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Synthesis And Biological Evaluation Of Benzimidazole Derivatives

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Abstract
Benzimidazoles are a class of heterocyclic compounds in which a benzene ring is fused to the 4 and 5 positions of an imidazole ring. Benzimidazole refers to the parent compound, while benzimidazoles are a class of heterocyclic compounds having similar ring structures, but different substituents. Benzimidazole derivatives possess a wide range of bioactivities including antimicrobial, anthelmintic, antiviral, anticancer, and antihypertensive activities. Many compounds possessing a benzimidazole skeleton have been employed as drugs in the market. The application of benzimidazoles in other fields has also been documented. The synthesis of benzimidazole derivatives has attracted much attention from chemists and numerous articles on the synthesis of this class of heterocyclic compound have been reported over the years. Present abstract deals with synthesis of benzimidazole derivatives. All the compounds were characterized by UV, IR, ^{1}H NMR, mass spectral data and CHN elemental analysis. The synthesized derivatives were screened for analgesic and anti-inflammatory activities. All the compounds showed significant effect at 100 mg/kg p.o. and the experimental data are statistically significant at $p < 0.01$ *level.*

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I. Introduction

Heterocycles are an important class of compounds, making up more than half of all known organic compound [1]. Heterocyclic moieties are present in a wide variety of drugs,most vitamins, many natural products, biomolecules, and biologically active compounds, including antitumor, antibiotic, anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic, herbicidal, fungicidal, and insecticidal agents. Heterocycles have been frequently found as a key structural unit in synthetic pharmaceuticals and agrochemicals [2]. Some of these compounds exhibit a significant solvatochromic, photochromic, and bio chemiluminescence properties. Most of the heterocycles possess important applications in materials science such as dyestuff, fluorescent sensor, brightening agents, information storage, plastics, and analytical reagents. In addition, they have applications in supra molecular and polymer chemistry, especially in conjugated polymers.

The medicinal chemists have been utilizing the heterocyclic moieties to synthesize a wide variety of libraries of compounds based on one core scaffold and to screen those compounds against different receptors, yielding several bioactive compounds. Almost unlimited combinations of fused heterocyclic structures can be designed, resulting in novel polycyclic or conjugated frameworks with the most diverse physical, chemical and biological properties.

Therefore, efficient methodologies to generate polycyclic structures from biologically active heterocyclic templates are always of interest to both organic and medicinal chemists [3]. The primary objective of medicinal chemistry is the design and discovery of new drug compounds. Benzimidazole is a heterocyclic aromatic organic compound. This bicyclic compound consists of the fusion of benzene and imidazole. Benzimidazole, in anextension of the well-elaborated imidazole system, has been used as carbon skeletons for N-heterocyclic carbenes. The NHCs are usually used as ligands for transition metal complexes. They are often prepared by deprotonating an N, N'-disubstituted benzimidazolium salt at the 2-position with a base [4]

Benzimidazole, as the name implies is a bicyclic ring system in which benzene has been fused to the 4 and 5 position of the hetero cycle (imidazole). A basis forinterest in the benzimidazole ring system as a nucleus from which to develop potential chemotherapeutic agents was established in the 1950's when it was found that 5,6, -dimethyl-l-(alpha-D-ribofuranosyl) benzimidazole was an integral part of thestructure of the vitamin B12 [5]

In recent times, benzimidazole has been acknowledged as the choice of moiety due to their role in different disease. Furthermore, it has been characterized as the main lead against the survivability of the different

gram-positive and gram-negative strains and even acts as an effective therapy against the antibacterial agents that causes bacterial resistance. Taking all these influences into consideration and their emergence in further validation and repurposing of benzimidazole, the study is targeted to explore the present evidence on benzimidazole and its derivatives for their respective reported pharmacological activities. The present paper focused on the major derivatives of benzimidazole and reported their pharmacological activities for further exploration of scientific facts about benzimidazole.

Experimental section

Melting point were determined in open capillary tubes and are uncorrected**.** The time required for the completion of the reaction was monitored by TLC using Silica gel G plates and spots were exposed in Iodine chamber.IR spectra were recorded on Perkin Elmer 1800(FTIR) spectrophotometer. IH NMR spectra (DMSO) were taken on a DRX – 300 spectrometer 300 MHz using TMS as internal standard and chemical shifts are expressed in ᵹ ppm.

II. Materials And Methods.

Methodology:

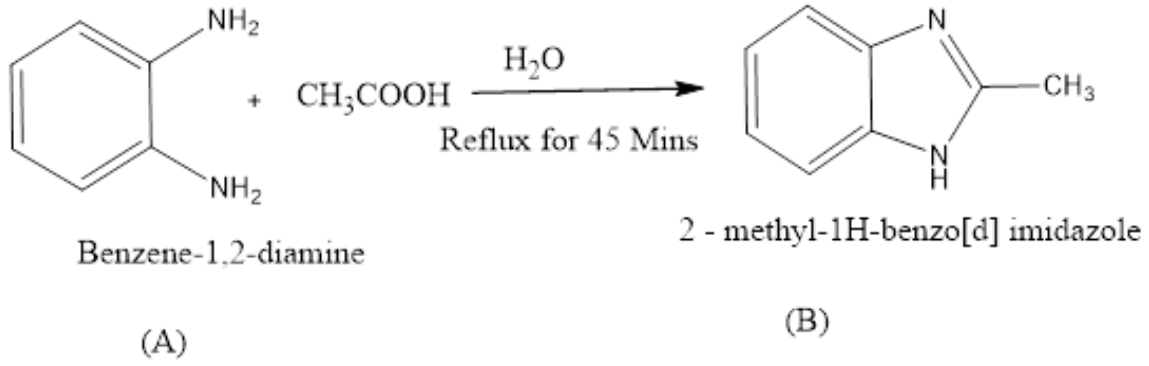
Synthesis

Scheme 1: Synthesis of conjugated system of benzimidazole and chromene

The scheme of synthesis of desired compounds is as follow –

Scheme 1(a)

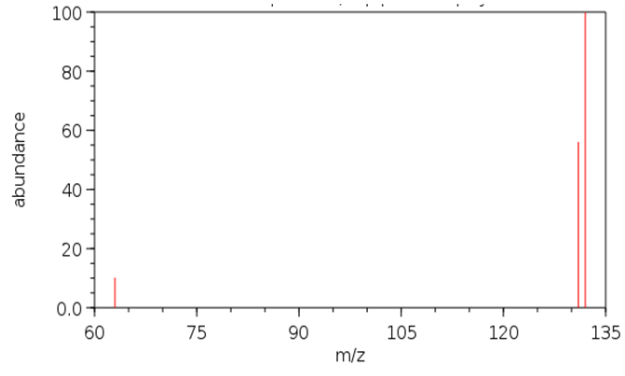
Step 1. Benzene 1,2 diamine (A) and acetic acid undergoes reaction in the presence of H_2O. Reflux the reaction mixture for 45 minutes to get the product 2 methyl-1H- benzo(d) Imidazole (B).



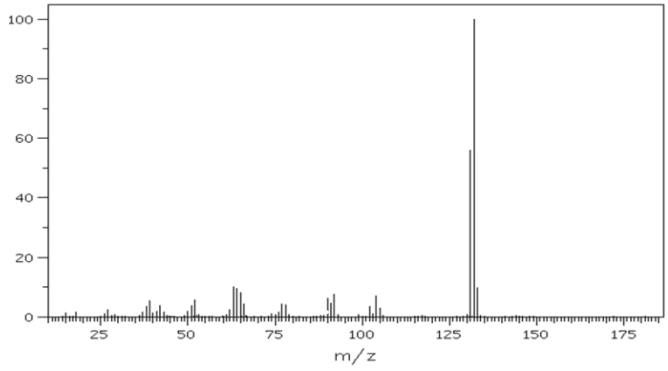
Compound B

It is a white or colourless solid that is highly soluble in polar organic solvents and water.
Appearance: Crystalline Powder
Yield: 39 %
Melting Point: 175-177 ^{0}C
Chemical Formula: C8 H8 N2
Molecular weight: 132
Density: 1.1083
Pka : 6.19 (at 25 ^{0}C)
Refractive index: 1.6313
Mass Fragmentation: 132$[M]^+$, 133 $[M+H]^+$
FTIR:

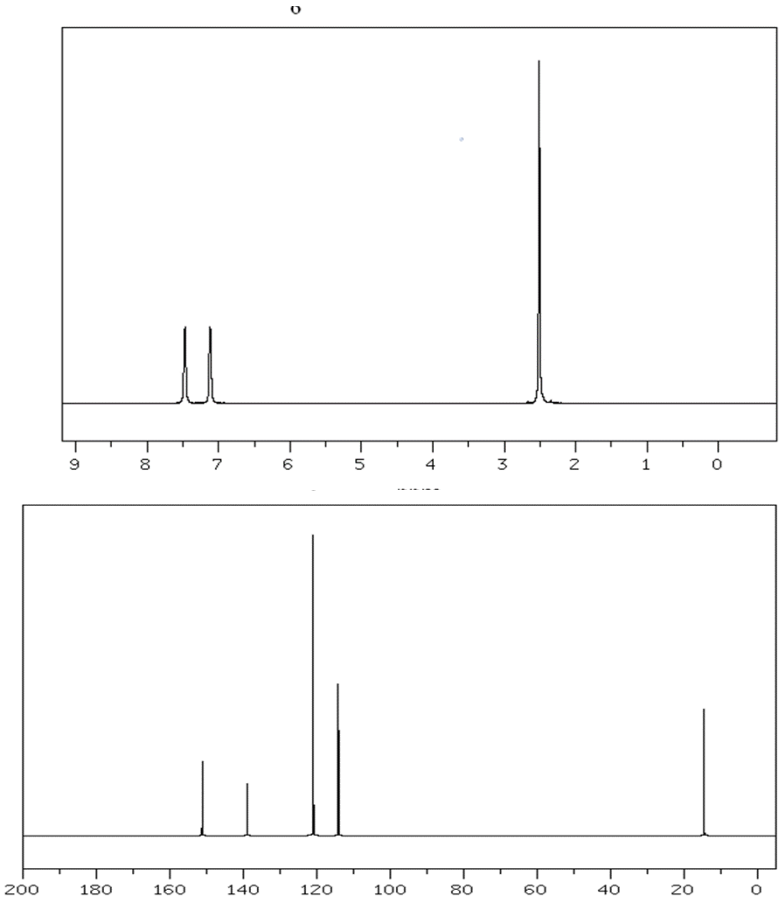
The F.T.I.R spectrum of this compound shows an absorption pack at 3178 cm-1 refers to (N-H) group and an absorption pack at 2916 cm-1 refers to (C-H) aliphatic.
^{1}HNMR (300 MHz) δ(ppm) Benz : (7.26t 2H and 7.71t 2H), N-H (2.45), CH3 (2.20s).



Mass Spectrum of Compound B

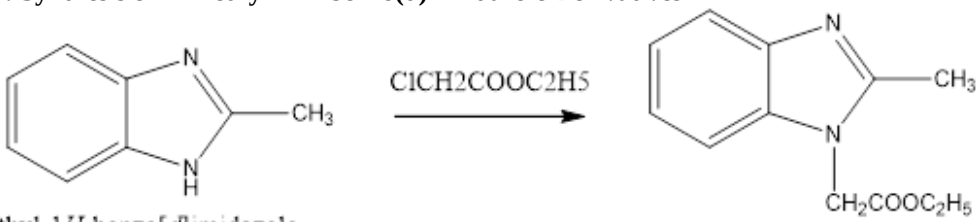


^{1}H NMR spectrum of Compound B



^{13}C NMR spectrum of Compound B

Scheme 2: Synthesis of 2- methyl-1H- benzo(d) Imidazole Derivatives



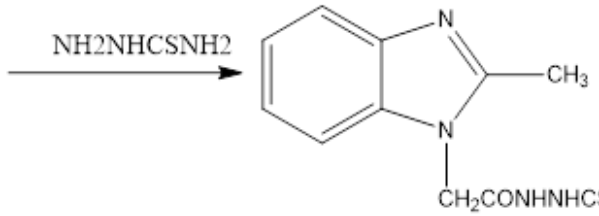
2-methyl-1*H*-benzo[*d*]imidazole
Chemical Formula: $C_8H_8N_2$
Molecular Weight: 132.17
m/z: 132.07 (100.0%), 133.07 (8.7%)

(B)

ethyl 2-(2-methyl-1*H*-benzo[*d*]imidazol-1-yl)acetate
Chemical Formula: $C_{12}H_{14}N_2O_2$
Molecular Weight: 218.26

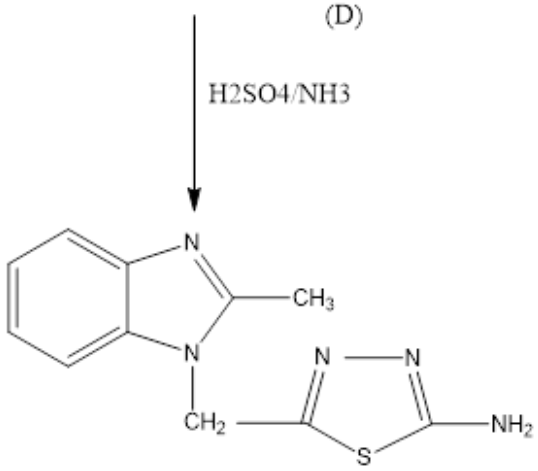
m/z: 218.11 (100.0%), 219.11 (13.0%)

(C)



2-(2-(2-methyl-1*H*-benzo[*d*]imidazol-1-yl)acetyl)hydrazine-1-carbothioamide
Chemical Formula: $C_{11}H_{13}N_5OS$
Molecular Weight: 263.32
m/z: 263.08 (100.0%), 264.09 (11.9%), 265.08 (4.5%), 264.08 (1.8%)

(D)



1-(λ^3-methyl)-2-methyl-1*H*-benzo[*d*]imidazole
1-(λ^2-azaneylidene)ethyl (*Z*)-*N*'-methylcarbamimidothioate

Chemical Formula: $C_9H_9N_2$
Molecular Weight: 145.19
m/z: 145.08 (100.0%), 146.08 (9.7%)

(E)

Synthesis of N-Ethylacetate-2-methyl-benzimidazole (C)

A mixture of 2-methyl–benzimidazole and ethyl-chloroacetate with K_2CO_3 was added and mixed thoroughly. The reaction mixture was air dried and subjected to microwave irradiation for 13 min. The completion of reaction was monitored by thin layer chromatography. The reaction mixture was cooled and separated, solid extracted with ethanol to give the desired product

It is a white or colourless crystalline solid that is highly soluble in polar organic solvents and water.

Appearance: Crystalline solid
Yield: 30 %
Melting Point: 214-217 ^{0}C
Chemical Formula: $C_{12}H_{14}N_2O_2$
Molecular weight: 218
Mass Fragmentation: 218$[M]^+$, 219 $[M+H]^+$
IR(cm^{-1}) : 1270, 1470 (-NCH_2), 1427(-CH_2 bending), 1384 (-CH_3bending),
1H NMR :1.90(t, 3H J=7.0 Hz, -$COOCH_2CH_3$), 4.19 (q, 2H, J=7.0 Hz, -CH_2CH_3), 2.64(s, 1H, --CH_3), 7.35 (m, 4H, Ar-H), 3.63 (s, 2H,-NCH_2)

Synthesis of N-Acetylthiosemicarbazide-2-methyl-benzimidazole (D)

The N^1-Ethylacetate-2-methyl-benzimidazole and thio semi carbazide was ground in a mortar using a pestle for uniform mixing. The mixture was kept inside a microwave irradiation for 12-15 mins. The completion of the reaction was monitored by thin layer chromatography. The product was recrystallized using ethanol.
It is a colourless crystalline solid soluble in polar organic solvents and water.
Appearance: Crystalline solid
Yield: 30 %
Melting Point: 312-314 ^{0}C
Chemical Formula: $C_{11}H_{13}N_5OS$
Molecular weight: 263
Mass Fragmentation: 263$[M]^+$, 264 $[M+H]^+$
IR (cm^{-1}): 1275,1470(-NCH2), 3273 (NH), 1127(>C=S), 2821(-CH3) 1602 (-C=N of benzimidazole ring),
1H NMR :8.24 (m, 4H, -NHNHCSNH2), 2.66(s, 1H, -CH3), 3.67(s, 2H, -NCH2), 7.36(m, 4H, Ar-H)

Synthesis of N-(2'-amino-5'-methylene)-1', 3',4'-thiadiazole-2-methyl-benzimidazole (E)

Equimolar solution of compound **D** dissolved in chloroform and concentrated H_2SO_4 was added in to above solution at room temperature. This reaction mixture was subjected to microwave irradiation for 18 mins. The sample was cooled in ice bath and irradiation was repeated several times. Completion of the reaction was monitored by TLC. The resulting product was neutralized with conc. Liq. ammonia. The final product was recrystallized from ethanol to give compound **E**.

It is a white or colourless crystalline solid that is highly soluble in polar organic solvents and water.
Appearance: Crystalline solid
Yield: 30 %
Melting Point: 293-295 0C
Chemical Formula: $C_9H_9N_2$
Molecular weight: 145
Mass Fragmentation: 145$[M]^+$, 146 $[M+H]^+$
IR (cm^{-1}): 1278, 1465(-NCH2), 3395(-NH2), 1406, 1631(C=N, C-N of benzimidazole ring), 1604(Thiadiazole ring), 2831 (-CH3)
1H NMR :4.81(s, 1H, -NH2), 2.64(s, 1H, -CH3), 7.24(m, 4H, Ar-H)

III. Results And Discussion

The reaction sequence involves microwave-induced preparation of N^1-Ethylacetate-2-methyl-benzimidazole from reaction of 2-methylbenzimidazole with ethyl-chloroacetate. Further reaction with thiosemicarbazide gives N^1-acetylthiosemicarbazide-2-methyl-benzimidazole. The compound on dehydrative annulation by sulfuric acid gives N^1-(2'-amino-5'-methylene)-1',3',4'-thiadiazole-2-methyl-benzimidazole.

2-Methyl benzimidazole (B) on reaction with ethyl-chloro ethanoate gives N1- Ethylacetate-2-methylbenzimidazole (C) which showed characteristic IR absorption band at 1428 (-CH2 bending), 1721 (C=O str) and 1640 cm-1 (C=N str). Compound (C) on reaction with thio semicarbazide gives N1-Acetylthiosemicarbazide-2-methyl-benzimidazole(D). Further on dehydrative annulation by mineral acid gives N1-(2′-amino-5′- methylene)-1′,3′,4′-thiadiazole-2-methyl-benzimidazole (E) [5-7].

Aanalgesic activity

The analgesic activity was carried out by Tail-flick method using Swiss albino mice. In this method, heat is used as a source of pain. Overnight fasted healthy and adult male Swiss albino mice weighing between 20 g and 25 g, in a group of six each were taken for the investigation. The animals were kept into a small cage with an opening for the tail at the rear wall. The tail was held gently and a light beam exerting radiant heat was directed to the proximal third of the tail. The tip of the tail of the mice was individually placed on the radiant heat source

at constant temperature 55 °C [8]. The cut-off reaction time was fixed at 15 s to avoid tissue damage. The tail flick response was measured at 0- 5 hours after treatment of test compounds by digital analgesiometer (INCO, Ambala, India). The drug pentazocine (3.9 mg/kg, i.p.) was used as standard drug for comparison and test groups received synthesized benzimidazole derivatives at 100 mg/kg p.o.

The analgesic activity

The analgesic activity revealed that almost all the compounds showed very potent analgesic activity when compared with standard pentazocine. Among the tested compounds **C D and E** showed profound analgesic activity. The rest of the compounds **1C**, **1D** and **1E s**howed moderate activity when compared with the control.

Table 1. Analgesic activity of benzimidazole derivatives on mice by using tail-flick method.

Compounds Scode	TW time in second (Mean ± SEM)				
	0 h	1 h	2 h	3 h	4 h
Control	1.76 ± 0.13	1.98 ± 0.14	2.53 ± 0.119	2.63 ± 0.20	2.89 ± 0.52
Standard	1.86 ± 0.56	4.5 ± 0.44	7.13 ± 0.21##	8.12 ± 0.27#	9.53 ± 0.29##
1C	2.4 ± 0.31	5.37 ± 0.19	4.19 ± 0.48#	6.13 ± 0.30#	5.16 ± 0.28##
1D	2.19 ± 0.27	4.22 ± 0.32	5.6 ± 0.41#	4.36 ± 0.27#	3.89 ± 0.45#
1E	2.47 ± 0.35	3.76 ± 0.21	4.14 ± 0.37#	4.61 ± 0.21#	2.59 ± 0.31##

n = 6 animals in each group.
# $p < 0.05$ vs control.
$p < 0.01$ vs control.

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