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Synthesis, Characterization and Biological Screening of novel N-[2-chloro-4-(trifluromethyl) phenyl]-4-(substituted phenyl)-3, 6-Dimethyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide

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ABSTRACT

N-[2-chloro-4-(trifluromethyl)phenyl]-4-(substitutedphenyl)-3,6-Dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4a-o) are synthesized. The synthesis of (4a-o) was achieved by acid catalysed cyclocondensation of N-(2-chloro-4-(trifluromethyl) phenyl)-3-oxobutanamide, N-methyl urea and benzaldehydes. The products were characterized by FT-IR, mass spectra, ^{1}H NMR and elemental analyses. The newly synthesized compounds were subjected to various biological activities *viz*., antimicrobial.

KEYWORDS

Pyrimidine, N-(2-chloro-4-(trifluromethyl) phenyl)-3-oxobutanamide, N-methyl urea, Multi component cyclocondensation.

INTRODUCTION

The importance of substituted pyrimidines, common source for the development of new potential therapeutic agents, [1] is well known. Among them, the pyrimido[4,5-d]pyrimidines and pyrimido[2,3-d]pyrimidines are an important class of annelated uracils with biological significance because of their connection with purine pteridine system.[2] Numerous reports delineate the antitumor,[3] antiviral,[4] antioxidant,[5] antifungal,[6] and hepatoprotective[7] activity of these compounds. Therefore, for the preparation of these complex molecules large efforts have been directed towards the synthetic manipulation of uracils. As result, a number of reports have appeared in literature, which usually requires forcing conditions, long reaction times, and complex synthetic pathway.[8-13]

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With the emphasis on the search for atom-efficient transformations of easily available starting materials into complex organic molecules, reactions that provide maximum diversity are especially desirable. Here, multicomponent reactions[14] (MCRs) have emerged as powerful strategy. MCRs are economically and environmentally very advantageous because multi-step syntheses produce considerable amounts of waste mainly due to complex isolation procedures often involving expensive, toxic and hazardous solvents after each step. The versatile biological properties of pyrimidine derivatives prompted us to take up this project to synthesize some novel derivatives using a cyclocondensation reaction of a 1, 3-diketone, an aldehyde, and N-methyl urea. So here in continuation to our earlier work[15] with keeping in mind various biomedical applications and with a view to further assess the pharmacological profile of these class of compounds, the novel series of N-

(2-chloro-4-(trifluoromethyl)phenyl)-4-(substitutedphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (4a-o) are synthesized. The synthesis of (4a-o) was achieved by acid catalysed cyclocondensation of N-(2-chloro-4-(trifluromethyl) phenyl)-3-oxobutanamide (1), N-methyl urea (2) and Benzaldehydes (3). The products were characterized by FT-IR, mass spectra, ^{1}H NMR and elemental analyses.

MATERIALS AND METHODS

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 method for the preparation of N-[2-chloro-4-(trifluromethyl) phenyl]-4-(substituted phenyl)-3,6-Dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide:

A mixture of N-(2-chloro-4-(trifluoromethyl)phenyl)-3-oxobutanamide (0.01 M), benzaldehydes (0.01 M), N-methyl urea (0.015 M) and catalytic amount of conc. hydrochloric acid (HCl) in ethanol (30 ml) was heated under reflux condition for 12 to 16 hrs. The reaction mixture was kept at room temperature for 24 hrs. The crystalline product obtained and recrystallized from ethanol.

(4a).*N*-[2-chloro-4-(trifluoromethyl)phenyl]-4-(2-methoxyphenyl)-3,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide: Yield: 68%; mp 204ºC; Anal. Calcd. for $C_{21}H_{19}ClF_3N_3O_3$

C, (55.58%) H (4.22%) N (9.26%) Found: C, 55.50; H, 4.20; N, 9.18 IR (KBr cm^{-1}): 3240, 3140 (N-H stretching of amide), 2970 (C-H stretching of aromatic ring), 1720 (C=O stretching of amide), 1074 (C-F stretching). ^{1}H NMR (DMSO-d_6) δ ppm: 2.38 (s, 3H, -CH_3), 3.02(s, 3H, –NCH_3), 3.81 (s, 3H, -OCH_3), 5.30 (s, 1H,-CH-), 7.05-7.19 (m,4H, Aromatic ring), 7.74-8.21 (m, 3H,Halogenated Aromatic ring), 9.98 (s, 1H,Pyrimidine-NH-), 9.50 (s, 1H, -NH-C=O).

(4b).4-(3-chlorophenyl)-*N*-[2-chloro-4-(trifluoromethyl)phenyl]-3,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. Yield: 63%; mp 222ºC; Anal. Calcd. for $C_{20}H_{16}Cl_2F_3N_3O_2$

C, 52.42; H, 3.52; N, 9.17 Found: C, 52.02; H, 3.46; N, 9.08. IR (KBr cm^{-1}): 3260,3130 (N-H stretching of amide), 2960 (C-H stretching of aromatic ring), 1715 (C=O stretching of amide), 1078 (C-F stretching), ^{1}H NMR (DMSO-d_6) δ ppm: 2.35 (s, 3H, -CH_3), 3.15 (s, 3H, –NCH_3), 5.10 (s, 1H,-CH-), 7.10-7.70 (m,4H, Aromatic ring), 7.70-8.24 (m, 3H,Halogenated Aromatic ring), 9.90 (s, 1H,Pyrimidine-NH-), 9.49 (s, 1H, -NH-C=O).

(4c).*N*-[2-chloro-4-(trifluoromethyl)phenyl]-4-(2-fluorophenyl)-3,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. Yield: 59%; mp 215ºC; Anal. Calcd. for $C_{20}H_{16}ClF_4N_3O_2$

C, 54.37; H, 3.65; N, 9.51 Found: C, 54.30; H, 3.52; N, 9.42. IR (KBr cm^{-1}): 3255,3120 (N-H stretching of amide), 2958 (C-H stretching of aromatic ring), 1718 (C=O stretching of amide), 1078 (C-F stretching), ^{1}H NMR (DMSO-d_6) δ ppm: 2.33 (s, 3H, -CH_3), 3.10 (s, 3H, –NCH_3), 5.30 (s, 1H,-CH-), 7.14-7.75 (m,4H, Aromatic ring), 7.65-8.20 (m, 3H,Halogenated Aromatic ring), 9.85 (s, 1H,Pyrimidine-NH-), 9.50 (s, 1H, -NH-C=O).

(4d).*N*-[2-chloro-4-(trifluoromethyl)phenyl]-4-(3,5-dimethoxyphenyl)-3,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. Yield: 64%; mp 216ºC; Anal. Calcd. For $C_{22}H_{21}ClF_3N_3O_4$

C, 54.61; H, 4.37; N, 8.68 Found: C, 54.40; H, 4.42; N, 8.52. IR (KBr cm^{-1}): 3253, 3122 (N-H stretching of amide), 2952 (C-H stretching of aromatic ring), 1710 (C=O stretching of amide), 1078 (C-F stretching).

(4e).N-[2-chloro-4-(trifluoromethyl)phenyl]-4-(4-methoxyphenyl)-3,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. Yield: 75%; mp 228ºC; Anal. Calcd. for $C_{21}H_{19}ClF_3N_3O_3$

C, 55.58; H, 4.22; N, 9.26 Found: C, 55.40; H, 4.32; N, 9.32. IR (KBr cm^{-1}): 3263, 3132 (N-H stretching of amide), 2962 (C-H stretching of aromatic ring), 1712 (C=O stretching of amide), 1078 (C-F stretching).

(4f).4-(4-chlorophenyl)-*N*-[2-chloro-4-(trifluoromethyl)phenyl]-3,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. Yield: 71%; mp 197ºC; Anal. Calcd. for $C_{20}H_{16}Cl_2F_3N_3O_2$

C, 52.42; H, 3.52; N, 9.17 Found: C, 52.40; H, 3.42; N, 9.12. IR (KBr cm^{-1}): 3267, 3135 (N-H stretching of amide), 2965 (C-H stretching of aromatic ring), 1715 (C=O stretching of amide), 1074 (C-F stretching).

(4g).*N*-[2-chloro-4-(trifluoromethyl)phenyl]-3,6-dimethyl-4-(4-methylphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. Yield: 69%; mp 201ºC; Anal. Calcd. for $C_{21}H_{19}ClF_3N_3O_2$

C, 57.61; H, 4.37; N, 9.60 Found: C, 57.50; H, 4.42; N, 9.52. IR (KBr cm^{-1}): 3257, 3125 (N-H stretching of amide), 2955 (C-H stretching of aromatic ring), 1709 (C=O stretching of amide), 1069 (C-F stretching).

(4h).N-[2-chloro-4-(trifluoromethyl)phenyl]-4-(4-fluorophenyl)-3,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. Yield: 55%; mp 205ºC; Anal. Calcd. for $C_{20}H_{16}ClF_4N_3O_2$

C, 54.37; H, 3.65; N, 9.51 Found: C, 54.50; H, 3.55; N, 9.52. IR (KBr cm^{-1}): 3252, 3129 (N-H stretching of amide), 2956 (C-H stretching of aromatic ring), 1711 (C=O stretching of amide), 1071 (C-F stretching).

(4i).4-(2-chlorophenyl)-*N*-[2-chloro-4-(trifluoromethyl)phenyl]-3,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. Yield: 70%; mp 189ºC; Anal. Calcd. for $C_{20}H_{16}Cl_2F_3N_3O_2$

C, 52.42; H, 3.52; N, 9.17 Found: C, 52.40; H, 3.55; N, 9.12. IR (KBr cm^{-1}): 3250, 3130 (N-H stretching of amide), 2951 (C-H stretching of aromatic ring), 1713 (C=O stretching of amide), 1073 (C-F stretching).

(4j).N-[2-chloro-4-(trifluoromethyl)phenyl]-4-(3,4-dichlorophenyl)-3,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. Yield: 71%; mp 232ºC; Anal. Calcd. for $C_{20}H_{15}Cl_3F_3N_3O_2$

C, 48.75; H, 3.07; N, 8.53 Found: C, 48.70; H, 3.10; N, 8.52. IR (KBr cm^{-1}): 3254, 3134 (N-H stretching of amide), 2954 (C-H stretching of aromatic ring), 1714 (C=O stretching of amide), 1074 (C-F stretching).

(4k).*N*-[2-chloro-4-(trifluoromethyl)phenyl]-4-(3-methoxyphenyl)-3,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. Yield: 59%; mp 222ºC; Anal. Calcd. for $C_{21}H_{19}ClF_3N_3O_3$

C, 55.58; H, 4.22; N, 9.26 Found: C, 55.52; H, 4.15; N, 9.22. IR (KBr cm^{-1}): 3244, 3124 (N-H stretching of amide), 2944 (C-H stretching of aromatic ring), 1704 (C=O stretching of amide), 1064 (C-F stretching).

(4l).*N*-[2-chloro-4-(trifluoromethyl)phenyl]-4-(2,4-dimethylphenyl)-3,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. Yield: 70%; mp 213ºC; Anal. Calcd. for $C_{22}H_{21}ClF_3N_3O_2$

C, 58.48; H, 4.68; N, 9.30 Found: C, 58.52; H, 4.65; N, 9.23. IR (KBr cm^{-1}): 3248, 3131 (N-H stretching of amide), 2955 (C-H stretching of aromatic ring), 1707 (C=O stretching of amide), 1069(C-F stretching).

(4m).4-(4-bromophenyl)-N-[2-chloro-4-(trifluoromethyl)phenyl]-3,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. Yield: 67%; mp 195ºC; Anal. Calcd. for $C_{20}H_{16}BrClF_3N_3O_2$

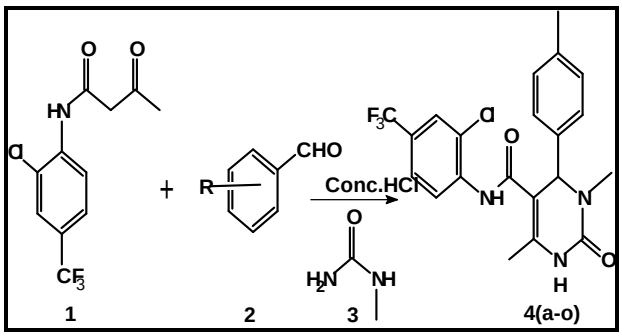
C, 47.78; H, 3.21; N, 8.36 Found: C, 47.60; H, 3.22; N, 8.33. IR (KBr cm^{-1}): 3247, 3135 (N-H stretching of amide), 2957 (C-H stretching of aromatic ring), 1712 (C=O stretching of amide), 1070(C-F stretching).

(4n).4-(3-bromophenyl)-*N*-[2-chloro-4-(trifluoromethyl)phenyl]-3,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. Yield: 70%; mp 216ºC; Anal. Calcd. for $C_{20}H_{16}BrClF_3N_3O$

C, 47.78; H, 3.21; N, 8.36 Found: C, 47.70; H, 3.15; N, 8.30. IR (KBr cm^{-1}): 3246, 3134 (N-H stretching of amide), 2956 (C-H stretching of aromatic ring), 1713 (C=O stretching of amide), 1071(C-F stretching).

(4o).*N*-[2-chloro-4-(trifluoromethyl)phenyl]-3,6-dimethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide. Yield: 72%; mp 232ºC; Anal. Calcd. for $C_{20}H_{17}ClF_3N_3O_2$

C, 56.68; H, 4.04; N, 9.91 Found: C, 56.56; H, 4.00; N, 9.90. IR (KBr cm^{-1}): 3245, 3131 (N-H stretching of amide), 2951 (C-H stretching of aromatic ring), 1718 (C=O stretching of amide), 1075(C-F stretching).



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 **4e, 4f, 4l, 4m** were active against C.albicans. while compounds **4b, 4c, 4h, 4j** were active against A.clavatus. Further in Antibacterial study shows compounds **4g, 4n** were moderately active against S.aures and compounds 4**j** shows moderate activity against S.pyrogenes. In case of E.coli compounds **4b, 4g, 4h, 4i, 4j, 4l** shows moderate activity while in case of P.aeruginosa compounds **4n** shows moderate activity. Remaining compounds did not show any promising activity against tested bacteria and fungi.

RESULTS AND DISCUSSION

The different *N*-[2-chloro-4-(trifluromethyl)phenyl]-4-(substituted phenyl)-3,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide were synthesised by the cyclocondensation of N-(2-chloro-4-(trifluromethyl)phenyl)-3-oxobutanamide,N-methyl urea, and various substituted benzaldehydes in presence of HCl. The M.P. of the synthesized compounds was checked by the given literatures. The purity of compounds was analyzed by TLC. The structures of all compounds were confirmed by IR, ^1H –NMR and Elemental analyses. The IR Spectrum of compounds showed band at 3240,3120 cm^{-1} (N-H stretching of amide), 2975 cm^{-1} (C-H stretching of aromatic ring),

1725 cm^{-1} (C=O stretching of amide), 1075 cm^{-1} (C-F stretching) which corresponds to Pyrimidine ring and carboxamide along with halogen substitution. The ^{1}H NMR spectrum of compounds shows two peaks at 5-5.5 ppms which were assigned as –CH- groups of pyrimidine ring. A peak in aromatic region at 7.1-8.5ppm confirms the presence of two substituted aromatic rings. The characteristic peaks of Pyrimidine –NH- between 8.5-10 ppm confirms the presence of Pyrimidine ring system. The other alkyl protons gave their characteristic peaks in the range of 2-3.5 ppm with proper multiplicity.

CONCLUSION

The newly synthesized compounds *N*-[2-chloro-4-(trifluromethyl)phenyl]-4-(substituted phenyl)-3,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide compound **4e, 4f, 4l, 4m ,4b, 4c, 4h, 4j** were found to be active in the study of antifungal activity . It can be concluded that this class of compounds certainly holds great promise towards the pursuit to discover novel classes of antimicrobial agents.

Table 1: Antibacterial and Antifungal activity of *N*-[2-chloro-4-(trifluromethyl)phenyl]-4-(substituted phenyl)-3,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (4a-o)

Compound No.	Zone diameter of growth inhibition in mm					
	Antibacterial Activity				Antifungal Activity	
	Gram +ve		Gram -ve			
	S. aureus	S. pyrogenes	E. coli	P. aeruginosa	C. albicans	A. clavatus
4a	11	14	12	11	18	16
4b	10	17	19	13	19	**23**
4c	21	09	16	08	17	**24**
4d	16	14	14	05	17	18
4e	19	15	10	06	**25**	19
4f	20	17	16	12	**22**	16
4g	22	10	19	09	15	16
4h	13	11	20	10	19	**23**
4i	12	19	23	08	17	18
4j	11	22	24	09	16	**24**
4k	16	13	11	13	15	17
4l	15	NA	17	12	**21**	09
4m	19	04	12	10	**20**	13
4n	23	05	09	16	16	11
4o	18	06	08	11	16	07
Amplicilline	**18**	**19**	**20**	**20**	-	-
Chloramphenicol	**21**	**20**	**23**	**21**	-	-
Fluconazole	-	-	-	-	**24**	**24**

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