IJMPR 2021, 5(6), 71-74

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Research Article
SJIF Impact Factor: 5.273

BIO ACTIVE SYNTHESIS OF 4-(HETERO AROMATIC ALDEHYDES)-6-METHYL-2-THIOXO-1, 2, 3, 4-TETRAHYDROPYRIMIDINE-5-CARBOXYLATE ESTERS USING METHANE SULFONIC ACID

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Received on: 25/10/2021
Revised on: 15/11/2021
Accepted on: 05/12/2021

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ABSTRACT

As a part of our research in the synthesis of pyrimidine derivatives containing biological activities, some new tetrahydropyrimidine derivatives (1-6) were synthesized. The present study, the synthesis of some novel Biginelli-type pyrimidine is reported. The prepared compounds are ethanone derivatives of 6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidines with a simple heteroarylaldehydes group at C-4 position of the pyrimidine ring. These compounds can be obtained the reaction of heteroaromatic aldehydes (1.2 mmol), acetyl acetone (1mmol), thiourea(1mmol) in the presence of Methanesulfonic acid at120^{0}C conditions. All the compounds were examined by advanced spectroscopic data (1H NMR, 13C NMR& LCMS) and the structural determination was calculated by elemental analysis. In addition to the all newly synthesized compounds were screened by their microbial activity .The antibacterial activity of some synthesized compounds was investigated against *Staphylococcus aureus*, *Esherichiacoli*, S.typhi, *BacillusSubstills*), Some of these compounds such as 4d,4e and exhibited a good to significant antibacterial activity.

KEYWORDS: Acetyl acetone, Hetero aromatic aldehydes, Methanesulfonic acid, ethanone derivatives of 6-methyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidines, biological activity.

INTRODUCTION

2-thioxo-1, 2, 3, 4-tetrahydropyrimidineis an interesting moiety which has attracted considerable attention of medicinal chemist's inthe last few decades.[1] This chemical is also called 1,2,3,4-tetrahydropyrimidine-2(1*H*)-thione was introduced to chemistry by the Italian chemist Pietro Biginelli. A broad range of biological effects, including calcium channel modulation.[2,3] adrenoceptorblocking.[4] antitumor.[5] antiviral,[6] anti-inflammatory,[7] and antimicrobial,[8] activities have been attributed to this class of heterocyclic compounds. Free radicals with a singlet electron in theirstructure play an important role in the pathogenesis of various disorders such as cancers, atherosclerosis, diabetes, Alzheimer, Parkinson and diseases related to aging process.[9,10]

Regarding the importance of the Biginelli reaction products, much work on improving the yield and reaction conditions has been actively pursued. For example, using Lewis acids as a catalyst such as $Cu(OTf)_2$.[11] $Yb(OTf)_3$.[12] Triethylammonium hydrogen sulfate.[13] $BiCl_3$.[14] and $Mn(OAc)_3.2H_2O$.[15] instead of acidic reagents significantly improved the reaction output with reduced reaction times. The polymer-supported, resin-bound isothiourea,[16] polymer nanocomposite,[17] and various other catalysts,[18,19] have been used for synthesis of Biginelli products. In general terms, this report is going to describe the synthesis of new tetrahydropyrimidine derivatives via the Biginelli reaction using Brownsted acid methane sulfonic acid as a catalyst. Biological activities of synthesis compounds were tested against gram-positive and gram-negative bacteria.

METHODS AND MATERIALS

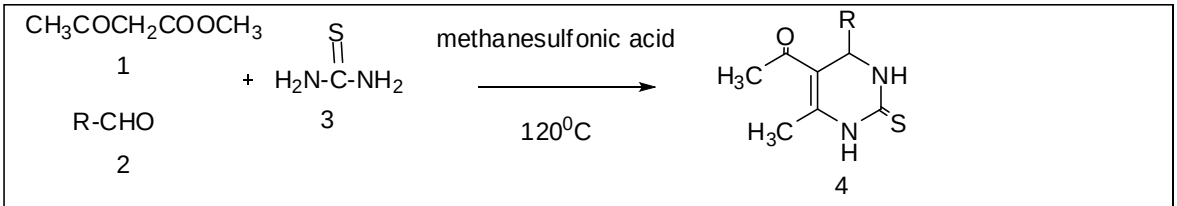
Experimental

All the chemicals, solvents and synthetic grade reagents can be procured from Sigma Aldrich India and Merck chemicals They were used without further purification. The progress of reaction was monitored by thin layer chromatography. The melting point of the all the newly synthesized derivatives were determined open at one end

and were uncorrected using an Electrochemical Mk3 apparatus. 1HNMR &13cNMR spectrum were recorded on 400MHz Brucker spectrometer in $CDCl_3$ as a solvent and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilanes (Me_4Si) as an internal standard. Molecular mass of the synthesized compound were determined by LCMS spectrometer.

General procedure for synthesis

A mixture of hetro aromatic aldehydes(1.2 mmol), Acetyl acetone (1mmol), thiourea (2mmol) are introduced in 100 ml of RB flask, Methanesulfonic acid was added gradually until the mixture was dissolved and The reaction mixture was carried out on the magnetic stirrer under 120^0C condition. The progress of the reaction was monitored by TLC in ethyl acetate: n-hexane (4:6). After completion of the reaction, the mixture was cooled to room temperature and poured on 100 ml ice cold water. The crude was filtered and washed with ethyl acetate and a saturated Braine solution several times. The solid product can be separated by column chromatography (Ethylacetate:n-hexane, 4:6) and desired compounds was recrystalized from ethanol. Scheme - I.



R = Furan, Tiophene, Pyrrole, pyridine-2-carbaldehyde, pyridine-3-carbaldehyde, Indole-3-carbaldehyde

Scheme-1

1).1-(4-(furan-2-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) ethanone(4a)

Paleyellow;yield-86%;m.p–228-230^{0}c;**^{1}HNMR** (400MHz,$CDCl_3$)δinppm: 7.365-7.214(m,5H,Ar-H), 6.617 (s,2H,NH2), 4.137 (s,1H,CH), 2.325(s,2HCH2). 2.122-1.823(m,2H),1.055(s,3H,CH_3). **^{13}CNMR** (100MHz,$CDCl_3$) δinppm:194.48, 158.17,153.86,143.66, 128.78,126.27,124.31,118.72,113.64,57.26,49.88,39.52,36.95,31.47,26.88;**LCMS(m/z):**293.85.**Molecularformula:** $C_{18}H_{18}N_2O_2$. **Elemental analysis**: Calculated: C-73.65, H-6.16, N- 9.52.Obtained: C-73.69,H-6.15,N-9.51.

2)1-(6-methyl-4-(1Hpyrrole-2-yl)-2-thioxo- 1,2,3,4-tetrahydropyrimidine-5-yl) ethanone (4b)

white solid; yield-85%; m.p – 205-206^{0}c;**^{1}HNMR (400MHz,$CDCl_3$)** δ in ppm: 9.328(s,1H,-OH),7.055-6.657 (m,4H,Ar-H).6.593(s,2H,NH_2), 4.126(s,1H,CH), 2.258(s,1H,CH_2),2.199-1.926 (m,2H,CH_2), 1.018 (s,3H,CH_2), 0.957 (s,3H,CH_3);**^{13} CNMR (100MHz, $CDCl_3$)** δinppm:195.15 157.56,155.24,153.88,135.64, 130.18, 118.87,116.09, 112.85, 56.56,50.21,38.43, 37.38,30.96,27.1. **LCMS** (m/z): 310.09. **Molecular formula**: $C_{18}H_{18}N_2O_3$. **Elemental analysis**: calculated: C-69.66,H-5.84 , N-9.03.Obtained: C-69.69, H-5.83, N-9.02.

3)1-(6-mrthyl-4-(thiophene-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl) ethanone(4c)

Pale yellow solid; yield-85%; m.p – 229^{0}c, **^{1}HNMR (400MHz, $CDCl_3$)** δ in ppm: 9.528(s,1H,-OH),6.877-6.648(m,3H,Ar-H),6.514(s,2H,NH_2), 4.216(s,1H,CH), 4.178-1.087(s,2H-,CH_2), 1.298 (t,J=7.6Hz,3H),2.209 (s,2H,CH_3), 2.037 (d,J=8.0Hz,2H),1.104 (s,3H,CH_3),1.01 (s,3H,-CH_2). **^{13}CNMR (100MHz,$CDCl_3$)** δinppm: 194.77, 157.88,153.91, 146.67,143.85, 134.63,121.58,118.75, 114.87,113.26,112.68,63.77,57.6 5,49.77, 38.49,37. 05,31.48, 26.29, 14.25.**LCMS**(m/z): 354.53. **Molecularformula**: $C_{20}H_{22}N_2O_4$. **Elemental analysis**: calculated: C-67.78, H-6.26, N-7.90. Obtained:C-67.82, H-6.25, N-7.89.

4).1-(6-methyl-4-(pyridine-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl) ethanone(4d)

White solid; yield-87%; m.p – 231^{0}c, **^{1}HNMR (400MHz, $CDCl_3$)** δ in ppm: 9.495(s,1H,OH), 6.878-6.675(m,3H,Ar-H),6.547(s,2H, NH_2), 4.187(s,1H,CH), 3.674(s, 3H, OCH_3), 2.266(s, 2H, CH_2), 2.227(d, J=8.0Hz, 2H), 1.855-1.818(m, 2H, CH_2), 1.067(s, 3H, CH_3), 0.971(s, 3H, CH_3). **^{13}CNMR (100MHz, $CDCl_3$)** δ in ppm: 164.92, 162.55, 155.49, 131.28, 128.46, 122.72, 118.98, 114.77, 110.89 & 55.455(OMe).**LCMS** (m/z):339.79. **Molecular formula**: $C_{19}H_{20}N_2O_4$. **Elemental analysis**: calculated: C-71.70, H-5.21, N-16.72. Obtained: C-71.65, H-5.20, N-16.70.

5).1-(6-methyl-4-(pyridine-3-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl) ethanone(4e)

white solid; yield-88%; m.p – 169-171^{0}c, **^{1}HNMR (400MHz, $CDCl_3$)** δ in ppm: 9.471 (s,2H,NH_2), 6.125 (s,1H,Ar-H), 6.077 (s,1H, Ar-H), 4.185(s,1H, CH), 3.475(s,9H,OCH_3), 1.933(s, 2H, CH_2),1.578(s, 2H, CH_2), 1.064(s,3H, CH_3), 0.885(s, 3H, CH_3). **^{13}CNMR (100MHz, $CDCl_3$)**δinppm:195.77,160.56, 158.54, 153.47,143.96,118.43,114.74,104.75,95.68,57.55, 54.77, 50.54,39.15,37.54,31.78,26.96. **LCMS** (m/z):354.39. **Molecularformula**: $C_{20}H_{22}N_2O_4$. **Elemental analysis**: calculated: C-67.78, H-6.26, N-7.89, Obtained: C- 67.74, H-6.25, N-7.89.

6).1-(4-(1H-indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl) ethanone(4f)
white solid; yield-89%; m.p – 235^0c, **^{1}HNMR (400MHz, $CDCl_3$)** δ in ppm:6.715(s,2H,NH_2), 6.074(s,1H,Ar-H), 4.188(s,1H, CH), 3.754(s,9H,OCH_3),2.334(s, 2H, CH_2),1.784(s, 2H, CH_2), 1.067(s,3H,CH_3), 0.881(s,3H,CH_3). **^{13}CNMR (100MHz, $CDCl_3$)**δinppm: 163.59,160.87, 159.21, 156.78,153.53,118.82, 113.51,100. 49,92.89, 57.73,54. 58,50.65,36.72,31.64, 24.44,26.78. **LCMS** (m/z): 384.28. **Molecular formula**: $C_{21}H_{24}N_2O_5$.**Elemental analysis**: Calculated: C-65.61, H-6.29, N-7.29. Obtained: 65.58, H-6.28, N-7.36.

Biological Activity
Anti Bacterial Activity
The anti bacterial activities of newly synthesized compounds are examined against 5 pathogenic bacteria strains. The result of antibiotic activity studies for the compounds. The gram negative bacteria screened were Escherichia Coli Pseudomonas aeruginosa were selected and tested by the disc diffusion method,[20] using Mueller–Hinton agar against. Normal saline was used for preparation of inoculants having turbidity equal to 0.5 McFarland standards. Tested compounds were dissolved in dimethy sulfoxide (DMSO) for the preparation of stock solution. The solvent control was included, although no antibacterial activity has been noted. The gram positive bacteria screened were S-aureas and Bacillus. Culture was carried out with sterile swab and micro tube suspension was cultured for 24 h and then inoculated onto Mueller Hinton agar. The target compounds were used at the concentration of 250 µglml and 500 µglml using DMSO as a solvent the amoxylin 10 µglml disc were used as a standard. The rest of the compounds were found to be moderate active against the tested micro organism. Cifrafloxin was used as the standard.

Anti Fungal Activity
Anti fungal activity of new synthesized compounds were examined by disc diffusion method against the organism of aspergillusniger and Candida albicans 1. Compared were treated at the concentrations of 500 µglml and 1000 µglml using DMSO as a solvent. The standard drug was used as ketoconazol 50 µglml against both organisms.

RESULT AND DISCUSSION

All newly titled synthesized compounds can be synthesized under elevated temperature such as 120^0C. These target compounds can be obtained, we used to Methanesulfonic acid and also used for solvent. This catalyst can be used to improve the reaction conditions and reaction is completed maximum 2 hours. The rate of reaction increased by using this catalyst. The yield of the titled compounds obtained from 85-89%. We used various substituted hetero aromatic aldehydes such as pyridine -2-carbaldehyde and pyridine -3-carbaldehyde, indole -3-carbalde gives maximum yeild than that of other hetero aromatic aldehyde. All the synthesized compounds were examined anti bacterial activity as well as antifungal Table-I.

Table-I: Antimicrobial activity screening activity synthesized scaffold.

Compound Code	*Zone of inhibition in (mm)					
	Bacteria				Fungi	
	S.aureus	E.coli	S. typhi	B.substills	A. niger	C. albicans
4a	10	11	09	11	08	09
4b	18	17	10	18	07	08
4c	22	19	12	18	08	10
4d	21	19	21	20	16	17
4e	20	22	20	19	16	15
4f	20	17	13	18	15	14
Cifrafloxin	25	25	22	22	NA	NA
Ketoconazol	NA	NA	NA	NA	20	20
DMSO	---	----	---	---	---	---

CONCLUSION

The reaction condition carried at elevated temperature for all the newly synthesised derivatives. The yield of the titled compounds obtained from 85-89%. The compound having pyridine -2-carbaldehyde and pyridine -3-carbaldehyde, indole -3-carbalde gives maximum yeild than that of other hetero aromatic aldehyde. The rate of reaction improved by using the methane sulfonic acid. All the titled compounds tested by anti microbial activity against gram positive, gram negitive and fungal. The compound having pyridine -2-carbaldehyde and pyridine -3-carbaldehyde, indole -3-carbalde gives maximum showed excelent active potential. Other wise the compounds having other hetero aromatic aldehyde.

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