© 2019 IJSRST | Volume 6 | Issue 3 | Print ISSN: 2395-6011 | Online ISSN: 2395-602X
Themed Section: Science and Technology
DOI : https://doi.org/10.32628/IJSRST1207250

Synthesis and biological Evaluation of Some Abbreviated New pyrimidine derivatives

Jatin Vora[1], Kartik Vyas[2]

[1]Department of Chemistry, Sheth L. H. Science College, Mansa, India (Scholars of Gujarat University, Ahmedabad), Gujarat, India

[2]Department of Chemistry, Sheth L. H. Science College, Mansa, Gujarat, India

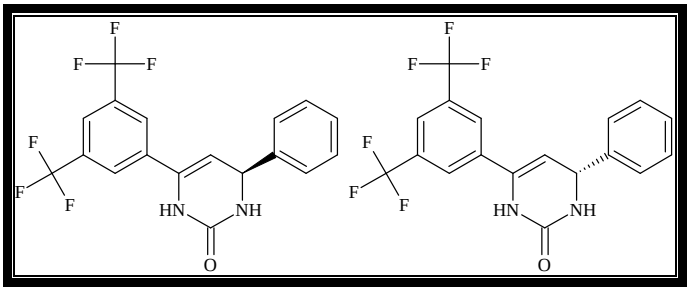
ABSTRACT

A cogent synthesis of completely new compound series of by ***6-(3,5-bis(trifluoromethyl)phenyl)-4-(4-chlorophenyl)-3,4-dihydro pyrimidine-2(1H)-one*** (***Biginelli reaction)*** was achieved by continue heating of (E)-1-(3,5-bis(trifluoromethyl)phenyl)-3-(substituted phenyl)prop-2-en-1-one and urea for 5 hours with 40% KOH and ethyl alcohol. (E)-1-(3,5-bis(trifluoromethyl)phenyl)-3-(substituted phenyl)prop-2-en-1-one is produced by Claisen-Schmidt Condensation. In this condensation 1-(3,5-bis(trifluoromethyl)phenyl)ethanone and different aldehyde are mixed. All the novel compound series were characterized by infrared and 1H nuclear magnetic resonance and mass spectroscopic techniques and by elemental analyses. The newly synthesized compounds were evaluated for their antibacterial and antifungal activity

Keywords : (E)-1-(3,5-bis(trifluoromethyl)phenyl)-3-(substituted phenyl)prop-2-en-1-one, Urea, KOH and Ethanol.

I. INTRODUCTION

The biginelli rection is the most efficient reaction for the preparation of di hydropyrimidines. Which is the multi-component and acid-catalyzed reaction [1]. The acid which is used in this reaction is copper (II) trifluoroacetate hydrate [2]. And boron trifluoride. The product forming during this method is used as a calcium channel blocker [3]. Antihypertensive agents antimicrobial and antifungal agents. In 1987, Atwal et al.[4][5] reported a modification to the Biginelli reaction that consistently generated higher yields. Atul Kumar has reported first enzymatic synthesis for Biginelli reaction via yeast catalyzed protocol in high yields.[6] The key advantage of the present method is the capability to allow variability of functional groups, short reaction times, easy workup, high yields, thus providing economic and environmental advantages. [7] 4 - (benzyloxy) – 3 - methoxy benzaldehyde, N - (substituted phenyl) – 3 - oxobutanamide and 2H-1,2,4-triazole-3-amine are three-component which are mainly responsible for highly efficient condensation



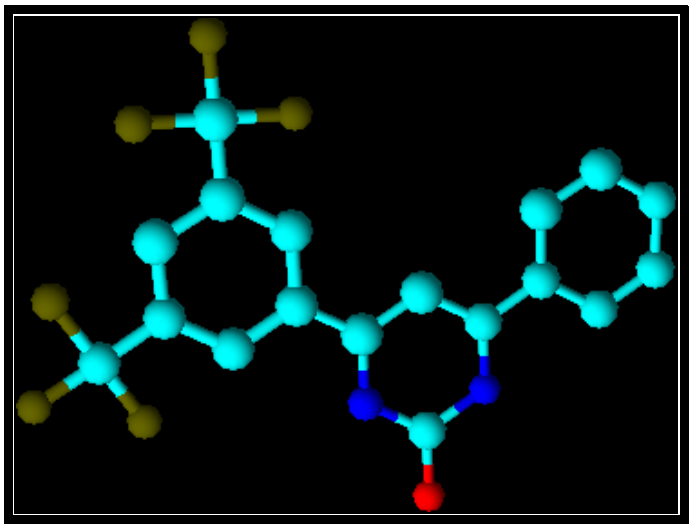
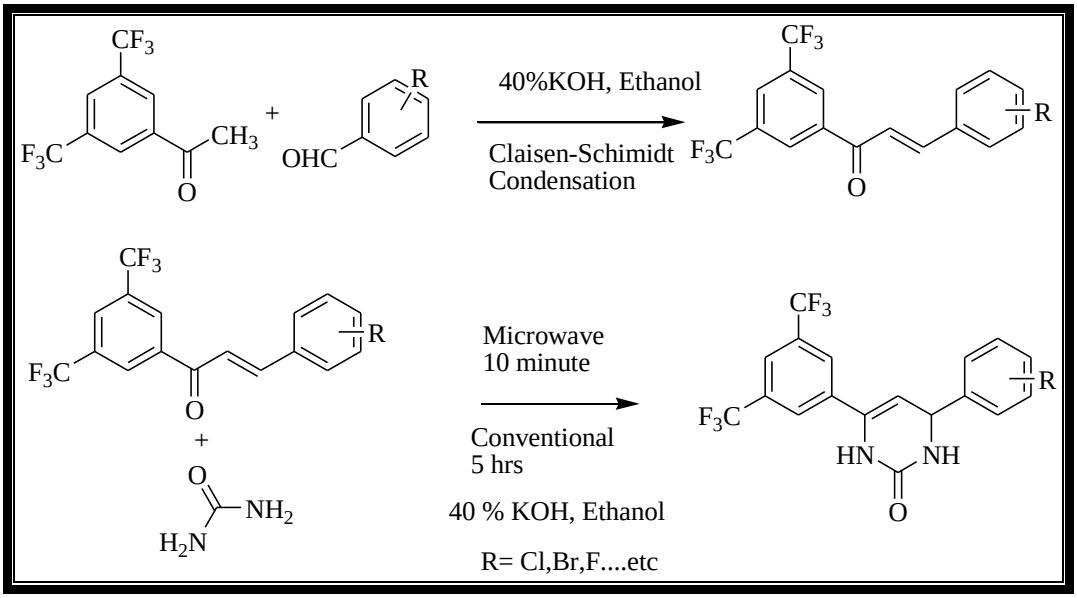


Figure 1. 3D Structure



II. EXPERIMENTAL

Typical untried procedure

A mixture of (E)-1-(3,5-bis(trifluoromethyl)phenyl)-3-(substituted phenyl)prop-2-en-1-one and Urea was refluxed in 40 % KOH in ethanol (20ml) on water bath for 5 hours. The solvent was distilled out under vacuum and neutralized with 20% HCl, filter out the solid product and crystalline from ethanol.

6-(3,5-bis(trifluoromethyl)phenyl)-4-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (4a)

M.P. 160ºC; Yield: 70%; IR(KBr)(cm^{-1}): 3092 (N-H), 2916 (C-H), 1610 (C=O), 1588, 1462 (C=C), 1095 (C-F); 754 (C-Cl); ^{1}H NMR (DMSO-*d6*) δ ppm: δ 5.50 (s, 2H, -CH- of pyrimidine ring), 6.96-6.98 (m, 1H, Ar-H), 7.23-7.33 (m, 2H, Ar-H), 7.43-7.44 (s, 1H, -Ar-H),7.53-7.57 (s, 2H, -Ar-H), 8.31-8.33 (s, 2H, -NH of pyrimidine), 8.61 (s, 1H, -Ar-H); MS: *m/z* 420. Anal. found: C, 51.79; H, 2.48; Cl, 8.87; F, 27.14; N, 6.53. $C_{18}H_{11}ClF_6N_2O$ requires: C, 51.38; H, 2.64; Cl, 8.43; F, 27.09; N, 6.66 %.

6-(3,5-bis(trifluoromethyl)phenyl)-4-(4-fluorophenyl)-3,4-dihydropyrimidin-2(1H)-one (4b)

M.P. 169ºC; Yield: 74%; IR(KBr)(cm-1): 3086 (N-H), 2931 (C-H), 1641 (C=O), 1581, 1465 (C=C), 1074 (C-F); 727 (C-Cl); ^{1}H NMR (DMSO-d6) δ ppm: δ 5.49 (s, 2H, -CH- of pyrimidine ring), 7.35-7.40 (m, 4H, Ar-H), 7.62-7.67 (m, 1H, Ar-H), 7.80 (s, 2H, -Ar-H), 7.93-7.95 (s, 2H, -NH of of pyrimidine); MS: *m/z* 404. Anal. found: C, 53.40; H, 2.84; F, 32.15; N, 6.63. $C_{18}H_{11}F_7N_2O$ requires: C, 53.48; H, 2.74; F, 32.90; N, 6.93 %.

6-(3,5-bis(trifluoromethyl)phenyl)-4-(4-bromophenyl)-3,4-dihydropyrimidin-2(1H)-one (4c)

M.P. 166ºC; Yield: 70%; IR(KBr)(cm-1): 3089 (N-H), 2964 (C-H), 1668 (C=O), 1577, 1460 (C=C), 1069 (C-F); 733 (C-Cl); ^{1}H NMR (DMSO-d6) δ ppm: δ 5.43 (s, 2H, -CH- of pyrimidine ring), 7.33-7.38 (m, 4H, Ar-H), 7.62-7.65 (m, 1H, Ar-H), 7.77 (s, 2H, -Ar-H), 7.88-7.90 (s, 2H, -NH of of pyrimidine); MS: *m/z* 465. Anal. found: C, 46.49; H, 2.39; Br, 17.11; F, 24.51; N, 6.07. $C_{18}H_{11}BrF_6N_2O$ requires: C, 46.47; H, 2.38; Br, 17.18; F, 24.50; N, 6.02%.

6-(3,5-bis(trifluoromethyl)phenyl)-4-(3-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (4d)

M.P. 162ºC; Yield: 63%; IR(KBr)(cm^{-1}): 3092 (N-H), 2916 (C-H), 1610 (C=O), 1588, 1462 (C=C), 1095 (C-F); 754 (C-Cl); ^{1}H NMR (DMSO-*d6*) δ ppm: δ 5.50 (s, 2H, -CH- of pyrimidine ring), 6.87-6.90 (m, 1H, Ar-H), 7.20-7.25 (m, 2H, Ar-H), 7.43-7.44 (s, 1H, -Ar-H),7.50-7.51 (s, 2H, -Ar-H), 8.22-8.22 (s, 2H, -NH of pyrimidine), 8.71 (s, 1H, -Ar-H); MS: *m/z* 420. Anal. found: C C, 51.34; H, 2.60; Cl, 8.41; F, 27.11; N, 6.42. $C_{18}H_{11}ClF_6N_2O$ requires: C, 51.38; H, 2.64; Cl, 8.43; F, 27.09; N, 6.66 %.

6-(3,5-bis(trifluoromethyl)phenyl)-4-(3-fluorophenyl)-3,4-dihydropyrimidin-2(1H)-one (4e)

M.P. 160ºC; Yield: 66%; IR(KBr)(cm^{-1}): 3108 (N-H), 2945 (C-H), 1679 (C=O), 1574, 1468 (C=C), 1088 (C-F); 741 (C-Cl); ^{1}H NMR (DMSO-*d6*) δ ppm: δ 5.43 (s, 2H, -CH- of pyrimidine ring), 6.93-6.95 (m, 1H, Ar-H), 7.29-7.31 (m, 2H, Ar-H), 7.38-7.40 (s, 1H, -Ar-H),7.48-7.50 (s, 2H, -Ar-H), 8.37-8.39 (s, 2H, -NH of pyrimidine), 8.74 (s, 1H, -Ar-H); MS: *m/z* 404. Anal. found: C, 53.47; H, 2.77; F, 32.96; N, 6.89. $C_{18}H_{11}F_7N_2O$ requires: C, 53.48; H, 2.74; F, 32.90; N, 6.93 %.

6-(3,5-bis(trifluoromethyl)phenyl)-4-(3-bromophenyl)-3,4-dihydropyrimidin-2(1H)-one (4f)

M.P. 170ºC; Yield: 70% IR(KBr)(cm^{-1}): 3111 (N-H), 2947 (C-H), 1644 (C=O), 1584, 1465 (C=C), 1090 (C-F); 742 (C-Cl); ^{1}H NMR (DMSO-*d6*) δ ppm: δ 5.59 (s, 2H, -CH- of pyrimidine ring), 7.07-7.09 (m, 1H, Ar-H), 7.27-7.29 (m, 2H, Ar-H), 7.44-7.46 (s, 1H, -Ar-H), 7.52-7.54 (s, 2H, -Ar-H), 8.43-8.45 (s, 2H, -NH of pyrimidine), 8.77 (s, 1H, -Ar-H); MS: *m/z* 465. Anal. found: C, 46.38; H, 2.40; Br, 17.28; F, 24.33; N, 6.11. $C_{18}H_{11}BrF_6N_2O$ requires: C, 46.47; H, 2.38; Br, 17.18; F, 24.50; N, 6.02%.

6-(3,5-bis(trifluoromethyl)phenyl)-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1H)-one (4g)

M.P. 159ºC; Yield: 60%; IR(KBr)(cm^{-1}): 3123 (N-H), 2967 (C-H), 1658 (C=O), 1568, 1456 (C=C), 1054 (C-F); 743 (C-Cl); ^{1}H NMR (DMSO-*d6*) δ ppm: δ 5.41 (s, 2H, -CH- of pyrimidine ring), 6.89-6.91 (m, 1H, Ar-H), 7.28-7.30 (m, 2H, Ar-H), 7.32-7.34 (s, 1H, -Ar-H),7.43-7.45 (s, 2H, -Ar-H), 8.42-8.45 (s, 2H, -NH of pyrimidine), 8.88 (s, 1H, -Ar-H); MS: *m/z* 400. Anal. found: C, 57.21; H, 3.64; F, 28.31; N, 7.12. $C_{19}H_{14}F_6N_2O$ requires: C, 57.01; H, 3.52; F, 28.47; N, 7.00%.

6-(3,5-bis(trifluoromethyl)phenyl)-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (4h)

M.P. 170ºC; Yield: 52%; IR(KBr)(cm^{-1}): 3084 (N-H), 2933 (C-H), 1668 (C=O), 1579, 1446 (C=C), 1065 (C-F); 745 (C-Cl); ^{1}H NMR (DMSO-*d6*) δ ppm: δ 5.48 (s, 2H, -CH- of pyrimidine ring), 6.88-6.90 (m, 1H, Ar-H), 7.28-7.30 (m, 2H, Ar-H), 7.40-7.42 (s, 1H, -Ar-H), 7.66-7.68 (s, 2H, -Ar-H), 8.10-8.12 (s, 2H, -NH of pyrimidine), 8.45 (s, 1H, -Ar-H); MS: *m/z* 416. Anal. found: C, 54.46; H, 3.41; F, 27.31; N, 6.70. $C_{19}H_{14}F_6N_2O_2$ requires: C, 54.81; H, 3.39; F, 27.38; N, 6.73%.

6-(3,5-bis(trifluoromethyl)phenyl)-4-(4-(trifluoromethyl)phenyl)-3,4-dihydropyrimidin-2(1H)-one (4i)

M.P. 166ºC; Yield: 64%; IR(KBr)(cm^{-1}): 3057 (N-H), 2949 (C-H), 1623 (C=O), 1567, 1446 (C=C), 1025 (C-F); 733 (C-Cl); ^{1}H NMR (DMSO-*d6*) δ ppm: δ 5.42 (s, 2H, -CH- of pyrimidine ring), 6.72-6.74 (m, 1H, Ar-H), 7.25-7.28 (m, 2H, Ar-H), 7.30-7.35 (s, 1H, -Ar-H),7.47-7.50 (s, 2H, -Ar-H), 8.36-8.39 (s, 2H, -NH of pyrimidine), 8.77 (s, 1H, -Ar-H); MS: *m/z* 454. Anal. found: C, 50.20; H, 2.40; F, 37.47; N, 6.56. $C_{19}H_{11}F_9N_2O$ requires: C, 50.23; H, 2.44; F, 37.64; N, 6.17%.

6-(3,5-bis(trifluoromethyl)phenyl)-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (4j)

M.P. 160ºC; Yield: 69%; IR(KBr)(cm^{-1}): 3102 (N-H), 2945 (C-H), 1666 (C=O), 1580, 1467 (C=C), 1054 (C-F); 744 (C-Cl); ^{1}H NMR (DMSO-*d6*) δ ppm: δ 5.23 (s, 2H, -CH- of pyrimidine ring), 6.90-6.93 (m, 1H, Ar-H), 7.20-7.25 (m, 2H, Ar-H), 7.40-7.43 (s, 1H, -Ar-H),7.50-7.54 (s, 2H, -Ar-H), 8.30-8.32 (s, 2H, -NH of pyrimidine), 8.76 (s, 1H, -Ar-H); MS: *m/z* 431. Anal. found: C, 50.18; H, 2.54; F, 26.51; N, 9.71. $C_{18}H_{11}F_6N_3O_3$ requires: C, 50.13; H, 2.57; F, 26.43; N, 9.74%.

III. BIOLOGICAL EVALUATION

Antimicrobial evaluation

All of the synthesized compounds **4a-j** were tested for their antibacterial and antifungal activity (MIC) in vitro by broth dilution method[8-10] with two Gram-positive bacteria Staphylococcus aureus MTCC-96, Streptococcus pyogenes MTCC 443, two Gram-negative bacteria Escherichia coli MTCC 442, Pseudomonas aeruginosa MTCC 441 and three fungal strains Candida albicans MTCC 227, Aspergillus Niger MTCC 282, Aspergillus clavatus MTCC 1323 taking ampicillin, chloramphenicol, norfloxacin, nystatin, and griseofulvin as standard drugs. The standard strains were procured from the Microbial Type Culture Collection (MTCC) and Gene Bank, Institute of Microbial Technology, Chandigarh, India. The minimal inhibitory concentration (MIC) values for all the newly synthesized compounds, specified as the humble concentration of the compound preventing the observable growth, were determined by using the microdilution broth method according to NCCLS(National Committee for Clinical Laboratory Standards) standards.

Serial dilutions of the test compounds and reference drugs were prepared in Mueller-Hinton agar. Drugs (10 mg) were dissolved in dimethylsulfoxide (DMSO, 1 mL). Further progressive dilutions with melted Mueller-Hinton agar were performed to obtain the required concentrations. In primary screening 1000 μg mL^{-1}, 500 μg mL^{-1} and 250 μg mL^{-1} concentrations of the synthesized drugs were taken. The active synthesized drugs found in this primary screening were further tested in the second set of dilution at 125 μg mL-1, 62.5 μg mL^{-1}, 50 μg mL^{-1}, 25 μg mL-1, 12.5 μg mL^{-1}, and 6.250 μg mL^{-1} concentration against all microorganisms. The tubes were inoculated with 108 CFU mL^{-1} (colony-forming unit/mL) and

incubated at 37 ºC for 24 h. The MIC was the lowest concentration of the tested compound that yields no visible growth (turbidity) on the plate. To ensure that the solvent did not affect the bacterial growth, a control was performed with the test medium supplemented with DMSO at the same dilutions as used in the experiments and it was observed that DMSO did not affect the microorganisms in the concentrations studied. The results obtained from antimicrobial susceptibility testing are depicted.

Table 1 :- *in vitro Antibacterial Screening Results for* (4a-j)

Code	**Minimal inhibition concentration (µg mL^{-1})**			
	Gram-positive		**Gram-negative**	
	GPA1	**GPA2**	**GNA3**	**GNA4**
4a	500	500	1000	100
4b	250	250	250	500
4c	1000	1000	200	250
4d	250	1000	250	250
4e	1000	250	250	250
4f	250	250	200	250
4g	1000	500	500	500
4h	500	500	250	250
4i	500	250	100	1000
4j	500	62.5	500	100
Ampicillin	250	100	100	100
Chloramphenicol	50	50	50	50
Norfloxacin	10	10	10	10
	Staphylococcus aureus	**GPA1**		
	Streptococcus pyogenes	**GPA2**		
	Escherichia coli	**GNA3**		
	Pseudomonas aeruginosa	**GNA4**		

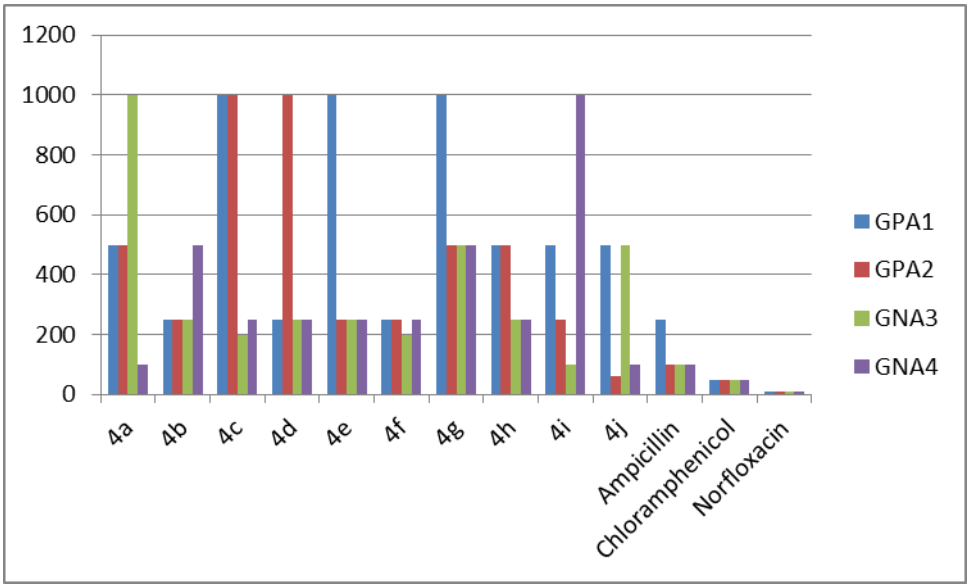
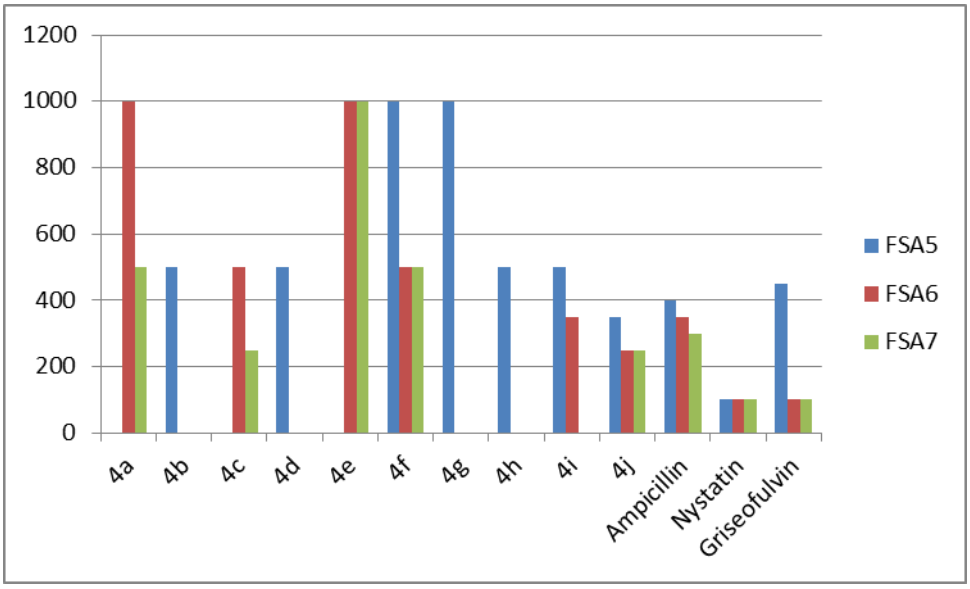


Table 2 :- *in vitro Antifungal Screening Results for* (4a-j)

Code	**Minimal inhibition concentration (µg mL-1)**		
	Fungal species		
	FSA5	**FSA6**	**FSA7**
4a	>1000	1000	500
4b	500	>1000	>1000
4c	>1000	500	250
4d	500	>1000	>1000
4e	>1000	1000	1000
4f	1000	500	500
4g	1000	>1000	>1000
4h	500	>1000	>1000
4i	500	350	>1000
4j	350	250	250
Ampicillin	400	350	300
Nystatin	100	100	100
Griseofulvin	450	100	100
		Candida albicans	**FSA5**
		Aspergillus Niger	**FSA6**
		Aspergillus clavatus	**FSA7**



IV. RESULT AND DISCUSSION

Here we test all synthesized compounds for the determination of their activity for four bacteria in which compound no. 4b and 4f found good inhibitors against staphylococcus aureus and compound no.4b, 4e, 4fand 4i exhibit good activity at 250 µg mL^{-1} against streptococcus pyogenes. 4c, 4i exhibit excellent activity at 100,200 µg mL^{-1} respectively. And 4d, 4e, 4h are good inhibitors against Escherichia coli. Compound no.4a and 4j show very good activity

against pseudomonas aeruginosa while others are moderate.

Three fungal strains are used for screening. In antifungal screening 4j compound is great inhibitors against all three fungal strains. 4b, 4d, 4i, and 4j are moderate inhibitors against candida Albicans .4i is an excellent inhibitor while 4f and 4c are good inhibitors against the aspergillus Niger .4c exhibit very good antifungal activity at 250 μg mL^{-1} 4f and 4f are moderate inhibitors.

V. CONCLUSION

In this paper, we present the method for preparing the triazolopymidine by bignelli reaction and the help of Clausen Schmidt condensation. By comparing results we found many antimicrobial and antifungal agents among them which will use to study of the determination of a variety of activities in triazolopyrimidine

VI. REFERENCES

[1]. Biginelli, P. (1891). "Ueber Aldehyduramide des Acetessigäthers". Chemische Berichte, 24: 1317–1319. doi:10.1002/cber.189102401228.

[2]. Song, Dailei; Wang, Runxia; Chen, Yongli; Zhang, Shaohua; Liu, Chunsheng; Luo, Genxiang (2008). "Copper(II) trifluoroacetate catalyzed synthesis of 3,4-dihydropyrimidin-2(1H)-ones under solvent-free conditions". Reaction Kinetics and Catalysis Letters. 95 (2).

[3]. Rovnyak, G. C.; Atwal, K. S.; Hedberg, A.; Kimball, S. D.; Moreland, S.; Gougoutas, J. Z.; O'Reilly, B. C.; Schwartz, J.; Malley, M. F. (1992). & quot; Dihydropyrimidine calcium channel blockers. 4. Basic 3-substituted-4-aryl-1,4-dihydropyrimidine-5-carboxylic acid esters. Potent antihypertensive agents & quot;. J. Med. Chem. 35 (17): 3254–3263.

[4]. Reilly, B. C.; Atwal, K. S. (1987). & quot; Synthesis of Substituted 1,2,3,4-Tetrahydro-6-methyl-2-thioxo-5-pyrimidinecarboxylic Acid Esters & quot Heterocycles. 26 (5): 1189–1192. doi:10.3987/R-1987-05-1189.

[5]. Kumar, Atul; Maurya, Ram Awatar (2007). "An efficient bakers' yeast catalysed synthesis of 3,4-dihydropyrimidin-2-(1H)-ones". Tetrahedron Letters. 48 (26): 4569.

[6]. Chetan K Jadhav, Amol S Nipate, Asha V Chate, Vishal D Songire, Anil P Patil, Charansingh H Gill (2019) Efficient Rapid Access to Biginelli for the Multicomponent Synthesis of 1,2,3,4-Tetrahydropyrimidines in Room-Temperature Diisopropyl Ethyl Ammonium Acetate, ACS Omega December 31, 4 (27): 22313-22324.

[7]. Shuyan Yu, Jingxin Wu, Hongbing Lan, Lihong Gao, Hengyu Qian, Kaiqi Fan, Zhigang Yin, “palladium and Bronsted acid co-catalyzed biginelli-like multicomponent reactions via in situ generated cyclic enol ether : Access tospirofuran- hydropyrimidines. Organic Letters 2019 December 18.

[8]. National Committee for Clinical and Laboratory Standards, Method for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically Approved Standard, fourth ed. NCCLS, Villanova, Italy, Document M 100-S7, S100-S157 (1997).

[9]. D.H. Isenberg, Essential Procedure for Clinical Microbiology, American Society for Microbiology, Washington, (1998).

[10]. J. R. Zgoda, J. R. Porter, Pharm. Biol., 39, 221-225 (2001).

Cite this article as :

Jatin Vora, Kartik Vyas, " Synthesis and biological Evaluation of Some Abbreviated New pyrimidine derivatives", International Journal of Scientific Research in Science and Technology (IJSRST), Online ISSN : 2395-602X, Print ISSN : 2395-6011, Volume 6 Issue 3, pp. 354-361, May-June 2019. Available at doi : https://doi.org/10.32628/IJSRST1207250
Journal URL : http://ijsrst.com/IJSRST1207250