IJMPR 2025, 9(4), 87-90

International Journal of Modern Pharmaceutical Research

www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Research Article

SJIF Impact Factor: 6.669

MULTI COMPONENT ONE POT SYNTHESIS OF METHYL- 6-METHYL-4-PHENYL-2-THIOXO-1, 2, 3, 4-TETRAHYDROPYRIMIDINE-5-CARBOXYLATE DERIVATIVES PROMOTED BY IODINE AS CATALYST

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Article Received on: 21/02/2025

Article Revised on: 12/03/2025

Article Accepted on: 02/04/2025

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ABSTRACT

The present study deals with 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 aromatic aldehyde, acetyl acetone and thiourea in the ethanol as a solvent followed by I_2 as a catalysed dehydration. The products were obtained in moderate to good yield under mild, solvent as well as catalysed conditions. The structure of these compounds has been evaluated 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. In addition to examined antimicrobial activities

KEYWORDS: Aacetyl acetone, aromatic aldehyde, thiourea, I_2, Biginelli cyclocondensation, antimicrobial activities.

1. INTRODUCTION

Nitrogen containing six-member heterocyclic compounds have been play an prominent in medicinal chemistry. Heterocyclic compounds are cyclic compounds with at least two different or same elements as ring members' atoms, the commonest atoms include nitrogen, oxygen and sculpture. The existence of many naturally occurring hetero cyclic molecules viz; as hormones, antibiotics, caffeine etc. are abundance in nature and are very significant in our lives.

Literature survey reported that the partially reduced pyridine and derivatives of Pyrimidines which having anti-hypertensive property of the clinically used calcium channel blockers such as nifedipine, amlodipine have 1,4-dihydropyridine ring system possess methyl carboxylate side chain at 3rd position of compound. 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, Pyrimidines derivatives possessing antitumor[19], antimicrobial.[20] Antibacterial[21], antifungal[22] and anti-infective[23] activities have also been reported in the literature. This protocol is an acid catalysed three component reaction between an substituted aromatic aldehyde, 1,3-dicorbanyal components and Thiourea.

The Pyrimidines skeleton available in a wide variety 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 solvent free conditions are of interest from both industrial and academic viewpoints.

2. METHODS AND MATERIALS

All the synthetic grade reagents and chemicals were procured by Sigma Aldrich. These chemicals, solvents and reagents were used without further purification. The melting points of newly synthesized compounds were determined by Agrawal thermometer in open capillaries and are uncorrected. ^{1}H NMR and ^{13}CNMR spectra were recorded on a Bruker 400MHz spectrometer using $CDCl_3$ as solutions. Molecular weight of the newly synthesized compounds was recorded by LCMS spectrometer. Elemental analysis was performed on a CarloErbaEA 1108 elemental analyser. Reaction mixture was monitored on Merck aluminium thin layer

chromatography (TLC, UV254nm) plates. Visualisation was accomplished either an UV chamber (or) in Iodine Vapour. Column chromatography was carried out on silica gel (100mesh) Merck chemicals.

2.1. GENERAL PROCEDURE

The synthesis of the Methyl 6-methyl-4-phenyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate-2-thiones analogue from a mixture of methyl acetate, substituted aromatic aldehyde and thiourea in ethanol as a solvent in the presence of I_2 was stirred and heated at 70^0c for 3hrs. The reaction mixture was monitored by thin layer chromatography (4:6 ethyl acetate: n-hexane**).** After completion of the reactants were consumed during the completion of the reaction conditions by using thiourea. The reaction mixture poured in a beaker containing ethyl acetate and washed with saturated solution of sodium bicarbonate. The distillation of Ethylacetae in crude under vacuum was distilled and compound recrystallization with ethanol.

2.2. SPECTRAL EVIDENCE

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

Yield: 84%, pale-yellow solid; mp-201-203ºC ;**^{1}H NMR** (400 MHz, $CDCl_3$): δ ppm:9.842(1H, s, NH-1), 9.514 (1H, s, NH-3), 7.645-7.326 (5H, m, Ar-H), 5.049 (1H, d, J = 7.0Hz, CH), 3.662 (s,3H, OCH_3), 2.230 (s,3H, CH_3); **^{13}C NMR (**100 MHz, $CDCl_3$): δ ppm:173.88, 164.56, 145.78, 143.03, 128.19, 127.76, 126.64, 101.72, 54.27, 49.48, 16.75; 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: 87%, pale-yellow solid; mp -212-214ºC;^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.815 (1H, s, NH-1),9.459(1H, s, NH-3), 8.984 (1H, s, OH), 6.978 (2H, s, Ar-H), 5.112 (1H, d, J = 7.6Hz, CH), 3.771 (s,3H, OCH_3), 3.758 (s,3H,OCH_3), 2.122 (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**:$C_{15}H_{18}N_2O_5S$.**Elemental Analysis** : 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: 90%, pale-yellow solid; mp-210-212ºC; ^{1}H NMR (400 MHz,$CDCl_3$)δ ppm: 9.730 (s,1H, NH-1),9.594 (s,1H, NH-3), 7.194 (d, J =7.2Hz,2H, Ar-H), 7.035 (t, J = 7.0Hz, Ar-H), 5.04 (s,1H, -CH-), 3.758 (s,3H, OCH_3),3.594 (3H, s, OCH_3), 2.530 (s,3H, CH_3); ^{13}C NMR(100MHz,$CDCl_3$)δppm:173.79,164.86,159.95,146.04,145.05,103.65,99.87,98.02,54. 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).Methyl4-(3,4,5-trimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine -5- carboxylate (4d)

Yield: 90%, pale-yellow solid; mp -215-217ºC; ^{1}H NMR (400 MHz,$CDCl_3$)δppm : 9.821(s,1H, NH-1), 8.997 (s,1H, NH-3), 7.075 (s,2H, Ar-H), 5.057 (d, J = 8.0Hz,1H, -CH), 3.757 (s,9H,OCH_3),2.343(s,3H,-CH_3);^{13}CNMR(100MHz,$CDCl_3$)δppm;177.15,165.08,152.77,146.86,137.75,135.46,103.08,101.72,60.59,55.44,53.67,49.73,16.85;LCMS(m/z)=352.74.

Molecularformule:$C_{16}H_{20}N_2O_5S$.**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: 854%, pale-yellow solid; mp-253-255ºC;^{1}H NMR(400 MHz, $CDCl_3$) δ ppm: 9.772 (s,1H, NH-1), 9.635 (s,1H, NH-3), 9.124 (s,1H,$NHCOCH_3$),7.874 (d, J = 8.4Hz,2H, Ar-H), 7.518 (d, J = 7.6Hz,2H Ar-H), 5.018 (d, J =7.8Hz, -CH), 3.758 (s,3H,- OCH_3), 2.532 (s,3H, CH_3),2.029(s,3H,CH_3);^{13}CNMR(100MHz,$CDCl_3$)δppm: 176.85,167.05,164.74,144.48,138.77,136.94,126.81,118.27,99.04,52.74,50.85,23.65,17.41; LCMS:(m/z)=319.38.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: 88%, Yellow solid; mp-221-223ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:9.746 (s,1H, NH-1), 9.520 (s,1H NH-3), 7.740 (d, J = 8.0Hz,2H, Ar-H), 7.417 (t, J = 8.8, 2H,Ar-H), 5.012(d, J = 7.6Hz,1H,-CH), 3.657 (s, 3H,-OCH_3), 2.233(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.Molecularformule:$C_{13}H_{13}FN_2O_2S$.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: 91%, pale-yellow solid; mp 214-216ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δppm = 9.878 (s,1H, NH-1), 9.634 (s,1H, NH-3), 7.840 (s,1H, Ar-H), 7.636-7.326 (m,2m, Ar-H), 5.148 (d, J=7.6Hz,1H,- CH), 3.741(s,3H,-OCH_3), 2.032 (s,3H,- CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm:174.59,165.28,146.42,139.08,133.58,130.36,129.09,128.84,127.51,98.09,50.57,49.43,16.07;LCMS(m/z)=331.22.Molecularformule:$C_{13}H_{12}Cl_2N_2O_2S$.ElementalAnalysis: Calculated :C-47.14, H-3.65.N-8.46,Obtained : C-47.10,H-3.64,N-8.51.

2.2.8).4-(5-(methoxycarbonyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-yl) benzoic acid (4h)
Yield: 85%, pale-yellow solid; mp (^oC): 236-238^{0}C; ^{1}HNMR (400 MHz, $CDCl_3$) δ ppm = 9.562(s,1H, NH-1),9.157 (s,1H, NH-3),7.851 (d, J = 8.8Hz,2H Ar-H), 7.536 (d, J = 8.0Hz, Ar-H), 5.126 (d, J =5.4Hz,1H,-CH), 3.769(3H,s, -OCH_3), 2.132 (s,3H,-CH_3); ^{13}C NMR (100MHz,$CDCl_3$)δppm:175.25,166.51,165.77,146.03,144.09,130.46,129.55,126.77,99.44,53.67,50.07,18.73;LC MS(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-54.85,H-4.59,N-9.19.

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 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.

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 250µglml and 500 µglml using DMSO as a solvent. The standard drug was used as fluconazole 50 µglml against both organisms.

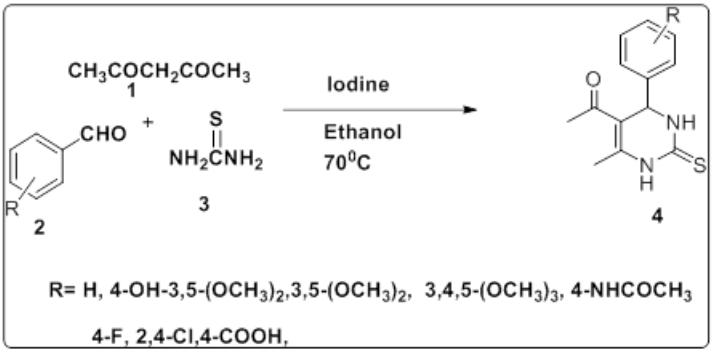
Table I: Antimicrobial activity screening activity synthesized scaffold.

Entry	*Zone of inhibition in (mm)					
	Bacteria				Fungi	
	P.aeruginosa	E.coli	S.aureus	B.substill	A. Niger	C. Albicans
4a	05	07	08	06	07	08
4b	18	16	18	15	10	12
4c	17	15	17	17	09	10
4d	21	20	19	19	15	16
4e	14	10	13	12	10	09
4f	17	18	15	18	13	16
4g	21	22	19	18	17	16
4h	10	12	12	13	16	16
Streptomycin	25	25	22	22	NA	NA
Fluconazole	NA	NA	NA	NA	20	20
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 I_2 and a one pot three component of starting from equimolar amounts of aromatic aldehyde and 2.5 molar equivalent of thiourea. However 70^{o}C 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 I_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 I2 as a promoter of Biginelli cyclocondensation reaction of acetyl acetone, aromatic aldehyde and thiourea at 70^{o}C.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 86-91% 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. 1HNMR 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 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** showed poor active potent. Anti-fungal activity of 4g was exhibited good 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. The compounds screened good anti-microbial activity.

6. AKNOWLEDGEMENT

Authors are thankful to Department of chemistry, PYDAH College (P.G.Courses), (Affiliated to Andhra university), Visakhapatnam, India.

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