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A One-pot Microwave Irradiation Synthesis of Pyrimido[1,2-a]benzimidazoles

Borisagar M*[1], Baldev A[1], Nimavat K[2], Ram H[3], Vyas K[4]

[1]*Research scholar of Shree J.J.T. University,Chudela (Rajasthan), India.*

[2] *Government Science College, Gandhinagar, India.*

[3]*Navin Fluorine International Limited , Surat, India.*

[4]*Sheth L.H. Science College, Mansa.Gujarat, India.*

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ABSTRACT

Synthesis of a series of pyrimido[1,2-a]benzimidazoles **(4a-j)** was achieved from different acetoacetamides, 3,4-dimethoxybenzaldehyde and 2-Aminobenzimedazole using microwave irradiation within 50 minutes with high yield. The structures of the products were supported by FTIR, PMR and mass spectral data.

KEYWORDS

Pyrimido[1,2-a]benzimidazoles; Acetoacetamides; 2-Aminobenzimedazole, microwave irradiation synthesis.

INTRODUCTION

The condensation of a ring of benzimedazole and another one of pyrimidine gives rise to the formation of bicyclic heterocycles known as Pyrimido[1,2-a]benzimidazoles. Among these isomeric families of compounds, Pyrimido[1,2-a]benzimidazoles derivatives Revisions surveying the synthesis, reactivity, spectroscopic characterization and crystallographic studies of 5,8-dihydroimidazolo[1,2-a]pyrimidines[1], benz[4,5]imidazo[1,2-a]pyrimidine[2] 3-hydroxy-1,2,3,4-tetrahydropyrimido [1,2-a]benzimidazoles[3] and 2,3-Diarylpyrimido[1,2-a]benzimidazole[4] have also been published. From the standpoint of biological activity, fused heteroaromatic systems are often of much greater interest than the constituent monocyclic compounds. Antimicrobial[5-8], antimalarial[9], antiproliferative[10], protein kinase inhibitor[11], T cell activation[12], angioprotein receptors and/or vascular endothelial growth factor receptor-2 (VEGFR-2) inhibitory activities[13], hypotensive, spasmolytic, and antiaggregant activities[14], anesthetic activity[15] and diuretic[16], antiInflammatory[17,18], antiamoebic[19], substance P receptor binding activity[20], antiarrhythmic[21], central nervous system-depressing[22], antidiabetics[23], benzodiazepine receptor binding activity[24], antiparasitic[25], herbicidal[26], DNA-topoisomerase I inhibitory activity[27], immunotropic activity[28], antineoplastic activity[29] etc. activities have been reported for certain pyrimido[1,2-a]benzimidazole derivatives.

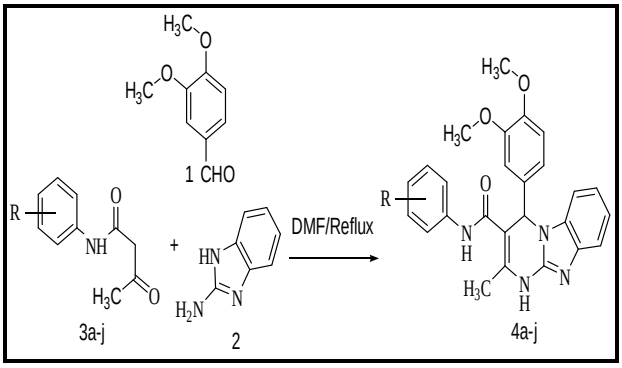
We have developed a new one-pot multi component synthesis of novel Pyrimido[1,2-a]benzimidazoles **(4a-j)** with the advantages of short reaction time, high yield and environmental friendliness **(Scheme-1)**.

***Address for Correspondence:**
Mahendra Borisagar
Shree J.J.T. University,Chudela,
Rajasthan, India.
E-Mail Id: mgborisagar@yahoo.com

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.



Scheme-1

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 Pyrimido[1,2-a]benzimidazoles.

A mixture of the 2-amino-benzimidazole (2 mmol), acetoacetaminde (1.5 mmol) and 3,4-dimethoxybenzaldehyde (1 mmol) in 0.4 ml of DMF was refluxed under microwave irradiation for 50 min. After cooling, methanol (~15 ml) was added. The reaction mixture was allowed to stand overnight and then filtered to give the solid Pyrimido[1,2-a]benzimidazoles products **(4a-j)**, which were crystallized from ethanol and subsequently dried in air.

N-(4-methoxyphenyl)-2-methyl-4-(3,4-dimethoxyphenyl)-1,4-dihydro-pyrimido[1,2-a]benzi- midazole-3-carboxamide (4a)

M. p. 180 ºC; white crystals; ^{1}H NMR (DMSO-d_6) δ ppm: (δ 1.13) (s, 3H, H_a), (δ 3.37) (s, 9H, H_b), (δ 5.69) (s, 1H, H_c), (δ 6.60-6.72) (m, 3H, $H_{d-f,}$), (δ 6.72-6.74) (d, 2H, $H_{gg'}$), (δ 7.22-7.24) (d, 2H, $H_{hh'}$), (δ 7.54-7.56) (d, 2H, $H_{ii'}$), (δ 7.76-7.78) (d, 2H, $H_{jj'}$), (δ 9.48) (s, 1H, H_k), (δ 9.78) (s, 1H, H_l). FT IR (cm-1): 3157 (N-H stretching of secondary amine), 3051 (C-H stretching of aromatic ring), 2958 (C-H asymmetrical stretching of CH3 group), 2899 (C-H asymmetrical stretching of CH3 group), 1683 (C=O stretching of amide), 1627 (N-H deformation of pyrimidine ring), 1575 and 1510 (C=C stretching of aromatic ring), 1454 (C-H asymmetrical deformation of CH3 group), 1365 (C-H symmetrical deformation of CH3 group), 1261 (C-O-C asymmetrical stretching of OCH3), 1174 (C-N stretching), 1095 (C-H in planedeformation of aromatic ring), 825 (C-H out of plane bending of 1,4-disubstituion); Mass: *m/z* 470; Anal. Calcd. for $C_{27}H_{26}N_4O_4$: C, 68.92; H, 5.57; N, 11.91; O, 13.60. Found: C, 68.67; H, 5.32; N, 11.74; O, 13.51%.

N-(4-chlorophenyl)-2-methyl-4-(3,4-dimethoxyphenyl)-1,4-dihydro-pyrimido[1,2-a]benzi- midazole-3-carboxamide (4b)

M. p. 179 ºC; white crystals; ^{1}H NMR (DMSO-d_6) δ ppm: (δ 1.17) (s, 3H, H_a), (δ 3.39) (s, 6H, H_b), (δ 5.66) (s, 1H, H_c), (δ 6.62-6.70) (m, 3H, $H_{d-f,}$), (δ 6.70-6.72) (d, 2H, $H_{gg'}$), (δ 7.20-7.24) (d, 2H, $H_{hh'}$), (δ 7.50-7.52) (d, 2H, $H_{ii'}$), (δ 7.72-7.74) (d, 2H, $H_{jj'}$), (δ 9.56) (s, 1H, H_k), (δ 9.88) (s, 1H, H_l). FT IR (cm-1): 3164 (N-H stretching of secondary amine), 3050 (C-H stretching of aromatic ring), 2925 (C-H asymmetrical stretching of CH3 group), 2856 (C-H asymmetrical stretching of CH3 group), 1677 (C=O stretching of amide), 1620 (N-H deformation of pyrimidine ring), 1558 and 1505 (C=C stretching of aromatic ring), 1429 (C-H asymmetrical deformation of CH3 group), 1327 (C-H symmetrical deformation of CH3 group), 1256 (C-O-C asymmetrical stretching of OCH3), 1178 (C-N stretching), 1077 (C-H in planedeformation of aromatic ring), 630 (C-Cl stretching), 822 (C-H out of plane bending of 1,4-disubstituion); Mass: *m/z* 458; Anal. Calcd. for $C_{26}H_{23}ClN_4O_3$: C, 68.11; H, 5.06; F, 4.14; N, 12.22; O, 10.47. Found: C, 68.05; H, 5.00; F, 4.05; N, 12.12; O, 10.24%.

N-(4-hydroxyphenyl)-2-methyl-4-(3,4-dimethoxyphenyl)-1,4-dihydro-pyrimido[1,2-a]benzi- midazole-3-carboxamide (4c)

M. p. 186 ºC; white crystals; ^{1}H NMR (DMSO-d_6) δ ppm: (δ 1.19) (s, 3H, H_a), (δ 3.29) (s, 6H, H_b), (δ 4.22) (s, 1H, H_c), (δ 5.67) (s, 1H, H_d), (δ 6.56-6.60) (m, 3H, $H_{e-g,}$), (δ 6.72-6.74) (d, 2H, $H_{hh'}$), (δ 7.20-7.24) (d, 2H, $H_{ii'}$), (δ 7.50-7.52) (d, 2H, $H_{jj'}$), (δ 7.72-7.74) (d, 2H, $H_{kk'}$), (δ 9.51) (s, 1H, H_l), (δ 9.79) (s, 1H, H_m). FT IR (cm-1):

3156 (N-H stretching of secondary amine), 3006 (C-H stretching of aromatic ring), 2953 (C-H asymmetrical stretching of CH3 group), 2846 (C-H asymmetrical stretching of CH3 group), 1672 (C=O stretching of amide), 1611 (N-H deformation of pyrimidine ring), 1548 and 1500 (C=C stretching of aromatic ring), 1451 (C-H asymmetrical deformation of CH3 group), 1312 (C-H symmetrical deformation of CH3 group), 1251 (C-O-C asymmetrical stretching of OCH3), 1187 (C-N stretching), 1094 (C-H in planedeformation of aromatic ring), 835 (C-H out of plane bending of 1,4-disubstituion); Mass: *m/z* 456; Anal. Calcd. for $C_{26}H_{24}N_4O_4$: C, 68.41; H, 5.30; N, 12.27; O, 14.02. Found: C, 68.24; H, 5.21; N, 12.20; O, 14.00 %.

N-(4-fluorophenyl)-2-methyl-4-(3,4-dimethoxyphenyl)-1,4-dihydro-pyrimido[1,2-a]benzi- midazole-3-carboxamide (4d)

M. p. 182 ºC; white crystals; ^{1}H NMR (DMSO-d_6) δ ppm: (δ 1.21) (s, 3H, H_a), (δ 3.28) (s, 6H, H_b), (δ 5.74) (s, 1H, H_c), (δ 6.64-6.72) (m, 3H, $H_{d\text{-}f}$,), (δ 6.75-6.77) (d, 2H, $H_{gg'}$), (δ 7.22-7.24) (d, 2H, $H_{hh'}$), (δ 7.52-7.56) (d, 2H, $H_{ii'}$), (δ 7.70-7.72) (d, 2H, $H_{jj'}$), (δ 9.50) (s, 1H, H_k), (δ 9.80) (s, 1H, H_l). FT IR (cm-1): 3123 (N-H stretching of secondary amine), 3046 (C-H stretching of aromatic ring), 2920 (C-H asymmetrical stretching of CH3 group), 2850 (C-H asymmetrical stretching of CH3 group), 1675 (C=O stretching of amide), 1624 (N-H deformation of pyrimidine ring), 1550 and 1500 (C=C stretching of aromatic ring), 1434 (C-H asymmetrical deformation of CH3 group), 1322 (C-H symmetrical deformation of CH3 group), 1251 (C-O-C asymmetrical stretching of OCH3), 1174 (C-N stretching), 1075 (C-H in planedeformation of aromatic ring), 1030 (C-F stretching), 827 (C-H out of plane bending of 1,4-disubstituion); Mass: *m/z* 458; Anal. Calcd. for $C_{26}H_{23}FN_4O_3$: C, 68.11; H, 5.06; F, 4.14; N, 12.22; O, 10.47. Found: C, 68.05; H, 5.00; F, 4.05; N, 12.12; O, 10.24%.

N-(4-bromophenyl)-2-methyl-4-(3,4-dimethoxyphenyl)-1,4-dihydro-pyrimido[1,2-a]benzi- midazole-3-carboxamide (4e)

M. p. 181 ºC; white crystals; ^{1}H NMR (DMSO-d_6) δ ppm: (δ 1.28) (s, 3H, H_a), (δ 3.24) (s, 6H, H_b), (δ 5.64) (s, 1H, H_c), (δ 6.46-6.50) (m, 3H, $H_{d\text{-}f}$,), (δ 6.72-6.74) (d, 2H, $H_{gg'}$), (δ 7.20-7.24) (d, 2H, $H_{hh'}$), (δ 7.56-7.58) (d, 2H, $H_{ii'}$), (δ 7.72-7.74) (d, 2H, $H_{jj'}$), (δ 9.60) (s, 1H, H_k), (δ 9.86) (s, 1H, H_l). FT IR (cm-1): 3145 (N-H stretching of secondary amine), 3057(C-H stretching of aromatic ring), 2987 (C-H asymmetrical stretching of CH3 group), 2846 (C-H asymmetrical stretching of CH3 group), 1654 (C=O stretching of amide), 1625 (N-H deformation of pyrimidine ring), 1575 and 1510 (C=C stretching of aromatic ring), 1445 (C-H asymmetrical deformation of CH3 group), 1341 (C-H symmetrical deformation of CH3 group), 1251 (C-O-C asymmetrical stretching of OCH3), 1154 (C-N stretching), 1071 (C-H in planedeformation of aromatic ring), 666 (C-Br stretching), 820 (C-H out of plane bending of 1,4-disubstituion); Mass: *m/z* 518; Anal. Calcd. for $C_{26}H_{23}BrN_4O_3$: C, 60.12; H, 4.46; Br, 15.38; N, 10.79; O, 9.24. Found: C, 60.10; H, 4.27; Br, 15.18; N, 10.69; O, 9.14%

N-(3-chloro,4-fluorophenyl)-2-methyl-4-(3,4-dimethoxyphenyl)-1,4-dihydro-pyrimido[1,2-a]benzi- midazole-3-carboxamide (4f)

M. p. 180 ºC; white crystals; ^{1}H NMR (DMSO-d_6) δ ppm: (δ 1.22) (s, 3H, H_a), (δ 3.21) (s, 6H, H_b), (δ 5.25) (s, 1H, H_c), (δ 6.46-6.48) (m, 2H, $H_{d\text{-}f}$,), (δ 6.70-6.72) (d, 2H, $H_{gg'}$), (δ 7.22-7.24) (d, 2H, $H_{hh'}$), (δ 7.54-7.56) (d, 2H, $H_{ii'}$), (δ 7.70-7.74) (d, 2H, $H_{jj'}$), (δ 9.65) (s, 1H, H_k), (δ 9.96) (s, 1H, H_l). FT IR (cm-1): 3125 (N-H stretching of secondary amine), 3054 (C-H stretching of aromatic ring), 2982 (C-H asymmetrical stretching of CH3 group), 2844 (C-H asymmetrical stretching of CH3 group), 1653 (C=O stretching of amide), 1626 (N-H deformation of pyrimidine ring), 1574 and 1518 (C=C stretching of aromatic ring), 1442 (C-H asymmetrical deformation of CH3 group), 1348 (C-H symmetrical deformation of CH3 group), 1258 (C-O-C asymmetrical stretching of OCH3), 1157 (C-N stretching), 1071 (C-H in planedeformation of aromatic ring), 1012 (C-F stretching), 666 (C-Cl stretching), 820 (C-H out

of plane bending of 1,4-disubstituion); Mass: *m/z* 493; Anal. Calcd. for $C_{26}H_{22}ClFN_4O_3$: C, 63.35; H, 4.50; Cl, 7.19; F, 3.85; N, 11.37; O, 9.74. Found: C, 63.12; H, 4.33; Cl, 7.11; F, 3.46; N, 11.27; O, 9.64%.

N-(3,4-dichlorophenyl)-2-methyl-4-(3,4-dimethoxyphenyl)-1,4-dihydro-pyrimido[1,2-a] benzimidazole-3-carboxamide (4g)

M. p. 179 ºC; white crystals; ^{1}H NMR (DMSO-d_6) δ ppm: (δ 1.24) (s, 3H, H_a), (δ 3.12) (s, 6H, H_b), (δ 5.45) (s, 1H, H_c), (δ 6.40-6.44) (m, 2H, $H_{d\text{-}f}$,), (δ 6.70-6.72) (d, 2H, $H_{gg'}$), (δ 7.22-7.24) (d, 2H, $H_{hh'}$), (δ 7.52-7.54) (d, 2H, $H_{ii'}$), (δ 7.72-7.74) (d, 2H, $H_{jj'}$), (δ 9.45) (s, 1H, H_k), (δ 9.90) (s, 1H, H_l). FT IR (cm-1): 3124 (N-H stretching of secondary amine), 3045 (C-H stretching of aromatic ring), 2957 (C-H asymmetrical stretching of CH3 group), 2846 (C-H asymmetrical stretching of CH3 group), 1657 (C=O stretching of amide), 1628 (N-H deformation of pyrimidine ring), 1575 and 1516 (C=C stretching of aromatic ring), 1457 (C-H asymmetrical deformation of CH3 group), 1346 (C-H symmetrical deformation of CH3 group), 1268 (C-O-C asymmetrical stretching of OCH3), 1164 (C-N stretching), 1057 (C-H in planedeformation of aromatic ring), 653 (C-Cl stretching), 829 (C-H out of plane bending of 1,4-disubstituion); Mass: *m/z* 509; Anal. Calcd. for $C_{26}H_{23}Cl_2N_4O_3$: C C, 61.31; H, 4.35; Cl, 13.92; N, 11.00; O, 9.42; Found: C, 61.13; H, 4.23; Cl, 13.81; N, 10.50; O, 9.23%.

N-(3-chlorophenyl)-2-methyl-4-(3,4-dimethoxyphenyl)-1,4-dihydro-pyrimido[1,2-a]benzi- midazole-3-carboxamide (4h)

M. p. 174 ºC; white crystals; ^{1}H NMR (DMSO-d_6) δ ppm: (δ 1.24) (s, 3H, H_a), (δ 3.57) (s, 6H, H_b), (δ 5.67) (s, 1H, H_c), (δ 6.48-6.50) (m, 3H, $H_{d\text{-}f}$,), (δ 6.70-6.74) (d, 2H, $H_{gg'}$), (δ 7.22-7.24) (d, 2H, $H_{hh'}$), (δ 7.66-7.68) (d, 2H, $H_{ii'}$), (δ 7.78-7.80) (d, 2H, $H_{jj'}$), (δ 9.46) (s, 1H, H_k), (δ 9.96) (s, 1H, H_l). FT IR (cm-1): 3142 (N-H stretching of secondary amine), 3055(C-H stretching of aromatic ring), 2987 (C-H asymmetrical stretching of CH3 group), 2847 (C-H asymmetrical stretching of CH3 group), 1657 (C=O stretching of amide), 1627 (N-H deformation of pyrimidine ring), 1577 and 1517 (C=C stretching of aromatic ring), 1448 (C-H asymmetrical deformation of CH3 group), 1348 (C-H symmetrical deformation of CH3 group), 1258 (C-O-C asymmetrical stretching of OCH3), 1184 (C-N stretching), 1084 (C-H in planedeformation of aromatic ring), 656 (C-Cl stretching), 827 (C-H out of plane bending of 1,4-disubstituion); Mass: *m/z* 475; Anal. Calcd. for $C_{26}H_{23}ClN_4O_3$: C, 65.75; H, 4.88; Cl, 7.46; N, 11.80; O, 10.11; Found: C, 65.45; H, 4.68; Cl, 7.26; N, 11.72; O, 10.01%

N-(3-bromophenyl)-2-methyl-4-(3,4-dimethoxyphenyl)-1,4-dihydro-pyrimido[1,2-a]benzi- midazole-3-carboxamide (4i)

M. p. 188 ºC; white crystals; ^{1}H NMR (DMSO-d_6) δ ppm: (δ 1.22) (s, 3H, H_a), (δ 3.47) (s, 6H, H_b), (δ 5.54) (s, 1H, H_c), (δ 6.40-6.48) (m, 3H, $H_{d\text{-}f}$,), (δ 6.70-6.76) (d, 2H, $H_{gg'}$), (δ 7.22-7.26) (d, 2H, $H_{hh'}$), (δ 7.46-7.50) (d, 2H, $H_{ii'}$), (δ 7.62-7.67) (d, 2H, $H_{jj'}$), (δ 9.70) (s, 1H, H_k), (δ 9.76) (s, 1H, H_l). FT IR (cm-1): 3144 (N-H stretching of secondary amine), 3051 (C-H stretching of aromatic ring), 2985 (C-H asymmetrical stretching of CH3 group), 2844 (C-H asymmetrical stretching of CH3 group), 1653 (C=O stretching of amide), 1628 (N-H deformation of pyrimidine ring), 1576 and 1514 (C=C stretching of aromatic ring), 1448 (C-H asymmetrical deformation of CH3 group), 1342 (C-H symmetrical deformation of CH3 group), 1257 (C-O-C asymmetrical stretching of OCH3), 1154 (C-N stretching), 1071 (C-H in planedeformation of aromatic ring), 646 (C-Br stretching), 829(C-H out of plane bending of 1,4-disubstituion); Mass: *m/z* 518; Anal. Calcd. for $C_{26}H_{23}BrN_4O_3$: C, 60.12; H, 4.46; Br, 15.38; N, 10.79; O, 9.24. Found: C, 60.08; H, 4.21; Br, 15.19; N, 10.59; O, 9.10%.

N-(3-methoxyphenyl)-2-methyl-4-(3,4-dimethoxyphenyl)-1,4-dihydro-pyrimido[1,2-a]benzi- midazole-3-carboxamide (4j)

M. p. 191 ºC; white crystals; ^{1}H NMR (DMSO-d_6) δ ppm: (δ 1.18) (s, 3H, H_a), (δ 3.47) (s, 9H, H_b), (δ 5.59) (s, 1H, H_c), (δ 6.60-6.70) (m, 3H, $H_{d\text{-}f}$,), (δ 6.74-6.78) (d, 2H, $H_{gg'}$), (δ 7.29-7.31) (d, 2H, $H_{hh'}$), (δ 7.46-7.52) (d, 2H, $H_{ii'}$), (δ 7.74-

7.76) (d, 2H, $H_{jj'}$), (δ 9.66) (s, 1H, H_k), (δ 9.78) (s, 1H, H_l). FT IR (cm-1): 3166 (N-H stretching of secondary amine), 3061 (C-H stretching of aromatic ring), 2968 (C-H asymmetrical stretching of CH3 group), 2869 (C-H asymmetrical stretching of CH3 group), 1663 (C=O stretching of amide), 1667 (N-H deformation of pyrimidine ring), 1565 and 1500 (C=C stretching of aromatic ring), 1464 (C-H asymmetrical deformation of CH3 group), 1366 (C-H symmetrical deformation of CH3 group), 1266 (C-O-C asymmetrical stretching of OCH3), 1164 (C-N stretching), 1095 (C-H in planedeformation of aromatic ring), 826 (C-H out of plane bending of 1,4-disubstituion); Mass: *m/z* 470; Anal. Calcd. for $C_{27}H_{26}N_4O_4$: C, 68.92; H, 5.57; N, 11.91; O, 13.60. Found: C, 68.61; H, 5.32; N, 11.70; O, 13.50%.

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