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Synthesis, Characterization and Biological Screening of Some Novel Triazolopyrimidine Derivatives Possessing Isopropyl Group

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ABSTRACT

Well organized Synthesis of a completely new series of N-(3-chloro-4-fluorophenyl)-7-(substitutedchlorophenyl)-4,7-dihydro-5-isopropyl-[1,2,4]triazolo [1,5-a]pyrimidine-6-carboxamide (4a-j) was achieved from condensation reaction of N-(3-chloro-4-fluorophenyl)-4-methyl-3-oxopentanamide, 3-amino-1,2,4-triazole and different aldehyde. After refluxing of 20 minutes with DMF and cooling product is obtained. these new compounds were characterized using some physical techniques like FT-IR spectra, Mass spectra, by the 1H-NMR spectra. Antimicrobial activity and antifungal activity were studied against example of gram - positive gram- negative bacterial and fungal strain.

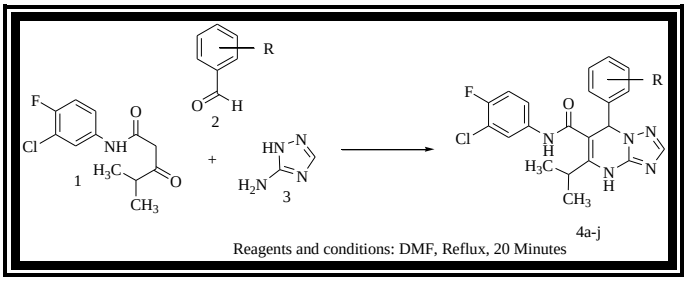
Keywords : 3-amino-1,2,4-triazole, N N-(3-chloro-4-fluorophenyl)-4-methyl-3-oxopentanamide and DMF.

I. INTRODUCTION

Biginelli reaction has been the way to the synthesis of a large number of compounds. [1] An advantage of this type of multicomponent reaction is that its higher efficiency, cost-effectiveness, easy to handle. Even though the method is quite old but it is found as power full weapon in the synthesis of a wide spectrum of biological function that dihydro pyriidone possesses. [2,3]

The activity of many compounds of these types as having antiviral, antibacterial, and antihypertensive effects, and they act as a calcium channel blocker. [4–7], and as multiple function resistance reversals [8, 9]. Antimicrobial and antifungal activity of some alkaloids isolated recently to 3,4 dihydropyrimidin-2(1H)-one compounds [10, 11]. Firstly was synthesized by Biginelli in 1893 this type of multicomponent reaction is widely known as a one-pott reaction. in this one-pot reaction, more than three or three-component are mixed either continuously or through a sequential-addition. By reducing the number of synthetic operations and expanding target-oriented synthesis and functional complexity. [6]

SCHEME



II. EXPERMENTAL DETAIL

EXPERMENTAL DETAIL
TYPICAL UNTRIED PROCEDURE

A mixture of the 3-amino-1,2,4-triazole, N-(substituedphenyl)-4-methyl-3-oxopentanamide and an appropriate aromatic aldehydes was refluxed in DMF for 20 min. After cooling, methanol was added. The reaction mixture was allowed to stand overnight and then filtered to give the solid triazolopyrimidine products (4a-j), which were recrystallized from ethanol.

N-(3-chloro-4-fluorophenyl)-7-(4-chlorophenyl)-4,7-dihydro-5-isopropyl-[1,2,4]triazolo [1,5-a]pyrimidine-6-carboxamide (4a)

Yield: 68%; mp 256ºC; Anal. Calcd. for $C_{21}H_{18}Cl_2FN_5O$: C, 56.51; H, 4.07; Cl, 15.89; F, 4.26; N, 15.69; O, 3.58; Found: C, 56.40; H, 4.00; Cl, 15.75; F, 4.15; N, 15.56; O, 3.42%; MS: m/z 445.

N-(3-chloro-4-fluorophenyl)-4,7-dihydro-5-isopropyl-7-p-tolyl-[-[1,2,4] triazolo [1,5-a] pyrimidine-6-carboxamide(4b)

Yield: 66%; mp 227ºC; Anal. Calcd. for $C_{22}H_{21}ClFN_5O$: C, 62.04; H, 4.97; Cl, 8.32; F, 4.46; N, 16.44; O, 3.76; Found: C, 61.89; H, 4.82; Cl, 8.20; F, 4.31; N, 16.36; O, 3.62; IR (cm^{-1}): 3377 (N-H stretching of secondary amine), 3022 (C-H stretching of aromatic ring), 2970 (C-H asymmetrical stretching of CH_3 group), 2870 (C-H asymmetrical stretching of CH_3 group), 1666 (C=O stretching of amide), 1577 (C=N stretching of triazole ring), 1550 (N-H deformation of pyrimidine ring), 1529 and 1500 (C=C stretching of aromatic ring), 1408 (C-H asymmetrical deformation of CH_3 group), 1307 (C-H symmetrical deformation of CH_3 group), 1282 (C-N stretching), 1078 (C-H in plane deformation of aromatic ring), 1141 (C-F stretching) 815 (C-H out of plane bending of 1,4-disubstituion), 667 (C-Cl stretching); MS: m/z 425; ^1H NMR (DMSO-d_6) δ ppm: 1.15-1.17 (d, 3H, H_a, J = 7.20 Hz), 1.27-1.29 (d, 3H, H_b, J = 7.20 Hz), 2.20 (s, 3H, H_c) 3.28-3.33 (m, 1H, H_d),) 6.42 (s, 1H, H_d), 6.93-6.97 (m, 1H, H_f), 7.01-7.03 (d, 2H, $H_{gg'}$, J = 8.00 Hz), 7.09-7.11 (d, 1H, $H_{hh'}$, J = 8.00 Hz), 7.25-7.29 (m, 1H, H_i), 7.49 (m, 1H, H_j), 7.62 (s, 1H, H_k), 9.65 (s, 1H, H_l), 9.74 (s, 1H, H_m).

N-(3-chloro-4-fluorophenyl)-4,7-dihydro-5-isopropyl-7-(4-methoxyphenyl) [1,2,4] triazolo[1,5-a]pyrimidine-6-carboxamide (4c)

Yield: 62%; mp 257ºC; Anal. Calcd. for $C_{22}H_{21}ClFN_5O_2$: C, 59.80; H, 4.79; Cl, 8.02; F, 4.30; N, 15.85; O, 7.24; Found: C, 59.70; H, 4.66; Cl, 7.89; F, 4.21; N, 15.74; O, 7.11; IR (cm^{-1}): 3369 (N-H stretching of secondary amine), 3084 (C-H stretching of aromatic ring), 2970 (C-H asymmetrical stretching of CH_3 group), 2868 (C-H asymmetrical stretching of CH_3 group), 1664 (C=O stretching of amide), 1664 (C=N stretching of triazole ring), 1573 (N-H deformation of pyrimidine ring), 1550 (C=C stretching of aromatic ring), 1468 (C-H asymmetrical deformation of CH_3 group), 1307 (C-H symmetrical deformation of CH_3 group), 1280 (C-N stretching), 1247 (C-O-C stretching),1035 (C-F stretching), 1076 (C-H in plane deformation of aromatic ring), 779 (C-H out of plane bending of 1,4-disubstituion), 663 (C-Cl stretching); MS: m/z 441; ^1H NMR (DMSO-d_6) δ ppm: 1.23-1.25 (d, 3H, H_a, J = 7.20 Hz), 1.36-1.38 (d, 3H, H_b, J = 7.20 Hz), 3.38-3.45 (m, 1H, H_c), 3.73-3.75 (s, 3H, H_d) 6.49 (s, 1H, H_e), 6.81-6.84 (d, 2H, $H_{ff'}$, J = 13.60 Hz), 7.00-7.04 (m, 1H, H_g), 7.24-7.27 (d, 2H, $H_{hh'}$, J = 11.60 Hz), 7.31-7.35 (m, 1H, H_i), 7.58 (s, 1H, H_j), 7.64 (s, 1H, H_k), 9.66 (s, 1H, H_l), 9.84 (s, 1H, H_m).

N-(3-chloro-4-fluorophenyl)-4,7-dihydro-5-isopropyl-7-(4-nitrophenyl)-[1,2,4]triazolo [1,5-a]pyrimidine-6-carboxamide (4d)

Yield: 71%; mp 247ºC; Anal. Calcd. for $C_{21}H_{18}ClFN_6O_3$: C, 55.21; H, 3.97; Cl, 7.76; F, 4.16; N, 18.40; O, 10.51; Found: C, 55.12; H, 3.84; Cl, 7.61; F, 4.03; N, 18.34; O, 10.41; MS: m/z 456.

N-(3-chloro-4-fluorophenyl)-4,7-dihydro-5-isopropyl-7-(4-fluorophenyl)[1,2,4]triazolo [1,5-a]pyrimidine-6-carboxamide (4e)

Yield: 72%; mp 233ºC; Anal. Calcd. for $C_{21}H_{18}ClF_2N_5O$: C, 58.68; H, 4.22; Cl, 8.25; F, 8.84; N, 16.29; O, 3.72; Found: C, 58.68; H, 4.11; Cl, 8.10; F, 8.68; N, 16.12; O, 3.62; IR (cm^{-1}): 3421 (N-H stretching of secondary amine), 3024 (C-H stretching of aromatic ring), 2924 (C-H asymmetrical stretching of CH_3 group), 2875 (C-H asymmetrical stretching of CH_3 group), 1668 (C=O stretching of amide), 1575 (C=N stretching of triazole ring), 1552 (N-H deformation of pyrimidine ring), 1498 (C=C stretching of aromatic ring), 1410 (C-H asymmetrical deformation of CH_3 group), 1305 (C-H symmetrical deformation of CH_3 group), 1242 (C-N stretching), 1087 (C-H in plane deformation of aromatic ring), 1012 (C-F stretching), 819 (C-H out of plane bending of 1,4-disubstituion), 686 (C-Cl stretching); MS: m/z 429; ^{1}H NMR (DMSO-d_6) δ ppm: 1.15-1.17 (d, 3H, H_a, J = 7.20 Hz), 1.27-1.29 (d, 3H, H_b, J = 7.20 Hz), 3.30-3.37 (m, 1H, H_c), 6.41 (s, 1H, H_d), 6.73-6.75 (d, 2H, $H_{ee'}$, J = 8.80 Hz), 6.82-6.87 (m, 2H, H_{fg}), 7.16-7.18 (d, 1H, H_h, J = 8.40 Hz), 7.36-7.40 (m, 1H, H_i), 7.48 (s, 1H, H_j), 7.67 (s, 1H, H_k) ,9.50 (s, 1H, H_l), 9.71 (s, 1H, H_m).

N-(3-chloro-4-fluorophenyl)-4,7-dihydro-5-isopropyl-7-(3-nitrophenyl)[1,2,4]triazolo [1,5-a]pyrimidine-6-carboxamide (4f)

Yield: 70%; mp 247ºC; Anal. Calcd. for $C_{21}H_{18}ClFN_6O_3$: C, 55.21; H, 3.97; Cl, 7.76; F, 4.16; N, 18.40; O, 10.51; Found: C, 55.21; H, 3.97; Cl, 7.76; F, 4.16; N, 18.40; O, 10.51%; MS: m/z 456.

N-(3-chloro-4-fluorophenyl)-4,7-dihydro-5-isopropyl-7-(3-chlorophenyl)[1,2,4]triazolo [1,5-a]pyrimidine-6-carboxamide (4g)

Yield: 63%; mp 235ºC; Anal. Calcd. for $C_{21}H_{18}Cl_2FN_5O$: C, 56.51; H, 4.07; Cl, 15.89; F, 4.26; N, 15.69; O, 3.58; Found: C, 56.43; H, 4.00; Cl, 15.72; F, 4.10; N, 15.54; O, 3.42%; MS: m/z 445.

N-(3-chloro-4-fluorophenyl)-4,7-dihydro-5-isopropyl-7-(2-nitrophenyl)-[1,2,4]triazolo [1,5-a]pyrimidine-6-carboxamide (4h)

Yield: 66%; mp 198ºC; Anal. Calcd. for $C_{21}H_{18}ClFN_6O_3$: C, 55.21; H, 3.97; Cl, 7.76; F, 4.16; N, 18.40; O, 10.51;Found: C, 55.10; H, 3.88; Cl, 7.64; F, 4.05; N, 18.31; O, 10.42%; MS: m/z 456.

N-(3-chloro-4-fluorophenyl)-4,7-dihydro-5-isopropyl-7-(4-nitrophenyl)-[1,2,4]triazolo [1,5-a]pyrimidine-6-carboxamide (4i)

Yield: 80%; mp 209 ºC; Anal. Calcd. for $C_{21}H_{19}ClFN_5O_2$: C, 58.95; H, 4.48; Cl, 8.29; F, 4.44; N, 16.37; O, 7.48; Found: C, 58.87; H, 4.34; Cl, 8.10; F, 4.34; N, 16.23; O, 7.34%; MS: m/z 427.

N-(3-chloro-4-fluorophenyl)-4,7-dihydro-5-isopropyl-7-(3-bromophenyl)[1,2,4]triazolo [1,5-a]pyrimidine-6-carboxamide (4j)

Yield: 73%; mp 219 ºC; Anal. Calcd. for $C_{21}H_{18}BrClFN_5O$: C, 51.40; H, 3.70; Br, 16.28; Cl, 7.22; F, 3.87; N, 14.27; O, 3.26; Found: C, 51.31; H, 3.61; Br, 16.15; Cl, 7.10; F, 3.76; N, 14.14; O, 3.12%; MS: m/z 489.

III. ANTIMICROBIAL ACTIVITY

Biological evaluation

All of the synthesized compounds were tested for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method[12-14]with two Gram-positive bacteria *Staphylococcus aureus* MTCC-96 and *Streptococcus pyogenes* MTCC 442, two Gram-negative bacteria *Escherichia coli* MTCC 443 and *Pseudomonas aeruginosa* MTCC 1688 and three fungal strains *Candida albicans* MTCC 227,

Aspergillus Niger MTCC 282 and *Aspergillus clavatus* MTCC 1323 taking gentamycin, ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin and greseofulvin as standard drugs. The standard strains were procured from the Microbial Type Culture Collection.

For all completely new synthesized compound the value if MIC is defined as minimum concentration of the synthesized compound which stopping the growth of microorganism which is determines by this method. According to NCCLS standards.

Minimal Inhibition Concentration [MIC]

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 37 ^{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 theoriginal inoculums) is compared.

Methods used for primary and secondary screening

Each synthesized compounds was diluted obtaining 2000 µg mL^{-1} concentration, as a stock solution. Size of inoculum is fixed to I 10^8 cfu (colony forming unit) per milliliter it is done by compairing turbidity of tube.

Primary screen: In primary screening 1000 µg mL^{-1}, 500 µg mL^{-1} and 250 µg mL^{-1} concentrations of the synthesized compounds were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms.

Secondary screen: The compounds found active in primary screening were similarly diluted to obtain 200 µg mL^{-1}, 100 µg mL^{-1}, 50 µg mL^{-1}, 25 µg mL^{-1}, 12.5 µg mL^{-1}, and 6.250 µg mL^{-1} concentrations.

Reading Result: The highest dilution showing at least 99 % inhibition zone is taken as MIC. The result of this is much affected by the size of the inoculums. The test mixture should contain 10^8 organism/mL.

Table-1 :- In vitro Antibacterial Screening Results for (4a-j)

Code	Minimal inhibition concentration (µg mL^{-1})			
	Gram-positive		Gram-negative	
	GPA1	GPA2	GNA3	GNA4
4a	250	250	250	250
4b	200	200	50	100
4c	250	250	500	500
4d	250	500	100	200
4e	100	200	100	250
4f	250	100	250	500
4g	200	50	50	100
4h	250	500	150	200
4i	500	1000	500	500
4j	100	100	500	250
Ampicillin	250	100	100	100
Chloramphenicol	50	50	50	50
Norfloxacin	10	10	10	10
	Staphylococcus aureus	GPA1		
	Streptococcus pyogenes	GPA2		
	Escherichia coli	GNA3		
	Pseudomonas aeruginosa	GNA4		

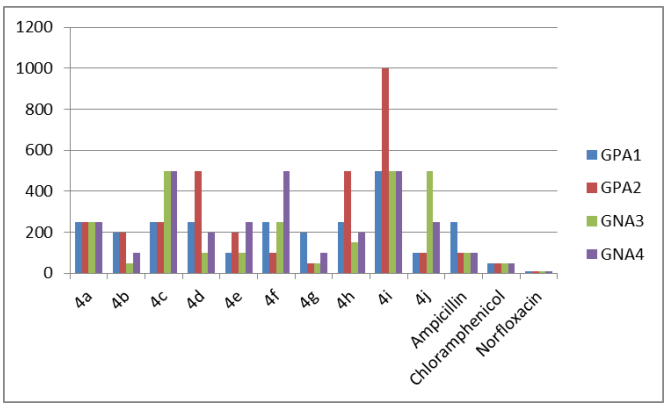
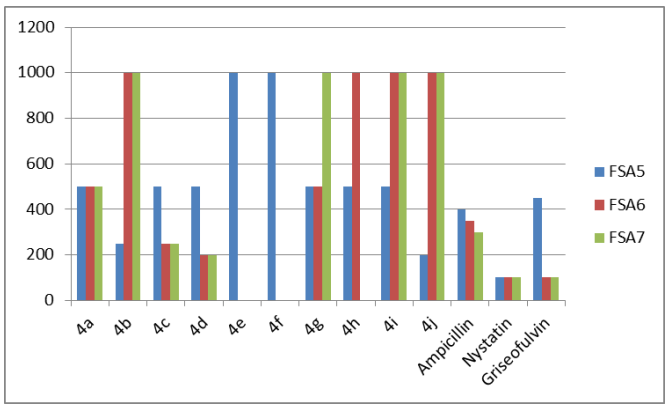


Table-2 :- In vitro Antifungal Screening Results for (4a-j)

Code	Minimal inhibition concentration (µg mL-1)		
	Fungal species		
	FSA5	FSA6	FSA7
4a	500	500	500
4b	250	1000	1000
4c	500	250	250
4d	500	200	200
4e	1000	>1000	>1000
4f	1000	>1000	>1000
4g	500	500	1000
4h	500	1000	>1000
4i	500	1000	1000
4j	200	1000	1000
Ampicillin	400	350	300
Nystatin	100	100	100
Griseofulvin	450	100	100
		Candida albicans	**FSA5**
		Aspergillus Niger	**FSA6**
		Aspergillus clavatus	**FSA7**



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