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Synthesis and spectral characterization of some 2-[(1-((substituted phenylamino) methyl)-1-benzoimidazol-2-yl) alkyl] isoindoline-1,3-diones for *in-vitro* anthelmintic screening

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ABSTRACT

Two series of isoindoline carrying benzimidazoles (6a-n) were synthesized by mannich reaction of 2-alkyl benzimidazolyl isoindoline-1,3-dione (4a-b) with different aromatic primary amines (5a-g) using formaldehyde as condensing agent. The pthalic anhydride (1) and aminoacids (2a-b) condensed at high temperature to give 2-(1,3-dioxoisoindolin-2-yl) carboxylic acids (3a-b). These acids undergo cyclization with orthophenylene diamine yields benzimidazoles (4a-b). The yield of the synthesized compounds ranged from 40-78%. The structures of the synthesized isoindolinedione compounds were verified by IR, ^{1}*H-NMR,* ^{13}*C-NMR, mass spectral data and physical analysis. The In-vitro anthelmintic screening of all benzimidazolyl isoindolines indicates that, have pronounced potency when compared to albendazole.*

Keywords: Benzimidazoles, benzimidazolyl isoindolines, isoindoline and anthelmintic.

INTRODUCTION

Heterocyclic's compounds have depicted a central position in the field of medicinal chemistry owing to their high reactivity, pharmacological properties and are widely implicated in various biochemical processes. Many heterocyclic's compounds especially five membered like imidazoles, pyrazoles, pyrroles, furans, thiazoles, oxazoles, isoxazoles, thiadiazole and six membered heterocyclic's like pyridine, pyrimidines, pyrazines, piper azines etc have shown diversified pharmacological activity ranging from anti-infective, antibacterial, antifungal, antiprotozoal, anti-tubercular, antiviral, analgesic, anti-inflam matory, anti epileptic, anti-ulcer [1], diuretics, anticancer, antihypertensive, anthelminitics , etc. Fused heterocyclic's compounds such as benzimidazole , phenothiazine, indole, benzofuran, benzoxacine, benzodiazepines, benzothiazine, purine, quinoline, pteridine have been well-recognized for their anti-infective,antibacterial, antifungal, antiprotozoal, anthelminitics ,CNS stimulant,diuretics, antimalarial, antiviral, antineoplastics, hypnotics, antihistamines, anti-inflammatory, antiarrhythmic,antipsychotic [2] etc.

Out of the above mentioned heterocyclic's, Imidazole and benzimidazole derivatives comprise the ring system in a number of naturally occurring compounds such as histamine, histidine, pilocarpine, hydantoin, purine, vitamin B_{12} etc and also many drugs have been synthesized with the above mentioned heterocyclic's derivatives to name a few, albendazole, antazoline, azathioprine, clonidine, clotrimazole,cimetidine, metronidazole, ketoconazole, tolazoline, phentolamine, phenytoin, dacarbazine, omeprazole etc. It was found that benzimidazole derivatives are displayed antimicrobial [3], antiviral [4], antitubercular [5], antiulcer [6], antioxidant [7], anthelminitic [8], analgesic [9], HIV-RT inhibitor [10], central nervous system depressant [11], anticancer [12] , DNA topoisomerase inhibitors [13], antibacterial [14] and antifungal [15] activities.

Indole is also an integral part of a variety of biologically active natural products such as psilocin and LSD as hallucinogens, ergotamine for migraine, vinca alkaloids as anti cancer, reserpine as antihypertensive [16] and some synthetic drugs, methisazone as antiviral, indomethazine and indoprofen as anti-inflammatory. Indolines and its analogs are of the most extensively studied nucleus, which can be used as the starting material or intermediate/subunit for the synthesis of numerous fused heterocyclic medicinal compounds [17]. The literature survey shows that indoline and isoindoline derivatives which have a wide range of biological activities such as antimicrobial [18], antibacterial [19], anti-inflammatory [20], antihistamine [21], antioxidant, antiproliferative [22], acetylcholinesterase inhibitors [23], inhibitor of human neuronal nitric oxide synthase [24].

Hence synthesis of new derivatives of heterocyclics is being continuously reported. Many reports have been published specifying wide variety of pharmacological activities. After carefully following literature survey, it was thought of interest to merge both of indoline and benzimidazole moieties attempted by synthesise which may enhance the drug activity of compounds up to some extent or might possess some of the above mentioned biological activities. So our research work involves the synthesis of various certain new benzimidazolyl isoindoline derivative heterocyclics and characterization of the derivatives by the help of IR HNMR,CNMR & mass spectra of the obtained derivatives followed by in-vitro anthelminitic screening evaluation of the derivatives.

MATERIALS AND METHOEDS

Synthesis of 2-glycyl and 2-alanyl isoindole-1,3 dione (3a&3b)
Weighed equimolecular quantity of pthalic anhydride (1) and aminoacids (glycine (2a) and alanine (2b)) in a beaker were kept in a heated sand bath (180-185^{o}C). The melted mixture was stirred continually during the first five minutes and any solid pthalic anhydride which sublimed into the melted reaction mixture till there was complete fusion occurs. The melted mixture was kept aside, undisturbed for 5minutes observe the liquid mass solidified. The white solid (3a-b) obtained was then recrystallised from ethanol.

Synthesis of 2-methyl and 2-ethyl benzimidazolyl-isoindole-1, 3-dione (4a&4b)
The 0.1 molar quantity of (3a-b) and 0.1 molar of orthophenylene diamine were refluxed in 30 ml of 4N HCl for two hours. The solution was cooling gave a precipitate (4a-b) which was filtered with ice cold water, dried and then recrystallised from ethanol.

Synthesis of 1H-substituted benzimidazolyl-2-alkyl derivatives of isoindole-1, 3-dione (6a-n)
The 0.1 molar quantity of (4a-b) was dissolved in 0.2 molar 35% formaldehyde mixed in acetic acid. To this 0.2 molar quantity of aromatic amines (5a-g) was added and the mixture was refluxed for 4 hours. The solution was cool to room temperature and pour in to a beaker containing ice cold water with stirring. The precipitated product (6a-n) was filtered, left over night in a freezer, dried and recrystallised from ethanol.

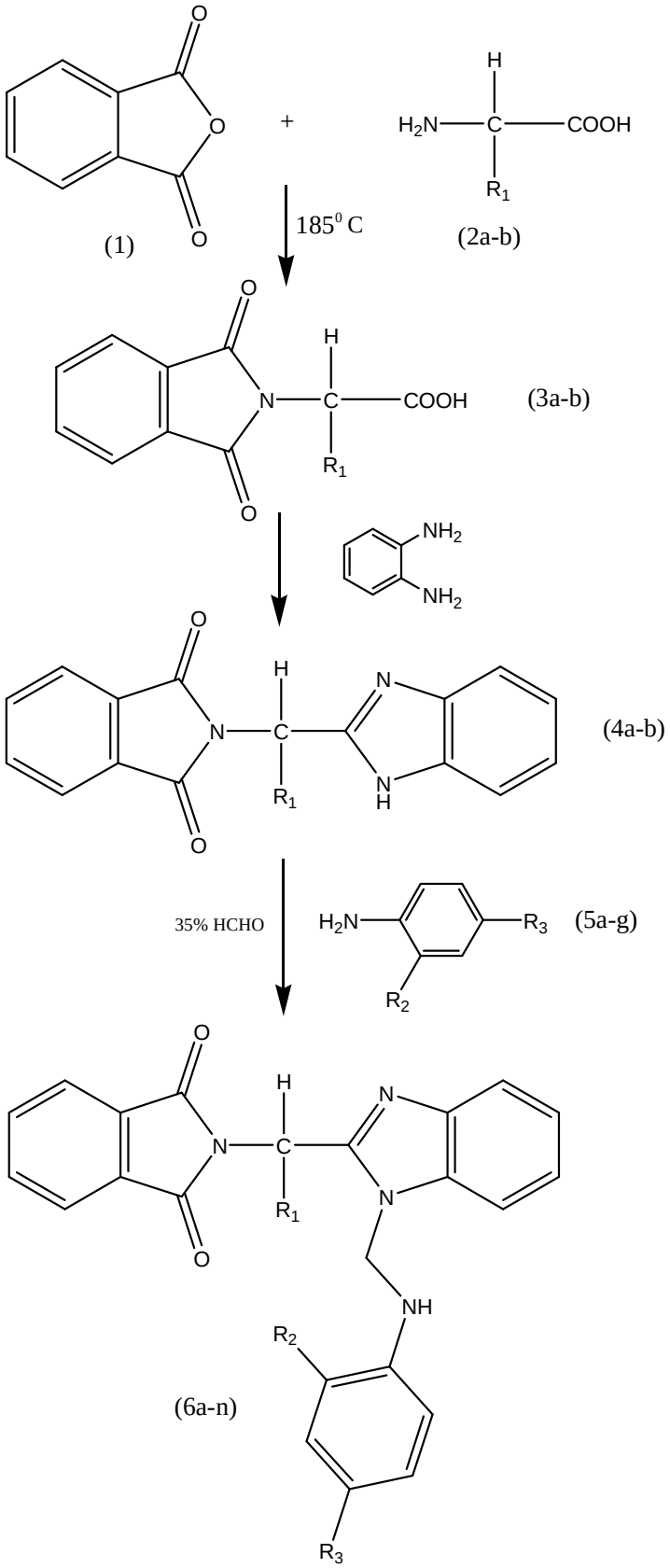
The melting points were taken by using a Thomas Hoover capillary melting point apparatus. The purity of the synthesized isoindolines was checked by TLC using silica gel-60 F_{254} aluminium sheets using chloroform: ethanol (8:2) as eluent and visualized in a ultra violet chamber (Table-1). IR spectra were recorded (in KBr) on FTIR 8300 Shimadzu spectrophotometer. The ^{1}HNMR and ^{13}CNMR spectras were recorded on a Bruker AC 300 MHZ FTNMR spectrophotometer in $CDCl_3$ and chemical shift were recorded in parts per million downfield from TMS. The mass spectra were recorded in JEOL GC MATE II GC/MS (EI).

Analytical and spectral *data:*
2-((1H-benzo imidazol-2-yl) methyl) isoindoline-1, 3-dione (compound 4a)
IR (v in cm^{-1}): 3352.64 (N–H,str), 3122.86-3026.41 (Aromatic,C–H,str), 2886.57- 2827.74 (CH_2,str), 1769.75-1759.14 (N–C=O,str), 1678.44 (C=N,str) , 1589.40-1503.56-1484.27 (Aromatic, C=C), 1453.41-1413.87-1382.04 (C–H,ben), 1301.99-1246.06 (C–N,str).

^{1}HNMR (δ in ppm): 4.072 (S, 2H, N– $C\underline{H}_2$–Ar), 7.262–7.792 (m,4H,Ar-H,Benzimidazole), 7.626–8.102 (m,4H,Ar-H, Isoindoline), 8.537 (S,1H,N–H).***^{13}CNMR (δ in ppm):*** 42.62 (N– $\underline{C}H_2$–Ar) , 115.16-123.43(Ar-C,Benzimidazole), 138.38 (fused C), 141.78 (C=N), 127.09-132.37 (Ar-C, Isoindoline), 169.45(C=O). ***MS (m/z,%):*** 85.61(30), 92.59 (24), 97.05 (52),105.22 (37), 117.04 (100),131.20 (68),146.08 (29),164.85 (18), 174.22 (39),191.57 (12), 213.31(17), 234.36 (10), 250.02 (11), 265.24(6), 277.13 (5).

2-(1-(1H-benzo imidazol-2-yl) ethyl) isoindoline-1,3-dione (compound 4b)
IR (v in cm^{-1}): 3408.33-3334.07 (N–H,str), 3063.06-3028.34 (Aromatic,C–H,str), 2983.98-2948.29 (CH_3,str), 2885.60- 2828.70(CH_2,str), 1767.82(N–C=O,str), 1681.02 (C=N,str) , 1593.25-1496.81(Aromatic, C=C), 1453.41-1394.58 (C–H,ben), 1317.43-1293.31 (C–N,str).

SCHEME



[1]HNMR (δ in ppm): 1.382–1.390 (d,2H, N– CH–C<u>H</u>$_3$–Ar), 4.165–4.223 (q,4H, N–C<u>H</u>–CH$_3$–Ar), 7.249–7.783 (m,4H,Ar-H,Benzimidazole), 7.625–8.102 (m,4H,Ar-H, Isoindoline), 8.524 (S,1H,N–H).***[13]CNMR (δ in ppm):*** 18.32 (N– CH–<u>C</u>H$_3$–Ar), 45.51 (N– <u>C</u>H–CH$_3$–Ar), 115.39-123.43 (Ar-C,Benzimidazole), 138.40 (fused C), 141.95 (C=N),

127.78-132.89 (Ar-C, Isoindoline), 168.12 (C=O).***MS (m/z,%):*** 77.05 (76), 91.08 (36), 106.06 (14), 117.25 (100), 132.07 (24), 145.02 (60), 164.10 (15), 172.36 (28), 188.12 (42), 210.27 (16), 222.10 (21), 235.08 (11), 250.55 (13), 264.74 (22), 275.26 (10), 291.10 (6),

Table-1: Physical analysis of synthesised benzimidazolyl isoindolines

S no	Samples	Molecular formula	R_1	R_2	R_3	Melting Point ^oC	R_f value	Yield %
1	4a	$C_{16}H_{11}N_3O_2$	H	-	-	186-187	0.76	78
2	4b	$C_{17}H_{13}N_3O_2$	CH_3	-	-	192-193	0.72	75
3	6a	$C_{23}H_{18}N_4O_2$	H	H	H	197-198	0.45	63
4	6b	$C_{24}H_{20}N_4O_2$	CH_3	H	H	201-202	0.42	61
5	6c	$C_{24}H_{18}N_4O_4$	H	H	COOH	253-254	0.78	67
6	6d	$C_{25}H_{20}N_4O_4$	CH_3	H	COOH	257-258	0.73	64
7	6e	$C_{24}H_{18}N_4O_4$	H	COOH	H	208-209	0.75	52
8	6f	$C_{25}H_{20}N_4O_4$	CH_3	COOH	H	213-214	0.70	48
9	6g	$C_{23}H_{18}N_4O_5S$	H	H	SO_3H	277-278	0.59	65
10	6h	$C_{24}H_{20}N_4O_5S$	CH_3	H	SO_3H	282-283	0.56	62
11	6i	$C_{23}H_{19}N_5O_4S$	H	H	SO_2NH_2	225-226	0.51	69
12	6j	$C_{24}H_{21}N_5O_4S$	CH_3	H	SO_2NH_2	233-234	0.48	66
13	6k	$C_{23}H_{18}N_4O_3$	H	OH	H	237-238	0.85	44
14	6l	$C_{24}H_{20}N_4O_3$	CH_3	OH	H	242-243	0.79	40
15	6m	$C_{23}H_{18}N_4O_3$	H	H	OH	246-247	0.87	57
16	6n	$C_{24}H_{20}N_4O_3$	CH_3	H	OH	251-252	0.81	54

2-((1-((phenylamino)methyl)-1H-benzo imidazol-2-yl) methyl) isoindoline-1,3-dione (compound 6a)

IR (ν in cm^{-1}): 3407.37-3384.22(N–H, str), 3113.21-3042.81 (Aromatic, C–H,str), 2945.40- 2884.64(CH_2, str), 1774.57(N–C=O,str),1680.05-1668.48(C=N,str),1595.18-1495.85 (Aromatic, C=C), 1456.30-1383.01 (C–H,ben), 1365.65-1318.39-1303.92 (C–N,str).

^{1}HNMR (δ in ppm): 3.027 (S, 1H, Ph–N<u>H</u>– CH_2), 4.093 (S, 2H, N– C<u>H</u>$_2$–Ar), 4.787–4.810 (d,2H,NH–C<u>H</u>$_2$–Ar), 7.247–7.782 (m,4H,Ar-H,Benzimidazole), 7.629–8.120 (m,4H,Ar-H, Isoindoline), 6.543–7.591(m,4H, Subs phenyl).***^{13}CNMR (δ in ppm):*** 34.75 (N– <u>C</u>H_2–Ar), 63.57(N–<u>C</u>H_2–NH),115.57-123.71(Ar-C,Benzimidazole),135.87-138.55(fusedC),142.61 (C=N),149.63(<u>Ar</u>–NH),127.05-133.52(Ar-C,Isoindoline),113.01-117.43-129.36(phenyl), 169.58 (C=O).***MS (m/z,%):*** 77.11 (73), 91.26 (50), 106.05 (20), 117.25 (100), 131.68 (46), 146.15 (52),162.10 (28),193.03 (23),207.14(21),221.36(37), 230.06 (33), 253.02 (35), 268.62 (20), 282.24 (27), 309.04 (11), 326.15 (16), 338.23 (8), 355.41 (5), 369.76 (4), 382.28 (6).

2-(1-(1-((phenylamino)methyl)-1H-benzo[d] imidazol-2-yl) ethyl) isoindoline-1,3-dione (compound 6b)

IR (ν in cm^{-1}): 3304.02(N–H,str), 3129.61-3065.95 (Aromatic,C–H,str),2981.08-2974.33 (CH_3,str), 2887.53-2945.40(CH_2,str),1774.57(N–C=O,str),1695.49-1683.91 (C=N,str) , 1591.33-1517.06(Aromatic, C=C), 1456.30-1433.16-1389.76 (C–H,ben), 1319.35-1299.10 (C–N,str).

^{1}HNMR (δ in ppm): 1.423–1.438 (d,2H, N– CH–C<u>H</u>$_3$–Ar), 3.043 (S, 1H, Ph–N<u>H</u>– CH_2), 4.233–4.288 (q,4H, N–C<u>H</u>–CH_3–Ar), 4.782–4.815 (d,2H,NH–C<u>H</u>$_2$–Ar), 6.589–7.593(m,4H,phenyl), 7.261–7.798 (m,4H,Ar-H,Benzimidazole), 7.629–8.140 (m,4H,Ar-H, Isoindoline).***^{13}CNMR (δ in ppm):*** 18.65 (N– CH–<u>C</u>H_3–Ar) , 37.66 (N– <u>C</u>H–CH_3–Ar),115.87-123.52 (Ar-C,Benzimidazole), 63.57 (N– <u>C</u>H_2–NH), 135.95-138.38 (fused C), 142.73 (C=N), 149.32, 168.56 (C=O), 127.36-133.56 (Ar-C, Isoindoline), 113.57-117.43-129.77 (phenyl). ***MS (m/z,%):*** 77.09 (64), 90.08 (41), 103.04 (30), 117.10 (100), 144.14 (51), 158.38 (38), 178.25(25),192.19(14),208.27(33),220.31(56),234.11(29),254.39(45),279.28(35), 295.24(48), 313.20(13),328.36 (28), 339.25 (15), 356.03 (7), 369.67 (5),380.31(3),396.34 (2).

4-((2-((1,3-dioxoisoindolin-2-yl) methyl)-1H-benzoimidazol-1-yl) methylamino) benzoicacid (compound 6c)

IR (ν in cm^{-1}): 3460.41 -2540.33(O–H,str), 3383.26-3364.93 (N–H,str), 3114.18-3025.45 (Aromatic,C–H,str), 2982.05- 2887.53 (CH_2,str), 1774.57-1722.49 (N–C=O,str), 1706.46 (HO–C=O,str), 1695.49 (C=N,str) ,1600.97-1550.25 (Aromatic, C=C), 1410.98-1386.86 (C–H,ben), 1324.18-1300.07 (C–N,str), 1210.37-1203.62 (C–O,str).

^{1}HNMR (δ in ppm): 3.056 (S, 1H, Ph–N<u>H</u>– CH_2), 4.126 (S, 2H, N– C<u>H</u>$_2$–Ar), 4.743–4.758 (d,2H,NH–C<u>H</u>$_2$–Ar),7.230 –7.839 (m,4H,Ar-H,Benzimidazole), 7.638–8.178 (m,4H,Ar-H, Isoindoline), 6.768–7.582 (m,4H, Subs phenyl), 10.540 (S, 1H, COOH).***^{13}CNMR (δ in ppm):*** 35.37 (N– <u>C</u>H_2–Ar), 64.65 (N– <u>C</u>H_2–NH), 115.61-124.63 (Ar-C,Benzimidazole), 134.38-138.54 (fused C), 142.82 (C=N), 152.63 (<u>Ar</u>–NH), 127.85-133.14 (Ar-C, Isoindoline), 114.42-117.67-131.13 (subs phenyl),169.48(C=O), 171.77(COOH).***MS (m/z,%):*** 77.85 (58), 103.42

(45), 117.20 (100), 121.44 (24), 130.22 (52), 147.45 (33), 189.46 (28), 205.49 (31), 236.21 (40), 260.00 (20), 276.00 (25), 305.20 (22), 329.37 (10), 354.46 (19), 381.24 (6), 409.35 (11), 426.22 (7).

4-((2-(1-(1,3-dioxoisoindolin-2-yl) ethyl)-1H-benzoimidazol-1-yl) methylamino) benzoicacid (compound 6d)

IR (ν in cm^{-1}): 3476.81 -2559.62 (O–H,str), 3335.03-3363.00 (N–H,str), 3054.38-3027.38 (Aromatic,C–H,str), 2983.01-2948.29 (CH_3,str), 2888.50- 2829.67 (CH_2,str), 1769.75-1730.21 (N–C=O,str), 1714.77 (HO–C=O,str), 1681.98-1671.37 (C=N,str) , 1596.15-1495.85 (Aromatic, C=C), 1454.38-1395.54 (C–H,ben), 1316.46-1292.35 (C–N,str), 1211.34-1173.72 (C–O,str).

^{1}HNMR (δ in ppm): 1.415–1.456 (d,2H, N– CH–C<u>H</u>$_3$–Ar), 3.065 (S, 1H, Ph–N<u>H</u>– CH_2), 4.135–4.289 (q,4H, N–C<u>H</u>–CH_3–Ar), 4.794–4.831 (d,2H,NH–C<u>H</u>$_2$–Ar), 6.710–7.590 (m,4H, Subs phenyl), 7.286–7.863 (m,4H,Ar-H,Benzimidazole), 7.643–8.227 (m,4H,Ar-H, Isoindoline), 10.538 (S, 1H, COOH).***^{13}CNMR (δ in ppm):*** 19.62 (N–CH–<u>C</u>H$_3$–Ar) , 38.42 (N– <u>C</u>H–CH_3–Ar), 64.75 (N– <u>C</u>H$_2$–NH), 114.46-118.49-131.10 (subs phenyl), 115.54-124.54 (Ar-C,Benzimidazole), 127.95-133.13 (Ar-C, Isoindoline), 134.40-138.50 (fused C), 142.85 (C=N), 152.72, 168.48 (C=O),171.55 (COOH).***MS (m/z,%):*** 69.84 (42), 77.37 (57),96.78 (34), 117.77(100), 137.68 (48), 144.51(64), 152.59 (40), 171.54 (45), 207.38 (26), 221.33 (38), 246.27 (31), 264.31(44), 290.34 (11), 319.08 (23), 364.31 (18), 390.68 (16), 413.74 (19), 440.34 (8).

2-((2-((1,3-dioxoisoindolin-2-yl) methyl)-1H-benzoimidazol-1-yl) methylamino) benzoicacid (compound 6e)

IR (ν in cm^{-1}): 3478.74-3254.02 (O–H,str), 3305.14 (N–H,str), 3097.78-3044.74 (Aromatic, C–H,str),2949.26-2883.68 (CH_2,str),1768.78-1760.10 (N–C=O,str),1714.77 -1702.24 (HO–C=O,str), 1697.41-1678.37 (C=N,str) , 1590.36-1504.53(Aromatic, C=C), 1454.38-1385.90 (C–H,ben), 1324.18-1302.96 (C–N,str),1210.37-1245.09 (C–O,str).

^{1}HNMR (δ in ppm): 3.335 (S, 1H, Ph–N<u>H</u>– CH_2), 4.097 (S, 2H, N– C<u>H</u>$_2$–Ar), 4.826–4.835 (d,2H,NH–C<u>H</u>$_2$–Ar), 7.236–7.773 (m,4H,Ar-H,Benzimidazole), 7.643–8.081 (m,4H,Ar-H, Isoindoline), 6.687–7.552 (m,4H, Subs phenyl), 10.823 (S, 1H, COOH).***^{13}CNMR (δ in ppm):*** 34.80 (N– <u>C</u>H$_2$–Ar), 64.76 (N– <u>C</u>H$_2$–NH), 115.76-124.35 (Ar-C,Benzimidazole), 134.80-138.63 (fused C), 142.72 (C=N), 151.88 (<u>Ar</u>–NH), 128.74-133.26 (Ar-C, Isoindoline), 107.09-117.74-131.14 (subs phenyl), 169.16(C=O), 170.57 (COOH).***MS (m/z,%):*** 77.80 (43), 97.44 (33), 117.14 (100),130.24 (55),146.10 (26),173.49 (28), 216.40 (41),244.50 (25), 265.47 (37), 279.53 (18), 290.59 (21), 329.52 (16), 353.56 (32), 381.34 (17), 394.10 (13), 409.04 (10), 426.04 (11).

2-((2-(1-(1,3-dioxoisoindolin-2-yl) ethyl)-1H-benzoimidazol-1-yl) methylamino) benzoicacid (compound 6f)

IR (ν in cm^{-1}): 3407.37 -2502.72 (O–H,str), 3274.27-3314.78 (N–H,str), 3172.04-3057.27 (Aromatic,C–H,str), 2974.33-2952.15 (CH_3,str), 2886.57- 2823.88 (CH_2,str), 1762.03-1731.17(N–C=O,str),1715.74(HO–C=O,str),1668.48-1652.09(C=N,str),1596.15-1496.81 (Aromatic,C=C), 1449.55-1387.43 (C–H,ben),1315.50-1279.81 (C–N,str), 1220.02-1212.30 (C–O,str).

^{1}HNMR (δ in ppm): 1.425–1.443 (d,2H, N– CH–C<u>H</u>$_3$–Ar), 3.264 (S, 1H, Ph–N<u>H</u>– CH_2), 4.069–4.236 (q,4H, N–C<u>H</u>–CH_3–Ar), 4.765–4.783 (d,2H,NH–C<u>H</u>$_2$–Ar), 7.233–7.767 (m,4H,Ar-H,Benzimidazole), 7.639–8.179 (m,4H,Ar-H, Isoindoline),6.798 –7.567 (m,4H, Subs phenyl), 10.786 (S, 1H, COOH).***^{13}CNMR (δ in ppm):*** 19.76 (N– CH–<u>C</u>H$_3$–Ar), 37.66 (N– <u>C</u>H–CH_3–Ar), 64.75 (N– <u>C</u>H$_2$–NH), 107.13-117.51-131.12 (subs phenyl), 128.67-133.13 (Ar-C, Isoindoline), 115.67-124.28 (Ar-C,Benzimidazole), 134.81-138.22 (fused C), 143.02 (C=N), 151.61, 168.28 (C=O), 170.43 (COOH). ***MS (m/z,%):*** 77.85 (60), 91.81 (40), 105.77 (49), 117.00(100),137.60 (29), 144.07 (46), 162.55 (33), 179.49 (21), 197.46 (42), 213.37 (18), 241.19 (55), 258.87 (15), 290.18 (36), 319.04 (20), 347.05 (10),364.35 (23), 396.67 (11), 413.04 (17), 440.84 (8).

4-((2-((1,3-dioxoisoindolin-2-yl) methyl)-1H-benzo[d]imidazol-1-yl) methylamino) benzene sulfonicacid (compound 6g)

IR (ν in cm^{-1}):3360.11(N–H,str), 3668.73 (S–OH,str), 3030.27-3099.71(Aromatic, C–H,str), 2948.29-2887.53(CH_2,str),1774.57-1722.49(N–C=O,str),1695.49-1651.02(C=N,str),1600.01- 1505.49(Aromatic, C=C), 1456.30-1418.69-1382.04(C–H,ben), 1350.36-1163.11 (SO_3H, str), 1324.18-1302.96 (C–N,str).

^{1}HNMR (δ in ppm): 2.736 (S,1H,SO_3H), 3.051 (S, 1H, Ph–N<u>H</u>– CH_2), 4.260 (S, 2H, N– C<u>H</u>$_2$–Ar), 4.839–4.853 (d,2H,NH–C<u>H</u>$_2$–Ar), 7.238–7.752 (m, 4H, Ar-H, Benzimidazole), 7.608–8.10(m, 4H, Ar-H, Isoindoline), 6.764–7.596(m,4H,Subs phenyl). ***^{13}CNMR (δ in ppm):*** 36.12 (N– <u>C</u>H$_2$–Ar), 65.29 (N– <u>C</u>H$_2$–NH), 115.12-124.25 (Ar-C,Benzimidazole), 134.50-137.49 (fused C), 141.24 (C=N), 152.60 (<u>Ar</u>–NH),128.00-132.34 (Ar-C, Isoindoline),114.52-129.31-139.30 (subs phenyl), 168.42 (C=O).***MS (m/z,%):*** 69.04 (52), 77.84 (63), 91.37 (36), 106.39 (18), 117.34 (100),130.10 (49), 160.38 (28), 191.78 (23), 209.61(27), 232.77 (36), 251.10 (17), 267.95 (11), 276.44 (32), 302.40 (20), 338.73 (16), 349.34 (14), 373.47 (12), 406.31 (15), 430.81 (8), 462.56 (6).

4-((2-(1-(1,3-dioxoisoindolin-2-yl)ethyl)-1H-benzoimidazol-1-yl) methylamino) benzene sulfonicacid (compound 6h)

IR (ν in cm^{-1}): 3336.96(N–H,str), 3611.83-3439.19 (S–OH,str), 3012.91(Aromatic,C–H,str), 2985.91-2949.26(CH_3,str),2886.57-2836.42(CH_2,str),1769.75-1731.17(N–C=O,str), 1697.41-1681.98 (C=N,str) , 1595.18-1495.85(Aromatic, C=C), 1456.30-1441.84-1395.54 (C–H,ben), 1346.36 (SO_3H, str), 1317.43-1292.35(C–N,str).

^{1}HNMR (δ in ppm): 1.405–1.492 (d,2H, N– CH–C<u>H</u>$_3$–Ar), 2.786 (S,1H,SO_3H), 3.065 (S, 1H, Ph–N<u>H</u>– CH_2), 4.126–4.201(q,4H, N–C<u>H</u>–CH_3–Ar), 4.808–4.843 (d,2H,NH–C<u>H</u>$_2$–Ar), 6.783–7.573 (m,4H, Subs phenyl), 7.223–7.778 (m,4H,Ar-H,Benzimidazole), 7.606–8.102 (m,4H,Ar-H, Isoindoline). ***^{13}CNMR (δ in ppm):*** 20.09 (N– CH–<u>C</u>H$_3$–Ar), 39.37 (N– <u>C</u>H–CH_3–Ar), 65.20 (N– <u>C</u>H$_2$–NH), 114.62-129.67-139.63(subsphenyl),115.24-124.41(Ar-C,Benzimidazole), 128.03-132.76 (Ar-C, Isoindoline), 134.13-137.21 (fused C), 141.54 (C=N), 152.53, 167.62 (C=O). ***MS (m/z,%):*** 65.24 (38), 78.64 (53), 90.52 (42), 106.30 (15), 117.36 (100),135.14 (33), 144.03 (67), 160.95 (16), 191.68 (9), 209.63 (40), 229.45 (22), 262.69 (11), 291.10 (28), 325.34 (17), 349.14 (12), 413.18 (7), 451.94 (10), 476.37 (6).

4-((2-((1,3-dioxoisoindolin-2-yl) methyl)-1H-benzoimidazol-1-yl) methylamino) benzene sulfonamide (compound 6i)

IR (ν in cm^{-1}): 3410.26(N–H, str), 3323.46-3220.27 (N–H_2, str), 3024.48-3062.10 (Aromatic, C–H, str), 2986.87-2829.67(CH_2, str), 1769.75-1762.03(N–C=O, str), 1653.05-1646.30 (C=N, str), 1594.22-1496.81(Aromatic, C=C), 1457.27-1450.52-1441.84-1387.83(C–H,ben), 1374.33-1346.36 (SO_2NH_2 str),1317.43-1293.31(C–N,str).

^{1}HNMR (δ in ppm): 2.485 (S,2H,SO_2NH_2), 3.061(S,1H,Ph–N<u>H</u>–CH_2),4.261(S,2H,N–C<u>H</u>$_2$–Ar), 4.846–4.858 (d,2H,NH–C<u>H</u>$_2$–Ar),7.254–7.782 (m,4H,Ar-H,Benzimidazole), 7.622–8.221 (m,4H,Ar-H, Isoindoline), 6.763–7.558 (m,4H, Subs phenyl).***^{13}CNMR (δ in ppm):*** 35.38 (N– <u>C</u>H$_2$–Ar), 64.57 (N– <u>C</u>H$_2$–NH), 115.32-123.13 (Ar-C, Benzimidazole), 138.54-136.46 (fused C), 142.36 (C=N),151.65 (<u>Ar</u>–NH), 127.94-132.32(Ar-C, Isoindoline),113.52-129.57-131.26 (substituted phenyl),169.39 (C=O).***MS (m/z,%):*** 57.99 (48), 77.87 (68), 89.54 (28), 106.40 (44), 117.32 (100), 130.19 (53), 160.98 (36), 192.78 (17), 216.61(22), 242.40 (9), 255.43 (12), 276.44 (25), 291.17 (32), 306.09 (14), 331.92 (16), 363.68 (4), 407.48 (7), 447.25 (8), 461.44 (6).

4-((2-(1-(1,3-dioxoisoindolin-2-yl)ethyl)-1H-benzoimidazol-1-yl) methylamino) benzene sulfonamide (compound 6j)

IR(ν in cm^{-1}): 3478.74-3366.86(N–H,str),3259.81-3336.0(N–H_2,str),3028.34-3064.03 (Aromatic,C–H,str),2952.15-2983.01(CH_3,str),2883.68-2828.70(CH_2,str),1777.46-1731.17 (N–C=O,str),1697.41-1659.80(C=N,str) ,1595.18-1504.53(Aromatic, C=C), 1455.34-1450.52 -1441.84-1386.86 (C–H,ben), 1373.36-1337.68 (SO_2NH_2 str), 1316.46-1305.85 (C–N,str).

^{1}HNMR (δ in ppm): 1.452–1.490 (d,2H, N– CH–C<u>H</u>$_3$–Ar), 3.084 (S, 1H, Ph–N<u>H</u>– CH_2), 2.453 (S,2H,SO_2NH_2), 4.183–4.251 (q, 4H, N–C<u>H</u>–CH_3–Ar), 4.783–4.864 (d, 2H, NH–C<u>H</u>$_2$–Ar), 7.246–7.793(m, 4H, Ar-H, Benzimidazole),7.632–8.135(m,4H,Ar-H, Isoindoline), 6.691–7.578 (m,4H, Subs phenyl).***^{13}CNMR (δ in ppm):*** 19.63 (N– CH–<u>C</u>H$_3$–Ar) , 38.36 (N– <u>C</u>H–CH_3–Ar), 64.65 (N– <u>C</u>H$_2$–NH), 113.68-129.12-131.14 (subs phenyl), 115.33-123.08 (Ar-C, Benzimidazole), 127.80-132.40 (Ar-C, Isoindoline), 135.45-138.58 (fused C), 141.60 (C=N), 150.41,168.55 (C=O).***MS (m/z,%):*** 57.00 (37), 78.64 (52), 89.54 (57), 117.31(100), 130.21 (46), 144.05(64), 166.92 (25), 192.77(20), 216.61 (6), 242.41 (30), 256.37 (12),282.20 (24), 290.56 (17), 308.06 (22), 331.87 (40), 357.76 (13), 371.71 (19), 407.45 (7), 435.20 (10), 446.76 (9), 475.96 (5).

2-((1-((2-hydroxyphenylamino)methyl)-1H-benzo[d] imidazol-2-yl) methyl) isoindoline-1,3-dione (compound 6k)

IR (ν in cm^{-1}): 3296.46-3272.34 (O–H,str), 3350.07 (N–H,str), 3114.18-3037.99 (Aromatic, C–H,str), 2949.26-2884.64 (CH_2,str), 1770.17-1722.49 (N–C=O,str), 1695.49-1615.44 (C=N,str) , 1588.43-1478.49 (Aromatic, C=C), 1456.30-1410.01 (C–H,ben), 1345.39-1301.99 (C–N,str), 1238.34-1202.66 (C–O,str).

^{1}HNMR (δ in ppm): 3.060 (S, 1H, Ph–N<u>H</u>– CH_2), 4.241(S, 2H, N– C<u>H</u>$_2$–Ar), 4.827–4.853 (d,2H,NH–C<u>H</u>$_2$–Ar), 5.167 (S, 1H, OH), 7.250–7.783 (m,4H,Ar-H,Benzimidazole), 7.632–8.156 (m,4H,Ar-H, Isoindoline), 6.237–7.505 (m,4H, Subs phenyl).***^{13}CNMR (δ in ppm):*** 35.13 (N– <u>C</u>H$_2$–Ar), 64.26 (N– <u>C</u>H$_2$–NH), 115.13-123.53 (Ar-C,Benzimidazole), 134.01-138.60 (fused C),142.54 (C=N),147.58 (<u>Ar</u>–NH),144.33 (<u>Ar</u>–OH), 127.71-132.97 (Ar-C, Isoindoline), 113.40-118.48-131.57 (subs phenyl), 168.50 (C=O).***MS (m/z,%):*** 77.15 (63), 90.10 (26), 105.08 (6), 117.11(100), 130.18 (51), 146.14 (13), 162.10 (17), 179.15 (4), 193.19 (12), 207.17 (10), 221.20 (43), 235.21 (34), 253.19 (23), 261.25 (16), 281.22 (40), 294.24 (20), 312.28 (5), 327.26 (11), 337.33 (7), 355.30 (3), 370.36 (2.7), 379.39 (1), 398.24 (2).

2-(1-(1-((2-hydroxyphenylamino)methyl)-1H-benzo imidazol-2-yl) ethyl) isoindoline-1,3-dione (compound 6l)
IR (v in cm^{-1}): 3565.53-3306.10 (O–H,str), 3408.33-3375.54 (N–H,str), 3062.10-3024.48 (Aromatic,C–H,str), 2981.08-2950.22 (CH_3,str), 2883.68-2840.28 (CH_2,str), 1768.78-1762.03 (N–C=O,str), 1653.05-1624.12 (C=N,str) , 1594.22-1496.81 (Aromatic, C=C), 1457.27-1396.51 (C–H,ben), 1317.43-1268.24 (C–N,str), 1212.30-1139.97 (C–O,str).

^{1}HNMR (δ in ppm): 1.460–1.493 (d,2H, N– CH–C<u>H</u>$_3$–Ar),3.064 (S, 1H, Ph–N<u>H</u>– CH_2), 4.122–4.200 (q,4H, N–C<u>H</u>–CH_3–Ar), 4.773–4.855 (d,2H,NH–C<u>H</u>$_2$–Ar), 5.154 (S, 1H, OH), 7.252–7.784 (m,4H,Ar-H,Benzimidazole), 7.635–8.173 (m,4H,Ar-H, Isoindoline), 6.254–7.512 (m,4H, Subs phenyl).***^{13}CNMR (δ in ppm):*** 18.44 (N– CH–<u>C</u>H$_3$–Ar), 39.65 (N– <u>C</u>H–CH_3–Ar),64.50 (N– <u>C</u>H$_2$–NH), 114.41-118.77-131.63 (subs phenyl), 115.22-123.52 (Ar-C,Benzimidazole), 127.36-132.92 (Ar-C, Isoindoline), 134.20-138.52 (fused C), 142.12 (C=N), 143.30, 145.05, 168.53 (C=O).***MS (m/z,%):*** 77.05 (76), 91.08 (49), 103.06 (8), 117.06 (100), 132.07 (25), 144.67 (59), 150.05 (7), 162.04 (21), 179.07 (6), 193.12 (14), 221.11(40), 235.13 (19), 253.08 (51), 261.16 (38), 281.12 (13), 294.02 (33), 312.10 (26), 327.04 (47), 337.10 (8), 357.43 (5), 378.74 (31), 392.41 (18), 412.64 (5).

2-((1-((4-hydroxyphenylamino)methyl)-1H-benzo imidazol-2-yl) methyl) isoindoline-1,3-dione (compound 6m)
IR (v in cm^{-1}): 3633.05-3281.99 (O–H,str), 3341.78 (N–H,str), 3094.89-3063.06 (Aromatic, C–H,str), 2981.08-2884.64 (CH_2,str), 1767.82-1722.49 (N–C=O,str),1650.80 (C=N,str), 1588.43-1478.49 (Aromatic, C=C), 1456.30-1386.86 (C–H,ben), 1301.99-1245.09 (C–N,str), 1211.34-1203.62 (C–O,str).

^{1}HNMR (δ in ppm): 3.075 (S, 1H, Ph–N<u>H</u>– CH_2), 4.140 (S, 2H, N– C<u>H</u>$_2$–Ar), 4.549 (S, 1H, OH), 4.823–4.882 (d,2H,NH–C<u>H</u>$_2$–Ar),7.268–7.761 (m,4H,Ar-H,Benzimidazole),7.624– 8.138 (m,4H,Ar-H, Isoindoline), 6.261–7.587 (m,4H, Subsphenyl). ***^{13}CNMR (δ in ppm):*** 36.59 (N– <u>C</u>H$_2$–Ar), 63.49 (N– <u>C</u>H$_2$–NH), 115.35-123.40 (Ar-C, Benz imidazole), 134.13-138.42 (fused C), 142.56 (C=N), 151.52 (<u>Ar</u>–NH), 148.13 (<u>Ar</u>–OH), 127. 78 -132.81 (Ar-C, Isoindoline), 113.89-116.81-130.47 (subs phenyl), 169.66 (C=O). ***MS (m/z,%):*** 77.12 (63), 90.10 (25), 105.08 (6), 117.25 (100), 130.00 (55), 146.13 (11), 162.40 (16), 179.13 (4), 193.19 (10), 208.16 (9), 221.49 (39), 235.21 (12), 253.18 (15), 265.47 (5), 279.53 (20), 290.59 (4), 312.28 (3), 327.25 (16), 339.52 (8), 353.56 (7), 370.41(3), 380.54 (1), 398.15 (2).

2-(1-(1-((4-hydroxyphenylamino)methyl)-1H-benzoimidazol-2-yl) ethyl) isoindoline-1,3-dione (compound 6n)
IR (v in cm^{-1}): 3646.55-3615.69-3275.24 (O–H,str), 3341.78 (N–H,str), 3026.41 (Aromatic, C–H,str), 2988.80-2948.29 (CH_3,str), 2886.57-2825.81 (CH_2,str), 1769.75-1731.17 (N–C=O, str),1651.12 (C=N,str) , 1593.25-1507.42 (Aromatic, C=C), 1454.38-1395.54 (C–H,ben), 1342.50-1316.46 (C–N,str), 1212.30-1172.76 (C–O,str).

^{1}HNMR (δ in ppm): 1.446–1.450 (d,2H, N– CH–C<u>H</u>$_3$–Ar),3.079 (S, 1H, Ph–N<u>H</u>– CH_2),4.190–4.289 (q,4H, N–C<u>H</u>–CH_3–Ar), 4.573(S, 1H, OH),4.810–4.871(d,2H,NH–C<u>H</u>$_2$–Ar),7.261–7.78 (m,4H,Ar-H, Benzimidazole), 7.628–8.134 (m,4H,Ar-H, Isoindoline), 6.226–7.564 (m,4H, Subs phenyl). ***^{13}CNMR (δ in ppm):***18.32 (N– CH–<u>C</u>H$_3$–Ar) , 38.23 (N– <u>C</u>H–CH_3–Ar), 64.54 (N– <u>C</u>H$_2$–NH),114.14-117.13-130.35 (subs phenyl), 115.31-123.43 (Ar-C,Benzimidazole), 127.60-132.90 (Ar-C, Isoindoline), 134.07-138.56 (fused C), 142.71(C=N), 147.03, 150.64, 167.39 (C=O).***MS (m/z,%):*** 78.16 (49), 85.11 (23), 98.12 (5), 117.11 (100), 127.20 (14), 141.15 (7), 144.62 (60), 157.11 (16), 174.15 (3), 188.20 (11), 202.18 (6), 216.21 (48), 248.20 (40), 256.27 (26), 276.24 (25), 289.26 (31), 322.08 (38), 332.35 (24), 350.31 (10), 365.41 (15), 387.68 (9), 412.67 (4).

ANTHELMINTIC EVALUATION

The synthesized isoindolines were tested for anthelmintic activity by in-vitro bioassay method. The south Indian adult earth worms *Pheretima posthuma of* 7-9cm in length and 0.2-0.3 cm in width were used for the invitro anthelmintic bio-assay due to its anatomical and physiological resemblance with the intestinal worm parasites of human beings. The earth worms of nearly equal size (8 ± 1cm) were selected randomly than washed thoroughly with normal saline solution to remove all fecal and adhering materials before they were released in to petridishes which containing drug in 15 ml of normal saline solution. The worms were divided into the control, standard and tested isoindolines groups of five earthworms in each group. All the tested isoindolines and the standard drug solution were freshly prepared before commencement of the experiments. The control group petridish contains 0.5ml of dimethylsulphoxide in 14.5ml of normal saline solution. The standard drug albendazole and tested isoindolines were prepared at a doses level of 10, 30,50 mg by dissolving in minimum quantity, about 0.5ml of dimethylsulphoxide and the volume was diluted to 15 ml with normal saline, then poured into petridishes. The five earth worms were placed in each petridishes at room temperature and time taken for the induction of complete paralysis and time taken for death of individual earthworms was noted. The time taken for worms to become motionless and do not revive even in normal saline was noted as paralysis time. The death time was ascertained by applying external stimuli unless placing the individual worms in warm water at 50^{o}C which stimulate and induce

movement of worms, if alive. The mean paralysis time and mean death time were calculated for each tested concentrations of the isoindolines.

Table-2 In vitro anthelminitic activity of synthesized indolines (4a-b & 6a-n)

indolines	Time taken for paralysis (P)			Time taken for death (D)		
	10 mg/ group	30 mg/ group	50 mg/ group	10 mg/ group	30 mg/ group	50 mg/ group
4a	54.35±1.64[a]	31.17±0.87[a]	18.08±0.35[a]	73.04±0.64[a]	52.05±0.39[a]	34.06±0.20[a]
4b	56.46±1.41[a]	33.47±1.05[a]	18.30±0.26[a]	78.28±0.45[a]	55.10±0.66[a]	34.41±0.17[a]
6a	61.21±1.55[a]	37.23±0.90[a]	18.52±0.39[a]	85.45±0.50[a]	59.24±0.45[a]	37.05±0.33[a]
6b	65.08±1.12[a]	40.44±0.76[a]	20.11±0.65[a]	88.07±0.71[a]	61.28±0.32[a]	38.30±0.24[a]
6c	72.27±1.08[a]	42.16±0.94[a]	23.03±0.51[a]	93.23±0.66[a]	65.20±0.41[a]	40.09±0.31[a]
6d	78.46±1.10[a]	44.26±0.91[a]	23.18±0.45[a]	98.27±0.48[a]	67.06±0.37[a]	40.24±0.35[a]
6e	83.19±1.44[a]	44.44±1.00[a]	23.32±0.43[a]	102.05±0.64[a]	70.02±0.43[a]	40.50±0.22[a]
6f	85.41±1.35[a]	47.19±1.04[a]	23.50±0.34[a]	107.25±0.51[a]	74.22±0.48[a]	41.04±0.19[a]
6g	91.07±1.60[a]	53.08±0.99[a]	25.16±0.46[a]	115.03±0.59[a]	79.03±0.34[a]	43.10±0.16[a]
6h	94.22±1.17[a]	58.40±1.09[a]	25.45±0.67[a]	121.22±0.67[a]	82.52±0.49[a]	43.51±0.12[a]
6i	42.16±1.14[a]	25.11±0.82[a]	19.15±0.29[a]	63.39±0.36[a]	45.13±0.36[a]	29.34±0.26[a]
6j	47.05±0.98[a]	27.04±0.94[a]	19.45±0.37[a]	68.49±0.39[a]	49.38±0.39[a]	32.02±0.21[a]
6k	36.17±1.29[a]	20.21±0.88[a]	16.05±0.36[a]	52.09±0.51[a]	37.32±0.46[a]	26.05±0.17[a]
6l	39.28±1.22[a]	22.39±0.86[a]	16.55±0.54[a]	57.20±0.62[a]	40.21±0.60[a]	27.31±0.20[a]
6m	34.30±1.24[a]	19.22±0.82[c]	15.25±0.33[b]	46.35±0.57[a]	33.11±0.35[a]	24.10±0.27[a]
6n	38.40±1.18[a]	21.25±0.85[a]	16.32±0.59[a]	54.05± 0.35[a]	39.26±0.42[a]	26.43±0.24[a]
ALZ	23.51±0.91	14.55±0.62	12.33±0.21	37.24±0.33	26.28±0.26	19.12±0.07

Each value represents the mean ±SEM (n=5). Significance levels c - P<0.5, b - P<0.01 and a - P<0.001 as compared with the respective standard drug (ALZ- Albendazole).

RESULTS AND DISCUSSION

The spectral data of synthesized compounds were conforming the molecular structure. In-vitro anthelmintic screening results of benzimidazolyl isoindolines were depicted in Table-2. The isoindolines acquired the anthelmintic activity at minimal dose of 10 mg/dish. The investigation of all tested groups of isoindolines at tested concentrations 10mg, 30mg and 50mg had shown significant anthelmintic activity compared to the standard drug albendazole. It was observed that while increasing the concentrations of isoindolines and albendazole significantly reduced the time taken for paralysis and death as well. In which isoindolines 6k, 6l, 6m and 6n showed excellent potent action for time taken to paralysis and death when compared to the standard drug albendazole. The isoindolines 6i, 6j were also registered comparably potent activity to the above mentioned compounds. The isoindolines 4a, 4b, 6a, 6b were also displayed good anthelmintic activity. The data also indicates that isoindolines 6c,6d,6e,6f exhibited appreciable activity but isoindolines 6g,6h were possess comparably less potent than other tested compounds.. A closer inspection of the results indicates that all tested isoindolines marked good anthelmintic activity at the higher 30mg and 50mg concentrations.

The structure activity relationship studies revealed that polar electron donating hydroxy group and sulphonamide groups are found to increase the anthelmintic properties, where as electron withdrawing acidic carboxylic acid and sulfonic acid substituents found to reduce anthelmintic potency. Among this 1- phenyl hydroxyl group substituted benzimidazolyl isoindolines were only potent anthelmintic activity but the 1- phenyl sulfonic acid group substituted benzimidazolyl isoindolines shows least anthelmintic activity. Meanwhile, the 1- phenyl group substituted benzimidazolyl isoindolines were less potent than 1H-un substituted benzimidazoles. From the results , which indicated that the , 2-ethyl substituted benzimidazolyl isoindolines (4b,6b,6d,6f,6h,6j,6l,6n) were marked less activity than 2-methyl substituted benzimidazolyl isoindolines (4a,6a,6c,6e,6g,6i,6k,6m). Moreover, the close examination of table 2 proves that the 1- phenyl para hydroxyl group and 1- phenyl para carboxylic acid substituted benzimidazolyl isoindolines were produced more activity then the corresponding ortho substitution on same nucleus.

CONCLUSION

Spectral structural elucidation is conforming the molecular formula of all the synthesized compounds. The anthelmintic investigation of all the tested benzimidazolyl isoindolines endowed with less time taken for death at 30mg and 50mg concentrations. Among this, 1-phenyl hydroxy substituted (6k, 6l, 6m and 6n) benzimidazolyl isoindolines were produced excellent anthelmintic activity but 1-phenyl free acid and sulfonic acid substituted analogues were shows comparably less potency then other tested benzimidazolyl isoindolines . Moreover, the 1-phenyl para substituted and 2-methyl substituted benzimidazolyl isoindolines were expressed elevated anthelmintic properties then the corresponding 1-phenyl ortho substituted and 2-ethyl substituted analogues.

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