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RESEARCH ARTICLE

SYNTHESIS, CHARACTERISATION AND ANTI-OXIDANT STUDY OF NEW FUSED IMINOPYRIMIDO-BENZIMIDAZOLE DERIVATIVES

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ABSTRACT

This manuscript describes the simple condensation of bis (methylthio) methylene malononitrile (1) with 2-amino benzimidazole (2) in DMF and catalytic amount of anhydrous K_2CO_3 gives 3-cyano-4-imino-2-metylthio-*4H*- pyrimido [1, 2-*a*] benzimidazole (3) in good yield and further refluxed with different nucleophiles such as aryl amines, heteryl amines, substituted phenols and active methylene compounds to equip its 2- substituted derivatives. All newly synthesized compounds were deduced by spectroscopic technique such as IR, MS, NMR (^{1}H & ^{13}C) and screened their antioxidant activity.

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INTRODUCTION

Biological evaluation of benzimidazole derivatives and their chemical properties are significant area of heterocyclic chemistry in a long history of research (Paul A. Friedman, Edward G. Platzer, 1978; Yasuhisa Kohara *et al*., 1996; Spasov *et al*., 1999). Benzimidazole is heterocyclic aromatic organic compound containing nitrogen as a hetero atom. It contains imidazole heterocycle fused with benzene ring. Fused benzimidazole heterocycles and its derivatives are essential synthetic protocol in the era of organic and medicinal chemistry. Benzimidazoles are confidential structural units not only in the pharmaceutical industry but also in several other fields such as electronic, polymer and agricultural chemistry (Perry and Wilson, 1993; Skalitzky *et al*., 2003). A large number of benzimidazole derivatives acting vital role in number of biologically important molecules (Marijana Hranjec Gordana Pavlovic *et al*., 2012). This ring system is present in various drugs like antidiabetics (Tamer *et al*., 2012), antimicrobial (Seenaiah *et al*., 2014; Hardik H. Jardosh *et al*., 2013), antiviral (Michele Tonelli *et al*., 2014), antiproliferative (Anna Nowicka *et al*., 2014), antioxidant (Vartale *et al*., 2014), anticancer (Nataraj Poomathi *et al*., 2014), anti-inflammatory. (Sham M. Sondhi *et al*., 200) Thus, because of its growing medicinal significance, great efforts have been made to develop an efficient and economical method for the synthesis of new imino pyrimido [1, 2-*a*] benzimidazole derivatives and to study their antioxidant potential in the present article.

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MATERIALS AND METHODS

A] Instrumentation

Chemicals and solvents used for synthesis purchased from analytical grade and used without further purification such as ethyl alcohol, methyl alcohol, chloroform, DMF. Bis (methylthio) methylene malononitrile was prepared in the laboratory. 2-amino benzimidazole was bought from Sigma Aldrich. Melting points of the products were determined in open capillary tubes on an electrothermal melting point apparatus and were uncorrected. All the reactions were monitored by Thin layer chromatography (TLC) which was carried out on silica gel plates (Merck) using pet ether – ethyl acetate (7:3) as eluant; zones were detected visually under ultraviolet irradiation. IR spectra were recorded on Shimadzu FT-IR spectrophotometer, ^{1}H-NMR spectra were obtained on

Bruker avance spectrophotometer 500 MHz in DMSO-d6 using tetramethylsilane as an internal standard. Chemical shifts were recorded in parts per million (ppm, **δ**). Mass spectra were recorded on GC-MS spectrometer using the ESI technique.

B] General Experimental Procedure

3-Cyano -4-imino-2-metylthio-*4H*-pyrimido [1, 2-*a*] benzimidazole (3)

A mixture of 2-amino benzimidazole (2) (0.01 mol) and bis (methylthio) methylene malononitrile (1) (0.01 mol) in 25 ml of N, N-dimethyl formamide (DMF) and anhydrous potassium carbonate (10mg) was refluxed for 5 to 6 hours. The progress of the reaction was monitored by thin layer chromatography (TLC). The reaction mixture was cooled to room temperature and poured in to ice cold water. The solid that separated out was filtered, washed with water and recrystalized from ethanol to obtain compound (**3)**.

2-Substituted derivatives of 3-cyano-4-imino-2-metylthio-*4H*-pyrimido[1,2-*a*] benzimidazole (4 -7)

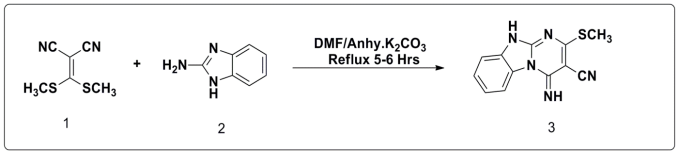
A mixture of (3) (0.001 mol) when reacted independently with various aromatic amines, substituted phenols, heteryl amines and compounds containing an active methylene group (0.001 mol) in N, N'-dimethyl formamide (20 ml) and catalytic amount of anhydrous potassium carbonate (10 mg) was refluxed for 5 – 6 hrs. The progress of the reaction was monitored by thin layer chromatography (TLC). The reaction mixture was cooled to room temperature and poured into ice cold water. The solid that separated out was filtered, washed with water and recrystalized from ethanol to get respective compounds 4 – 7.

RESULTS AND DISCUSSION

A] Chemistry:

In the present work, we have reported one pot synthesis of 3-cyano-4-imino-2-methylthio-*4H*-pyrimido [1, 2-*a*] benzimidazole (3) and their 2- substituted derivatives. Reaction started with 2-amino benzimidazole (2) and bis (methylthio) methylene malononitrile (1) were refluxed in N, N'-dimethyl formamide and catalytic amount of anhydrous potassium carbonate to afford compound (**3)**.

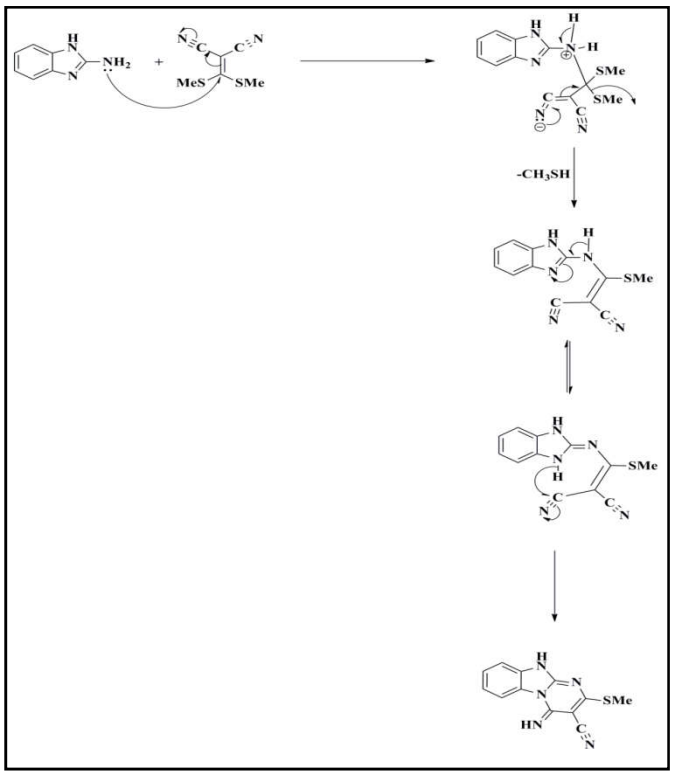
Scheme 1:



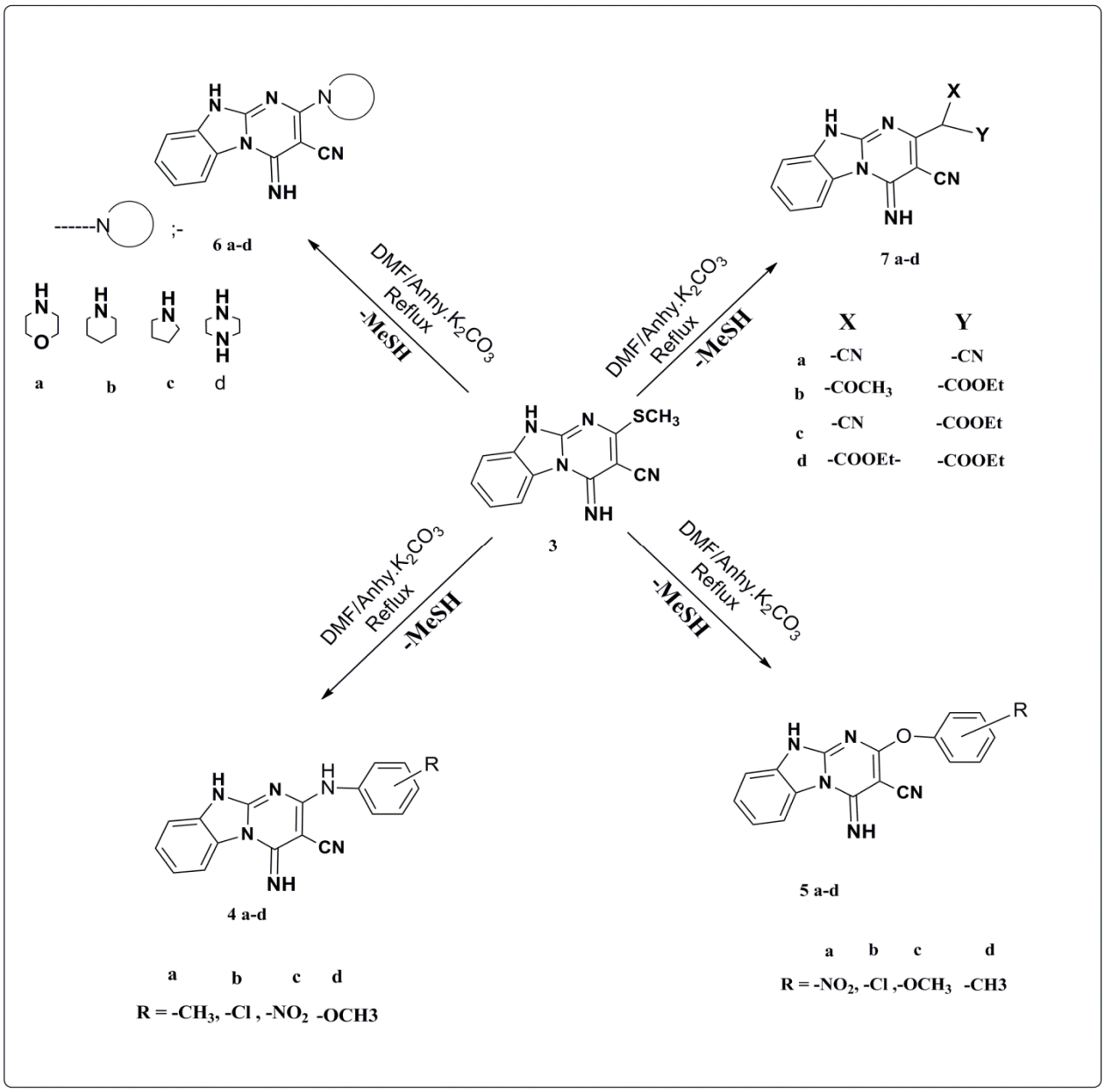
Scheme 1: 3-Cyano -4-imino-2-metylthio-*4H*-pyrimido [1, 2-*a*] benzimidazole [3]

Parent molecule **(3)** containing methylthio as a good leaving group at 2- position. electronegative ring 1-nitrogen atom and electron withdrawing 3-cyano group makes 2-position more susceptible towards nucleophilic substitution. As the number of nitrogen atoms in compound (3) increases, the ring pi electrons become less energetic towards electrophilic substitution reaction while nucleophilic substitution becomes easier. Therefore different types of nitrogen, oxygen & carbon nucleophiles can easily substitute the methylthio group from 2-position in compound (3) and obtained its novel derivatives.

A plausible Mechanism



The compound **(3)** reacted with selected nitrogen, oxygen and carbon containing nucleophiles like aryl amines, substituted phenols, heteryl amines and active methylene compounds to equip corresponding pyrimido benzimidazole derivatives. compound **(3)** refluxed with p-methyl aniline, o-chloro aniline, p-nitro aniline, p- methoxy aniline in N,N'-dimethyl formamide and catalytic amount of anhydrous potassium carbonate to give 3-cyano-4-imino-2-(4-methyl aniline/ 2-chloro aniline/ 4-nitro aniline/p-methoxy aniline)- *4H*-pyrimido [1,2-*a*] benzimidazole 4a, 4b ,4c, 4d respectively in **(scheme -2)**. Under similar experimental condition compound **(3)** treated with different substituted phenols to furnish 3-cyano-4-imino-2-(2-nitro phenol/4- chloro phenol/ 4-methoxy phenol/4-methyl phenol) -*4H*-pyrimido [1, 2-*a*] benzimidazole 5a, 5b, 5c, 5d respectively in **(scheme-2)**. Under similar experimental condition compound **(3)** reacted with heteryl amines like morpholine, piperidine pyrrolidine andpiperazine to yield 3-cyano-4-imino-2-(morpholino/piperidino/ pyrrolidino/piperazino)-*4H*-pyrimido[1,2-*a*]benzimidazole 6a, 6b, 6c, 6d respectively shown in **(scheme-2)** and also under similar experimental condition compound **(3)** reacted with different compounds having active methylene groups to afford 3-cyano-4-imino-2-(malonyl / α-ethyl acetoacetyl / α-ethyl cyano acetyl / diethyl malonyl) -*4H*-pyrimido [1,2-*a*] benzimidazole 7a, 7b, 7c, 7d respectively as shown in (**scheme-2).**



Scheme 2: Synthesis of 2-substituted derivatives of 3-Cyano -4-imino-*4H*-pyrimido [1, 2- *a*] benzimidazole [4 - 7]

C] Spectroscopic Data

The structures of newly synthesized compounds were deduced on the basis of spectral properties such as IR, Mass, ^{1}H and ^{13}C NMR. in compounds 4a-d, 5a-d, 6a-d and 7a-d shows IR absorption band in the range of 3436 cm^{-1} to 3460 cm^{-1} and 2198 cm^{-1} to 2210 cm^{-1} due to =N-H and- CN stretching respectively. The characteristic =N-H singlet peak appears at 8.6 ppm and ring nitrogen protons at 3.81 ppm in ^{1}H NMR and Mass spectral data are also in good agreement.

3-Cyano-4-imino-2-metylthio-*4H*-pyrimido [1, 2-*a*] benzimidazole (3)

Color: Yellow powder, Yield: 85 %, m.p : $321^{0}C$ - $324^{0}C$. M.F: $C_{12}H_9N_5S$, M.W: 255, IR : 2210 cm^{-1} (-CN), 3436 cm^{-1}(=NH), ^{1}H NMR: (500 MHz, DMSO-d_6) δ: 2.6 (s, 3H, SCH_3), 3.81 (s, 1H,-NH), 7.3-8.4(m, 4H, Ar- H), 8.6 (s, 1H, =NH) ppm; Mass: m/z = 256 (M + 1). ^{13}C NMR (500 MHz, DMSO-d_6) δ: 121,118,126,127,153,150,115,167, 13ppm.

3-Cyano--4-imino-2-(4'-methyl anilino)-*4H*-pyrimido [1, 2-*a*] benzimidazole (4a)

Color: Faint yellow powder, Yield: 78%, m.p: 314 - 318°C, M.F. C_{18} H_{14} N_6, IR: 2206 cm^{-1} (-CN), 3460 cm^{-1} (=NH). ^{1}H NMR (500 MHz, DMSO-d_6): δ: 2.6 (s, 3H, CH_3), 3.81 (s, 2H, -NH), 6.6 - 8.4 (m, 8H, Ar-H), 8.6 (s, 1H, =NH) ppm, Mass: m/z = 315 (M +1).

3-Cyano--4-imino-2-(2'-chloro anilino)-*4H*-pyrimido [1, 2-*a*] benzimidazole (4b)

Color: yellow powder, Yield: 75%, m.p: 310 - 314°C, M.F: $C_{17}H_{11}ClN_6$, IR: 2206 cm^{-1} (-CN), 3420 cm^{-1} (=NH).

3-Cyano--4-imino-2-(4'-nitro anilino)-*4H*-pyrimido [1, 2-*a*] benzimidazole (4c)

Color: yellow powder, Yield: 77%, m.p: 317 - 320°C. M.F: $C_{17}H_{11}N_7O_2$, IR: 2208 cm^{-1} (-CN), 3440 cm^{-1} (=NH).

3-Cyano--4-imino-2-(4'-methoxy anilino)-*4H*-pyrimido [1, 2-*a*] benzimidazole (4d)

Color: yellow powder, Yield: 79%, m.p: 317 - 320°C. M.F: $C_{18}H_{14}N_6O$.

3-Cyano-4-imino-2-(2'-nitro phenol)-*4H*-pyrimido [1, 2-*a*] benzimidazole (5a)

Color: Yellow powder, Yield: 75%, m.p : 308-312 °C (dec.). M.F : C_{17} H_{10} N_6 O_3, IR : 2206 cm^{-1} (-CN), 3437 cm^{-1} (=NH), ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.81 (s,1H,-NH), 6.6-8.4 (m, 8H, Ar-H), 8.6 (s,1H,=NH) ppm; Mass: m/z: 346(M^+) , 347(M+1), 348 (M+2).

3-Cyano-4-imino-2-(4'-chloro phenol)-*4H*-pyrimido [1, 2-*a*] benzimidazole (5b)

Color: Yellow powder, Yield: 72%, m.p: 309-313 °C (dec.). M.F: $C_{17}H_{10}ClN_5O$, IR: 2206 cm^{-1} (-CN), 3435 cm^{-1} (=NH).

3-Cyano-4-imino-2-(4'-methoxy phenol)-*4H*-pyrimido [1, 2-*a*] benzimidazole (5c)

Color: Yellow powder, Yield: 75%, m.p: 316-319 °C (dec.), M.F: C_{18} $H_{13}N_5O_2$, IR: 2206 cm^{-1} (-CN), 3450 cm^{-1} (=NH).

3-Cyano-4-imino-2-(4'-methyl phenol)-*4H*-pyrimido [1, 2-*a*] benzimidazole (5d)

Color: Yellow powder, Yield: 77%, m.p: 308-312 °C (dec.), M.F: C_{18} H_{13} N_5O, IR: 2206 cm^{-1} (-CN), 3437 cm^{-1} (=NH).

3-Cyano-4-imino-2-(morpholino)-*4H*-pyrimido [1, 2-*a*] benzimidazole (6a)

Color: Yellow powder, Yield: 78%, m.p: 315-318 °C (dec.).M.F: C_{15} $H_{14}N_6O$, IR: 2198 cm^{-1} (-CN), 3460 cm^{-1} (=NH). ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.5(t, 4H,-N-CH_2), 3.7(t, 4H,-O-CH_2) 3.81 (s, 1H, -NH), 7.3-8.4 (m, 4H, Ar-H), 8.6 (s, 1H, =NH) ppm; Mass: m/z: 294(M^+), 295(M+1), 296(M+2).

3-Cyano-4-imino-2-(piperidino)-*4H*-pyrimido [1, 2-*a*] benzimidazole (6b)

Color: Yellow powder, Yield: 74%, m.p: 318-321 °C (dec.).M.F: $C_{16}H_{16}N_6$, IR: 2198 cm^{-1} (-CN), 3454 cm^{-1} (=NH).

3-Cyano-4-imino-2-(pyrrolidino)-*4H*-pyrimido [1, 2-*a*] benzimidazole (6c)

Color: Yellow powder, Yield: 82%, m.p: 311-315 °C (dec.), M.F: C_{15} H_{14} N_6, IR: 2200 cm^{-1} (-CN), 3445 cm^{-1} (=NH).

3-Cyano-4-imino-2-(piperazino)-*4H*-pyrimido [1, 2-*a*] benzimidazole (6d)

Color: Yellow powder, Yield: 80%, m.p: 321-325 °C (dec.). M.F: $C_{15}H_{15}N_7$, IR: 2202 cm^{-1} (-CN), 3456 cm^{-1} (=NH).

3-Cyano-4-imino-2-(α-malonyl)-*4H*-pyrimido [1, 2-*a*] benzimidazole (7a)

Color: brown, Yield: 80%, m.p: 326-329 °C (dec.). M.F: $C_{14}H_7N_7$, IR: 2202 cm^{-1} (-CN), 3437 cm^{-1} (=NH). ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.81 (s, 1H, -NH), 4.1(s, 1H,-CH), 7.3-8.4(m, 4H, Ar-H), 8.6 (s, 1H, =NH) ppm. Mass: m/z: 274 (M+1), 275(M+2).

3-Cyano-4-imino-2-(α-ethyl acetoacetyl)-*4H*-pyrimido [1, 2-*a*] benzimidazole (7b)

Color: brown, **Yield:** 80%, **m.p:** 324-328 °C (dec.). **M.F:** C_{17} H_{15} N_5 O_3, **IR:** 2202 cm^{-1} (-CN), 3440 cm^{-1} (=NH).

3-Cyano-4-imino-2-(α-ethyl cyano acetyl)-*4H*-pyrimido [1, 2-*a*] benzimidazole (7c)

Color: brown, Yield: 80%, m.p: 323-327 °C (dec.).M.F: $C_{15}H_{10}N_6O$, IR: 2206 cm^{-1} (-CN), 3450 cm^{-1} (=NH).

3-Cyano-4-imino-2-(diethyl malonyl)-*4H*-pyrimido [1, 2-*a*] benzimidazole (7d)

Color: brown, Yield: 80%, m.p: 330-333 °C (dec.). M.F: $C_{17}H_{15}N_5O_4$.

B] Antioxidant activity

Sr. No.	Compound Tested	Antioxidant Activity (%)	
		DPPH radical scavenging activity	OH radical scavenging activity
1	3	43.3 ± 0.321	32.1 ± 0.547
2	4a	41.2 ± 0.632	24.7 ± 0.921
3	4b	42.4 ± 0.630	25.2± 0.723
4	5a	34.5 ± 0.214	24.9+ 0.842
5	5b	29.1 ± 0.311	38.9 ± 0.254
6	5c	32.3 ± 0.215	35.8+ 0.346
7	6a	15.1 ± 0.714	38.1 ± 0.329
8	6b	25.6 ± 0.518	33.4.+ 0.419
9	7c	14.5 ± 0.625	25.25 ± 0.275
10	Ascorbic Acid (Vit. C)	78.48 ± 0.13	02.67 ± 0.24

The outcomes of antioxidant potential of newly synthesized imino pyrimido [1, 2-*a*] benzimidazole derivatives are summarized in above table. The effectiveness 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 imino pyrimido [1, 2-*a*] benzimidazole derivatives were in a range of 14.5 ± 0.625 to 43.3 ± 0.321 % as compared to the standard ascorbic acid (78.48 ± 0.13 %). The highest proton radical scavenging activity was exhibited by 3 shows least action. The study of

table clearly indicates comparatively good OH radical scavenging activity of newly synthesized imino pyrimido [1, 2-*a*] benzimidazole derivatives in a range of 24.7 ± 0.921 to 38.9 ± 0.254% as compared with standard ascorbic acid (02.67 ± 0.24 %). It is significant to note that compound 5b demonstrated highest OH free radical scavenging activity (38.9 ± 0.254 %).

Conclusion

In the present work we have synthesized different 2-substituted imino pyrimido [1, 2-*a*] benzimidazole derivatives in good yields. Selected newly synthesized derivatives were evaluated in vitro to determine their free radical scavenging activities using DPPH and OH free radicals. It is important to state that the series of imino pyrimido [1, 2-*a*] benzimidazole derivatives were comparatively good in stabilizing the hydroxyl free radical as compared with the proton radical stabilization. In view of present work it can positively concluded that the imino pyrimido [1, 2-*a*] benzimidazole derivatives are crucial to enhance the antioxidant activity. The present investigation opens new trend for researchers to find out the different possible pharmacological activities by using or modifying the novel series of 2-substituted imino pyrimido [1, 2-*a*] benzimidazole derivatives.

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