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SYNTHESIS, CHARACTERIZATION AND OF NOVEL *N*-[2-CHLORO-4-(TRIFLUOROMETHYL) PHENYL]-2-OXO-4-(SUBSTITUTED PHENYL)-6-(PROPAN-2-YL)-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXAMIDE

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Abstract:

N-[2-chloro-4-(trifluoromethyl)phenyl]-2-oxo-4-(substitutedphenyl)-6-(propan-2-yl)-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-(trifluoromethyl)phenyl]-4-methyl-3-oxopentanamide, 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.

Key Words: Pyrimidine, *N*-[2-chloro-4-(trifluoromethyl) phenyl]-4-methyl-3-oxopentanamide, urea, Multi component cyclocondensation.

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Introduction:

In the family of heterocyclic compounds, nitrogen-containing Heterocycles are an important class of compounds in medicinal chemistry. There has been considerable interest in the development of preparative methods for the production of Pyrimidine. This seems to be because Pyrimidine represent one of the most active classes of compounds, possessing a wide Spectrum of biological activity[1-3]. Pyrimidines and their ring-fused derivatives have a broad Spectrum

of biological activity; best known as the heterocyclic core of the nucleic acid bases. These ring systems are often incorporated into drugs designed for anticancer[4, 5], antiviral[6], antihypertensive[7], analgesic[8], antipyretic[9], antiinflammetry[10], antipsoriasis[11] agents. Some of them are active on the blood circulatory system[12] and can stimulate the skin preparative regeneration and increase the efficacy of antibiotic therapy of *Staphylococcus* and *Proteu s*infected wounds[13]. Similarly, derivatives of naphthofurans have attracted the attention of manyorganic chemists owing to their well pronounced activities such as anticancer[14], antifungal andcytotoxic[15] and in the treatment of metabolic disorders[16] 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 urea. So here in continuation to our earlier work[17,18,19]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]-2-oxo-4-(substitutedphenyl)-6-(propan-2-yl)-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-(trifluoromethyl) phenyl]-4-methyl-3-oxopentanamide, urea and Benzaldehydes. 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-(trifluoromethyl) phenyl]-2-oxo-4-(substituted phenyl)-6-(propan-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide:

A mixture of *N*-[2-chloro-4-(trifluoromethyl) phenyl]-4-methyl-3-oxopentanamide (0.01 M), benzaldehydes (0.01 M), 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]-2-oxo-4-(2-methoxy)phenyl-6-(propan-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide: Yield: 62%; mp 217ºC; Anal. Calcd. for $C_{22}H_{21}ClF_3N_3O_3$: C, 56.48; H, 4.52; Cl, 7.58; F, 12.18; N, 8.98; O, 10.26. Found: C, 56.38; H, 4.42; Cl, 7.48; F, 12.08; N, 8.88; O, 10.16%; IR (cm^{-1}): 3439 (N-H stretching of amide), 3013 (C-H stretching of aromatic ring), 2985 (C-H asymmetrical stretching of CH_3 group), 2855 (C-H symmetrical stretching of CH_3 group), 1651 (C=O stretching of amide), 1597 (C=O stretching of cyclic) 1597 (N-H deformation of pyrimidine ring), 1529 (C=C stretching of aromatic ring), 1475 (C-H asymmetrical deformation of CH_3 group), 1402 (C-H symmetrical deformation of CH_3 group), 1346 (C-N-C stretching vibration of pyrimidine ring), 1274 (C-N stretching), 1194 (C-O-C asymmetrical stretching OCH_3), 1064 (C-F stretching), 1038 (C-O-C symmetrical stretching OCH_3) 835 (para-substituted), 682 (C-Cl streching); MS: *m/z* 468; ^{1}H NMR (DMSO-d_6) δ ppm: 1.47 (s, 3H, H_a), 1.58 (s, 3H, H_b), 3.32 (s, 3H, H_c), 3.85 (s, 1H, H_d), 4.83 (s, 1H, H_e), 7.09-7.11 (d, 1H, H_f,), 7.27-7.29 (d, 1H, H_g), 7.38-7.40 (d, 1H, H_h,), 7.43-7.46 (m, 1H, H_i), 7.50-7.54 (m, 1H, H_j), 7.90 (s, 1H, H_k), 7.93-7.95 (m, 1H, H_l), 8.47-8.50 (m, 1H, H_m), 8.90 (s, 1H, H_n), 10.09 (s, 1H, H_o).

(4b).4-(3-chlorophenyl)-*N*-[2-chloro-4-(trifluoromethyl)phenyl]-2-oxo-6-(propan-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide: Yield: 68%; mp 207ºC; Anal. Calcd. for $C_{21}H_{18}Cl_2F_3N_3O_2$: C, (53.40%) H (3.84%) N (8.90%) Found: C, 53.50; H, 3.74; N, 8.88 (C-H stretching of aromatic ring), 2980 (C-H asymmetrical stretching of CH_3 group), 2850 (C-H symmetrical stretching of CH_3 group), 1653 (C=O stretching of amide), 1599 (C=O stretching of cyclic) 1593 (N-H deformation of pyrimidine ring), 1523 (C=C stretching of aromatic ring), 1475 (C-H asymmetrical deformation of CH_3 group), 1401 (C-H symmetrical deformation of CH_3 group), 1345 (C-N-C stretching vibration of pyrimidine ring), 1275 (C-N stretching), 1067 (C-F stretching), 837 (para-substituted), 685 (C-Cl stretching. MS: *m/z* 472. ^{1}H NMR (DMSO-d_6) δ ppm: 1.47 (s, 3H, H_a), 1.58 (s, 3H, H_b), 3.85 (s, 1H, Hc), 4.83 (s, 1H, H_d), 7.09-7.11 (d, 1H, H_e), 7.27-7.29 (d, 1H, H_f), 7.38-7.40 (d, 1H, H_g,), 7.43-7.46 (m, 1H, H_h), 7.50-7.54 (m, 1H, H_i), 7.90 (s, 1H, H_j), 7.93-7.95 (m, 1H, H_k), 8.47-8.50 (m, 1H, H_l), 8.90 (s, 1H, H_m), 10.09 (s, 1H, H_n).

(4c).*N*-[2-chloro-4-(trifluoromethyl)phenyl]-4-(2-fluorophenyl)-2-oxo-6-(propan-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide: Yield: 59%; mp 203ºC; Anal. Calcd. for $C_{21}H_{18}ClF_4N_3O_2$: C, (55.33%) H (3.98%) N (9.22%) Found: C, 55.35; H, 3.94; N, 9.21 IR (KBr cm^{-1}): 3245, 3140 (N-H stretching of amide), 2970 (C-H stretching of aromatic ring), 1710 (C=O stretching of amide), 1070 (C-F stretching). MS: *m/z* 456.

(4d).N-[2-chloro-4-(trifluoromethyl)phenyl]-2-oxo-4-(3,4-dimethoxy)phenyl-6-(propan-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide: Yield: 60%; mp 202ºC; Anal. Calcd. for $C_{23}H_{23}ClF_3N_3O_4$: C, 55.48; H, 4.66; N, 8.44; O, 12.85; Found: C, 55.28; H, 4.36; N, 8.14; O, 12.45; IR (KBr cm^{-1}): 3240, 3135 (N-H stretching of amide), 2972 (C-H stretching of aromatic ring), 1712 (C=O stretching of amide), 1072 (C-F stretching). MS: *m/z* 498.

(4e).*N*-[2-chloro-4-(trifluoromethyl)phenyl]-2-oxo-4-(4-methoxy)phenyl-6-(propan-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide: Yield: 65%; mp 205ºC; Anal. Calcd. for $C_{22}H_{21}ClF_3N_3O_3$: C, 56.48; H, 4.52; N, 8.98; O, 10.26; Found: C, 56.18; H, 4.22; N, 8.58; O, 10.06; IR (KBr cm^{-1}): 3242, 3137 (N-H stretching of amide), 2971 (C-H stretching of aromatic ring), 1715 (C=O stretching of amide), 1070 (C-F stretching) MS: *m/z* 468.

(4f).4-(4-chlorophenyl)-N-[2-chloro-4-(trifluoromethyl)phenyl]-2-oxo-6-(propan-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide: Yield: 67%; mp 204ºC; Anal. Calcd. for $C_{21}H_{18}Cl_2F_3N_3O_2$: C, 53.40; H, 3.84; N, 8.90; O, 6.78; Found: C, 53.60; H, 3.54; N, 8.40; O, 6.48%; IR (KBr cm^{-1}): 3240, 3133 (N-H stretching of amide), 2975 (C-H stretching of aromatic ring), 1712 (C=O stretching of amide), 1076 (C-F stretching) MS: *m/z* 472;

(4g).*N*-[2-chloro-4-(trifluoromethyl)phenyl]-2-oxo-4-(4-methyl)phenyl-6-(propan-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide: Yield: 60%; mp 211ºC; Anal. Calcd. for $C_{22}H_{21}ClF_3N_3O_2$: C, 58.48; H, 4.68; N, 9.30; O, 7.08; Found: C, 58.28; H, 4.68; N, 9.10; O, 7.04%; IR (KBr cm^{-1}): 3238, 3135 (N-H stretching of amide), 2972 (C-H stretching of aromatic ring), 1710 (C=O stretching of amide), 1075 (C-F stretching) MS: *m/z* 452.

(4h).N-[2-chloro-4-(trifluoromethyl)phenyl]-4-(4-fluorophenyl)-2-oxo-6-(propan-2-yl)-1,2,3,4 tetrahydropyrimidine-5-carboxamide: Yield: 59%; mp 195ºC; Anal. Calcd. for $C_{21}H_{18}ClF_4N_3O_2$: C, 55.33; H, 3.98; N, 9.22; O, 7.02; Found: C, 55.13; H, 3.74; N, 9.02; O, 7.12%; IR (KBr cm^{-1}): 3239, 3134 (N-H stretching of amide), 2976 (C-H stretching of aromatic ring), 1709 (C=O stretching of amide), 1073 (C-F stretching) MS: *m/z* 456.

(4i).4-(2-chlorophenyl)-*N*-[2-chloro-4-(trifluoromethyl)phenyl]-2-oxo-6-(propan-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide: Yield: 74%; mp 187ºC; Anal. Calcd. for $C_{21}H_{18}Cl_2F_3N_3O_2$: C, 53.40; H, 3.84; N, 8.90; O, 6.78; Found: C, 53.12; H, 3.86; N, 8.80; O, 6.72%; IR (KBr cm^{-1}): 3239, 3134 (N-H stretching of amide), 2976 (C-H stretching of aromatic ring), 1709 (C=O stretching of amide), 1073 (C-F stretching) MS: *m/z* 472

(4j).*N*-[2-chloro-4-(trifluoromethyl)phenyl]-4-(3,4-dichlorophenyl)-2-oxo-6-(propan-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide: Yield: 70%; mp 215ºC; Anal. Calcd. for $C_{21}H_{17}Cl_3F_3N_3O_2$: C, 49.77; H, 3.38; N, 8.29; O, 6.31; Found: C, 49.71; H, 3.30; N, 8.20; O, 6.26%; IR (KBr cm^{-1}): 3235, 3130 (N-H stretching of amide), 2970 (C-H stretching of aromatic ring), 1708 (C=O stretching of amide), 1072 (C-F stretching) MS: *m/z* 506.

(4k).N-[2-chloro-4-(trifluoromethyl)phenyl]-2-oxo-4-(3-methoxy)phenyl-6-(propan-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide: Yield: 63%; mp 217ºC; Anal. Calcd. for $C_{22}H_{21}ClF_3N_3O_3$: C, 56.48; H, 4.52; N, 8.98; O, 10.26. Found: C, 56.20; H, 4.34; N, 8.90; O, 10.12%; IR (KBr cm^{-1}): 3236, 3131 (N-H stretching of amide), 2976 (C-H stretching of aromatic ring), 1710 (C=O stretching of amide), 1073 (C-F stretching) MS: *m/z* 468.

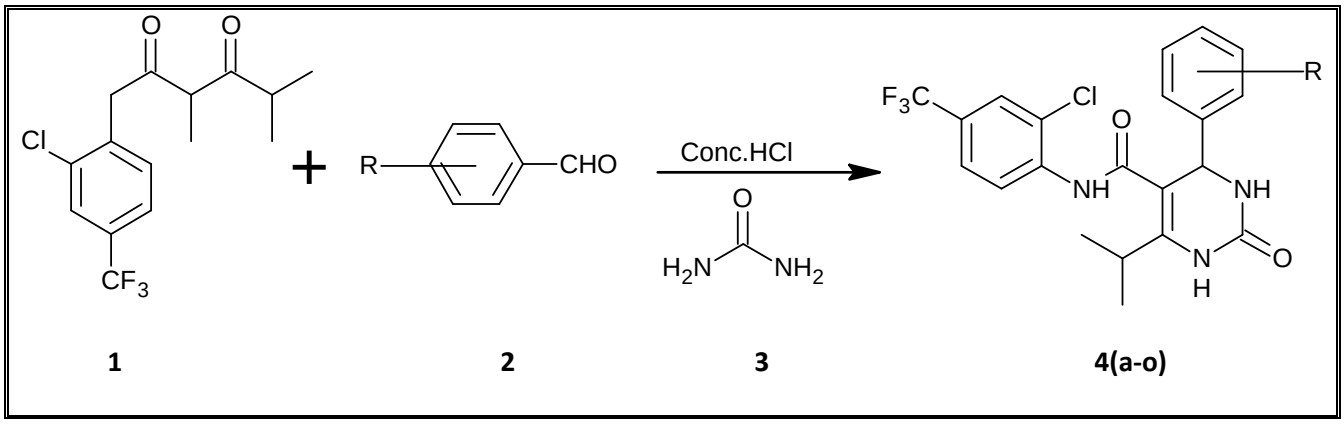
(4l).*N*-[2-chloro-4-(trifluoromethyl)phenyl]-2-oxo-4-(2,4-dimethyl)phenyl-6-(propan-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide: Yield: 57%; mp 213ºC; Anal. Calcd. for $C_{23}H_{23}ClF_3N_3O_2$: C, 59.29; H, 4.98; N, 9.02; O, 6.87; Found: C, 59.21; H, 4.81; N, 9.02; O, 6.87; IR (KBr cm^{-1}): 3233, 3130 (N-H stretching of amide), 2973 (C-H stretching of aromatic ring), 1712 (C=O stretching of amide), 1074 (C-F stretching) MS: *m/z* 466.

(4m).4-(4-bromophenyl)-N-[2-chloro-4-(trifluoromethyl)phenyl]-2-oxo-6-(propan-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide: Yield: 68%; mp 211ºC; Anal. Calcd. for $C_{21}H_{18}BrClF_3N_3O_2$: CC, 48.81; H, 3.51; N, 8.13; O, 6.19; Found: C, 48.80; H, 3.50; N, 8.02; O, 6.10; IR (KBr cm^{-1}): 3232, 3130 (N-H stretching of amide), 2975 (C-H stretching of aromatic ring), 1711 (C=O stretching of amide), 1070 (C-F stretching) MS: *m/z* 517.

(4n).4-(3-bromophenyl)-*N*-[2-chloro-4-(trifluoromethyl)phenyl]-2-oxo-6-(propan-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide: Yield: 65%; mp 187ºC; Anal. Calcd. for $C_{21}H_{18}BrClF_3N_3O_2$: C, 48.81; H, 3.51; N, 8.13; O, 6.19; Found: C, 48.72; H, 3.41; N, 8.05; O, 6.01%; IR (KBr cm^{-1}): 3232, 3130 (N-H stretching of amide), 2975 (C-H stretching of aromatic ring), 1711 (C=O stretching of amide), 1070 (C-F stretching) MS: *m/z* 517.

(4o).*N*-[2-chloro-4-(trifluoromethyl)phenyl]-2-oxo-4-phenyl-6-(propan-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide:

Yield: 67%; mp 203ºC; Anal. Calcd. for $C_{21}H_{19}ClF_3N_3O_2$: C, 57.61; H, 4.37; N, 9.60; O, 7.31; Found: C, 57.45; H, 4.12; N, 9.42; O, 7.12; IR (KBr cm^{-1}): 3232, 3130 (N-H stretching of amide), 2975 (C-H stretching of aromatic ring), 1711 (C=O stretching of amide), 1070 (C-F stretching) MS: *m/z* 438.



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