WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 16, 1017-1028. Research Article ISSN 2277– 7105

SYNTHESIS AND ANTIOXIDANT ACTIVITY OF NEW PYRAZOLES OF 6-METHYLBENZIMIDAZOLES

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Article Received on
01 July 2018,

Revised on 22 July 2018,
Accepted on 14 August 2018,

DOI: 10.20959/wjpr201816-13159

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ABSTRACT

The synthesis of new series of pyrazole derivatives of 6-methylbenzimidazoles was achieved in excellent yields by the oxidation of 6-methylbenzimidazole pyrazolines with iodobenzene diacetate in dichloromethane. The synthesized compounds were tested for antioxidant activity. The results show that some of the compounds have exhibited good antioxidant activity.

KEYWORDS: Benzimidazoles, chalcones, pyrazolines, pyrazoles Antioxidant activity.

INTRODUCTION

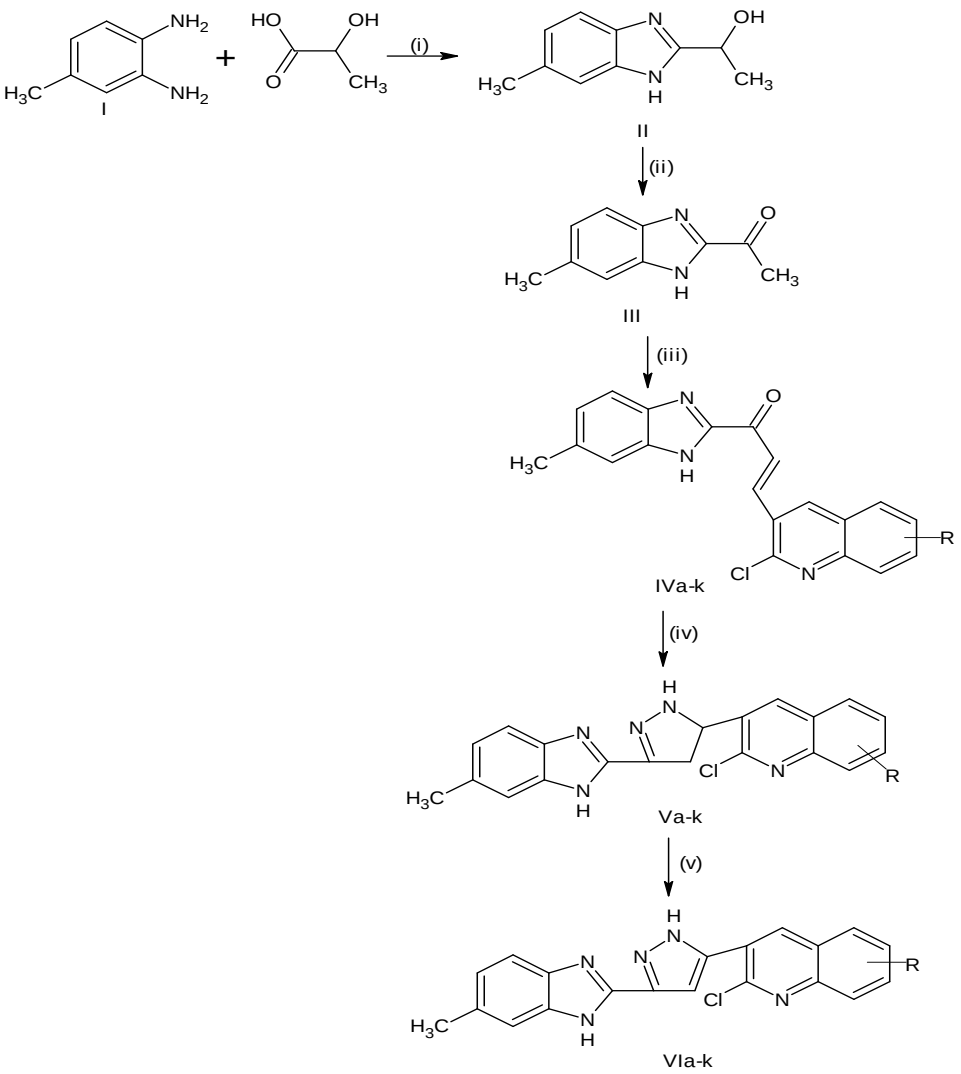
Benzimidazole is a versatile heterocyclic pharmacophore with diverse range of medicinal properties as evaluated by numerous research groups.[1] Benzimidazoles have been exploited over the past few decades because of the wide range of activities displayed by this class of heterocycles.

Pyrazoles represent one of the most active classes of compounds possessing wide spectrum of biological activities. Pyrazoles show analgesic[2], antipyretic[3], anti-inflammatory[4], germicidal[5], antifungal[6], anticancer[7] and antioxidant[8] activities, and act as hepatoselective HMG-CoA reductase.[9]

Antioxidants are nutrients that help protect cells from a normal but harmful physiological process known as "oxidative stress." These nutrients are part of the natural composition of many types of foods, especially fruits and vegetables. They should also be added to some

foods and are available in the form of nutritional supplements. The active oxygen molecules such as superoxide, hydroxyl and peroxyl radicals play an important role in the oxidative stress that leads to carcinogenesis in the pathogenesis of various diseases such as Alzheimer's, Parkinson's, Cataracts and DNA damage.[10]

Today, antioxidants arouse the interest of researchers in medicinal plants and synthetic compounds. In the course of the synthesis of bioactive benzimidazoles, some new benzimidazoles have been prepared which contain pyrazoles to study the addictive effects of these in order to increase biological activity.



R= (a)-6-Meo; (b)-7-Meo (c)-8-CH_3; (d) -6-Cl; (e)-8-Meo; (f) -7-Cl; (g)-7-CH_3; (h) -6-CH_3; (i)-6-Br; (j)-6-F; (k)-H.

Reagents and conditions: (i) 4 N HCl, lactic acid reflux with microwave irradiation, 320 mins, (ii) $K_2Cr_2O_7$, dilute H_2SO_4, 2 hrs, (iii) 2-chloroquinoline-3-carbaldehydes, EtOH, 10%

NaOH, 0.5 hrs, (iv) $NH.NH_2$, EtOH, CH_3COOH, reflux 4 hrs, (v) iodobenzene diacetate , dichloromethane, 4hrs.

MATERIALS AND METHODS

All solvents and reagents were purchased and used as such. The melting points were checked by the open capillary tube method and are not corrected. IR spectra of the compounds were recorded on the Shimadzu FTIR 8400S spectrometer by using the KBr pellet method. The NMR spectra were recorded on the Bruker Avance II spectrometer from 400 NMR and MASS spectra on a Waters spectrometer, Q-TOF Microma SS.

Synthesis of 6-methyl-2-(α-hydroxyethyl)benzimidazole (II)

An equal amount of 4-methyl-O-phenylenediamine (0.01 mole) and lactic acid (0.01 mole), 4N HCl are refluxed in microwave oven at the intensity of 65% (450 W) for 320 mins. TLC was monitored for the completion of the reaction. Then the reaction mixture was neutralized with sodium bicarbonate ($NaHCO_3$). The filtered product was washed with water, dried and recrystallized from ethanol m.p-186-88ċ.[11-14]

Synthesis of 6-methyl-2-acetylbenzimidazole (III)

To a reaction mixture of 6-methyl-2-(α-hydroxyethyl) benzimidazole (9.8 g, 50 mmole) in dilute H_2SO_4 (5%, 40 mL), a solution of $K_2Cr_2O_7$ (44 g , 150 mmole) in aqueous H_2SO_4 (25%, v/v; 80 ml) was added drop wise over a period of 20 mins. Stirring continued for 2 hrs at room temperature, the product (constituting the chromium complex), was filtered and suspended in 50 ml of water. Aqueous ammonia (1:1) was used to adjust the pH at 6-6.5. Then the solid product was filtered, washed with water and dried. The final product is recrystallized from ethyl acetate to get a pure compound m.p-195-97ċ.[15]

Synthesis of Chalcone derivatives of 6-methyl-benzimidazoles (IV)

To a reaction mixture of 6-methyl-2-acetylbenzimidazole (10 mmole, 1.74 g) in aqueous NaOH (10%, 30 ml) was added 2-chloro-3-formylquinolines (10 mmole, 1.91 g) and stirring continued up to 30 minutes at room temperature. On the completion of the reaction, the solid product was separated by filtration, washed and dried. In addition, it was recrystallized from ethanol.[16-22]

Similarly, **chalcone derivatives of 6-methyl-benzimidazoles (IVa-k)** were synthesized.

IVh: yield 77%, m.p-250-52ċ; IR (KBr): 3275, 3064, 2918, 1658, 1579, 1427, 1217, 763 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.79 (s, 3H, CH_3), 7.53-7.52 (d, 1H, CO-CH=CH), 7.26-7.83 (m, 11H, ArH), 8.72 (s, 1H, NH), MS: *m/z* 361 (M+•).

IVa: yield 86%, m.p-262-64ċ; IR (KBr): 3271, 3192, 2848, 1664, 1554, 1234, 804 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.92 (s, 3H, OCH_3), 7.196-7.190 (d, 1H, CO-CH=CH), 6.97-7.70 (m, 9H, ArH), 8.13(s, 1H, NH) MS: *m/z* 377 (M+•).

IVd: yield 88%, m.p-278-80ċ; IR (KBr): 3282, 2850, 1660, 1566, 1413, 1334, 802,719 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.18-7.17 (d, 1H, CO-CH=CH), 7.17-7.94 (m, 9H, ArH), 8.15 (s, 1H, NH) MS: *m/z* 382 (M+•).

Synthesis of Pyrazolines of 6-methyl-benzimidazoles (V)

To a reaction mixture of chalcone (3.47 g, 0.01 mole) dissolved in ethanol (40 ml) hydrazine hydrate (0.75 g, 0.015 mol) and glacial acetic acid (10 ml), was added and the reaction mixture was heated to reflux on water bath for 4 hrs. The solvent was reduced to half its volume. The crystalline product deposited on cooling was filtered, washed with water, dried and crystallized from ethanol to get pure product.[23]

Similarly, **pyrazoline derivatives of 6-methyl-benzimidazoles (Va-k)** were synthesized.

Vh: yield 52%, m.p-118-20ċ; IR (KBr): 3190, 3053, 1654, 1579, 1479, 1278, 767 cm^{-1}; ^1H NMR($CDCl_3$, 400 MHz): δ 2.75 (s, 3H, CH_3), 3.43 (dd, 2H, CH_2-Pyrazoline), 5.85 (dd,1H, Pyrazoline), 7.03-7.68 (m, 11H, Ar-H), 8.16 (s, 1H, NH), MS: *m/z* 375 (M+•).

Vc: yield 60%, m.p-115-17ċ; IR (KBr): 3217, 3047, 1658, 1579, 1479, 1228, 767 cm^{-1}; ^1H NMR($CDCl_3$, 400 MHz): δ 2.65 (s, 3H, CH_3), 3.44 (dd, 2H, CH_2-Pyrazoline), 5.80 (dd,1H, Pyrazoline), 7.03-7.86 (m, 11H, Ar-H), 8.34 (s, 1H, NH), MS: *m/z* 375 (M+•).

Vb: yield 58%, m.p-109-10ċ; IR (KBr): 3215, 3086, 1666, 1570, 1492, 1228, 804 cm^{-1}; ^1H NMR($CDCl_3$, 400 MHz): δ 3.87 (s, 3H, OCH_3), 3.46 (dd, 2H, CH_2-Pyrazoline), 5.30 (dd,1H, Pyrazoline), 6.88-7.60 (m, 11H, Ar-H), 7.80 (s, 1H, NH), MS: *m/z* 391 (M+•).

Vd: yield 64%, m.p-112-14ċ; IR (KBr): 3227, 3066, 1654, 1570, 1494, 1278, 825, 806 cm^{-1}; ^1H NMR($CDCl_3$, 400 MHz): δ 3.47 (dd, 2H, CH_2-Pyrazoline), 5.45 (dd,1H, Pyrazoline), 7.04-7.70 (m, 9H, Ar-H), 8.23 (s, 1H, NH), MS: *m/z* 396 (M+•).

Synthesis of Pyrazoles of 6-methyl-benzimidazoles (VI)

To a stirred solution of pyrazoline derivative (0.361 g, 0.01 mole) in dichloromethane (20 ml) was added iodobenzene diacetate (0.386 g, 0.0012 mole) at room temperature. The resulting mixture was stirred for 4 hours. The dichloromethane was distilled off in a steam bath to give a gum which was triturated with petroleum ether to remove the iodobenzene and then purified by recrystallization from ethanol to get the pure compound.[24]

Similarly, **pyrazole derivatives of 6-methyl-benzimidazoles (VIa-k)** were synthesized.

VIh: yield 74%, m.p-82-84ċ; IR (KBr): 3059, 2958, 2850 1612, 1522, 1517 1450, 1220, 744 cm^{-1}; ^1H NMR($CDCl_3$, 400 MHz): δ 2.74 (s, 3H, CH_3), 7.26 (s, 1H, -CH=C), 7.72 (s, 1H, -N=CH), 6.90-8.19 (m, 10H, Ar-H), 8.74 (s, 1H, NH), MS: *m/z* 373 (M+•).

VIa: yield 68%, m.p-86-88ċ; IR (KBr): 3184, 3064, 2918, 1620, 1543, 1492 1450, 1228, 746 cm^{-1}; ^1H NMR($CDCl_3$, 400 MHz): δ 3.85 (s, 3H, OCH_3), 7.29 (s, 1H, -CH=C), 7.62 (s, 1H, -N=CH), 6.88-7.69 (m, 10H, Ar-H), 7.82 (s, 1H, NH), MS: *m/z* 389 (M+•).

VId: yield 72%, m.p-78-80ċ; IR (KBr): 3157, 3063, 2958, 1622, 1496, 1230, 746 cm^{-1}; ^1H NMR($CDCl_3$, 400 MHz): δ 7.26 (s, 1H, -CH=C), 7.69 (s, 1H, -N=CH), 6.88-7.94 (m, 10H, ArH), 8.05 (s, 1H, NH), MS: *m/z* 394 (M+•).

VIf: yield 77%, m.p-87-89ċ; IR (KBr): 3182, 3061, 2918, 1656, 1539, 1273, 827 cm^{-1}; ^1H NMR($CDCl_3$, 400 MHz): δ 7.26 (s, 1H, -CH=C), 7.52 (s, 1H, -N=CH), 7.12-7.78 (m, 10H, ArH), 8.40 (s, 1H, NH), MS: *m/z* 394 (M+•).

RESULTS AND DISCUSSION

Condensation of 4-methyl-O-phenylenediamine **(I)** with lactic acid gives 6-methyl-2-(α-hydroxyethyl)benzimidazole **(II)**. Attempted oxidation of **(II)** with $K_2Cr_2O_7$ in dilute H_2SO_4 gives 6-methyl-2-acetylbenzimidazole **(III).** Further condensation with 2-chloro-3-formylquinolines gives chalcone derivatives of 6-methyl-benzimidazoles **(IVa-k).** These on treatment with hydrazine hydrate in ethanol and glacial acetic acid, gives pyrazolines of 6-methyl-benzimidazoles **(Va-k).** Which yield the title compounds when treated with iodobenzene diacetate in dichloromethane. **(VIa-k).**

The IR spectrum of **IVh** showed characteristic absorption peaks at 3275 (NH), 1658 (C=O) and 1579 (C=N). The ^{1}H NMR spectrum of IVh showed a singlet observed at δ 2.79, which was assigned to the CH_3 protons. A multiplet at δ 7.26-7.83 (11H) was accounted for aromatic protons. A doublet was observed at δ 7.53-7.52 responsible for (CO-CH = CH) of the chalcone moiety.

The IR spectrum of **Vh** showed characteristic absorption peaks at 3190 (NH), 1654 (C=O) and 1579 (C=N). The ^{1}H NMR spectrum of **Vh** showed a singlet for the CH_3 proton at δ 2.75. A singlet of $-CH_2$ protons of the pyrazoline core was at δ 3.43 and a singlet at δ 5.85 of the pyrazoline core were also observed. A multiplet of aromatic protons was observed at δ 7.03-7.68 (11H) and one NH at δ 8.16.

The IR spectrum of **VIh** showed characteristic absorption peaks at 3059 (NH), 1612 (C=O), and 1522 (C=N). The ^{1}H-NMR spectrum of **IVh** showed a singlet that was at δ 2.74, which was assigned to the CH3 protons. A singlet observed at δ 7.26 and δ 7.72 of -CH=C and -N=CH of the pyrazole nucleus, respectively. A multiplet at δ 6.90-8.19 (10H) represented the aromatic protons and NH at δ 8.74.

In the same way, the structures of the remaining compounds were confirmed by the spectral data. In addition, they were tested to determine antioxidant activity.

Table No. 1: Physical Data of pyrazole derivatives of 6-methyl-benzimidazoles (VIa-k).

Sl. No.	Compoud Code	R	Molecular Formula	Molecular Weight	M.P.C.	C%	H%	Cl%	N%
1	VIa	6-Ome	$C_{21}H_{16}ClN_5O$	389.83	86	64.70	4.14	9.09	17.96
2	VIb	7-Ome	$C_{21}H_{16}ClN_5O$	389.83	88	64.70	4.14	9.09	17.96
3	VIc	8-CH_3	$C_{21}H_{16}ClN_5$	373.83	82	67.47	4.31	9.48	18.73
4	VId	6-Cl	$C_{20}H_{13}Cl_2N_5$	394.25	87	60.93	3.32	17.78	17.76
5	VIe	8-Ome	$C_{21}H_{16}ClN_5O$	389.83	86	64.70	4.14	9.09	17.96
6	VIf	7-Cl	$C_{20}H_{13}Cl_2N_5$	394.25	89	60.93	3.32	17.78	17.76
7	VIg	7-CH_3	$C_{21}H_{16}ClN_5$	373.83	84	67.47	4.31	9.48	18.73
8	VIh	6-CH_3	$C_{21}H_{16}ClN_5$	373.83	82	67.47	4.31	9.48	18.73
9	VIi	6-Br	$C_{20}H_{13}BrClN_5$	438.70	88	54.75	2.99	8.08	15.96
10	VIj	6-F	$C_{20}H_{13}FClN_5$	377.80	90	63.58	3.47	9.38	18.54
11	VIk	H	$C_{20}H_{14}ClN_5$	359.81	83	66.76	3.92	9.85	19.46

BIOLOGICAL EVALUATION

Antioxidant activity

The synthesized compounds were screened for antioxidant activity by an in vitro method, by using 2,2-diphenyl-1-picrylhydrazyl (DPPH) and hydrogen peroxide scavenging activity.

Free Radical Scavenging Activity

Free radical scavenging activity of the synthesized compounds was measured using 2,2-diphenyl-1-picrylhydrazyl (DPPH).[25-27] Ascorbic acid was used as standard. Percentage inhibition was calculated and compared to the standard. The results are shown in Table No. 2.

Table No. 2: DPPH radical Scavenging Assay of Synthesized Compounds.

Comp Code	% inhibition					
	10µg/ml	50 µg/ml	100 µg/ml	150 µg/ml	200 µg/ml	250 µg/ml
VIa	14.86	29.15	36.44	45.18	52.76	62.53
VIb	09.62	12.68	23.46	31.63	43.29	59.03
VIc	15.16	29.83	38.04	49.12	56.26	61.22
VIg	34.83	37.31	40.23	43.44	48.10	52.47
VIh	36.58	39.06	44.89	49.85	53.35	57.87
VIi	08.30	11.51	21.72	31.63	42.27	53.35
Ascorbic acid	36.05	43.53	48.97	56.46	61.22	67.34

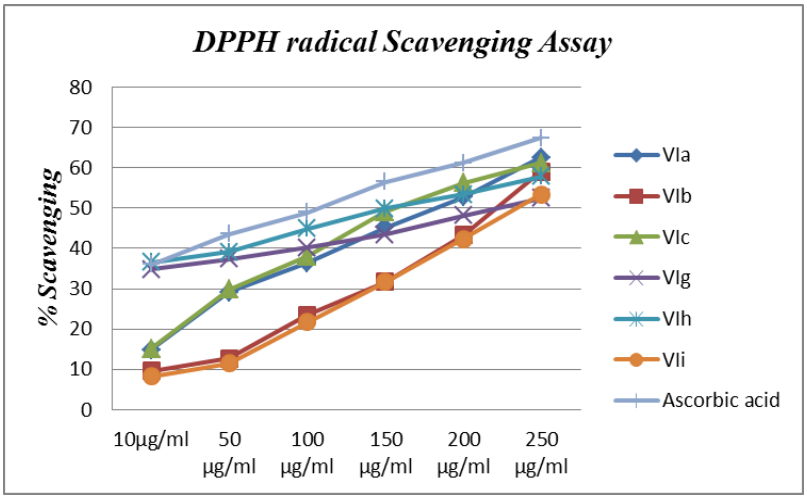


Figure 1: DPPH radical scavenging assay results of synthesized compounds.

Hydrogen Peroxide Scavenging Activity

The hydrogen peroxide binding activity of the synthesized compounds was measured using hydrogen peroxide (30% v/v).[28] Ascorbic acid was used as standard. Percentage inhibition was calculated and compared to the standard. The results are shown in Table No. 3.

Table No. 3: Hydrogen Peroxide Scavenging Activity of Synthesized Compounds.

Comp Code	% inhibition					
	10µg/ml	50 µg/ml	100 µg/ml	150 µg/ml	200 µg/ml	250 µg/ml
VIa	10.34	16.32	29.83	37.31	49.85	61.22
VIb	08.16	14.96	27.21	35.37	44.21	53.06
VIc	12.53	22.74	32.94	43.87	54.81	62.09
VIg	34.69	42.12	46.20	50.87	56.26	62.09
VIh	35.86	38.04	42.41	53.35	60.20	65.01
VIi	09.52	11.56	25.85	38.77	48.29	55.78
Ascorbic acid	35.56	44.07	52.06	60.05	68.81	75.60

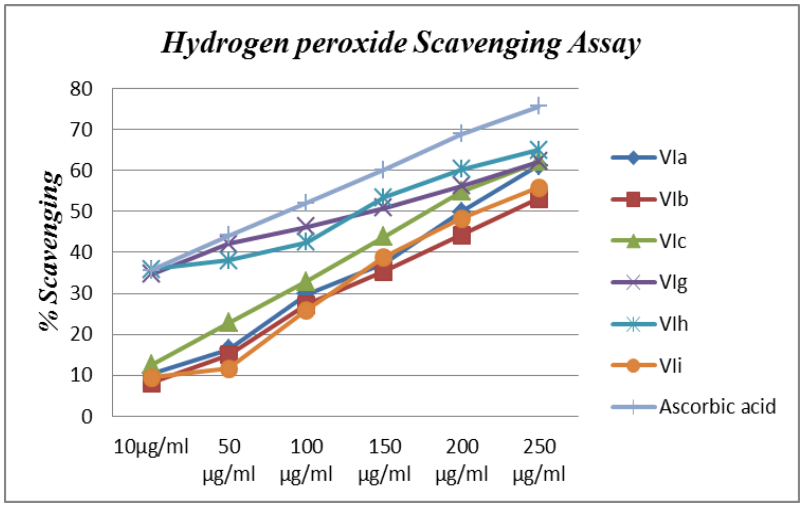


Figure 2: Hydrogen peroxide scavenging assay results of synthesized compounds.

Table No. 4: IC_{50} Values for DPPH radical Scavenging Assay of Synthesized Compounds.

Comp Code	IC $_{50}$
VIa	4.584
VIb	5.522
VIc	4.416
VIg	5.557
VIh	4.196
VIi	5.837
Ascorbic acid	3.135

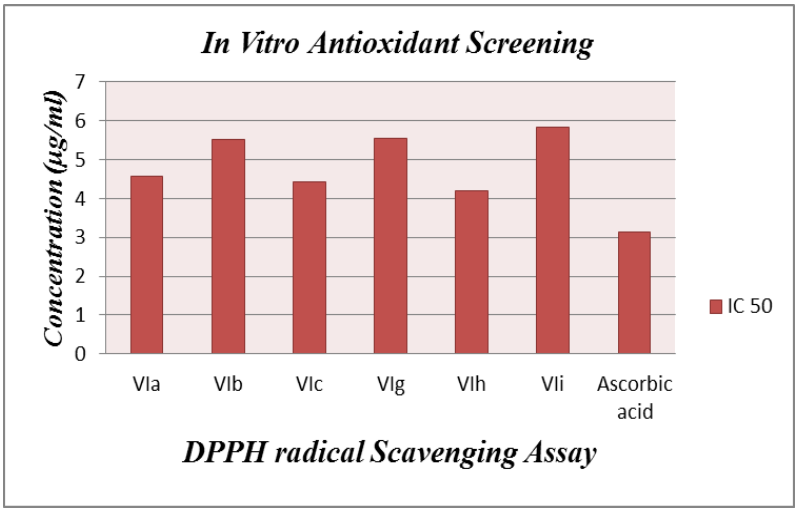


Figure 3: IC_{50} Values for DPPH radical scavenging assay results of synthesized compounds.

Table No. 5: IC_{50} Values for Hydrogen Peroxide Scavenging Activity of Synthesized Compounds.

Comp Code	IC $_{50}$
VIa	4.627
VIb	5.630
VIc	4.667
VIg	3.747
VIh	3.635
VIi	5.317
Ascorbic acid	2.754

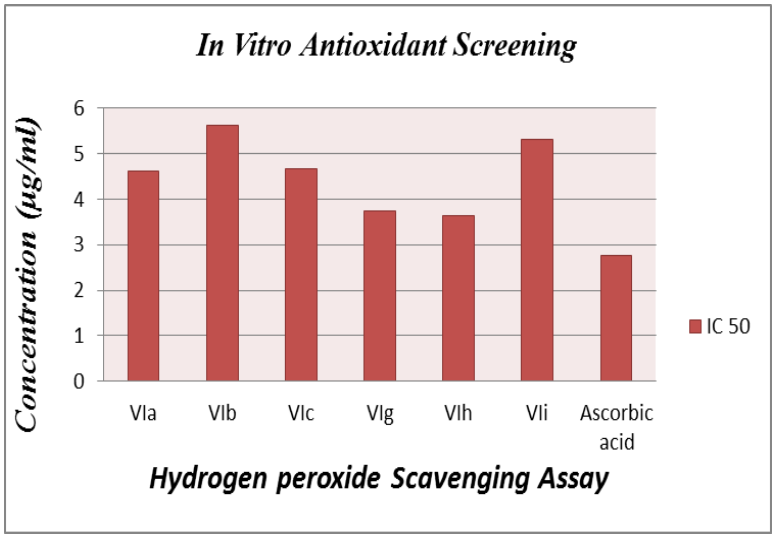


Figure 4: IC_{50} Values for Hydrogen peroxide scavenging assay results of synthesized compounds.

From the above studies, it was observed that as the concentration increases, the trapping amount for the test compounds increases linearly with the standard. All compounds showed excellent antioxidant activity compared to standard ascorbic acid. After careful investigation of the results of the DPPH assay and the hydrogen peroxide scavenging assay, it shows that the VIc, VIg and VIh have potent antioxidant activity, of which VIh is the best compared to ascorbic acid. It means the role of the steric as well as the electron-releasing group CH_3 as a substituent for the inhibition of free radicals.

CONCLUSION

A new series of pyrazoles of 6-methyl-benzimidazole derivatives (VIa-k) was synthesized. The synthesized compounds were confirmed by their spectral studies. Further, these compounds were tested for antioxidant activity. Most of the compounds tested showed significant activity.

ACKNOWLEDGEMENT

The authors thank the Rajiv Gandhi University of Health Sciences, Bangalore for financial support and also the head and management of the BLDEA SSM College of Pharmacy and Research Center, Vijayapur, Karnataka for the provision of facilities.

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