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An Efficient Approach Towards Synthesis of Pyrimidine Derivatives Bearing Pyridine Nucleus Using L-Proline as a Catalyst

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ABSTRACT

Pyridine and pyrimidine containing compounds found to possess various biological activities. Biginelli reaction is one of the finest approaches to synthesize pyrimidine derivatives that offer diverse choice of substitutions. This paper describes an efficient approach towards synthesis of pyrimidine derivatives bearing pyridine nucleus using L-proline as a catalyst. Twenty compounds were synthesized in high purity using a simple synthetic program. All the compounds were characterized by NMR, IR and mass spectroscopy.

Keywords: Pyrimidine, Pyridine, Biginelli reaction, biological activities, NMR, L-proline

I. INTRODUCTION

Biginelli P. reported the synthesis of functionalized 3,4-dihydropyrimidin-2(1H)-ones (DHPMs) via three-component condensation reaction of an aromatic aldehydes, urea and ethyl acetoacetate. In the past decade, this multicomponent reaction has experienced a remarkable revival, mainly due to the interesting pharmacological properties associated with this dihydropyrimidine scaffold. The classical three-component Biginelli condensation is usually carried out in alcoholic solution containing a few drops of concentrated hydrochloric or sulfuric acid as catalyst, although other systems such as tetrahydrofuran/hydrochloric acid (THF/HCl), dioxane/hydrochloric acid or acetic acid/hydrochloric acid has also been employed. Multicomponent reactions (MCRs) occupy an outstanding position in organic and medicinal chemistry for their high degree of atom economy, applications in combinatorial chemistry and diversity-oriented synthesis [1].

The venerable Biginelli reaction, one pot cyclocondensation of aldehyde, 1,3-ketoester and urea or thiourea, is inarguably one of the most useful MCRs [2]. Polyfunctionalized dihydropyrimidines (DHPMs) represent a heterocyclic system of remarkable pharmacological activity.

The mechanism of the Biginelli reaction has been the subject of some debate over the past decades. Early work by Folkers K. et al. suggested that bisureide i.e., the primary bimolecular condensation product of benzaldehydes and urea is the first intermediate in this reaction [3]. In 1973 Sweet F. et al. proposed that a carbenium ion, produced by an acid-catalyzed aldol reaction of benzaldehyde with ethyl acetoacetate, is the key intermediate and is formed in the first and limiting step of the Biginelli reaction [4].

Kappe O. et al. reinvestigated the mechanism in 1997 using ^{1}H and ^{13}C NMR spectroscopy and have established that the first step in this reaction involves the acid-catalyzed formation of an N-acyliminium ion intermediate from the aldehydes and urea component. Interception of the iminium ion by ethyl acetoacetate, possibly through its enol tautomer, produces an open-chain ureide which subsequently cyclize to dihydropyrimidine. Although the highly reactive N-acyliminium ion species could not be isolated or directly observed, further evidence for the proposed mechanism was obtained by isolation of intermediates, employing sterically bulky [5] or electron-deficient acetoacetates [6] respectively. The relative stereochemistry in hexahydropyrimidine was established by an X-ray analysis.

Different catalysts have been employed for these types of reaction are: Ferric chloride (FeCl3)/tetraethyl orthosilicate [7], triflates [8, 9], metal bromide [10, 11], polyoxometalate [12], strontium (II) nitrate [13], cerium (III) chloride [14], lithium trifluoromethanesulfonate or

lithium triflate (LiOTf) [15], lanthanide triflates-$Ln(OTf)_3$ [16], heteropolyacids [17], ion exchange resins, polymer based solid acid [18], L-proline [19, 20], chiral phosphoric acid [21], trimethylsilyl chloride (TMSCl) [22], zirconium tetrachloride ZrCl4 [23], dowex [24], Boron trifluoride-etharate (BF_3-etharate) [25], BF_3-etharate/cuprous chloride (CuCl) [26], vanadium trichloride (VCl_3) [27], lithium perchlorate ($LiClO_4$) [28], stannous chloride ($SnCl_2.2H_2O$) [29], $AlCl_3$/KI [30], $CoCl_2/MnCl_2$ [31], $AlCl_3/AlBr_3$ [32], P_2O_5 [33], Bismuth oxide perchlorate ($BiOClO_4.xH_2O$) [34], $CaCl_2$ [35], 1,3-Dibromo-5,4-dimethylhydantoin, Zinc tetrafluoroborate [36].

II. EXPERIMENTAL

Materials and methods

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine. IR spectra were recorded Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. ^{1}H NMR was determined in DMSO-d6 solution on a Bruker Ac 400 MHz spectrometer.

Reaction Scheme

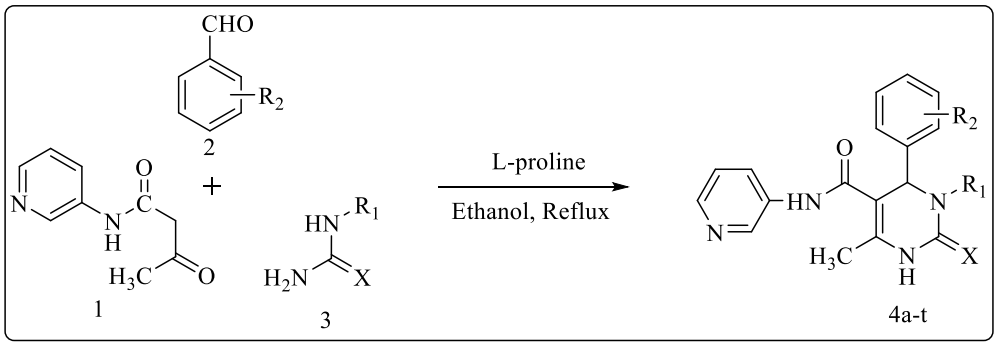


Table 1. Physical data for synthesized compounds

Code	R_1	X	R_2	M.F.	M.W.	M.P. ºC	Yield %	R_{f1}	R_{f2}
4a	H	O	H	$C_{17}H_{16}N_4O_2$	308	160-162	66	0.42	0.66
4b	H	O	4-CH_3	$C_{18}H_{18}N_4O_2$	322	191-193	64	0.50	0.69
4c	H	O	4-OCH_3	$C_{18}H_{18}N_4O_3$	338	221-223	63	0.49	0.73
4d	H	O	4-Cl	$C_{17}H_{15}ClN_4O_2$	342	199-201	76	0.46	0.68
4e	H	O	4-F	$C_{17}H_{15}FN_4O_2$	326	198-200	80	0.54	0.75
4f	H	O	4-NO_2	$C_{17}H_{15}N_5O_4$	353	183-185	69	0.50	0.70
4g	H	O	3-NO_2	$C_{17}H_{15}N_5O_4$	353	192-194	65	0.53	0.72
4h	H	O	2-NO_2	$C_{17}H_{15}N_5O_4$	353	226-228	79	0.50	0.65
4i	H	O	3-Cl	$C_{17}H_{15}ClN_4O_2$	342	153-155	58	0.55	0.67
4j	H	O	2-Cl	$C_{17}H_{15}ClN_4O_2$	342	223-225	62	0.48	0.77
4k	H	S	H	$C_{17}H_{16}N_4OS$	324	167-169	64	0.50	0.61
4l	H	S	4-CH_3	$C_{18}H_{18}N_4OS$	338	231-233	74	0.58	0.67
4m	H	S	4-OCH_3	$C_{18}H_{18}N_4O_2S$	354	181-183	70	0.41	0.74
4n	H	S	4-Cl	$C_{17}H_{15}ClN_4OS$	358	216-218	72	0.56	0.66
4o	H	S	4-F	$C_{17}H_{15}FN_4OS$	342	209-211	77	0.53	0.60
4p	H	S	4-NO_2	$C_{17}H_{15}N_5O_3S$	369	236-238	65	0.50	0.58
4q	H	S	3-NO_2	$C_{17}H_{15}N_5O_3S$	369	229-231	63	0.54	0.61
4r	H	S	2-NO_2	$C_{17}H_{15}N_5O_3S$	369	234-236	68	0.57	0.64
4s	H	S	3-Cl	$C_{17}H_{15}ClN_4OS$	358	188-190	62	0.48	0.57
4t	H	S	2-Cl	$C_{17}H_{15}ClN_4OS$	358	238-240	59	0.58	0.70

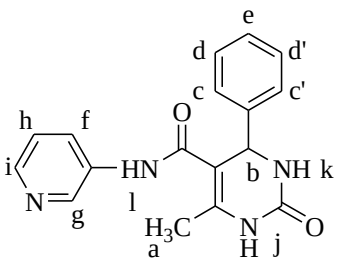
Synthesis of N-(pyridin-3-yl)-3-oxo-butanamide

Synthesis of N-(pyridin-3-yl)-3-oxo-butanamide was achieved using previously published methods [45].

General procedure for the synthesis of 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-aryl-N-(pyridin-3-yl)pyrimidine-5-carboxamides (4a-j)

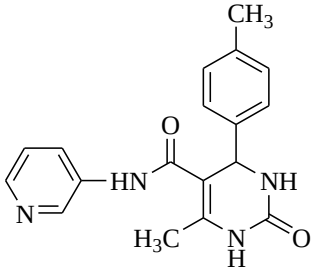
A mixture of N-(pyridin-3-yl)-3-oxo-butanamide (0.01 mol), appropriate aromatic aldehyde (0.01 mol), urea (0.015 mol) and catalytical amount of L-proline in ethanol (30 ml) was heated under reflux condition for 8 to10 hrs. The reaction mixture was kept at room temperature for 24 hrs. The product obtained was isolated and recrystallized from ethanol.

1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenyl-N-(pyridin-3-yl)pyrimidine-5-carboxamide (4a)



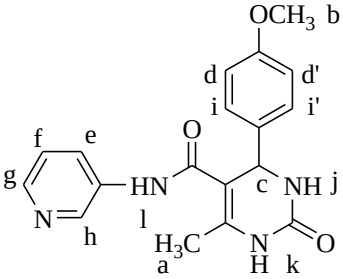
Yield: 66%; mp 160-162 ºC; IR (cm-1): 3331 (N-H stretching of primary amide), 3294 (N-H stretching of pyrimidine ring), 3059 (C-H symmetrical stretching of CH3 group), 3024 (C-H stretching of aromatic ring), 2931 (C-H asymmetrical stretching of CH3 group), 1699 (C=O stretching of amide), 1631 and 1525 (C=C stretching of aromatic ring), 1593 (N-H deformation of pyrimidine ring), 1460 (C-H asymmetrical deformation of CH3 group), 1342 (C-H symmetrical deformation of CH3 group), 1323 (C-N-C stretching of pyrimidine ring), 1282 (C-N stretching of pyrimidine ring), 1234 (C-H in plane deformation of aromatic ring), 759 and 713 (C-H out of plane deformation of mono substituted benzene ring); 1H NMR (DMSO-d6) δ ppm: 2.25 (s, 3H, Ha), 5.43 (s, 1H, Hb), 7.21-7.36 (m, 6H, Hcc'-f), 7.67 (s, 1H, Hg), 7.95-7.97 (d, 1H, Hh, J = 8.0 Hz), 8.20-8.21 (d, 1H, Hi, J = 4.0 Hz), 8.69 (s, 1H, Hk), 9.76 (s, 1H, Hl): m/z 308;

1,2,3,4-tetrahydro-6-methyl-2-oxo-N-(pyridin-3-yl)-4-p-tolylpyrimidine-5-carboxamide (CPV-102)



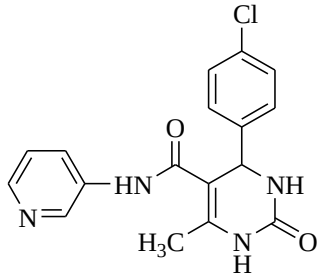
Yield: 64%; mp 191-193 ºC; MS: m/z 322;

1,2,3,4-tetrahydro-4-(4-methoxyphenyl)-6-methyl-2-oxo-N-(pyridin-3-yl)pyrimidine-5-carboxamide (4c)



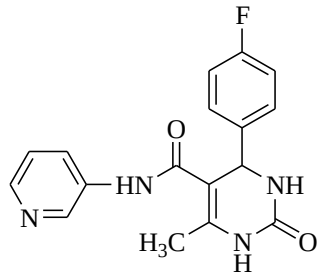
Yield: 63%; mp 221-223 ºC; IR (cm^{-1}): 3498 (N-H stretching of primary amide), 3230 (N-H stretching of pyrimidine ring), 3115 (C-H symmetrical stretching of CH_3 group), 2937 (C-H asymmetrical stretching of CH_3 group), 1712 (C=O stretching of amide), 1641 (N-H deformation of pyrimidine ring), 1525 and 1483 (C=C stretching of aromatic ring), 1435 (C-H asymmetrical deformation of CH_3 group), 1408 (C-N-C stretching of pyrimidine ring), 1340 (C-H symmetrical deformation of CH_3 group), 1276 (C-N stretching of pyrimidine ring), 1240 (C-O-C asymmetrical stretching of ether linkage), 1174 (C-H in plane deformation of aromatic ring), 1062 (C-O-C symmetrical stretching of ether linkage), 866 (C-H out of plane deformation of 1,4-disubstitution); ^{1}H NMR (DMSO-d_6) δ ppm: 2.11 (s, 3H, H_a), 3.73 (s, 3H, H_b), 5.44 (s, 1H, H_c), 6.82-6.84 (d, 2H, $H_{dd'}$, J = 8.0 Hz), 7.18-7.25 (m, 3H, H_{e-g}), 7.49 (s, 1H, H_h), 7.99-8.00 (d, 2H, $H_{ii'}$, J = 4.0 Hz), 8.17-8.18 (d, 1H, H_j, J = 4.0 Hz), 8.70 (s, 2H, H_{kj}), 9.60 (s, 1H, H_l); MS: m/z 338; Anal. Calcd. for $C_{18}H_{18}N_4O_3$: C, 63.89; H, 5.36; N, 16.56; O, 14.19. Found: C, 63.81; H, 5.30; N, 16.50; O, 14.11%.

4-(4-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxo-N-(pyridin-3-yl)pyrimidine-5-carboxamide (4d)



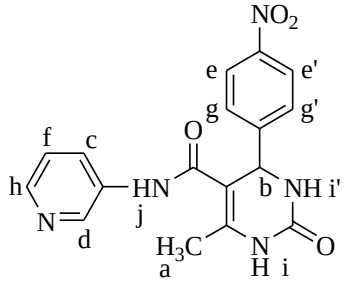
Yield: 76%; mp 199-201 ºC; MS: m/z 342;

4-(4-fluorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxo-N-(pyridin-3-yl)pyrimidine-5-carboxamide (4e)



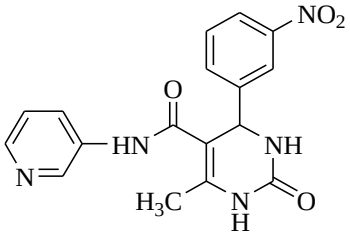
Yield: 80%; mp 198-200 ºC; MS: m/z 326;

1,2,3,4-tetrahydro-6-methyl-4-(4-nitrophenyl)-2-oxo-N-(pyridin-3-yl)pyrimidine-5-carboxamide (4f)



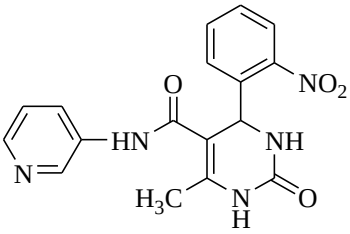
Yield: 69%; mp 183-185 ºC; IR (cm^{-1}): 3298 (N-H stretching of primary amide), 3234 (N-H stretching of pyrimidine ring), 3026 (C-H symmetrical stretching of CH_3 group), 2829 (C-H asymmetrical stretching of CH_3 group), 1689 (C=O stretching of amide), 1600 and 1471 (C=C stretching of aromatic ring), 1583 (C-NO_2 symmetrical stretching), 1521 (N-H deformation of pyrimidine ring), 1423 (C-N stretching of pyrimidine ring), 1390 (C-H asymmetrical deformation of CH_3 group), 1348 (C-N-C stretching of pyrimidine ring), 1309 (C-H symmetrical deformation of CH_3 group), 1244 (C-H in plane deformation of aromatic ring), 798 (C-H out of plane deformation of 1,4-disubstitution); ^1H NMR (DMSO-d_6) δ ppm: 2.19 (s, 3H, H_a), 5.63 (s, 1H, H_b), 7.18-7.22 (m, 1H, H_c), 7.49 (s, 1H, H_d), 7.59-7.61 (d, 2H, $H_{ee'}$, J = 8.0 Hz), 8.01-8.03 (d, 1H, H_f, J = 8.0 Hz), 8.14-8.16 (d, 2H, $H_{gg'}$, J = 8.0 Hz), 8.23-8.24 (d, 1H, H_h, J = 4.0 Hz), 8.71-8.73 (d, 2H, $H_{ii'}$, J = 8.0 Hz), 9.60 (s, 1H, H_j); MS: m/z 353;

1,2,3,4-tetrahydro-6-methyl-4-(3-nitrophenyl)-2-oxo-N-(pyridin-3-yl)pyrimidine-5-carboxamide (4g)



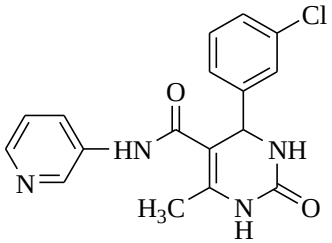
Yield: 65%; mp 192-194 ºC; MS: m/z 353;

1,2,3,4-tetrahydro-6-methyl-4-(2-nitrophenyl)-2-oxo-N-(pyridin-3-yl)pyrimidine-5-carboxamide (4h)



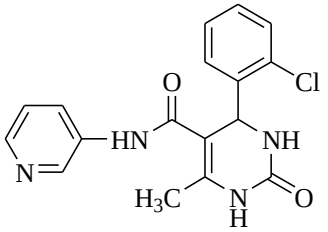
Yield: 79%; mp 226-228 ºC; MS: m/z 353;

4-(3-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxo-N-(pyridin-3-yl)pyrimidine-5-carboxamide (4i)



Yield: 58%; mp 153-155 ºC; MS: m/z 342;

4-(2-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxo-N-(pyridin-3-yl)pyrimidine-5-carboxamide (4j)

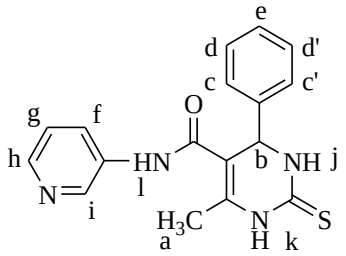


Yield: 62%; mp 223-225 ºC; MS: m/z 342;

General procedure for the synthesis of 1,2,3,4-tetrahydro-6-methyl-4-aryl-N-(pyridin-3-yl)-2-thioxopyrimidine-5-carboxamides (4k-t)

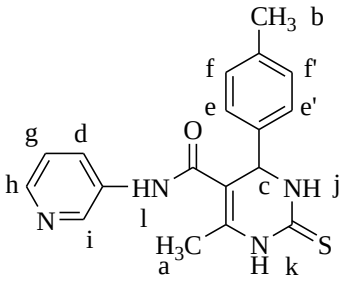
A mixture of N-(pyridin-3-yl)-3-oxo-butanamide (0.01 mol), appropriate aromatic aldehyde (0.01 mol), thiourea (0.015 mol) and catalytical amount of L-proline in ethanol (30 ml) was heated under reflux condition for 8 to10 hrs. The reaction mixture was kept at room temperature for 24 hrs. The product obtained was isolated and recrystallized from ethanol.

1,2,3,4-tetrahydro-6-methyl-4-phenyl-N-(pyridin-3-yl)-2-thioxopyrimidine-5-carboxamide (4k)



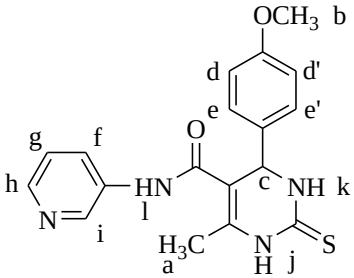
Yield: 64%; mp 167-169 ºC; IR (cm^{-1}): 3290 (N-H stretching of primary amide), 3192 (N-H stretching of pyrimidine ring), 3099 (C-H symmetrical stretching of CH_3 group), 2874 (C-H asymmetrical stretching of CH_3 group), 1662 (C=O stretching of amide), 1589 (N-H deformation of pyrimidine ring), 1523 and 1471 (C=C stretching of aromatic ring), 1433 (C-H asymmetrical deformation of CH_3 group), 1338 (C-N-C stretching of pyrimidine ring), 1290 (C-H symmetrical deformation of CH_3 group), 1242 (C-N stretching of pyrimidine ring), 1201 (C=S stretching), 1031 (C-H in plane deformation of aromatic ring), 758 and 721 (C-H out of plane deformation of mono substituted benzene ring); ^1H NMR (DMSO-d_6) δ ppm: 2.50 (s, 3H, H_a), 5.43 (s, 1H, H_b), 7.24-7.38 (m, 6H, $H_{cc'-f}$), 7.96-7.98 (d, 1H, H_g, J = 8.0 Hz), 8.22-8.24 (d, 1H, H_h, J = 8.0 Hz), 8.70 (s, 1H, H_i,), 9.53 (s, 1H, H_j), 9.94 (s, 1H, H_k), 10.08 (s, 1H, H_l); MS: m/z 324.

1,2,3,4-tetrahydro-6-methyl-N-(pyridin-3-yl)-2-thioxo-4-p-tolylpyrimidine-5-carboxamide (4l)



Yield: 74%; mp 231-233 ºC; IR (cm^{-1}): 3271 (N-H stretching of secondary amide), 3036 (C-H symmetrical stretching of CH_3 group), 2924 (C-H asymmetrical stretching of CH_3 group), 1708 (C=O stretching of amide), 1629 (N-H deformation of pyrimidine ring), 1591 and 1512 (C=C stretching of aromatic ring), 1408 (C-H asymmetrical deformation of CH_3 group), 1338 (C-H symmetrical deformation of CH_3 group), 1263 (C-N-C stretching of pyrimidine ring), 1236 (C-N stretching of pyrimidine ring), 1149 (C=S stretching); ^1H NMR (DMSO-d_6) δ ppm: 2.11 (s, 3H, H_a), 2.53-2.55 (s, 3H, H_b), 5.46-5.47 (s, 1H, H_c), 7.19-7.23 (m, 1H, H_d), 7.31 (s, 4H, $H_{e-f'}$), 7.62 (s, 1H, H_g), 7.97-8.00 (m, 1H, H_h), 8.18-8.20 (m, 1H, H_i), 8.70-8.71 (d, 1H, H_j, J = 4.0 Hz), 8.80 (s, 1H, H_k), 9.68 (s, 1H, H_l); MS: m/z 338.

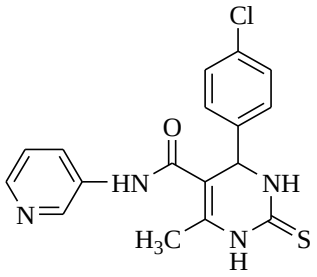
1,2,3,4-tetrahydro-4-(4-methoxyphenyl)-6-methyl-N-(pyridin-3-yl)-2-thioxopyrimidine-5-carboxamide (4m)



Yield: 70%; mp 181-183 ºC; IR (cm^{-1}): 3363 (N-H stretching of primary amide), 3319 (N-H stretching of pyrimidine ring), 3099 (C-H symmetrical stretching of CH_3 group), 2966 (C-H asymmetrical stretching of CH_3 group), 1672 (C=O stretching of amide), 1566 (N-H deformation of pyrimidine ring), 1516 and 1481 (C=C stretching of aromatic ring), 1415 (C-H asymmetrical deformation of CH_3 group), 1388 (C-H symmetrical deformation of CH_3 group), 1340 (C-N-C stretching of pyrimidine ring), 1280 (C-N stretching of pyrimidine ring), 1197 (C-O-C asymmetrical stretching of ether linkage), 1187 (C=S stretching), 1033 (C-O-C symmetrical stretching of ether linkage), 954 (C-H in

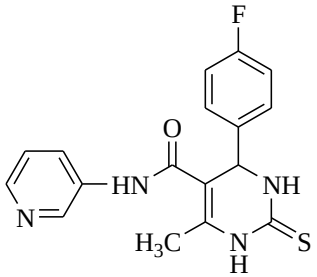
plane deformation of aromatic ring), 804 (C-H out of plane deformation of 1,4-disubstitution); ^{1}H NMR (DMSO-d_6) δ ppm: 2.15 (s, 3H, H_a), 3.74 (s, 1H, H_b), 5.45 (s, 1H, H_c), 6.83-6.85 (d, 2H, $H_{dd'}$, J = 8.0 Hz), 7.19-7.25 (m, 3H, H_{e-f}), 7.99-8.01 (d, 1H, H_g, J = 8.0 Hz), 8.20-8.22 (d, 1H, H_h, J = 8.0 Hz), 8.70-8.71 (d, 1H, H_i, J = 4.0 Hz), 9.35 (s, 1H, H_j), 9.74 (s, 1H, H_k), 9.88 (s, 1H, H_l); MS: m/z 354.

4-(4-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-N-(pyridin-3-yl)-2-thioxopyrimidine-5-carboxamide (4n)



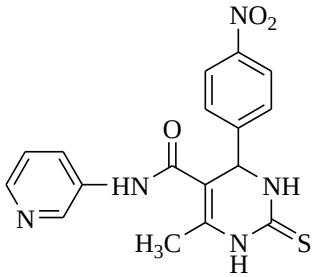
Yield: 72%; mp 216-218 ºC; MS: m/z 358;

4-(4-fluorophenyl)-1,2,3,4-tetrahydro-6-methyl-N-(pyridin-3-yl)-2-thioxopyrimidine-5-carboxamide (4o)



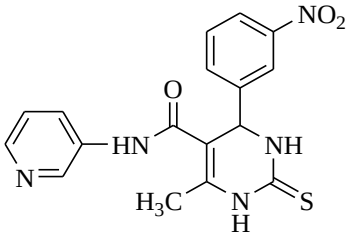
Yield: 77%; mp 209-211 ºC; MS: m/z 342; Anal. Calcd. for $C_{17}H_{15}FN_4OS$: C, 59.63; H, 4.42; N, 16.36; O, 4.67; S, 9.37. Found: C, 59.57; H, 4.36; N, 16.28; O, 4.62; S, 9.30%.

1,2,3,4-tetrahydro-6-methyl-4-(4-nitrophenyl)-N-(pyridin-3-yl)-2-thioxo pyrimidine-5-carboxamide (4p)



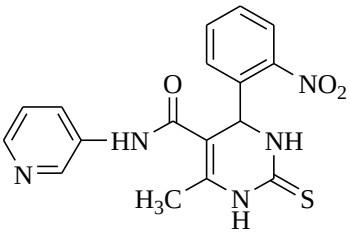
Yield: 65%; mp 236-238 ºC; MS: m/z 369.

1,2,3,4-tetrahydro-6-methyl-4-(3-nitrophenyl)-N-(pyridin-3-yl)-2-thioxopyrimidine-5-carboxamide (4q)



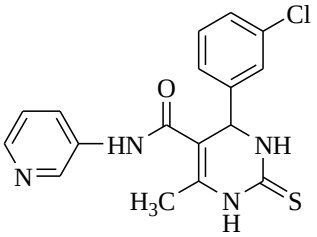
Yield: 63%; mp 229-231 ºC; MS: m/z 369.

1,2,3,4-tetrahydro-6-methyl-4-(2-nitrophenyl)-N-(pyridin-3-yl)-2-thioxopyrimidine-5-carboxamide (CPV-118)



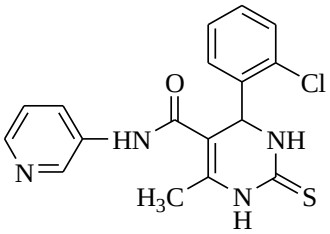
Yield: 68%; mp 234-236 ºC; MS: m/z 369.

4-(3-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-N-(pyridin-3-yl)-2-thioxo pyrimidine-5-carboxamide (4r)



Yield: 62%; mp 188-190 ºC; MS: m/z 358.

4-(2-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-N-(pyridin-3-yl)-2-thioxopyrimidine-5-carboxamide (4t)



Yield: 59%; mp 238-240 ºC; MS: m/z 359.

III. RESULTS AND DISCUSSION

The chemistry of pyrimidines and its derivatives has been studied for over a century due to their diverse biological activities. The 1,2,3,4-tetrahydropyrimidine ring system is of special biological interest because it has numerous pharmacological and medicinal applications viz, antitumour, antiviral, antimalarial, antitubarcular etc.

Keeping in mind various biomedical applications and with a view to further assess, the pharmacological profile of these class of compounds, two novel series of 1,2,3,4-tetrahydropyrimidine (4a-t) are synthesized. The synthesis of these thirty compounds was achieved by the Biginelli reaction of acetoacetanilide, urea derivatives and corresponding aldehydes. The reaction is catalysed by L-proline. The synthetic route for the preparation of dihydropyrimidines derivatives (4a-t) is summarized in Scheme 1. Various aldehydes (1a-e) bearing a range of electron withdrawing and electron releasing substituents, viz., 4-F; 4-Cl; 4-Br; 4-NO_2; 4-CH_3 were prepared according to the previously reported procedure. The aldehydes thus obtained, were used along with 1,3-diketones and urea derivatives as adducts for the multi-component Biginelli reaction. All the dihydropyrimidines derivatives (4a-t) were synthesized by the three-component coupling reaction involving substituted aldehydes, acetoacetanilide and urea derivatives. The yields of the products were obtained in the range of 60–74%. Designed series of molecules (Table 1) were characterized by ^{1}H NMR, IR, and Mass spectrometry techniques.

IV. CONCLUSION

In nutshell, we report herein synthesis of twenty compounds of pyrimidine bearing pyridine scaffolds in good purity. The present report explores the diversity of the Biginelli reaction and offer large range of substitution possibilities. L-proline is an efficient catalyst for Biginelli reaction and it provides a good opportunity to researchers for exploring newer dimensions associated with the Biginelli reactions. All the compounds were characterized by various spectroscopic techniques and the data were in agreement with the structures assigned. The newly synthesized compounds can be subjected to various biological activities that is future plan as far as this work is concerned.

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