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# SYNTHESIS OF SOME NOVEL 2- SUBSTITUTED BENZIMIDAZOLE DERIVATIVES & THEIR ASSESSMENT FOR ANTIMICROBIAL & ANTHELMINTIC ACTIVITY

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## ABSTRACT

Heterocyclic compounds are the greatest invention by the scientists in the present scenario. Now-a days they are the ultimate goal for solving several health complexities. Presence of hetero atoms in a molecule as pharmacophore is responsible for wide variety of therapeutical activity. Objective of this work is to improvement of humble and relaxed method for generation of 2-substituted benzimidazole derivatives. It involves insertion of aromatic aldehyde into the 2$^{nd}$ position of benzimidazole nucleus. Which results a number of derivatives. Each derivatives were interpreted through IR spectroscopy & evaluated for antimicrobial & anthelmintic activity. Antimicrobial activity was confirmed by disc diffusion methods. Minimum zone of inhibition (7 mm) was found in case of compound, 2C (*E.coli*) & Maximum zone of inhibition (14 mm) was found in case of compound 2D (*S.aureus)* followed by 12 mm in case of 2B (*E.coli*). All derivatives also found to possess anthelmintic activity when we compare with the a standard drug albendazole.

**KEYWORDS:** Derivatives, Synthetic, Disc diffusion, anthelmintic.

## INTRODUCTION

Benzimidazole nucleus are the master class among the hetocyclic nucleus. They are included in various classification of drug such as analgesic, antiulcer and antihypertensive anti-inflammatory, antibacterial, antifungal, antiviral, antianthelminitic, anticonvulsant, anticancer, antiulcer and antihypertensive etc. Systhesis of benzimidazole derivatives are

keen interest of so many because of its wide range of pharmacological activity. They are weakly basic in nature.[1]

**Objective**

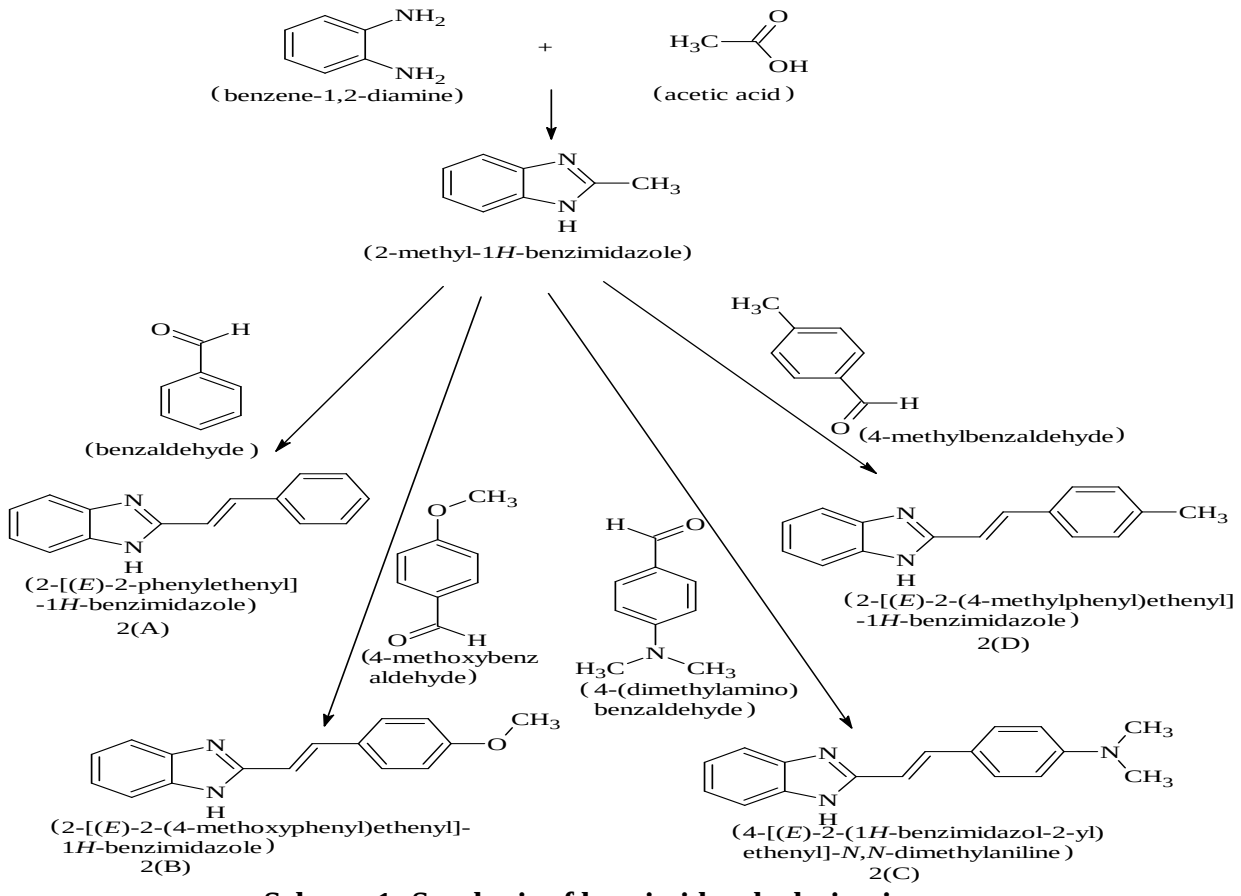
Benzimidazole is one of the well known heterocyclic nucleus. Modification in this nucleus is always interesting one. So another attempt has been made to substitute its structure by adding some extra pharmacophoric groups. Benzimidazole itself having a lot of pharmacological activity.

The main motto behind this research is to reorganise the benzimidazole nucleus in such a way that it must possess various pharmacological activity such as anti-microbial, anthelmintic etc. basing on the idea obtained from the literature survey.

**EXPERIMENTAL METHODS**

All the chemicals used are of analytical grade.

Various derivative of benzimidazole are synthesized by conventional methods as follows. (Scheme-1).




**Scheme 1: Synthesis of benzimidazole derivatives.**

**Step-I**: *O*-phenylenediamine dihydrochloride (0.03 mol), 20 ml of water, acetic acid (0.09 mol) were heated together under reflux for 45 minutes. It was cooled & the reaction mixture was made distinctly basic by the gradual addition of the concentrated ammonia solution, the precipitated product was collected and recrystallised from 10% ethanol.

**Step-II: 2(A)**: Benzaldehyde (10mmol) was added to step-1 product (1.5 g, 10 mmol) in ethanol solution of sodium hydroxide (75 mmol sodium hydroxide in 40 ml of ethanol). The reaction mixture was subsequently stirred at room temperature for 5 hr and neutralized with a solution of 30% acetic acid leading to a precipitate. It was filtered, dried and recrystallized in toluene to get the pure compound.

**Step-II: 2(B):** 4-methoxybenzaldehyde (10mmol) was added to step-1 product (1.5 g, 10 mmol) in ethanol solution of sodium hydroxide (75 mmol sodium hydroxide in 40 ml of ethanol). The reaction mixture was subsequently stirred at room temperature for 5 hr and neutralized with a solution of 30% acetic acid leading to a precipitate. It was filtered, dried and recrystallized in toluene to get the pure compound.

**Step-II: 2(C)**: 4-(dimethylamino)benzaldehyde (10mmol) was added to step-1 product (1.5 g, 10 mmol) in ethanol solution of sodium hydroxide (75 mmol sodium hydroxide in 40 ml of ethanol). The reaction mixture was subsequently stirred at room temperature for 5 hr and neutralized with a solution of 30% acetic acid leading to a precipitate. It was filtered, dried and recrystallized in toluene to get the pure compound.

**Step-II: 2(D)**: 4-methylbenzaldehyde (10mmol) was added to step-1 product (1.5 g, 10 mmol) in ethanol solution of sodium hydroxide (75 mmol sodium hydroxide in 40 ml of ethanol). The reaction mixture was subsequently stirred at room temperature for 5 hr and neutralized with a solution of 30% acetic acid leading to a precipitate. It was filtered, dried and recrystallized in toluene to get the pure compound.

**Qualitative anti microbial test:** Antimicrobial test was performed by disc diffusion method & minimum inhibitory concentration by preparation of various concentration of synthesized compound against the standard Ciprofloxacin & DMF as control.

**In-vitro anthelmintic test:** The test was performed on indian earthmorm & wormicidal activity was determined against the standard drug Albendazole.[2]

## RESULTS AND DISCUSSION

**Interpretation:** All the synthesized structure was confirmed by the IR data (Schimadzu) as follows.

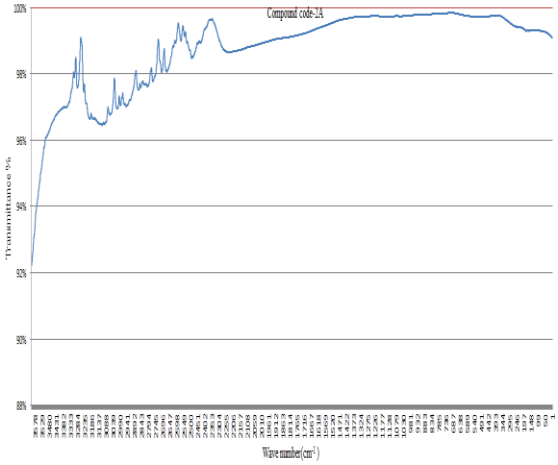



**Fig. 1: IR spectra of 2A.**

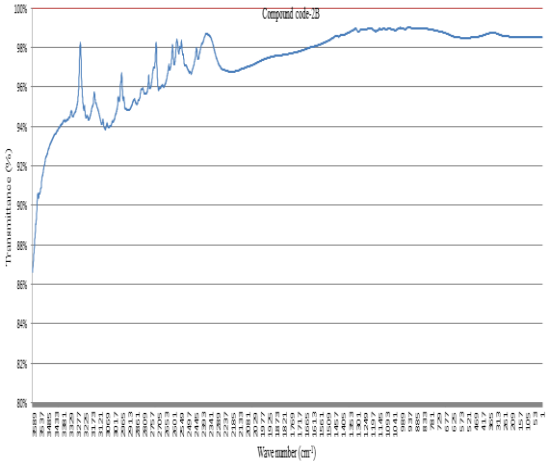



**Fig. 2: IR spectra of 2B.**

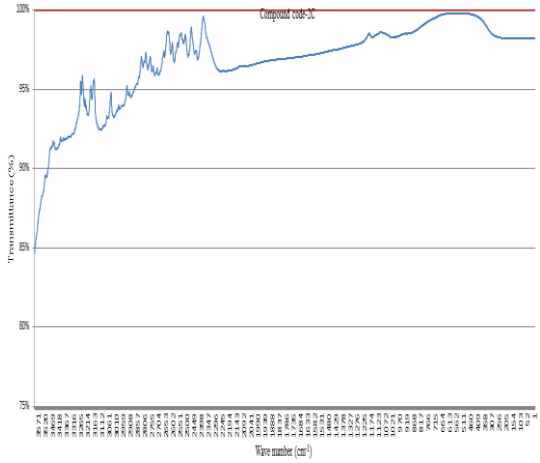



**Fig. 3: IR spectra of 2C.**

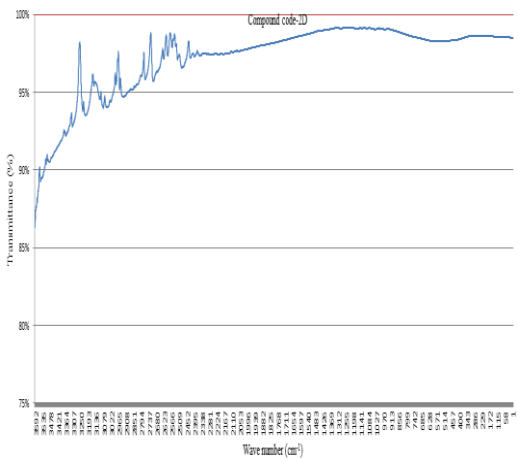



**Fig. 4: IR spectra of 2D.**

**Table 1: (Interpretation chart).**

| Comp. Code | IR DATA ($cm^{-1}$) |
|---|---|
| **2(A)** | 3480 (N-H stretching), 2243 (C=N stretching), 1680(C=C stretching), 3333(C-H stretching), 3235, 3186, 3088,3050, 3039 (C-H stretching), 2990, 2941 (C-H stretching), 2892(C-H stretching), 2843 (C-H stretching), 2796, 2745, 2690, 2598, 2549, 2500 (C-H stretching), 2255 (C=C stretching) |
| **2(B)** | 1405 (C-O stretching), 3485 (N-H stretching), 1665 (C=C stretching), 2340 (C-H stretching), 1457 (C=C stretching,aromatic), 2237 (C=N stretching), 1301 (C-O stretching), 729 (C-H bending) |
| **2(C)** | 1174,1123, 1103 (C-N stretching), 1405 (C-O stretching), 3485 (N-H stretching), 1665 (C=C stretching), 2340 (C-H stretching), 1457 (C=C stretching, aromatic), 2237 (C=N stretching), 1301 (C-O stretching), 729 (C-H bending) |
| **2(D)** | 3030 (C-H stretching aromatic), 3485 (N-H stretching), 1665 (C=C stretching), 2340 (C-H stretching), 1457 (C=C stretching,aromatic), 2237 (C=N stretching), 1301 (C-O stretching), 729 (C-H bending) |

**Table 2: (Properties of Synthesized compounds).**

| Compound code | 2(A) | 2(B) | 2(C) | 2(D) |
|---|---|---|---|---|
| **Mol. Formula** | $C_{15}H_{12}N_2$ | $C_{16}H_{14}N_2O$ | $C_{17}H_{17}N_3$ | $C_{16}H_{14}N_2$ |
| **Formula Weight** | 220.26918 | 250.29516 | 263.33698 | 234.29576 |
| **Composition** | C(81.79%) H(5.49%) N(12.72%) | C(76.78%) H(5.64%) N(11.19%) O(6.39%) | C(77.54%) H(6.51%) N(15.96%) | C(82.02%) H(6.02%) N(11.96%) |
| **Molar Refractivity** | 74.01 ± 0.3 $cm^3$ | 80.6 ±0.3$cm^3$ | 88.32 ± 0.3 $cm^3$ | 78.83 ± 0.3 $cm^3$ |
| **Molar Volume** | 178.3 ± 3.0 $cm^3$ | 202.3 ± 3.0 $cm^3$ | 216.2 ± 3.0 $cm^3$ | 194.5 ± 3.0 $cm^3$ |
| **Parachor** | 499.5 ± 4.0 $cm^3$ | 556.2 ± 4.0 $cm^3$ | 601.5 ± 4.0 $cm^3$ | 537.1 ± 4.0 $cm^3$ |
| **Index of Refraction** | 1.768 ± 0.02 | 1.729 ± 0.02 | 1.752 ± 0.02 | 1.744 ± 0.02 |
| **Surface Tension** | 61.6 ± 3.0 dyne/cm | 1.729 ± 0.02 dyne/cm | 59.8 ± 3.0 dyne/cm | 58.0 ± 3.0 dyne/cm |
| **Density** | 1.235 ± 0.06 $g/cm^3$ | 1.237 ± 0.06 $g/cm^3$ | 1.217 ± 0.06 $g/cm^3$ | 1.204 ± 0.06 $g/cm^3$ |
| **Polarizability** | 29.34 ± 0.5 $10^{-24}cm^3$ | 31.98 ± 0.5 $10^{-24}$ $cm^3$ | 35.01 ± 0.5 $10^{-24}cm^3$ | 31.25 ± 0.5 $10^{-24}cm^3$ |
| **Monoisotopic Mass** | 220.100048 Da | 250.110613Da | 263.142248 Da | 234.115698 Da |
| **Nominal Mass** | 220 Da | 250 Da | 263 Da | 234 Da |
| **Average Mass** | 220.2692 Da | 250.2952 Da | 263.337 Da | 234.2958 Da |

**Anti bacterial activity chart**

**Table 3: (Zone of inhibition chart).**

| Compound Code | Molecular formula | Zone of Inhibition (mm) | | | Zone of Inhibition (mm) | | |
|---|---|---|---|---|---|---|---|
| | | *E.coli.* conc.(µg /ml) | | | *S.aureus* conc.(µg /ml) | | |
| | | 30 | 40 | 50 | 30 | 40 | 50 |
| **2(A)** | $C_{15}H_{12}N_2$ | 8 | 10 | 11 | 8 | 9 | 9 |
| **2(B)** | $C_{16}H_{14}N_2O$ | 8 | 10 | 12 | 8 | 8 | 10 |
| **2(C)** | $C_{17}H_{17}N_3$ | 7 | 7 | 8 | 8 | 9 | 10 |
| **2(D)** | $C_{16}H_{14}N_2$ | 8 | 9 | 9 | 11 | 12 | 13 |
| **STD** | $C_{18}H_{19}FN_2O_3$ | | | 16 | | | 17 |
| **Solvent** | DMF | 0 | 0 | 0 | 0 | 0 | 0 |

**Table 4: (Evaluation Table for Anthelmintic Activity).**

| S.N | Compound Code | Concentration (µg /ml) | Time taken for paralysis | Time taken for death |
|---|---|---|---|---|
| 1 | Albendazole (Std.) | 30 | 35.43 ± 1.00 | 00.59 ± 1.16 |
| | | 40 | 30.40 ± 1.10 | 00.57 ± 1.20 |
| | | 50 | 31.50 ± 1.10 | 00.57 ± 2.50 |
| 1 | 2(A) | 30 | 36.43 ± 1.22 | 01.05 ± 1.16 |
| | | 40 | 34.40 ± 1.17 | 00.59 ± 1.21 |
| | | 50 | 31.73 ± 1.10 | 00.58 ± 2.54 |
| 2 | 2(B) | 30 | 35.30 ± 1.22 | 01.03 ± 2.14 |
| | | 40 | 33.25 ± 1.17 | 01.00 ± 1.25 |
| | | 50 | 30.50 ± 2.01 | 0.57 ± 1.50 |
| 3 | 2(C) | 30 | 29.43 ± 1.20 | 01.05 ± 2.15 |
| | | 40 | 29.45 ± 1.16 | 01.13 ± 1.24 |
| | | 50 | 28.73 ± 2.01 | 0.58 ± 1.54 |
| 4 | 2(D) | 30 | 35.43 ± 1.26 | 01.00 ± 1.16 |
| | | 40 | 34.40 ± 1.20 | 01.01 ± 1.21 |
| | | 50 | 33.75 ± 1.01 | 0.56 ± 3.54 |

Values are expressed as mean ± SEM, $n = 6$.

Various concentration of our synthesized compound (30 µg/ml, 40 µg/ml, 50 µg/ml) were tested using agar disc diffusion methods. Ciprofloxacin, sulphanilamide were used as standard & DMF as control. The zone of inhibition was measured. It was found that zone of inhibition was increased proportionately with increase the concentration of the synthesized compound. Minimum zone of inhibition (7 mm) was found in case of compound, 2C (*E.coli*). Maximum zone of inhibition (14 mm) was found in case of compound 2D (*S.aureus)* followed by 12 mm in case of 2B (*E.coli*).

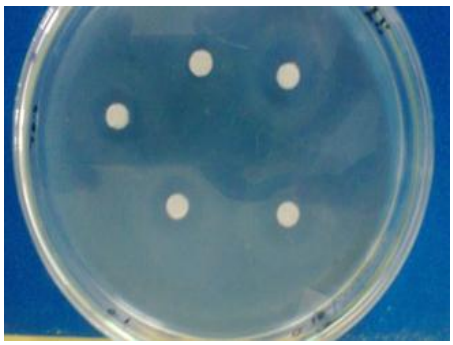


**Fig. 1: Zone of inhibition of 2D (S.Aureus).**

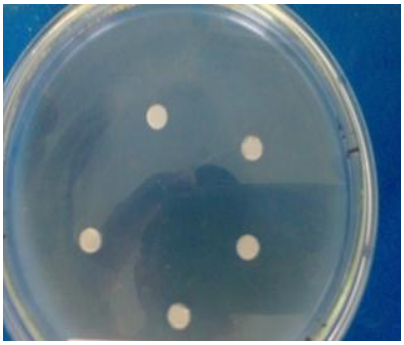


**Fig. 2: Zone of inhibition of 2C (E.Coli).**

Synthesized drugs were compared with one of the effective anthelmintic standard drug albendazole with different concentration (30 µg/ml, 40 µg/ml, 50 µg/ml). When 30µg/ml solution of the standard albendazole & our sample was tested then it was found that albendazole take 35.43 ± 1.00 min for paralysis & 00.59 ± 1.16 min for death whereas synthesized drugs (2A, 2B, 2C & 2D) at the same concentration takes 36.43 ± 1.22, 35.30 ± 1.22, 29.43 ± 1.20, 35.43 ± 1.26 mins respectively for paralysis & 01.05 ± 1.16, 01.03 ± 2.14, 01.05 ± 2.15, 01.00 ± 1.16 mins respectively for death. From this we can say that our synthesized compound has definitely some anthelmintic activity.

From above discussed matter it confirmed that all our synthesized benzimidazole derivatives have moderate antimicrobial activity as well as anthelmintic activity.

## CONCLUSION

It was enumerated that all the synthesized compound possess appreciable amount of antimicrobial & anthelmintic activity as compared to respective standard drugs. So future of this nucleus is become brighten.

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