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Research Article

Synthesis, characterization and *in vivo* anthelmintic activity of some newer benzimidazole derivatives

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Abstract

The medicinal chemistry is devoted to the discovery and development of new agents for cure and prevention of diseases. A new drug discovery is exceeding complex and involves selection of moiety, establishing their synthesis and recogination of biological activity. Benzimidazole is a bicyclic ring system in which benzene ring fused with 4- and 5- position of the imidazole ring, imidazole ring contain two nitrogen atoms at nonadjacent position. Benzimidazole is a very important pharmacophore in drug discovery, and its derivatives are used as an important class of bioactive molecules in the field of new drug development. The structures of the newly synthesized benzimidazole derivatives were accomplished through IR, ^{1}H NMR and mass spectral data. All derivatives showed moderate to good anthelmintic activity against *Phaeritima posthuma* species of earthworm at the concentration of 75.0 mg/ml, when compared with piperazine citrate as reference compound. Among all the synthesized compounds, the compound *N*-{(2'-Methyl-1*H*-benzo[*d*]imidazol-1-yl)methyl}-4-nitrobenzenamine **(1a)**, 4-Chloro-*N*-{(2'-methyl-1*H*-benzo[*d*]imidazol-1-yl) methyl} benzenamine **(1c)**, *N*-{(4'-Fluorophenyl)(2''-methyl-1*H*-benzo[*d*]imidazol-1-yl)methyl}-4-nitrobenzenamine **(2b)**, *N*-{(3'-Nitrophenyl)(2''-methyl-1*H*-benzo[*d*]imidazol-1-yl)methyl}-4-chlorobenzenamine **(2d)**, 1-{(4'-Nitrophenylamino) methyl}-1*H*-benzo[*d*]imidazole-2-thiol **(3a)**, 1-{(4'-Chlorophenylamino) methyl}-1*H*-benzo[*d*]imidazole-2-thiol **(3c)**, 1-{(4'-Nitrophenylamino)(4''-fluorophenyl)methyl}-1*H*-benzo[*d*]imidazole-2-thiol **(4b)**, 1-{(4'-Chlorophenylamino)(3''-nitrophenyl)methyl}-1*H*-benzo[*d*]imidazole-2-thiol **(4d)** were found to be most potent towards anthelmintic activity.

Keywords: Benzimidazole, piperazine, anthelmintic activity.

Introduction

Helminthes are recognized as a major problem to livestock production throughout tropics [1]. Most diseases caused by helminthes are of a chronic and debilitating in nature; they probably cause more morbidity and greater economic and social deprivation among humans and animals than any single group of parasites. The parasitic gastroenteritis is caused by mixed infection with several species of stomach and intestinal worms, which results in weakness, loss of appetite, decreased feed efficiency, reduced weight gain and decreased productivity [2]. Chemotherapy is the only treatment and effective tool to cure and control helminth infection, as effective vaccines against have not been developed so far. Indiscriminate use of synthetic anthelmintics can lead to resistance of parasites [3]. Benzimidazole is a very important pharmacophore in drug

discovery, and its derivatives are used as an important class of bioactive molecules in the field of new drug development [4]. Benzimidazole nucleus has capability to inhibit the growth of various bacteria, yeast, fungi, protozoa and helminthes [5]. Benzimidazole are the versatile pharmacophore havig various biological activities like antibacterial [6], antifungal [7], Anthelmintic [8], antiprotozoal [9], anticoagulant [10], analgesic, anti-inflammatory [11], anticancer [12], anti-HIV [13], antiulcer [14], antiviral [15], antihistaminic [16], antioxidant [17], anticonvulsant [18], hypolipidemic activities [19].

This study focused on the synthesis of some newer benzimidazole derivatives through mannish reaction, and their significant role in anthelmintic activity.

Materials and Methods

Melting points were taken in open capillary tube and were uncorrected. The purity of all the newly synthesized compounds was checked by TLC on silica gel G plates. The solvent system was chloroform: methanol: 1: 1. The UV spectra were recorded on a SHIMADZU spec-1700, IR spectra on a SHIMADZU 8400S spectrophotometer, ^{1}H NMR spectra on a Brucker DRX 300 in DMSO using TMS (Tetramethyl silane) as an internal standard and Mass spectrum on an MS-ESI (SHIMADZU-2010 AT, software class VP). Elemental analysis was carried out on elemental vario EL III Carlo Erba 1108.

Procedure for synthesis of 2-Methyl-1*H*-benzo[*d*]imidazole

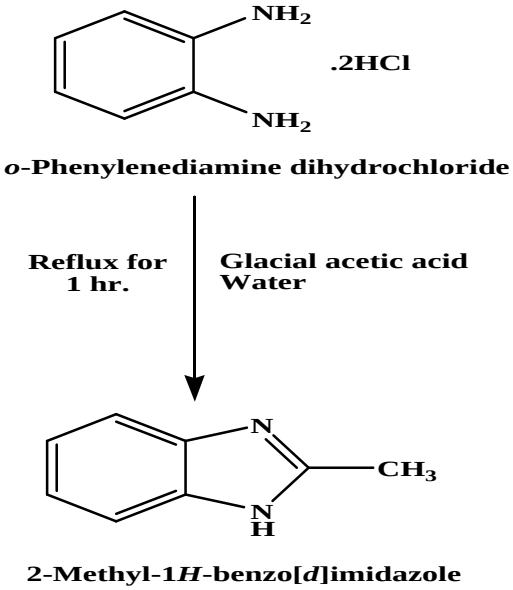
o-Phenylenediamine dihydrochloride (10 mmol), water 5 ml and acetic acid (30 mmol) were added to the flask and the reaction mixture was refluxed for 1 hr. The flask was then removed, cooled at room temperature and conc. ammonia solution was added slowly with constant stirring until the reaction mixture become alkaline. The product was precipitated out, washed with ice cold water, filtered, dried and recrystallized from aqueous ethanol.

Procedure for Synthesis of *N*-{(2-Methyl/Mercapto-1*H*-benzo[*d*]imidazol-1-yl)methyl}substituted benzenamine (1a-1c) & (3a-3c),*N*-{(2-Methyl/Mercapto-1*H*-benzo [*d*]imidazol-1-yl) (substituted phenyl)methyl}substituted benzenamine (2a-2d) & (4a-4d)

Eqimolar quantities of compound 2-Methyl/Mercapto benzimidazole (10 mmol), Substituted aryl amine (10 mmol) and formaldehyde/Substituted benzaldehyde (10 mmol) were taken in 15 ml. of ethanol and refluxed for 10-24 hrs. On cooling, the product formed was filtered, dried and purified by recrystallization with 40% aq. Ethanol.

Scheme-1:

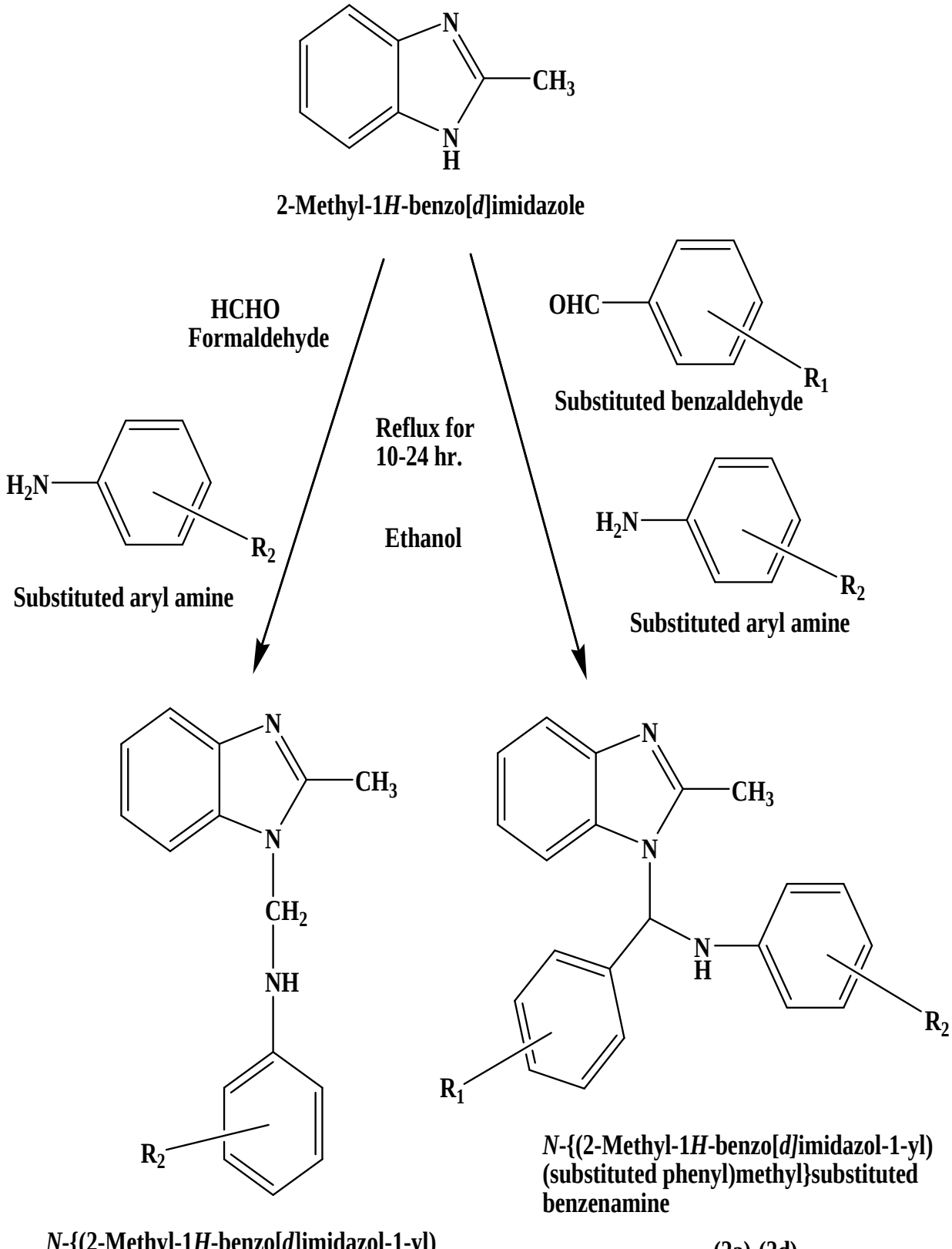
Step-1:



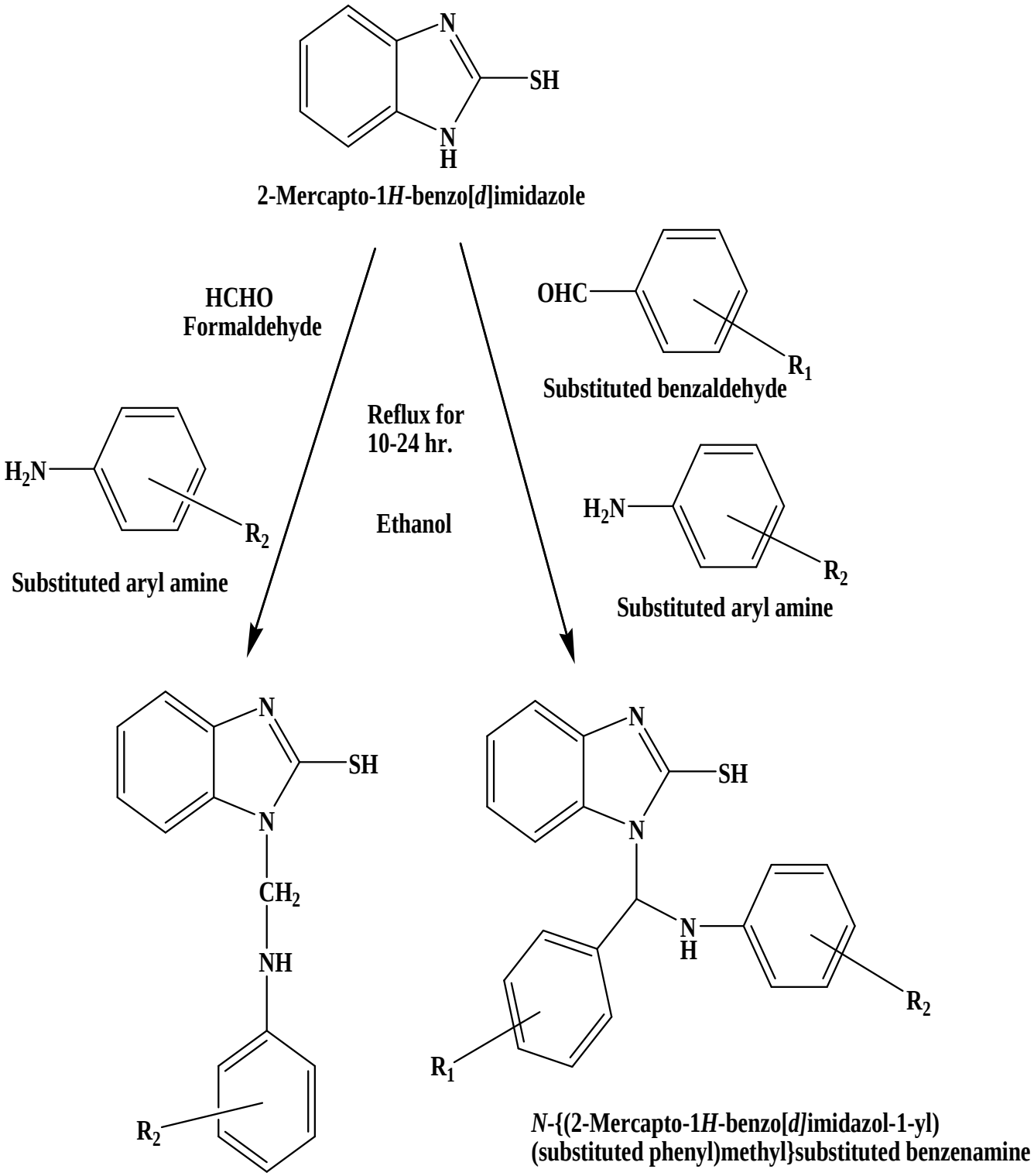
***o*-Phenylenediamine dihydrochloride**

2-Methyl-1*H*-benzo[*d*]imidazole

Step-2:


2-Methyl-1H-benzo[d]imidazole
HCHO
Formaldehyde
Reflux for
10-24 hr.
Ethanol
Substituted aryl amine
Substituted benzaldehyde
Substituted aryl amine
N-{(2-Methyl-1H-benzo[d]imidazol-1-yl)
methyl}substituted benzenamine
(1a)-(1c)
N-{(2-Methyl-1H-benzo[d]imidazol-1-yl)
(substituted phenyl)methyl}substituted
benzenamine
(2a)-(2d)

Scheme-2:


2-Mercapto-1H-benzo[d]imidazole
HCHO
Formaldehyde
Reflux for
10-24 hr.
Ethanol
Substituted aryl amine
Substituted benzaldehyde
Substituted aryl amine
N-{(2-Mercapto-1H-benzo[d]imidazol-1-yl)
methyl}substituted benzenamine
(3a)-(3c)
N-{(2-Mercapto-1H-benzo[d]imidazol-1-yl)
(substituted phenyl)methyl}substituted benzenamine
(4a)-(4d)

Compound No.	R_1	R_2
1a	-	*p*-NO_2
1b	-	*m*-OCH_3
1c	-	*p*-Cl
2a	*p*-OH	*p*-NO_2
2b	*p*-F	*p*-NO_2
2c	*m*-OCH_3	*p*-NO_2
2d	*m*-NO_2	*p*-Cl
3a	-	*p*-NO_2
3b	-	*m*-OCH_3
3c	-	*p*-Cl
4a	*p*-OH	*p*-NO_2
4b	*p*-F	*p*-NO_2
4c	*m*-OCH_3	*p*-NO_2
4d	*m*-NO_2	*p*-Cl

Compound detail

N-{(2'-Methyl-1*H*-benzo[*d*]imidazol-1-yl)methyl}-4-nitrobenzenamine (1a):

Yield: 81.41 %, m.p. 144-146°C; Elemental analysis Calcd for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.80; H, 5.01; N, 19.81 %; FTIR (KBr, $\nu_{max,}$ cm^{-1}): 3365 (N-H str. (2°amine)), 3051 (Aromatic C-H str.), 2935 (Aliphatic C-H str.), 1677 (C=N str.), 1630 (Aromatic C⋯C str.), 1585 (Aromatic C-C str.), 1419 (N-O str.), 1315 (Aromatic C-N str.), 1174 (Aliphatic C-N str.), 813 (C-H *p*-disubstituted benzene (def.)); ^{1}H NMR **(**DMSO-d_6**)** δ(ppm)**:** 2.70 (s, 3H, CH_3), 4.10 (s, 1H, N-H, D_2O exchangeable), 4.32 (s, 2H, CH_2), 7.203-7.249 (t, 2H, Ar–H), 7.410-7.425 (d, 2H, Ar–H), 7.501-7.527 (d, 2H, Ar–H), 7.854-7.895 (d, 2H, Ar–H); MS (ESI) m/z [% rel. abundance]: 282 (100) $[M]^+$, 283 (16) $[M+1]^+$.

3-Methoxy-*N*-{(2'-methyl-1*H*-benzo[*d*]imidazol-1-yl)methyl}benzenamine (1b):

Yield: 75.7 %, m.p. 164-166°C; Elemental analysis Calcd for $C_{16}H_{17}N_3O$: C, 71.89; H, 6.41; N, 15.72. Found: C, 71.87; H, 6.40; N, 15.69 %; FTIR (KBr, $\nu_{max,}$ cm^{-1}): 3350 (N-H str. (2°amine)), 3056 (Aromatic C-H str.), 2921 (Aliphatic C-H str.), 1687 (C=N Str.), 1620 (Aromatic C⋯C str.), 1271 (Aromatic C-N str.), 1209 (Aliphatic C-N str.), 1084 (C-O-C str.), 693 (C-H *m*-disubstituted benzene (def.)); ^{1}H NMR **(**DMSO-d_6**)** δ(ppm)**:** 2.320 (s, 3H, CH_3), 3.734 (s, 3H, OCH_3), 4.122 (s, 1H, N-H, D_2O exchangeable), 4.601 (s, 2H, CH_2), 6.080-6.093 (d, 1H, Ar–H), 6.408 (s, 1H, Ar–H), 6.700-6.777 (t, 1H, Ar-H), 6.940-6.957 (d, 1H, Ar-H), 7.260-7.283 (t, 2H, Ar–H), 7.509-7.525 (d, 2H, Ar–H); MS (ESI) m/z [% rel. abundance]: 267 (100) $[M]^+$, 268 (18) $[M+1]^+$.

4-Chloro-*N*-{(2'-methyl-1*H*-benzo[*d*]imidazol-1-yl) methyl} benzenamine (1c):

Yield: 63.71 %, m.p. 180-182°C; Elemental analysis Calcd for $C_{15}H_{14}N_3Cl$: C, 66.30; H, 5.19; N, 15.12; Cl, 13.05. Found: C, 66.27; H, 5.18; N, 15.09; Cl, 13.01 %; FTIR (KBr, $\nu_{max,}$ cm^{-1}): 3356 (N-H str. (2°amine)), 3037 (Aromatic C–H str.), 2935 (Aliphatic C-H str.), 1664 (C=N str.), 1623 (C=C ring str.), 1282 (Aromatic C-N str.), 1164 (Aliphatic C-N str.), 1092 cm^{-1} (Aromatic C-Cl str.), 829 (C-H *p*-disubstituted benzene (def.)); ^{1}H NMR **(**DMSO-d_6**)** δ(ppm)**:** 2.102 (s, 3H, CH_3), 4.00 (s, 1H, N-H, D_2O exchangeable), 4.410 (s, 2H, CH_2), 7.053-7.109 (t, 2H, Ar–H), 7.210-7.235 (d, 2H, Ar–H), 7.421-7.439 (d, 2H, Ar–H), 7.654-7.690 (d, 2H, Ar–H); MS (ESI) m/z [% rel. abundance]: 271 (100) $[M]^+$, 272 (16) $[M+1]^+$, 273 (27) $[M+2]^+$.

4-{(4'-Nitrophenylamino)(2''-methyl-1*H*-benzo[*d*]imidazol-1-yl)methyl}phenol (2a):

Yield: 78.2 %, m.p. 178-180°C; Elemental analysis Calcd for $C_{21}H_{18}N_4O_3$: C, 67.37; H, 4.85; N, 14.96. Found: C, 67.35; H, 4.84; N, 14.93 %; FTIR (KBr, $\nu_{max,}$ cm^{-1}): 3640 (O-H str.), 3361 (N-H str. (2°amine)), 3072 (Aromatic C-H str.), 2896 (Aliphatic C-H str.), 1675 (C=N Str.), 1625 (Aromatic C⋯C str.), 1483 (N-O Str.), 1313 (Aromatic C-N str.), 1186 (Aliphatic C-N str.), 840 (C-H *p*-disubstituted benzene (def.)); ^{1}H NMR **(**DMSO-d_6**)** δ(ppm)**:** 2.803 (s, 3H, CH_3), 4.502 (s, 1H, N-H, D_2O exchangeable), 5.20 (s, 1H, OH, D_2O exchangeable), 6.106 (s, 1H, CH), 6.603-6.625 (d, 2H, Ar–H), 6.804-6.829 (d, 2H, Ar–H), 6.904-6.983 (t, 2H, Ar–H), 6.259-6.285 (d, 2H, Ar-H), 7.310-7.329 (d, 2H, Ar–H), 7.901-7.925 (d, 2H, Ar–H); MS (ESI) m/z [% rel. abundance]: 374 (100) $[M]^+$, 375 (16) $[M+1]^+$.

***N*-{(4'-Fluorophenyl)(2''-methyl-1*H*-benzo[*d*]imidazol-1-yl)methyl}-4-nitrobenzenamine (2b):**

Yield: 85.3 %, m.p. 134-136°C; Elemental analysis Calcd for $C_{21}H_{17}FN_4O_2$: C, 67.01; H, 4.55; F, 5.05; N, 14.89. Found: C, 67.02; H, 4.52; F, 5.02; N, 14.86 %; FTIR (KBr, $\nu_{max,}$ cm^{-1}): 3357 (N-H str. (2°amine)), 3055 (Aromatic C-H str.), 2889 (Aliphatic C-H str.), 1680 (C=N str.), 1616 (Aromatic C⋯C str.), 1431 (N-O Str.), 1313 (Aromatic C-N str.), 1205 (C-F Str.), 1103 (Aliphatic C-N str.), 820 (C-H *p*-disubstituted benzene (def.)); ^{1}H NMR **(**DMSO-d_6**)** δ(ppm)**:** 2.401 (s, 3H, CH_3), 4.00 (s, 1H, N-H, D_2O exchangeable), 6.10 (s, 1H, CH), 6.920-6.957 (d, 2H, Ar–H), 7.240-7.248 (d, 2H, Ar–H), 7.303-7.399 (t, 2H, Ar–H), 7.512-7.528 (d, 2H, Ar-H), 7.802-7.815 (d, 2H, Ar–H), 7.902-7.957 (d, 2H, Ar–H); MS (ESI) m/z [% rel. abundance]: 376 (100) $[M]^+$, 377 (12) $[M+1]^+$, 378 (24) $[M+2]^+$.

***N*-{(3-Methoxyphenyl)(2''-methyl-1*H*-benzo[*d*]imidazol-1-yl)methyl}-4-nitrobenzenamine (2c):**

Yield: 83.5 %, m.p. 152-154°C; Elemental analysis Calcd for $C_{22}H_{20}N_4O_3$: C, 68.03; H, 5.19; N, 14.42. Found: C, 68.01; H, 5.16; N, 14.41 %; FTIR (KBr, $\nu_{max,}$ cm^{-1}): 3361 (N-H str. (2°amine)), 3062 (Aromatic C-H str.), 2898 (Aliphatic C-H str.), 1687 (C=N str.), 1610 (Aromatic C⋯C str.), 1476 (N-O str.), 1313 (Aromatic C-N str.), 1190 (C-O-C str.), 1125 (Aliphatic C-N str.), 812 (C-H *p*-disubstituted benzene (def.)), 705 (C-H *m*-disubstituted benzene (def.)); ^{1}H NMR **(**DMSO-d_6**)** δ(ppm)**:** 2.203 (s, 3H, CH_3), 3.734 (s, 3H, OCH_3), 4.312 (s, 1H, N-H, D_2O exchangeable), 6.280 (s, 1H, CH), 6.093-6.548 (d, 1H, Ar–H), 6.600 (s, 1H, Ar–H), 6.738-6.840 (t, 1H, Ar–H), 6.957-7.060(d, 1H, Ar-H), 7.269-7.299 (t, 2H, Ar–H), 7.305-7.359 (d, 2H, Ar–H), 7.505-7.529 (d, 2H, Ar–H), 7.925-7.945 (d, 2H, Ar–H); MS (ESI) m/z [% rel. abundance]: 388 (100) $[M]^+$, 389 (16) $[M+1]^+$.

***N*-{(3'-Nitrophenyl)(2''-methyl-1*H*-benzo[*d*]imidazol-1-yl)methyl}-4-chlorobenzenamine (2d):**

Yield: 68.97 %, m.p. 218-220°C; Elemental analysis Calcd for $C_{21}H_{17}N_4O_2Cl$: C, 64.21; H, 4.36; N, 14.26; Cl, 9.02. Found: C, 64.19; H, 4.35; N, 14.23; Cl, 9.01%; FTIR (KBr, $\nu_{max,}$ cm^{-1}): 3380 (N-H str. (2°amine)), 3049 (Aromatic C-H str.), 2910 (Aliphatic C-H str.), 1664 (C=N str.), 1610 (Aromatic C⋯C str.), 1446 (N-O str.), 1332 (Aromatic C-N str.), 1226 (Aliphatic C-N str.), 1092 (C-Cl str.), 834 (C-H *p*-Disubstituted

benzene (def.)), 691 (C-H *m*-disubstituted benzene (def.)); ^{1}H NMR **(**DMSO-d_6**)** δ(ppm)**:** 2.300 (s, 3H, CH_3), 4.207 (s, 1H, N-H, D_2O exchangeable), 6.103 (s, 1H, CH), 7.103-7.179 (t, 2H, Ar–H), 7.210-7.243 (d, 2H, Ar–H), 7.302-7.349 (d, 2H, Ar–H), 7.410-7.435 (d, 1H, Ar-H), 7.501-7.584 (t, 1H, Ar–H), 7.605-7.641 (d, 2H, Ar–H), 7.907 (s, 1H, Ar–H), 7.914-8.025 (d, 1H, Ar–H); MS (ESI) m/z [% rel. abundance]: 392 (100) $[M]^+$, 393 (12) $[M+1]^+$, 394 (23) $[M+2]^+$.

1-{(4'-Nitrophenylamino) methyl}-1*H*-benzo[*d*]imidazole-2-thiol (3a):

Yield: 87.7 %, m.p. 236-238°C; Elemental analysis Calcd for $C_{14}H_{12}N_4O_2S$: C, 55.99; H, 4.03; N, 18.65; S, 10.68. Found: C, 55.97; H, 4.01; N, 18.63; S, 10.62 %; FTIR (KBr, $\nu_{max,}$ cm^{-1}): 3370 (N-H str. (2°amine)), 3075 (Aromatic C-H str.), 2925 (Aliphatic C-H str.), 2559 (S-H Str.), 1635 (Aromatic C=C Str.), 1623 (C=N Str.), 1593 (Aromatic C-C str.), 1454 (N-O Str.), 1325 (Aromatic C-N str.), 1180 (Aliphatic C-N str.), 806 (C-H *p*-disubstituted benzene (def.)); ^{1}H NMR **(**DMSO-d_6**)** δ(ppm)**:** 3.007 (s, 1H, SH, D_2O exchangeable), 4.000 (s, 1H, N-H, D_2O exchangeable), 4.502 (s, 2H, CH_2), 7.215-7.269 (t, 2H, Ar–H), 7.304-7.325 (d, 2H, Ar–H), 7.610-7.630 (d, 2H, Ar–H), 7.904-7.923 (d, 2H, Ar–H); MS (ESI) m/z [% rel. abundance]: 300 (100) $[M]^+$, 301 (15) $[M+1]^+$.

1-{(3'-Methoxyphenylamino) methyl}-1*H*-benzo[*d*]imidazole-2-thiol (3b):

Yield: 83.8 %, m.p. 220-222°C; Elemental analysis Calcd for $C_{15}H_{15}N_3OS$: C, 63.13; H, 5.30; N, 14.73; S, 11.24. Found: C, 63.11; H, 5.28; N, 14.71; S, 11.22 %; FTIR (KBr, $\nu_{max,}$ cm^{-1}): 3364 (N-H str. (2°amine)), 3072 (Aromatic C-H str.), 2879 (Aliphatic C-H str.), 2572 (S-H Str.), 1682 (C=N str.), 1614 (Aromatic C=C str.), 1274 (Aromatic C-N str.), 1190 (Aliphatic C-N Str.), 1107 (C-O-C Str.), 710 (C-H *m*-Disubstituted benzene (def.)); ^{1}H NMR **(**DMSO-d_6**)** δ(ppm)**:** 3.220 (s, 1H, SH, D_2O exchangeable), 3.730 (s, 3H, OCH_3), 4.000 (s, 1H, N-H, D_2O exchangeable), 4.302 (s, 2H, CH_2), 6.110-6.133 (d, 1H, Ar–H), 6.408 (s, 1H, Ar–H), 6.701-6.767 (t, 1H, Ar-H), 6.940-6.953 (d, 1H, Ar-H),7.310-7.364 (t, 2H, Ar–H), 7.733-7.765 (d, 2H, Ar–H); MS (ESI) m/z [% rel. abundance]: 285 (100) $[M]^+$, 286 (15) $[M+1]^+$.

1-{(4'-Chlorophenylamino) methyl}-1*H*-benzo[*d*]imidazole-2-thiol (3c):

Yield: 83.4 %, m.p. 252-254°C; Elemental analysis Calcd for $C_{14}H_{12}N_3SCl$: C, 58.03; H, 4.17; N, 14.50; S, 11.07; Cl, 12.23. Found: C, 58.01; H, 4.15; N, 14.47; S, 11.02; Cl, 12.21 %; FTIR (KBr, $\nu_{max,}$ cm^{-1}): 3362 (N-H str. (2°amine)), 3071 (Aromatic C–H str.), 2952 (Aliphatic C-H str.), 2571 (S-H str.), 1683 (C=N str.), 1602 (C=C ring str.), 1317 (Aromatic C-N str.), 1182 (Aliphatic C-N str.), 1095 cm^{-1} (Aromatic -Cl str.), 835 (C-H *p*-disubstituted (def.)); ^{1}H NMR **(**DMSO-d_6**)** δ(ppm)**:** 3.102 (s, 1H, SH, D_2O exchangeable), 4.010 (s, 1H, N-H, D_2O exchangeable), 4.402 (s, 2H, CH_2), 7.043-7.103 (t, 2H, Ar–H), 7.216-7.243 (d, 2H, Ar–H), 7.401-7.435 (d, 2H, Ar–H), 7.509-7.524 (d, 2H, Ar–H); MS (ESI) m/z [% rel. abundance]: 289 (100) $[M]^+$, 290 (15) $[M+1]^+$, 291 (26) $[M+2]^+$.

4-{(4'-Nitrophenylamino)(2''-mercapto-1*H*-benzo[*d*]imidazol-1-yl)methyl}phenol (4a):

Yield: 69.6 %, m.p. 210-212°C; Elemental analysis Calcd for $C_{20}H_{16}N_4O_3S$: C, 61.21; H, 4.11; N, 14.28; S, 8.17. Found: C, 61.18; H, 4.09; N, 14.25; S, 8.14 %; FTIR (KBr, $\nu_{max,}$ cm^{-1}): 3620 (O-H str.), 3359 (N-H str. (2°amine)), 3063 (Aromatic C-H str.), 2893 (Aliphatic C-H str.), 2570 (S-H Str.), 1661 (C=N str.), 1631 (Aromatic C=C str.), 1469 (N-O Str.), 1303 (Aromatic C-N str.), 1176 (Aliphatic C-N str.), 823 (C-H *p*-disubstituted benzene (def.)); ^{1}H NMR **(**DMSO-d_6**)** δ(ppm)**:** 3.401 (s, 1H, SH, D_2O exchangeable), 4.300 (s, 1H, N-H, D_2O exchangeable), 5.000 (s, 1H, OH, D_2O exchangeable), 6.206 (s, 1H, CH), 6.603-6.625 (d, 2H, Ar–H), 6.807-6.823 (d, 2H, Ar–H), 7.156-7.181 (d, 2H, Ar–H), 7.309-7.385 (t, 2H, Ar-H), 7.479-7.505 (d, 2H, Ar–H), 7.810-7.844 (d, 2H, Ar–H); MS (ESI) m/z [% rel. abundance]: 392 (100) $[M]^+$, 393 (12) $[M+1]^+$.

1-{(4'-Nitrophenylamino)(4''-fluorophenyl)methyl}-1*H*-benzo[*d*]imidazole-2-thiol (4b):

Yield: 84.76 %, m.p. 240-242°C; Elemental analysis Calcd for $C_{20}H_{14}FN_3O_2S$: C, 63.31; H, 3.72; F, 5.03; N, 11.08; S, 8.45. Found: C, 63.16; H, 3.53; F, 5.01; N, 11.02; S, 8.20; %; FTIR (KBr, $\nu_{max,}$ cm^{-1}): 3386 (N-H str. (2°amine)), 3089 (Aromatic C-H str.), 2887 (Aliphatic C-H str.), 2557 (S-H Str.), 1685 (C=N str.), 1620 (Aromatic C=C str.), 1413 (N-O str.), 1299 (Aromatic C-N str.), 1208 (C-F str.), 1145 (Aliphatic C-N str.), 820 (C-H *p*-disubstituted benzene (def.)); ^{1}H NMR **(**DMSO-d_6**)** δ(ppm)**:** 3.100 (s, 1H, SH, D_2O exchangeable), 4.010 (s, 1H, N-H, D_2O exchangeable), 6.109 (s, 1H, CH), 6.932-6.951 (d, 2H, Ar–H), 7.210-7.283 (t, 2H, Ar–H), 7.311-7.334 (d, 2H, Ar–H), 7.602-7.629 (d, 2H, Ar-H), 7.832-7.853 (d, 2H, Ar–H), 7.941-7.959 (d, 2H, Ar–H); MS (ESI) m/z [% rel. abundance]: 394 (100) $[M]^+$, 395 (12) $[M+1]^+$, 396 (25) $[M+2]^+$.

1-{(4'-Nitrophenylamino)(3''-methoxyphenyl)methyl}-1*H*-benzo[*d*]imidazole-2-thiol (4c):

Yield: 80.7 %, m.p. 226-228°C; Elemental analysis Calcd for $C_{21}H_{17}N_3O_3S$: C, 64.43; H, 4.38; N, 10.73; S, 8.19. Found: C, 64.41; H, 4.36; N, 10.71; S, 8.16 %; FTIR (KBr, $\nu_{max,}$ cm^{-1}): 3361 (N-H str. (2°amine)), 3040 (Aromatic C-H str.), 2881 (Aliphatic C-H str.), 2578 (S-H str.), 1675 (C=N str.), 1618 (Aromatic C=C str.), 1467 (N-O str.), 1313 (Aromatic C-N str.), 1186 (C-O-C str.), 1110 (Aliphatic C-N str.), 820 (C-H *p*-disubstituted benzene (def.)), 708 (C-H *m*-disubstituted benzene (def.)); ^{1}H NMR **(**DMSO-d_6**)** δ(ppm)**:** 3.200 (s, 1H, SH, D_2O exchangeable), 3.704 (s, 3H, OCH_3), 4.212 (s, 1H, N-H, D_2O exchangeable), 6.120 (s, 1H, CH), 6.193-6.528 (d, 1H, Ar–H), 6.600 (s, 1H, Ar–H), 6.728-6.900 (t, 1H, Ar–H), 6.927-7.030 (d, 1H, Ar-H), 7.209-7.289 (t, 2H, Ar–H), 7.305-7.399 (d, 2H, Ar–H), 7.605-7.629 (d, 2H, Ar–H), 7.813-7.845 (d, 2H, Ar–H); MS (ESI) m/z [% rel. abundance]: 406 (100) $[M]^+$, 407 (12) $[M+1]^+$.

1-{(4'-Chlorophenylamino)(3''-nitrophenyl)methyl}-1*H*-benzo[*d*]imidazole-2-thiol (4d):

Yield: 73.05 %, m.p. 190-192°C; Elemental analysis Calcd for $C_{20}H_{15}N_4O_2SCl$: C, 58.46; H, 3.68; N, 13.64; S, 7.80; Cl, 8.63. Found: C, 58.45; H, 3.63; N, 13.62; S, 7.76; Cl, 8.61 %; FTIR (KBr, $\nu_{max,}$ cm^{-1}): 3380 (N-H str. (2°amine)), 3080 (Aromatic C-H str.), 2958 (Aliphatic C-H str.), 2559 (S-H Str.), 1685 (C=N str.), 1602 (Aromatic C=C str.), 1421 (N-O str.), 1326 (Aromatic C-N str.), 1180 (Aliphatic C-N str.), 1090 (C-Cl str.), 812 (C-H *p*-disubstituted benzene (def.)), 703 (C-H *m*-disubstituted benzene (def.)); ^{1}H NMR **(**DMSO-d_6**)** δ(ppm)**:** 3.102 (s, 1H, SH, D_2O exchangeable), 4.102 (s, 1H, N-H, D_2O exchangeable), 6.107 (s, 1H, CH), 7.103-7.189 (t, 2H, Ar–H), 7.212-7.240 (d, 2H, Ar–H), 7.303-7.342 (d, 1H, Ar–H), 7.401-7.437 (d, 2H, Ar-H), 7.510-7.574 (t, 1H, Ar–H), 7.705-7.731 (d, 2H, Ar–H), 7.907 (s, 1H, Ar–H), 7.915-8.035 (d, 1H, Ar–H); MS (ESI) m/z [% rel. abundance]: 410 (100) $[M]^+$, 411 (12) $[M+1]^+$, 412 (25) $[M+2]^+$.

Results and Discussion

The novel benzimidazole derivatives were synthesized successfully in moderate to good yields. The newly synthesized compounds were identified on the basis of R_f values; melting point range; solubility in different solvents; FTIR, ^{1}H NMR, mass spectral analysis and elemental analysis. All the newly synthesized benzimidazole derivatives were screened for anthelmintic activity against *Phaeritima posthuma* species of earthworm, compared to standard drug piperazine citrate.

Anthelmintic activity

Anthelmintic activity was evaluated on earthworm, *Phaeritima posthuma*. Earthworms were divided into fourteen groups (5 each). The first group served as normal control which received Tween 80 (0.5%) and distilled water only, second group received the standard drug i.e Piperazine citrate in Tween 80 (0.5%), distilled water and a dose level of 75.0 mg/ml and other test groups received various doses of synthesized compounds in Tween 80 (0.5%) and distilled water. Observations were made for the time taken to cause paralysis and death of individual worms for two hours. The paralyzing and death times were noted and their mean was calculated for triplicate sets. The results of anthelmintic activity are shown in table **1**. It was concluded that among all the synthesized compounds **1a, 1c, 2b, 2d, 3a,**

3c, 4b, 4d showed potent anthelmintic activity against *Phaeritima posthuma* species of earthworm, compared to standard drug piperazine citrate.

Table 1. anthelmintic activity of compounds

Compound code	Compound conc. (mg/ml)	*Phaeritima Posthuma*	
		Mean paralyzing time (min)	Mean death time (min)
1**a**	37.5	15.33±0.52	24.66±0.33
	75.0	13.66±0.70	21.33±0.64
	150.0	11.66±0.34	19.33±0.40
1**b**	37.5	59.33±0.40	69.66±0.40
	75.0	52.33±0.48	62.33±0.52
	150.0	42.33±0.26	57.33±0.44
1**c**	37.5	17.66±0.48	23.33±0.56
	75.0	22.66±0.32	21.33±0.56
	150.0	19.66±0.29	22.33±0.45
2a	37.5	57.67±0.90	78.30±0.87
	75.0	44.60±0.30	57.38±0.48
	150.0	33.38±0.78	36.32±0.86
2b	37.5	11.33±0.35	19.33±0.80
	75.0	19.33±0.48	27.33±0.29
	150.0	12.33±0.91	20.66±0.32
2c	37.5	52.22±0.81	57.66±0.47
	75.0	41.66±0.47	51.00±0.81
	150.0	34.33±0.94	42.00±0.81
2d	37.5	27.66±0.48	42.33±0.48
	75.0	21.33±0.60	36.33±0.66
	150.0	19.33±0.81	29..33±0.38
3a	37.5	15.33±0.49	18.66±0.75.0
	75.0	14.33±0.35	17.66±0.43
	150.0	10.33±0.41	16.33±0.29
3b	37.5	50.13±0.28	78.32±0.87
	75.0	41.60±0.77	57.38±0.48
	150.0	29.19±0.83	36.32±0.86
3c	37.5	12.66±0.75.0	18.66±0.42
	75.0	13.33±0.64	24.66±0.92
	150.0	17.66±0.29	21.33±0.85
4a	37.5	59.33±0.32	67.66±0.59
	75.0	46.66±0.65	57.33±0.61
	150.0	37.33±0.81	47.33±0.89
4b	37.5	19.33±0.40	23.66±0.40
	75.0	18.66±0.83	25.66±0.89
	150.0	18.33±0.39	24.33±0.39
4c	37.5	59.33±0.40	69.66±0.40
	75.0	48.66±0.83	57.66±0.89
	150.0	38.33±0.39	48.33±0.39
4d	37.5	19.33±0.40	24.66±0.40
	75.0	18.66±0.83	27.66±0.89
	150.0	18.33±0.39	26.33±0.39
Piperazine citrate(standard)	75.0	28.66±0.82	34.66±0.79
Control	-	-	-

Data are given as mean ± S.D (n=3); S.D = standard deviation

We demonstrated in this study a significant increase in serum Ghrelin 6 months after insertion of BIB. These findings are in concordance with the data obtained by Marek Bužga et al who stated that the levels of ghrelin increased significantly

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