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Original Article

Antioxidant and antimicrobial evaluation of pyrimido [1, 2-*a*] benzimidazoles

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ABSTRACT

When ethyl 2-cyano-3,3-bis(methylthio)acrylate **(2)** on treatment with 2-amino benzimidazole **(1)** in N,N-dimethyl formamide (DMF) and catalytic amount of anhydrous potassium carbonate, gives 3-cyano-2-metylthio-4-oxo-*4H*- pyrimido [1,2-*a*] benzimidazole **(3)**.The latter were further reacted with selected N-,O- and C- nucleophiles such as aryl amines, heteryl amines, substituted phenols and compounds containing an active methylene group to afforded 2-cyano-3-metylthio-4-oxo-4H-pyrimido [1,2-*a*] benzimidazole and their 2-substituted derivatives. All newly synthesized compounds were evaluated and characterized by spectroscopic techniques and screened their very excellent antioxidant and antimicrobial activities.

Keywords: 2-Amino benzimidazole, ethyl cyano bismethylthio acrylate, DMF, Anhydrous K_2CO_3.

INTRODUCTION

Benzimidazole is a heterocyclic aromatic organic compound. It is an important pharmacophore and a privileged structure in medicinal chemistry. This compound is bicyclic in nature which consist of the fusion of benzene and imidazole. Now a day, it is a moiety of choice which possesses many pharmacological properties. The most prominent benzimidazole compound in nature is N-ribosyl-dimethyl benzimidazole, which serves as an axial ligand for cobalt in vitamin B-12[1]. Literature survey shows that among the benzimidazole derivatives, 2-substituted ones are found to be pharmacologically more potent. Hence the design and synthesis of 2-substituted benzimidazole are the potential area of research[2-3]. Some new benzimidazole derivatives shows antimicrobial activity[4-5]. The synthesis of 1, 3-diaryl pyrazinobenzimidazole derivatives have been reported and the investigated for their anticancer activities [6]. Benzimidazole derivatives play important role in medical field with so many pharmacological activities such as antileukemic agent[7], antimicrobial[8], antiviral [9], anti-diabetic [10-11] and anticancer activity [12-16]. Recently we reported efficient synthesis and their antioxidant activity[17]. The potency of these clinically useful drugs in treatment of microbial infections and other activities encouraged us for the development of some more potent and significant compounds[4-5]. In the present work we report new method for synthesis of 3-cyano-2-metylthio-4-oxo-*4H*-pyrimido [1,2-*a*] benzimidazole and its 2-substituted derivatives. Some of the selected compounds shows very good to excellent antioxidant and antimicrobial activities.

MATERIAL AND METHODS

General: Melting points was determined by open capillary tubes and were uncorrected. All the reactions monitored by thin layer chromatography which was carried out on 0.2 mm silica gel-C plates using iodine vapors for detection. Infrared spectra were recorded in Nujol or as potassium bromide pallets on infrared spectrophotometer. Nuclear magnetic resonance spectra were obtained on brukner advance spectrophotometer 400 MHz. Mass spectra were recorded on FT-VC-7070 H Mass spectrometer using the EI technique at 70 eV. All the reaction were carried out under ambient atmosphere. Elemental analysis was performed on a Heraeus CHN-O rapid analyzer.

Procedure for the synthesis of 3-cyano-2-metylthio-4-oxo-*4H*-pyrimido [1, 2-*a*] benzimidazole (3): A mixture of 2-amino benzimidazole (1) (0.01 mol) and ethyl 2-cyano-3,3-bis(methylthio) acrylate (2) (0.01 mol) in 20

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mL of N, N'- dimethyl formamide and anhydrous potassium carbonate (10 mg) was refluxed for 4 hours. The reaction mixture was cooled to room temperature and poured in to ice cold water. The separated solid product was filtered, washed with water and recrystallized from dimethyl formamide-ethanol mixture [2:8] to give pure (3).

Procedure for the synthesis of 2-substituted derivatives of 3-cyano-2-metylthio-4-oxo-*4H*-pyrimido[1,2-a]benzimidazole (3) (4a-c, 5a-c, 6a-c and 7a-c): A mixture of (3) (0.001 m mol) when reacted independently with various aromatic amines , heteryl amines, substituted phenols and compounds containing an active methylene group respectively (0.001 m Mol) in N, N'- dimethyl formamide (15 mL) and catalytic amount of anhydrous potassium carbonate (10 mg) was refluxed for 4-6 hrs. The reaction mixture was cooled to room temperature and poured into ice cold water. The separated solid product was filtered, washed with water and recrystallized from dimethyl formamide-ethanol mixture [2:8] to give pure **4a-c, 5a-c, 6a-c** and **7a-c**

3-Cyano-2-metylthio-4-oxo-*4H*-pyrimido [1, 2-*a*] benzimidazole (3): Orange powder, Yield 88%, m.p 325°C (dec.). IR (KBr/cm^{-1}) 2231 cm^{-1} (CN), 1645 cm^{-1} (CO), ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.0 (s, 1H,-NH), 2.43 (s, 3H, SCH_3), 6.38-6.82(m, 4H,Ar-H) ppm; EI-MS(m/z:RA%): 256.(M^+1).^{13}C NMR(300MHz, $CDCl_3$) δ:18, 114, 119, 97, 110, 120, 128, 130, 156, 152ppm , Anal. Calcd. For: $C_{12}H_8N_4OS$; (C: 56.24; H: 3.15; N: 21.86; O: 6.24; S: 12.51). Found: (C:56.10; H:2.95; N:21.46; O: 6.14; S:12.34).

3-Cyano-2-(4'-methyl anilino)-4-oxo-*4H*-pyrimido[1,2-*a*] benzimidazole (4a): Brown powder, Yield 80%, m.p 337°C (dec.). IR (KBr/cm^{-1}) 2226 cm^{-1} (CN), 1630 cm^{-1} (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.0 (s, 1H, -NH), 2.31 (s, 3H, CH_3), 6.32-6.96 (m, 8H, Ar-H), ppm; EI-MS (m/z: RA %): 315(100%). Anal. Calcd. For: $C_{18}H_{13}N_5O$; (C: 68.56; H: 4.16; N: 22.21). Found: (C, 68.36; H, 4.06; N, 21.96).

3-Cyano-2-(4'-methoxy anilino)-4-oxo-*4H*-pyrimido [1, 2-*a*] benzimidazole (4b): Brown powder, Yield 77%, m.p 339°C (dec.). IR (KBr/cm^{-1}) 2221 cm^{-1} (CN), 1625 cm^{-1} (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.0 (s, 1H, -NH), 3.83 (s, 3H, -OCH_3), 6.33-6.82(m, 8H, Ar-H) ppm; EI-MS (m/z: RA %): 331(100%); Anal. Calcd. For: $C_{18}H_{13}N_5O_2$; (C: 65.25; H: 3.95; N: 21.14). Found: (C, 65.05; H, 3.65; N, 20.94).

3-Cyano-2-(3'-chloro anilino)-4-oxo-*4H*-pyrimido [1, 2-*a*] benzimidazole (4c): Brown powder, Yield 83%, m.p 335°C (dec.). IR (KBr/cm^{-1}) 2225 cm^{-1} (CN),1638 cm^{-1} (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.0 (s, 1H, -NH), 6.31-7.14(m, 8H,Ar-H) ppm; EI-MS (m/z: RA %): 335(100%); Anal. Calcd. For: $C_{17}H_{10}ClN_5O$; (C: 60.81; H: 3.00; N, 20.86). Found: (C: 60.63; H: 2.91.00; N: 20.54).

3-Cyano-2-(pyrrolidino)-4-oxo-*4H*-pyrimido [1, 2-*a*] benzimidazole (5a): Brown powder, Yield 83%, m.p 328°C (dec.). IR (KBr/cm^{-1}) 2225 cm^{-1} (CN),1634 cm^{-1} (CO); ^{1}H NMR (400 MHz,DMSO-d_6): δ 4.0 (s, 1H, -NH), 6.38-6.82(m, 4H,Ar-H),2.63(t,4H,-N-CH_2),1.70(t,4H,-CH_2) ppm; EI-MS(m/z:RA %): 279 (100%), Anal. Calcd. For: $C_{15}H_{13}N_5O$; (C, 64.51; H, 4.69; N, 25.07). Found: (C, 64.21; H, 4.25; N, 24.87).

3-Cyano-2-(piperidino)-4-oxo-*4H*-pyrimido [1, 2-*a*] benzimidazole (5b): Brown powder, Yield 81%, m.p 331°C (dec.). IR (KBr/cm-1) 2224 cm^{-1} (CN), 1633 cm^{-1} (CO); ^{1}H NMR(400MHz,DMSO-d_6): δ 4.0(s, 1H, -NH), 6.38-6.82(m, 4H,Ar-H), 1.53(t,4H, CH_2), 3.17(t,4H,N-CH_2),1.59(q,2H,-CH_2) ppm; EI-MS (m/z: RA %): 293(100%), Anal. Calcd. For: $C_{16}H_{15}N_5O$; (C: 65.52; H: 5.15; N: 23.88). Found: (C: 65.11; H: 5.05; N: 23.62).

3-Cyano-2-(morpholino)-4-oxo-*4H*-pyrimido [1, 2-*a*] benzimidazole (5c): Brown powder, Yield 78%, m.p 329° C (dec.). IR (KBr/cm^{-1}) 2226 cm^{-1} (CN), 1636 cm^{-1} (CO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.0 (s, 1H, -NH), 3.15(t, 4H,-N-CH_2), 3.65(t, 4H,-O-CH_2) 6.38-6.82(m, 4H, Ar-H), ppm; EI-MS (m/z: RA %): 295 (100.0%), Anal. Calcd. For: $C_{15}H_{13}N_5O_2$; (C: 61.01; H: 4.44; N: 23.72). Found: (C: 60.81; H: 4.19; N: 23.41).

3-Cyano-2-(4'-chloro phenoxy)-4-oxo-*4H*-pyrimido [1, 2-*a*] benzimidazole (6a): Brown powder, Yield 80%, m.p 336°C (dec.). IR (KBr/cm^{-1}) 2225 cm^{-1} (CN), 1633 cm^{-1} (CO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.0 (s, 1H,-NH), 6.38-7.32(m, 8H, Ar-H)ppm; EI-MS (m/z: RA %): 336 (100%), Anal. Calcd. For: $C_{17}H_9ClN_4O_2$ (C: 60.64; H: 2.69; N: 16.64). Found: (C, 60.24; H, 2.18; N, 16.31).

3-Cyano-2-(4'-methoxy phenoxy)-4-oxo-*4H*-pyrimido [1, 2-*a*] benzimidazole (6b): Brown powder, Yield 74%, m.p 337°C (dec.). IR (KBr/cm^{-1}) 2223 cm^{-1} (CN), 1632 cm^{-1} (CO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.0 (s, 1H, -NH), 3.8(s, 1H,-OCH_3), 6.38-6.84(m, 8H, Ar-H) ppm; EI-MS (m/z: RA %): 332 (100%), Anal. Calcd. For: $C_{18}H_{12}N_4O_3$;(C: 65.06; H: 3.64; N: 16.86). Found: (C: 64.83; H: 3.32; N: 16.55).

3-Cyano-2-(2'-chloro phenoxy)- 4 – oxo-*4H*-pyrimido [1, 2-*a*] benzimidazole (6c): Brown powder, Yield 81%, m.p 234°C (dec.). IR (KBr/cm^{-1}

^{1}) 2227 cm^{-1} (CN), 1635 cm^{-1} (CO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.0 (s, 1H,-NH), 6.28-7.43(m, 8H, Ar-H)ppm; EI-MS (m/z: RA %): 337 (100%), Anal. Calcd. For: $C_{17}H_9ClN_4O_2$; (C: 60.64; H: 2.69; N: 16.64). Found: (C: 60.24; H: 2.18; N, 16.31).

3-Cyano-2-(α-ethylacetoacetyl)-4-oxo-*4H*-pyrimido [1, 2-*a*] benzimidazole (7a): Brown powder, Yield 79%, m.p 335°C (dec.). IR (KBr/cm^{-1}) 2281 cm^{-1} (CN), 1660 cm^{-1} (CO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29(t,3H,-CH_3),2.13(s,3H,-$COCH_3$) 3.87(s,1H,-CH), 4.0 (s, 1H, -NH), 4.21 (q,2H,-OCH_2), 6.38-6.82(m,4H Ar-H), ppm. EI-MS (m/z: RA %): 338 (100 %), Anal. Calcd. For: $C_{17}H_{14}N_4O_4$; (C: 60.35; H: 4.17; N: 16.56). Found: (C: 60.15; H: 4.04; N; 16.39).

3-Cyano-2-(α-ethylcyanoacetyl)-4-oxo-*4H*-pyrimido [1, 2-*a*] benzimidazole (7b): Brown powder, Yield 72%, m.p 331°C (dec.). IR (KBr/cm^{-1}) 2266 cm^{-1} (CN), 1655 cm^{-1} (CO); ^{1}H NMR (400 MHz,DMSO-d_6) δ 4.0 (s, 1H, -NH), 1.29(t,3H,-CH_3), 4.18(s,1H,-CH),4.21(q,2H,-OCH_2), 6.38-6.82(m,4H, Ar-H) ppm. EI-MS (m/z: RA %): 321 (100%), Anal. Calcd. For: $C_{16}H_{11}N_5O_3$; (C: 59.81; H: 3.45; N: 21.80). Found: (C: 59.68; H: 3.21; N: 21.55).

3-Cyano-2-(α-malononitriyl)-4-oxo-*4H*-pyrimido [1, 2-*a*] benzimidazole (7c): Brown powder, Yield 81%, m.p 327°C (dec.). IR (KBr/cm^{-1}) 2256 (CN), 1650 cm^{-1} (CO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.0 (s, 1H, -NH), 4.18(s,1H,-CH), 6.38-6.82(m,4H, Ar-H), ppm. EI-MS (m/z: RA %): 274 (100%), Anal. Calcd. For: $C_{14}H_6N_6O$; (C: 61.32; H: 2.21; N: 30.65). Found: (C: 61.12; H: 2.10; N: 30.49).

RESULT AND DISCUSSION

In the present investigation, we have reported one pot synthesis of 3-cyano-2-metylthio-4-oxo-*4H*-pyrimido [1, 2-*a*] benzimidazole **(3)** and their substituted derivatives. **(4)** Our method gives single product with high yield. The reaction started with 2-amino benzimidazole **(1)** and ethyl 2-cyano-3,3-bis(methylthio)acrylate **(2)** were refluxed in N,N-dimethyl formamide (DMF) in presence of catalytic amount of anhydrous potassium carbonate to afford **(3) (Scheme-1).**

Compound **(3)** posses a replicable active methylthio group at 2- position which is activated by ring 1-nitrogen atom and electron withdrawing group 3-cyano group. Compound **(3)** reacted with selected N-,O-, C- nucleophiles like aryl amines, heteryl amines, substituted phenols and compounds containing an active methylene groups. The compound **(3)** on reactions with p-methoxy aniline, 2-chloro aniline, 4-chloro aniline, in N,N'-dimethyl formamide and catalytic amount of anhydrous potassium carbonate to afforded 3-cyano-4-oxo-2-(4-methoxy aniline/ 4-methyl aniline/3-chloro aniline)- *4H*-pyrimido [1,2-*a*] benzimidazole respectively **(scheme -2)**. Under similar experimental condition compound **(3)** reacted with heteryl amines like pyrolidine, piperidine and morpholine to yielded 3-cyano-4-oxo-2(pyrolidino /piperidino/ morpholino) - *4H*-pyrimido [1,2-*a*] benzimidazole respectively **(scheme-2)**.

Under similar experimental condition compound **(3)** reacted independently with different substituted phenols in N,N'-dimethyl formamide and catalytic amount of anhydrous potassium carbonate, afforded 3-cyano-4-oxo-2-(4-chloro phenol/4-methoxy phenol/ 2-chloro phenol) -*4H*-pyrimido [1,2-*a*] benzimidazole **(scheme-3)**. and also under similar experimental condition compound **(3)** reacted independently with different substituted active methylene group like ethyl acetoacetate, ethyl cyano acetate, malononitrile in presence of N,N'-dimethyl formamide and catalytic amount of anhydrous potassium carbonate to afforded 3-cyano-4-oxo-2-(α-ethyl acetoacetonyl / α-ethyl cyano acetonyl /malonyl) -*4H*-pyrimido [1,2-*a*] benzimidazole respectively.

Compounds 4a-c, 5a-c, 6a-c and 7a-c show absorption bands in their IR spectra in the range of 1630 cm^{-1} to 1660 cm^{-1} and 2221 cm^{-1} to 2281 cm^{-1} due to CO and CN stretching respectively. ^{1}H NMR and Mass spectral data are also in agreement with structures of newly synthesized compounds 4a-c, 5a-c, 6a-c and 7a-c. These newly synthesized compounds possess good antioxidant and antimicrobial activities.

ANTIOXIDANT AND ANTIMICROBIAL ACTIVITY

1) DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging assay: DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging assay was carried out as per reported method[17]. In brief, 1 ml (1 m Mol) of the test compound is added to equal quantity of 0.1 m Mol solution of DPPH in ethanol. After 20 min of incubation at room temperature, the DPPH reduction was measured by reading the absorbance at 517 nm. Ascorbic acid (1 m Mol) was used as the reference compound.

2) OH radical scavenging assay: The OH radical scavenging activity was demonstrated with Fenton's reaction[18]. The reaction mixture contained, 60 µL of FeC_2 (1 m Mol), 90 µL of 1–10 phenathroline (1 m Mol), 2.4 mL of phosphate buffer (0.2 M, pH 7.8), 150 µl of H_2O_2 (0.17 M)

and 1.5 mL of individual compound (1 m Mol). The reaction was started by adding H_2O_2.After 5 min. incubation at room temperature, the absorbance was recorded at 560 nm. Ascorbic acid (1 m Mol) was used as a reference compound.

Antioxidant activity:

The results of antioxidant potential of novel synthesized pyrimido[1, 2-*a*]benzimidazole derivatives are summarized in Table No. 1. The efficiency of antioxidant potential was determined in terms of percent DPPH and OH radical scavenging assay. The DPPH radical scavenging assay has been used for preliminary screening of the samples for antioxidant activity. The proton radical scavenging action is known as an important mechanism of antioxidants. The overall DPPH radical scavenging activity of tested pyrimido[1, 2-*a*]benzimidazole derivatives were in a range of 15.1 + 0.714 to 83.8 + 0.215 % as compared to the standard ascorbic acid (78.48 + 0.13 %). The highest proton radical scavenging activity was exhibited by 4a exhibit least action. Out of four tested derivatives, compound 7c failed to stabilize proton radical under experimental condition.

The perusal of Table No. 1 clearly indicates comparatively good OH radical scavenging activity of newly synthesized pyrimido[1, 2-*a*]benzimidazole compounds in a range of 11.7 + 0.137 to 69.2 + 0.257 % as compared with standard ascorbic acid (02.67 + 0.24 %). The 6b demonstrated highest OH radical scavenging activity (69.2 + 0.257 %). It is crucial to state that the series of pyrimido[1, 2-*a*]benzimidazole compounds were comparatively good in stabilizing the hydroxyl free radical as compared with the proton radical stabilization. In view of present work it can decisively concluded that the pyrimido benzimidazole fused derivatives are essential to boost the antioxidant activity. The present investigation opens a new trends for researchers to find out the diverse plausible pharmacological activities by using or modifying the novel series of 2-substituted pyrimidobenzimidazole compounds.

Antimicrobial activity

Materials and Methods: The bacterial strain, *Escherichia coli* (DH5-α) and *Bacillus subtilis* (MTCC 7424) were obtained from the Microbial Culture Depository Section, School of Life Sciences, S. R. T. M. University, Nanded. (MS) while the culture of *Salmonella typhi* (NCIM No. 5274) were obtained from the National Collection of Industrial Microorganisms (NCIM), National Chemical Laboratory, Pune. All the cultures were maintained in their respective Liquid Broth (LB). All slant cultures were kept at 37°C for 24 hours before testing biological activities. The newly synthesized pyrimido[1, 2-*a*]benzimidazole derivatives were tested at concentration of 200 µg/ml for their antimicrobial activity against *E. coli*, *B. subtilis* and *S. typhi* using agar diffusion assay with Amoxicillin and Ciprofloxacin (2.5 mg/ml) as a standard drug. The results of antimicrobial activity are presented in the Table No. 2. Amongst the pyrimido[1, 2-*a*]benzimidazole derivatives, the most of the derivatives exhibited potential antimicrobial activity against *B. subtilis*.

CONCLUSION

In summary, we report the first time synthesis of 3-cyano-2-metylthio-4-oxo-*4H*-pyrimido [1, 2-*a*] benzimidazole and its 2-substituted derivatives by simple and efficient method. These synthesized pyrido [1, 2-*a*] pyrimidine derivatives exhibit promising antibacterial activity and some of the selected compounds shows moderate to excellent antioxidant activity. Hence, it has enough scope for further study in developing these as good lead compounds. Moreover, this preliminary study is encouraging to further investigate their broad spectrum pharmacological activities.

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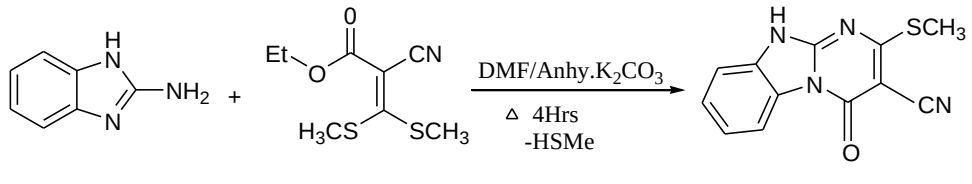
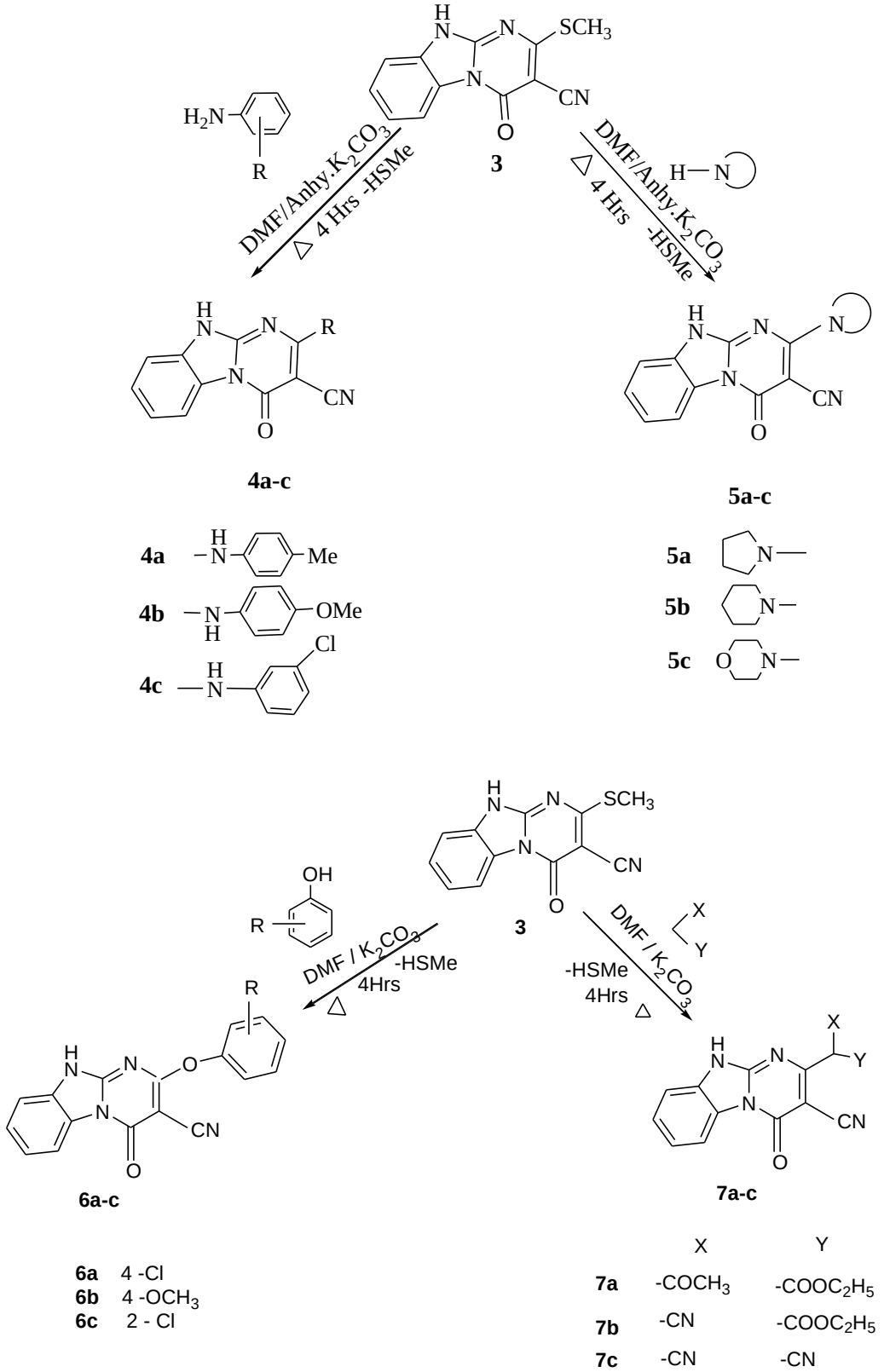


1 **2** **3**

Scheme - 1:Synthesis of compound (3)



Scheme-3: Synthesis of 2-substituted derivatives of 4H-pyrimido [1,2-*a*] benzimidazole

Table No.1: Antioxidant potential of tested pyrimido[1, 2-*a*]benzimidazole derivatives.

Sr. No.	Compound Tested	Antioxidant Activity (%)	
		DPPH radical scavenging activity	OH radical scavenging activity
1	3	38.7 ± 0.517	31.9 ± 0.927
2	4a	83.8 ± 0.215	69.2 ± 0.257
3	6b	16.7 ± 0.279	11.7 ± 0.137
4	7c	NR	NR
5	Ascorbic Acid (Vit. C)	78.48 ± 0.13	02.67 ± 0.24

Note: Results presented here are the mean values from three independent experiments ± S.D., NR = No reaction under experimental condition.

Table 2: Antimicrobial activity of pyrimido[1, 2-*a*]benzimidazole derivatives.

Sr. No.	Compound Tested (200 µg/ml)	*E. coli*	*B. subtilis*	*S. typhi*
1	3	- -	+ +	- -
2	4a	- -	+ +	- -
3	4b	- -	+ +	- -
4	5c	- -	+ +	- -
5	6b	- -	+ +	- -
6	7c	- -	+ +	- -

Note: + + sign shows the considerable zone of inhibition.

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