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SYNTHESIS & CHARACTERIZATION OF NOVEL 4-(2,3,5-TRIFLUOROPHENYL)-N-(SUBSTITUTEDPHENYL)-1,2,3,4-TETRAHYDRO-6-METHYL-2-OXOPYRIMIDINE-5-CARBOXAMIDE DERIVATIVES WITH THEIR BROAD SPECTRUM ANTIMICROBIAL POTENCY

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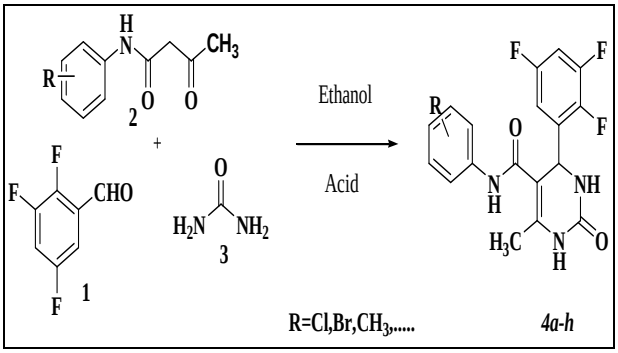
ABSTRACT
The title compounds 4-(2,3,5-trifluorophenyl)-N-(substitutedphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide have been synthesized for the development of antimicrobial agents. Newly synthesized compounds were evaluated for their in vitro antibacterial activity against Gram-positive bacteria (Pseudomonas aeruginosa, Streptococcus pyogenes), Gram-negative bacteria (Escherichia coli, Staphylococcus aureus), and antifungal activity (Candida albicans, Aspergillus niger, Aspergillus clavatus). The structures of the compounds were characterized by infrared, ^{1}H NMR, mass spectroscopic techniques and elemental analysis. The synthesized compounds showed potent antimicrobial activity against tested microorganisms.

KEYWORDS: 2,3,5-trifluorobenzaldehyde, N-(substitutedphenyl)-3-oxobutanamide, Urea, Conc. HCl and Ethanol.

INTRODUCTION
A medicinal Chemistry has its roots in several branches of chemistry and biology. However, essentially it worries with the understanding of mechanisms of action of drugs. It efforts to set up relationship flanked by structure and function and to link biodynamic behavior with chemical reactivity and physical properties. In medicinal chemistry pyrimidine derivatives have been very well branded for their beneficial application.

The majority simple and straightforward procedure for the synthesis of DHPMs was first reported by the Italian chemist Pietro Biginelli in 1893, it involves a three-component one-pot condensation of benzaldehyde, ethyl acetoacetate and urea under strongly acidic conditions.[1] Multicomponent reactions (MCRs) are highely important reaction for organic chemists, especially in medicinal chemistry field.[2,3] Biginelli reaction is one of the most studied reaction in the area of multicomponent re-actions[4] and dihydropyrimidin-2(1H)-ones (DHPMs) by the condensation of aldehyde, β-keto ester and urea in the presence of acid.[5] Dihydropyrimidinones (DHPMs) and their derivatives have displayed a captivating assortment in natural, synthetic, pharmacological, therapeutic and bioorganic chemistry.

Dihydropyrimidine (DHPM) and tetrahydropyrimidine which are a Nitrogen-containimg heterocycles have attracted much attention from the researchers for last few decades. The tremendously growing number of publications and patents on the di and tetra hydropyrimidines are mainly due to the fact that the multi functionalized dihydropyrimidine scaffold (DHPMs, "Biginelli compounds") represents a heterocylic system of remarkable pharmacological efficiency. Pyrimidines exhibit a broad variety of biological activity such as antimicrobial[6-14], anticancer[15-17], antitumor[18-21], anti-inflammatory[22-23], analgesic[24], antiviral[25], anti-HIV[26], anti-Hepatitis[27] and tyrosine kinase inhibitors activities.[28-31] Several pyrimidine analogues drugs like Pyrimethamine, Trimethoprim, Minoxidil and Pipemidic acid trihydrate are used as biological active agents.



Experimental

Typical untried procedure

A mixture of N-(substitutedphenyl)-3-oxobutanamide, 2,3,5-trifluorobenzaldehyde, Urea and catalytic amount of conc. HCL in ethanol was heated under reflux condition for 10 hrs. The reaction mixture was kept at room temperature for 24 hrs. The crystalline product obtained and recrystallized from ethanol.

Physical Data

4-(2,3,5-trifluorophenyl)-N-(4-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (4a): Yield: 60%; mp 171ºC; Elemental analysis calcd. For $C_{18}H_{13}ClF_3N_3O_2$: C, 54.63; H, 3.31; Cl, 8.96; F, 14.40; N, 10.62; O, 8.09; Found: C, 54.62; H, 3.30; Cl, 8.97; F, 14.41; N, 10.62; O, 8.09 %; MS: *m/z* 396; IR (cm^{-1}): 3171 (N-H stretching of amide), 3080 (C-H stretching of aromatic ring), 2967 (C-H asymmetrical stretching of CH_3 group), 2877 (C-H symmetrical stretching of CH_3 group), 1674 (C=O stretching of amide), 1620 (C=O stretching of cyclic) 1600 (N-H deformation of pyrimidine ring), 1490 (C=C stretching of aromatic ring), 1380 (C-H asymmetrical deformation of CH_3 group), 1282 (C-N stretching), 1112, 1084 (C-H in plane deformation of aromatic ring), 1060 (C-F stretching), 773 (C-Cl stretching) 842 (para-substituted); ^{1}H NMR (DMSO-*d6*) δ ppm: 1.71 (s, 3H, H_a), 5.56 (s, 1H, H_b), 6.47 (s, 1H, H_c), 6.52 (s, 1H, H_d), 7.25-7.58 (dd', 4H, $H_{ee',ff'}$), 7.95-7.99 (s, 1H, H_g), 8.82 (s, 2H, H_{hi}).

4-(2,3,5-trifluorophenyl)-N-(4-bromophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (4b): Yield: 58%; mp 177ºC; Elemental analysis calcd. for $C_{18}H_{13}BrF_3N_3O_2$: C, 49.11; H, 2.98; Br, 18.15; F, 12.95; N, 9.55; O, 7.27; Found: C, 49.19; H, 2.99; Br, 18.19; F, 12.95; N, 9.50; O, 7.20%; MS: *m/z* 440.

4-(2,3,5-trifluorophenyl)-N-(4-fluorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (4c): Yield: 54%; mp 173ºC; Elemental analysis calcd. For $C_{18}H_{13}F_4N_3O_2$: C, 57.00; H, 3.45; F, 20.03; N, 11.08; O, 8.44; Found: C, 57.02; H, 3.49; F, 20.09; N, 11.00; O, 8.40%; MS: *m/z* 379.

4-(2,3,5-trifluorophenyl)-N-(4-methoxyphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (4d): Yield: 60%; mp 176ºC; Elemental analysis calcd. for $C_{19}H_{16}F_3N_3O_3$: C, 58.31; H, 4.12; F, 14.56; N, 10.74; O, 12.26; Found: C, 58.31; H, 4.13; F, 14.57; N, 10.78; O, 12.20%; MS: *m/z* 391.

4-(2,3,5-trifluorophenyl)-N-(4-methylphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (4e): Yield: 57%; mp 164ºC; Elemental analysis calcd. for $C_{19}H_{16}F_3N_3O_2$: C, 60.80; H, 4.30; F, 15.18; N, 11.20; O, 8.53; Found: C, 60.74; H, 4.33; F, 15.11; N, 11.21; O, 8.51%; MS: *m/z* 375.

4-(2,3,5-trifluorophenyl)-N-(3-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (4f): Yield: 51%; mp 159ºC; Elemental analysis calcd. For $C_{18}H_{13}ClF_3N_3O_2$: C, 54.63; H, 3.31; Cl, 8.96; F, 14.40; N, 10.62; O, 8.09; Found: C, 54.61; H, 3.30; Cl, 8.94; F, 14.41; N, 10.60; O, 8.04 %; MS: *m/z* 396.

4-(2,3,5-trifluorophenyl)-N-(3-bromophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (4g): Yield: 55%; mp 167ºC; Elemental analysis calcd. for $C_{18}H_{13}BrF_3N_3O_2$: C, 49.11; H, 2.98; Br, 18.15; F, 12.95; N, 9.55; O, 7.27; Found: C, 49.10; H, 2.94; Br, 18.14; F, 12.93; N, 9.53; O, 7.27%; MS: *m/z* 440.

4-(2,3,5-trifluorophenyl)-N-(3-fluorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (4h): Yield: 53%; mp 161ºC Elemental analysis calcd. For $C_{18}H_{13}F_4N_3O_2$: C, 57.00; H, 3.45; F, 20.03; N, 11.08; O, 8.44; Found: C, 57.04; H, 3.11 F, 20.00; N, 11.08; O, 8.40%; MS: *m/z* 379.

BIOLOGICAL EVALUATION

Antimicrobial evaluation

Total of the Prepared compounds were experienced for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method 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 ***gentamycin, chloramphenicol, norfloxacin, nystatin and greseofulvin*** as regular drugs.

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 micro dilution broth method according to NCCLS(National Committee for Clinical Laboratory Standards) standards.

Minimal Inhibition Concentration [MIC]

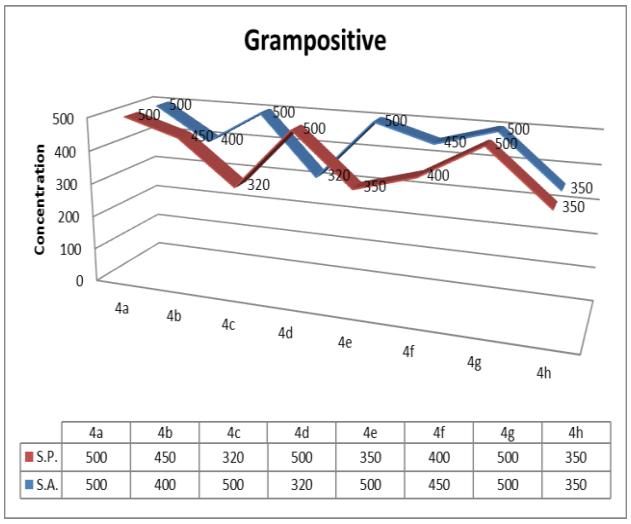
The main advantage of the 'Broth Dilution Method' for MIC determination lies in the fact that it can readily be converted to determine the MIC as well.

- Serial dilutions were prepared in primary and secondary screening.

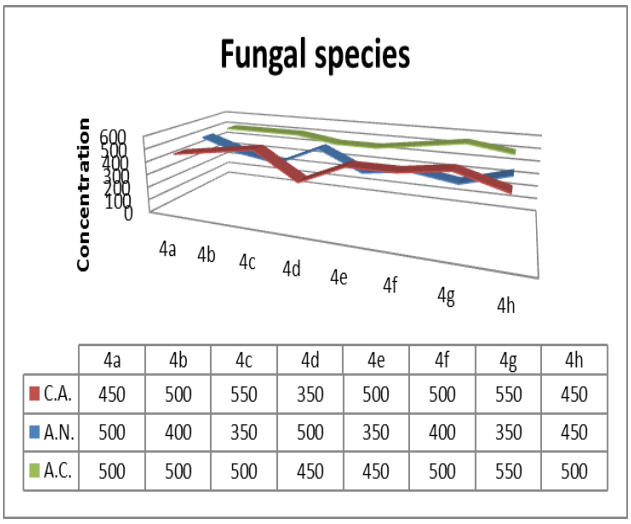
- The control tube containing no antibiotic is immediately subcultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 35 ^{0}C overnight.
- The MIC of the control organism is read to check the accuracy of the drug concentrations.
- The lowest concentration inhibiting growth of the organism is recorded as the MIC.
- The amount of growth from the control tube before incubation (which represents the original inoculums) is compared.

Table. 1: *in vitro Antimicrobial Screening Results for* (4a-h).

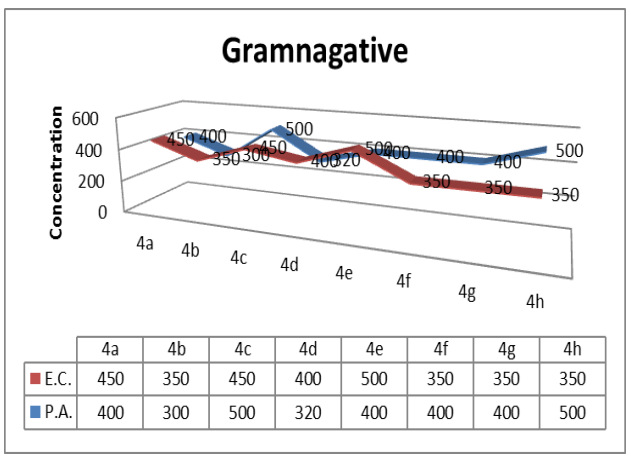
Code	Minimal inhibition concentration (µg mL^{-1})						
	Gram-positive		Gram-negative		Fungal species		
	S.a.	***S. p.***	***E.c.***	***P.a.***	***C. a.***	***A. n.***	***A.c.***
4a	500	500	450	400	450	500	500
4b	400	450	350	300	500	400	500
4c	500	320	450	500	550	350	500
4d	320	500	400	320	350	500	450
4e	500	350	500	400	500	350	450
4f	450	400	350	400	500	400	500
4g	500	500	350	400	550	350	550
4h	350	350	350	500	450	450	500
Ampicillin	250	100	100	100	-	-	-
Chloramphenicol	50	50	50	50	-	-	-
Norfloxacin	10	10	10	10	-	-	-
Nystatin	-	-	-	-	100	100	100
Griseofulvin	-	-	-	-	450	100	100



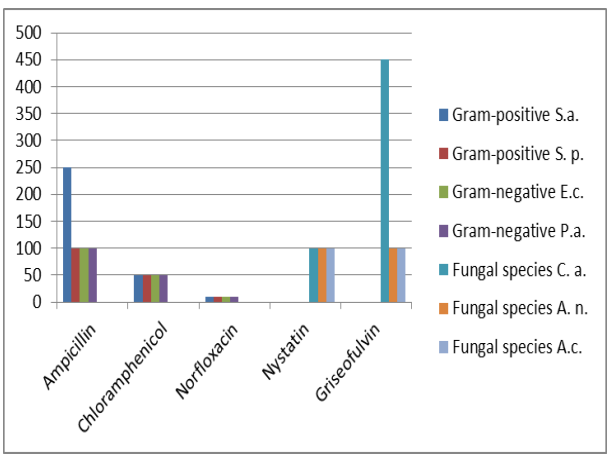
	4a	4b	4c	4d	4e	4f	4g	4h
S.P.	500	450	320	500	350	400	500	350
S.A.	500	400	500	320	500	450	500	350



	4a	4b	4c	4d	4e	4f	4g	4h
C.A.	450	500	550	350	500	500	550	450
A.N.	500	400	350	500	350	400	350	450
A.C.	500	500	500	450	450	500	550	500



	4a	4b	4c	4d	4e	4f	4g	4h
E.C.	450	350	450	400	500	350	350	350
P.A.	400	300	500	320	400	400	400	500



CONCLUSION

In put up, we obtained in create of inventive pyrimidine derivatives using devoid of any troubles and suitable process. By method produces these products in good quality yield and unproblematic work on. Product is isolated by unforced filtration. The isolated products are much unadulterated and do not require any another purification. Here pyrimidine derivative is use further reaction because secondary amine is presence in a structure so the in further research program, it will a use.

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