCH₃)₂),7.590(s,3H,OCH₃),2.471(s,3H,-CH₃),1.687(s,3H,-CH₃);¹³CNMR (100MHz, CDCl₃)δppm;175.54,161.78,154.78,147.86, 137.75, 135.46, 104.09, 102.72, 60.58, 55.44, 53.67, 48.73, 18.85; LCMS (m/z) - 352.74(M+H), Molecular formulae: C₁₆H₂₀N₂O₅S; Elemental Analysis: 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-tetrahydro pyrimidine-5-carboxylate(4e).

Yield: 85%, pale brown solid; M.P-241-243°C;¹H NMR(400 MHz, CDCl₃)δppm: 9.812 (s,1H, NH), 9.514 (s,1H, NH), 9.325 (s,1H,NHCOCH₃),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,-OCH₃),2.512(s,3H, CH₃),2.020 (s,3H,CH₃);¹³CNMR(100MHz,CDCl₃)δppm:178.18, 167.84, 164.14, 144.69, 138.54, 137.18, 127.80, 119.22, 98.57, 53.71, 50.85, 24.18,17.40; LCMS:(m/z) = 319.56(M+H); Molecular formulae:C₁₅H₁₇N₂O₅S; Elemental Analysis: Calculated: C-56.41, H-5.37. N-13.16; Obtained:C-56.35, H-5.36, N-13.22.

2.2.6. Methyl 4-(4-fluorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4f):

Yield: 87%, Yellow powder; M.P-237-239°C; ¹H NMR (400 MHz, CDCl₃) δ ppm : 9.848 (s, 1H, NH), 9.208 (s, 1H, NH), 7.718 (d, J = 8.0 Hz, 2H, Ar-H), 7.385 (t, J = 9.0, 2H, Ar-H), 5.247 (d, J = 7.2 Hz, 1H, -CH), 3.769 (s, 3H, -OCH₃), 2.412 (s, 3H, -CH₃), 1.498 (s, 3H, -CH₃); ¹³C NMR (100 MHz, CDCl₃) δ ppm: 172.45, 167.52, 163.58, 146.16, 138.58, 128.59, 115.29, 102.78, 53.27, 51.45, 17.38; LCMS (m/z): 280.87 (M+H). Molecular formula: C₁₃H₁₃FN₂O₂S. Elemental analysis: Calculated: C-55.70, H-4.67, N-9.99, Obtained: C-55.65, H-4.65, N-10.06

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

Yield: 81%, Yellow solid; M.P-242-244°C; ¹H NMR (400 MHz, CDCl₃) δ ppm: 9.741 (s, 1H, NH), 9.541 (s, 1H, NH), 7.848 (s, 1H, Ar-H), 7.728-7.414 (m, 2m, Ar-H), 5.214 (d, J=7.8 Hz, 1H, -CH), 3.717 (s, 3H, -OCH₃), 2.254 (s, 3H, -CH₃), 1.452 (s, 3H, -CH₃); ¹³C NMR (100 MHz, CDCl₃) δ ppm: 174.18, 164.54, 142.25, 138.28, 133.74, 130.15, 128.94, 128.08, 127.05, 102.12, 52.57, 49.45, 16.48; LCMS (m/z); 331.2 (M+2). Molecular formula: C₁₃H₁₂Cl₂N₂O₂S. Elemental Analysis: 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: 83%, Yellow solid; M.P (°C): 244-246°C; ¹H NMR (400 MHz, CDCl₃) δ ppm: 9.625 (s, 1H, NH), 9.308 (s, 1H, NH), 7.880 (d, J = 7.8 Hz, 2H, Ar-H), 7.557 (d, J = 8.4 Hz, Ar-H), 5.226 (d, J=8.8 Hz, 1H, -CH), 3.728 (3H, s, -OCH₃), 2.245 (s, 3H, -CH₃), 1.745 (s, 3H, -CH₃); ¹³C NMR (100 MHz, CDCl₃) δ ppm: 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 (M+); Molecular formula: C₁₄H₁₄N₂O₂S. Elemental Analysis: 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 compounds are screened against 5 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 µg/ml and 500 µg/ml using DMSO as a solvent the streptomycin 10 µg/ml disc were used as a standard. The rest of the compounds were found to be moderate active against the tested microorganism.

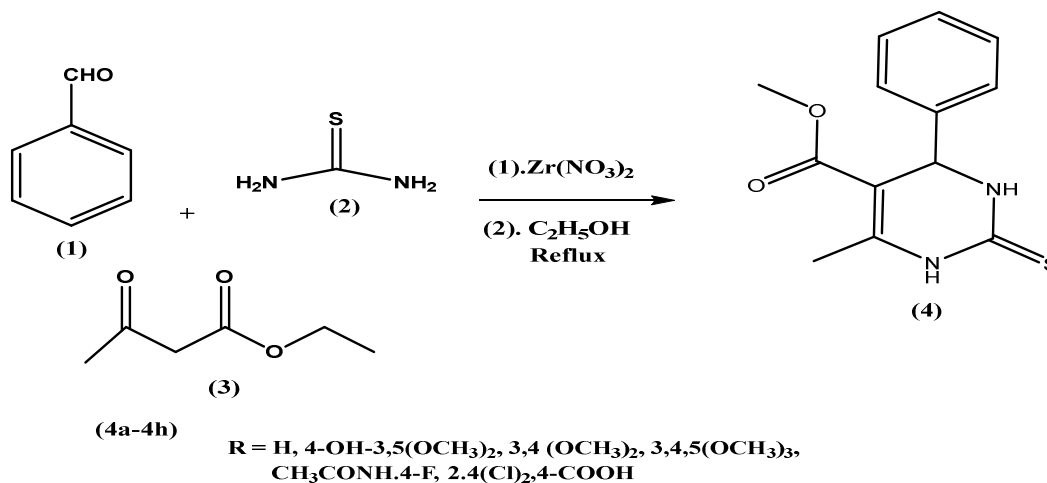
3.2. ANTI-FUNGAL ACTIVITY:

Anti-fungal activity of desired compounds was evaluated by disc diffusion method against the organism of A.Niger and C.albicans. The compounds were compared and they were

treated at the concentrations of 250 µg/ml and 500 µg/ml using DMSO as a solvent. The standard drug was used as fluconazole 50 µg/ml against both organisms.

4. RESULTS AND DISCUSSION:

4.1. Chemistry



(Scheme-1)

The fast method for the synthesis of this Methyl-6-methyl-4-phenyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate derivate was based on the application of $\text{Zr}(\text{NO}_3)_2$ and a one pot three component of beginning from equimolar amounts of aromatic aldehyde, thiourea and ethyl acetoacetate. This work deals with Biginelli-type reactions that can be found in scientific literature. Nevertheless, the crude product combination is poured over the crushed material after being heated to 75°C , filtered to remove the precipitated yellow solid, and then recrystallized from ethanol.

The various catalysts, catalyst concentrations, and solvents were used to optimize these similar processes. In contrast to oxidative related catalysts like magnesium nitrate ($\text{Mg}(\text{NO}_3)_2$), titanium dioxide (TiO_2), and zinc chloride ($\text{ZnCl}_2 \cdot 5\text{H}_2\text{O}$), the highest product of the derivatives was obtained in the presence of Lew's acid catalyst, such as zirconium nitrate ($\text{Zr}(\text{NO}_3)_2$). (Table I).

Table-I: The effect of catalyst for preparation of titled derivatives

Entry	Catalyst	Time (hrs.)	Yield (%)
1	$\text{Mg}(\text{NO}_3)_2$	3	55
2	$\text{ZnCl}_2 \cdot 5\text{H}_2\text{O}$	3	69
3	TiO_2	3	75
4	$\text{Zr}(\text{NO}_3)_2$	3	92

Reaction of aromatic aldehydes, ethylacetoacetate and thiourea in presence of $\text{Zr}(\text{NO}_3)_2$ under conventional method and solvent conditions, b; Isolated yield

The model reaction under investigation employed a variety of solvents, including DMF, isopropanol acetonitrile, ethanol, and methanol. It was found to be the most efficient medium for the reaction with an 89% product yield. Because of its greater yield, ease of work-up, and environmental friendliness, it was used as the solvent for subsequent processes. Ethanol has a vital role as a solvent.

Table-II: The effect of solvent for preparation of titled derivatives

Entry	Catalyst	Time (hrs.)	Yield (%)
1	CH ₃ CN	5	50
2	MeOH	5	67
3	DMF	5	55
4	EtOH	5	92

Reaction of aromaticldehydes, ethylacetoacetate and thiourea in presence of Zr (NO₃)₂ under conventional method and solvent conditions, b; Isolated yield

Table-III showed that the named derivatives had much improved, with 5c's yield reaching 92%. It also showed the amount of catalyst used in the synthesis, its impact on the product yield, and the rate of reaction and Table III shows that the alteration in the loaded catalyst was found to improve the product. The results were not improved by using the maximum amount of the catalyst. Table III illustrates how the yield unexpectedly dropped to 35% even though the reaction time was reduced to one hour by using 4.0 mmol% Zr(NO₃)₂.

Table-III: The effect of loaded for preparation of titled ^{(a)*}

Derivative	Amount catalyst(mmol)	Time (hrs)	Yield (%) ^{b*}
1	1.0	5	15
2	2.0	5	46
3	4.0	5	92
4	6.0	5	92

Reaction of aromaticldehydes, ethylacetoacetate and thiourea in presence of Zr (NO₃)₂ under conventional method and solvent conditions, b; Isolated yield

After obtaining these investigation findings, our goal was to boost the product's yield from the previous study. The sole goal was to add different amounts of appropriate catalyst and solvents to improve the current method's efficiency in terms of reaction time and product yield. It was determined to use this system for our reaction after taking this into account and knowing about the recently studied methanesulphonic acid reaction medium.

The fact that the model reaction utilizing this reaction medium was finished in just 90 minutes (1.5 hours) and that it was taking place at a temperature between 60 and 70°C, which allowed for a good product yield, thrilled us. In order to determine the proper amounts for the reaction and achieve the ideal experimental circumstances, additional experiments were conducted using different concentrations of water and methanesulphonic acid. According to our research, the maximum product yield is obtained when 0.50 g of warmed fly ash is added to water for the reaction.

4.2. ANTIMICROBIAL ACTIVITY OF COMPOUNDS

The micro broth dilution method was used to assess the target compounds' in vitro antibacterial and antifungal properties. Gram-positive (*B. subtilis* and *S. aureus*) and gram-negative (*E. coli* and *P. aeruginosa*) microorganisms were used to test the invitro antibacterial activity. *A. niger* and *C. albicans* microorganisms were used to test the invitro antifungal activity. Ketonazole and streptomycin were the standard medications employed in this investigation for both antifungal and antibacterial screening. The Culture Collection and Geneank (MTCC), located in Chandigarh, India, was the commercial source of the standard strains used to screen for antibacterial and antifungal properties. Sabouraud dextrose broth was utilized for the growth of fungi and Mueller Hinton broth as a nutritional medium for bacteria. By comparing the turbidity, the inoculum size for the test strain was changed to 10⁸ CFU/mL. Primary and secondary evaluations were used to document the outcomes. The compounds under investigation and conventional medications were diluted twice to create the stock solution (2000 µg/mL).

Table-IV. Antimicrobial activity of compounds (5a-5h):

Entry	Antibacterial MIC (µg/mL)				Antifungal MIC (µg/mL)		
	Strains	<i>B. subtilis</i>	<i>S. aureus</i>	<i>P. aeruginosa</i>	<i>E. coli</i>	<i>A. Niger</i>	<i>C. Albicans</i>
4a		08	10	09	07	07	09
4b		23	22	23	19	16	17
4c		21	18	20	15	14	16
4d		19	20	21	22	16	15
4e		19	20	18	20	16	16
4f		22	21	20	22	19	18
4g		11	12	12	14	10	09
4h		11	13	07	08	04	06
Streptomycin		27	27	27	27	-	-
Ketonazole		-	-	-	-	25	25
DMSO							

The aromatic aldehydes bearing both electron-attracting and electron-releasing group of substituent moieties, were effected as reactants, the synthesis of titled derivatives being in low reaction times, using a small amount of $Zr(NO_3)_2$ and ethanol as solvent and Lewis acid catalyst under reflux (Scheme -1). The isolated product were generally an 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 $Zr(NO_3)_2$ as employed of Biginelli cyclocondensation reaction of acetyl acetone, substituted aromatic aldehyde and thiourea at 75°C. The role of this $Zr(NO_3)_2$ acts as catalyst. The yields of the products acquired as good to excellent yield and in this synthesis, the product of the synthesized compound can be obtained 85-94% of the yield.

¹HNMR signals of N-H protons showed at 9.72-8.8.91. This values indicate that two different protons is the Pyrimidines ring. ¹HNMR values of –OH protons of 4b compounds exhibited 7.80. The proton values of ¹HNMR values of –OCH₃ 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 microbial activity of titled compound was 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-IV.

5. CONCLUSIONS:

An appropriate procedure for the preparation of pyrimidine-2-thione derivatives 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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7. REFERENCES:

1. Rambhau P. Gore and Ambarsing P. Rajput. A Review on recent progress in multicomponent Reactions of pyrimidine synthesis. *Drug Invention Today* 2013;5(2);148-152
2. Mounir A. I. Salem, Magda I. Marzouk, Marwa S. Salem, and Ghazala A. Alshibani. One-pot Synthesis of 1, 2, 3, 4-Tetrahydropyrimidine-2(1*H*)-thione derivatives and their biological Activity, *Journal of Heterocyclic Chemistry* 2016;53;545.
3. Pozharsk Ali Af, Sodatemkov At and Kartritzky Ar. *Heterocycle in Life and Society: An Introduction to Heterocyclic Chemistry. Biochemistry and Applications, Second Edition, 1997;6(4);301.*
4. Sharana Basappa B Patil. Biological and medicinal significance of pyrimidines: A Review. *International J. Pharm Sci and Res.* 2018;9(1);44
5. R. Kumar, A. Mittal and U. Ramachandran, "Design and synthesis of 6-methyl-2-oxo-1,2,3,4- tetrahydropyrimidine-5- carboxylic acid derivatives as PPAR γ activators", *Bioorg. Med. Chem. Lett.*, 2007, 17, 4613-4618.
6. R. L. Sawant and M. S. Bhatia, "Synthesis, screening and qsar studies of 3-formyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine analogues as antibacterial agents", *Bull. Chem. Soc. Ethiopia*, 2008, 22, 391-402.
7. K. Satyavathi, K. T. Naga Ravi, R. P. Bhoja and M. Sharmila, "Synthesis and screening of 3-formyl-2-thio-1, 2, 3, 4-tetrahydro pyrimidine analogues as antibacterial agents," *Asian J. Chem.*, 2010, 22, 5182-5186

8. S. N. Darandale, D. N. Pansare, N. A. Mulla and D. B. Shinde, "Green synthesis of tetrahydropyrimidine analogues and evaluation of their antimicrobial activity", *Bioorg. Med. Chem. Lett.*, 2013, *23*, 2632-2635.
9. H. S. Basavaraja, P. Basavaraj, M. Vijaykumar, M. M. Hussain and B. N. Chidananda, "Synthesis and antimicrobial screening of some substituted INH- and THPHM-linked pyrimidines," *Ind. J. Heterocycl. Chem.*, 2011, *20*, 237-240
10. M. K. Manal, M. R. Sameha, A. A. Mohamed, K. A. Eman and F. L. Phoebe, "Design, synthesis and cytotoxic activity of some novel compounds containing pyrazolo[3,4-d]pyrimidine nucleus", *Der Pharma Chem.*, 2013, *5*, 109-124.
11. K. Weinhardt, M. B. Wallach and M. Marx, "Synthesis and antidepressant profiles of phenyl-substituted 2-amino- and 2-[(alkoxycarbonyl)amino]-1,4,5,6-tetrahydro pyrimidines," *J. Med. Chem.*, 1985, *28*, 694-698.
12. A. Balkan, B. Tozkoparan, M. Ertan, Y. Sara and N. Ertekin, "New thiazolo [3, 2-a]pyrimidine derivatives, synthesis and calcium antagonistic activities," *Boll. Chim. Farma.*, 1996, *135*, 648-652.
13. K. Kaur and E. Knaus, "Synthesis of alkyl 6-methyl-4-(2-pyridyl)-1,2,3,4-tetrahydro-2H-pyrimidine-2-one-5-carboxylates for evaluation as calcium channel antagonists," *J. Heterocycl. Chem.*, 2007, *44*, 745-747.
14. Y. Ji-Xin, C. Xiao-Qing, C. Di-Mei and H. Mao-Lin, "Synthesis, structure analysis, and antitumor activity of (*R*)-2,4-dioxo-5-fluoro-1(methoxycarbonyl) ethylamino carbonyl methyl] 1,2,3,4 tetrahydro pyrimidine," *Chin. J. Chem.*, 2007, *25*, 417-421
15. V. Virsodia, R. R. S. Pissurlenkar, D. Manvar, C. Dholakia, P. Adlakha, A. Shah and E. V. Coutinho, "Synthesis, screening for antitubercular activity and 3D-QSAR studies of substituted *N*-phenyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-pyrimidine-5-carboxamides" *Eur. J. Med. Chem.*, 2008, *43*, 2103-2115
16. S. Mokale, S. Shinde, R. Elgire, J. Sangshetti and D. Shinde, "Synthesis and anti-inflammatory activity of some 3-(4,6-disubstituted 2-thioxo-1,2,3,4 tetrahydro pyrimidin-5-yl)propanoic acid derivatives," *Bioorg. Med. Chem. Lett.*, 2010, *20*, 4424-4426
17. R. Dhankar, A. M. Rahatgaonkar, R. Shukla, M. Chorghade and A. Tiwari, "Computer simulation of the invitro and in vivo anti-inflammatory activities of dihydropyrimidines acid derivatives through the inhibition of cyclooxygenase-2", *Med. Chem. Res.*, 2013, *22*, 2493-2504
18. N. Arora and S. Pandeya, "Synthesis and analgesic activity of novel pyrimidine derivatives" *Int. J. Pharma. Sci. Rev. Res.*, 2011, *11*, 48-52
19. M. Mansouri, A. Movahedian, M. Rostami and A. Fassihi, "Synthesis and antioxidant evaluation of 4-(furan-2-yl)-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate esters", *Res. Pharma. Sci.*, 2012, *7*, 257-264

