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Synthesis, Characterization and Biological Activity Of 1, 4-Dihydropyrimido [1,2-A] Benzimidazole

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ABSTRACT

An effectual direct synthesis of 1,4-dihydropyrimido[1,2-a]benzimidazole (C-01 to C-10) was developed from 1H-benzo[d]imidazol-2-amine, 4-(benzyloxy)-3-methoxybenzaldehyde, N-(substituted phenyl)-3-oxobutanamide by adding few drop of DMF and in presence of conc.HCL. The product was obtained after about 5 hours of heating in refluxing condition. The synthesized compounds were characterized by different spectral and elemental analysis. Some of the obtained compounds showed a promising antimicrobial activity on screening against Gram-positive and Gram-negative bacterial strains.

Keywords : 1,4-dihydropyrimido[1,2-a]benzimidazole, 1H-benzo[d]imidazol-2-amine, 4-(benzyloxy)-3-methoxybenzaldehyde, N-(substituted phenyl)-3-oxobutanamide, Antimicrobial activity.

I. INTRODUCTION

Recently, an emerging bacterial infection has become more challenging worldwide due to the increasing number of multidrug resistant (MDR) microbes[1-7]. This creates the crucial need to develop new more efficient anti-microbial agents. From a medicinal chemistry perspective, developing therapeutic molecules with improved pharmacological properties and drug-tolerance profile, as well as fewer side effects, is an ultimate goal[8]. Hence, libraries with privileged heterocyclic scaffolds are frequently utilized in the development of new potent drugs[9].

Heterocyclic nucleus are most important in developing bioactive drug molecules. They have vital role in our biological system as they forms an integral part of many pharmacologically active molecules, natural products and nucleic acids. Heterocyclic compound are also present in large variety of drug candidate like antitumor, antibiotic, anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic, herbicidal, fungicidal and insecticidal agents[10]. In the recent years much attention has been focused on the synthesis of pyrimidines & other nitrogeneous heterocycles, because of their biological & medicinal importance. Of nitrogenous heterocycles, azoloazines containing fragments similar to the

natural heterocycles purines and pyrimidines are currently of great practical importance. A numerous compounds containing benzimidazole scaffold which are isosteres of the nitrogenous bases of nucleic acids are of great significance[11].Compounds containing the benzimidazole moiety are found to exhibit various types of biological activity, including analgesic[12], antibacterial[13], anticancer[14-15], antifungal[16], antiHIV[17], anti-inflammatory[18], antimalarial[19], antimicrobial[20], antioxidant activity[21], as well as anti-tuberculosis[22] and varied antiviral activities[23]. Thus, the creation of pharmacologically active benzimidazole derivatives is a significant task that requires complex synthetic approaches. Among the structural modification of benzimidazole scaffolds, polycyclic condensed analogs with the participation of five- and six-membered structures is of particular interest and independent significance. Of the large number of fused or polycyclic derivatives of benzimidazoles, pyrimido[1,2-a]benzimidazoles are of significant interest, having structural similarity both with benzimidazoles and with various azolo[1,5-a]pyrimidines which have also proven themselves as structures with relevant biological properties, including antiviral, antibacterial24, anti-septic[25-26], anticancer[27] and anti-glycation[28] effects.

We have synthesize 1,4-dihydropyrimido[1,2-a]benzimidazole derivatives by the refluxing 1H-benzo[d]imidazol-2-amine, 4-(benzyloxy)-3-methoxybenzaldehyde, N-(substituted phenyl)-3-oxobutanamide in solvent, with the addition of DMF and few drops of HCL on constant stirring.. The structures of the newly synthesized compounds were characterized by the elemental analyses, IR, 1H NMR and mass spectral data. The antimicrobial activity was assayed by by the broth dilution method by measuring the minimal Inhibitory Concentration in μg/ml. All the compounds were screened against varieties of bacterial strains such as *Staphylococcus aureus* MTCC-96, *Streptococcus pyogenes* MTCC 443), two Gram-negative bacterial strains (*Escherichia coli* MTCC 442, *Pseudomonas aeruginosa* MTCC 441) and three fungal strains (Candida *albicans* MTCC 227, *Aspergillus Niger* MTCC 282, *Aspergillus clavatus* at different concentration. Standard drugs like Ampicillin, Chloramphenicol and Norfloxacin were used for the comparison purpose.

II. MATERIAL AND METHODS

Melting points were determined in an open capillary tubes and are uncorrected. Thin layer chromatography using silica gel plates were used to access the reactions and purity of the synthesized compounds. All the products have been characterized by elemental analysis, IR, 1H NMR and mass spectral study. IR spectra were recorded on SHIMADZU FTIR-8400 spectrophotometer in KBr disc. 1H NMR spectra were recorded on BRUKER spectrometer (400 MHz) using TMS as an internal standard, chemical shift in δ ppm. Mass spectra were determined using direct inlet probe on a GCMS-QP2010 mass spectrometer.

III. EXPERIMENTAL

General Procedure for the Synthesis of 1,4-dihydropyrimido[1,2-a]benzimidazole (C-01 to C-10)

To a mixture of 1H-benzo[d]imidazol-2-amine, 4-(benzyloxy)-3-methoxybenzaldehyde, N-(substituted phenyl)-3-oxobutanamide in the solvent, few drops of DMF and few drops of con. HCl was added with constant stirring. The resulting mixture was heated for 5 hrs. in refluxing condition. After completion the reaction mixture was kept at room temperature for 20 hrs. The separated crystalline product was filtered and washed with methanol.

ANALYTICAL DATA

4-(4-(benzyloxy)-3-methoxyphenyl)-N-(4-chlorophenyl)-2-methyl-1,4-dihydropyrimido[1,2-a]benzimidazole-3-carboxamide C-01

M.P. 191ºC; Yield: 76% IR (KBr) υ, cm-1: 3149, 2829 (C-H), 3304 (N-H), 1655 (C=O), 1605, 1529 (Aromatic skeletons), 1223 (C-O-C),779 (C-Cl); 1H NMR (400 MHz, DMSO) : δH 2.07 (singlet, 3H, methyl), 3.60 (singlet, 3H, methoxy), 4.93 (singlet, 2H, -CH2-O), 6.58 (singlet, 1H, -CH- of pyrimidine ring), 6.68-7.59 (multiplet, 16H, Aromatic -H), 9.81 (singlet, 1H, NH-CO), 9.81 (singlet, 1H, -NH- Aromatic-NH); MS: m/z 551.03.Anal.found: C, 69.75; H, 4.94; Cl, 6.43; N, 10.17; O, 8.71. for $C_{32}H_{27}ClN_4O_3$

4-(4-(benzyloxy)-3-methoxyphenyl)-N-(3-chlorophenyl)-2-methyl-1,4-dihydropyrimido[1,2-a]benzimidazole-3-carboxamide C-02

M.P. 184ºC; Yield: 68% IR (KBr) υ, cm-1: 3146, 2822 (C-H), 3310 (N-H), 1657 (C=O), 1603, 1523 (Aromatic skeletons), 1227 (C-O-C),772 (C-Cl); 1H NMR (400 MHz, DMSO) : δH 2.26 (singlet, 3H, methyl), 3.83 (singlet, 3H, methoxy), 5.04 (singlet, 2H, -CH2-O), 5.66 (singlet, 1H, -CH- of pyrimidine ring), 6.68-7.99 (multiplet, 16H, Aromatic -H), 10.12 (singlet, 1H, NH-CO), 9.79 (singlet, 1H, -NH- Aromatic-NH); Elemental Analysis for $C_{32}H_{27}ClN_4O_3$; MS: m/z 551.03.

4-(4-(benzyloxy)-3-methoxyphenyl)-N-(2-chlorophenyl)-2-methyl-1,4-dihydropyrimido[1,2-a]benzimidazole-3-carboxamide C-03

M.P. 193ºC; Yield: 72% IR (KBr) υ, cm-1: 3138, 2818 (C-H), 3302 (N-H), 1649 (C=O), 1602, 1527 (Aromatic skeletons), 1219 (C-O-C),776 (C-Cl); 1H NMR (400 MHz, DMSO) : δH 2.23 (singlet, 3H, methyl), 3.87 (singlet, 3H, methoxy), 5.16 (singlet, 2H, -CH2-O), 6.37 (singlet, 1H, -CH- of pyrimidine ring), 6.62-8.04 (multiplet, 16H, Aromatic -H), 10.12 (singlet, 1H, NH-CO), 9.80 (singlet, 1H, -NH- Aromatic-NH); Elemental Analysis for $C_{32}H_{27}ClN_4O_3$; MS: m/z 551.03.

4-(4-(benzyloxy)-3-methoxyphenyl)-N-(4-fluorophenyl)-2-methyl-1,4-dihydropyrimido[1,2-a]benzimidazole-3-carboxamide C-04

M.P. 190ºC; Yield: 78%;IR(KBr) υ cm-1: 3160, 2862 (C-H), 3300 (N-H), 1652 (C=O), 1593,1528 (Aromatic skeletons), 1188 (C-O-C), 1070 (C-F); ^{1}H NMR (400 MHz, DMSO) : δ H 1.76 (singlet, 3H, methyl), 3.38 (singlet, 3H, methoxy), 4.35-4.56 (singlet, 2H, -CH2-O), 6.71-7.68 (multiplet, 16H, Aromatic–H), 8.20-8.21 (singlet, 1H, Aromatic–H), 10.12 (singlet, 1H, NH-CO), 9.80 (singlet, 1H, -NH- Aromatic-NH); MS: m/z 534.58. Anal.found: C, 71.97; H, 5.04; F, 3.53; N, 10.47; O, 8.91% for $C_{32}H_{27}FN_4O_3$.

4-(4-(benzyloxy)-3-methoxyphenyl)-N-(3-fluorophenyl)-2-methyl-1,4-dihydropyrimido[1,2-a]benzimidazole-3-carboxamide C-05

M.P. 183ºC; Yield: 65%;IR(KBr) υ cm-1: 3163, 2861 (C-H), 3308 (N-H), 1657 (C=O), 1591,1529 (Aromatic skeletons), 1191 (C-O-C), 1073 (C-F); ^{1}H NMR (400 MHz, DMSO) : δ H 1.79 (singlet, 3H, methyl), 3.43 (singlet, 3H, methoxy), 4.35-5.02 (singlet, 2H, -CH2-O), 6.71-7.75(multiplet, 16H, Aromatic–H), 8.20-8.25 (singlet, 1H, Aromatic–H), 10.12 (singlet, 1H, NH-CO), 9.81 (singlet, 1H, -NH- Aromatic-NH), Elemental Analysis for $C_{32}H_{27}FN_4O_3$; MS: m/z 534.58.

4-(4-(benzyloxy)-3-methoxyphenyl)-N-(2-fluorophenyl)-2-methyl-1,4-dihydropyrimido[1,2-a]benzimidazole-3-carboxamide C-06

M.P. 193ºC; Yield: 73%;IR(KBr) υ cm-1: 3156, 2858 (C-H), 3303 (N-H), 1651 (C=O), 1592,1526 (Aromatic skeletons), 1186 (C-O-C), 1071 (C-F); ^{1}H NMR (400 MHz, DMSO) : δ H 1.76 (singlet, 3H, methyl), 3.36 (singlet, 3H, methoxy), 4.32-4.87 (singlet, 2H, -CH2-O), 6.71-7.70 (multiplet, 16H, Aromatic–H), 8.20-8.25 (singlet, 1H, Aromatic–H), 10.12 (singlet, 1H, NH-CO), 9.80 (singlet, 1H, -NH- Aromatic-NH), Elemental Analysis for $C_{32}H_{27}FN_4O_3$; MS: m/z 534.58.

4-(4-(benzyloxy)-3-methoxyphenyl)-N-(4-bromophenyl)-2-methyl-1,4-dihydropyrimido[1,2-a]benzimidazole-3-carboxamide C-07

M.P. 196ºC; Yield: 69% IR (KBr) υ, cm-1: 3149, 2829 (C-H), 3304 (N-H), 1655 (C=O), 1605, 1529 (Aromatic skeletons), 1223 (C-O-C),645 (C-Br); 1H NMR (400 MHz, DMSO) : δH 2.12 (singlet, 3H, methyl), 3.63 (singlet, 3H, methoxy), 5.07 (singlet, 2H, -CH2-O), 6.51 (singlet, 1H, -CH- of pyrimidine ring), 6.68-7.72

(multiplet, 16H, Aromatic -H), 9.79 (singlet, 1H, NH-CO), 9.81 (singlet, 1H, -NH- Aromatic-NH); MS: m/z 595.49.Anal.found: C, 64.55; H, 4.56; Br, 13.42; N, 9.41; O, 8.06. for $C_{32}H_{27}BrN_4O_3$.

4-(4-(benzyloxy)-3-methoxyphenyl)-N-(3-bromophenyl)-2-methyl-1,4-dihydropyrimido[1,2-a]benzimidazole-3-carboxamide C-08

M.P. 179ºC; Yield: 75% IR (KBr) υ, cm-1: 3142, 2823 (C-H), 3301 (N-H), 1652 (C=O), 1602, 1523 (Aromatic skeletons), 1221 (C-O-C),639 (C-Br); 1H NMR (400 MHz, DMSO) : δH 2.08 (singlet, 3H, methyl), 3.57 (singlet, 3H, methoxy), 5.04 (singlet, 2H, -CH2-O), 6.35 (singlet, 1H, -CH- of pyrimidine ring), 6.68-7.80 (multiplet, 16H, Aromatic -H), 9.74 (singlet, 1H, NH-CO), 9.79 (singlet, 1H, -NH- Aromatic-NH), Elemental Analysis for $C_{32}H_{27}BrN_4O_3$; MS: m/z 595.49.

4-(4-(benzyloxy)-3-methoxyphenyl)-N-(2-bromophenyl)-2-methyl-1,4-dihydropyrimido[1,2-a]benzimidazole-3-carboxamide C-09

M.P. 192ºC; Yield: 72% IR (KBr) υ, cm-1: 3145, 2828 (C-H), 3303 (N-H), 1654 (C=O), 1603, 1527 (Aromatic skeletons), 1225 (C-O-C),642 (C-Br); 1H NMR (400 MHz, DMSO) : δH 2.10 (singlet, 3H, methyl), 3.61 (singlet, 3H, methoxy), 5.06 (singlet, 2H, -CH2-O), 6.48 (singlet, 1H, -CH- of pyrimidine ring), 6.63-7.79 (multiplet, 16H, Aromatic -H), 9.77 (singlet, 1H, NH-CO), 9.83 (singlet, 1H, -NH- Aromatic-NH), Elemental Analysis for $C_{32}H_{27}BrN_4O_3$; MS: m/z 595.49.

4-(4-(benzyloxy)-3-methoxyphenyl)-N-(4-methylphenyl)-2-methyl-1,4 dihydropyrimido[1,2-a]benzimidazole-3-carboxamide C-10

M.P. 161ºC; Yield: 58% IR (KBr) υ, cm-1: 3132, 2756 (C-H), 3312 (N-H), 1659 (C=O), 1601, 1522 (Aromatic skeletons), 1222 (C-O-C); 1H NMR (400 MHz, DMSO) : δH 2.16 (singlet, 6H, methyl), 3.64 (singlet, 3H, methoxy), 5.02 (singlet, 2H, -CH2-O), 6.41 (singlet, 1H, -CH- of pyrimidine ring), 6.63-7.59 (multiplet, 16H, Aromatic -H), 10.08 (singlet, 1H, NH-CO), 9.77 (singlet, 1H, -NH- Aromatic-NH), Elemental Analysis; C, 74.70; H,5.70; N,10.56; O,9.05. for $C_{32}H_{27}BrN_4O_3$; MS: m/z 530.62.

ANTIMICROBIAL ACTIVITY

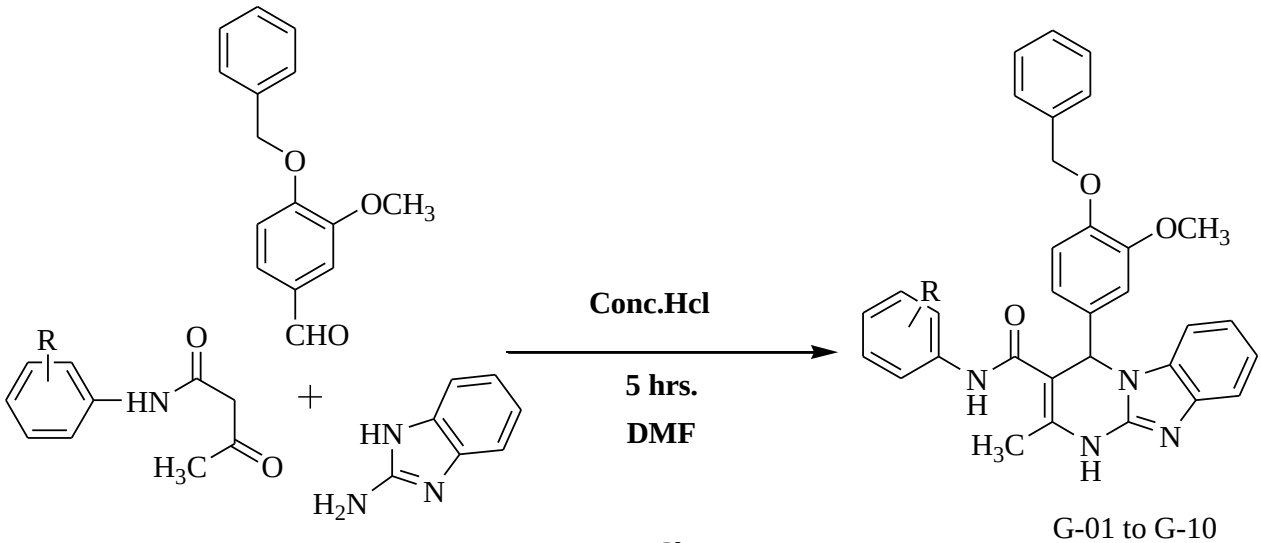
The "*in vitro*" analysis of biological activity of all the synthesized compounds **C1 to C10** was carried out against standard strains of Gram +ve and Gram -ve bacteria and of Fungi. The standard strains were procured from the Microbial Type Culture Collection (MTCC), Gene Bank, Institute of Microbial Technology, Chandigarh, India. The determination of their antimicrobial activity was done by the broth dilution method. Determination of their activity was done against two gram positive bacterial strains, (*Staphylococcus aureus* MTCC-96, *Streptococcus pyogenes* MTCC 443), two Gram-negative bacterial strains (*Escherichia coli* MTCC 442, *Pseudomonas aeruginosa* MTCC 441) and three fungal strains (Candida *albicans* MTCC 227, *Aspergillus Niger* MTCC 282, *Aspergillus clavatus* MTCC 1323) by minimum concentration inhibition method. Here ampicillin, nystatin chloramphenicol, griseofulvin and norfloxacin were used as standard drugs.

The minimal inhibitory concentration (MIC) values determined in vitro analysis by broth dilution method for all the compounds **C1 to C10**, is specified as the minimum concentration of the compound to stop the detectable growth of specific microorganism. Mueller-hinton broth was used for serial dilutions of test compounds and reference drugs. The sample solution was prepared by dissolving the compound in DMSO, Drugs(10gm/mL). Further serially diluted with melted Mueller Hinton agar to obtain the desired concentrations. In primary screening 1000 µg mL^{-1}, 500 µg mL^{-1} and 250 µg mL^{-1} concentrations of synthesized compounds were taken. The synthesized compounds which found active in primary screening were further tested in second set of dilution at 125 µg mL^{-1}, 62.5 µg mL^{-1},50 µg mL^{-1}, 25 µg mL^{-1} and 12.5 µg mL^{-1} concentrations against microorganism. The tubes were inoculated with 10^8cfu mL^{-1} and incubated 37˚C

for 24hrs. The MIC were the minimum or lowest concentration of the tested compounds that yields no turbidity on the plate indicated no growth. To ensure the solvent is inert on the bacterial growth, a control was tested with the test medium supplemented with DMSO at the same dilutions as used in experiment and it was observed that DMSO had no effect on microorganisms in concentrations studied. The results obtained from antimicrobial susceptibility testing are depicted in Table-1.

IV. RESULT AND DISCUSSION

Our investigation was focused on the synthesis of the diversely functionalised and active dihydropyrimido[1,2-a]benzimidazole derivatives.



Scheme-1: Reagents and Reaction Conditions: 1,4-dihydropyrimido[1,2-a]benzimidazole, 1H-benzo[d]imidazol-2-amine, 4-(benzyloxy)-3-methoxybenzaldehyde, N-(substituted phenyl)-3-oxobutanamide. DMF, reflux, 5hrs.

Table-1:- *in vitro Antimicrobial Screening Results for* (C1 to C10)

Compound	Minimal Inhibition Concentration (µg ml^{-1})			
	Gram-Positive		Gram-Negative	
	s.aureus.	*s. pyogene*	*e. coli*	*p.aeruginosa*
C1	250	125	250	250
C2	500	125	250	500
C3	250	250	500	250
C4	500	250	500	250
C5	125	125	125	500
C6	250	500	125	500
C7	500	250	125	250

C8	500	250	250	125
C9	125	250	250	125
C10	250	250	250	250
Ampicillin	250	100	100	100
Chloramphenicol	50	50	50	50
Norfloxacin	10	10	10	10

Here some of the compound showed good antimicrobial acitivty at 250 **µg mL^{-1},** while others are moderate inhibitor or inactive.

Table-2 :- Anti-Fungal Activity

Compound	Minimal Inhibition Concentration(µg mL^{-1})		
	Fungal Species		
	c.a.	a.n.	a.c
C1	250	125	500
C2	250	500	125
C3	250	125	125
C4	250	500	125
C5	500	125	250
C6	250	500	125
C7	500	125	125
C8	250	500	250
C9	250	125	125
C10	500	500	250
Nystatin	100	100	100
Griseofulvin	450	100	100

In this screening compound show efficient antifungal activity with 125 **µg mL^{-1}**.

V. CONCLUSION

The facile one-pot method is efficient to develop diversely functionalised and active pyrimidine derivatives. The method is quite easy and gives the products in better yield and purity. Products can be isolated by simple filtration method so can avoid much tedious purification work. The newly synthesized triazolopyridines possess a promising antibacterial and antifungal activity. Further, the newly synthesized compounds established more SAR evidence of its biological importance in detail.

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