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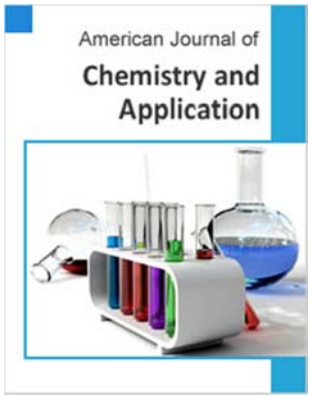

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Synthesis and Analgesic Activity Evaluation of Some New Benzimidazole Derivatives

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Abstract
A series of *N*-substituted benzimidazole derivatives (1-5) was synthesized. Benzimidazole nucleus was acylated in 1-position with benzoyl chloride in basic medium at room temperature to form *N*-acylated benzimidazole (1). Reaction of the *N*-acylated benzimidazole (1) with different amines yields the desired *N*-substituted benzimidazole derivatives (2-5). All the synthesized compounds (1-5) were evaluated *in vivo* for analgesic activity by acetic acid induced writhing and hot plate tests in mice. In comparison to the standard drug aspirin at the same dose (50mg/kg), compound 4 was the most potent as it decreased the number of writings to 17% comparing to control. However, aspirin resulted in a decrease equal to 12% of the control. In addition, all the test compounds except 5 produced some reduction in reaction time for hot plate test. Markedly, the effect was statistically significant with compounds 3 and 4.

1. Introduction

Benzimidazole nucleus is a constituent of many bioactive heterocyclic compounds that are of wide interest because of their diverse biological and clinical applications [1]. This interest in benzimidazole chemistry has been increased by the discovery that the 5, 6-dimethylbenimidazole moiety is part of chemical structure of vitamin B12 [2]. This created interest for researchers who have synthesized variety of benzimidazole derivatives and screened them for their various biological activities [3-7]. Recent review revealed that compounds containing benzimidazole nucleus exert remarkable biological and pharmacological activities. Such activities include anticancer, antimicrobial, antitubercular, antimalarial, antiprotozoal, antiviral, antidiabetic, antihistaminic, anticonvulsant, anti-HIV, antihypertensive, antioxidant, and antiulcer [8]. Analgesic and anti-inflammatory activities of various benzimidazole derivatives were also reported in the literature [9-13].

2. Experimental Procedure

A series of *N*-substituted benzimidazole derivatives were synthesized to determining their analgesic activity. The new *N*-substituted benzimidazole derivatives were synthesized from benzimidazole and benzoyl chloride to produce compound (1). The reaction of compound (1) with various appropriate amines produces the desired compounds (2-5).

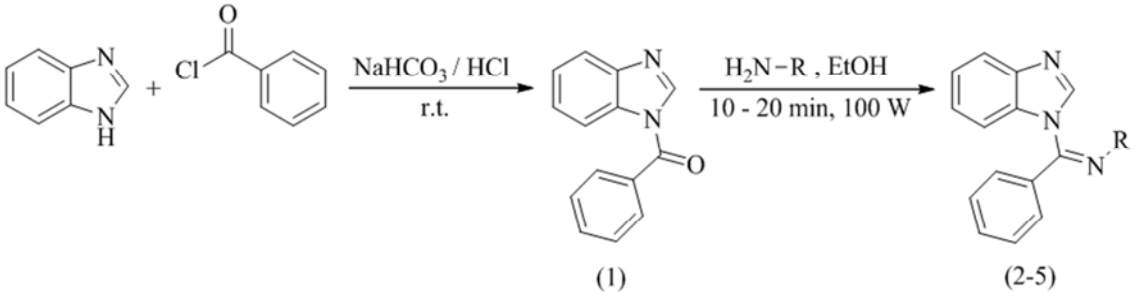


Figure 1. *The synthetic pathways for preparation of the compounds (1-5).*

3. Materials and Methods

All reagents and solvents used in this work were purchased from Merck and Sigma Aldrich. The melting points were determined in open capillary tubes on Buchi B-540 Laboratories melting point apparatus and were uncorrected. The purity of the synthesized compounds was confirmed by TLC using silica gel Aluminum sheets as stationary phase (60 F254). The IR spectra were recorded in potassium bromide on a Victor 22/Varian FT-IR spectrometer.

3.1. Synthesis of (1*H*-Benzimidazol-1-yl) (Phenyl) Methanone (1) [14]

4.23 mmol (0.5 g) of benzimidazole was dissolved in 10 mL of 10% sodium hydrogen carbonate and 1 mL of benzoyl chloride was added. The reaction mixture was shaken vigorously in a stoppered test tube at room temperature for approximately 20 min. The mixture was then acidified with 1N hydrochloric acid and filtered by vacuum pump. The product was dried and recrystallized from ethanol.

3.2. General Method for Synthesis of Compounds (2-5) [15]

The compounds 2, 3, 4 and 5 were prepared by mixing compound 1 (4 mmol, 0.89 g) with 3-amino-1, 2, 4-triazole, 4-aminophenazone, 4-aminoazobenzene and 4-aminobenzoic acid (4 mmol) respectively in 30 mL ethanol. The mixture was irradiated in domestic microwave at (100 watt) for 10 min (20 min for compound 4). After completion of the reaction, the final product was filtered off, dried and recrystallized from ethanol and petroleum ether.

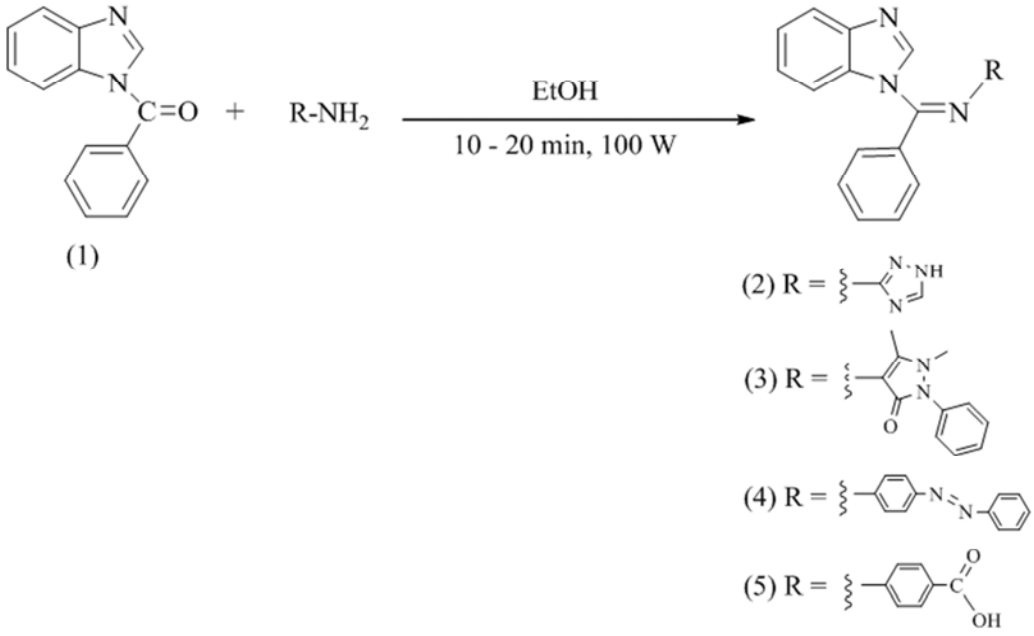


Figure 2. *The synthetic scheme for preparation of the compounds (**2-5**).*

4. Pharmacology

4.1. Animals

Male Albino mice were used for different experiments. Animals were bred in the animal house of Tripoli University, each group consisted at least of 4 animals, was housed separately in a cage. Standard food pallet diet and water were available ad lib. The animals were kept at constant room temperature (20-25°C), with 12 hours dark/light cycle. All the experiments in this article were approved by institutional animal ethical committee (IAEC).

4.2. Drug Administration

Test drugs were suspended in 1% w/v carboxymethylcellulose. Control and test animals (n ≥4) were injected intraperitoneally either by test drug or vehicle control in dose 50mg/kg and volume of 1mL/100g. Tests for analgesic activity were performed 30 minutes after drug administration.

4.3. Hot Plate Method

The animals were placed on hot plate at 55-56°C. End point was recorded when the animal licked its four-limbs or jumped out of the plate. The cut-off time of the experiment was 30 seconds [16].

4.4. Induction of Pain by Acetic Acid

Albino mice (treated and control groups) were injected intraperitoneally with 1mL/100g of 3% acetic acid, the number of writhings was recorded for a period of 10 minutes ignoring the period of first 10 minutes after injection of acetic acid [17].

4.5. Statistical Analysis

Generated data were statically assessed using ANOVA test using SPSS package (v16.0), followed by *post hoc* test (Bonferroni or Dunnett) to test significance between the vehicle and treated groups. Data was statistically significant if p value was ≤0.05.

5. Results and Discussion

5.1. Chemistry

In the present study, new N-substituted benzimidazole derivatives (1-5), have been synthesized. The synthetic pathway for preparation of the desired products listed in table 1 is shown in figure 1. Compound 1 was prepared in 94.5% yield by acylation of benzimidazole in 1-position with benzoyl chloride in basic medium at room temperature following the reported procedure [14].

Treatment of *N*-acylated benzimidazole (1) with 3-amino-1, 2, 4-triazole, 4-aminophenazone, 4-aminoazobenzene and 4-aminobenzoic acid (4 mmol) respectively in ethanol under microwave conditions gave the corresponding substituted benzimidazole derivatives (2-5) (figure 2) in 30-43%. Their structures were confirmed by IR spectra and their physicochemical parameters are given in Table 1.

Table 1. *Physicochemical properties of the newly synthesized compounds (1-5).*

Comp. Nr	M. Formula (M. Wt)	R_f	m.p. (°C)	Yield (%)	IR spectral data (ν cm^{-1})
1	$C_{14}H_{10}N_2O$ (222.24)	0.64	318–319	94.5	ν (cm^{-1}) = 1670 (C=O), 3234, 3293 (C-H), 1481, 1507 (C=C), 1279 (C-N).
2	$C_{16}H_{12}N_6$ (288.31)	0.37	292–293	43	ν (cm^{-1}) = 1690 (C=N imine), 3000 (C-H), 1430, 1526 (C=C), 3300 (N-H).
3	$C_{25}H_{21}N_5O$ (407.47)	0.29	193–194	32.5	ν (cm^{-1}) = 1584 (C=N imine), 3051, 3185 (C-H), 2872 (C-H) 1485 (C=C), 1719 (C=O), 1317 (C-N).
4	$C_{26}H_{19}N_5$ (401.46)	0.51	114	42.5	ν (cm^{-1}) = 1603 (C=N imine), 3053 (C-H), 1503 (C=C), 1401 (N=N), 1300 (C-N).
5	$C_{21}H_{15}N_3O_2$ (341.36)	0.31	265–266	30	ν (cm^{-1}) = 1520 (C=N imine), 3003 (C-H), 1601, 1625 (C=C), 1691 (C=O), 3309 (O-H), 1313 (C-N).

5.2. Pharmacology

Table 2. *Peripheral analgesic activity results.*

Treatments	Number of writhing
control	51.2 ± (6.5)
Test compound 1	22.1* ± (4.2)
Test compound 2	18.5* ± (6.6)
Test compound 3	13.25* ± (4.6)
Test compound 4	9* ± (2.8)
Test compound 5	14.5* ± (3.5)

Values in the table mean ± standard deviations.

The investigated compounds 1-5 were assessed on the behavioral animal tests based on the reactivity to pain stimulus using thermally induced pain by hot plate method and chemically induced pain by acetic acid. The results are shown in tables 2 and 3.

Table 3. *Effect of test drugs on hot plate time.*

Treatments	Reaction time
control	7.9±1.3
Test compound 1	7.8± (2.7)
Test compound 2	6.5± (1.3)
Test compound 3	5.7± (1.2)
Test compound 4	5.5* ± (1.1)
Test compound 5	7.4* ± (3)

Values in the table mean ± standard deviations

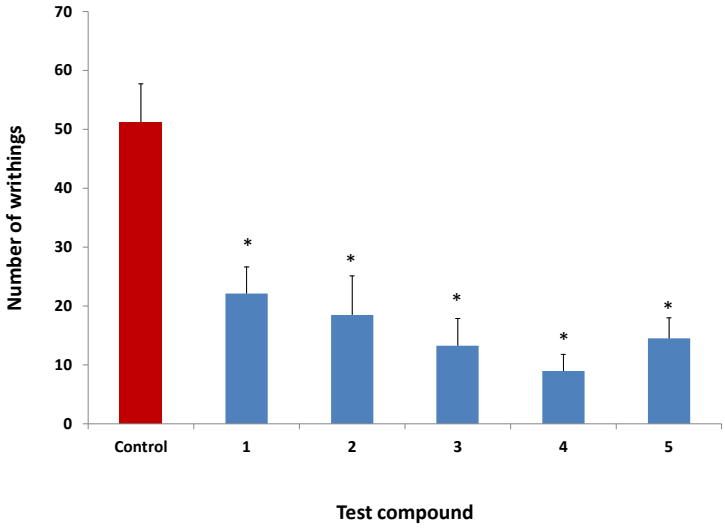


Figure 3. *Effect of test drugs on chemically induced pain by acetic acid.*

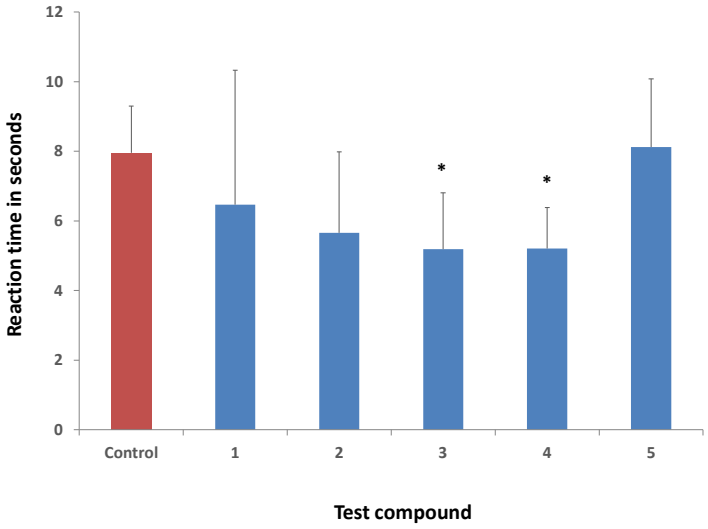


Figure 4. *Effect of test drugs on thermally induced pain by hot plate.*

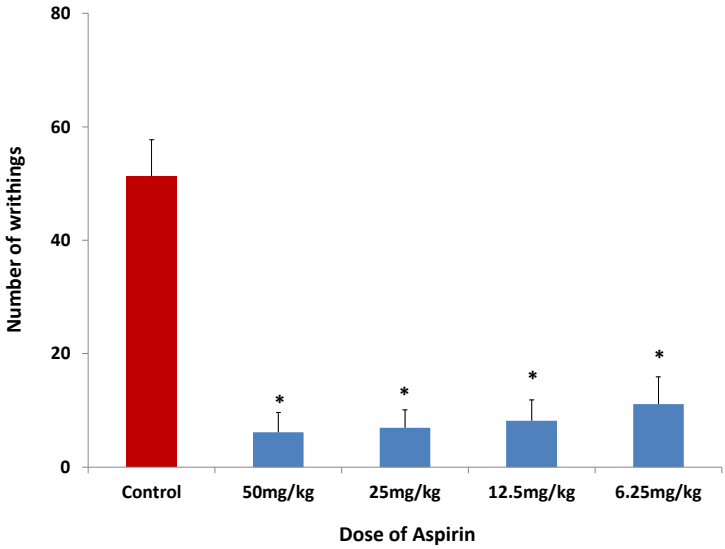
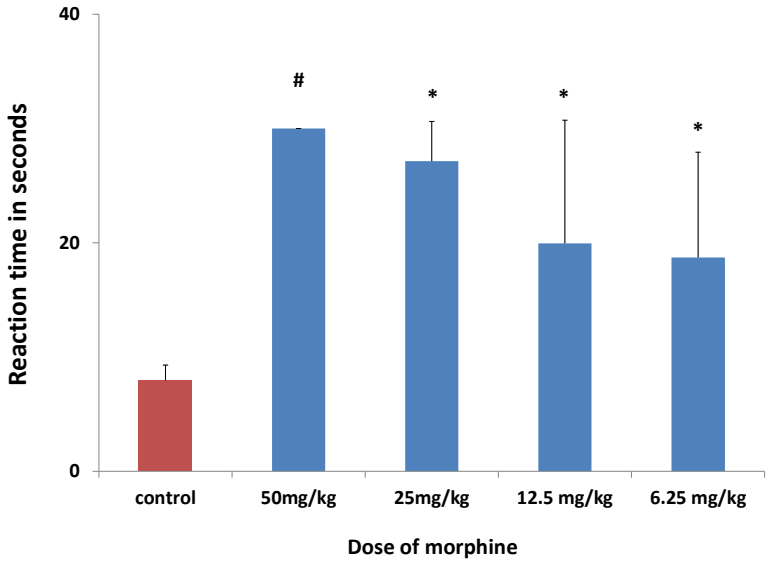


Figure 5. *Effect of aspirin on acetic acid induced pain.*



[#] means the reaction time was longer than 30 seconds.

Figure 6. *Effect of morphine on thermally induced pain.*

In the present work, 5 newly synthesized benzimidazole derivatives were investigated for analgesic activity. The pilot analgesic activity screening was undertaken using two models to generate pain. Chemically induced pain generated by acetic acid to asses any action similar to peripherally acting analgesics [17, 18]. The hot plate test model was used to investigate the central analgesic activity of the tested compounds.

All tested benzimidazole derivatives caused significant decreases in the number of writhings after acetic acid injection (figure. 3). The possible activity concluded from acetic acid test led us to carry out a comparative study to the classical non steroidal anti-inflammatory drug (NSAID) aspirin [19]. At 50 mg/kg dose, the tested benzomidazole derivatives 1, 2, 3, 4 and 5 produced inhibiting activity for writhing of 27, 32, 46, 67 and 42% respectively in comparison to aspirin at the same doses. Therefore these compounds might retain activity similar to NSAID [20]. On the other hand none of the compounds under test showed any noticeable increase in hot plate test, except compound 5 which resulted in some non-significant increase. Nevertheless, apart from compound 5, all the compounds produced some reduction in reaction time for hot plate test (figure. 4), which excludes the centrally acting analgesic activity of these compounds. A group of animals were treated with various doses of morphine in order to serve as a standard and positive control for hot plate test (figure. 6).

6. Conclusion

New *N*-substituted benzimidazole derivatives were synthesized and tested for analgesic activity. These newly synthesized benzimidazole derivatives seemed to have NSAIDs like activity, so further investigations are needed to identify the mechanism of action. Also studying the anti-inflammatory activity of these compounds possibly could lead to positive results as many drugs share both analgesic and anti-inflammatory activity.

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