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A one-pot multi component synthesis of triazolopyrimidines

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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 multi component synthesis within 30-45 minutes with high yield. The structures of the products were supported by FTIR, PMR and mass spectral data.

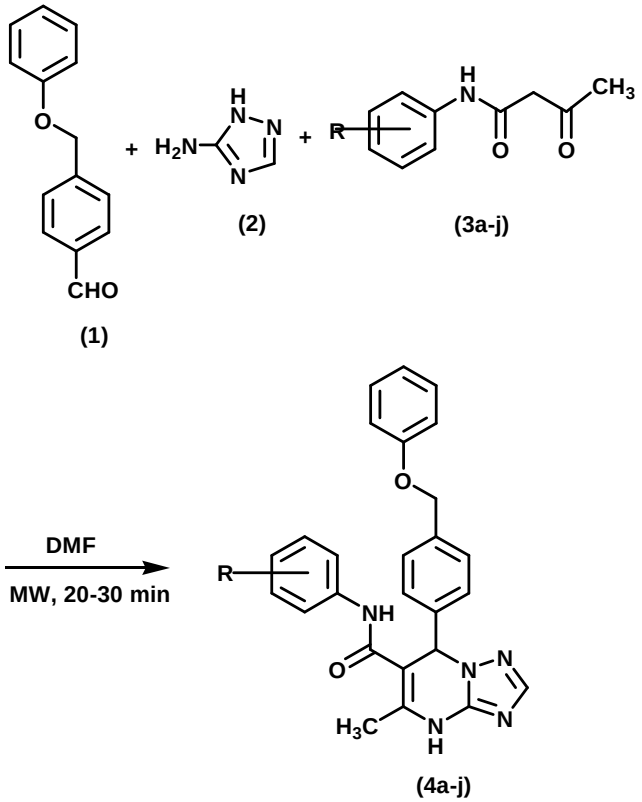
KEYWORDS

Triazolo[1,5-a]pyrimidines;
Acetoacetamides;
5-Amino-1,2,4-triazole;
Multi component 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-triazolopyrimi-dines. 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], Acetohydro-xyacid synthase inhibitor[11], CDK-2 inhibitors[12], Anti-inflammatory[13], fungicidal activities[14], antimycoba-cterial 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

EXPERIMENTAL

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 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.

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 ºC; 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 °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 °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 pyrimidine 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 °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 °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 °C; 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 °C; 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 °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%.

REFERENCES

[1] G.Fischer; Adv.Heterocycl.Chem., **57**, 81 **(1993)**.
[2] M.A.E.Shaban, A.E.A.Morgan; Adv.Heterocycl. Chem., **77**, 345 **(2002)**.
[3] M.A.E.Shaban, A.E.A.Morgan; Adv.Heterocycl. Chem., **73**, 131 **(2002)**.
[4] M.A.E.Shaban, A.E.A.Morgan; Adv.Heterocycl. Chem., **75**, 243 **(2002)**.
[5] N.Zhang, A.K.Semiramis, N.Thai et al.; J.Med. Chem., **50**, 319 **(2007)**.
[6] L.Havlicek, K.Fuksova, V.Krystof, et al.; Bioorg. Med.Chem., **13**, 5399 **(2009)**.
[7] M.E.Fraley, W.F.Hoffman, R.S.Rubino; Bioorg. Med.Chem.Lett., **12**, 2767 **(2002)**.
[8] Q.Chen, X.L.Zhu, Z.M.Liu, et al.; Eur.J.Med. Chem., **43**, 595 **(2008)**.
[9] S.Uryu, S.Tokuhiro, T.Murasugi, et al.; Brain Research, **46**, 298 **(2002)**.
[10] C.F.Beyer, N.Zhang, R.Hernandez, D.Vitale, J.Lucas, T.Nguyen, C.Discafani, S.Ayral-Kaloustian, J.Gibbons; J.Cancer Res., **68**, 2292 **(2008)**.
[11] Q.Chen, X.Zhu, L.Jiang, Z.Liu, G.Yang; European Journal of Medicinal Chemistry, **43**, 595 **(2008)**.
[12] H.Li, J.Tatlock, A.Linton, J.Gonzalez, T.Jewell, L.Patel, S.Ludlum, M.Drowns, S.V.Rahavendran, H.Skor, R.Hunter, S.T.Shi, K.J.Herlihy, H.Parge, M.Hickey, X.Yu, F.Chau, J.Nonomiya, C.Lewis; J.Med.Chem., **52**, 1255 **(2009)**.
[13] C.Chen, L.Lv, F.Ji, Q.Chen, H.Xu, C.Niu, Z.Xi, G.Yang; Bioorg.Med.Chem., **17**, 3011 **(2009)**.
[14] Q.Chen, Z.M.Liu, C.N.Chen, L.L.Jiang, G.F.Yang; Chem.Biodivers., **6(8)**, 1254-1265 **(2009)**.
[15] Arch Pharm, Weinheim, **342(2)**, 94-99 **(2009)**.
[16] H.Peng, G.Kumaravel, G.Yao, L.Sha, J.Wang, H.Van Vlijmen, T.Bohnert, C.Huang, C.B.Vu, C.L.Ensinger, H.Chang, T.M.Engber, E.T.Whalley, R.C.Petter; J.Med.Chem., **47**, 6218 **(2004)**.
[17] V.Ram, P.Srivastava, S.K.Singh, M.Kandpal, B.L.Tekwani; Bioorg.Med.Chem.Lett., **7**, 1087 **(1997)**.