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Synthesis and characterization of benzimidazole derivatives by sonogashira coupling and evaluation of anthelmintic activity

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ABSTRACT

Series of new benzimidazole derivatives have been prepared starting with synthesis of 2-(6-bromo-2-naphthyl)-1H-benzimidazole by using ortho-phenyl diamine and 6-bromo-2-naphthoic acid. The compounds were further alkylated and acylated. The acetylene linkage was incorporated by reacting 6-ethynyl-4,4-dimethylthiochromanwith2-(6-bromo-2-naphthyl)-1H-benzimidazolevia Sonogashira coupling resulted2-(6-((4,4-dimethylthio chroman-6-yl)ethynyl)naphthalen-2-yl)-1H-benzo[d]imidazole. The newer benzimidazole derivatives were alkylated and acylated to obtained library of newer compounds. All the compounds were characterized by IR, ^{1}H NMR, ^{13}CMR and Mass spectroscopies. All newly synthesized benzimidazole derivatives were subjected for anthelmintic activity. To study the Anthelmintic activity Indian earthworm (Pheretima posthuma) was used at the concentration 10 mg/ml and 20 mg/ml. Albendazole is used as reference standard. Overall study exhibited that all the compounds have moderate to excellent activity.

Keywords: Benzimidazole derivatives, sonogashira coupling, anthelmintic activity.

INTRODUCTION

In humans parasitic worms are responsible for the macroparasitic disease called as helminthiasis. Parasitic worms such as Nematodes or Cestodes are exist in liver, muscles, lungs, skin, lymph, eye, brain and other tissues [1]. The wide verities of anthelmintic drugs areavailable in market which used to destroy such worms from the human body. But some infectious disease cannot be treated and parasite cannot be irradiated completely from human body by present drug [2]. Particularly filariasis diagnosis in early stage can be help for its treatment. After advancement of parasitic infection, it cannot be curved completely. The benzimidazole derivative e.g. Albendazole andOxibondazole is the choice of medical practioner. The potency of the benzimidazole as biologically active compound prompted as to synthesis newer derivation and study of anthelmintic activity. The sonogashira coupling is employed to obtain final compounds.

Sonogashira coupling is the palladium catalyzed coupling of terminal alkynes with aryl and vinyl halides in the presence of CuI and an amino base and is one of the important and widely used carbon-carbon bond forming reactions in organic synthesis [3].This method has been successfully applied for the synthesis of natural products [4], biologically active molecules [5], new organic materials for optical and microelectronic applications [6], dendrimeric, oligomeric, polymeric materials [7], macromolecules with acetylenic links [8], polyalkynylated molecules and generally as a route to new intriguing molecules architectures [9]. In present work we report evaluation of anthelmintic activity and preparation of benzimidazole derivatives via sonogashira coupling.

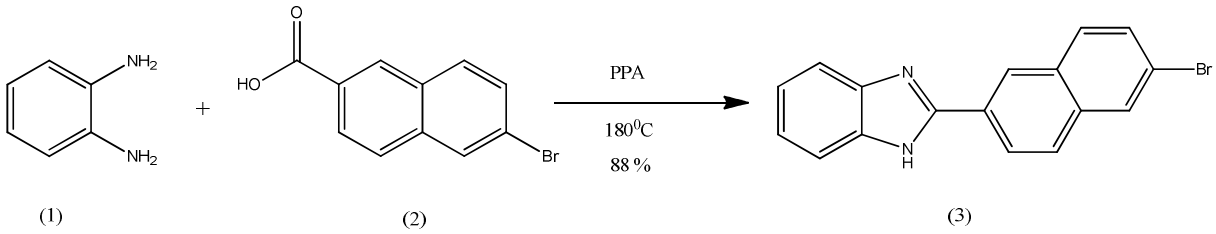
MATERIALS AND METHODS

Melting points are uncorrected and were recorded on a Polomon instrument. TLC carried out using pre-coated silica gel plates and visualization was done using Iodine/UV lamp. IR spectra were recorded on a Shimadzu FT-IR spectrometer using KBr.1H-NMR spectra were recorded on a Varian Mercury Vx SWBB 300 Hz spectrometer and 13C-NMR spectra were recorded on a Varian Mercury Vx SWBB 75 Hz spectrometer with DMSO-d_6 as a solvent unless otherwise mentioned. O-phenyldiamine, 6-bromo naphthoic acid, alkylating agent and acylating agents used were of synthetic grade. 6-ethynyl-4,4-dimethylthiochroman was prepared according to reported procedure from thiophenol.

Experimental:

Synthesis of 2-(6-bromo-2-naphthyl)-1H-benzimidazole (Compound 3):

A mixture of o-phenylenediamine**1** (10.3 g, 95 mmol), 6-bromo napthoic acid **2** (26.3 g, 104 mmol) and polyphosphoric acid (120 ml) was refluxed for 4h at 180°C,monitored on TLC (mobile phase, Chloroform : Methanol 9:1).The reaction mixture was cooled and neutralized with aqueous solution of sodium hydroxide. The precipitate was filtered off and recrystallized from ethyl acetate afforded light yellowish solid of compound **3** (27.1 g, 88 %).



(1) (2) (3)

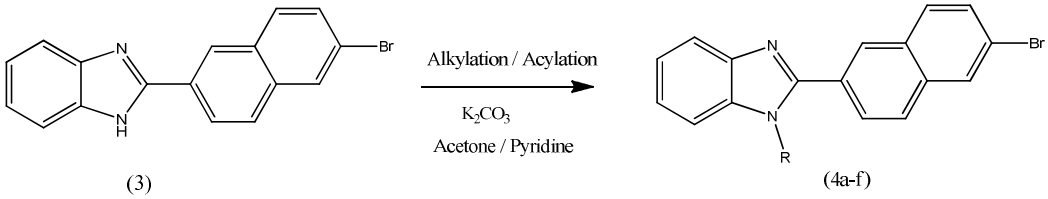
Scheme -1

General procedure for the synthesis of compound 4a-e:

To a mixture of compound 2-(6-bromo-2-naphthyl)-1H-benzimidazole**3** (2 mmol) in acetone (12ml) was added finely ground anhydrous K_2CO_3 (4mmol), triethylbenzyl ammonium chloride (TEBAB, 0.1 mmol) followed by the addition of respective alkyl halide (3 mmol). The reaction mixture was then refluxed for 3-10 hrs, monitored by TLC (mobile phase Chloroform: Methanol, 9:1). Acetone was evaporated under vacuum; water was added to the residue and extracted with dichloromethane. The dichloromethane layer was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded the corresponding N-substituted derivatives 4a-e. The crude compounds were purified by flash column chromatography (silica gel) to obtain pure products.

General procedure for the synthesis of compound 4f:

To a mixture of compound 2-(6-bromo-2-naphthyl)-1H-benzimidazole**3,** (2 mmole) in pyridine (6 ml) was added respective alkyl formate (4 mmol). The reaction mixture was then stirred for 10-15 hrs, monitored by TLC (Ethyl acetate: n-Hexane, 8:2). After completion of the reaction, the reaction mixture was quenched in water (50 ml) and extracted using dichloromethane (2 X 20 ml). The dichloromethane layer was washed with water and dried over anhydrous Sodium sulfate. Evaporation of the solvent yielded the corresponding N-substituted derivative **4f**. The crude compound was recrystallized from hot ethyl acetate to obtain pure products.



(3) (4a-f)

4a, R = Methyl; 4b, R = Ethyl; 4c, R = Propyl; 4d, R = Butyl;
4e, R = Benzyl; 4f, R = Ethoxycarbonyl

Scheme – 2

Physical and spectral data of compound (3) and (4a-4f):

2-(6-bromonaphthalen-2-yl)-1H-benzo[d]imidazole (Compound 3):

Yield : 88% ***M.P.:*** 112-114^{0}C.; ***IR (KBr) (υ in cm-1) :***746.45 ,885.33, 1060.85, 1276.88, 1423.47, 3408.22; ***^{1}H-NMR (DMSO-d_6) (δ in ppm):*** 7.21 (broad singlet, 2H, Ar-H), 7.54-7.71(m, 3H, Ar-H), 7.95-8.1 (m, 2H, Ar-H), 8.27-8.43 (m, 2H, Ar-H), 8.72 (s, 1H. Ar-H), 13.06 (s, 1H, -NH).; ***^{13}C-NMR (CD_3OD) (δ in ppm):***122.27, 124.12, 124.19, 125.94, 126.25, 127.34, 128.49, 128.87, 129.08, 129.85, 130.99, 131.27, 131.42, 132.36, 133.07, 136.40, and 152.84; ***EI-MS*** :323/325 [M+1].

2-(6-bromonaphthalen-2-yl)-1-methyl-1H-benzo[d]imidazole (Compound 4a):

Yield: 81%. ***M.P.:*** 138-141^{0}C; ***IR (KBr) (υ in cm-1):***740.67, 879.54,1060.85,1282.66, 1456.26, 1593.20.; ***^{1}H-NMR (DMSO-d_6) (δ in ppm):***3.97 (s, 3H, N-$\underline{CH_3}$), 7.23-7.28 (m, 2H, Ar-H),7.53-7.71(m,3H,Ar-H),7.99-8.15(m,3H,Ar-H), 8.27- 8.32 (m, 1H, Ar-H), 8.47-8.54 (m,1H,Ar-H).; ***EI-MS***: 337/339 [M+1].

2-(6-bromonaphthalen-2-yl)-1-ethyl-1H-benzo[d]imidazole (Compound 4b):

Yield : 91%. ***M.P.:*** 173-176^{0}C.; ***IR (KBr) (υ in cm-1):***746.45, 815.89, 883.40,1271.09,1444.68, 1471.69.; ***^{1}H-NMR (DMSO-d_6) (δ in ppm):***1.34 (m, 3H,-CH2-CH3),4.4 (m,2H, N-CH2-CH3),7.28 (m,1H,Ar-H) ,7.69-7.7 (m, 2H,Ar-H),8.08 (m, 1H,Ar-H),8.21 (m, 2H,Ar-H),8.28 (m, 2H,Ar-H),8.47 (m, 1H,Ar-H), 8.56 (m, 1H,Ar-H).; ***EI-MS:***351/353 [M+1].

2-(6-bromonaphthalen-2-yl)-1-propyl-1H-benzo[d]imidazole (Compound 4c):

Yield : 89 %. ***M.P.:*** 165-168 ^{0}C.; ***^{1}H-NMR (DMSO-d_6) (δ in ppm):***0.72 (m,3H,CH_2-CH_2-CH_3), 1.71(m,2H, CH_2-CH_2-CH_3), 4.29 (m,3H, N-CH_2-CH_2-CH_3),7.29(m,2H,Ar-H),7.72-7.77 (m, 3H,Ar-H),7.98 (m,1H,Ar-H),8.1 (m, 1H,Ar-H),8.25-8.4(m,3H,Ar-H).; ***EI-MS:***365/367 [M+1].

2-(6-bromonaphthalen-2-yl)-1-butyl-1H-benzo[d]imidazole (Compound 4d):

Yield: 88 %. ***M.P.:*** 89-92^{0}C.; ***IR (KBr) (υ in cm-1):***742.5, 879.5, 1109.7, 1170.7, 1463.97, 1624.0, 2958.8, 3055.24. ***^{1}H-NMR (DMSO-d_6) (δ in ppm):***0.74 (m,3H, -CH_2-CH_2-CH_3),1.19 (m,2H, CH_2-CH_2-CH_3), 1.77(m,2H,-CH_2-CH_2-CH_2), 4.53(m,2H, N-CH_2-CH_2), 7.63 (m,2H, Ar-H),7.84 (m,2H,Ar-H),8.02 (m, 4H,Ar-H),8.45 (m, 1H,Ar-H),8.6 (m, 1H,Ar-H).; ***EI-MS:***379/381[M+1].

1-benzyl-2-(6-bromonaphthalen-2-yl)-1H-benzo[d]imidazole (Compound 4e):

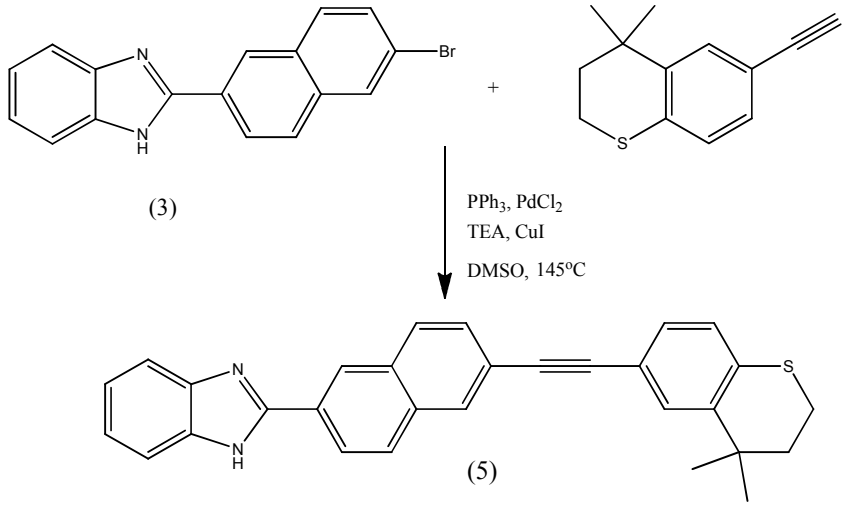
Yield: 76% ***M.P.:*** 125-128^{0}C; ***IR (KBr) (υ in cm-1):***744.52, 804.32, 875.68, 1060.85, 1276.88, 1427.32.; ***^{1}H-NMR (DMSO-d_6) (δ in ppm):***5.69 (s,2H,N-CH2-Ph),7.0 (m, 2H,Ar-H), 7.25 (m, 5H,Ar-H),7.55(m,2H,Ar-H),7.74 (m, 2H,Ar-H),7.92 (m, 2H,Ar-H), 8.28-8.32 (m, 2H,Ar-H).; ***EI-MS:***413/415[M+1].

Ethyl 2-(6-bromonaphthalen-2-yl)-1H-benzo[d]imidazole-1-carboxylate (Compound 4f):

Yield: 92%. ***M.P.:*** 68-71^{0}C.; ***IR (KBr) (υ in cm-1):***744.52, 804.32, 875.68, 1060.85, 1276.88, 1427.32,1757.15. ***^{1}H-NMR (DMSO-d_6) (δ in ppm):***1.1 (m, 3H, CH_2-CH_3), 4.32 (m, 2H, O-CH_2-CH_3),7.46 (m, 2H, Ar-H),7.71-7.8 (m, 2H, Ar-H),7.9-8.04(m, 4H,Ar-H),8.32 (m 2H,Ar-H).; ***EI-MS:***395/397 [M+1].

Synthesis of compound 2-(6-((4,4-dimethylthiochroman-6-yl) ethynyl)naphthalen-2-yl)-1H-benzo[d]imidazole (5):

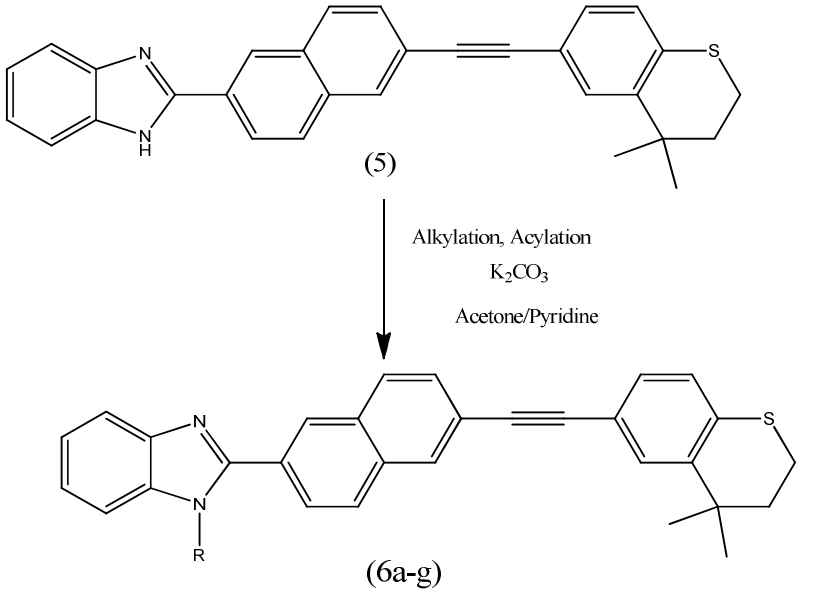
A mixture of triphenylphosphine(0.93mmol) and palladium chloride (0.45mmol) in dimethylsulfoxide (90 ml) was heated to 140-145°C for 10 min under argon atmosphere to obtain a clear solution. The reaction mixture was then allowed to cool to room temperature and to this solution, a mixture of **3** (17 mmol), 6-ethynyl-4,4-dimethylthiochroman (3.5 g,17 mmol),triethylamine (2.88g, 28.58 mmol) and copper iodide (0.614 mmol) in dimethylsulfoxide (20 ml) was slowly added. The resulting mixture was heated with stirring at 95°C. The progress of reaction was monitored by TLC (Mobile phase, Chloroform : Methanol , 9:1). The reaction mixture was then cooled to room temperature and filtered on a celite pad, followed by washing with ethyl acetate (2 X 150 ml).The filtrate was then washed with water (2 X 150 ml), brine (2 X 100 ml) and dried over anhydrous magnesium sulphate .The solvent was evaporated under vacuum yielded the crude product which was recrystallized from acetone to obtain pure yellow color product (**5**).



Scheme – 3.

General procedure for preparation 2-[4-(1-Cyclohexyl-1H-tetrazol-5-yl)-butylsulfanyl]-1-alkyl -1H-benzimidazole [6a-e]:

To a mixture of compound 1 (2mmol) in acetone (50 ml) ,finely ground anhydrous K_2CO_3 (4mmol), triethylbenzylammonium bromide (TEBAB, 1 mmol) were added, followed by of alkylating agent (3 mmol).The reaction mixture was then refluxed for 03-10 hrs, monitored by TLC (mobile phase Ethyl acetate: n-Hexane, 7:3). Acetone was evaporated under vacuum, and then water was added to the residue and extracted in dichloromethane. The dichloromethane layer was washed with water and dried over anhydrous Sodium sulfate. Evaporation of the solvent yielded the corresponding alkylated product.



6a, R = Methyl; 6b, R = Ethyl; 6c, R = Propyl; 6d, R = Butyl;
6e, R = Benzyl; 6f, R = Ethoxycarbonyl; 6g, R = Phenoxycarbonyl

Scheme – 4.

General procedure for the synthesis of compound 6f-g:

To a mixture of compound 2-(6-((4,4-dimethylthiochroman-6-yl)ethynyl)naphthalen-2-yl)-1H-benzo[d]imidazole (**5**, 2 mmole) in pyridine (6 ml) corresponding alkyl formate was added (4 mmol). The reaction mixture was then stirred for 10-15 hrs, monitored by TLC (mobile phase, Ethyl acetate :n-Hexane, 7:3) . After completion of the reaction, the reaction mixture was quenched in water (50 ml) and extracted using dichloromethane (2 X 20 ml). The dichloromethane layer was washed with water and dried over anhydrous Sodium sulfate. After removals of solvent, corresponding N-substituted derivatives were obtained **6f-g**. The crude compounds were recrystallized from ethyl acetate to obtain pure products.

Physical and spectral data of compound (5) and (6a-6g):

2-(6-((4,4-dimethylthiochroman-6-yl)ethynyl)naphthalen-2-yl)-1H-benzo[d]imidazole (Compound 5):
Yield: 92 %***M.P.:*** 189-201^{0}C; ***IR (KBr) (υ in cm-1):***742.59,813.96, 889.18, 1053.13,1097.50, 1278.81, 1392.61, 1421.54, 1444.68, 1541.12, 2200.78, 2956.87, 3051.39; ***^{1}H-NMR (DMSO-d_6) (δ in ppm):***1.32(s ,6H,(C-$(CH_3)_2$),1.90 (m,2H,C-CH_2-CH_2-S), 3.06 (m,2H, CH_2-CH_2-S) ,7..8-7.10 (d,1H, J=8.4 Hz, Ar-H),7.19-7.26 (m,3H,Ar-H),7.54-7.70 (m, 4H,Ar-H), 8.03-8.09 (t, 2H, J = 8.4Hz, Ar-H) , 8.20 (s, 1H, Ar-H), 8.31-8.34(d, 1H, J= 8.3Hz,Ar-H), 8.72(s, 1H, Ar-H),13.08 (s, 1H, -NH).; ***13C-NMR: (DMSO-d_6) (δ in ppm):*** 22.63, 29.84, 32.83, and 36.78 (aliphatic carbon), 89.21(acetylene carbon) 91.21(acetylene carbon), 117.66, 121.11, 122.52, 124.96, 125.83, 126.73, 128.61, 128.64, 129.02, 129.09, 129.23, 129.81, 131.08, 132.35, 133.29, 133.69, 142.54, 151.13 (aromatic carbon).; ***EI-MS:***444.42 [M+1].

2-(6-((4,4-dimethylthiochroman-6-yl)ethynyl)naphthalen-2-yl)-1-methyl-1H-benzo[d]imidazole (Compound 6a):
Yield:76% ***M.P.:*** 167-171^{0}C; ***IR (KBr) (υ in cm-1):***744.52, 815.89, 889.18, 889.18, 1053.13, 1109.07, 1261.47, 1460.11, 14477.47, 1622.13, 2200.78, 2926.01, 2958.87; ***^{1}H-NMR (DMSO-d_6) (δ in ppm):***1.32(s, 6H, C-$(CH_3)_2$),1.91(m, 2H,-CH_2-CH_2),3.07 (m, 2H,CH_2-CH_2-S),3.96(s, 3H,N-CH_3), 7.11 (d, 1H,J = 8 Hz,Ar-H),7.28(m, 2H,Ar-H),7.77(m, 4H,Ar-H), 7.95(d, 1H,Ar-H),8.13(m,3H,Ar-H), 8.27(t,1H,J = 9Hz,Ar-H),8.53(s, 1H,Ar-H).
EI-MS:459.53 [M+1].

2-(6-((4,4-dimethylthiochroman-6-yl)ethynyl)naphthalen-2-yl)-1-ethyl-1H-benzo[d]imidazole (Compound 6b):
Yield:79% ***M.P.:*** 78-81 ^{0}C; ***IR (KBr) (υ in cm-1):***744.52, 817.82, 891.11, 1053.11, 1109.07, 1269.16, 1386.82, 1442.75, 1477.47, 1624.06, 2200.78,2931.80, 2960.73; ***^{1}H-NMR (DMSO-d_6) (δ in ppm):***1.32 (s,6H, C-$(CH_3)_2$,1.35(m,3H,CH_2-CH_3),1.9 (m,2H,-CH_2-CH_2),3.06 (m, 2H, CH_2-CH_2-S),4.31-4.33 (q,2H,N-CH_2),7.08 (m,1H,Ar-H),7.24-7.38(m,2H,Ar-H),7.6(m,2H,Ar-H),8.0(d,1H J =8.3 Hz,Ar-H), 8.21(m,2H,Ar-H), 8.43(m,2H,Ar-H), 8.43(m,2H,Ar-H), 8.53(t,1H,J =9.3 Hz,Ar-H), 8.73(s,1H,Ar-H); ***EI-MS:***473.38 [M+1]

2-(6-((4,4-dimethylthiochroman-6-yl)ethynyl)naphthalen-2-yl)-1-propyl-1H-benzo[d]imidazole (Compound 6c):
Yield:86% ***M.P.:*** 86-91^{0}C; ***IR (KBr) (υ in cm-1):***742.59, 813.96, 889.18, 1053.13, 1105.21, 1261.45, 1452.40, 1585.49, 2200.78, 2929.87, 2960.73; ***^{1}H-NMR (DMSO-d_6) (δ in ppm):***0.91 (m, 3H, CH_2-CH_3),1.31(m,6H,C-$(CH_3)_2$),1.91(m,4H, CH_2-CH_2; N-CH_2-CH_2-CH_3),3.05 (m,2H,CH_2-CH_2-S),4.37 (m,2H, N-CH_2),7.06 (m,1H,Ar-H), 7.22 (m, 1H,Ar-H), 7.42 (m, 2H,Ar-H), 7.58 (m, 3H,Ar-H), 7.76 (m, 4H,Ar-H),8.06 (m, 1H,Ar-H),8.36 (m, 1H,Ar-H).; ***EI-MS:***487.42 [M+1]

1-butyl-2-(6-((4,4-dimethylthiochroman-6-yl)ethynyl)naphthalen-2-yl)-1H-benzo[d]imidazole (Compound 6d):
Yield: 79 % ***M.P.:*** 83-86^{0}C; ***IR (KBr) (υ in cm-1):***742.59, 813.96, 887.26, 1053.13, 1107.14, 1261.45, 1450.47, 1587.42, 2202.71, 2929.15, 2958.80, 3053.32; ***^{1}H-NMR (DMSO-d_6) (δ in ppm):***0.85-.9(t,3H, CH_2-CH_3),1.28-1.37 (m, 8H, C-$(CH_3)_2$;CH_2-CH_2-CH_3), 1.85-1.9(m, 4H, CH_2-CH_2; N-CH_2-CH_2-CH_2), 3.05 (m, 2H,CH_2-CH_2-S), 4.39 (m,2H,N-CH_2),7.06 (m,1H,Ar-H),7.21 (m,1H,Ar-H), 7.41-7.43 (m,2H,Ar-H),7.54 (m,2H,Ar-H), 7.65-7.67 (m, 1H,Ar-H),7.88-7.94 (m, 3H,Ar-H), 7.97 (m, 1H,Ar-H),8.31 (m, 1H,Ar-H), 8.43 (m,1H,Ar-H).; ***EI-MS:***501.45 [M+1]

1-benzyl-2-(6-((4,4-dimethylthiochroman-6-yl)ethynyl)naphthalen-2-yl)-1H-benzo[d]imidazole (Compound 6e):
Yield :92% ***M.P.:*** 113-115^{0}C; ***IR (KBr) (υ in cm-1):***696.30, 744.52, 815.89, 1053.13, 1111.00, 1454.33, 1473.62, 1622.13, 2198.85, 2958.80; ***^{1}H-NMR (DMSO-d_6) (δ in ppm):***1.36 (s,6H, C-$(CH_3)_2$),1.97 (m,2H, CH_2-CH_2),3.06 (m,2H, CH_2-CH_2-S),5.76 (m, 2H, N-CH_2-Ph),7.01 (m,3H),7.16-7.22(m,3H,Ar-H),7.43 (m,2H,Ar-H), 7.67(m, 2H,Ar-H), 7.98 (m, 2H,Ar-H), 8.7 (m, 1H,Ar-H).; ***EI-MS:***534.7 [M+1].

ethyl2-(6-((4,4-dimethylthiochroman-6-yl)ethynyl)naphthalen-2-yl)-1H-benzo[d]imidazole-1-carboxylate (Compound 6f):

Yield:81% ***M.P.:*** 67-71^{0}C; ***IR (KBr) (υ in cm-1):***740.67, 821.68, 889.18, 1053.13, 1109.07, 1384.89, 1444.68, 1541.12, 1631.78, 2202.71, 2958.80; ***^{1}H-NMR (DMSO-d_6) (δ in ppm):***1.10-1.12 (t, 3H, CH2-CH-3)1.32 (s,6H,C-$(CH3)_2$), 1.91 (m,2H, CH_2-CH-$_2$),3.07 (m,2H, CH_2-CH_2-S), 4.31-4.38 (m, 2H,O-CH_2-CH_3), 7.11-7.13(d, 1H,Ar-H), 7.26-7.29(d,1H,Ar-H),7.38-7.51 (m, 2H,Ar-H), 7.57-7.67 (m, 2H,Ar-H), 7.70-7.92 (m, 2H,Ar-H),8.01-8.07 (m, 3H,Ar-H),8.26 (s,1H,Ar-H), 8.38 (s,1H,Ar-H).; ***EI-MS:***516.8 [M+1].

Benzyl-2-(6-((4,4-dimethylthiochroman-6-yl)ethynyl)naphthalen-2-yl)-1H-benzo[d]imidazole-1-carboxylate (Compound 6g):

Yield :75% ***M.P.:*** 123-130^{0}C, ***IR (KBr) (υ in cm-1):***742.59, 819.75, 891.11, 1055.06, 1205.51, 1317.38, 1450.47, 1753.29, 2202.71, 2927.94, 2958.80; ***^{1}H-NMR (DMSO-d_6) (δ in ppm):***1.33 (s,6H,C-$(CH_3)_2$),1.93-1.93 (t,2H, CH_2-CH_2),3.03-3.05 (t, 2H,CH_2-CH_2-S),5.17 (s, 2H, CH_2-Ph),7.01-7.041(d, 1H,Ar-H), 7.19-7.26 (m,3H,Ar-H),7.36 (m, 3H,Ar-H),7.48-7.53(m, 3H,Ar-H), 7.58-7.68 (m, 4H,Ar-H), 7.88-7.93 (m, 1H,Ar-H),8.07-8.11 (m, 2H,Ar-H), 8.71 (m, 1H,Ar-H).; ***EI-MS:***578.2[M+1].

Anthelmintic activity:

To study the Anthelmintic activity Indian earthworm (*Pheretimaposthuma*) was used. Earthworms are utilized for the activity were thoroughly cleaned by washing with saline water get rid of all unwanted material. The anatomically and physiologically earthworms are resembles tointestinal roundworm parasites present in human being. These earthworms were used to investigate anthelmintic activity of synthesized newer benzimidazole.The solution of benzimidazole derivation of each concentration 10 mg/ml and 20 mg/ml were prepared in saline water using tween-80 as surfactant. The 10 ml of solution were taken in petridish. In each petridish group of three earthworms were placed Albendazole (10 mg/ml and 20 mg/ml saline solutions) used as standard. The selected worms were placed in each solution. The time taken for complete paralysis and death was recorded at room temperature. Paralyzed and death worms are shown in figure 1. The mean paralyzed and death time was recorded out of three earthworms which are in petridish.

Table-3. Anthelmintic activity of synthesized Compounds

Compound	Paralysis time (min)		Death time (min)	
	10 mg/ml	20 mg/ml	10 mg/ml	20 mg/ml
3	5	4.3	10.6	9.3
4a	2.33	1.66	8	6
4b	3	1	4.6	2.3
4c	2.33	1.3	3.66	2.3
4d	1.6	1	3.3	2
4e	2.3	1.6	3.6	2.3
4f	3.3	2.3	5.3	3.3
5	3.0	2	4.6	3.3
6a	1.66	1	7.0	3.6
6b	4.6	3.0	9.0	6.0
6c	5	3.6	7.6	6
6d	2.6	2.33	4.3	3.3
6e	3.3	2.6	4.6	3.3
6f	2.6	3.3	4.3	4
Albendazole (Standard)	0.6	0.3	2	1

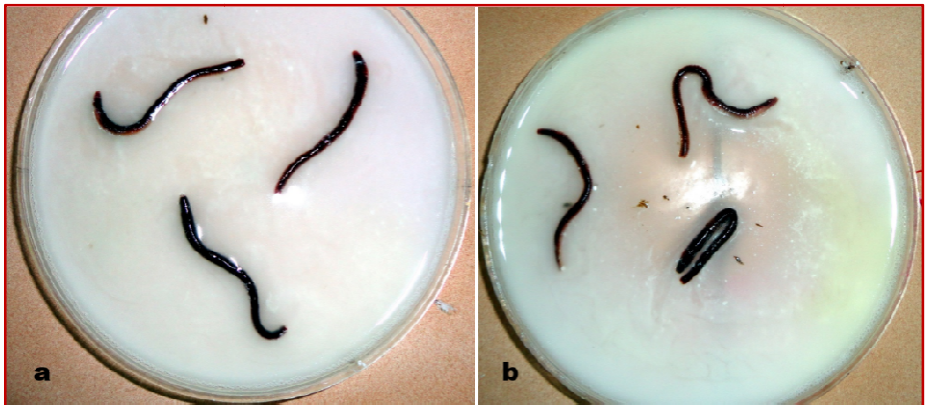


Figure 1. Images of earthworms a) Paralyzed earthworms b) death earthworms

RESULTS AND DISCUSSION

In present work all synthesized compound were tested for *in vitro* anthelmintic activity. The activity was carried out using Indian earthworms(*Pheretimaposthuma*). It resembles anatomically and physiologicallyto intestinal roundworm parasites present in human being. All derivative of the benzimidazole exhibit good activity in comparison with Albendazole(standard). Compound 6a to 6f demonstrated better activity due to presence of acetylene linkage. Furthermore the alkylated derivative of compound (4) and (6) exhibited better activity as compare to parent moiety.

CONCLUSION

All newly synthesized benzimidazole derivative shows the potent anthelmintic activity. The derivative synthesized via sonogashira coupling. In conclusion the benzimidazole derivative demonstrated promising activity. It is observed that the acylated compound obtained by replacing hydrogen of nitrogen of benzimidazole enhance the activity. The series of compound 6a-6g were synthesized by sonogashira coupling. The improvement of anthelmintic activity may attributed to the incorporation of alkyl linkage.

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