



RESEARCH ARTICLE

An Efficient Multi Component Synthesis: Novel Triazolopyrimidines

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ABSTRACT

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

KEYWORDS

Pyrimidines, acetoacetamides, triazole condensation 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, so four different isomeric families of compounds are defined (see Fig. 1). Among these, 1,2,4-triazolo[1,5-a]pyrimidine derivatives are thermodynamically more stable and, thus, the most studied ones¹, 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]pyrimidines² 1,2,4-triazolo[4,3-a]pyrimidines³ and 1,2,4-triazolo[4,3-c]pyrimidines⁴ have also been published.

The studies about the coordination chemistry of triazolopyrimidines have been exclusively focused till now in the 1,5-a series. These compounds, which are structurally similar and may be regarded as mimic of isomeric purines, have displayed a rich coordination chemistry, a

considerable number of new compounds with interesting structural features having been characterized⁵, including simple mononuclear compounds with monodentately coordinated ligands^{6,7} and di or polynuclear compounds in which either the triazolopyrimidine ligand⁸ or other auxiliary ligands⁹ bridge the metalatoms.

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.^{10,11-15} Most of these are based on modification of the classical one-pot Biginelli reaction^{10,11-14} and in some cases on more

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complex multi-step processes involving harsh reaction conditions and long reaction times.¹⁶⁻¹⁷

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 pyrimidines (**4a-j**) with the advantage of short reaction time, high yield and environmentally friendliness (**Scheme-a**).

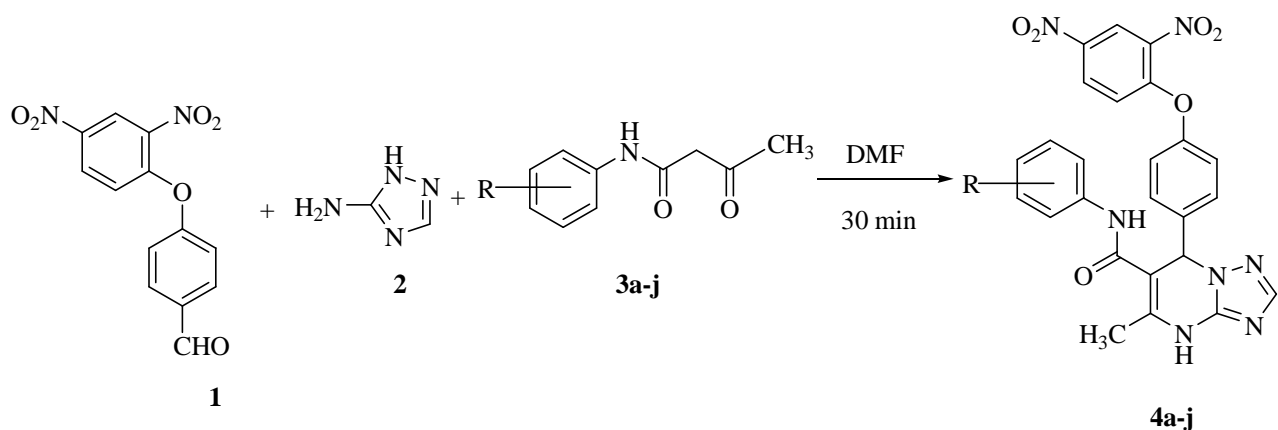


Fig.:-1

Scheme-a

EXPERIMENTAL

Melting points were measured in open capillaries and are uncorrected. ¹H NMR spectra were recorded on Bruker 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. Thin Layer Chromatography was performed on silica gel-G using hexane: ethylacetate solvent system.

Typical experimental procedure for the synthesis of triazolopyrimidines.

A mixture of the 5-amino-1,2,4-triazole (2 mmol), an appropriate acetoacetamide (1 mmol) and 4-(2,4-dinitrophenoxy)benzaldehyde (1 mmol) was refluxed in 0.5 ml of DMF for 30

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.

7-(4-(2,4-dinitrophenoxy)phenyl)-N-(3-chlorophenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide 4a. m.p. 202°C; white crystals; ¹H NMR (DMSO-d₆) δ ppm: (δ 2.13) (s, 3H, H_a), (δ 6.46) (s, 1H, H_b), (δ 6.73-6.75) (d, 2H, H_{cc}), (δ 6.86-6.88) (d, 1H, H_d), (δ 7.04-7.08) (t, 2H,

H_{cc'}), (δ 7.17-7.21) (t, 1H, H_f), (δ 7.27-7.35) (m, 3H, H_{g-i}), (δ 7.48-7.52) (dd, 2H, H_{jk}), (δ 7.61) (s, 1H, H_l), (δ 9.78) (s, 1H, H_m), (δ 10.19) (s, 1H, H_n). FT IR (cm⁻¹): 3259 (N-H stretching of secondary amine), 3032 (C-H stretching of aromatic ring), 2920 (C-H asymmetrical stretching of CH₃ group), 2875 (C-H asymmetrical stretching of CH₃ 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 CH₃ group), 1410 (C-H symmetrical deformation of CH₃ group), 1330 (C-N stretching), 1274 (C-NO₂ symmetrical deformation of NO₂ group), 1247 (C-O-C stretching), 1028 (C-H in plane deformation of aromatic ring), 821 (C-H out of plane bending of 1,4-disubstitution), 736 (C-Cl stretching), Mass: m/z 548; Anal. Calcd. for

C₂₅H₁₈ClN₇O₆: C, 54.80; H, 3.31; Cl, 6.47; N, 17.89; O, 17.52; Found: C, 54.75; H, 3.25; Cl, 6.24; N, 17.75; O, 17.23%.

7-(4-(2,4-dinitrophenoxy)phenyl)-N-(4-fluorophenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-

carboxamide 4b. m.p. 201 °C; white crystals; ¹H NMR (DMSO-d₆) δ ppm: (δ 2.24) (s, 3H, H_a), (δ 6.41) (s, 1H, H_b), (δ 6.67-6.76) (d, 2H, H_{cc'}), (δ 6.82-6.89) (d, 1H, H_d), (δ 7.03-7.09) (t, 2H, H_{ee'}), (δ 7.17-7.37) (dd' dd', 4H, H_{ff-gg'}), (δ 7.49-7.54) (dd, 2H, H_{hi}), (δ 7.63) (s, 1H, H_j), (δ 9.67) (s, 1H, H_k), (δ 10.13) (s, 1H, H_l). FT IR (cm⁻¹): 3249 (N-H stretching of secondary amine), 3022 (C-H stretching of aromatic ring), 2911 (C-H asymmetrical stretching of CH₃ group), 2863 (C-H asymmetrical stretching of CH₃ group), 1657 (C=O stretching of amide), 1608 (C=N stretching of triazole ring), 1545 (N-H deformation of pyrimidine ring), 1512 and 1474 (C=C stretching of aromatic ring), 1454 (C-H asymmetrical deformation of CH₃ group), 1408 (C-H symmetrical deformation of CH₃ group), 1324 (C-N stretching), 1278 (C-NO₂ symmetrical deformation of NO₂ group), 1249 (C-O-C stretching), 1029 (C-H in plane deformation of aromatic ring), 826 (C-H out of plane bending of 1,4-disubstitution), 738 (C-Cl stretching), Mass: m/z 531; Anal. Calcd. for C₂₅H₁₈FN₇O₆: C, 56.50; H, 3.41; F, 3.57; N, 18.45; O, 18.06; Found: C, 56.24; H, 3.31; F, 3.51; N, 18.40; O, 18.00%.

7-(4-(2,4-dinitrophenoxy)phenyl)-N-(4-chlorophenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-

carboxamide 4c. m.p. 211 °C; white crystals; ¹H NMR (DMSO-d₆) δ ppm: (δ 2.15) (s, 3H, H_a), (δ 6.34) (s, 1H, H_b), (δ 6.57-6.68) (d, 2H, H_{cc'}), (δ 6.78-6.84) (d, 1H, H_d), (δ 7.05-7.12) (t, 2H, H_{ee'}), (δ 7.20-7.41) (dd' dd', 4H, H_{ff-gg'}), (δ 7.45-7.50) (dd, 2H, H_{hi}), (δ 7.69) (s, 1H, H_j), (δ 9.64) (s, 1H, H_k), (δ 10.05) (s, 1H, H_l). FT IR (cm⁻¹): 3189 (N-H stretching of secondary amine), 3002 (C-H stretching of aromatic ring), 2901 (C-H asymmetrical stretching of CH₃ group), 2803 (C-H asymmetrical stretching of CH₃ group), 1607 (C=O stretching of amide),

1602 (C=N stretching of triazole ring), 1525 (N-H deformation of pyrimidine ring), 1502 and 1464 (C=C stretching of aromatic ring), 1444 (C-H asymmetrical deformation of CH₃ group), 1401 (C-H symmetrical deformation of CH₃ group), 1334 (C-N stretching), 1268 (C-NO₂ symmetrical deformation of NO₂ group), 1239 (C-O-C stretching), 1019 (C-H in plane deformation of aromatic ring), 834 (C-H out of plane bending of 1,4-disubstitution), 729 (C-Cl stretching), Mass: m/z 548; Anal. Calcd. for C₂₅H₁₈ClN₇O₆: C, 54.80; H, 3.31; Cl, 6.47; N, 17.89; O, 17.52; Found: C, 54.68; H, 3.23; Cl, 6.25; N, 17.71; O, 17.12%.

7-(4-(2,4-dinitrophenoxy)phenyl)-N-(4-nitrophenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-

carboxamide 4d. m.p. 223 °C; white crystals; ¹H NMR (DMSO-d₆) δ ppm: (δ 2.10) (s, 3H, H_a), (δ 6.30) (s, 1H, H_b), (δ 6.50-6.60) (d, 2H, H_{cc'}), (δ 6.71-6.79) (d, 1H, H_d), (δ 7.02-7.08) (t, 2H, H_{ee'}), (δ 7.15-7.34) (dd' dd', 4H, H_{ff-gg'}), (δ 7.41-7.46) (dd, 2H, H_{hi}), (δ 7.56) (s, 1H, H_j), (δ 9.58) (s, 1H, H_k), (δ 10.02) (s, 1H, H_l). FT IR (cm⁻¹): 3230 (N-H stretching of secondary amine), 3022 (C-H stretching of aromatic ring), 2926 (C-H asymmetrical stretching of CH₃ group), 2853 (C-H asymmetrical stretching of CH₃ group), 1656 (C=O stretching of amide), 1623 (C=N stretching of triazole ring), 1555 (N-H deformation of pyrimidine ring), 1516 and 1453 (C=C stretching of aromatic ring), 1423 (C-H asymmetrical deformation of CH₃ group), 1409 (C-H symmetrical deformation of CH₃ group), 1345 (C-N stretching), 1253 (C-NO₂ symmetrical deformation of NO₂ group), 1229 (C-O-C stretching), 1028 (C-H in plane deformation of aromatic ring), 843 (C-H out of plane bending of 1,4-disubstitution), 738 (C-Cl stretching), Mass: m/z 558; Anal. Calcd. for C₂₅H₁₈N₈O₈: C, 53.77; H, 3.25; N, 20.06; O, 22.92; Found: C, 53.58; H, 3.12; N, 20.00; O, 22.86%.

7-(4-(2,4-dinitrophenoxy)phenyl)-N-(3-nitrophenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-

carboxamide 4e. m.p. 189°C; white crystals; ¹H

NMR (DMSO- d_6) δ ppm: (δ 2.11) (s, 3H, H_a), (δ 6.43) (s, 1H, H_b), (δ 6.71-6.73) (d, 2H, $H_{cc'}$), (δ 6.82-6.84) (d, 1H, H_d), (δ 7.02-7.06) (t, 2H, $H_{e'e'}$), (δ 7.12-7.16) (t, 1H, H_f), (δ 7.23-7.31) (m, 3H, H_{g-i}), (δ 7.42-7.46) (dd, 2H, H_{jk}), (δ 7.63) (s, 1H, H_l), (δ 9.65) (s, 1H, H_m), (δ 10.23) (s, 1H, H_n). FT IR (cm^{-1}): 3267 (N-H stretching of secondary amine), 3025 (C-H stretching of aromatic ring), 2922 (C-H asymmetrical stretching of CH_3 group), 2845 (C-H asymmetrical stretching of CH_3 group), 1665 (C=O stretching of amide), 1615 (C=N stretching of triazole ring), 1524 (N-H deformation of pyrimidine ring), 1516 and 1452 (C=C stretching of aromatic ring), 1413 (C-H asymmetrical deformation of CH_3 group), 1411 (C-H symmetrical deformation of CH_3 group), 1363 (C-N stretching), 1251 (C-NO₂ symmetrical deformation of NO₂ group), 1213 (C-O-C stretching), 1032 (C-H in plane deformation of aromatic ring), 823 (C-H out of plane bending of 1,4-disubstitution), 738 (C-Cl stretching), Mass: m/z 558; Anal. Calcd. for $C_{25}H_{18}N_8O_8$: C, 53.77; H, 3.25; N, 20.06; O, 22.92; Found: C, 53.60; H, 3.13; N, 19.89; O, 22.82%.

7-(4-(2,4-dinitrophenoxy)phenyl)-N-(4-hydroxyphenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide 4f. m.p. 198 °C; white crystals; ¹H NMR (DMSO- d_6) δ ppm: (δ 2.14) (s, 3H, H_a), (δ 4.42) (s, 1H, H_b), (δ 6.32) (s, 1H, H_c), (δ 6.48-6.58) (d, 2H, $H_{d,d'}$), (δ 6.64-6.74) (d, 1H, H_e), (δ 7.05-7.11) (t, 2H, $H_{f,f'}$), (δ 7.16-7.29) (dd' dd', 4H, $H_{g,g'-h,h'}$), (δ 7.42-7.48) (dd, 2H, H_{ij}), (δ 7.62) (s, 1H, H_k), (δ 9.52) (s, 1H, H_l), (δ 10.11) (s, 1H, H_m). FT IR (cm^{-1}): 3256 (N-H stretching of secondary amine), 3054 (C-H stretching of aromatic ring), 2958 (C-H asymmetrical stretching of CH_3 group), 2868 (C-H asymmetrical stretching of CH_3 group), 1652 (C=O stretching of amide), 1641 (C=N stretching of triazole ring), 1525 (N-H deformation of pyrimidine ring), 1509 and 1452 (C=C stretching of aromatic ring), 1413 (C-H asymmetrical deformation of CH_3 group), 1401 (C-H symmetrical deformation of CH_3 group), 1354 (C-N stretching), 1235 (C-NO₂

symmetrical deformation of NO₂ group), 1234 (C-O-C stretching), 1021 (C-H in plane deformation of aromatic ring), 834 (C-H out of plane bending of 1,4-disubstitution), 728 (C-Cl stretching), Mass: m/z 529; Anal. Calcd. for $C_{25}H_{19}N_7O_7$: C, 56.71; H, 3.62; N, 18.52; O, 21.15; Found: C, 56.54; H, 3.51; N, 18.23; O, 21.01%.

7-(4-(2,4-dinitrophenoxy)phenyl)-N-(2-chlorophenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide 4g. m.p. 194°C; white crystals; ¹H NMR (DMSO- d_6) δ ppm: (δ 2.23) (s, 3H, H_a), (δ 6.25) (s, 1H, H_b), (δ 6.71-6.73) (d, 2H, $H_{cc'}$), (δ 6.78-6.80) (d, 1H, H_d), (δ 7.00-7.04) (t, 2H, $H_{e'e'}$), (δ 7.10-7.15) (t, 1H, H_f), (δ 7.20-7.24) (m, 5H, H_{g-k}), (δ 7.41-7.51) (dd, 2H, H_{lm}), (δ 7.52) (s, 1H, H_n), (δ 9.52) (s, 1H, H_o), (δ 10.02) (s, 1H, H_p). FT IR (cm^{-1}): 3245 (N-H stretching of secondary amine), 3023 (C-H stretching of aromatic ring), 2917 (C-H asymmetrical stretching of CH_3 group), 2864 (C-H asymmetrical stretching of CH_3 group), 1651 (C=O stretching of amide), 1612 (C=N stretching of triazole ring), 1524 (N-H deformation of pyrimidine ring), 1502 and 1484 (C=C stretching of aromatic ring), 1424 (C-H asymmetrical deformation of CH_3 group), 1405 (C-H symmetrical deformation of CH_3 group), 1356 (C-N stretching), 1254 (C-NO₂ symmetrical deformation of NO₂ group), 1256 (C-O-C stretching), 1012 (C-H in plane deformation of aromatic ring), 831 (C-H out of plane bending of 1,4-disubstitution), 732 (C-Cl stretching), Mass: m/z 548; Anal. Calcd. for $C_{25}H_{18}ClN_7O_6$: C, 54.80; H, 3.31; Cl, 6.47; N, 17.89; O, 17.52; Found: C, 54.72; H, 3.21; Cl, 6.20; N, 17.70; O, 17.20%.

7-(4-(2,4-dinitrophenoxy)phenyl)-N-(4-methoxyphenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide 4h. m.p. 202°C; white crystals; ¹H NMR (DMSO- d_6) δ ppm: (δ 2.23) (s, 3H, H_a), (δ 3.23) (s, 3H, H_b), (δ 3.46) (s, 2H, H_c), (δ 6.25) (s, 1H, H_d), (δ 6.71-6.73) (d, 2H, $H_{e'e'}$), (δ 6.78-6.80) (d, 1H, H_f), (δ 7.00-7.04) (t, 2H, H_g), (δ 7.10-7.15) (t, 1H, H_h), (δ 7.20-7.24) (m,

5H, H_{i-k}), (δ 7.41-7.51) (dd, 2H, H_{lm}), (δ 7.52) (s, 1H, H_n), (δ 9.52) (s, 1H, H_o), (δ 10.02) (s, 1H, H_p). FT IR (cm⁻¹): 3240 (N-H stretching of secondary amine), 3020 (C-H stretching of aromatic ring), 2913 (C-H asymmetrical stretching of CH₃ group), 2860 (C-H asymmetrical stretching of CH₃ group), 1650 (C=O stretching of amide), 1610 (C=N stretching of triazole ring), 1521 (N-H deformation of pyrimidine ring), 1500 and 1480 (C=C stretching of aromatic ring), 1411 (C-H asymmetrical deformation of CH₃ group), 1401 (C-H symmetrical deformation of CH₃ group), 1323 (C-N stretching), 1251 (C-NO₂ symmetrical deformation of NO₂ group), 1250 (C-O-C stretching), 1011 (C-H in plane deformation of aromatic ring), 821 (C-H out of plane bending of 1,4-disubstitution), 723 (C-Cl stretching), Mass: m/z 543; Anal. Calcd. for C₂₆H₂₁N₇O₇: C, 57.46; H, 3.89; N, 18.04; O, 20.61; Found: C, 57.34; H, 3.54; N, 18.00; O, 20.53%.

7-(4-(2,4-dinitrophenoxy)phenyl)-N-(4-bromophenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide 4i. m.p. 210 °C; white crystals; ¹H NMR (DMSO-d₆) δ ppm: (δ 2.02) (s, 3H, H_a), (δ 6.13) (s, 1H, H_b), (δ 6.54-6.66) (d, 2H, H_{cc}), (δ 6.76-6.82) (d, 1H, H_d), (δ 7.04-7.10) (t, 2H, H_{ee}), (δ 7.16-7.36) (dd' dd', 4H, H_{ff-gg}), (δ 7.48-7.52) (dd, 2H, H_{hi}), (δ 7.80) (s, 1H, H_j), (δ 9.54) (s, 1H, H_k), (δ 10.13) (s, 1H, H_l). FT IR (cm⁻¹): 3289 (N-H stretching of secondary amine), 3022 (C-H stretching of aromatic ring), 2923 (C-H asymmetrical stretching of CH₃ group), 2832 (C-H asymmetrical stretching of CH₃ group), 1612 (C=O stretching of amide), 1600 (C=N stretching of triazole ring), 1554 (N-H deformation of pyrimidine ring), 1511 and 1431 (C=C stretching of aromatic ring), 1421 (C-H asymmetrical deformation of CH₃ group), 1400 (C-H symmetrical deformation of CH₃ group), 1344 (C-N stretching), 1223 (C-NO₂ symmetrical deformation of NO₂ group), 1201 (C-O-C stretching), 1054 (C-H in plane deformation of aromatic ring), 832 (C-H out of plane bending of 1,4-disubstitution), 730 (C-Br stretching), Mass: m/z 591; Anal. Calcd. for

C₂₅H₁₈BrN₇O₆: C, 50.69; H, 3.06; Br, 13.49; N, 16.55; O, 16.21; Found: C, 50.62; H, 3.00; Br, 13.32; N, 16.23; O, 16.02%.

7-(4-(2,4-dinitrophenoxy)phenyl)-N-(3-bromophenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxamide 4j. m.p. 191 °C; white crystals; ¹H NMR (DMSO-d₆) δ ppm: (δ 2.12) (s, 3H, H_a), (δ 6.21) (s, 1H, H_b), (δ 6.52-6.64) (d, 2H, H_{cc}), (δ 6.74-6.80) (d, 1H, H_d), (δ 7.00-7.08) (t, 2H, H_{ee}), (δ 7.12-7.30) (dd' dd', 4H, H_{ff-gg}), (δ 7.40-7.42) (dd, 2H, H_{hi}), (δ 7.64) (s, 1H, H_j), (δ 9.67) (s, 1H, H_k), (δ 10.54) (s, 1H, H_l). FT IR (cm⁻¹): 3223 (N-H stretching of secondary amine), 3001 (C-H stretching of aromatic ring), 2954 (C-H asymmetrical stretching of CH₃ group), 2856 (C-H asymmetrical stretching of CH₃ group), 1602 (C=O stretching of amide), 1598 (C=N stretching of triazole ring), 1525 (N-H deformation of pyrimidine ring), 1500 and 1456 (C=C stretching of aromatic ring), 1409 (C-H asymmetrical deformation of CH₃ group), 1397 (C-H symmetrical deformation of CH₃ group), 1357 (C-N stretching), 1228 (C-NO₂ symmetrical deformation of NO₂ group), 1211 (C-O-C stretching), 1042 (C-H in plane deformation of aromatic ring), 838 (C-H out of plane bending of 1,4-disubstitution), 729 (C-Br stretching), Mass: m/z 591; Anal. Calcd. for C₂₅H₁₈BrN₇O₆: C, 50.69; H, 3.06; Br, 13.49; N, 16.55; O, 16.21; Found: C, 50.54; H, 3.00; Br, 13.27; N, 16.20; O, 16.00%.

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