Synthesis of 1, 2, 4-triazolo[1,5-a]Pyrimidines Derivatives as Antimicrobial Agents

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Abstract:
The condensation of a ring of 1,2,4-triazole and another one of pyrimidine gives rise to the formation of bicyclic heterocycles known as 1,2,4-triazolopyrimidines. Four different possibilities exist for the relative orientation of both rings, so four different isomeric families of compounds are defined: 1,2,4-triazolo[1,5-a]pyrimidine, 1,2,4-triazolo[1,5-c]pyrimidine, 1,2,4-triazolo[4,3-a]pyrimidine and 1,2,4-triazolo[4,3-c]pyrimidine. Among these isomeric families of compounds, 1,2,4-triazolo[1,5-a]pyrimidine derivatives are thermodynamically more stable and, thus, the most studied ones [1], a few of them being commercially available. Revisions surveying the synthesis, reactivity, spectroscopic characterization and crystallographic studies of 1,2,4-triazolo[1,5-c]pyrimidines [2], 1,2,4-triazolo[4,3-a]pyrimidines [3] and 1,2,4-triazolo[4,3-c]pyrimidines [4] have also been published. From the standpoint of biological activity, fused heteroaromatic systems are often of much greater interest than the constituent monocyclic compounds. Recently, 1,2,4-triazolo[1,5-a]pyrimidines have aroused increasing attention from the chemical and biological view points, due to their diverse pharmacological activities, such as antitumor potency [5, 6], inhibition of KDR kinase [7], antifungal effect [8] and macrophage activation [9]. They have proved to be promising anticancer agents with dual mechanisms of tubulin polymerization promotion [5, 6] as well as cyclin dependent kinases 2 inhibition [10]. Some examples of published derivatives of 1,2,4-triazolo[1,5-a]pyrimidine with their biological activities are as following.

Keywords: *Triazolo, Pyrimidines Derivatives*

1. Experimental

1.1 Materials and Methods

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine. IR spectra were recorded Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. ^{1}H NMR was determined in DMSO-d_6 solution on a Bruker Ac 400 MHz spectrometer. Elemental analysis of the all the synthesized compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned.

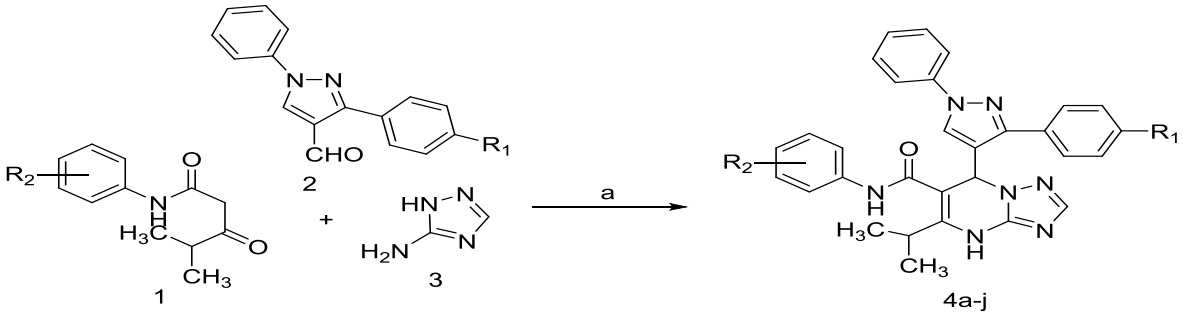
2. Synthesis of 4-methyl-3-oxo-N-(aryl)pentanamide

Synthesis of 4-methyl-3-oxo-N-(aryl)pentanamide was achieved using previously published methods [11].

3. General procedure for the synthesis of 7-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,7-dihydro-5-isopropyl-N-(aryl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (VP 31-60)

A mixture of the 5-amino-1,2,4-triazole (0.01 mol), 4-methyl-3-oxo-N-(aryl)pentanamide (0.01 mol) and 3-(4-chlorophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (0.01 mol) was refluxed in 0.4 mL of

DMF for 12-15 min. After cooling, methanol (~10 mL) was added. The reaction mixture was allowed to stand overnight and then filtered to give the solid triazolopyrimidine products 4a-t, which were crystallized from ethanol and subsequently dried in air.



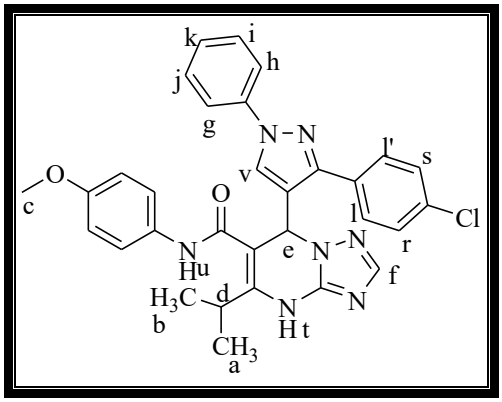
Reagents and conditions: (a) DMF, Reflux, 12-15 Minutes

Table 1: Physical data of synthesized compounds (4a-t)

Code	R_1	R_2	M.F.	M. W.	M.P. °C	Yield %	R_{f1}	R_{f2}
4a	4-OCH_3	4-Cl	$C_{31}H_{28}ClN_7O_2$	566	209-211	78	0.56	0.71
4b	4-F	4-Cl	$C_{30}H_{25}ClFN_7O$	554	183-185	72	0.51	0.69
4c	4-NO_2	4-Cl	$C_{30}H_{25}ClN_8O_3$	581	250-252	82	0.48	0.64
4d	4-Cl	4-Cl	$C_{30}H_{25}Cl_2N_7O$	570	170-172	69	0.50	0.68
4e	3-Cl	4-Cl	$C_{30}H_{25}Cl_2N_7O$	570	248-250	80	0.53	0.70
4f	4-Br	4-Cl	$C_{30}H_{25}BrClN_7O$	614	193-195	75	0.44	0.74
4g	3-NO_2	4-Cl	$C_{30}H_{25}ClN_8O_3$	581	204-206	69	0.51	0.70
4h	2-Cl	4-Cl	$C_{30}H_{25}Cl_2N_7O$	570	254-256	76	0.50	0.63
4i	2-NO_2	4-Cl	$C_{30}H_{25}ClN_8O_3$	581	177-179	82	0.41	0.62
4j	2-F	4-Cl	$C_{30}H_{25}ClFN_7O$	554	199-201	70	0.49	0.74
4k	4-OCH_3	4-F	$C_{31}H_{28}FN_7O_2$	549	246-248	73	0.52	0.69
4l	4-F	4-F	$C_{30}H_{25}F_2N_7O$	537	232-234	85	0.56	0.68
4m	4-NO_2	4-F	$C_{30}H_{25}FN_8O_3$	564	250-252	78	0.50	0.66
4n	4-Cl	4-F	$C_{30}H_{25}ClFN_7O$	554	250-252	72	0.52	0.69
4o	3-Cl	4-F	$C_{30}H_{25}ClFN_7O$	554	216-218	76	0.61	0.77
4p	4-Br	4-F	$C_{30}H_{25}BrFN_7O$	598	240-242	66	0.54	0.61
4q	3-NO_2	4-F	$C_{30}H_{25}FN_8O_3$	564	233-235	78	0.53	0.71

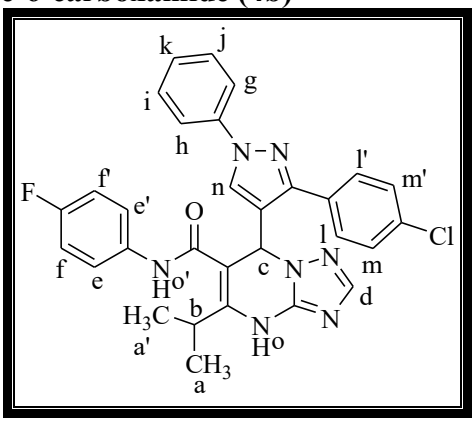
4r	2-Cl	4-F	$C_{30}H_{25}ClFN_7O$	554	190-192	71	0.64	0.78
4s	2-NO_2	4-F	$C_{30}H_{25}FN_8O_3$	564	202-204	65	0.48	0.62
4t	2-F	4-F	$C_{30}H_{25}F_2N_7O$	537	236-238	79	0.61	0.72

7-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,7-dihydro-5-isopropyl-N-(4-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4a)



Yield: 78%; mp 209-211 ºC; Anal. Calcd. for $C_{31}H_{28}ClN_7O_2$: C, 65.78; H, 4.99; N, 17.32; Found: C, 65.88; H, 4.89; N, 17.22%; IR (cm^{-1}): 3379 (N-H stretching of secondary amine), 3059 (C-H stretching of aromatic ring), 3012 (C-H symmetrical stretching of CH_3 group), 2895 (C-H asymmetrical stretching of CH_3 group), 1676 (C=O stretching of amide), 1645 (C=N stretching of triazole ring), 1552 (N-H deformation of pyrimidine ring), 1514 and 1458 (C=C stretching of aromatic ring), 1429 (C-H asymmetrical deformation of CH_3 group), 1329 (C-H symmetrical deformation of CH_3 group), 1301 (C-N stretching), 1145 (C-O-C asymmetrical stretching of ether linkage), 1064 (C-O-C symmetrical stretching of ether linkage), 1031 (C-H in plane deformation of aromatic ring), 840 (C-H out of plane deformation of 1,4-disubstitution); MS: m/z 566; ^{1}H NMR (DMSO-d_6) δ ppm: 1.19-1.21 (d, 3H, H_a, J = 6.84 Hz), 1.29-1.31 (d, 3H, H_b, J = 6.72 Hz), 3.73 (s, 3H, H_c), 6.69-6.75 (t, 3H, H_{d-f}), 7.28-7.33 (m, 5H, H_{g-k}), 7.41-7.45 (t, 2H, $H_{ll'}$), 7.50 (s, 1H, H_r), 7.64-7.70 (m, 4H, H_{n-q}), 7.82 (s, 1H, H_v), 8.20 (s, 1H, H_s), 9.40 (s, 1H, H_t), 9.63 (s, 1H, H_u).

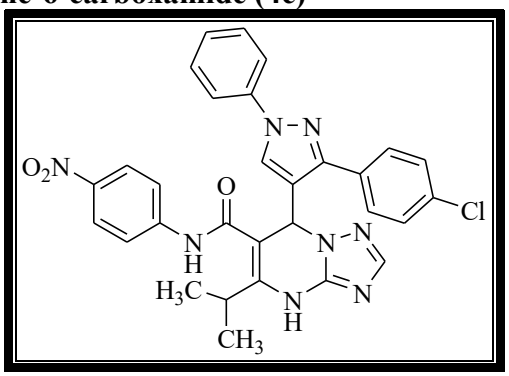
7-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-N-(4-fluorophenyl)-4,7-dihydro-5-isopropyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4b)



Yield: 72%; mp 183-185 ºC; Anal. Calcd. for $C_{30}H_{25}ClFN_7O$: C, 65.04; H, 4.55; N, 17.70%; Found: C, 65.14; H, 4.45; N, 17.80%; MS: m/z 554; ^{1}H NMR (DMSO-d_6) δ ppm: 1.08-1.11 (t, 6H, $H_{aa'}$), 2.36-2.40 (t, 1H, H_b), 4.46 (s, 1H, H_c), 6.20 (s, 1H, H_d), 7.29-7.31 (d, 2H, $H_{ee'}$, J = 7.04 Hz), 7.35-7.37 (d, 2H, $H_{ff'}$, J = 8.04

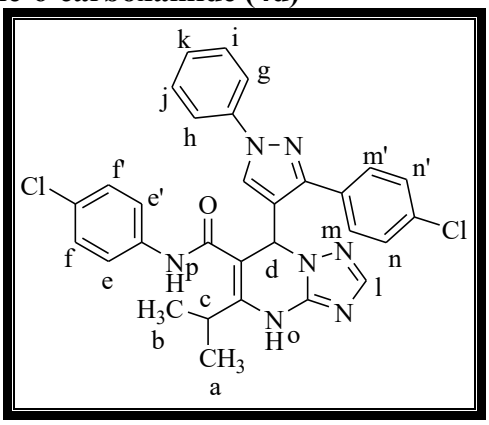
Hz), 7.43-7.49 (m, 5H, $H_{g\text{-}k}$), 7.63-7.65 (d, 2H, $H_{ll'}$, J = 8.08 Hz), 7.74-7.76 (d, 2H, $H_{mm'}$, J = 7.76 Hz), 8.11 (s, 1H, H_n), 9.29 (s, 2H, $H_{oo'}$).

7-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,7-dihydro-5-isopropyl-N-(4-nitrophenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4c)



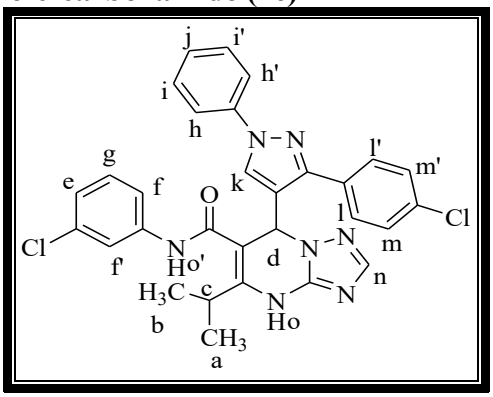
Yield: 82%; mp 250-252 ºC; Anal. Calcd. for $C_{30}H_{25}ClN_8O_3$: C, 62.01; H, 4.34; N, 19.29%; Found: C, 62.11; H, 4.24; Cl, 6.20; N, 19.19; O, 8.36 %; MS: m/z 581.

N-(4-chlorophenyl)-7-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,7-dihydro-5-isopropyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4d)



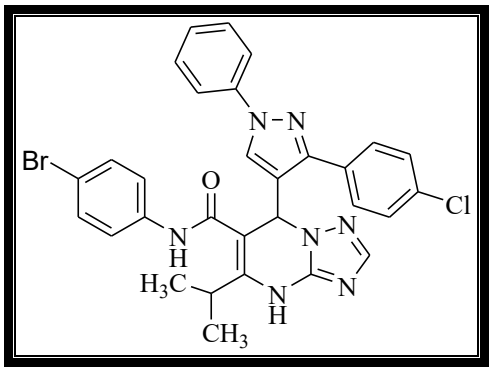
Yield: 69%; mp 170-172 ºC; Anal. Calcd. for $C_{30}H_{25}Cl_2N_7O$: C, C, 63.16; H, 4.42; N, 17.19%: Found: C, 63.06; H, 4.52; N, 17.29%; MS: m/z 570; ^{1}H NMR (DMSO-d_6) δ ppm: 1.19-1.20 (d, 3H, H_a, J = 7.00 Hz), 1.28-1.29 (d, 3H, H_b, J = 6.88 Hz), 2.56 (s, 1H, H_l), 3.20-3.24 (t, 1H, H_c), 6.72 (s, 1H, H_d), 7.15-7.18 (d, 2H, $H_{ee'}$, J = 8.76 Hz), 7.25-7.32 (m, 2H, $H_{ff'}$), 7.40-7.44 (m, 5H, $H_{g\text{-}k}$), 7.51 (s, 1H, H_q), 7.60-7.62 (d, 2H, $H_{mm'}$, J = 8.36 Hz), 7.67-7.68 (d, 2H, $H_{nn'}$, J = 7.80 Hz), 8.18 (s, 1H, H_o), 9.76 (s, 1H H_p).

N-(3-chlorophenyl)-7-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,7-dihydro-5-isopropyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4e)



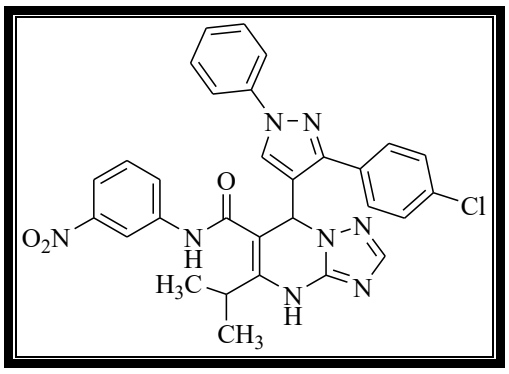
Yield: 80%; mp 248-250 ºC; Anal. Calcd. for $C_{30}H_{25}Cl_2N_7O$: C, 63.16; H, 4.42; N, 17.19%; Found: C, 63.09; H, 4.62; N, 17.39%; MS: m/z 570; ^{1}H NMR (DMSO-d_6) δ ppm: 1.18-1.20 (d, 3H, H_a, J = 7.00 Hz), 1.28-1.29 (d, 3H, H_b, J = 6.88 Hz), 3.19-3.23 (t, 1H, H_c), 6.72 (s, 1H, H_d), 6.97-6.99 (t, 1H, H_e), 7.15-7.19 (t, 1H, H_g), 7.15-7.17 (d, 2H, $H_{ff'}$, J = 8.08 Hz), 7.25-7.27 (d, 2H, $H_{hh'}$, J = 6.88 Hz), 7.41-7.45 (t, 2H, $H_{ii'}$), 7.52 (s, 1H, H_j), 7.56 (s, 1H, H_k), 7.60-7.62 (d, 2H, $H_{ll'}$, J = 8.32 Hz), 7.69-7.71 (d, 2H, $H_{nn'}$, J = 7.84 Hz), 8.23 (s, 1H, H_n), 9.82 (s, 2H $H_{oo'}$);.

N-(4-bromophenyl)-7-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,7-dihydro-5-isopropyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4f)



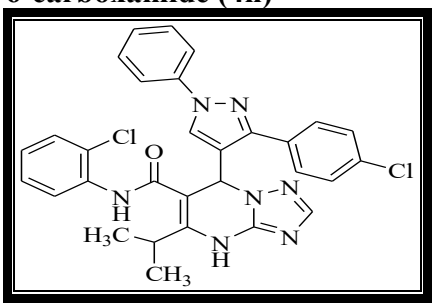
Yield: 75%; mp 193-195 ºC Anal. Calcd. for $C_{30}H_{25}BrClN_7O$: C, 58.60; H, 4.10; N, 15.94. Found: C, 58.70; H, 4.00; N, 15.84%; MS: m/z 614.

7-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,7-dihydro-5-isopropyl-N-(3-nitrophenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4g)



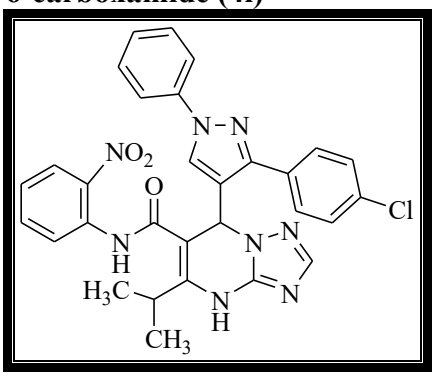
Yield: 69%; mp 204-206 ºC; Anal. Calcd. for $C_{30}H_{25}ClN_8O_3$: C, 62.01; H, 4.34; N, 19.29. Found: C, 61.90; H, 4.24; N, 19.49%; MS: m/z 581.

N-(2-chlorophenyl)-7-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,7-dihydro-5-isopropyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4h)



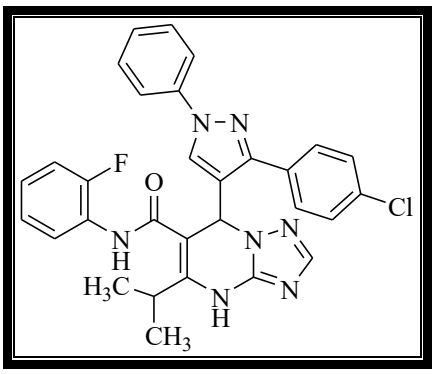
Yield: 76%; mp 254-256 ºC; Anal. Calcd. for $C_{30}H_{25}Cl_2N_7O$: C, 63.16; H, 4.42; N, 17.19. Found: C, 62.98; H, 4.52; N, 17.39%; MS: m/z 570.

7-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,7-dihydro-5-isopropyl-N-(2-nitrophenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4i)



Yield: 82%; mp 177-179 ºC; Anal. Calcd. for $C_{30}H_{25}ClN_8O_3$: C, 62.01; H, 4.34; N, 19.29. Found: C, 61.80; H, 4.24; N, 19.39%; MS: m/z 581.

7-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-N-(2-fluorophenyl)-4,7-dihydro-5-isopropyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4j)

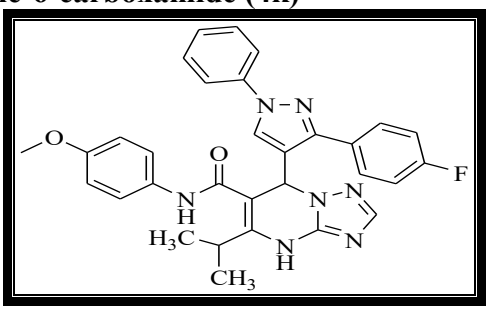


Yield: 70%; mp 199-201 ºC; Anal. Calcd. for $C_{30}H_{25}ClFN_7O$: C, 65.04; H, 4.55; N, 17.70. Found: C, 66.01; H, 4.65; N, 17.60 %; MS: m/z 554.

General procedure for the synthesis of 7-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,7-dihydro-5-isopropyl-N-(aryl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4k-t)

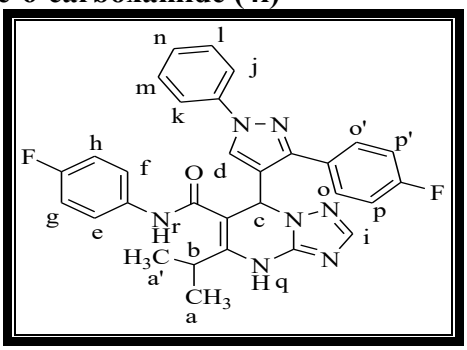
A mixture of the 5-amino-1,2,4-triazole (0.01 mol), 4-methyl-3-oxo-N-(aryl)pentanamide (0.01 mol) and 3-(4-fluorophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (0.01 mol) was refluxed in 0.4 mL of DMF for 12-15 min. After cooling, methanol (~10 mL) was added. The reaction mixture was allowed to stand overnight and then filtered to give the solid triazolopyrimidine products VP-41 to 50, which were crystallized from ethanol and subsequently dried in air.

7-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,7-dihydro-5-isopropyl-N-(4-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4k)



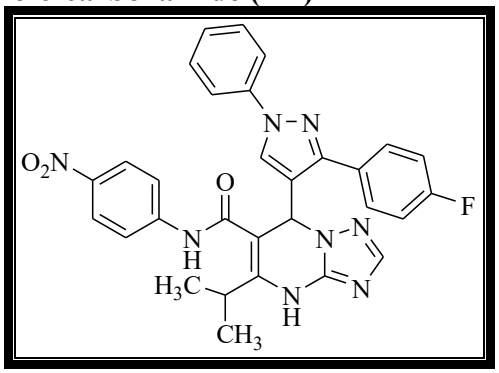
Yield: 73%; mp 246-248 ºC; Anal. Calcd. for $C_{31}H_{28}FN_7O_2$: C, 67.75; H, 5.14; N, 17.84. Found: C, 67.05; H, 5.04; N, 17.94%; MS: m/z 549;

N-(4-fluorophenyl)-7-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,7-dihydro-5-isopropyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4l)



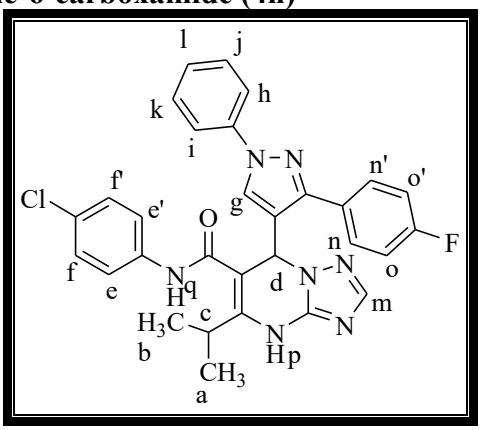
Yield: 85%; mp 232-234 ºC; Anal. Calcd. for $C_{30}H_{25}F_2N_7O$: C, 67.03; H, 4.69; N, 18.24. Found C, 66.04; H, 4.79; N, 18.14%; IR (cm^{-1}): 3159 (N-H stretching of secondary amine), 3099 (C-H stretching of aromatic ring), 3041 (C-H symmetrical stretching of CH_3 group), 2897 (C-H asymmetrical stretching of CH_3 group), 1664 (C=O stretching of amide), 1593 (C=N stretching of triazole ring), 1533 (N-H deformation of pyrimidine ring), 1512 and 1481 (C=C stretching of aromatic ring), 1417 (C-H asymmetrical deformation of CH_3 group), 1329 (C-H symmetrical deformation of CH_3 group), 1284 (C-N stretching), 1149 (C-O-C asymmetrical stretching of ether linkage), 1093 (C-O-C symmetrical stretching of ether linkage), 1035 (C-H in plane deformation of aromatic ring), 833 (C-H out of plane deformation of 1,4-disubstitution); MS: m/z 537; ^{1}H NMR (DMSO-d_6) δ ppm: 1.07-1.10 (t, 6H, $H_{aa'}$), 2.33-2.38 (m, 1H, H_b), 4.46 (s, 1H, H_c), 6.18 (s, 1H, H_d), 7.10-7.14 (t, 4H, H_{e-h}), 7.27-7.30 (t, 1H, H_i), 7.44-7.48 (m, 5H, H_{j-n}), 7.64-7.68 (m, 2H, $H_{oo'}$), 7.80-7.82 (d, 2H, $H_{pp'}$, J = 7.92 Hz), 8.29 (s, 1H, H_q), 9.40 (s, 2H, H_r).

7-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,7-dihydro-5-isopropyl-N-(4-nitrophenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4m)



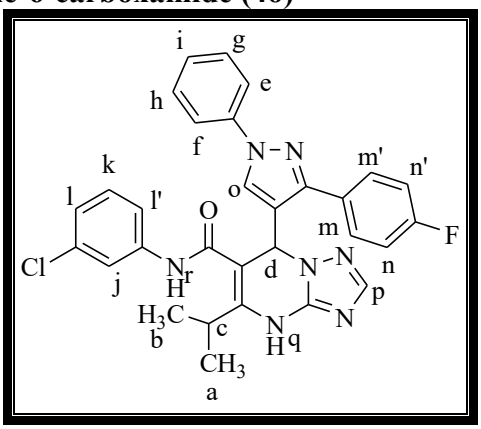
Yield: 78%; mp 250-252 ºC; Anal. Calcd. for $C_{30}H_{25}FN_8O_3$: C, 63.82; H, 4.46; N, 19.85. Found C, 63.52; H, 4.56; N, 19.65%; MS: m/z 564;

N-(4-chlorophenyl)-7-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,7-dihydro-5-isopropyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4n)



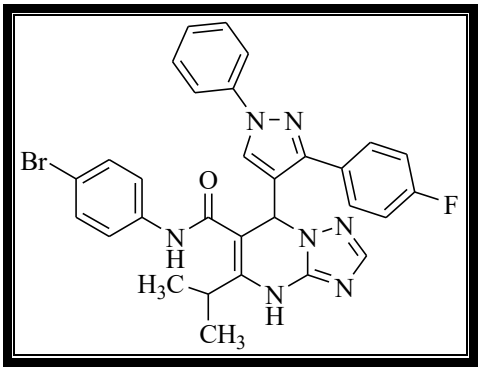
Yield: 72%; mp 250-252 ºC; Anal. Calcd. for $C_{30}H_{25}ClFN_7O$: C, 65.04; H, 4.55; N, 17.70. Found: C, 65.94; H, 4.45; N, 17.90%; MS: m/z 554; ^{1}H NMR (DMSO-d_6) δ ppm: 1.17-1.19 (d, 3H, H_a, J = 7.00 Hz), 1.27-1.28 (d, 3H, H_b, J = 6.88 Hz), 3.17-3.20 (t, 1H, H_c), 6.68 (s, 1H, H_d), 7.05-7.09 (t, 2H, $H_{ee'}$), 7.17-7.25 (t, 2H, $H_{ff'}$), 7.27 (t, 1H, H_g), 7.29-7.45 (m, 5H, H_{h-l}), 7.52 (s, 1H, H_m), 7.62-7.64 (t, 2H, $H_{nn'}$), 7.65-7.72 (t, 2H, $H_{oo'}$), 9.78 (s, 1H, H_p), 9.82 (s, 1H, H_q).

N-(3-chlorophenyl)-7-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,7-dihydro-5-isopropyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4o)



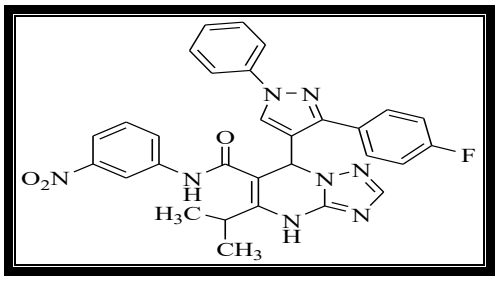
Yield: 76%; mp 216-218ºC; Anal. Calcd. for $C_{30}H_{25}ClFN_7O$: C, 65.04; H, 4.55; N, 17.70. Found C, 65.94; H, 4.25; N, 17.90%; MS: m/z 554; ^{1}H NMR (DMSO-d_6) δ ppm: 1.16-1.19 (d, 3H, H_a, J = 7.12 Hz), 1.27-1.28 (d, 3H, H_b, J = 6.88 Hz), 2.55-2.57 (m, 1H, H_c), 4.19 (s, 1H, H_d), 7.24-7.28 (m, 5H, H_{e-i}), 7.36-7.40 (t, 1H, H_j), 7.51-7.55 (t, 2H, $H_{ll'}$), 7.83 (s, 1H, H_k), 7.84-7.92 (m, 2H, $H_{mm'}$), 7.94-7.96 (d, 2H, $H_{nn'}$), 8.00 (s, 1H, H_o), 9.03 (s, 1H, H_p), 9.24 (s, 1H, H_q), 13.81 (s, 1H, H_r).

N-(4-bromophenyl)-7-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,7-dihydro-5-isopropyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4p)



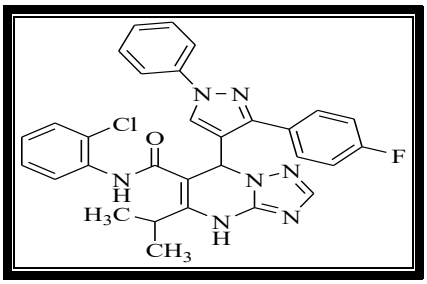
Yield: 66%; mp 240-242 ºC; Anal. Calcd. for $C_{30}H_{25}BrFN_7O$: C, 60.21; H, 4.21; N, 16.38. Found C, 61.01; H, 4.11; N, 16.48%; MS: m/z 598.

7-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,7-dihydro-5-isopropyl-N-(3-nitrophenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4q)



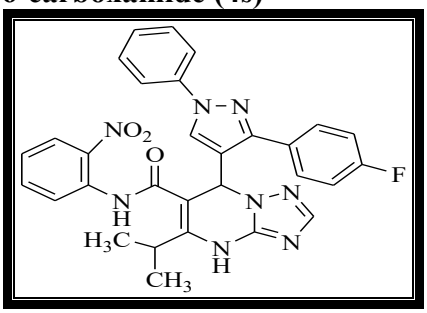
Yield: 78%; mp 233-235ºC; Anal. Calcd. for $C_{30}H_{25}FN_8O_3$: C, 63.82; H, 4.46; N, 19.85. Found: C, 63.12; H, 4.56; N, 19.65%. MS: m/z 564.

N-(2-chlorophenyl)-7-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,7-dihydro-5-isopropyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4r)



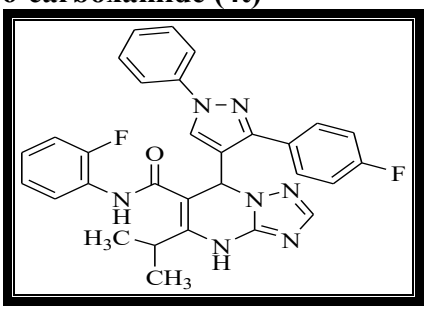
Yield: 71%; mp 190-192 ºC; Anal. Calcd. for $C_{30}H_{25}ClFN_7O$: C, 65.04; H, 4.55; N, 17.70. Found: C, 64.50; H, 4.35; N, 17.90%. MS: m/z 553.

7-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,7-dihydro-5-isopropyl-N-(2-nitrophenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4s)



Yield: 65%; mp 202-204 ºC; Anal. Calcd. for $C_{30}H_{25}FN_8O_3$: C, 63.82; H, 4.46; N, 19.85. Found: C, 64.02; H, 4.26; N, 19.65%. MS: m/z 564

N-(2-fluorophenyl)-7-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4,7-dihydro-5-isopropyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide (4t)



Yield: 79%; mp 236-238 ºC; MS: m/z 509; Anal. Calcd. for $C_{30}H_{25}F_2N_7O$: C, 67.03; H, 4.69; N, 18.24. Found C, 67.93; H, 4.79; N, 18.64%.

4. Antimicrobial evaluation

All of the synthesized compounds (4a-t) 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, 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, ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin and greseofulvin as standard drugs. The standard strains were procured from the Microbial Type Culture Collection (MTCC), Institute of Microbial Technology, Chandigarh, India. The minimal inhibitory concentration (MIC) values for all the newly synthesized compounds, defined as the lowest concentration of the compound preventing the visible growth, were determined by using micro dilution broth method according to NCCLS standards [12].

Table 2: Antibacterial and antifungal activity of synthesized compounds (4a-t)

Code	Minimum 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	500	>1000	100	500	250
4b	1000	500	1000	1000	500	500	100
4c	500	1000	1000	500	500	100	500
4d	62.5	100	250	125	1000	>1000	1000
4e	1000	500	500	1000	500	100	500
4f	100	125	500	500	250	500	100
4g	250	1000	1000	250	500	1000	1000

	4h	100	250	100	500	500	1000	1000
	4i	250	125	250	250	100	1000	250
	4j	62.5	100	100	250	250	500	250
	4k	1000	100	100	500	250	100	250
5.	4l	125	100	100	500	500	250	1000
	4m	500	500	1000	>1000	1000	500	125
	4n	125	100	50	250	500	1000	500
	4o	100	1000	250	1000	1000	500	1000
	4p	50	500	250	250	>1000	1000	>1000
	4q	500	1000	500	1000	500	500	100
	4r	125	25	100	100	500	>1000	500
	4s	125	500	500	250	100	1000	250
	4t	>1000	250	>1000	500	1000	1000	500
	Ampicillin	250	100	100	100	-	-	-
	Chloramphen.	50	50	50	50	-	-	-
	Ciprofloxacin	50	50	25	25	-	-	-
	Norfloxacin	10	10	10	10	-	-	-
	Nystatin	-	-	-	-	100	100	100
	Griseofulvin	-	-	-	-	500	100	100

Results and discussion

The biological importance of 1,2,4-triazolo[1,5-a]pyrimidines is well documented. Over the years, various substituted derivatives of these heterocycles have shown utility against a range of biological targets. For example, they have demonstrated activity against malaria and bronchospasm and shown activity as coronary vasodilators, antihypertensive agents, leishmanicides, antibiotics, adenosine A_{2a} antagonists, immunosuppressants, antitumor agents, fungicides, xanthine oxidase inhibitors, and phosphodiesterase inhibitors.

One of the synthetic pathways to 1,2,4-triazolo[1,5-a]pyrimidines is based on the Biginelli like cyclocondensation of aromatic aldehydes and acetoacetic acid derivatives with aminoazoles containing a guanidine fragment. There are literary data about the synthesis of triazolopyrimidines by treatment of 5-amino-1,2,4-triazole or 5-aminotetrazole with aldehydes and ethyl acetoacetate or cyclic β-diketones. The cyclocondensations were realized by heating of the starting materials in ethanol with catalytic amounts of hydrochloric acid under reflux conditions or using DMF as solvent. The use of acetoacetamides in these or similar reactions has not been described.

Recognizing these facts, we have synthesised four new series of 1,2,4-triazolo[1,5-a]pyrimidines (4a-t) containing an acetoacetamide fragment. The structures of all the newly synthesized compounds were elucidated by FT-IR, mass spectra, ^{1}H NMR and elemental analysis. The newly synthesized compounds were subjected to antimicrobial activitiy.

6. Conclusion

In this paper, we have synthesized diverse 1,2,4-triazolo[1,5-a]pyrimidines derivatives with potential antimicrobial activities. The observed activities follow a specific pattern according to substitution on phenyl ring. Thus the study contributes a lot to structure activity relationship of the synthesized 1,2,4-triazolo[1,5-a]pyrimidines derivatives.

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