Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2012, 4(5):2687-2691

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

An one-pot multi component synthesis of novel 1,2,4-triazolo[1,5-a]pyrimidines

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ABSTRACT

*Synthesis of a series of triazolopyrimidines **(4a-j)** was achieved from different acetoacetamides, name of aldehyde and triazole using microwave irradiation within 30 min with high yield. The triazolopyrimidines of the products were supported by FTIR, PMR and mass spectral data.*

Keywords: pyrimidines, acetoacetamides, triazole microwave assisted synthesis.

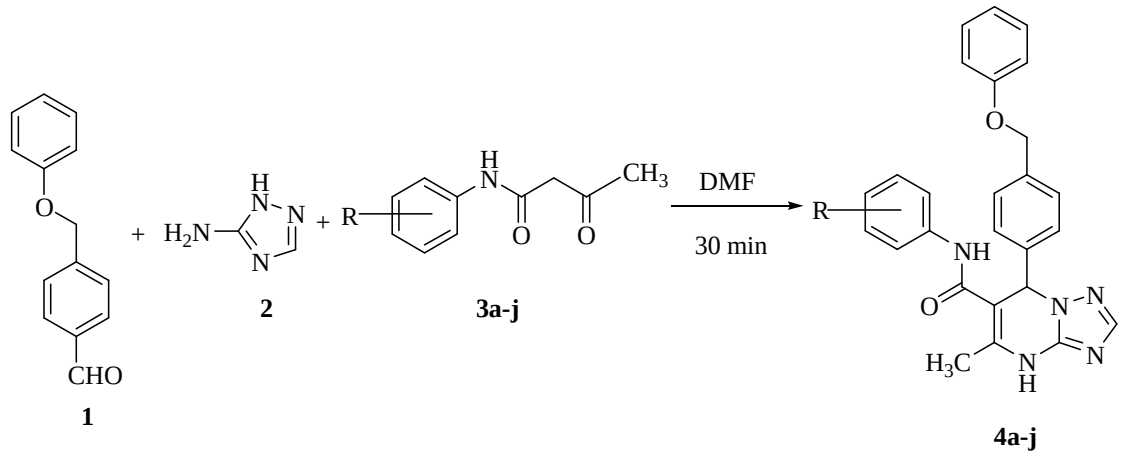
INTRODUCTION

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. Four different possibilities exist for the relative orientation of both rings in 1,2,4-triazolo[1,5-a]pyrimidines. This Pyrimidine and its derivatives have been studied for over a century due to their variety of important chemical and biological applications. pyrimidine derivatives are of interest because of their pharmacological properties [1-13] including antiviral, 2 antitumour, 5 antibacterial [6-10] and antihypertensive 4.

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, inhibition of KDR kinase, antifungal effect and macrophage activation. They have proved to be promising anticancer agents with dual mechanisms of tubulin polymerization promotion as well as cyclin dependent kinases 2 inhibition. Some examples of published derivatives of 1,2,4-triazolo[1,5-a]pyrimidine with their biological activities.

Several synthetic strategies have been reported for the preparation of triazolopyrimidine derivatives.[5, 13-18] Most of these are based on modification of the classical one-pot Biginelli reaction[5, 14-17] and in some cases on more complex multi-step processes involving harsh reaction conditions and long reaction times.[18-19] One major drawback of the classical Biginelli protocol is the low yield that is frequently encountered when using sterically more demanding aldehydes.

To circumvent these problems, we have developed a new microwave assisted protocol for the synthesis of novel pyridmidines **(4a-j)** with the advantage of short reaction time, high yield and environmentally friendliness **(Scheme-a)**.



Scheme-a

EXPERIMENTAL SECTION

Melting points were measured in open capillaries and are uncorrected. ^{1}HNMR spectra were recorded on Brukur spectrophotometer (400MHz). 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. Thin Layer Chromatography 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), an appropriate acetoacetaminde (1 mmol) and 4-(phenoxymethyl)benzaldehyde (1 mmol) was refluxed in 0.5 ml of DMF for 15 min. After cooling, methanol (~15 ml) was added. The reaction mixture was allowed to stand overnight and then filtered to give the solid triazolopyrimidine products, which were crystallized from ethanol .

N-(3-chlorophenyl)-4,7-dihydro-5-methyl-7-(4-(phenoxymethyl)phenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide 4a. m.p. 219 ºC; white crystals; ^{1}H NMR (DMSO-d_6) δ ppm: (δ 2.13) (s, 3H, H_a), (δ 3.33) (s, 2H, H_b), (δ 6.46) (s, 1H, H_c), (δ 6.73-6.75) (d, 2H, $H_{dd'}$,), (δ 6.86-6.88) (d, 1H, H_e,), (δ 7.04-7.08) (t, 2H, $H_{ff'}$), (δ 7.17-7.21) (t, 1H, H_g), (δ 7.27-7.35) (m, 5H, H_{h-l}), (δ 7.48-7.52) (dd, 2H, H_{mn}), (δ 7.61) (s, 1H, H_o), (δ 9.78) (s, 1H, H_p),(δ 10.19) (s, 1H, H_q). FT IR (cm^{-1}): 3259 (N-H stretching of secondary amine), 3032 (C-H stretching of aromatic ring), 2920 (C-H asymmetrical stretching of CH_3 group), 2875 (C-H asymmetrical stretching of CH_3 group), 1668 (C=O stretching of amide), 1606 (C=N stretching of triazole ring), 1550 (N-H deformation of pyrimidine ring), 1514 and 1480 (C=C stretching of aromatic ring), 1440 (C-H asymmetrical deformation of CH_3 group), 1410 (C-H symmetrical deformation of CH_3 group), 1330 (C-N stretching), 1247 (C-O-C stretching), 1028 (C-H in plane deformation of aromatic ring), 821 (C-H out of plane bending of 1,4-disubstituion), 736 (C-Cl stretching), Mass: *m/z* 472; Anal. Calcd. for $C_{26}H_{22}ClN_5O_2$: C, 66.17; H, 4.70; N, 14.84. Found: C, 66.01; H, 4.52; N, 14.73%.

N-(4-fluorophenyl)-4,7-dihydro-5-methyl-7-(4-(phenoxymethyl)phenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide 4b. m.p. 179 ºC; white crystals; 1H NMR (DMSO-d6) δ ppm: (δ 1.76) (s, 3H, Ha), (δ 4.96) (m, 2H, Hb), (δ 6.86) (s, 1H, Hc), (δ 6.73) (s, 1H, Hd), (δ 6.85-6.86) (d, 1H, He,), (δ 6.98-7.07) (m, 4H, Hf-i), (δ 7.17-7.34) (m, 5H, Hj-n), (δ 7.42-7.44) (s, 1H, Ho), (δ 7.59-7.62) (d, 2H, Hp,q,), (δ 9.33 (s, 1H, Hr), (δ 10.01) (s, 1H, Hs). FT IR (cm-1): 3217 (N-H stretching of secondary amine), 3045 (C-H stretching of aromatic ring), 2964 (C-H asymmetrical stretching of CH3 group), 2872 (C-H asymmetrical stretching of CH3 group), 1666 (C=O stretching of amide), 1595 (C=N stretching of triazole ring), 1516 (N-H deformation of pyrimidine ring), 1440, 1400 (C=C stretching of aromatic ring), 1411 (C-H asymmetrical deformation of CH3 group), 1344 (C-H symmetrical deformation of CH3 group), 1280 (C-N stretching), 1247 (C-O-C stretching), 1033 (C-H in plane deformation of aromatic ring), 819 (C-H out of plane bending of 1,4-disubstituion). Mass: m/z 455; Anal. Calcd. for C26H22FN5O2: C, 68.56; H, 4.87; N, 15.38. Found: C, 68.32; H, 4.67; N, 15.29%.

N-(4-chlorophenyl)-4,7-dihydro-5-methyl-7-(4-(phenoxymethyl)phenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide 4c. m. p. 257 ^{o}C; white crystals; 1H NMR (DMSO-d6) δ ppm: (δ 2.14) (s, 3H, Ha), (δ 4.95) (t, 2H, Hb), (δ 6.48) (s, 1H, Hc), (δ 6.73-6.75) (d, 2H, Hd,e,), (δ 6.86-6.88 (d, 1H, Hd,), (δ 7.17-7.21) (t, 1H, Hf,), (δ 7.27-7.35) (m, 6H, Hg-l), (δ 7.40-7.43) (t, 1H, Hn), (δ 7.63) (s, 2H, Hm), (δ 7.79-7.81) (m, 1H, Ho-q), (δ 9.92) (s, 1H, Hr), (δ 10.27) (s, 1H, Hs). FT IR (cm-1): 3269 (N-H stretching of secondary amine), 3024 (C-H stretching of aromatic ring), 2922 (C-H asymmetrical stretching of CH3 group), 2868 (C-H asymmetrical stretching of CH3 group), 1666 (C=O stretching of amide), 1618 (C=N stretching of triazole ring), 1550 (N-H deformation of pyrimidine ring), 1510, 1479 and 1442 (C=C stretching of aromatic ring), 1413 (C-H asymmetrical deformation of CH3 group), 1329 (C-H symmetrical deformation of CH3 group), 1280 (C-N stretching), 1247 (C-O-C stretching), 1033 (C-H in plane deformation of aromatic ring), 825 (C-H out of plane bending of 1,4-disubstituion. MS: m/z 471; Anal. Calcd. for C26H22ClN5O2: C, 66.17; H, 4.70; N, 14.84; O, 6.78. Found: C, 64.38; H, 4.29; N, 14.75%.

N-(4-nitrophenyl)-4,7-dihydro-5-methyl-7-(4-(phenoxymethyl)phenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide 4d. m. p. 179 ^{o}C; white crystals; ^{1}H NMR (DMSO-d_6) δ ppm: (δ 2.03) (s, 3H, H_a), (δ 3.13) (s, 2H, H_b), (δ 6.33) (s, 1H, H_c), (δ 6.70-6.72) (d, 2H, $H_{dd'}$,), (δ 6.80-6.84) (d, 1H, H_e,), (δ 7.00-7.04) (t, 2H, $H_{ff'}$), (δ7.11-7.15) (t, 1H, H_g), (δ 7.23-7.25) (m, 5H, H_{h-l}), (δ 7.46-7.50) (dd, 2H, H_{mn}), (δ 7.58) (s, 1H, H_o), (δ 9.74) (s, 1H, H_p),(δ 10.16) (s, 1H, H_q).

FT IR (cm-1): 3309 (N-H stretching of secondary amine), 3014 (C-H stretching of aromatic ring), 2952 (C-H asymmetrical stretching of CH3 group), 2858 (C-H asymmetrical stretching of CH3 group), 1656 (C=O stretching of amide), 1608 (C=N stretching of triazole ring), 1540 (N-H deformation of pyrimidine ring), 1511, 1469 and 1432 (C=C stretching of aromatic ring), 1403 (C-H asymmetrical deformation of CH3 group), Nitro: (N-O 1365), 1319 (C-H symmetrical deformation of CH3 group), 1229 (C-N stretching), 1227 (C-O-C stretching), 1031 (C-H in plane deformation of aromatic ring), 820 (C-H out of plane bending of 1,4-disubstituion. MS: m/z 482; Anal. Calcd. for C26H22N6O4: C, 64.72; H, 4.60;N,17.42; O, 13.26. Found: C, 64.61; H, 4.50; N, 17.24%.

N-(3-nitrophenyl)-4,7-dihydro-5-methyl-7-(4-(phenoxymethyl)phenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide 4e. m. p. 199 ^{o}C; white crystals; ^{1}H NMR (DMSO-d_6) δ ppm: (δ 2.11) (s, 3H, H_a), (δ 3.58) (s, 2H, H_b), (δ 6.01) (s, 1H, H_c), (δ 6.46-6.66) (d, 2H, $H_{dd'}$,), (δ 6.62-6.70) (d, 1H, H_e,), (δ 7.11-7.13) (t, 2H, $H_{ff'}$), (δ 7.15-7.17) (t, 1H, H_g), (δ 7.22-7.26) (m, 5H, H_{h-l}), (δ 7.46-7.52) (dd, 2H, H_{mn}), (δ7.53) (s, 1H, H_o), (δ 9.87) (s, 1H, H_p),(δ 10.25) (s, 1H, H_q).

FT IR (cm-1): 3312 (N-H stretching of secondary amine), 3001 (C-H stretching of aromatic ring), 2924 (C-H asymmetrical stretching of CH3 group), 2822 (C-H asymmetrical stretching of CH3 group), 1605 (C=O stretching of amide), 1600 (C=N stretching of triazole ring), 1527 (N-H deformation of pyrimidine ring), 1509, 1456 and 1435 (C=C stretching of aromatic ring), 1405 (C-H asymmetrical deformation of CH3 group), Nitro: (N-O 1316), 1300 (C-H symmetrical deformation of CH3 group), 1257 (C-N stretching), 1213 (C-O-C stretching), 1010 (C-H in plane deformation of aromatic ring), 835 (C-H out of plane bending of 1,4-disubstituion. mp 274 ºC; MS: m/z 482; Anal. Calcd. for C26H22N6O4: C, 64.72; H, 4.60; N, 17.42; O, 13.26. Found: C, 64.10; H, 4.54; N, 16.89%.

N-(4-hydroxyphenyl)-4,7-dihydro-5-methyl-7-(4-(phenoxymethyl)phenyl)-[1,2,4]triazolo- [1,5-a]pyrimidine-6-carboxamide 4f. m.p. 222 ºC); white crystals; 1H NMR (DMSO-d6) δ ppm: (δ 1.66) (s, 3H, Ha), (δ 4.89) (m, 2H, Hb), (δ 6.81) (s, 1H, Hc), (δ 6.75 (s, 1H, Hd), (δ 6.85-6.86) (d, 1H, He,), (δ 6.56-7.00) (m, 4H, Hf-i), (δ 7.05-7.09) (m, 5H, Hj-n), (δ 7.23-7.33) (s, 1H, Ho), (δ 7.48-7.59) (d, 2H, Hp,q,), (δ 9.13) (s, 1H, Hr), (δ 10.01) (s, 1H, Hs). FT IR (cm-1): 3599 (Free -OH) 3317 (N-H stretching of secondary amine), 3056 (C-H stretching of aromatic ring), 2960 (C-H asymmetrical stretching of CH3 group), 2852 (C-H asymmetrical stretching of CH3 group), 1616 (C=O stretching of amide), 1592 (C=N stretching of triazole ring), 1501 (N-H deformation of pyrimidines ring), 1430, 1412 (C=C stretching of aromatic ring), 1405 (C-H asymmetrical deformation of CH3 group), 1342 (C-H symmetrical deformation of CH3 group), 1275 (C-N stretching), 1237 (C-O-C stretching), 1023 (C-H in plane deformation of aromatic ring), 811 (C-H out of plane bending of 1,4-disubstituion). Maas: m/z 453; Anal. Calcd. for C26H23N5O3: C, 68.86; H, 5.11; N, 15.44; O, 10.58. Found: C, 67.08; H, 4.39;N, 20.61%.

N-(2-chlorophenyl)-4,7-dihydro-5-methyl-7-(4-(phenoxymethyl)phenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide 4g. m. p. 227 ^{o}C; white crystals; 1H NMR (DMSO-d6) δ ppm: (δ 2.11) (s, 3H, Ha), (δ 4.85) (t, 2H, Hb), (δ6 .59) (s, 1H, Hc), (δ 6.65-6.69) (d, 2H, Hd,e, (δ 6.68-6.78) (d, 1H, Hd,), (δ 7.12-7.18) (t, 1H, Hf,), (δ 7.15-7.26) (m, 6H, Hg-l), (δ 7.36-7.40) (t, 1H, Hn), (δ 7.56) (s, 2H, Hm),(δ 7.78-7.81) (m, 1H, Ho-q), (δ 9.98) (s, 1H,

Hr), (δ10.25) (s, 1H, Hs). FT IR (cm-1): 3259 (N-H stretching of secondary amine), 3031 (C-H stretching of aromatic ring), 2912 (C-H asymmetrical stretching of CH3 group), 2858 (C-H asymmetrical stretching of CH3 group), 1661 (C=O stretching of amide), 1610 (C=N stretching of triazole ring), 1558 (N-H deformation of pyrimidine ring), 1511, 1485 and 1441 (C=C stretching of aromatic ring), 1410 (C-H asymmetrical deformation of CH3 group), 1312 (C-H symmetrical deformation of CH3 group), 1275 (C-N stretching), 1241 (C-O-C stretching), 1016 (C-H in plane deformation of aromatic ring), 832 (C-H out of plane bending of 1,4-disubstituion.Mass: m/z 471; Anal. Calcd. for C26H22ClN5O2: C, 66.17; H, 4.70; N, 14.84; O, 6.78. Found: C, 65.86; H, 4.45; N, 14.58%.

N-(4-methoxyphenyl)-4,7-dihydro-5-methyl-7-(4-(phenoxymethyl)phenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide 4h. m. p. 199 ^{o}C; white crystals; ^{1}H NMR (DMSO-d_6) δ ppm: (δ 2.23) (s, 3H, H_a), (δ 3.46) (s, 2H, H_b), (δ 6.25) (s, 1H, H_c), (δ 6.71-6.73) (d, 2H, $H_{dd'}$,), (δ 6.78-6.80) (d, 1H, H_e,), (δ 7.00-7.04) (t, 2H, $H_{ff'}$), (δ 7.10-7.15) (t, 1H, H_g), (δ 7.20-7.24) (m, 5H, H_{h-l}), (δ 7.41-7.51) (dd, 2H, H_{mn}), (δ 7.52) (s, 1H, H_o), (δ 9.72) (s, 1H, H_p),(δ 10.10) (s, 1H, H_q). FT IR (cm-1): 3354 (N-H stretching of secondary amine), 3015 (C-H stretching of aromatic ring), 2959 (C-H asymmetrical stretching of CH3 group), 2855 (C-H asymmetrical stretching of CH3 group), 1652 (C=O stretching of amide), 1615 (C=N stretching of triazole ring), 1554 (N-H deformation of pyrimidine ring), 1521, 1462 and 1438 (C=C stretching of aromatic ring), 1416 (C-H asymmetrical deformation of CH3 group), Nitro: (N-O 1346), 1315 (C-H symmetrical deformation of CH3 group), 1265 (C-N stretching), 1221 (C-O-C stretching), 1013 (C-H in plane deformation of aromatic ring), 823 (C-H out of plane bending of 1,4-disubstituion. mp 274 ºC; MS: m/z 467; Anal. Calcd. for C27H25N5O3: C, 69.36; H, 5.39; N, 14.9. Found: C, 68.86; H, 5.09; N, 14.18%.

N-(4-bromophenyl)-4,7-dihydro-5-methyl-7-(4-(phenoxymethyl)phenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide 4i. m.p. 189 ºC); white crystals; 1H NMR (DMSO-d6) δ ppm: (δ 1.60) (s, 3H, Ha), (δ 4.54) (m, 2H, Hb), (δ 6.74) (s, 1H, Hc), (δ 6.65) (s, 1H, Hd), (δ 6.75-6.76) (d, 1H, He,), (δ 6.66-7.00) (m, 4H, Hf-i), (δ 7.11-7.14) (m, 5H, Hj-n), (δ 7.22-7.29) (s, 1H, Ho), (δ 7.47-7.52) (d, 2H, Hp,q,), (δ 9.11) (s, 1H, Hr), (δ 10.00) (s, 1H, Hs). FT IR (cm-1): 3544 (Free -OH) 3300 (N-H stretching of secondary amine), 3012 (C-H stretching of aromatic ring), 2952 (C-H asymmetrical stretching of CH3 group), 2854 (C-H asymmetrical stretching of CH3 group), 1600 (C=O stretching of amide), 1554 (C=N stretching of triazole ring), 1500 (N-H deformation of pyrimidine ring), 1423, 1402 (C=C stretching of aromatic ring), 1400 (C-H asymmetrical deformation of CH3 group), 1305 (C-H symmetrical deformation of CH3 group), 1255 (C-N stretching), 1277 (C-O-C stretching), 1015 (C-H in plane deformation of aromatic ring), 806 (C-H out of plane bending of 1,4-disubstituion). Maas: m/z 516; Anal. Calcd. for C26H22BrN5O2: C, 60.47; H, 4.29; N, 13.56; . Found: C, 60.01; H, 3.89; N, 12.46%.

N-(3-bromophenyl)-4,7-dihydro-5-methyl-7-(4-(phenoxymethyl)phenyl)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide 4j. m. p. 168 ^{o}C; white crystals; 1H NMR (DMSO-d6) δ ppm: (δ 2.01) (s, 3H, Ha), (δ 4.05) (t, 2H, Hb), (δ 6.48) (s, 1H, Hc), (δ 6.54-6.59) (d, 2H, Hd,e, (δ 6.58-6.68) (d, 1H, Hd,), (δ 7.09-7.12) (t, 1H, Hf,), (δ 7.18-7.26) (m, 6H, Hg-l), (δ 7.34-7.41) (t, 1H, Hn), (δ 7.51) (s, 2H, Hm), (δ 7.68-7.72) (m, 1H, Ho-q), (δ 9.89) (s, 1H, Hr), (δ 10.20) (s, 1H, Hs). FT IR (cm-1): 3333 (N-H stretching of secondary amine), 3165 (C-H stretching of aromatic ring), 2956 (C-H asymmetrical stretching of CH3 group), 2854 (C-H asymmetrical stretching of CH3 group), 1662 (C=O stretching of amide), 1626 (C=N stretching of triazole ring), 1551 (N-H deformation of pyrimidine ring), 1502, 1421 and 1401 (C=C stretching of aromatic ring), 1356 (C-H asymmetrical deformation of CH3 group), 1302 (C-H symmetrical deformation of CH3 group), 1265 (C-N stretching), 1223 (C-O-C stretching), 1010 (C-H in plane deformation of aromatic ring), 823 (C-H out of plane bending of 1,4-disubstituion. Maas: m/z 516; Anal. Calcd. for C26H22BrN5O2: C, 60.47; H, 4.29; N, 13.56; . Found: C, 60.01; H, 3.89; N, 12.46%.

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