Acta Chimica & Pharmaceutica Indica

Acta Chim. Pharm. Indica: 2(2), 2012, 101-105
ISSN 2277-288X

A ONE-POT MICROWAVE IRRADIATION SYNTHESIS OF 1,2,4-TRIAZOLO [1,5-A] PYRIMIDINES

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(*Received : 23.03.2012; Revised : 01.04.2012; Accepted : 04.04.2012*)

ABSTRACT

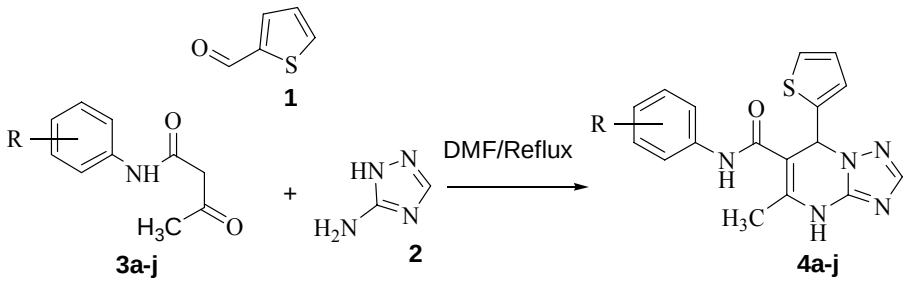
Synthesis of a series of triazolopyrimidines (4a-j) was achieved from different acetoacetamides, 4-(phenoxymethyl) benzaldehyde and 5-amino-1,2,4-triazole using microwave irradiation within 20-30 minutes with high yield. The structures of the products were supported by FTIR, PMR and mass spectral data.

Key words: Triazolo [1,5-a] pyrimidines, Acetoacetamides, 5-Amino-1,2,4-triazole, Microwave irradiation synthesis.

INTRODUCTION

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. 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]. 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. Pharmacological activities, such as antitumor potency[5,6], inhibition of KDR kinase[7], antifungal effect[8] and macrophage activation[9]. Anticancer acticity[10], Acetohydroxyacid synthase inhibitor[11], CDK-2 inhibitors[12], Anti-inflammatory[13], fungicidal activities[14], antimycobacterial agents[15], A2A adenosine receptor antagonists[16], latent leishmanicidal activity[17].

We have developed a new one-pot multi component synthesis of novel triazolo [1,5-a] pyridmidines (4a-j) with the advantages of short reaction time, high yield and environmental friendliness (Scheme-1).



Scheme 1

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EXPERIMENTAL

Melting points were measured in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded on Brukur spectrophotometer (400 MHz). Chemical shifts are expressed in units relative to TMS signal as internal reference. IR spectra were recorded on FT-IR Shimadzu-FT-IR 8400 spectrophotometer on KBr pallets. Mass spectra were recorded on GCMS QP2010 Gas Chromatograph Shimadzu. Thin Layer Chromatography (TLC) was performed on Silica gel-G using hexane: ethylacetate solvent system.

Typical exaperimental procedure for the synthesis of 1,2,4 triazolopyrimidines

A mixture of the 5-amino-1,2,4-triazole (2 mmol), acetoacetaminde (1 mmol) and 4-(phenoxymethyl) benzaldehyde (1 mmol) in 0.4 mL of DMF was refluxed under microwave irradiation for 20-30 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-j), which were crystallized from ethanol and subsequently dried in air.

4,7-dihydro-N-(4-methoxyphenyl)-5-methyl-7-(thiophen-2-yl)-[1,2,4] triazolo [1,5-a] pyrimidine-6-carboxamide (4a)

M. P. 219^{o}C; white crystals; ^{1}H NMR (DMSO-d_6) δ ppm: (δ 1.71) (s, 3H, H_a), (δ 3.37) (s, 3H, H_b), (δ 5.66) (s, 1H, H_c), (δ 6.60-6.72) (d, 2H, $H_{dd'}$,), (δ 6.75) (t, 2H, $H_{ee'}$), (δ 6.91) (d, 1H, H_f,), (δ 7.53) (t, 2H, $H_{gg'}$), (δ 8.10) (s, 1H, H_h), (δ 8.43) (s, 1H, H_i), (δ 9.78) (s, 1H, H_j). FT IR (cm^{-1}): 3150 (N-H stretching of secondary amine), 3002 (C-H stretching of aromatic ring), 2913 (C-H asymmetrical stretching of CH_3 group), 2856 (C-H asymmetrical stretching of CH_3 group), 1660 (C = O stretching of amide), 1600 (C = N stretching of triazole ring), 1545 (N-H deformation of pyrimidine ring), 1511 and 1465 (C = C stretching of aromatic ring), 1445 (C-H asymmetrical deformation of CH_3 group), 1406 (C-H symmetrical deformation of CH_3 group), 1353(C = S stretching), 1323 (C-N stretching), 1242 (C-O-C stretching), 1021 (C-H in plane deformation of aromatic ring), 823 (C-H out of plane bending of 1,4-disubstituion), Mass: *m/z* 367; Anal. Calcd. for $C_{18}H_{17}N_5O_2S$: C, 58.84; H, 4.66; N, 19.06; O, 8.71; S, 8.73. Found: C, 58.61; H, 4.34; N, 19.00; O, 8.42; S, 8.53 %.

N-(4-chlorophenyl)-4,7-dihydro-5-methyl-7-(thiophen-2-yl)-[1,2,4] triazolo [1,5-a] pyrimidine-6-carboxamide (4b)

M. P. 179^{o}C; white crystals; 1H NMR (DMSO-d6) δ ppm: (δ 1.77) (s, 3H, H_a), (δ 5.06) (s, 1H, H_b), (δ 6.61-6.77) (d, 2H, $H_{cc'}$,), (δ 6.79) (t, 2H, $H_{dd'}$), (δ 6.93) (d, 1H, H_e,), (δ 7.59) (t, 2H, $H_{ff'}$), (δ 8.15) (s, 1H, H_g), (δ 8.49) (s, 1H, H_h), (δ 9.78) (s, 1H, H_i). FT IR (cm^{-1}): 3133 (N-H stretching of secondary amine), 3010 (C-H stretching of aromatic ring), 2921 (C-H asymmetrical stretching of CH_3 group), 2853 (C-H asymmetrical stretching of CH_3 group), 1659 (C = O stretching of amide), 1610 (C = N stretching of triazole ring), 1535 (N-H deformation of pyrimidine ring), 1510 and 1460 (C = C stretching of aromatic ring), 1440 (C-H asymmetrical deformation of CH_3 group), 1401 (C-H symmetrical deformation of CH_3 group), 1358 (C = S stretching), 1333 (C-N stretching), 1023 (C-H in plane deformation of aromatic ring), 832 (C-H out of plane bending of 1,4-disubstituion), 736 (C-Cl stretching). Mass: *m/z* 371; Anal. Calcd. for $C_{17}H_{14}ClN_5OS$: C, 54.91; H, 3.79; Cl, 9.53; N, 18.83; O, 4.30; S, 8.62. Found: C, 54.51; H, 3.53; Cl, 9.23; N, 18.45; O, 4.22; S, 8.55%.

4,7-dihydro-5-methyl-7-(thiophen-2-yl)-N-p-tolyl-[1,2,4] triazolo [1,5-a] pyrimidine-6-carboxamide (4c)

M. p. 257^{o}C; white crystals; ^{1}H NMR (DMSO-d_6) δ ppm: (δ 1.63) (s, 3H, H_a), (δ 2.07) (s, 3H, H_b), (δ 5.45) (s, 1H, H_c), (δ 6.54-6.70) (d, 2H, $H_{dd'}$,), (δ 6.73) (t, 2H, $H_{ee'}$), (δ 6.95) (d, 1H, H_f,), (δ 7.54) (t, 2H, $H_{gg'}$),

(δ 8.23) (s, 1H, H_h), (δ 8.89) (s, 1H, H_i), (δ 9.70) (s, 1H, H_j). FT IR (cm^{-1}): 3144 (N-H stretching of secondary amine), 3020 (C-H stretching of aromatic ring), 2953 (C-H asymmetrical stretching of CH_3 group), 2850 (C-H asymmetrical stretching of CH_3 group), 1656 (C = O stretching of amide), 1601 (C = N stretching of triazole ring), 1553 (N-H deformation of pyrimidine ring), 1515 and 1443 (C = C stretching of aromatic ring), 1421 (C-H asymmetrical deformation of CH_3 group), 1400 (C-H symmetrical deformation of CH_3 group), 1350 (C = S stretching), 1311 (C-N stretching), 1020 (C-H in plane deformation of aromatic ring), 833 (C-H out of plane bending of 1,4-disubstituion), Mass: *m/z* 367; Anal. Calcd. for $C_{18}H_{17}N_5OS$: C, 61.52; H, 4.88; N, 19.93; O, 4.55; S, 9.12. Found: C, 61.21; H, 4.23; N, 19.54; O, 4.42; S, 9.10 %.

N-(4-fluorophenyl)-4,7-dihydro-5-methyl-7-(thiophen-2-yl)-[1,2,4] triazolo [1,5-a] pyrimidine-6-carboxamide (4d)

M. P. 179°C; white crystals; ^1H NMR (DMSO-d6) δ ppm: (δ 1.83) (s, 3H, H_a), (δ 5.53) (s, 1H, H_b), (δ 6.64-6.74) (d, 2H, $H_{cc'}$,), (δ 6.79) (t, 2H, $H_{dd'}$), (δ 6.90) (d, 1H, H_e,), (δ 7.61) (t, 2H, $H_{ff'}$), (δ 8.13) (s, 1H, H_g), (δ 8.76) (s, 1H, H_h), (δ 9.88) (s, 1H, H_i). FT IR (cm^{-1}): 3150 (N-H stretching of secondary amine), 3021 (C-H stretching of aromatic ring), 2924 (C-H asymmetrical stretching of CH_3 group), 2851 (C-H asymmetrical stretching of CH_3 group), 1656 (C = O stretching of amide), 1609 (C = N stretching of triazole ring), 1531 (N-H deformation of pyrimidine ring), 1510 and 1453 (C = C stretching of aromatic ring), 1453 (C-H asymmetrical deformation of CH_3 group), 1424 (C-H symmetrical deformation of CH_3 group), 1353 (C = S stretching), 1323 (C-N stretching), 1032 (C-H in plane deformation of aromatic ring), 823 (C-H out of plane bending of 1,4-disubstituion), 736 (C-F stretching). Mass: *m/z* 355; Anal. Calcd. for $C_{17}H_{14}FN_5OS$: C, 57.45; H, 3.97; F, 5.35; N, 19.71; O, 4.50; S, 9.02. Found: C, 57.35; H, 3.82; F, 5.12; N, 19.65; O, 4.21; S, 8.89%.

N-(4-bromophenyl)-4,7-dihydro-5-methyl-7-(thiophen-2-yl)-[1,2,4] triazolo [1,5-a] pyrimidine-6-carboxamide (4e)

M. P. 199°C; white crystals; ^1H NMR (DMSO-d6) δ ppm: (δ 1.56) (s, 3H, H_a), (δ 5.65) (s, 1H, H_b), (δ 6.54-6.72) (d, 2H, $H_{cc'}$,), (δ 6.78) (t, 2H, $H_{dd'}$), (δ 6.90) (d, 1H, H_e,), (δ 7.54) (t, 2H, $H_{ff'}$), (δ 8.10) (s, 1H, H_g), (δ 8.75) (s, 1H, H_h), (δ 9.75) (s, 1H, H_i). FT IR (cm^{-1}): 3124 (N-H stretching of secondary amine), 3011 (C-H stretching of aromatic ring), 2922 (C-H asymmetrical stretching of CH_3 group), 2853 (C-H asymmetrical stretching of CH_3 group), 1653 (C = O stretching of amide), 1603 (C = N stretching of triazole ring), 1535 (N-H deformation of pyrimidine ring), 1514 and 1456 (C = C stretching of aromatic ring), 1451 (C-H asymmetrical deformation of CH_3 group), 1421 (C-H symmetrical deformation of CH_3 group), 1352 (C = S stretching), 1328 (C-N stretching), 1045 (C-H in plane deformation of aromatic ring), 823 (C-H out of plane bending of 1,4-disubstituion), 751 (C-Br stretching). Mass: *m/z* 416; Anal. Calcd. for $C_{17}H_{14}BrN_5OS$: C, 49.05; H, 3.39; Br, 19.19; N, 16.82; O, 3.84; S, 7.70. Found: C, 49.00; H, 3.24; Br, 19.12; N, 16.68; O, 3.64; S, 7.65%.

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

M. P. 222°C; white crystals; ^1H NMR (DMSO-d6) δ ppm: (δ 1.74) (s, 3H, H_a), (δ 5.64) (s, 1H, H_b), (δ 6.54-6.72) (d, 2H, $H_{cc'}$,), (δ 6.89) (t, 1H, H_d), (δ 6.95) (d, 1H, H_e,), (δ 7.54-7.59) (t, 2H, $H_{ff'}$), (δ 8.21) (s, 1H, H_g), (δ 8.79) (s, 1H, H_h), (δ 9.81) (s, 1H, H_i). FT IR (cm^{-1}): 3164 (N-H stretching of secondary amine), 3068 (C-H stretching of aromatic ring), 2964 (C-H asymmetrical stretching of CH_3 group), 2861 (C-H asymmetrical stretching of CH_3 group), 1660 (C = O stretching of amide), 1608 (C = N stretching of triazole ring), 1553 (N-H deformation of pyrimidine ring), 1514 and 1454 (C = C stretching of aromatic ring), 1445 (C-H asymmetrical deformation of CH_3 group), 1428 (C-H symmetrical deformation of CH_3 group), 1354

(C = S stretching), 1328 (C-N stretching), 1042 (C-H in plane deformation of aromatic ring), 832 (C-H out of plane bending of 1,4-disubstituion), 751 (C-Cl stretching), 659 (C-F stretching). Mass: *m/z* 390; Anal. Calcd. for $C_{17}H_{13}ClFN_5OS$: C, 52.38; H, 3.36; Cl, 9.09; F, 4.87; N, 17.96; O, 4.10; S, 8.23. Found: C, 52.12; H, 3.24; Cl, 9.01; F, 4.56; N, 17.84; O, 4.01; S, 8.12%.

N-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-7-(thiophen-2-yl)-[1,2,4] triazolo [1,5-a] pyrimidine-6-carboxamide (4g)

M. P. 227°C; white crystals; ^{1}H NMR (DMSO-d6) δ ppm: (δ 1.64) (s, 3H, H_a), (δ 5.64) (s, 1H, H_b), (δ 6.60-6.72) (d, 2H, $H_{cc'}$,), (δ 6.89) (t, 1H, H_d), (δ 6.92) (d, 1H, H_e,), (δ 7.56-7.60) (t, 2H, $H_{ff'}$), (δ 8.24) (s, 1H, H_g), (δ 8.82) (s, 1H, H_h), (δ 9.86) (s, 1H, H_i). FT IR (cm^{-1}): 3156 (N-H stretching of secondary amine), 3065 (C-H stretching of aromatic ring), 2966 (C-H asymmetrical stretching of CH_3 group), 2856 (C-H asymmetrical stretching of CH_3 group), 1656 (C = O stretching of amide), 1645 (C = N stretching of triazole ring), 1565 (N-H deformation of pyrimidine ring), 1512 and 1456 (C = C stretching of aromatic ring), 1456 (C-H asymmetrical deformation of CH_3 group), 1421 (C-H symmetrical deformation of CH_3 group), 1353 (C = S stretching), 1328 (C-N stretching), 1042 (C-H in plane deformation of aromatic ring), 833 (C-H out of plane bending of 1,4-disubstituion), 751 (C-Cl stretching). Mass: *m/z* 406; Anal. Calcd. for $C_{17}H_{13}C_{l2}N_5OS$: C, 50.26; H, 3.23; Cl, 17.45; N, 17.24; O, 3.94; S, 7.89. Found: C, 50.11; H, 3.12; Cl, 17.42; N, 17.13; O, 3.64; S, 7.43%.

N-(3-chlorophenyl)-4,7-dihydro-5-methyl-7-(thiophen-2-yl)-[1,2,4] triazolo [1,5-a] pyrimidine-6-carboxamide (4h)

M. P. 199°C; white crystals; ^{1}H NMR (DMSO-d6) δ ppm: (δ 1.45) (s, 3H, H_a), (δ 5.58) (s, 1H, H_b), (δ 6.56-6.70) (d, 2H, $H_{cc'}$,), (δ 6.80) (t, 1H, H_d), (δ 6.92-7.08) (d, 2H, H_{ef},), (δ 7.52) (d, 1H, $H_{g'}$), (δ 7.52) (d, 1H, $H_{h'}$), (δ 8.33) (s, 1H, H_i), (δ 8.86) (s, 1H, H_j), (δ 9.78) (s, 1H, H_k). FT IR (cm^{-1}): 3165 (N-H stretching of secondary amine), 3055 (C-H stretching of aromatic ring), 2975 (C-H asymmetrical stretching of CH_3 group), 2853 (C-H asymmetrical stretching of CH_3 group), 1642 (C = O stretching of amide), 1644 (C = N stretching of triazole ring), 1561 (N-H deformation of pyrimidine ring), 1508 and 1451 (C = C stretching of aromatic ring), 1445 (C-H asymmetrical deformation of CH_3 group), 1412 (C-H symmetrical deformation of CH_3 group), 1356 (C = S stretching), 1324 (C-N stretching), 1041 (C-H in plane deformation of aromatic ring), 843 (C-H out of plane bending of 1,4-disubstituion), 752 (C-Cl stretching). Mass: *m/z* 388; Anal. Calcd. for $C_{18}H_{18}ClN_5OS$: C, 55.74; H, 4.68; Cl, 9.14; N, 18.06; O, 4.12; S, 8.27. Found: C, 55.65; H, 4.46; Cl, 9.08; N, 18.00; O, 4.04; S, 8.11%.

N-(3-bromophenyl)-4,7-dihydro-5-methyl-7-(thiophen-2-yl)-[1,2,4] triazolo [1,5-a] pyrimidine-6-carboxamidede (4i)

M. P. 189ºC; white crystals; ^{1}H NMR (DMSO-d6) δ ppm: (δ 1.24) (s, 3H, H_a), (δ 5.49) (s, 1H, H_b), (δ 6.43-6.64) (d, 2H, $H_{cc'}$,), (δ 6.72) (t, 1H, H_d), (δ 6.86-7.00) (d, 2H, H_{ef},), (δ 7.59) (d, 1H, $H_{g'}$), (δ 7.65) (d, 1H, $H_{h'}$), (δ 8.21) (s, 1H, H_i), (δ 8.98) (s, 1H, H_j), (δ 9.89) (s, 1H, H_k). FT IR (cm^{-1}): 3213 (N-H stretching of secondary amine), 3023 (C-H stretching of aromatic ring), 2959 (C-H asymmetrical stretching of CH_3 group), 2835 (C-H asymmetrical stretching of CH_3 group), 1624 (C = O stretching of amide), 1635 (C = N stretching of triazole ring), 1556 (N-H deformation of pyrimidine ring), 1511 and 1449 (C = C stretching of aromatic ring), 1442 (C-H asymmetrical deformation of CH_3 group), 1419 (C-H symmetrical deformation of CH_3 group), 1346 (C = S stretching), 1314 (C-N stretching), 1029 (C-H in plane deformation of aromatic ring), 846 (C-H out of plane bending of 1,4-disubstituion), 689 (C-Br stretching). Mass: *m/z* 432; Anal. Calcd. for $C_{18}H_{18}BrN_5OS$: C, 50.01; H, 4.20; Br, 18.48; N, 16.20; O, 3.70; S, 7.42. Found: C, 49.46; H, 4.04; Br, 18.34; N, 16.10; O, 3.63; S, 7.33%.

N-(3-methoxyphenyl)-4,7-dihydro-5-methyl-7-(thiophen-2-yl)-[1,2,4] triazolo [1,5-a] pyrimidine-6-carboxamide (4j)

M. P. 168^{o}C; white crystals; ^{1}H NMR (DMSO-d6) δ ppm: (δ 1.17) (s, 3H, H_a), (δ 5.24) (s, 1H, H_b), (δ 6.41-6.66) (d, 2H, $H_{cc'}$,), (δ 6.78) (t, 1H, H_d), (δ 6.87-7.12) (d, 2H, H_{ef},), (δ 7.64) (d, 1H, $H_{g'}$), (δ 7.87) (d, 1H, $H_{h'}$), (δ 8.33) (s, 1H, H_i), (δ 8.43) (s, 1H, H_j), (δ 9.46) (s, 1H, H_k). FT IR (cm^{-1}): 3245 (N-H stretching of secondary amine), 3022(C-H stretching of aromatic ring), 2954 (C-H asymmetrical stretching of CH_3 group), 2831 (C-H asymmetrical stretching of CH_3 group), 1626 (C = O stretching of amide), 1612 (C = N stretching of triazole ring), 1564 (N-H deformation of pyrimidine ring), 1524 and 1487 (C = C stretching of aromatic ring), 1453 (C-H asymmetrical deformation of CH_3 group), 1413 (C-H symmetrical deformation of CH_3 group), 1335 (C = S stretching), 1313 (C-N stretching), 1023 (C-H in plane deformation of aromatic ring), 846 (C-H out of plane bending of 1,4-disubstituion), 689 (C-Br stretching). Mass: *m/z* 383; Anal. Calcd. for $C_{19}H_{21}N_5O_2S$: C, 59.51; H, 5.52; N, 18.26; O, 8.34; S, 8.36. Found: C, 59.23; H, 5.13; N, 18.15; O, 8.23; S, 8.31%.

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