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Synthesis, Characterization And Biological Screening Of novel N-(2-chloro-4-(trifluoromethyl) phenyl)-4-(substitutedphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide

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ABSTRACT

Synthesis of various (N-(2-chloro-4-(trifluoromethyl) phenyl)-4-(substitutedphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide 3(a-o) from N-(2-chloro-4-(trifluoromethyl) phenyl)-3-oxobutanamide, Substituted benzaldehydes and urea in presence of Conc.HCl. The structures of the synthesized compounds were confirmed on the basis of spectral and elemental analysis. The synthesized compounds were screened for antimicrobial activity.

Keywords: Oxopyrimidine carboxamide, beginelli reaction, multicomponant cyclocondensation.

INTRODUCTION

The tremendously growing number of publications and patents on the dihydropyrimidine is mainly due to the fact that the multifunctionalized dihydropyrimidine scaffold (DHPMs, “Biginelli compounds”) represents a heterocylic system of remarkable pharmacological efficiency. In the past decades, a broad range of biological effects, including antiviral, antitumor, antibacterial, and anti-inflammatory activities, has been ascribed to these partly reduced pyrimidine derivatives. More recently, appropriately functionalized DHPMs have emerged as, e.g., orally active antihypertensive agents [1-4] or adrenoceptor-selective antagonists [5,6]. A very recent highlight in this context has been the identification of the structurally rather simple dihydropyrimidine (DHPM) monastrol as a novel cell-permeable molecule that blocks normal bipolar spindle assembly in mammalian cells and therefore causes cell cycle arrest [7] . Monastrol specifically inhibits the mitotic kinesin motor protein and can be considered as a new lead for the development of anticancer drugs [8]. Furthermore, apart from synthetic DHPM derivatives, several marine natural products with interesting biological activities containing the dihydropyrimidine-5-carboxylate have recently been isolated [9]. Most notable among these are the batzelladine alkaloids A and B, which inhibit the binding of Human immunodeficiency virus (HIV) envelope glycoprotein (protein gp-120) to human cluster of differentiation 4 (CD^4) cells and, therefore, are potential new leads for Acquired immunodeficiency syndrome (AIDS) therapy [10]. Also its been reported pyrimidine derivatives act as anti-colorectal cancer drugs. [11]

A number of improved variants in traditional Biginelli reaction employing new reagents, catalyst, methodologies and technique have emerged. Numerous synthetic method for the preparation of these compounds have been

reported using indium (III) chloride ($InCl_3$) [12], lanthanide triflate [13], diethoxytrifluoroborane (BF_3•OEt_2) [14], polyphosphate ester (PPE) [15], KSF clay [16], lanthanum(III) chloride ($LaCl_3$) [17], sulphuric acid (H_2SO_4) [18],PTSA [19],Phenyl phosphonic acid [20].

EXPERIMENTAL SECTION

The solvents and reagents used in the synthetic work were of analytical grade obtained from Hi-media and were purified by distillation or crystallization where necessary and their boiling or melting points were compared with the available literature values. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded FTIR Unicorn Maltson 1000 spectrophotometer**.**1H-NMR spectra were recorded on Bruker Ac-80 (80 MHz) spectrometer (300MHz in DMSO-d6) using TMS as internal standard and chemical shifts are indicated in δ (ppm). The progress of the reaction was monitored on precoated silica gel 60 F 254 plates (Merck) using different solvent systems and visualizing the spots under ultraviolet light and iodine chamber. Elemental analyses for C, H and N were carried out using a Perkin -Elmer C, H, and N analyzer.

General procedure for the synthesis N-(2-chloro-4-(trifluoromethyl) phenyl)-4-(substitutedphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide.(3a-o)
A mixture of N-(2-chloro-4-(trifluoromethyl)phenyl)-3-oxobutanamide (0.01 M), Substituted benzaldehyde (0.01 M), urea derivatives (0.015 M) and catalytic amount of conc. hydrochloric acid (HCl) in ethanol (30 ml) was heated under reflux condition for 10 to 12 hrs. The reaction mixture was kept at room temperature for 24 hrs. The crystalline product obtained and recrystallized from ethanol.

(3a) N-(2-chloro-4-(trifluoromethyl) phenyl)-4-(2-methoxyphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide: Yield: 68%; mp 207ºC; Anal. Calcd. for $C_{20}H_{17}ClF_3N_3O_3$: C, 54.62; H, 3.90; Cl, 8.06; F, 12.96; N, 9.55; O, 10.91 Found: C, 54.42; H, 3.81; Cl, 8.00; F, 12.90; N, 9.55; O, 10.91%; IR (cm^{-1}): 3410 (N-H stretching of amide), 3070 (C-H stretching of aromatic ring), 1693 (C=O stretching of amide), 1600 (N-H deformation of pyrimidine ring), 1525 (C=C stretching of aromatic ring), 1344 (C-N-C stretching vibration of pyrimidine ring),1247 (C-O-C asymmetrical stretching OCH_3), 1074 (C-F stretching),; MS: m/z 440; ^{1}H NMR (DMSO-d_6) δ ppm: 2.28 (s, 3H, $-CH_3$), 3.72 (s, 3H, $-OCH_3$), 5.15 (s, 1H,-CH-), 6.84-7.31 (m,4H,Aromatic ring), 7.75-8.21 (m, 3H,Halogenated Aromatic ring), 9.62,9.95(s, 2H,Pyrimidine-NH-), 8.90 (s, 1H, -NH-C=O).

(3b) N-(2-chloro-4-(trifluoromethyl) phenyl) -4-(3-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide: Yield: 63%; mp 217ºC; Anal. Calcd. for $C_{19}H_{14}Cl_2F_3N_3O_2$: C, 51.37; H, 3.18; Cl, 15.96; F, 12.83; N, 9.46; O, 7.20; Found: C, 51.12; H, 3.02; Cl, 15.85; F, 12.49; N, 9.23; O, 7.12%; MS: m/z 445.
Similarly remaining compounds were confirmed by elemental analysis and their Mass spectra.

(3c) N-(2-chloro-4-(trifluoromethyl) phenyl) -4-(2-fluorophenyl)-1, 2, 3, 4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide: Yield: 59%; mp 202ºC; Anal. Calcd. For $C_{19}H_{14}ClF_4N_3O_2$: C, 53.35; H, 3.30; Cl, 8.29; F, 17.76; N, 9.82; O, 7.48; Found: C, 53.21; H, 3.10; Cl, 8.08; F, 17.12; N, 9.71; O, 7.40%; MS: m/z 428.

(3d) N-(2-chloro-4-(trifluoromethyl) phenyl) -4-(3, 4 dimethoxyphenyl)-1, 2, 3, 4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide: Yield: 70%; mp 212ºC; Anal. Calcd. for $C_{21}H_{19}ClF_3N_3O_4$: C, 53.68; H, 4.08; Cl, 7.55; F, 12.13; N, 8.94; O, 13.62; Found: C, 53.68; H, 4.08; Cl, 7.55; F, 12.13; N, 8.94; O, 13.62%; MS: m/z 470.

(3e) N-(2-chloro-4-(trifluoromethyl)phenyl)-4-(4-methoxyphenyl)-1,2,3,4-tetrahydro -6-methyl -2-oxopyrimidine-5-carboxamide: Yield: 75%; mp 205ºC; Anal. Calcd. for $C_{20}H_{17}ClF_3N_3O_3$: C, 54.62; H, 3.90; Cl, 8.06; F, 12.96; N, 9.55; O, 10.91; Found: C, 54.31; H, 3.81; Cl, 8.00; F, 12.24; N, 9.41; O, 10.20%; MS: m/z 440.

(3f) N-(2-chloro-4-(trifluoromethyl)phenyl)-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl -2-oxopyrimidine-5-carboxamide: Yield: 71%; mp 224ºC; Anal. Calcd. for $C_{19}H_{14}Cl_2F_3N_3O_2$: C, 51.37; H, 3.18; Cl, 15.96; F, 12.83; N, 9.46; O, 7.20; Found: C, 51.20; H, 3.03; Cl, 15.56; F, 12.66; N, 9.22; O, 7.10%; MS: m/z 445

(3g) N-(2-chloro-4-(trifluoromethyl) phenyl)-4-(4-methylphenyl)-1, 2, 3, 4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide: Yield: 69%; mp 201ºC; Anal. Calcd. for $C_{20}H_{17}ClF_3N_3O_2$: C, 56.68; H, 4.04; Cl, 8.37; F, 13.45; N, 9.91; O, 7.55; Found: C, 56.24; H, 4.00; Cl, 8.22; F, 13.24; N, 85; O, 7.35%; MS: m/z 424.

(3h) N-(2-chloro-4-(trifluoromethyl) phenyl)-4-(4-fluorophenyl)-1, 2, 3, 4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide: Yield: 55%; mp 195ºC; Anal. Calcd. for $C_{19}H_{14}ClF_4N_3O_2$: C, 53.35; H, 3.30; Cl, 8.29; F, 17.76; N, 9.82; O, 7.48; Found: C, 53.09; H, 3.12; Cl, 8.11; F, 17.23; N, 9.45; O, 7.24%; MS: m/z 428.

(3i) N-(2-chloro-4-(trifluoromethyl)phenyl)-4-(2-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl -2-oxopyrimidine-5-carboxamide: Yield: 74%; mp 187ºC; Anal. Calcd. for $C_{19}H_{14}Cl_2F_3N_3O_2$: C, 51.37; H, 3.18; Cl, 15.96; F, 12.83; N, 9.46; O, 7.20; Found: C, 51.20; H, 3.03; Cl, 15.56; F, 12.66; N, 9.22; O, 7.10%; MS: m/z 445;

(3j) N-(2-chloro-4-(trifluoromethyl) phenyl)-4-(3, 4-dichlorophenyl)-1, 2, 3, 4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide: Yield: 75%; mp 235ºC; Anal. Calcd. for $C_{19}H_{13}Cl_3F_3N_3O_2$: C, 47.67; H, 2.74; Cl, 22.22; F, 11.91; N, 8.78; O, 6.68; Found: C, 47.43; H, 2.34; Cl, 22.01; F, 11.23; N, 8.42; O, 6.12%; MS: m/z 479.

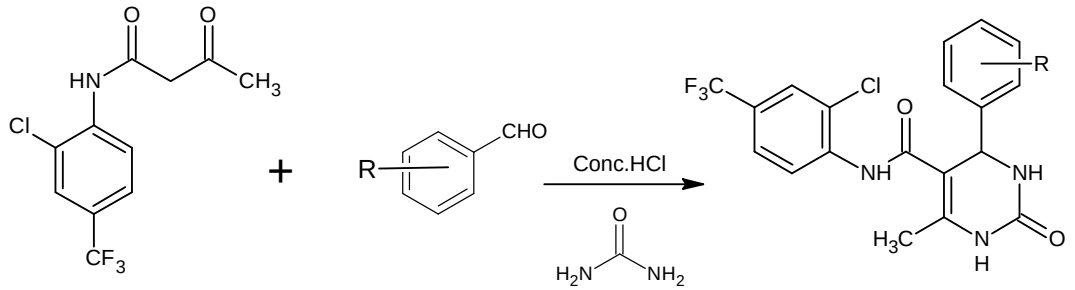
(3k) N-(2-chloro-4-(trifluoromethyl) phenyl) -4-(3-methoxyphenyl)-1, 2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide: Yield: 68%; mp 207ºC; Anal. Calcd. for $C_{20}H_{17}ClF_3N_3O_3$: C, 54.62; H, 3.90; Cl, 8.06; F, 12.96; N, 9.55; O, 10.91 Found: C, 54.42; H, 3.81; Cl, 8.00; F, 12.90; N, 9.55; O, 10.91%; MS: m/z 440.

(3l) N - (2-chloro-4-(trifluoromethyl) phenyl) -4-(2,4 -dimethylphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide: Yield: 58%; mp 233ºC; Anal. Calcd. for $C_{21}H_{19}ClF_3N_3O_2$: C, 57.61; H, 4.37; Cl, 8.10; F, 13.02; N, 9.60; O, 7.31; Found: C, 57.33; H, 4.22; Cl, 8.01; F, 12.56; N, 9.13; O, 7.21%; MS: m/z 438.

(3m) N-(2-chloro-4-(trifluoromethyl) phenyl) -4-(4-bromophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide: Yield: 68%; mp 211ºC; Anal. Calcd. for $C_{19}H_{14}BrClF_3N_3O_2$: C, 46.70; H, 2.89; Br, 16.35; Cl, 7.25; F, 11.66; N, 8.60; O, 6.55; Found: C, 46.61; H, 2.75; Br, 16.13; Cl, 7.11; F, 11.22; N, 8.21; O, 6.12%; MS: m/z 489.

(3n) N-(2-chloro-4-(trifluoromethyl) phenyl) -4-(3-bromophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide: Yield: 70%; mp 200ºC; Anal. Calcd. for $C_{19}H_{14}BrClF_3N_3O_2$: C, 46.70; H, 2.89; Br, 16.35; Cl, 7.25; F, 11.66; N, 8.60; O, 6.55; Found: C, 46.61; H, 2.75; Br, 16.13; Cl, 7.11; F, 11.22; N, 8.21; O, 6.12%; MS: m/z 489.

(3o) N-(2-chloro-4-(trifluoromethyl) phenyl)-4-phenyl-1, 2, 3, 4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide: Yield: 67%; mp 213ºC; Anal. Calcd. for $C_{19}H_{15}ClF_3N_3O_2$: C, 55.69; H, 3.69; Cl, 8.65; F, 13.91; N, 10.25; O, 7.81; Found: C, 55.46; H, 3.41; Cl, 8.60; F, 13.81; N, 10.10; O, 7.58%; MS: m/z 410.



1 **2** **3(a-o)**

Antimicrobial activity

The in vitro antibacterial activity was performed against Gram-positive bacteria including *Staphylococcus aureus* (**MTCC 96**), *Streptococcus pyogenes* (**MTCC 442**) and Gram negative bacteria including *Escherichia coli* (**MTCC 443**), *Pseudomonas aeruginosa* (**MTCC 424**). Yeast including *Candida albicans* (**MTCC 227**) and fungi *Aspergillus clavatus* (**MTCC 1323**) were used to test antifungal activity. Known antibiotics like **Amplicilline** and **Chloramphenicol** (the reference anti bacterial drugs) and **Fluconazole** (the reference antifungal drug) were used for comparison. The anmicrobial activities are summarized in Table 1.

From the result of antifungal data, compounds **3e, 3f** were active against C.albicans. while compounds **3c, 3h, 3f, 3n** were active against A.clavatus. Further in Antibacterial study shows compounds **3f, 3g, 3o** were active against S.aures and compounds **3a, 3c, 3i, 3j** shows activity against S.pyrogenes. In case of E.coli compounds **3h, 3i, 3m, 3n, 3o** shows good activity while in case of P.aeruginosa compounds **3a, 3e, 3l, 3o** shows good activity. Remaining compounds did not show any promising activity against tested bacteria and fungi.

RESULTS AND DISCUSSION

The different N-(2-chloro-4-(trifluoromethyl) phenyl)-4-(substitutedphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide were synthesised by the cyclocondensation of N-(2-chloro-4-(trifluoromethyl)phenyl)-3-oxobutanamide,Urea and various substituted benzaldehydes in presence of HCl .The M.P. of the synthesised compounds was checked by the given literatures . The purity of compounds was analyzed by TLC. The structures of the synthesized compounds 1a-j were confirmed on the basis of spectral and elemental analysis. The IR spectrum of these compounds exhibited bands due to 3410 (N-H stretching of amide), 3070 (C-H stretching of aromatic ring), 1693 (C=O stretching of amide), 1600 (N-H deformation of pyrimidine ring), 1525 (C=C stretching of aromatic ring), 1344 (C-N-C stretching vibration of pyrimidine ring),1247 (C-O-C asymmetrical stretching OCH_3), 1074 (C-F stretching).Further in their ^1H NMR spectrum (DMSO-d_6) δ ppm: 2.28 (s, 3H, -CH_3), 3.72 (s, 3H, -OCH_3), 5.15 (s, 1H,-CH-), 6.84-7.31 (m,4H,Aromatic ring), 7.75-8.21 (m, 3H,Halogenated Aromatic ring), 9.62,9.95(s, 2H,Pyrimidine-NH-), 8.90 (s, 1H, -NH-C=O) peaks confirms the formation of title compounds.

Table-.1: Antimicrobial activity of compounds 3a-o.

Compound No.	Zone of inhibition (in mm)					
	Antibacterial activity				Antifungal activity	
	Gram +ve		Gram -ve			
	S. aureus	*S. pyrogenes*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A.clavatus*
3a	16	**18**	17	**19**	19	22
3b	17	17	17	18	21	22
3c	16	**19**	16	17	21	**24**
3d	16	16	14	15	21	17
3e	16	17	16	**21**	**23**	17
3f	**18**	17	16	18	**23**	**23**
3g	**18**	17	18	16	21	20
3h	17	15	**21**	15	17	**23**
3i	15	**19**	**19**	17	15	20
3j	16	**18**	12	17	12	19
3k	13	14	15	16	21	18
3l	14	13	17	**19**	19	20
3m	17	18	**19**	13	18	20
3n	15	17	**20**	16	21	**23**
3o	**18**	13	**19**	**19**	13	19
Amplicilline	**18**	**19**	**20**	**20**	-	-
Chloramphenicol	**21**	**20**	**23**	**21**	-	-
Fluconazole	-	-	-	-	**24**	**24**

CONCLUSION

The newly synthesized compounds N-(2-chloro-4-(trifluoromethyl) phenyl)-4-(substitutedphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide, compound 3e, 3n were found to be active. In the study of antifungal activity compounds 3c, 3e, 3h, 3f, 3n were active . It can be concluded that this class of compounds certainly holds great promise towards the pursuit to discover novel classes of antimicrobial agents.

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