Available online at www.pelagiaresearchlibrary.com

Pelagia Research Library

Der Chemica Sinica, 2012, 3(6):1352-1357

Pelagia Research Library
ISSN: 0976-8505
CODEN (USA) CSHIA5

An efficient synthesis of novel pyrimido[1,2-*a*]benzimidazole derivatives and evaluation of their biological activity

***Ranjit S. Pada, Ram N. Nandaniya and Viresh. H. Shah.**

Department of Chemistry Krantiguru Shyamji Krishna Verma Kachchh University, Bhuj – Kachchh 370 001, Gujarat, (INDIA) .

ABSTRACT

*Synthesis of pyrimido[1,2-a]benzimidazole derivatives (**4a-j**) is based on the Biginelli like cyclocondensation of aromatic aldehydes and acetoacetamide derivatives with 2-amino benzimidazole containing a guanidine fragment. An efficient synthesis of novel pyrimido[1,2-a]benzimidazoles was achieved from The cyclocondensations were achieved by heating of the starting materials in dimethylformamide (DMF) under reflux conditions. Synthesized compounds were characterized by analytical and spectral (IR, ^{1}H NMR, mass spectral and elemental analyses) data and have been screened for their antimicrobial activity.*

Keywords: pyrimido[1,2-a]benzimidazole, benzimidazole, acetoacetamides, Biginelli like cyclocondensation.

INTRODUCTION

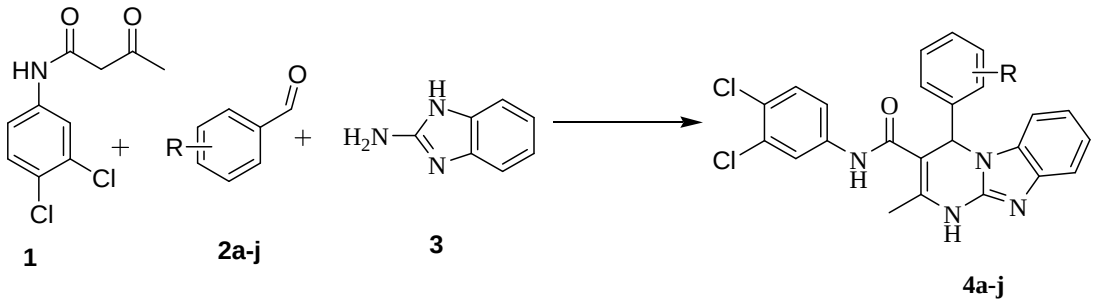
Pyrimidines occupy a distinct and unique place in our life. This heterocyclic moiety has great biological and medicinal significance. A large array of pyrimidine drugs possesses a variety of medicinal properties. Polysubstituted pyrimido [1,2-a]benzimidazoles possess a wide spectrum of biological activities and they are structurally related to natural purine bases. Biological activity of fused heteroaromatic systems are often of much greater interest than the constituent monocyclic compounds. Antimicrobial [1-4], antimalarial [5], antiproliferative [6], protein kinase inhibitory [7], T cell activation [8], angioprotein receptors and/or vascular endothelial growth factor receptor-2 (VEGFR-2) inhibitory [9], hypotensive; spasmolytic; and antiaggregant [10], anesthetic [11] and diuretic [12], antiInflammatory [13, 14], etc. activities have been reported for certain pyrimido[1,2-a]benzimidazole derivatives.

Pyrimido[1,2-a]benzimidazol-2-ones are generally synthesized by the reaction of propiolic esters [15, 16] and α,β-unsaturated esters [17, 19] with 2-aminobenzimidazole. Recently, many one pot synthetic approaches are reported for the synthesis of various substituted pyrimido[1,2-a]benzimidazoles[20-22]. Despite the variety of methods available for the synthesis of pyrimidobenzimidazoles, multi-component synthesis involving use of acetoacetamides is not reported in the literature.

One of the synthetic pathways to pyrimido [1,2-a]benzimidazoles is based on the Biginelli like cyclocondensation of aromatic aldehydes and acetoacetic acid derivatives with 2-amino benzimidazole containing a guanidine fragment. There are literary data about the synthesis of pyrimido [1,2-a]benzimidazoles by treatment of 2-amino benzimidazole with aldehydes and ethyl acetoacetate or cyclic β-diketones. The cyclocondensations were achieved by heating of the starting materials in ethanol with catalytic amounts of hydrochloric acid under reflux conditions or using dimethylformamide (DMF) as solvent. The use of acetoacetamides in these or similar reactions has not been described.

In continuation to our work on bioactive heterocycles we report herein for the first time a rapid efficient, clean and environmentally benign exclusive An efficient synthesis of novel pyrimido[1,2-a]benzimidazole derivatives (**4a-j**) **(Scheme-a)**. An improved method for the synthesis of some new pyrimido[1,2-a]benzimidazoles from aromatic aldehydes, acetoacetamide and 2-amino benzimidazole with significant enhancement in reaction rates, short reaction time (30 min h.), good to excellent yields (59-80%) and ambient temperature. The biological evaluation revealed that the newly synthesized compounds (**4a-j**) and exhibited good antimicrobial activity and moderate antimycobacterial activity.

Reaction Scheme



(Scheme-a) R = 4-OCH3 (a), 4-F (b), 4-CH3 (c), 4-Cl (d), 4-Br (e), 3-Cl (f), 4-NO2 (g), 3-NO2 (h), 2-NO2 (i), 4-OH (j)

MATERIALS AND METHODS

Experimental

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine. IR spectra were recorded Shimadzu FT-IR-8400 instrument using potassium bromide (KBr) pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct injection probe technique. ^{1}H NMR was determined in DMSO-d_6 solution on a bruker Ac 400 MHz spectrometer. Elemental analysis of the all the synthesized compounds was carried out on elemental vario EL III carlo erba 1108 model and the results are in agreements with the structures assigned.

General procedure for the synthesis of N-(3,4-dichlorophenyl)-2-methyl-4-(substitutedphenyl)-1,4-dihydropyrimido[1,2-a]benzimidazole-3-carboxamide(4a-j)

Synthesis of N-(3,4-dichlorophenyl)-3-oxobutanamide (**1**) was achieved using previously published method [23]. A mixture of the 2-amino benzimidazole (**3**) (0.01mol), N-(3,4-dichlorophenyl)-3-oxobutanamide (**1**) (0.01mol) and appropriate aromatic aldehydes (**2a-j**) (0.01mol) was refluxed in 4 ml of DMF for 30 min. using iodine as catalyst. After cooling, methanol (~12 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.

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

^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 2.32 (3H, s, -CH_3), 3.71 (3H, s, -OCH_3), 6.59 (1H, s, -CH), 6.75-6.77 (2H, dd, aromatic), 6.92-6.97 (2H, m, aromatic), 7.03-7.24 (2H, m, aromatic), 7.22-7.24 (2H, dd, aromatic), 7.39-7.45 (2H, m, aromatic), 7.81-7.83 (1H, dd, aromatic), 9.59 (1H, s, -NH), 10.20 (1H, s, -NH-CO); MS: m/z 479(M^+). Yield: 70%; mp 202 ºC;; Anal. Calcd. for $C_{25}H_{20}Cl_2N_4O_2$: C, 62.64; H, 4.21; N, 11.69; Found: C, 62.58; H, 4.14; N, 11.59%; IR (cm^{-1}): 3227 (N-H stretching of secondary amine), 3049 (C-H stretching of aromatic ring), 2975 (C-H asymmetrical stretching of CH_3 group), 2883 (C-H asymmetrical stretching of CH_3 group), 1651 (C=O stretching of amide), 1631 (N-H deformation of pyrimidine ring), 1622, 1564 and 1519 (C=C stretching of aromatic ring), 1456 (C-H asymmetrical deformation of CH_3 group), 1392 (C-H symmetrical deformation of CH_3 group), 1298 and 1247 (C-N stretching), 1078 (C-H in plane deformation of aromatic ring), 825 (C-H out of plane bending of 1,4-disubstituion) 738 and 680 (C-Cl stretching);.

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

^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 1.36 (3H, s, -CH_3), 6.60 (1H, s, -CH_3), 6.88-7.00 (4H, m, aromatic), 7.03-7.08 (1H, m, aromatic), 7.10-7.12 (1H, d, aromatic H_h, J = 8.92), 7.27-7.32 (2H, m, aromatic), 7.36-7.38 (1H, d, aromatic, J = 7.92 Hz), 7.40-7.44 (1H, m, aromatic), 7.79-7.82 (1H, dd, aromatic), 9.77 (1H, s, -NH), 9.97 (1H, s, -NH-CO); MS: m/z 467 (M^+). Yield: 68%; mp 221 ºC; Anal. Calcd. for $C_{24}H_{17}Cl_2FN_4O$: C, 61.68; H, 3.67; N, 11.99; Found: C, 61.53; H, 3.49; N, 11.77%; IR (cm^{-1}): 3273 (N-H stretching of secondary amine), 3057 (C-H stretching of aromatic ring), 2970 (C-H asymmetrical stretching of CH_3 group), 2895 (C-H asymmetrical stretching of CH_3 group), 1637 (C=O stretching of amide), 1688 (N-H deformation of pyrimidine ring), 1508 and 1467 (C=C stretching of aromatic ring), 1410 (C-H asymmetrical deformation of CH_3 group), 1357 (C-H symmetrical deformation of CH_3 group), 1294 and 1228 (C-N stretching), 1087 (C-H in plane deformation of aromatic ring), 1012 (C-Cl stretching), 819 (C-H out of plane bending of 1,4-disubstituion.

N-(3,4-dichlorophenyl) -2-methyl-4-(4-methylphenyl)-1,4-dihydropyrimido- [1,2-a] benzimidazole-3-carboxamide (4c)

^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 1.8 (3H, s, -CH_3), 2.59 (3H, s, -CH_3), 6.60 (1H, s,-CH), 6.91-6.95 (2H, m, aromatic)), 7.05-7.12 (2H, m, aromatic)), 7.19-7.27 (m, 4H,aromatic), 7.39-7.44 (2H, m, aromatic), 7.79-7.81 (1H, dd, aromatic), 9.87 (1H, s, -NH), 9.89 (1H, s, -NH-CO); MS: m/z 463(M^+). Yield: 61%; mp 212 ºC; Anal. Calcd. for $C_{25}H_{20}Cl_2N_4O$: C, 64.80; H, 4.35N, 12.09; Found: C, 64.62; H, 4.12; N, 11.89 %; IR (cm^{-1}): 3288 (N-H stretching of secondary amine), 3055 (C-H stretching of aromatic ring), 2978 (C-H asymmetrical stretching of CH_3 group), 2824 (C-H asymmetrical stretching of CH_3 group), 1651 (C=O stretching of amide), 1624 (N-H deformation of pyrimidine ring), 1562 and 1510 (C=C stretching of aromatic ring), 1458 (C-H asymmetrical deformation of CH_3 group), 1280 (C-H symmetrical deformation of CH_3 group), 1228 (C-N stretching), 1076 (C-H in plane deformation of aromatic ring), 833 (C-H out of plane bending of 1,4-disubstituion), 738 (C-Cl stretching).

N-(3,4-dichlorophenyl)-2-methyl-4-(4-chlorophenyl)-1,4-dihydropyrimido [1,2-a]benzimidazole-3-carboxamide (4d)

^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 1.36 (3H, s,-CH_3), 6.60 (3H, s,-CH_3), 6.88-7.00 (4H, m, aromatic), 7.03-7.08 (1H, m, aromatic), 7.10-7.12 (1H, d, aromatic), 7.27-7.32 (2H, m, aromatic), 7.36-7.38 (1H, d, aromatic), 7.40-7.44 (1H, m, aromatic), 7.79-7.82 (1H, dd, aromatic), 9.77 (1H, s, -NH), 9.97 (1H, s, -NHCO). MS: m/z 483(M^+). Yield: 72%; mp 251 ºC; Anal. Calcd. for $C_{24}H_{17}Cl_3N_4O$: C, 59.58; H, 3.54; N, 11.58; Found: C, 59.39; H, 3.42; N, 11.41%%; IR (cm^{-1}): 3273 (N-H stretching of secondary amine), 3057 (C-H stretching of aromatic ring), 2970 (C-H asymmetrical stretching of CH_3 group), 2895 (C-H asymmetrical stretching of CH_3 group), 1637 (C=O stretching of amide), 1688 (N-H deformation of pyrimidine ring), 1508 and 1467 (C=C stretching of aromatic ring), 1410 (C-H asymmetrical deformation of CH_3 group), 1357 (C-H symmetrical deformation of CH_3 group), 1294 and 1228 (C-N stretching), 1087 (C-H in plane deformation of aromatic ring), 845 (C-H out of plane bending of 1,4-disubstituion), 745 and 680 (C-Cl stretching).

N-(3,4-dichlorophenyl) -2-methyl-4-(3-bromophenyl)-1,4-dihydropyrimido [1,2-a]benzimidazole-3-carboxamide (4e)

^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 1.80 (3H, s, -CH_3), 6.60 (1H, s, -CH), 6.88-7.00 (4H, m, aromatic), 7.03-7.08 (1H, m, aromatic), 7.10-7.12 (1H, d, aromatic), 7.27-7.32 (2H, m, aromatic), 7.36-7.38 (1H, d, aromatic), 7.40-7.44 (1H, m, aromatic), 7.79-7.82 (1H, dd, aromatic), 9.69 (1H, s, -NH), 9.85(1H, s, -NHCO); MS: m/z 528 (M^+). Yield: 64%; mp 218 ºC; Anal. Calcd. for $C_{24}H_{17}BrCl_2N_4O$: C, 54.57; H, 3.24; 13.42; N, 10.61; Found: C, 54.46; H, 3.07; 13.21; N, 10.39%; IR (cm^{-1}): 3273 (N-H stretching of secondary amine), 3057 (C-H stretching of aromatic ring), 2970 (C-H asymmetrical stretching of CH_3 group), 2895 (C-H asymmetrical stretching of CH_3 group), 1637 (C=O stretching of amide), 1688 (N-H deformation of pyrimidine ring), 1508 and 1467 (C=C stretching of aromatic ring), 1410 (C-H asymmetrical deformation of CH_3 group), 1357 (C-H symmetrical deformation of CH_3 group), 1294 and 1228 (C-N stretching), 1087 (C-H in plane deformation of aromatic ring), 780 (C-H out of plane bending of 1,3-disubstituion), 750 (C-Cl stretching) , 610 (C-Br stretching).

N-(3,4-dichlorophenyl) -2-methyl-4-(3-chlorophenyl)-1,4-dihydropyrimido [1,2-a]benzimidazole-3-carboxamide (4f)

^{1}H NMR (400 MHz, DMSO-d_6, δ / ppm): 1.86 (3H, s, -CH_3), 6.60 (1H, s, -CH), 6.88-7.00 (4H, m, aromatic), 7.03-7.08 (1H, m, aromatic), 7.10-7.12 (1H, d, aromatic), 7.27-7.32 (2H, m, aromatic), 7.36-7.38 (1H, d, aromatic, J = 7.94 Hz), 7.40-7.44 (1H, m, aromatic), 7.79-7.82 (1H, dd, aromatic), 9.77 (1H, s, -NH), 9.89 (1H, s, -NHCO); MS: m/z 483(M^+). Yield: 72%; mp 211ºC; Anal. Calcd. for $C_{24}H_{17}Cl_3N_4O$: C, 63.04; H, 4.27; N, 11.31; Found: C, 63.00; H, 4.13; N, 11.24% IR (cm^{-1}): 3273 (N-H stretching of secondary amine), 3057 (C-H stretching of aromatic ring), 2970 (C-H asymmetrical stretching of CH_3 group), 2895 (C-H asymmetrical stretching of CH_3 group), 1637 (C=O stretching of amide), 1688 (N-H deformation of pyrimidine ring), 1508 and 1467 (C=C stretching of aromatic ring),

1410 (C-H asymmetrical deformation of CH_3 group), 1357 (C-H symmetrical deformation of CH_3 group), 1294 and 1228 (C-N stretching), 1087 (C-H in plane deformation of aromatic ring), 790 (C-H out of plane bending of 1,3-disubstituion), 755 and 680 (C-Cl stretching).

N-(3,4-dichlorophenyl) -2-methyl-4-(4-nitrophenyl)-1,4-dihydropyrimido [1,2-a]benzimidazole-3-carboxamide (4g)

^{1}H NMR (400 MHz, DMSO-d_6, δ / ppm): 1.36 (3H, s, -CH_3), 6.60 (1H, s, -CH), 6.88-7.00 (4H, m, aromatic), 7.03-7.08 (1H, m, aromatic), 7.10-7.12 (1H, d, aromatic), 7.27-7.32 (2H, m, aromatic), 7.36-7.38 (1H, d, aromatic, J = 7.92 Hz), 7.40-7.44 (1H, m, aromatic), 7.79-7.82 (1H, dd, aromatic), 9.77 (1H, s, -NH), 9.97 (1H, s, -NHCO); MS: m/z 493(M^+). Yield: 71%; mp 242 ºC;; Anal. Calcd. for $C_{24}H_{17}Cl_2N_5O_3$: C, 58.31; H, 3.47; N, 14.17; Found: C, 58.20; H, 3.28; N, 14.01% IR (cm^{-1}): 3273 (N-H stretching of secondary amine), 3057 (C-H stretching of aromatic ring), 2970 (C-H asymmetrical stretching of CH_3 group), 2895 (C-H asymmetrical stretching of CH_3 group), 1637 (C=O stretching of amide), 1688 (N-H deformation of pyrimidine ring), 1508 and 1467 (C=C stretching of aromatic ring), , 1357 (C-H symmetrical deformation of CH_3 group), 1340 (N-O of NO_2 group), 1294 and 1228 (C-N stretching), 1087 (C-H in plane deformation of aromatic ring), 805 (C-H out of plane bending of 1,4-disubstituion), 745 (C-Cl stretching).

N-(3,4-dichlorophenyl) -2-methyl-4-(3-nitrophenyl)-1,4-dihydropyrimido [1,2-a]benzimidazole-3-carboxamide (4h)

^{1}H NMR (400 MHz, DMSO-d_6, δ / ppm): 1.36 (3H, s, -CH_3), 6.60 (1H, s, -CH), 6.88-7.00 (4H, m, aromatic), 7.03-7.08 (, 1H, m , aromatic), 7.10-7.12 (1H, d, aromatic), 7.27-7.32 (2H, m, aromatic), 7.36-7.38 (1H, d, aromatic, J = 8.0 Hz), 7.40-7.44 (1H, m, aromatic), 7.79-7.82 (1H, dd, aromatic), 9.77 (1H, s, -NH), 9.97 (1H, s, -NHCO); MS: m/z 493(M^+). Yield: 72%; mp 207 ºC; Anal. Calcd. for $C_{24}H_{17}Cl_2N_5O_3$: C, 58.31; H, 3.47; N, 14.17; Found: C, 58.12; H, 3.20; N, 14.01%; IR (cm^{-1}): 3273 (N-H stretching of secondary amine), 3057 (C-H stretching of aromatic ring), 2970 (C-H asymmetrical stretching of CH_3 group), 2895 (C-H asymmetrical stretching of CH_3 group), 1637 (C=O stretching of amide), 1688 (N-H deformation of pyrimidine ring), 1508 and 1467 (C=C stretching of aromatic ring), 1410 (C-H asymmetrical deformation of CH_3 group), 1357 (C-H symmetrical deformation of CH_3 group), 1360 (N-O of NO_2 group), 1294 and 1228 (C-N stretching), 1087 (C-H in plane deformation of aromatic ring), 775 (C-H out of plane bending of 1,3-disubstituion), 738 (C-Cl stretching).

N-(3,4-dichlorophenyl) -2-methyl-4-(2-nitrophenyl)-1,4-dihydropyrimido [1,2-a]benzimidazole-3-carboxamide (4i)

^{1}H NMR (400 MHz, DMSO-d_6, δ / ppm): 1.36 (3H, s, -CH_3), 6.60 (1H, s, -CH), 6.88-7.00 (4H, m, aromatic), 7.03-7.08 (1H, m, aromatic), 7.10-7.12 (1H, d, aromatic), 7.27-7.32 (2H, m, aromatic), 7.36-7.38 (1H, d, aromatic, J = 7.92 Hz), 7.40-7.44 (1H, m, aromatic), 7.79-7.82 (1H, dd, aromatic), 9.77 (1H, s, -NH), 9.97 (1H, s, -NHCO); MS: m/z 493(M^+). Yield: 72%;mp 227 ºC; Anal. Calcd. for $C_{24}H_{17}Cl_2N_5O_3$: C, 58.31; H, 3.47; N, 14.17; Found: C, 58.07; H, 3.39; N, 14.02 %; IR (cm^{-1}): 3273 (N-H stretching of secondary amine), 3057 (C-H stretching of aromatic ring), 2970 (C-H asymmetrical stretching of CH_3 group), 2895 (C-H asymmetrical stretching of CH_3 group), 1637 (C=O stretching of amide), 1688 (N-H deformation of pyrimidine ring), 1508 and 1467 (C=C stretching of aromatic ring), 1410 (C-H asymmetrical deformation of CH_3 group), 1357 (C-H symmetrical deformation of CH_3 group), 1330 (N-O of NO_2 group), 1294 and 1228 (C-N stretching), 1087 (C-H in plane deformation of aromatic ring), 1012 (C-Cl stretching), 740 (C-H out of plane bending of 1,2-disubstituion), 765 (C-Cl stretching).

N-(3,4dichlorophenyl) -2-methyl-4-(4-hydroxyphenyl)-1,4-dihydropyrimido [1,2-a]benzimidazole-3-carboxamide (4j)

^{1}H NMR (400 MHz, DMSO-d_6, δ / ppm): 1.36 (3H, s, -CH_3), 5.40 (1H, s, -OH), 6.60 (1H, s, -CH), 6.88-7.00 (4H, m, aromatic), 7.03-7.08 (1H, m, aromatic), 7.10-7.12 (1H,d, aromatic J = 8.92), 7.27-7.32 (2H, m, aromatic), 7.36-7.38 (1H,d, aromatic, J = 7.92 Hz), 7.40-7.44 (1H,m, aromatic), 7.79-7.82 (1H, dd, aromatic), 9.77 (1H, s, -NH), 9.97 (1H, s, -NHCO); MS: m/z 465(M^+). Yield: 66%;mp 210 ºC; Anal. Calcd. for $C_{24}H_{18}Cl_2N_4O_2$: C, 61.95; H, 3.90; N, 12.04; Found: C, 61.71; H, 3.78; N, 11.91%; IR (cm^{-1}): 3315 (C-O stretching of phenol), 3273 (N-H stretching of secondary amine), 3057 (C-H stretching of aromatic ring), 2970 (C-H asymmetrical stretching of CH_3 group), 2895 (C-H asymmetrical stretching of CH_3 group), 1637 (C=O stretching of amide), 1688 (N-H deformation of pyrimidine ring), 1508 and 1467 (C=C stretching of aromatic ring), 1410 (C-H asymmetrical deformation of CH_3 group), 1357 (C-H symmetrical deformation of CH_3 group), 1294 and 1228 (C-N stretching), 1087 (C-H in plane deformation of aromatic ring), 1012 (C-Cl stretching), 819 (C-H out of plane bending of 1,4-disubstituion), 725 (C-Cl stretching).

Antimicrobial evaluation

All the isolated compound (4a-j) was tested for its antibacterial and antifungal activity (MIC) in vitro by broth dilution method with [24-26] two Gram-positive bacteria Staphylococcus aureus MTCC 96, Streptococcus

pyogenes MTCC 443, two Gram-negative bacteria Escherichia coli MTCC 442, Pseudomonas aeruginosa MTCC 441 and three fungal strains Candida albicans MTCC 227, Aspergillus niger MTCC 282, Aspergillus clavatus MTCC 1323 taking ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin, and greseofulvin as standard drugs. In primary screening 1000 µg mL^{-1}, 500 µg mL^{-1} and 250 µg mL^{-1} concentrations of the synthesized drugs were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms. The drugs found active in primary screening were similarly diluted to obtain 200 µg mL^{-1}, 100 µg mL^{-1}, 50 µg mL^{-1}, 25 µg mL^{-1}, 12.5 µg mL^{-1}, and 6.250 µg mL^{-1} concentrations. The highest dilution showing at least 99 % inhibition zone is taken as MIC. The result of this is much affected by the size of the inoculums. The test mixture should contain 10^8 organism/mL.

Table-I:- In vitro Antimicrobial Screening Results for 4a-j

Code	Minimal inhibition concentration (µg mL^{-1})						
	Gram-positive		Gram-negative		Fungal species		
	S.a.	S. p.	E.c.	P.a.	C. a.	A. n.	A.c.
4a	1000	500	1000	500	250	500	500
4b	250	500	250	500	250	250	500
4c	500	500	1000	1000	500	1000	500
4d	150	250	150	500	500	1000	500
4e	1000	150	500	500	500	1000	250
4f	1000	250	150	150	500	500	1000
4g	250	500	100	250	500	>1000	1000
4h	1000	500	250	200	500	250	1000
4i	200	500	250	200	500	500	1000
4j	250	1000	200	500	1000	1000	500
Gentamycin	0.25	0.5	0.05	1	-	-	-
Ampicillin	250	100	100	100	-	-	-
Chloramphenicol	50	50	50	50	-	-	-
Iprofloxacin	50	50	25	25	-	-	-
Norfloxacin	10	10	10	10	-	-	-
Nystatin	-	-	-	-	100	100	100
Greseofulvin	-	-	-	-	500	100	100

RESULTS AND DISCUSSION

Novel series of Pyrimido[1,2-a]benzimidazoles (**4a-j**) was synthesized by the Biginelli like cyclocondensation of aromatic aldehydes (**2a-j**) and of N-(3,4-dichloro)-4-methyl-3- oxobutanamide (**1**) with 2-amino benzimidazole (**3**) containing a guanidine fragment. For 1,4-dihydropyrimido[1,2-a]benzimidazoles (**4a-j**), confirmatory bands for secondary amine and amidic carbonyl groups were observed at 3414-3282 cm^{-1} and 1690-1600 cm^{-1} respectively. Another characteristic C=N stretching band of imidazole ring was observed at 1626-1500 cm^{-1}. ^1H NMR spectra showed a singlet for the methine proton of pyrimidine ring at 6.00-6.90 δ ppm, and singlets for amino and amide group protons at 7.50-9.90 and 9.45-10.50 δ ppm, respectively. The aromatic ring protons and J value were found to be in accordance with substitution pattern on phenyl ring. Further, mass spectrum shows M^+ according to the structures, which suggested formation of desired products (**4a-j**). The newly synthesized compounds were subjected to antimicrobial activity. The results obtained are depicted in table I.

CONCLUSION

In connection with our ongoing work on multi-component domino synthesis and in view of our interest in the efficient and rapid one-pot three-component preparation of pyrimido[1,2-a]benzimidazoles **(4a-j)** derivatives. We have demonstrated a simple route for the synthesis of the present methodology offers very attractive features such as short reaction time, mild reaction condition, good to excellent product yields, minimum environmental effects and commercially viable. This protocol is general and provides pyrimido[1,2-a]benzimidazoles in good to excellent yields depending on the reactivity of arylaldehydes. The newly synthesized compounds **4a-j** exhibited good antimycobacterial and antibacterial activities.

Acknowledgment
Authors are thankful to his PH.D. Guide Dr.Viresh H. Shah. Authors are also thankful to Department of Chemistry KSKV Kachchh University for providing laboratory facilities. Authors are also thankful to RSIC Chandigarh for providing ^1H NMR spectral analysis of the compounds.

REFERENCES

[1] Abdelhamid, Abdou O.; Abdelall, Eman K. A.; Abdel-Riheem, Nadia A.; Ahmed, Sayed A. Phosphorus, *Sulfur and Silicon and the Related Elements* **2010**, 185(4), 709-718.

[2] *Central European Journal of Chemistry* (**2009**), 7(3), 337-342. Publisher: Springer GmbH, CODEN: CEJCAZ ISSN: 1895-1066.
[3] Shaabani, M. R. Heterocycles **2008**, 75(12), 3005-3014.
[4] Bayomi, S. M.; Amin, K. M.; Al-Obaid, A. M.; Hares, N. G. *Egyptian Journal of Pharmaceutical Sciences* **1993**, 34(1-3), 117-30.
[5] Werbel, L. M.; Curry, A.; Elslager, E. F.; Hess, C. A.; Hutt, M. P.; Youngstrom, C. *Journal of Heterocyclic Chemistry* **1969**, 6(6), 787-96.
[6] Nawrocka, W. P.; Sztuba, B.; Drys, A.; Wietrzyk, J.; Kosendiak, J.; Opolski, A. *Polish Journal of Chemistry* **2006**, 80(2), 279-287.
[7] Nunes, J. J.; Zhu, X. T.; Ermann, M.; Ghiron, C.; Johnston, D. N.; Saluste, C. G. P. WO 2005021551, **2005** [Chem. Abstr.**2005**, 142, 298123].
[8] Nunes, J. J.; Zhu, X. T.; Amouzegh, P.; Ghiron, C.; Johnston, D. N.; Power, E. C. WO 2005009443, **2005** [Chem. Abstr.**2005**, 142, 198088].
[9] Cheung, M.; Harris, P. A.; Hasegawa, M.; Ida, S.; Kano, K.; Nishigaki, N.; Sato, H.; Veal, J. M.; Washio, Y.; West, R. I. WO 2002044156, 2002 [Chem. Abstr. **2002**, 137, 6179].
[10] Anisimova, V. A.; Osipova, M. M.; Spasov, A. A.; Turchaeva, A. F.; Dudchenko, G. P.; Larionov, N. P.; Kovalev, S. G. *Pharmaceutical Chemistry Journal* **2002**, 36(9), 468-473.
[11] Kreutzberger A; Leger M, *Archiv der Pharmazie* **1982**, 315(7), 651-3.
[12] Wahe, H.; Asobo, P. F.; Cherkasov, R. A.; Nkengfack, A. E.; Folefoc, G. N.; Fomum, Z. T.; Doepp, D. *Arkivoc* (Gainesville, FL, United States) **2003**, (14), 170-177.
[13] Sondhi, S. M.; Magan, A.; Sahu, R.; Mahesh, V. K.; Shukla, R.; Patnaik, G. K. *Synthesis* **1994**, (11), 1175-80.
[14] Martin, M. W.; Newcomb, J.; Nunes, J. J.; Boucher, C.; Chai, L.; Epstein, L. F.; Faust, T.; Flores, S.; Gallant, P.; Gore, A.; Gu, Y.; Hsieh, F.; Huang, X.; Kim, J. L.; Middleton, S.; Morgenstern, K.; Oliveira-dos-Santos, A.; Patel, V. F.; Powers, D.; Rose, P.; Tudor, Y.; Turci, S. M.; Welcher, A. A.; Zack, D.; Zhao, H. *J. Med. Chem*. **2008**, 51(6), 1637-1648.
[15] Wade, J. J.; Hegel, R. F.; Toso, C.B.. *J Org. Chem*. **1979**, 44, 1811.
[16] Chow, A. W.; Jakas, D. R.; Trotter, B. P.; Hall, N. M.; Hoover, J. R. E. *J. Heterocycl. Chem*. **1973**, 10, 71.
[17] Nawrocka, W.; Sztuba, B.; Kowalska, M. W.; Liszkiewicz, H.; Wietrzyk, J.; Nasulewicz, A.; Pelczynska,M.; Opolski, A. *Il Farmaco* **2004**, 59, 83.
[18] Da Settimo, A.; Primofiore, G.; Da Settimo, F.; Pardi, G.; Simorini, F.; Marini, A. M. *J. Heterocycl. Chem*. **2002**, 39, 1007.
[19] Elnagdi, M. H.; Wamhoff, H. *Chem. Lett*. **1981**, 419.
[20] T. S. Saleh, T. M. Eldebss, H. M. Albishri, *Ultrason Sonochem*., **2012**, 19, 49-55.
[21] M. V. Goryaeva, Ya. V. Burgart, V. I. Saloutin, O. N. Chupakhin, *Chem. Heterocycl. Comp*., **2012**, 48, 372-376.
[22] G. Li, Z.-T. Zhang, L.-Y. Dai, Y.-L. Du, D. Xue, *Helvetica Chimica Acta*, **2012**, 95, 989-997.
[23] Miriyala, B.; Williamson, J. S. *Tetrahedron Lett*. **2003**, 44, 7957.
[24] National Committee for Clinical and Laboratory Standards, Method for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically Approved Standard, fourth ed. NCCLS, Villanova, Italy, **1997**, Document M 100-S7. S100-S157.
[25] D.H. Isenberg, Essential Procedure for Clinical Microbiology, American Society for Microbiology, Washington, **1998**.
[26] Zgoda, J. R.; Porter, J. R. *Pharm. Biol*. **2001**, 39, 221.