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Research Article

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Synthesis of some new 1,4-dihydropyrimido[1,2-a]benzimidazoles and evaluation of their biological activity

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ABSTRACT

*Synthesis of a series of pyrimido[1,2-a]benzimidazoles **(4a-j)** was achieved from acetoacetamides, name of aldehyde and benzimidazole using refluxing with DMF and isolated by methanol with high yield and purity. The pyrimido[1,2-a]benzimidazoles of the products were supported by FTIR, PMR and mass spectral data.*

Keywords: pyrimidines, acetoacetamides, benzimidazole synthesis.

INTRODUCTION

An improved method for the synthesis of some new 1,4-dihydropyrimido[1,2-a]benz-imidazoles from aromatic aldehydes, Acetoacetamide compounds 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. crystisation using ethanol. The biological evaluation revealed that the newly synthesized compounds **(4a-j)** and exhibited good antimicrobial activity and moderate antimycobacterial activity.

Polysubstituted pyrimido[1,2-*a*]benzimidazoles possess a wide spectrum of biological activities and they are structurally related to natural purine bases.

From the standpoint of biological activity, fused heteroaromatic systems are often of much greater interest than the constituent monocyclic compounds. Antimicrobial [1-4], antimalarial [5], antiproliferative [6], protein kinase inhibitor, [7], T cell activation, [8], angioprotein receptors and/or vascular endothelial growth factor receptor-2 (VEGFR-2) inhibitory activities. [9], hypotensive, spasmolytic, and antiaggregant activities [10], anesthetic activity [11] and diuretic [12], antiInflammatory [13, 14], etc. activities have been reported for certain pyrimido[1,2-*a*]benzimidazole derivatives.

To circumvent these problems, we have developed a new protocol for the synthesis of novel pyrimido[1,2-*a*]benzimidazoles **(4a-j)** with the advantage of short reaction time, high yield and environmentally friendliness **(Scheme-a)**.

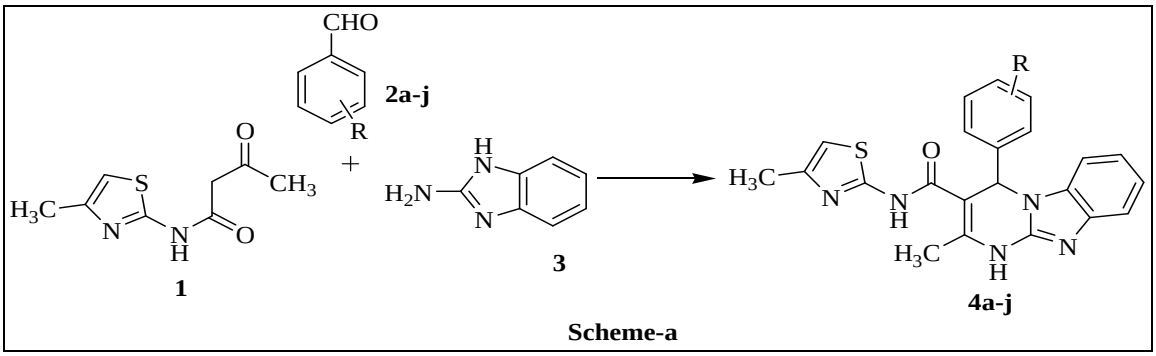
EXPERIMENTAL SECTION

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.

Typical exaperimental procedure for the synthesis of 1,4-dihydropyrimido[1,2-a]benz-imidazoles.
A mixture of the 2-amino benzimidazole (0.01mol), *N*-(4-methylthiazol-2-yl)-3-oxobutanamide (0.01mol) and an appropriate aromatic aldehyde (0.01mol) was refluxed in 10 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 1,4-dihydropyrimido[1,2-*a*]benzimidazoles products **4a-j**, which were crystallized from ethanol. Thin Layer Chromatography was performed on silica gel-G using hexane: ethylacetate solvent system.

Reaction Scheme



Scheme-a

4-(4-chlorophenyl)-2-methyl-N-(4-methyl-1,3-thiazol-2-yl)-1,4dihydropyr- imido[1,2-a] benzimidazole-3-carboxamide (4a)
mp 198 ºC; white crystals ; ^{1}H NMR (DMSO-d_6) δ ppm: 1.25 (s, 3H, H_a), 2.50 (s, 3H, H_b), 6.50 (s, 1H, H_c), 7.12-7.16 (m, 2H, $H_{d,e}$), 7.21-7.25 (m, 2H, $H_{f,g}$), 7.59-7.32 (d, 2H, $H_{hh'}$), 7.49-7.52(d, 2H, $H_{ii'}$) 7.66 (s, 1H, H_j), 10.02 (s, 1H, H_k), 10.09 (s, 1H, H_l). FT IR (cm^{-1}): 3308 (N-H stretching of secondary amine), 3051 (C-H stretching of aromatic ring), 2976 (C-H asymmetrical stretching of CH_3 group), 2827 (C-H asymmetrical stretching of CH_3 group), 1670 (C=O stretching of amide), 1618 (N-H deformation of pyrimidine ring), 1583 and 1508 (C=C stretching of aromatic ring), 1454 (C-H asymmetrical deformation of CH_3 group), 1386 (C-H symmetrical deformation of CH_3 group), 1296 (C-N stretching), 1045 (C-H in plane deformation of aromatic ring), 798 (C-H out of plane bending of 1,4-disubstituion), 736 (C-Cl stretching);; MS: *m/z* 435; Anal. Calcd. for $C_{22}H_{18}ClN_5OS$: C, 60.61; H, 4.16; N, 3.67; Found: C, 60.25; H, 4.02; N, 3.32 %; Yield: 68%.

4-(4-fluorophenyl)-2-methyl-N-(4-methyl-1,3-thiazol-2-yl)-1,4-dihydropyr- imido[1,2-a]benzimidazole-3-carboxamide (4b)
mp 185 ºC; ^{1}H NMR (DMSO-d_6) δ ppm: 1.34 (s, 3H, H_a), 2.24 (s, 3H, H_b), 5.29 (s, 1H, H_c), 6.58 (s, 1H, H_d), 6.92-7.93 (d, 2H, $H_{ee'}$), 7.05-7.09 (m, 2H, $H_{ff'}$), 7.18-7.24 (m, 2H, $H_{gg'}$) 7.39-7.41 (d, 2H, $H_{hh'}$), 9.35 (s, 1H, H_i), 9.56 (s, 1H, H_j). FT IR (cm^{-1}): 3274 (N-H stretching of secondary amine), 3053 (C-H stretching of aromatic ring), 2976 (C-H asymmetrical stretching of CH_3 group), 2845 (C-H asymmetrical stretching of CH_3 group), 1651 (C=O stretching of amide), 1608 (N-H deformation of pyrimidine ring), 1560,1529 and 1504 (C=C stretching of aromatic ring), 1458 (C-H asymmetrical deformation of CH_3 group), 1392 (C-H symmetrical deformation of CH_3 group), 1280 and 1253 (C-N stretching), 1074 (C-H in plane deformation of aromatic ring), 1074 (C-F stretching), 812 (C-H out of plane bending of 1,4-disubstituion). MS: *m/z* 419; Anal. Calcd. for $C_{22}H_{18}FN_5OS$: C, 62.99; H, 4.33; N, 16.70. Found: C, 62.23; H, 4.02; N, 16.28%;; Yield: 66%.

4-(4-methylphenyl)-2-methyl-N-(4-methyl-1,3-thiazol-2-yl)-1,4-dihydro pyri- mido[1,2-a]benzimidazole-3-carboxamide (4c)
mp 250 ºC; ^{1}H NMR (DMSO-d_6) δ ppm: 1.27 (s, 3H, H_a), 2.25 (s, 3H, H_b), 2.72 (s, 3H, H_c), 6.47 (s, 1H, H_d), 7.05-7.10 (m, 4H, H_{e-h}), 7.29-7.31 (d, 2H, H_{ij} ,), 7.53-7.55 (d, 2H, H_{kl} , *J*=8.40 Hz), 7.64 (s, 1H, H_m), 9.96 (s, 1H, H_n), 10.10 (s, 1H, H_o). FT IR (cm^{-1}): 3288 (N-H stretching of secondary amine), 3057 (C-H stretching of aromatic ring), 2976 (C-H asymmetrical stretching of CH_3 group), 2888 (C-H asymmetrical stretching of CH_3 group), 1651 (C=O stretching of amide), 1624 (N-H deformation of pyrimidine ring), 1562,1529 and 1502 (C=C stretching of aromatic ring), 1458 (C-H asymmetrical deformation of CH_3 group), 1394 (C-H symmetrical deformation of CH_3 group), 1257 and 1220 (C-N stretching), 1078 (C-H in plane deformation of aromatic ring), 817 (C-H out of plane bending of 1,4-disubstituion). MS: *m/z* 416; Anal. Calcd. for $C_{23}H_{21}N_5OS$: C, 66.48; H, 5.09; N, 16.85. Found: C, 66.14; H, 4.91; N, 16.11 %;; Yield: 76%.

4-(4-methoxyphenyl)-2-methyl-N-(4-methyl-1,3-thiazol-2-yl)-1,4-dihydro pyri- mido[1,2-a]benzimidazole-3-carboxamide (4d)

mp 211ºC; ^{1}H NMR (DMSO-d_6) δ ppm: 1.27 (s, 3H, H_a), 3.25 (s, 3H, H_b), 2.72 (s, 3H, H_c), 6.47 (s, 1H, H_d), 7.05-7.10 (m, 4H, H_{e-h}), 7.29-7.31 (d, 2H, H_{ij}), 7.53-7.55 (d, 2H, H_{kl} ,), 7.64 (s, 1H, H_m), 9.96 (s, 1H, H_n), 10.10 (s, 1H, H_o). FT IR (cm^{-1}): 3288 (N-H stretching of secondary amine), 3057 (C-H stretching of aromatic ring), 2976 (C-H asymmetrical stretching of CH_3 group), 2888 (C-H asymmetrical stretching of CH_3 group), 1651 (C=O stretching of amide), 1624 (N-H deformation of pyrimidine ring), 1562,1529 and 1502 (C=C stretching of aromatic ring), 1458 (C-H asymmetrical deformation of CH_3 group), 1394 (C-H symmetrical deformation of CH_3 group), 1257 and 1220 (C-N stretching), 1241 (C-O-C stretching), 1078 (C-H in plane deformation of aromatic ring), 817 (C-H out of plane bending of 1,4-disubstituion).MS: *m/z* 431; Anal. Calcd. for $C_{23}H_{21}N_5O_2S$: C, 64.02; H, 4.91; N, 16.23. Found: C, 63.85; H, 4.51; N, 16.02%. Yield: 71%.

4-(3-bromophenyl)-2-methyl-N-(4-methyl-1,3-thiazol-2-yl)-1,4-dihydro pyrimido[1,2-a]benzimidazole-3-carboxamide (4e)

mp 240 ºC; ^{1}H NMR (DMSO-d_6) δ ppm: 1.34 (s, 3H, H_a), 2.24 (s, 3H, H_b), 5.29 (s, 1H, H_c), 6.58 (s, 1H, H_d), 6.92-7.93 (d, 2H, $H_{ee'}$), 7.05-7.09 (m, 2H, $H_{ff'}$), 7.18-7.24 (m, 2H, $H_{gg'}$) 7.39-7.41 (d, 2H, $H_{hh'}$), 9.35 (s, 1H, H_i), 9.56 (s, 1H, H_j). FT IR (cm^{-1}): 3274 (N-H stretching of secondary amine), 3053 (C-H stretching of aromatic ring), 2976 (C-H asymmetrical stretching of CH_3 group), 2845 (C-H asymmetrical stretching of CH_3 group), 1651 (C=O stretching of amide), 1608 (N-H deformation of pyrimidine ring), 1560,1529 and 1504 (C=C stretching of aromatic ring), 1458 (C-H asymmetrical deformation of CH_3 group), 1392 (C-H symmetrical deformation of CH_3 group), 1280 and 1253 (C-N stretching), 1074 (C-H in plane deformation of aromatic ring), 1080 (C-Br stretching), 819 (C-H out of plane bending of 1,3-disubstituion). MS: *m/z* 479; Anal. Calcd. for $C_{22}H_{18}BrN_5OS$: C, 55.01; H, 3.78; N, 14.58. Found: C, 54.79; H, 3.45; N, 14.19%: Yield: 80%.

4-(3-chlorophenyl)-2-methyl-N-(4-methyl-1,3-thiazol-2-yl)-1,4-dihydro pyrimido[1,2-a]benzimidazole-3-carboxamide (4f)

mp 200 ºC; ^{1}H NMR (DMSO-d_6) δ ppm: 1.34 (s, 3H, H_a), 2.24 (s, 3H, H_b), 5.29 (s, 1H, H_c), 6.58 (s, 1H, H_d), 6.92-7.93 (d, 2H, $H_{ee'}$), 7.05-7.09 (m, 2H, $H_{ff'}$), 7.18-7.24 (m, 2H, $H_{gg'}$) 7.39-7.41 (d, 2H, $H_{hh'}$), 9.35 (s, 1H, H_i), 9.56 (s, 1H, H_j). FT IR (cm^{-1}): 3274 (N-H stretching of secondary amine), 3053 (C-H stretching of aromatic ring), 2976 (C-H asymmetrical stretching of CH_3 group), 2845 (C-H asymmetrical stretching of CH_3 group), 1651 (C=O stretching of amide), 1608 (N-H deformation of pyrimidine ring), 1560,1529 and 1504 (C=C stretching of aromatic ring), 1458 (C-H asymmetrical deformation of CH_3 group), 1392 (C-H symmetrical deformation of CH_3 group), 1280 and 1253 (C-N stretching), 1074 (C-H in plane deformation of aromatic ring), 1074 (C-Cl stretching), 805 (C-H out of plane bending of 1,3-disubstituion).MS: *m/z* 435.Anal. Calcd. for $C_{22}H_{18}ClN_5OS$: C, 60.61; H, 4.16; N, 16.07. Found: C, 60.22; H, 4.01; N, 15.77%: Yield: 77%.

2-methyl-N-(4-methyl-1,3-thiazol-2-yl)-4-(4-nitrophenyl)-1,4-dihydro pyrimido[1,2-a]benzimidazole-3-carboxamide (4g)

mp 203 ºC; ^{1}H NMR (DMSO-d_6) δ ppm: 1.34 (s, 3H, H_a), 2.24 (s, 3H, H_b), 5.29 (s, 1H, H_c), 6.58 (s, 1H, H_d), 6.92-7.93 (d, 2H, $H_{ee'}$), 7.05-7.09 (m, 2H, $H_{ff'}$), 7.18-7.24 (m, 2H, $H_{gg'}$) 7.39-7.41 (d, 2H, $H_{hh'}$), 9.35 (s, 1H, H_i), 9.56 (s, 1H, H_j). FT IR (cm^{-1}): 3274 (N-H stretching of secondary amine), 3053 (C-H stretching of aromatic ring), 2976 (C-H asymmetrical stretching of CH_3 group), 2845 (C-H asymmetrical stretching of CH_3 group), 1651 (C=O stretching of amide), 1608 (N-H deformation of pyrimidine ring), 1560,1529 and 1504 (C=C stretching of aromatic ring), 1458 (C-H asymmetrical deformation of CH_3 group), 1392 (C-H symmetrical deformation of CH_3 group), 1316 (Nitro N-O),1280 and 1253 (C-N stretching), 1074 (C-H in plane deformation of aromatic ring), 812 (C-H out of plane bending of 1,4-disubstituion). MS: *m/z* 446. Anal. Calcd. for $C_{22}H_{18}N_6O_3S$: C, 59.18; H, 4.06; N, 18.82. Found: C, 59.04; H, 3.88; N, 18.56%: Yield: 58%.

2-methyl-N-(4-methyl-1,3-thiazol-2-yl)-4-(3-nitrophenyl)-1,4-dihydro pyrimido[1,2-a]benzimidazole-3-carboxamide (4h)

mp 201ºC; ^{1}H NMR (DMSO-d_6) δ ppm: 1.34 (s, 3H, H_a), 2.24 (s, 3H, H_b), 5.29 (s, 1H, H_c), 6.58 (s, 1H, H_d), 6.92-7.93 (d, 2H, $H_{ee'}$), 7.05-7.09 (m, 2H, $H_{ff'}$), 7.18-7.24 (m, 2H, $H_{gg'}$) 7.39-7.41 (d, 2H, $H_{hh'}$), 9.35 (s, 1H, H_i), 9.56 (s, 1H, H_j). FT IR (cm^{-1}): 3274 (N-H stretching of secondary amine), 3053 (C-H stretching of aromatic ring), 2976 (C-H asymmetrical stretching of CH_3 group), 2845 (C-H asymmetrical stretching of CH_3 group), 1651 (C=O stretching of amide), 1608 (N-H deformation of pyrimidine ring), 1560,1529 and 1504 (C=C stretching of aromatic ring), 1458 (C-H asymmetrical deformation of CH_3 group), 1392 (C-H symmetrical deformation of CH_3 group), 1316 (Nitro N-O), 1280 and 1253 (C-N stretching), 1074 (C-H in plane deformation of aromatic ring), 712 (C-H out of plane bending of 1,3-disubstituion). MS: *m/z* 446. Anal. Calcd. for $C_{22}H_{18}N_6O_3S$: C, 59.18; H, 4.06; N, 18.82. Found: C, 59.02; H, 3.82; N, 18.57%.: Yield: 60%;

2-methyl-N-(4-methyl-1,3-thiazol-2-yl)-4-(2-nitrophenyl)-1,4-dihydro pyrimido[1,2-a]benzimidazole-3-carboxamide (4i)

mp 189 ºC; MS: ^{1}H NMR (DMSO-d_6) δ ppm: 1.34 (s, 3H, H_a), 2.24 (s, 3H, H_b), 5.29 (s, 1H, H_c), 6.58 (s, 1H, H_d), 6.92-7.93 (d, 2H, $H_{ee'}$), 7.05-7.09 (m, 2H, $H_{ff'}$), 7.18-7.24 (m, 2H, $H_{gg'}$) 7.39-7.41 (d, 2H, $H_{hh'}$), 9.35 (s, 1H, H_i), 9.56 (s, 1H, H_j). FT IR (cm^{-1}): 3274 (N-H stretching of secondary amine), 3053 (C-H stretching of aromatic ring), 2976 (C-H asymmetrical stretching of CH_3 group), 2845 (C-H asymmetrical stretching of CH_3 group), 1651 (C=O stretching of amide), 1608 (N-H deformation of pyrimidine ring), 1560,1529 and 1504 (C=C stretching of aromatic ring), 1458 (C-H asymmetrical deformation of CH_3 group), 1392 (C-H symmetrical deformation of CH_3 group), 1316 (Nitro N-O), 1280 and 1253 (C-N stretching), 1074 (C-H in plane deformation of aromatic ring), 640 (C-H out of plane bending of 1,2-disubstituion). MS: *m/z* 446; Anal. Calcd. for $C_{22}H_{18}N_6O_3S$: C, 59.18; H, 4.06; N, 18.82. Found: C, 59.02; H, 3.82; N, 18.55%: Yield: 72%;

4-(4-hydroxyphenyl)-2-methyl-N-(4-methyl-1,3-thiazol-2-yl)-1,4-dihydro pyrimido[1,2-a]benzimidazole-3-carboxamide. (4j)

mp 186 ºC; ^{1}H NMR (DMSO-d_6) δ ppm: 1.27 (s, 3H, H_a), 10.25 (s, 1H, H_b), 2.72 (s, 3H, H_c), 6.47 (s, 1H, H_d), 7.05-7.10 (m, 4H, H_{e-h} ,), 7.29-7.31 (d, 2H, H_{ij} ,), 7.53-7.55 (d, 2H, H_{kl} ,), 7.64 (s, 1H, H_m), 9.96 (s, 1H, H_n), 10.10 (s, 1H, H_o). FT IR (cm^{-1}): 3599 (Free -OH),3288 (N-H stretching of secondary amine), 3057 (C-H stretching of aromatic ring), 2976 (C-H asymmetrical stretching of CH_3 group), 2888 (C-H asymmetrical stretching of CH_3 group), 1651 (C=O stretching of amide), 1624 (N-H deformation of pyrimidine ring), 1562,1529 and 1502 (C=C stretching of aromatic ring), 1458 (C-H asymmetrical deformation of CH_3 group), 1394 (C-H symmetrical deformation of CH_3 group), 1257 and 1220 (C-N stretching), 1078 (C-H in plane deformation of aromatic ring), 817 (C-H out of plane bending of 1,4-disubstituion). MS: *m/z* 417; Anal. Calcd. for $C_{22}H_{19}N_5O_2S$: C, 63.29; H, 4.59; N, 16.78. Found: C, 63.06; H, 4.12; N, 16.47%: Yield: 70%;

RESULTS AND DISCUSSION

The synthesis of 1,4-dihydropyrimido[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. Synthesis of *N*-(4-methylthiazol-2-yl)-3-oxobutanamide was achieved using previously published method [15].

There are literary data about the synthesis of 1,4-dihydropyrimido[1,2-*a*]benzimidazoles by treatment of 2-amino benzimidazole with aldehydes and ethyl acetoacetate . The cyclocondensations were achieved by heating of the starting materials in ethanol with catalytic amounts of hydrochloric acid under reflux conditions . The use of acetoacetamides in these or similar reactions has not been described [16-21].

Recognizing these facts, we have synthesised new series of 1,4-dihydropyrimido[1,2-*a*]benzimidazoles **(4a-j)** containing an acetoacetamide fragment. The structures of all the newly synthesized compounds were elucidated by FT-IR, mass spectra, ^{1}H NMR and elemental analyses. The newly synthesized compounds were subjected to antimicrobial activity.

Biological evaluation

Table-1:- *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	200	200	62.5	200	>1000	>1000	>1000
4b	250	250	50	200	>1000	>1000	>1000
4c	500	500	250	250	>1000	>1000	>1000
4d	100	100	250	250	>1000	500	500
4e	200	250	100	100	>1000	>1000	>1000
4f	500	500	100	200	250	1000	1000
4g	1000	250	1000	500	250	1000	1000
4h	150	250	500	250	500	>1000	1000
4i	100	200	100	250	500	500	1000
4j	150	500	250	250	500	>1000	>1000
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

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