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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME BENZIMIDAZOLE DERIVATIVE WITH IBUPROFEN

K. Seiyadu Ibrahim*[1] and Jesima Begum [2]

King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia
Periyar College of Pharmacy [2], Trichy, India, India

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Correspondence to Author:

K. Seiyadu Ibrahim

Clinical Pharmacist, King Khalid Hospital, Riyadh, Kingdom of Saudi Arabia

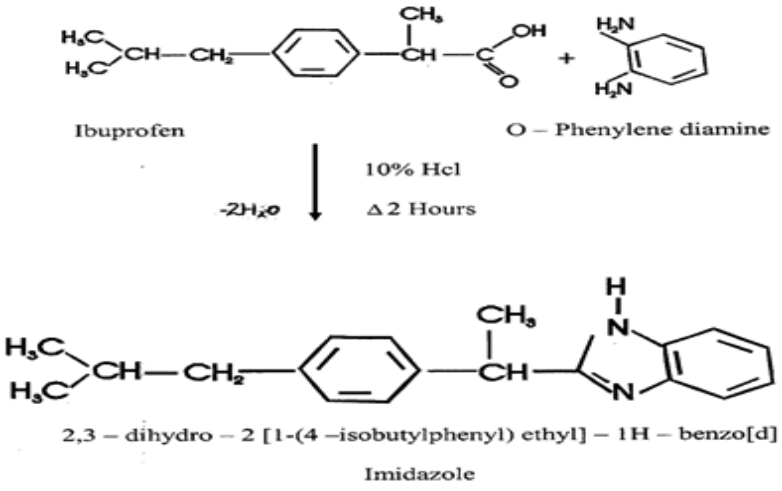
ABSTRACT

Some novel benzimidazole derivatives were synthesized with ibuprofen and evaluated for its activity. This compound showed notable antibacterial activity against gram-positive organisms and antifungal activity against when compared with respective standards.

INTRODUCTION: Benzimidazole nucleus is an important heterocyclic ring, because of its synthetic utility and broad range of pharmacological activities. Some benzimidazole derivatives with different pharmacological effects, including antifungal [1], anti-helmintic [2], anti-HIV [3], antihistaminic [4-6], antiulcer [7, 8], cardio tonic [9], antihypertensive [10, 11] and neuroleptic [12], are in clinical use. In order to obtain more effective chemotherapeutic agents, a variety of reports have been presented on the synthesis and biological evaluation of new benzimidazole derivatives [13]. Many reports have revealed that the influence of the substitution at the 1, 2 and 5 positions of the benzimidazole ring is very important for their pharmacological effects [14, 15]. 2-(substituted phenyl)-benzimidazoles with various types of biological activities, such as antibacterial 16, antiviral [17], antitumoral [18, 19] and anti-inflammatory [20], has been reported. Ibuprofen [21] having analgesic and anti-inflammatory based on the reference Ibuprofen undergoes reaction with O-phenylenediamine and replace the -OOH group in the presence of dilute hydrochloric acid. In connection with these studies, a series of some novel Benzimidazole derivatives with Ibuprofen was prepared with the corresponding O-phenylenediamines for evaluation of their biological activities.

Experimental: All melting points were determined using a Buchi SMP-20 melting point apparatus and were uncorrected. IR spectra were recorded on a Jasco FT/IR 420 spectrophotometer as potassium bromide disks (**fig. 1a & 1b**). 1H NMR analyses were performed with a Bruker AC400NMR spectrometer (**fig. 2a & ab**). Silica gel plates (Merck F254) and silica gel 60 (Merck; 230-400 mesh ATSM) were used for analytical and column chromatography, respectively. The Ibuprofen, Hydrochloric acid, Sodium hydroxide and Ethanol and O-Phenylenediamine used in this study were purchased from Aldrich Chemical Company.

Synthesis of 2, 3-dihydro -2-[1-(4-isobuty1 phenyl) ethyl]-lH benzo [d] Imidazole: A mixture of 1.08gm (0.lmole) of O-Phenylene diamine, 2.06gm (0.1 mole) of Ibuprofen, 5ml of dilute hydrochloric acid were taken into a 250ml round bottomed flask. And the mixture was heated on a water bath at 100°C for two hours, then it was cooled and 10% sodium hydroxide solution was added slowly with constant whirling of flask, until the mixture was just alkaline to litmus, filtered the crude product with the pump, washed with ice cold water, drained well and washed again with ice cold water and dried. The yield of the product was found to be 2 gm, and the melting point was 235°C with decomposition (**scheme 1**).



SCHEME 1: SYNTHESIS OF THE COMPOUND 2, 3-DIHYDRO-2-[1-(4-ISOBUTY1 PHENYL) ETHYL]-LH BENZO [D] IMIDAZOLE

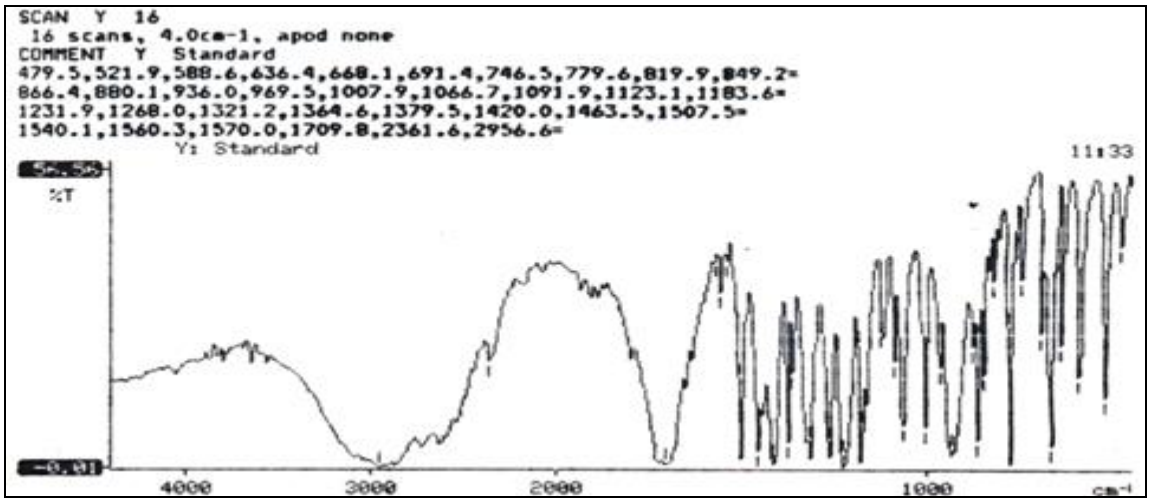


FIG. 1a: IR SPECTRAL ACTIVITY STANDARD IBUPROFEN (Y)

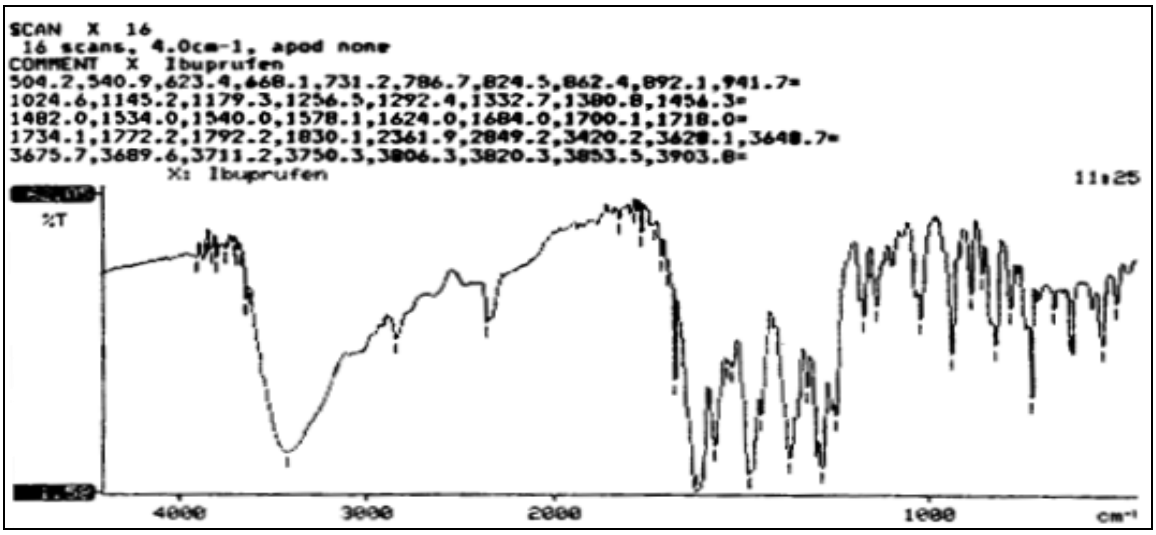


FIG. 1b: IR SPECTRAL ACTIVITY OF SYNTHESIZED COMPOUND

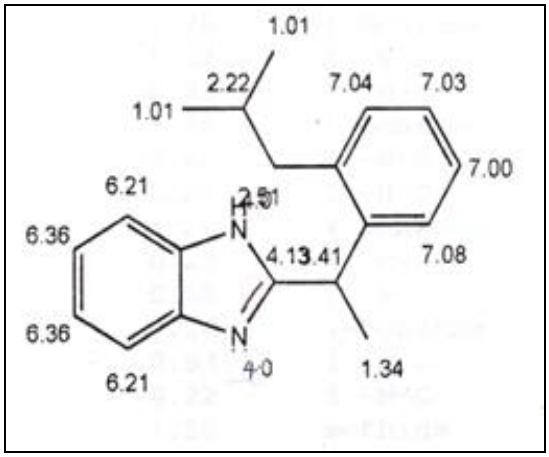


FIG. 2a: CHEM NMR H-1 ESTIMATION

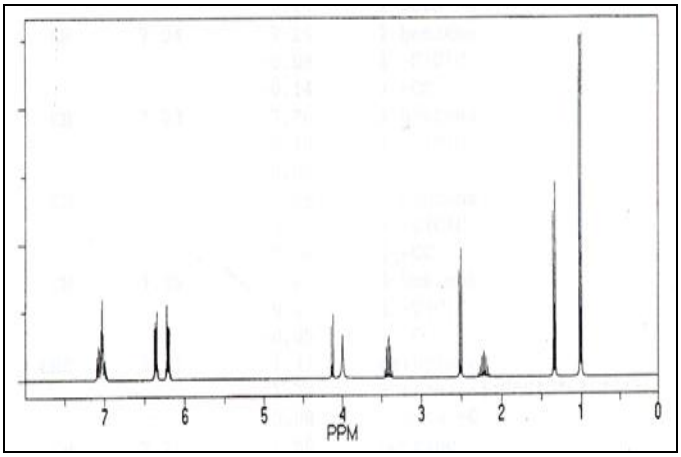


FIG. 2b: ESTIMATION QUALITY: BLUE- GOOD, MAGENTA-MEDIUM, RED- ROUGH

Antimicrobial activity: The in vitro antimicrobial activity of the compounds was tested by the tube dilution technique [4]. Test and reference compounds (Amikacin, Ampicillin trihydrate, Flucanazole and Cotrimoxazole) were dissolved in 12.5% DMSO, at concentrations of 200 mg/ml, further dilutions of the compounds and standards in the test medium were prepared at the required concentrations of 100, 50, 25, 12.5, 6.25, 3.12, 1.56, 0.78 mg/ml. The final inoculum size was 10 CFU/ml. The minimum inhibitory concentrations (MIC) were defined as the lowest concentrations of the compounds that prevented visible growth. It was determined that the solvent had no antimicrobial activity against any of the test microorganism. All the compounds were tested for their in vitro growth inhibitory activity against *Staphylococcus aureus* ATCC 250, *Pseudomonas aeruginosa* ATCC 25619, *Klebsilla pneumoniae* ATCC 10031 as Gram positive and *Escherichia coli* RSKK 313 as Gram negative bacteria and a fungus *Candida albicans* RSKK 628. MIC values have new and reference compounds are presented in **Table 1**.

TABLE 1: **ANTIMICROBIAL ACTIVITIES OF THE SYNTHESIZED COMPOUND**

Compound	*C. albicans*	*S. aureus*	*K. aerugenes*	*P. aerugmosa*	*E. coli*
2,3-dihydro -2-[1-(4-isobuty1 phenyl) ethyl]-lH benzo [d] Imidazole	25	50	25	50	100
Ampicillin	Not tested	6.25	12.5	6.25	3.125
Amikacin	Not tested	25	12.5	12.5	6.25
Cotrimoxazole	25	Not tested	Not tested	Not tested	Not tested
Fluconazole	50	Not tested	Not tested	Not tested	Not tested

* Minimum inhibitory concentration

Antibacterial Activity Assay: The cultures were obtained in Mueller-Hinton Broth (Difco) for all the bacteria after 18–24 h of incubation at 37.91^{o}C. Testing was carried out in Mueller-Hinton Broth at pH- 7.4 and two-fold dilution technique was applied. A set of tubes containing only inoculated broth was kept as controls. After incubation for 18-24 h at 37.91^{o}C, the last tube with no growth of microorganism was recorded to represent MIC expressed in mg/ml.

Antifungal activity assay: The yeast *C. albicans* was maintained in Sabouraud Dextrose Broth (Difco) after incubation for 48 h at 25.91^{o}C. Testing was performed in Sabouraud Dextrose Broth at pH 7.4 and the two-fold dilution technique was applied. A set of tubes containing only inoculated broth was kept as controls. After incubation for 48 h at 25.91^{o}C, the last tube with no growth of yeast was recorded to represent MIC expressed in mg/ml.

RESULTS AND DISCUSSION: 2, 3-dihydro -2-[1-(4-isobuty1 phenyl) ethyl]-lH benzo [d] Imidazole (Scheme 1) was synthesized from ibuprofen and O-Phenyl diamine by hydrolysis [22]. The amine group of O-Phenyl diamine was coupled with ibuprofen. In these reaction two molecules of water has been released in presence of catalyst Hydrochloric acid and heating. IR spectral data of synthesized compound has been explained in **table 2** and protocol of the H-1 NMR prediction in **table 3.** Compound 2, 3-dihydro -2-[1-(4-isobuty1 phenyl) ethyl]-lH benzo [d] Imidazole was evaluated for its antimicrobial activity against *S. aureus*, *E. coli, K. aerugenes, P. aerugmosa* and *C. albicans* by tube dilution technique. Its antibacterial and antifungal activities were determined as MIC values. **Table 1** shows the results of *in vitro* activity determination by a tube dilution method. The synthesized compound showed better activity than fluconazole against *C. albicans* and equal to that of Cotrimoxazole**.**

TABLE 2: IR SPECTRAL DATA OF SYNTHESIZED COMPOUND

Frequency in cm^{-1}	Types of vibration
3675.7	N-H stretching vibration
1798.2 -1734.1	Saturated, aryl acyclic
1700.1	Aryl
1684.0	C = N–stretching vibration
1624.0	N=N –stretching vibration
1578.1 -1540	N-H Binding
1292.4	C –N stretching
892.1	C-C bending [Aromatic]

TABLE 3: **PROTOCOL OF THE H-1 NMR PREDICTION**

Node	Shift	Base + Inc.	Comment (ppm rel. to TMS)
CH	4.13	1.50 2.26 0.38 -0.01	Methine 2 alpha – N 1 beta – 1: c*c*c*c*c*c* 1 1 beta –c
NH	4.0	4.00	aromatic c-NH
NH	4.0	4.00	aromatic c –NH
CH	6.21	7.26 -0.22 -0.86	1 – benzene 1 – N-c 1 – N-c
CH	6.36	7.26 -0.68 -0.22	1 – benzene 1-N-c 1-N-c
CH	6.36	7.26 -0.22 -0.68	1- benzene 1-N-c 1-N-c
CH	6.21	7.26 -0.83 -0.22	1-benzene 1-N-c 1-N-c
CH	3.41	1.50 0.17 1.28 0.46	methine 1 alpha –c 1 alpha -1:c*c*c*c*c*c* 1 2 beta –N
CH3	1.34	0.86 0.38 0.10	methyl 1 beta -1:c*c*c*c*c*c* 1 1 beta –c-R
CH	7.04	7.26 -0.08 -0.14	1 – benzene 1-c (c) c 1-cc
CH	7.03	7.26 -0.18 -0.05	1- benzene 1-c (c) c 1- cc
CH	7.00	7.26 -0.08 -0.18	1- benzene 1-c (c) c 1- cc
CH	7.08	7.26 -0.13 -0.05	1-benzene 1-c (c) c 1- cc
CH2	2.51	1.37 1.22 -0.08	Methylene 1 alpha -1:c*c*c*c*c*c*1 2 beta –c
CH	2.22	1.50 0.34 0.38	Methane 2 alpha –c 1 beta -1:c*c*c*c*c*c*1
CH3	1.01	0.86 0.10 0.05	Methyl 1 beta –c-R 1 beta –c
CH3	1.01	0.86 0.10 0.05	Methyl 1 beta –c-R 1 beta –c

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