ARTICLE

A Rapid One-Pot Synthesis and Biological Evaluation of Novel 1,2,4-Triazolo[1,5-*a*]-pyrimidines

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ABSTRACT

The synthesis of 10 novel 1,2,4-triazolo[1,5-*a*]pyrimidine derivatives have been undertaken by involving Biginelli type three components reaction of 1-phenyl-3-aryl-1*H*-pyrazole-4-carbaldehydes, 3-amino-1,2,4-triazole and ethyl acetoacetate in DMF. The structure of all the compounds have been established by IR, FT-IR, ^{1}H NMR, ^{13}C NMR, mass spectra and elemental analyses. The antimicrobial activity against *S. aureus* MTCC-96 (Gram positive), *E. coli* MTCC-443 (Gram negative) and antifungal activity against *A. niger* MTCC-282 and *C. albicans* MTCC-227 at different concentrations using micro-dilution broth method according to NCCLS standards. The antimicrobial activity was compared with ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin and greseofulvin as standard drugs at same different concentration. The compounds such as **A-2**, **A-4**, **A-5**, **A-6**, **A-8**, **A-9**, **A-10** showed moderate antibacterial activity against *Staphylococcus aureus* (Gram positive) at the concentration of 250, 100, 250, 200, 250, 250, 250 µg/mL while compounds **A-3** and **A-6** showed remarkable antibacterial activity against *Streptococcus pyogenes* (Gram positive) at the concentration of 100 µg/mL. Moreover, the compounds **A-3** and **A-9**, found to be potent against *Escherichia coli* (Gram negative) at the concentration of 62.5, 62.5 (µg/mL) and against *Pseudomonas aeruginosa* (Gram negative) with the concentration of 100 µg/mL.

KEYWORDS

1,2,4-Triazolo[1,5-*a*]pyrimidines, 3-amino-1,2,4-triazole, Biological screening, Biginelli reaction.

INTRODUCTION

1,2,4-Triazoles derivatives have been investigated as anticonvulsants [1], 5-lipoxygenase inhibitors [2] and as anticancer drugs [3]. Rizatriptan containing 1,2,4-triazoles moiety used as agents for acute treatment of migraine headaches are commercially available drugs [4]. However, they are also still a topic of intensive research [5]. Purine analogs are widely used against various diseases like cancer. The clinical application of 6-mercaptopurine [6] and thioguanine [7] in cancer treatment and the development of potent purine based CDK inhibitors. Pyrimidines mainly use in pharmacology as a anticancer, anti-HIV and antituberculoses and also exhibit pharmacological activities such as CNS depressant [8], neuroleptic [9] and turberculostatic [10].

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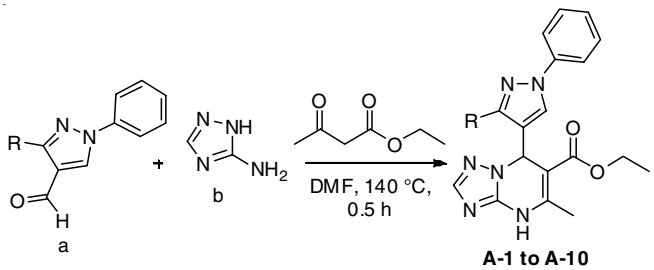
[1,2,4]triazolo[1,5-*a*]pyrimidines, a sub-type of purine bioisosteric analogs, were also reported to possess potential antitumor activities. Polycyclic systems containing [1,2,4]triazolo-[1,5-*a*]pyrimidine moiety are reported as antitumor [11], as corticotrophin releasing factor 1 receptor antagonists [12] or calcium channel modulators [13]. They can be used for treatment of Alzheimer's disease [14] and insomnia [15]. The aim of incorporating, 3-amino-1,2,4-triazole ring with pyrimidines can be justified by their various biological activity such as antitumor potency [16,17], inhibition of KDR kinase [18], antifungal effect [19] and macrophage activation [14]. From the standpoint of biological activity, fused heteroaromatic system [1,2,4]triazolo[1,5-*a*]pyrimidines, are often of much greater interest than the constituent monocyclic compounds. The synthesis of 1,2,4-triazolo[1,5-*a*]pyrimidine derivatives have been undertaken by involving Biginelli type three components reaction of 1-phenyl-3-aryl-1*H*-pyrazole-4-carbaldehydes, 3-amino-1,2,4-triazole and ethyl acetoacetate in DMF.

EXPERIMENTAL

All the chemicals were purchased from Sigma-Aldrich and used as such. Reactions were monitored by thin-layer chromatography (TLC) on precoated silica gel GF_{254} plates from E-Merck Co. and compounds visualized either by exposure to UV. Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on SHIMADZU-FTIR-8400 spectrophotometer using KBr pellet method. ^1H and ^{13}C NMR spectra were recorded on Bruker 300-MHz NMR spectrometer in $CDCl_3$ with TMS as internal standard. Mass spectrum was recorded on JOEL SX 102/DA-600-Mass spectrometer and elemental analysis was carried out using Heraus C,H,N rapid analyzer.

All the compounds *i.e.*, ethyl 4,7-dihydro-5-methyl-7-(1-phenyl-3-aryl-1*H*-pyrazol-4-yl)-[1,2,4]triazolo-[1,5-*a*]-pyrimidine-6-carboxylates (**A-1** to **A-10**) were synthesized by multi-component Biginelli type three components reaction of 1-phenyl-3-aryl-1*H*-pyrazole-4-carbaldehydes (a), 3-amino-1,2,4-triazole (b) and ethyl acetoacetate (c) in DMF (**Scheme-I**). Designed mole-cules series (Table-1) were characterized by ^1H NMR, ^{13}C NMR and mass spectrometry techniques and their purity were checked by elemental analysis.

Synthesis of 1-phenyl-3-aryl-1*H*-pyrazole-4-carbaldehyde (**a**) was achieved by known literature method.



where, **A1** = 4-NO_2-C_6H_5, **A2** = 3-NO_2-C_6H_5
A3 = 4-Cl-C_6H_5, **A4** = 4-OCH_3-C_6H_5
A5 = 4-CH_3-C_6H_5, **A6** = 4-F-C_6H_5
A7 = 4-Br-C_6H_5, **A8** = C_6H_5
A9 = 2-OCH_3-C_6H_5, **A10** = 2,4-di-Cl-C_6H_4

Scheme-I

General procedure for synthesis of ethyl 4,7-dihydro-5-methyl-7-(1-phenyl-3-aryl-1*H*-pyrazol-4-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylate (A-1 to A-10): A mixture of 1-phenyl-3-aryl-1*H*-pyrazole-4-carbaldehyde (**a**) (0.01 mol), 3-amino-1,2,4-triazole (**b**) (0.01 mol) and ethyl acetoacetate (**c**) (0.01 mol)/cyclohexane-1,3-dione (0.01 mol)/dimedone (0.01 mol) was refluxed in 1 mL of DMF for 30 min. After cooling, methanol (~10 mL) was added and the reaction mixture was allowed to stand overnight and then filtered the solid products (**A-1** to **A-10**), which were crystallized from ethanol and subsequently dried in air.

Antimicrobial activity: All the synthesized compounds (**A-1** to **A-10**) were tested 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 ampicillin, chloramphenicol, nystatin, ciprofloxacin, norfloxacin and greseofulvin as standard drugs. The standard strains were procured from the Microbial Type Culture Collection (MTCC) and Gene Bank, 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 [14]. Serial dilutions of the test compounds and reference drugs were prepared in Mueller-Hinton

TABLE-1
ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY OF SYNTHESIZED COMPOUNDS **A-1** TO **A-10**

Compd.	Minimum inhibition concentration (µg/mL)						
	Gram-positive		Gram-negative		Fungal species		
	S. aureus	*S. pyogenes*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*	*A. clavatus*
A-1	500	250	500	500	1000	1000	1000
A-2	250	500	500	500	200	500	250
A-3	500	100	62.5	100	1000	500	> 1000
A-4	100	500	500	1000	250	500	500
A-5	250	250	250	250	> 1000	500	1000
A-6	200	100	> 1000	500	1000	1000	250
A-7	500	500	1000	1000	1000	1000	1000
A-8	250	500	500	500	250	> 1000	> 1000
A-9	250	500	62.5	500	1000	500	500
A-10	250	500	250	500	1000	500	> 1000

agar. Drugs (10 mg) were dissolved in DMSO (1 mL). Further progressive dilutions with melted Mueller-Hinton agar were performed to obtain the required concentrations. In primary screening 1000, 500 and 250 μg mL^{-1} concentrations of the synthesized drugs were taken. The compounds found active in this primary screening were further tested in a second set of dilution at 200, 100, 50, 25, 12.5 and 6.25 μg mL^{-1} concentration against all microorganisms. The tubes were inoculated with 10^8 cfu mL^{-1} (colony forming unit/mL) and incubated at 37 ºC for 24 h. The MIC was the lowest concentration of the tested compound that yields no visible growth (turbidity) on the plate. To ensure that the solvent had no effect on the bacterial growth, a control was performed with the test medium supplemented with DMSO at the same dilutions as used in the experiments and it was observed that DMSO had no effect on the microorganisms in the concentrations studied. The antimicrobial activity of A-1 to A-10 is reported in Table-1.

Spectral data

Ethyl 4,7-dihydro-5-methyl-7-(3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylate (A-1): Yield: 70 %; m.p. 188 ºC, m.f. $C_{24}H_{21}N_7O_4$, m.w. 471, R_f: 0.57; IR (KBr, ν_{max}, cm^{-1}): 3122 (N-H *str*.), 3022 (C-H *str*. arom. ring), 2970, 2858 (C-H *str*. alkane), 1739 (C=O *str*. carbonyl of ester), 1674 (C=N *str*.), 1587, 1415 (C=C *str*. arom. ring), 1506 (C-NO_2 *str*.), 1363, 1292, 1259 (C-H bend. alkane), 1330 (C-NO_2 bend.), 1259 (C-O *str*.), 1068 (C-O-C *str*.), 794 (C-H bend. *p*-disubstituted arom. ring), 688 (C-H bend. five adj. H-atom of mono substituted arom. ring); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 0.800-0.836 (t, 3H, H_a), 2.413 (s, 3H, H_b), 3.774-3.923 (m, 2H, $H_{cc'}$), 6.546 (s, 1H, H_d), 7.322-7.359 (t, 1H, H_e, *J* = 7.4 Hz), 7.481-7.520 (t, 2H, $H_{ff'}$, *J* = 7.8 Hz), 7.733 (s, 1H, H_g), 7.907-7.927 (d, 2H, $H_{hh'}$, *J* = 8 Hz), 8.235-8.256 (d, 2H, $H_{ii'}$, *J* = 8.4 Hz), 8.390-8.412 (d, 2H, $H_{jj'}$, *J* = 8 Hz), 8.641 (s, 1H, H_k), 10.836 (s, 1H, H_l); ^{13}C NMR (DMSO-d_6, 400 MHz) δ ppm: 13.70, 18.56, 50.44, 59.17, 96.66, 118.39, 123.76, 125.16, 126.80,128.91, 129.26, 129.48, 138.92, 139.37, 146.50, 146.73, 147.03, 148.57, 150.12, 165.00; MS: *m/z* 471; Anal. (%) calcd. (found) for $C_{24}H_{21}N_7O_4$: C, 61.14 (61.27); H, 4.49 (4.56); N, 20.80 (21.03).

Ethyl 4,7-dihydro-5-methyl-7-(3-(3-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylate (A-2): Yield: 65 %; m.p. 216 ºC, m.f. $C_{24}H_{21}N_7O_4$, m.w. 471, R_f: 0.45; IR (KBr, ν_{max}, cm^{-1}): 3129 (N-H *str*.), 3033 (C-H *str*. arom. ring), 2970, 2858 (C-H *str*. alkane), 1739 (C=O *str.* carbonyl of ester), 1674 (C=N *str*.), 1587, 1415 (C=C *str*. arom. ring), 1506 (C-NO_2 *str*.), 1363, 1278, 1259 (C-H bend. alkane), 1339 (C-NO_2 bend.), 1259 (C-O *str*.), 1068 (C-O-C *str*.), 698-723 (C-H bend. *m*-disubstituted arom. ring), 695 (C-H bend. five adj. H atom of monosubstituted arom. ring); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 1.201-1.410 (t, 3H, H_a), 2.301 (s, 3H, H_b), 3.891-4.101 (m, 2H, $H_{cc'}$), 5.931 (s, 1H, H_d), 7.322-7.359 (t, 1H, H_e, *J* = 7.4 Hz), 7.481-7.520 (t, 2H, $H_{ff'}$, *J* = 7.8 Hz), 7.721 (s, 1H, H_g), 7.901-7.933 (d, 2H, $H_{hh'}$, *J* = 8 Hz), 8.231-8.256 (d, 2H, $H_{ii'}$, *J* = 8.4 Hz), 8.390-8.412 (d, 2H, $H_{jj'}$, *J* = 8 Hz), 8.741 (s, 1H, H_k), 11.121 (s, 1H, H_l); ^{13}C NMR (DMSO-d_6, 400 MHz) δ ppm: 13.91, 17.41, 53.01, 60.72, 102.66, 114.19, 120.04, 127.01, 128.39, 129.91, 130.26, 138.48, 139.92, 143.37, 145.50, 146.73, 147.03, 148.57, 150.12, 166.00; MS: *m/z* 471.17; Anal. (%) calcd. (found) for $C_{24}H_{21}N_7O_4$: C, 61.14 (61.27); H, 4.49 (4.56); N, 20.80 (21.03).

Ethyl 4,7-dihydro-5-methyl-7-(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylate (A-3): Yield: 77 %; m.p. 164 ºC, m.f. $C_{24}H_{21}N_6O_2Cl$, m.w. 460, R_f: 0.41; IR (KBr, ν_{max}, cm^{-1}): 3125 (N-H *str*.), 3016 (C-H *str*. arom. ring), 2890, 2858 (C-H *str*. alkane), 1749 (C=O *str*. carbonyl of ester), 1675 (C=N str.), 1557, 1415 (C=C *str*. arom. ring), 790-600 (C-Cl *str*.), 1363, 1292, 1259 (C-H bend. alkane), 1210 (C-Cl bend.), 1259 (C-O *str*.), 1068 (C-O-C *str*.), 762 (C-H bend. *p*-disubstituted arom. ring), 691 (C-H bend. five adj. H-atom of mono substituted arom. ring); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 0.991-1.012 (t, 3H, H_a), 2.164 (s, 3H, H_b), 3.929-4.014 (m, 2H, $H_{cc'}$), 5.916 (s, 1H, H_d), 7.422-7.442 (t, 1H, H_e, *J* = 8.4 Hz), 7.489-7.526 (t, 2H, $H_{ff'}$, *J* = 7.9 Hz), 7.431 (s, 1H, H_g), 7.520-7.541 (d, 2H, $H_{hh'}$, *J* = 8.2 Hz), 8.336-8.358 (d, 2H, $H_{ii'}$, *J* = 8.4 Hz), 8.398-8.418 (d, 2H, $H_{jj'}$, *J* = 8.2 Hz), 9.123 (s, 1H, H_k), 11.421 (s, 1H, H_l); ^{13}C NMR (DMSO-d_6, 400 MHz) δ ppm: 14.41, 16.81, 52.29, 60.28, 99.03, 119.06, 120.16, 123.91, 126.20, 129.26, 129.98, 133.83, 139.71, 143.81, 147.29, 151.23, 156.03, 165.03; MS: *m/z* 460.14; Anal. (%) calcd. (found) for $C_{24}H_{21}N_6O_4Cl$: C, 62.54 (62.27); H, 4.59 (4.56); N, 18.23 (19.25).

Ethyl 4,7-dihydro-7-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylate (A-4): Yield: 68 %; m.p. 174 ºC, m.f. $C_{25}H_{24}N_6O_3$, m.w. 456, R_f: 0.59; IR (KBr, ν_{max}, cm^{-1}): 3120 (N-H *str*.), 3022 (C-H *str*. arom. ring), 2970, 2845 (C-H *str*. alkane), 1737 (C=O *str*. carbonyl of ester), 1670 (C=N *str*.), 1558, 1527, 1456 (C=C *str*. arom. ring), 1365, 1328, 1288 (C-H bend. alkane), 1255 (C-O *str*.), 1064 (C-O-C *str*.), 790 (C-H bend. *p*-disubstituted arom. ring), 686 (C-H bend. five adj. H-atom of mono substituted arom. ring); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 0.818-0.851 (t, 3H, H_a), 2.424 (s, 3H, H_b), 3.839-3.893 (t, 5H, H_{cd}), 6.489 (s, 1H, H_e), 7.087-7.106 (d, 2H, $H_{ff'}$, *J* = 7.6 Hz), 7.265-7.298 (t, 1H, H_g, *J* = 6.6 Hz), 7.447-7.483 (t, 2H, $H_{hh'}$, *J* = 7.2 Hz), 7.745 (s, 1H, H_i), 7.879-7.933 (q, 4H, $H_{jj'kk'}$), 8.509 (s, 1H, H_l), 10.644-10.695 (d, 1H, H_m); ^{13}C NMR (DMSO-d_6, 400 MHz) δ ppm: 13.66, 18.49, 50.70, 55.09, 59.06, 97.13, 113.79, 117.99, 124.17, 125.20, 126.10, 127.96, 129.34, 129.61, 139.22, 146.31, 149.61, 149.92, 150.71, 159.20, 165.08; MS: *m/z* 456; Anal. (%) calcd. (found) for $C_{25}H_{24}N_6O_3$: C, 65.78 (65.92); H, 5.30 (5.43); N, 18.41 (18.58).

6,7-Dihydro-9-(1-phenyl-3-*p*-tolyl-1*H*-pyrazol-4-yl)-[1,2,4]triazolo[5,1-*b*]quinazolin-8(4*H*,5*H*,9*H*)-one (A-5): Yield: 75 %; m.p. 143 ºC, m.f. $C_{25}H_{24}N_6O_2$, m.w. 440, R_f: 0.56; IR (KBr, ν_{max}, cm^{-1}): 3248 (N-H *str*.), 3028 (C-H *str*. arom. ring), 2910 (C-H *str*. alkane), 1722 (C=O *str.* carbonyl of cyclic ketone), 1643 (C=N *str*.), 1575, 1504, 1452, 1411 (C=C *str*. arom. ring), 1357, 1336 (C-H bend. alkane), 1263 (C-O *str*.), 827 (C-H bend. *p*-disubstituted arom. ring), 692 (C-H bend. five adj. H-atom of monosubstituted aromatic ring); ^{1}H NMR (DMSO-d_6) δ ppm: 1.919 (bs, 2H, H_a), 2.202-2.222 (d, 2H, H_b), 2.386 (s, 3H, H_c), 2.587 (bs, 2H, H_d),6.394 (s, 1H, H_e), 7.290-7.309 (d, 3H, $H_{ff'f''}$, *J* = 7.6 Hz), 7.446-7.484 (t, 2H, $H_{gg'}$, *J* =7.6 Hz), 7.700 (s, 1H, H_h), 7.784-7.802 (d, 2H, $H_{ii'}$, *J* = 7.2 Hz), 7.840-7.859 (d, 2H, $H_{jj'}$, *J* = 7.6 Hz), 8.498 (s, 1H, H_k), 11.077 (s, 1H,

H_l); ^{13}C NMR (DMSO-d_6) δ ppm: 20.47, 24.47, 26.48, 36.30, 49.13, 106.51, 118.19, 119.10, 123.83, 126.36, 127.45, 128.76, 129.66, 130.47, 138.72, 139.11, 146.13, 149.74, 149.89, 152.20, 193.47; MS: *m/z* 422; Anal. (%) calcd. (found) for $C_{25}H_{22}N_6O$: C, 71.07 (70.92); H, 5.25 (5.37); N, 19.89 (20.08).

Ethyl 4,7-dihydro-5-methyl-7-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylate (A-6): Yield: 64 %; m.p. 205 ºC, m.f. $C_{24}H_{21}N_6O_2F$, m.w. 444, R_f: 0.61; IR (KBr, ν_{max}, cm^{-1}): 3042 (N-H *str*.), 3022 (C-H *str*. arom. ring), 2870, 2857 (C-H *str*. alkane), 1737 (C=O *str.* carbonyl of ester), 1675 (C=N *str*.), 1578, 1415 (C=C *str*. arom. ring), 1360-1102 (C-F *str*.), 1363, 1292, 1259 (C-H bend. alkane), 1430 (C-F bend.), 1259 (C-O *str*.), 1068 (C-O-C *str*.), 768 (C-H bend. *p*-disubstituted arom. ring), 693 (C-H bend. of five adj. H-atom of monosubstituted arom. ring); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 0.913-0.923 (t, 3H, H_a), 2.260 (s, 3H, H_b), 3.774-3.923 (m, 2H, $H_{cc'}$), 6.107 (s, 1H, H_d), 7.320-7.341 (t, 1H, H_e, *J* = 7.6 Hz), 7.449-7.467 (t, 2H, $H_{ff'}$, *J* = 7.8 Hz), 7.692 (s, 1H, H_g), 7.317-7.339 (d, 2H, $H_{hh'}$, *J* = 8 Hz), 8.0.21-8.061 (d, 2H, $H_{ii'}$, *J* = 8.4 Hz), 8.431-8.479 (d, 2H, $H_{jj'}$, *J* = 8 Hz), 8.942 (s, 1H, H_k), 11.430 (s, 1H, H_l); ^{13}C NMR (DMSO-d_6, 400 MHz) δ ppm: 13.90, 17.21, 53.21, 59.71, 102.31, 115.90, 120.01, 123.00, 127.03,129.09, 130.21, 131.42, 131.42, 139.78, 142.59, 146.31, 150.86, 162.91, 166.00; MS: *m/z* 444.17; Anal. (%) calcd. (found) for $C_{24}H_{21}N_6O_4F$: C, 64.86 (63.27); H, 4.76 (4.69); N, 18.91 (17.63); O, 7.20 (6.42).

Ethyl 4,7-dihydro-5-methyl-7-(3-(4-bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylate (A-7): Yield: 69 %; m.p. 198 ºC, m.f. $C_{24}H_{21}N_6O_2Br$, m.w. 505, R_f: 0.56; IR (KBr, ν_{max}, cm^{-1}): 3125 (N-H *str*.), 3041 (C-H *str*. arom. ring), 2975, 2862 (C-H *str*. alkane), 1746 (C=O *str*. carbonyl of ester), 1674 (C=N *str*.), 1587, 1415 (C=C *str*. arom. ring), 742-492 (C-Br *str*.), 1363, 1292, 1259 (C-H bend. alkane), 1012 (C-Br bend.), 1252 (C-O *str*.), 1068 (C-O-C *str*.), 820 (C-H bend. *p*-disubstituted arom. ring), 689 (C-H bend. five adj. H-atom of monosubstituted arom. ring); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 0.930-0.961 (t, 3H, H_a), 2.430 (s, 3H, H_b), 3.931-4.012 (m, 2H, $H_{cc'}$), 5.836 (s, 1H, H_d), 7.422-7.452 (t, 1H, H_e, *J* = 7.4 Hz), 7.530-7.561 (t, 2H, $H_{ff'}$, *J* = 7.8 Hz), 7.689 (s, 1H, H_g), 7.741-7.787 (d, 2H, $H_{hh'}$, *J* = 8 Hz), 7.931-7.969 (d, 2H, $H_{ii'}$, *J* = 8.4 Hz), 8.012-8.069 (d, 2H, $H_{jj'}$, *J* = 8 Hz), 8.349 (s, 1H, H_k), 11.420 (s, 1H, H_l); ^{13}C NMR (DMSO-d_6, 400 MHz) δ ppm: 14..23, 17.63, 52.31, 60.32, 102.71, 117.21, 119.87, 123.23, 128.40,127.01, 129.42, 132.09, 139.78, 143.68, 147.30, 151.62, 166.10; MS: *m/z* 504.09; Anal. (%) calcd. (found) for $C_{24}H_{21}N_6O_4Br$: C, 57.04 (58.62); H, 4.19 (4.22); N, 16.63 (18.71).

Ethyl 4,7-dihydro-5-methyl-7-(phenyl)-1-phenyl-1*H*-pyrazol-4-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylate (A-8): Yield: 82 %; m.p. 244 ºC, m.f. $C_{24}H_{22}N_6O_2$, m.w. 426, R_f: 0.50; IR (KBr, ν_{max}, cm^{-1}): 3132 (N-H *str*.), 3022 (C-H *str*. arom. ring), 3010, 2961 (C-H *str*. alkane), 1746 (C=O *str*. carbonyl of ester), 1648 (C=N *str*.), 1587, 1415 (C=C *str*. arom. ring), 1363, 1292, 1259 (C-H bend. alkane), 1259 (C-O *str*.), 1068 (C-O-C *str*.), 695 (C-H bend. of five adj. H-atom of mono substituted arom. ring); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 0.993-1.012 (t, 3H, H_a), 2.279 (s, 3H, H_b), 3.885-4.017 (m, 2H, $H_{cc'}$), 5.921 (s, 1H, H_d), 7.421-7.443 (t, 1H, H_e, *J* = 8.4 Hz), 7.481-7.520 (t, 2H, $H_{ff'}$, *J* = 7.8 Hz), 7.739 (s, 1H, H_g), 7.907-7.929 (d, 2H, $H_{hh'}$, *J* = 8 Hz), 8.012-8.031 (d, 2H, $H_{ii'}$, *J* = 8.4 Hz), 8.421-8.429 (d, 2H, $H_{jj'}$, *J* = 8 Hz), 8.612 (s, 1H, H_k), 10.914 (s, 1H, H_l); ^{13}C NMR (DMSO-d_6, 400 MHz) δ ppm: 13.90, 17.02, 52.91, 61.99, 103.40, 116.22, 118.91, 122.07, 125.86, 127.01, 129.33, 130.03, 132.46, 138.61, 142.12, 148.30, 151.38, 152.03, 165.01; MS: *m/z* 426.18; Anal. (%) calcd. (found) for $C_{24}H_{22}N_6O_2$: C, 67.59 (66.79); H, 5.20 (4.99); N, 19.71 (20.02).

Ethyl 4,7-dihydro-5-methyl-7-(3-(2-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylate (A-9): Yield: 77 %; m.p. 222 ºC, m.f. $C_{25}H_{24}N_6O_3$, m.w. 456, R_f: 0.43; IR (KBr, ν_{max}, cm^{-1}): 3143 (N-H *str*.), 3022 (C-H *str*. arom. ring), 2970, 2858 (C-H *str*. alkane), 1733 (C=O *str*. carbonyl of ester), 1618 (C=N *str*.), 1587, 1415 (C=C *str*. arom. ring), 1363, 1292, 1259 (C-H bend. alkane), 1259 (C-O *str*.), 1068 (C-O-C *str*.), 766 (C-H bend. *o*-disubstituted arom. ring), 696 (C-H bend. of five adj. H-atom of monosubstituted arom. ring); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 0.931-0.968 (t, 3H, H_a), 2.276 (s, 3H, H_b), 3.495 (s, 1H, $H_{c'}$), 3.931-4.013 (m, 2H, H_{dd}), 5.931 (s, 1H, $H_{e'}$), 7.101-7.123 (d, 1H, $H_{f'}$, *J* = 8.8 Hz), 7.431-7.463 (d, 2H, H_{gg}, *J* = 8.8 Hz), 7.512 (d, 1H, $H_{h'}$, *J* = 8 Hz), 7.441-7.468 (d, 2H, $H_{ii'}$, *J* = 7.9 Hz), 7.543 (d, 1H, $H_{j'}$, *J* = 7.4 Hz,), 7.690-7.712 (d, 2H, H_{kk}, *J* =8.8 Hz), 7.912 (s, 1H, H_l), 8.017-8.034 (d, 1H, H_m, *J* = 8.8 Hz), 8.512-8.529 (d, 1H, H_n, *J* = 8.8 Hz), 10.332 (s, 1H, H_o); ^{13}C NMR (DMSO-d_6, 400 MHz) δ ppm: 13.91, 16.98, 53.81, 55.10, 61.71, 101.38, 110.91, 117.43, 119.23,120.01, 121.18, 125.87, 129.68, 130.82, 137.72, 142.38, 147.39, 150.82, 157.63, 165.04; MS: *m/z* 456.19; Anal. (%) calcd. (found) for $C_{25}H_{22}N_6O_3$: C, 65.78 (64.23); H, 5.30 (5.28); N, 18.41 (19.42); O, (10.51) (9.38).

Ethyl 4,7-dihydro-5-methyl-7-(3-(2,4dichlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylate (A-10): Yield: 80 %; m.p. 156 ºC, m.f. $C_{24}H_{20}N_6O_2Cl_2$, m.w. 495, R_f: 0.49; IR (KBr, ν_{max}, cm^{-1}): 3210 (N-H *str*.), 3041 (C-H *str*. arom. ring), 3070, 2958 (C-H *str*. alkane), 1742 (C=O *str*. carbonyl of ester), 1678 (C=N *str*.), 1585, 1415 (C=C *str*. arom. ring), 845-635 (C-Cl *str*.), 1365, 1288, 1271 (C-H bend. alkane), 1222 (C-Cl bend.), 1259 (C-O *str*.), 1068 (C-O-C *str*.), 688-712 (C-H bend. disubstituted arom. ring), 692 (C-H bend. of five adj. H-atom of mono-substituted arom. ring); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 0.931-0.966 (t, 3H, H_a), 2.342 (s, 3H, H_b), 3.941-4.012 (m, 2H, $H_{cc'}$), 5.942 (s, 1H, H_d), 7.432-7.451 (s, 1H, H_e, *J* = 7.4 Hz), 7.448-7.469 (d, 1H, $H_{f'}$, *J* = 8.2 Hz), 7.520-7.543 (d, 1H, H_{gJ} = 7.4 Hz,), 7.612-7.628 (d, 2H, $H_{hh'}$, *J* = 8 Hz), 7.731-7.761 (d, 2H, $H_{ii'}$, *J* = 8.4 Hz), 7.831 (s, 1H, $H_{j'}$), 8.031 (s, 1H, H_k), 10.931 (s, 1H, H_l); ^{13}C NMR (DMSO-d_6, 400 MHz) δ ppm: 13.91, 17.48, 53.01, 60.91, 101.71, 117.21, 119.01, 121.42, 125.01, 127.31, 129.48, 130.34, 133.64, 135.71, 139.46, 143.01, 148.01, 149.63, 150.81, 165.03; MS: *m/z* 494.10; Anal. (%) calcd. (found) for $C_{24}H_{20}N_6O_2Cl_2$: C, 58.19 (59.21); H, 4.07 (4.56); N, 16.97 (15.31); O, 6.46 (5.93); Cl, 14.31 (15.30).

RESULTS AND DISCUSSION

Various 1,2,4-triazolo[1,5-*a*]pyrimidines bearing a range of electron withdrawing and electron releasing substituents, *viz*. 4-NO_2-C_6H_5; 3-NO_2-C_6H_5; 4-Cl-C_6H_5; 4-OCH_3-C_6H_5; 4-CH_3-C_6H_5; 4-F-C_6H_5; 4-Br-C_6H_5; C_6H_5; 2-OCH_3-C_6H_5; 2,4-di-

Cl-C_6H_4 were prepared. The structure of all the synthesized compounds (**A-1** to **A-10**) has been elucidated by FTIR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analyses. For compounds **A-1** to **A-10**, confirmatory bands for -NH and carbonyl groups were observed at 3248-3120 and 1760-1720 cm^{-1}, respectively. Another characteristic C=N stretching bands of triazole and pyrazole ring were observed at 1680-1640 cm^{-1}, which suggest formation of desired products **A-1** to **A-10**. ^{1}H NMR signals of a singlet of -NH of pyrazole ring at 7.69-7.74 δ ppm, a singlet of -NH of triazole ring at 8.50-8.70 δ ppm and a singlet of pyrimidine ring at 10.60-11.07 δ ppm. In ^{13}C NMR spectra, a signal of methyl carbon observed in the region of 10-20 δ ppm and a signal of tertiary carbon of pyrimidine ring was observed at near 60 δ ppm.

Compounds **A-2**, **A-4**, **A-5**, **A-6**, **A-8**, **A-9**, **A-10** showed moderate antibacterial activity against *Staphylococcus aureus* at the concentration of 250, 100, 200, 250, 250, 250, 250 µg/mL while compounds **A-3** and **A-7** showed remarkable antibacterial activity against *Staphylococcus aureus* at the concentration of 100 µg/mL. Moreover, compounds **A-3**, **A-9** and **A-10** found to be potent against *Escherichia coli* at the concentration of 62.5 µg/mL and against *Pseudomonas aerug-inosa* at the concentration of 100 µg/mL (Table-1).

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REFERENCES

1. C. Ainsworth, N.R. Easton, M. Livezey, D.E. Morrison and W.R. Gibson, The Anticonvulsant Activity of 1,2,4-Triazoles, *J. Med. Chem.*, **5**, 383 (1962); https://doi.org/10.1021/jm01237a016.
2. T. Mano, R.W. Stevens, Y. Okumura, M. Kawai, T. Okumura and M. Sakakibara, 5-Lipoxygenase Inhibitors: Convenient Synthesis of 4-[3-(4-Heterocyclylphenylthio)phenyl]-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxamide Analogues, *Bioorg. Med. Chem. Lett.*, **15**, 2611 (2005); https://doi.org/10.1016/j.bmcl.2005.03.041.
3. B.S. Holla, B. Veerendra, M.K. Shivananda and B. Poojary, Synthesis, Characterization and Anticancer Activity Studies on Some Mannich Bases Derived from 1,2,4-Triazoles, *Eur. J. Med. Chem.*, **38**, 759 (2003); https://doi.org/10.1016/S0223-5234(03)00128-4.
4. C. Dahlof and C. Lines, Rizatriptan: a New 5-HT1B/1D Receptor Agonist for the Treatment of Migraine, *Expert Opin. Investig. Drugs*, **8**, 671 (1999); https://doi.org/10.1517/13543784.8.5.671.
5. F. Sternfeld, R. Baker, H.B. Broughton, A.R. Guiblin, R.A. Jelley, V.G. Matassa, A.J. Reeve, M.S. Beer, J.A. Stanton, R.J. Hargreaves, S.L. Shepheard, J. Longmore, Z. Razzaque, M.I. Graham, B. Sohal and L.J. Street, The Chemical Evolution of N,N-Dimethyl-2-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl]ethylamine (L-741,604) and Analogues: Potent and Selective Agonists for 5-HT_{1D} Receptors, *Bioorg. Med. Chem. Lett.*, **6**, 1825 (1996); https://doi.org/10.1016/0960-894X(96)00324-1.
6. P. Ordentlich, Identification of the Antineoplastic Agent 6-Mercaptopurine as an Activator of the Orphan Nuclear Hormone Receptor Nurr1, *J. Biochem.*, **278**, 24791 (2003); https://doi.org/10.1074/jbc.M302167200.
7. M. Hoffmann, M. Chrzanowska, T. Hermann and J. Rychlewski, Modeling of Purine Derivatives Transport across Cell Membranes Based on Their Partition Coefficient Determination and Quantum Chemical Calculations, *J. Med. Chem.*, **48**, 4482 (2005); https://doi.org/10.1021/jm0495273.
8. J. Tani, Y. Yamada, T. Oine, T. Ochiai, R. Ishida and I. Inoue, Studies on Biologically Active Halogenated Compounds. 1. Synthesis and Central Nervous System Depressant Activity of 2-(Fluoromethyl)-3-Aryl-4(3*H*)-Quinazolinone Derivatives, *J. Med. Chem.*, **22**, 95 (1979); https://doi.org/10.1021/jm00187a021.
9. P. Adnet, P. Lestavel and R. Krivosic-Horber, Neuroleptic Malignant Syndrome, *Br. J. Anaesth.*, **85**, 129 (2000); https://doi.org/10.1093/bja/85.1.129.
10. G. Dorothy, A. Smith and S. Waksman, Tuberculostatic and Tuberculocidal Properties of Streptomycin1, *J. Bacteriol.*, **54**, 253 (1947).
11. (a) X.-L. Zhao, Y.-F. Zhao, S.-C. Guo, H.-S. Song, D. Wang and P. Gong, *Molecules*, **12**, 1136 (2007); https://doi.org/10.3390/12051136.
(b) G.S. Hassan, M.A. El-Sherbeny, M.B. El-Ashmawy, S.M. Bayomi, A.R. Maarouf and F.A. Badriacd, Synthesis and Antitumor Testing of Certain New Fused Triazolopyrimidine and Triazoloquinazoline Derivatives, *Arab. J. Chem.*, **10**, S1345 (2017); https://doi.org/10.1016/j.arabjc.2013.04.002.
12. T. Saito, T. Obitsu, C. Minamoto, T. Sugiura, N. Matsumura, S. Ueno, A. Kishi, S. Katsumata, H. Nakai and M. Toda, Pyrazolo[1,5-*a*]pyrimidines, Triazolo[1,5-*a*]pyrimidines and their Tricyclic Derivatives as Corticotropin-Releasing Factor 1 (CRF_1) Receptor Antagonists, *Bioorg. Med. Chem.*, **19**, 5955 (2011); https://doi.org/10.1016/j.bmc.2011.08.055.
13. C. Hougaard, S. Hammami, B.L. Eriksen, U.S. Sorensen, M.L. Jensen, D. Strobaek and P. Christophersen, Evidence for a Common Pharmacological Interaction Site on $K_{Ca}2$ Channels Providing Both Selective Activation and Selective Inhibition of the Human $K_{Ca}2.1$ Subtype, *Mol. Pharmacol.*, **81**, 210 (2012); https://doi.org/10.1124/mol.111.074252.
14. S. Uryu, S. Tokuhiro, T. Murasugi and T. Oda, *Brain Res.*, **946**, 298 (2002); https://doi.org/10.1016/S0006-8993(02)02898-6.
15. C. Mustazza, M.R.D. Giudice, A. Borioni and F. Gatta, A Novel Compound, RS-1178, Specifically Inhibits Neuronal Cell Death Mediated By β-Amyloid-Induced Macrophage Activation *in vitro*, *Heterocycl. Chem.*, **38**, 1119 (2001); https://doi.org/10.1002/jhet.5570380516.
16. N. Zhang, S. Ayral-Kaloustian, T. Nguyen, J. Afragola, R. Hernandez, J. Lucas, J. Gibbons and C. Beyer, Synthesis and SAR of [1,2,4]Triazolo-[1,5-*a*]pyrimidines, A Class of Anticancer Agents with a Unique Mechanism of Tubulin Inhibition, *J. Med. Chem.*, **50**, 319 (2007); https://doi.org/10.1021/jm060717i.
17. L. Havlicek, K. Fuksova, V. Krystof, M. Orsag, B. Vojtesek and M. Strnad, 8-Azapurines as New Inhibitors of Cyclin-Dependent Kinases, *Bioorg. Med. Chem.*, **13**, 5399 (2005); https://doi.org/10.1016/j.bmc.2005.06.007.
18. M.E. Fraley, W.F. Hoffman, R.S. Rubino, R.W. Hungate, A.J. Tebben, R.Z. Rutledge, R.C. McFall, W.R. Huckle, R.L. Kendall, K.E. Coll and K.A. Thomas, Synthesis and Initial SAR Studies of 3,6-Disubsti-tuted Pyrazolo[1,5-*a*]pyrimidines: A New Class of KDR Kinase Inhibitors, *Bioorg. Med. Chem. Lett.*, **12**, 2767 (2002); https://doi.org/10.1016/S0960-894X(02)00525-5.
19. Q. Chen, X.-L. Zhu, L.-L. Jiang, Z.-M. Liu and G.-F. Yang, Synthesis, Antifungal Activity and CoMFA Analysis of Novel 1,2,4-Triazolo[1,5-*a*]-pyrimidine Derivatives, *Eur. J. Med. Chem.*, **43**, 595 (2008); https://doi.org/10.1016/j.ejmech.2007.04.021.