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Chemistry and Biological Evaluation of Some New Triazolopyrimidine Derivatives Containing Isopropyl Group

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ABSTRACT

An efficient Synthesis of a novel series of **N,7-bis(substitutedphenyl)-4,7-dihydro-5-isopropyl-[1,2,4]triazolo-[1,5-a]pyrimidine-6-carboxamide** ***(4a-j)*** was accomplished from N-(substituedphenyl)-4-methyl-3-oxopentanamide, 3-amino-1,2,4-triazole and different aldehyde reflex 20 min with DMF and then after the cooling product was obtained. All the recently synthesized compounds were characterized by the Mass, IR, ^{1}H-NMR and mass spectroscopic techniques and by elemental analyses. The newly synthesized compounds were assessed for their antibacterial and antifungal activity.

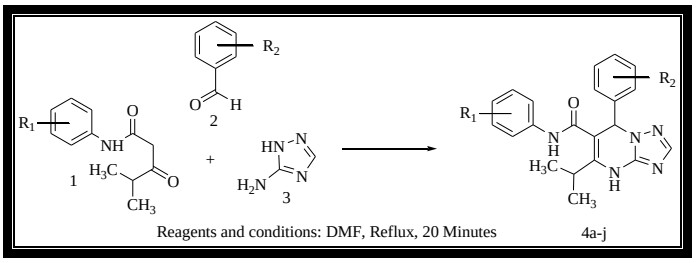
Keywords : 3-amino-1,2,4-triazole N-(substituedphenyl)-4-methyl-3-oxopentanamide and DMF.

I. INTRODUCTION

Nowdays there are various reserch in medical science in pharmasutical sector. cytotoxic drugs remains the main backbone for cancer treatment[1]. Drugs which affect DNA biosynthesis have received much attention and amongst them pyrimidine derivatives remain the most important[2]. Many pyrimidine incorporating compounds constitute an assortment of drugs which have pyrimidine nucleotides act effectively as naturalist metabolites, thus interfering in substantial cellular processes, for example nucleic acids synthesis.

Pyrimidinone Pyrimidinones type of compound are attractive claas of of pharmacologicaly active compounds are present a class of such compounds attracting much interest because of their interesting pharmacological properties, as antitumor[3], antiviral[4], anti-parkinsonism[5] and antimicrobial[6] agents in addition to their application as building blocks for synthesizing new molecules[7]. A variety of pyrimidine derivatives fused with other heterocyclic has been found as anticancer agents used in clinics or in clinical trials[8,9,10]. Derivatives of the [1, 2, 4] triazolo[4,3-a]pyrimidine ring system have been revealed to possess antitumor activity[11,12,13]. On the other hand, a number of glycosides were investigated and have shown high anticancer activity[14].

REACTION SCHEME



II. EXPERMENTAL DETAIL

TYPICAL UNTRIED PROCEDURE

A mixture of the 3-amino-1,2,4-triazole (0.01 M), N-(substituedphenyl)-4-methyl-3-oxopentanamide (0.01 M) and an appropriate aromatic aldehydes (0.01 M) was refluxed in DMF (4 ml) for 20 min. After cooling,

methanol (~10 ml) was added. after overnight cooling, the reaction mixture is filtered to obtain triazolopyrimidine product (4a-j) and this product is further recrystallized by ethyl alcohol.

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

Yield: 66%; mp 202ºC; Anal. Calcd. for $C_{21}H_{19}Cl_2N_5O$: C, 58.89; H, 4.47; Cl, 16.55; N, 16.35; O,3.74. Found: C, 58.79; H, 4.37; Cl, 16.33; N, 16.24; O,3.66%; IR (cm^{-1}): 3344 (N-H stretching of secondary amine), 3070 (C-H stretching of aromatic ring), 2901 (C-H asymmetrical stretching of CH_3 group), 2802 (C-H asymmetrical stretching of CH_3 group), 1687 (C=O stretching of amide), 1599 (C=N stretching of triazole ring), 1531 (N-H deformation of pyrimidine ring), 1492 (C=C stretching of aromatic ring), 1381 (C-H asymmetrical deformation of CH_3 group), 1309 (C-H symmetrical deformation of CH_3 group), 1247(C-N stretching), 1093 (C-H in plane deformation of aromatic ring), 833 (C-H out of plane bending of 1,4-disubstituion), 661 (C-Cl stretching); MS: *m/z* 428; ^{1}H NMR (DMSO-d_6) δ ppm: 1.15-117 (d, 3H, H_a, *J* = 10.00 Hz), 1.25-1.27 (d, 3H, H_b, *J* = 6.80 Hz), 3.20-3.27 (m, 1H, H_c), 6.50 (s, 1H, H_d), 7.12-7.16 (m, 2H, $H_{ee'}$), 7.21-7.25 (m, 2H, $H_{ff'}$, *J* = 14.00 Hz), 7.29-7.32 (d, 2H, $H_{gg'}$, *J* = 8.80 Hz), 7.49-7.52 (d, 2H, $H_{hh'}$, *J* = 8.80 Hz), 7.66 (s, 1H, H_i), 10.02 (s, 1H, H_j),10.09 (s, 1H, H_k).

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

Yield: 69%; mp 181ºC; Anal. Calcd. for $C_{21}H_{19}Cl_2N_5O$: C, 58.89; H, 4.47; Cl, 16.55; N, 16.35; O, 3.74; Found: C, 58.79; H, 4.37; Cl, 16.33; N, 16.24; O, 3.66%; IR (cm^{-1}): 3383 (N-H stretching of secondary amine), 3030 (C-H stretching of aromatic ring), 2970 (C-H asymmetrical stretching of CH_3 group), 2872 (C-H asymmetrical stretching of CH_3 group), 1674 (C=O stretching of amide), 1550 (C=N stretching of triazole ring), 1519 (N-H deformation of pyrimidine ring), 1492 (C=C stretching of aromatic ring), 1402 (C-H asymmetrical deformation of CH_3 group), 1342 (C-H symmetrical deformation of CH_3 group), 1244 (C-N stretching), 1138 (C-H in plane deformation of aromatic ring), 827(C-H out of plane bending of 1,4-disubstituion), 661 (C-Cl streching); MS: *m/z* 407; ^{1}H NMR (DMSO-d_6) δ ppm: 1.00-119 (d, 3H, H_a), 1.25-1.27 (d, 3H, H_b, *J* = 6.80 Hz),2.22 (s, 3H, H_c) 3.24-3.30 (m, 1H, H_d), 6.47 (s, 1H, H_e), 7.05-7.10 (m, 4H, $H_{ff'-gg'}$), 7.29-7.31 (d, 2H, $H_{hh'}$, *J* = 8.40 Hz), 7.53-7.55 (d, 2H, $H_{ii'}$, *J* = 8.40 Hz), 7.64 (s, 1H, H_j), 9.96 (s, 1H, H_k) 10.09 (s, 1H, H_l).

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

Yield: 78%; mp 257ºC; Anal. Calcd. for $C_{22}H_{22}ClN_5O_2$: C, 62.34; H, 5.23; Cl, 8.36; N, 16.52; O, 7.55; Found: C, 62.22; H, 5.00; Cl, 8.20; N, 16.40; O, 7.42%; IR (cm^{-1}): 3292 (N-H stretching of secondary amine), 3070 (C-H stretching of aromatic ring), 2994 (C-H asymmetrical stretching of CH_3 group), 2868 (C-H asymmetrical stretching of CH_3 group), 1631 (C=O stretching of amide), 1593 (C=N stretching of triazole ring), 1558 (N-H deformation of pyrimidine ring), 1491 (C=C stretching of aromatic ring), 1398 (C-H asymmetrical deformation of CH_3 group), 1342 and 1303 (C-NO_2 stretching), 1300 (C-H symmetrical deformation of CH_3 group), 1244 (C-O-C asymmetrical stretching of OCH_3), 1236 (C-N stretching), 1206 (C-O-C asymmetrical stretching of OCH_3), 1033 (C-H in plane deformation of aromatic ring), 1012 (C-O-C symmetrical stretching of OCH_3), 825 (C-H out of plane bending of 1,4-disubstituion), 661 (C-Cl stretching); MS: *m/z* 423;^{1}H NMR (DMSO-d_6) δ ppm: 1.12-1.17 (d, 3H, H_a), 1.28-1.29 (d, 3H, H_b, *J* = 6.80 Hz), 3.29-3.31 (m, 1H, H_c, *J* = 7.20 Hz), 3.68 (s, 3H, H_d) 6.50 (s, 1H, H_e), 6.84-6.87 (d, 2H, $H_{ff'}$, *J* = 8.80 Hz), 7.13-7.15 (d, 2H, $H_{gg'}$, *J* = 8.40 Hz), 7.54-7.58 (d, 1H, H_h, *J* = 8.40 Hz), 7.65 (s, 1H, H_i), 7.85-7.89 (m, 2H, H_{jk}) 8.54 (s, 1H, H_l) 10.03 (s, 1H, H_m) 10.41 (s, 1H, H_n).

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

Yield: 70%; mp 222ºC; Anal. Calcd. for $C_{21}H_{19}ClN_6O_3$: C, 57.47; H, 4.36; Cl, 8.08; N, 19.15; O, 10.94; Found: C, 57.35; H, 4.25; Cl, 8.01; N, 19.00; O, 10.86%; MS: m/z 438.

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

Yield: 81%; mp 261ºC; Anal. Calcd. for $C_{21}H_{19}ClFN_5O$: C, 61.24; H, 4.65; Cl, 8.61; F, 4.61; N, 17.00; O, 3.88; Found: C, 61.14; H, 4.54; Cl, 8.45; F, 4.50; N, 16.89; O, 3.75; MS: m/z 411.

N-(4-chlorophenyl)-4,7-dihydro-5-isopropyl-7-(3-nitrophenyl)- [1,2,4] triazo- lo[1,5-a] pyrimidine-6-carboxamide (4f)

Yield: 71%; mp 201ºC; Anal. Calcd. for $C_{21}H_{19}ClN_6O_3$: C, 57.47; H, 4.36; Cl, 8.08; N, 19.15; O, 10.94; Found: C, 57.35; H, 4.25; Cl, 8.01; N, 19.00; O, 10.86%; MS: m/z 438.

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

Yield: 59%; mp 244ºC; Anal. Calcd. for $C_{21}H_{19}Cl_2N_5O$: C, 58.89; H, 4.47; Cl, 16.55; N, 16.35; O, 3.74; Found: C, 58.74; H, 4.34; Cl, 16.45; N, 16.24; O, 3.64%; MS: m/z 428.

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

Yield: 64%; mp 216ºC; Anal. Calcd. for $C_{21}H_{19}ClN_6O_3$: C, 57.47; H, 4.36; Cl, 8.08; N, 19.15; O, 10.94; Found: C, 57.33; H, 4.23; Cl, 8.00; N, 19.05; O, 10.88%; MS: m/z 438.

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

Yield: 67%; mp 199 ºC; Anal. Calcd. for $C_{21}H_{20}ClN_5O_2$: C, 61.54; H, 4.92; Cl, 8.65; N, 17.09; O, 7.81; Found: C, 61.35; H, 4.85; Cl, 8.53; N, 17.00; O, 7.71%; MS: m/z 409.

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

Yield: 70%; mp 183ºC; Anal. Calcd. for $C_{21}H_{19}BrClN_5O$: C, 53.35; H, 4.05; Br, 16.90; Cl, 7.50; N, 14.81; O, 3.38; Found: C, 53.13; H, 4.00; Br, 16.81; Cl, 7.41; N, 14.72; O, 3.23%; MS: m/z 472.

III. ANTIMICROBIAL ACTIVITY

Biological evaluation of synthesized Indole-3-yl-glyoxylamide derivatives.

All of the synthesized compounds were tested for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method[15-17]with two Gram-positive bacteria *Streptococcus pyogenes* MTCC 442 and *Staphylococcus aureus* MTCC-96 and two Gram-negative bacteria *Escherichia coli* MTCC 443 and *Pseudomonas aeruginosa* MTCC 1688 and three fungal strains *Aspergillus Niger* MTCC 282 *Candida albicans* MTCC 227 and *Aspergillus clavatus* MTCC1323.here we are *Candida albicans* MTCC 227 here we are taking ampicillin ,nystatin ,narfloxacine this method is, gentamycin chloramphenicol, ciprofloxacin, norfloxacin, nystatin and greseofulvin as standard drugs. This all strains are collected from MTCC.

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.[21]

Minimal Inhibition Concentration [MIC]

The important benefit of **Broth Dilution Method** is that it can easily convertible too MIC Serial dilutions were prepared in primary and secondary screening.

1. 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.
2. The MIC of the control organism is read to check the accuracy of the drug concentrations.
3. The lowest concentration inhibiting growth of the organism is recorded as the MIC.
4. The amount of growth from the control tube before incubation (which represents the original 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 set to 10^8 cfu (colony forming unit) per milliliter fot test.this is done by comparing the turbidity of tubes.

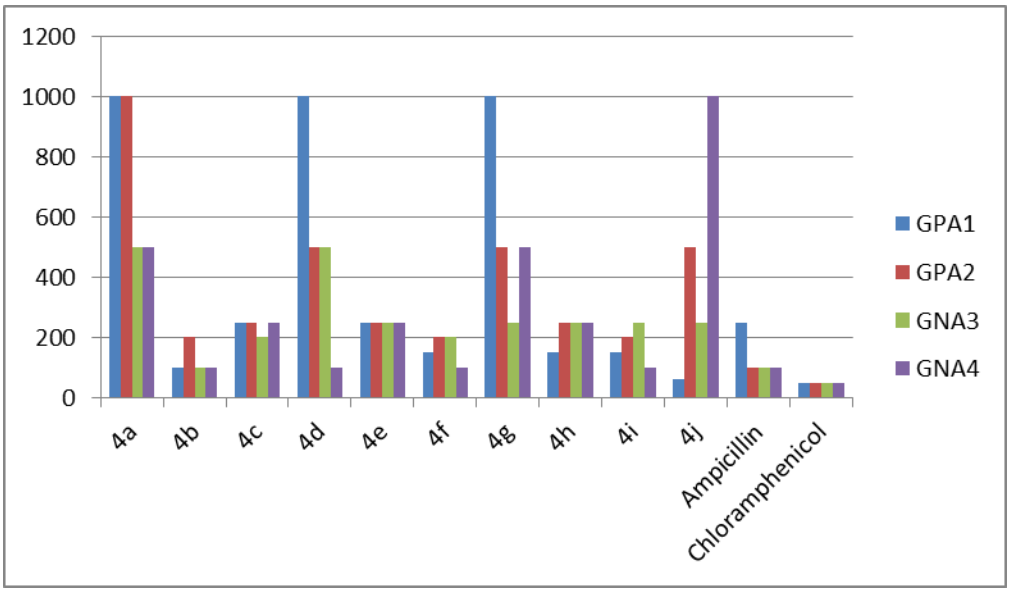
Primary screen: In primary screening 1000 µg mL^{-1}, 500 µg mL^{-1} and 250 µg mL^{-1} concentrations of the synthesized compounds were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms.

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.

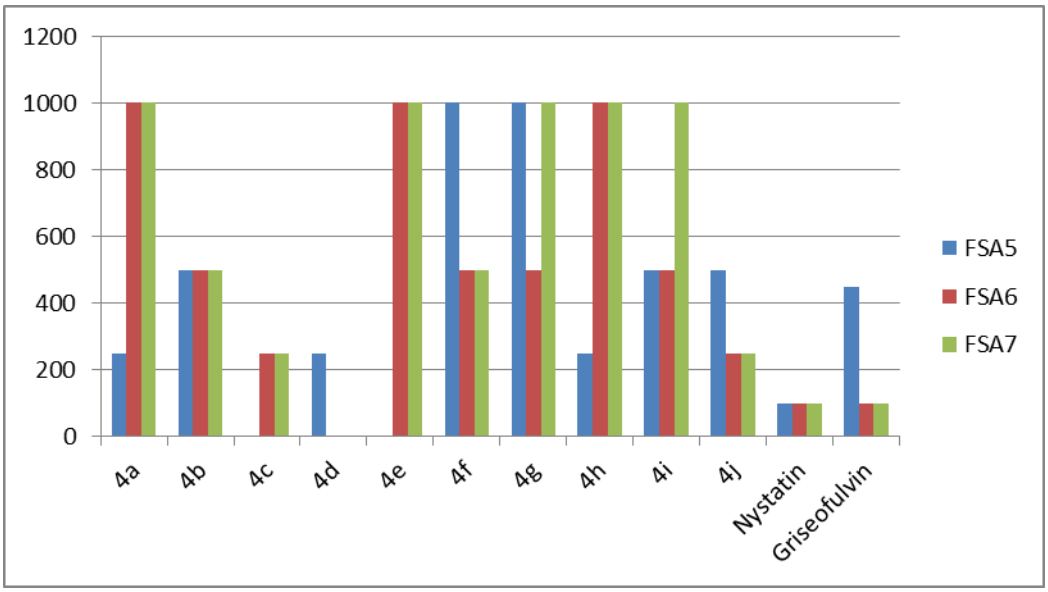
Reading Result: MIC is the inhibition zone which is created by hughest dilution taken . The result of this is much affected by the size of the inoculums. The test mixture should contain 10^8 organism/mL.

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

Compound	Minimal inhibition concentration (µg mL^{-1})			
	Gram-positive		Gram-negative	
	GPA1	GPA2	GNA3	GNA4
4a	1000	1000	500	500
4b	100	200	100	100
4c	250	250	200	250
4d	1000	500	500	100
4e	250	250	250	250
4f	150	200	200	100
4g	1000	500	250	500
4h	150	250	250	250
4i	150	200	250	100
4j	62.5	500	250	1000
Ampicillin	250	100	100	100
Chloramphenicol	50	50	50	50
	Staphylococcus aureus	GPA1		
	Streptococcus pyogenes	GPA2		
	Escherichia coli	GNA3		
	Pseudomonas aeruginosa	GNA4		



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



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