Al-Qadisiyah Journal of Pure Science

Volume 27 | Number 1 Article 26

2022

Synthesis and Characterization of New benzimidazole-nitrone Derivatives and Study of Their Effect as Anti-fungal

Meaad A. Fadel
Department of chemistry, College of Science, University of Basrah, Iraq, meaad.fadel@uobasrah.edu.iq

Dawood S. Ali
Department of chemistry, College of Science, University of Basrah, Iraq, dawood.ali@uobasrah.edu.iq

Hanaa K. Mousa
Department of chemistry, College of Science, University of Basrah, Iraq, hanan.mousa@uobasrah.edu.iq

Al-Qadisiyah Journal of Pure Science
ISSN(Printed): 1997-2490 ISSN(Online): 2411-3514
DOI:10.29350/2411-3514.1222
https://qjps.researchcommons.org/home/vol27/iss1/26

Synthesis and Characterization of New benzimidazole-nitrone Derivatives, and Study of Their Effect as Anti-fungal

Authors Names

Meaad A. Fadel[1], Dawood S. Ali[2] , Hanaa K. Mousa[3]

Keywords: Benzimidazole, nitrone, candida and aspergillus fungi, anti-fungal

ABSTRACT

New benzimidazole derivatives (benzimidazole-nitrone) were synthesized from the condensation of o-phenylene diamine with p-amino benzaldehyde in the presence of (P-TSOH\EtOH) then the benzimidazole compounds that containing an imine group were oxidized to obtain a nitrone group by used peracetic acid and identified by FT-IR, H1-NMR spectra, and elemental analysis. all compounds applied to the candida and aspergillus fungi gave a different result. The compounds have Ph, OH and N(CH3)2 groups as substituted in synthesized benzimidazole derivatives were showed reactivity as anti-fungal.

Introduction

The heterocyclic compounds have vital for life cycle and greatly dispersed in the natural world. The major role have been performed through heterocyclic compounds in the metabolism of all the live cells. A nitrogen built heterocyclic compound be significant position intended for manhood. Specifically, benzimidazole have the enormous significance not just biologically but also industrially as well as a whole nitrogen built heterocyclic compound. First benzimidazole derivative have created by Hobrecker in 1872[1].

[1,2,3]Department of chemistry/ College of Science/ University of Basrah/ Iraq

[1]meaad.fadel@uobasrah.edu.iq [2]hanan.mousa@uobasrah.edu.iq [3]dawood.ali@uobasrah.edu.iq

lately, the occurrence of general fungal contamination have grown into an significant complications and the eloquent effect of trouble and fatal accident in immune - compromised persons for example patient role that take off by anticancer chemotherapy or organs implants. benzimidazole have developing the original option for investigators and scientists In neoteric therapeutic chemistry and drug projection [2,3], because of its probable biological activity [4].

generality, the benzimidazole derivatives have recognized for its various valuable functions for example anti-inflammatory [5– 7] anti-bacterial [8–12] anti-fungal [13–16] anti-oxidant [17–22] anti-malarial [23], anti-cancer [24,25], anti-parasitic [26].

the benzimidazole ring system is to some extent popular at heterocyclic pharmacophore. That substructures have oftentimes known as ‘privileged’ because its diverse repetition in bioactivity compounds. In addendum, there are considerable confession used for benzimidazole ligand and its structural chemistry compounds, A prime concentrate is their biological activities. Benzimidazole medications shows abroad domain of various groups of biological activities because the exchanging substitution groups in main structure. In the pharmaceutical, veterinary and agrochemical fields, plentiful derivative of benzimidazole have taken to well-lit containing misonidazole, cimetidine, antihistamines, clotrimazole,azomycin, thiabendazole, omeprazole, misonidazole and astemizole. [27,28]

Anti-fungal

the fungus has slightly associate of a group of the eukaryotic organisms which contains microorganisms for example yeast and mold, in addition of the more familiar mushroom. That organisms have ordered as a kingdom, distinctly from other eukaryotic kingdoms, Plantae, Animalia, Protozoa, and Chromista[29] . Fungi were in all places. From time to time, they are too small to see with the nude eye. Fungi live in many places with the human, it coexists outdoors on plants or people's skin and inside the body or indoors on surfaces and air, figure (1) [30]:

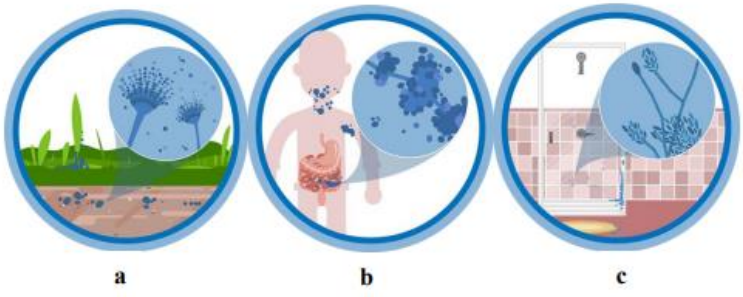


Figure (1): Fungus areas: (a) Outdoors, (b) On people’s skin, (c) Indoors, on surfaces.

There are millions of fungal species, but only a few hundred of them can make people sick. The most common fungal diseases came from candida and aspergillus fungi [31].

Materials and Methods:

The melting point was measured with the Electrothermal Melting Point apparatus. Infra-red spectra were recorded using (KBr disk) on Shimadzu FT-IR-8300 Spectrophotometers in Basrah University, Science college, Chemistry department. H^1-NMR spectra were measured in Tehran University (IRAN) on Avance DRX 500 MHz (from Bruker), using dimethylsulphoxide (DMSO) as internal standards.

Preparation of benzimidazole

(1 mmol) 1,2-diaminobenzene with aromatic aldehydes (2 mmol) in presence of p-TsOH in abs.ethanol. After 6 hours the product isolated by filtration and washed with ethanol and was recrystallized by mixture from DMF and ethanol. [32]

preparation of Schiff base

(0.01 mol) of amine dissolve in ethanol abs. in 100 ml conical flask stirring at room temperature. And then add a solution of aldehyde (0.01 mol) with ethanol abs. and continued to stirrer then the product precipitate over (30 min) as a powder. the product isolated by filtration and washed with small quantities of ethanol abs. to remove any remained starting materials. The product have recrystallized by ethanol abs. [33]

preparation of nitrone

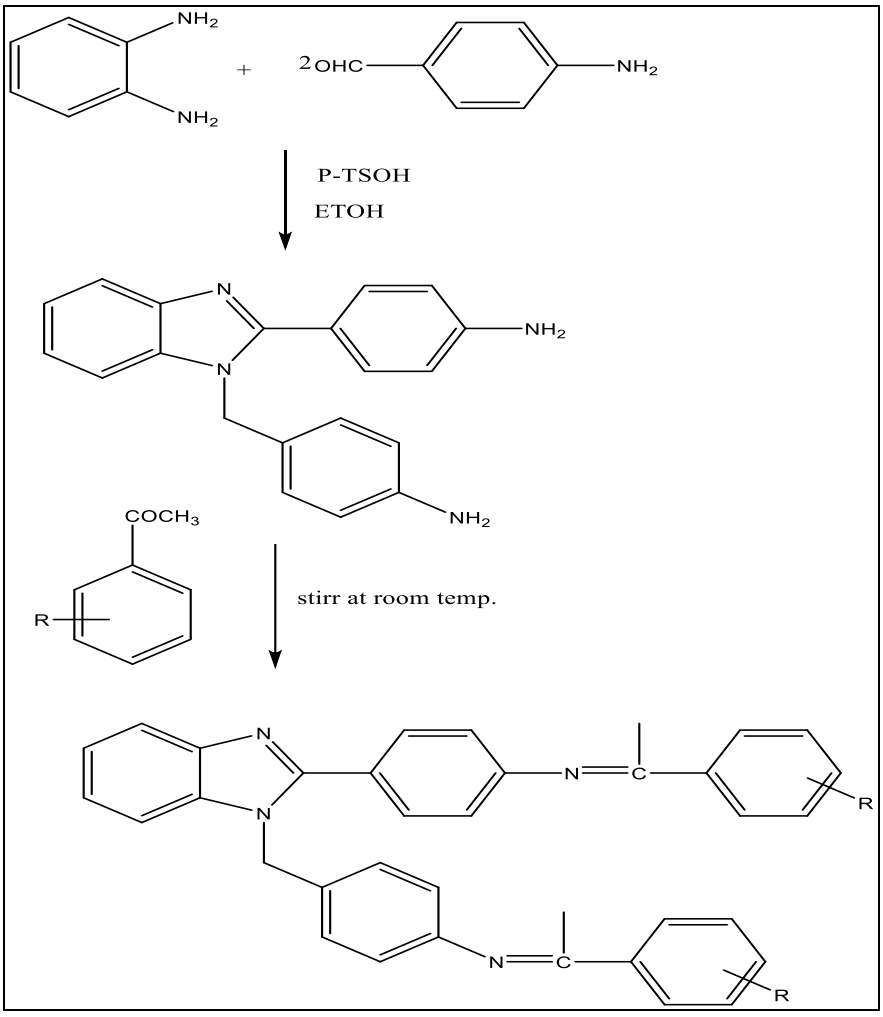
(0.00422 mol) of Schiff bases was add to a mixture of (2.282mL) of H_2O_2% 36 and (5.08ml) of acetic acid glacial in a round. It reacted severely with the emission of intense heat and was left to stir in an ice bath for (6 h). And then leave the output for (24 h) at (0 C^0). [34]

Test- antifungal [35]:

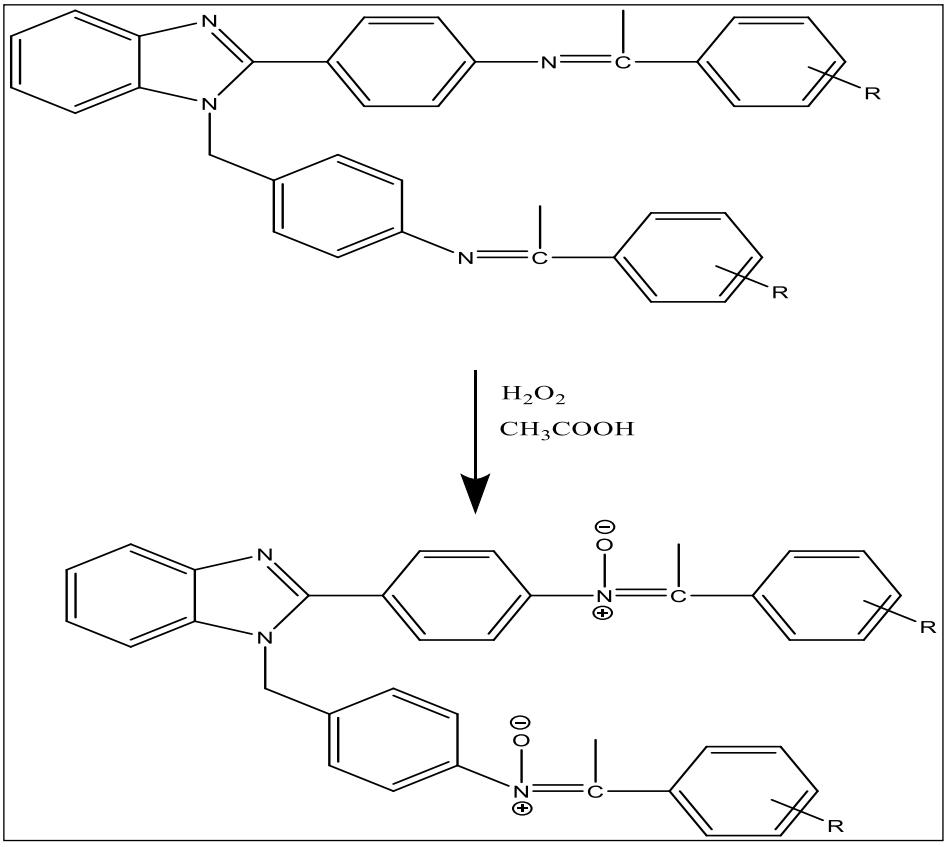
anti-fungal activity for samples have assayed by the fungi screening through the diffusion technique in the PDA growing medium . A fungal suspension were standardized to (10^6 conidia/mL) in the sterile saline solution (0.85%), and (100 µL) of each fungal suspension were feast into the surface of Petri dish. Then after (10 min) of relaxation, (6-mm) diameter holes have pressed and full with (50 µL) of the beforehand prepared excerpt sample. As regulator sample for all experiments, DMSO, hydroethanolic solution were used at (70%) and a fungicide tebuconazole (TEB) were used at (0.1%). Afterward, A plates have incubated at (28 ± 2) °C. Each excerpt form have assessed with three repetition. An assessment have conducted after about (72 h) through measurement the diameter of inhibition of a fungi growth (inhibition formed of clear zone round have reflected revealing for anti-fungal activity).

Results and discussion:

the treatment of o-phenylenediamine (1 mmol) with aromatic aldehydes (2 mmol) in the presence of 5 mol% of p-TsOH in absolute ethanol resulted in the formation of 2-aryl 1-arlymethyl-1H-benzimidazole [36] as showe in scheme (1)


NH2
NH2
+
2OHC
NH2
P-TSOH
ETOH
N
N
NH2
NH2
COCH3
R
stirr at room temp.
N
N
N
C
R
N
C
R

The benzimidazole compounds containing an imine group were oxidized to obtain a nitrone group by used peracetic acid. The reaction occurs by attacking the free electron pair of the imine group on the acid oxygen, forming the nitrone group [37], as shown in scheme (2)



The physical properties are shown in (Table1). The products were characterized by infra-red (Table2), H-NMR (Table3), and elemental analysis (Table 4).

Table (1) physical properties of synthesized compounds.

No. of comp.	IUBAC name	M.P. C^0	Color	M.wt	Yield %
3 (R=H)	(Z)-N-(4-(1-(4-(oxido((Z)-1-phenylethylidene)azanyl)benzyl)-1H-benzo[d]imidazol-2-yl)phenyl)-1-phenylethan-1-imine oxide	102-104	Light green	550	50
4 (R=OH)	(Z)-1-(4-hydroxyphenyl)-N-(4-(1-(4-(((Z)-1-(4-hydroxyphenyl)ethylidene)oxidoazanyl)benzyl)-1H-benzo[d]imidazol-2-yl)phenyl)ethan-1-imine oxide	132-133	Yellow	582	52
5 (R=N(CH_3)$_2$	(Z)-1-(4-(dimethylamino)phenyl)-N-(4-(1-(4-(((Z)-1-(4-(dimethylamino)phenyl)ethylidene)oxidoazanyl)benzyl)-1H-benzo[d]imidazol-2-yl)phenyl)ethan-1-imine oxide	161-163	Brown	636	41
9 (R=F)	(Z)-1-(4-fluorophenyl)-N-(4-(1-(4-(((Z)-1-(4-fluorophenyl)ethylidene)oxidoazanyl)benzyl)-1H-benzo[d]imidazol-2-yl)phenyl)ethan-1-imine oxide	151-154	Black	586	53
10 (R=CH_2-Ph-Cl)	(Z)-1-(4-chlorophenyl)-N-(4-(1-(4-(((Z)-1-(4-chlorophenyl)ethylidene)oxidoazanyl)benzyl)-1H-benzo[d]imidazol-2-yl)phenyl)ethan-1-imine oxide	175-178	Yellow	619	45

FT-IR spectral data:

The spectra of these compounds that showed in the region (3024-3090) cm^{-1}, which were attributed to the (C-H) aromatic group, and strong bands in the (1606-1658) cm^{-1} to the (C=N) stretching, all spectra showed absorption bands in the (1519-1543)cm^{-1} belong to the (C=C) stretching vibration aromatic ring also in the range (1161-1167)cm^{-1} due to the (N-O) stretching, and the (C-N) stretching appear in (1334-1388)cm^{-1}. The absorption bands data of these compounds are shown in Table (2) refer to the infrared

spectra of the prepared compounds [38], and infra-red spectrum of the compounds were shown in the Figures (2)-(6) :

Table (2): infra-red Spectra data for the synthesized compounds

Comp.	C=N Str.	C-N Str.	N-O Str.	C=C Ar. Str.	C-H Ar. Str.	C-H aliph. Str.
3	1635	1377	1167	1519	3066	2955
4	1606	1373	1165	1519	3066	2947
5	1631	1377	1167	1519	3066	2928
9	1606	1377	1161	1519	3066	2958
10	1608	1373	1161	1519	3066	2943

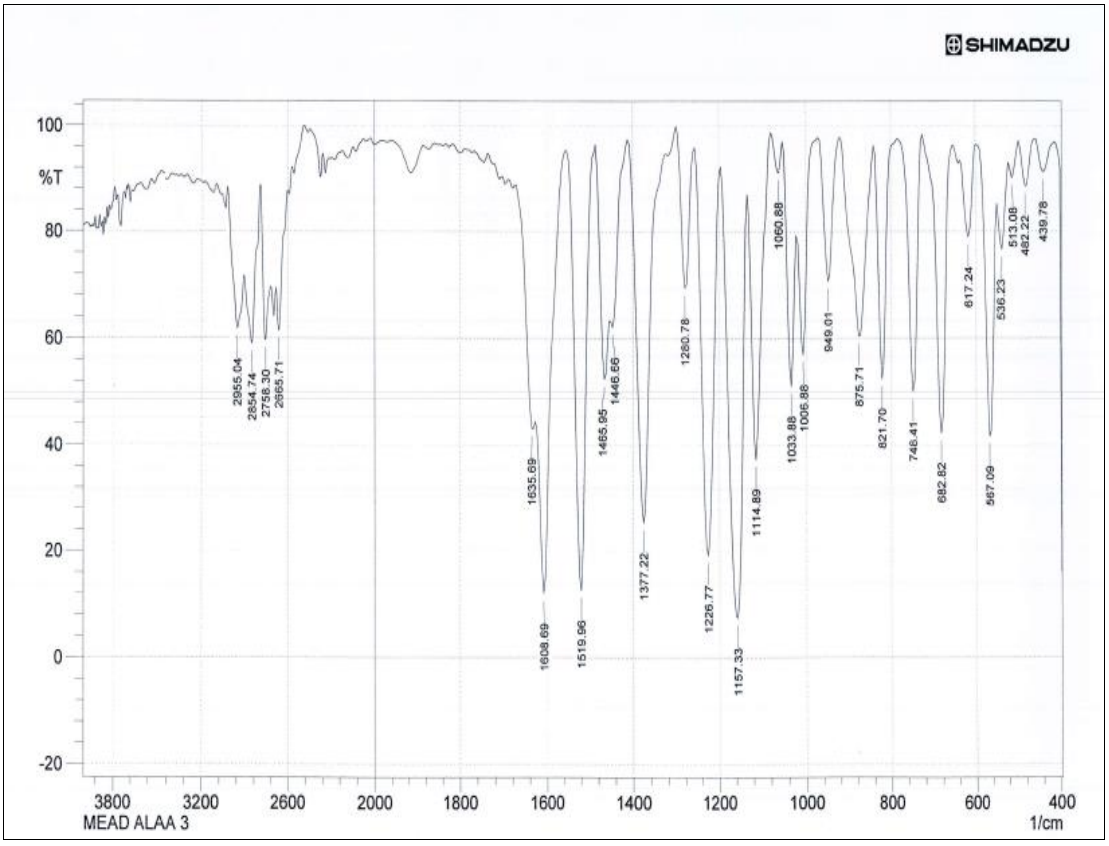


Figure (2): The infra-red Spectrum for the comp. 3

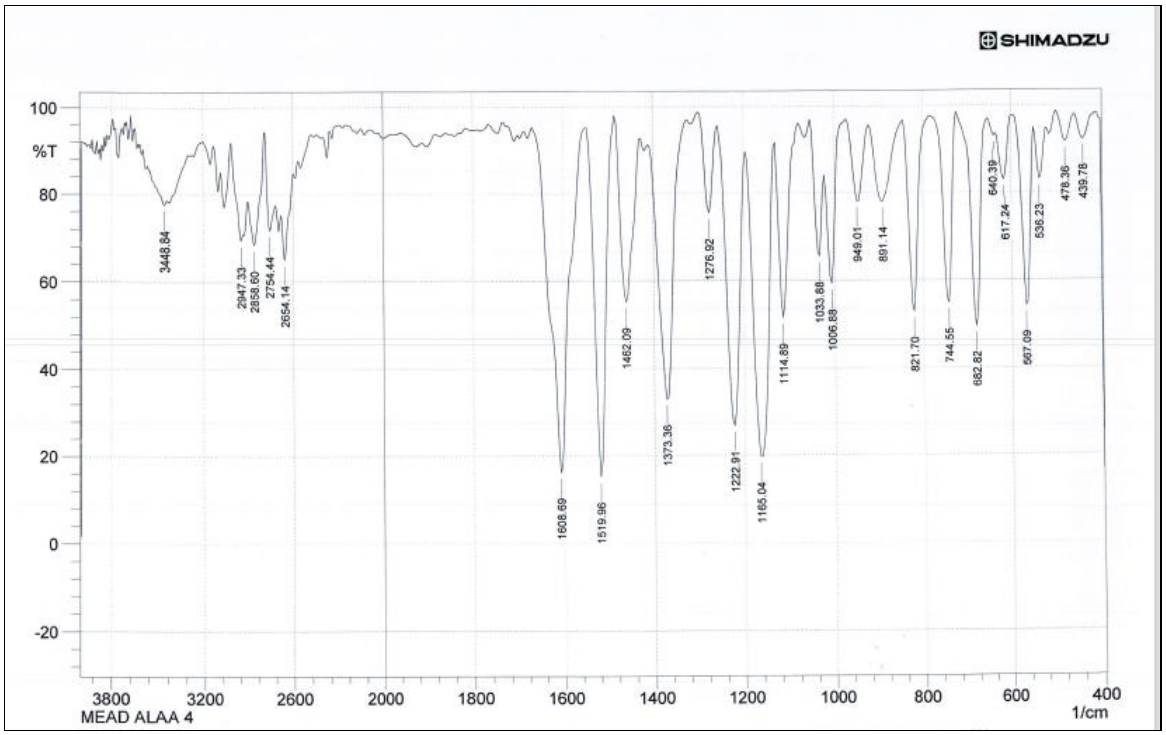


Figure (3): The infra-red Spectrum for the comp. 4

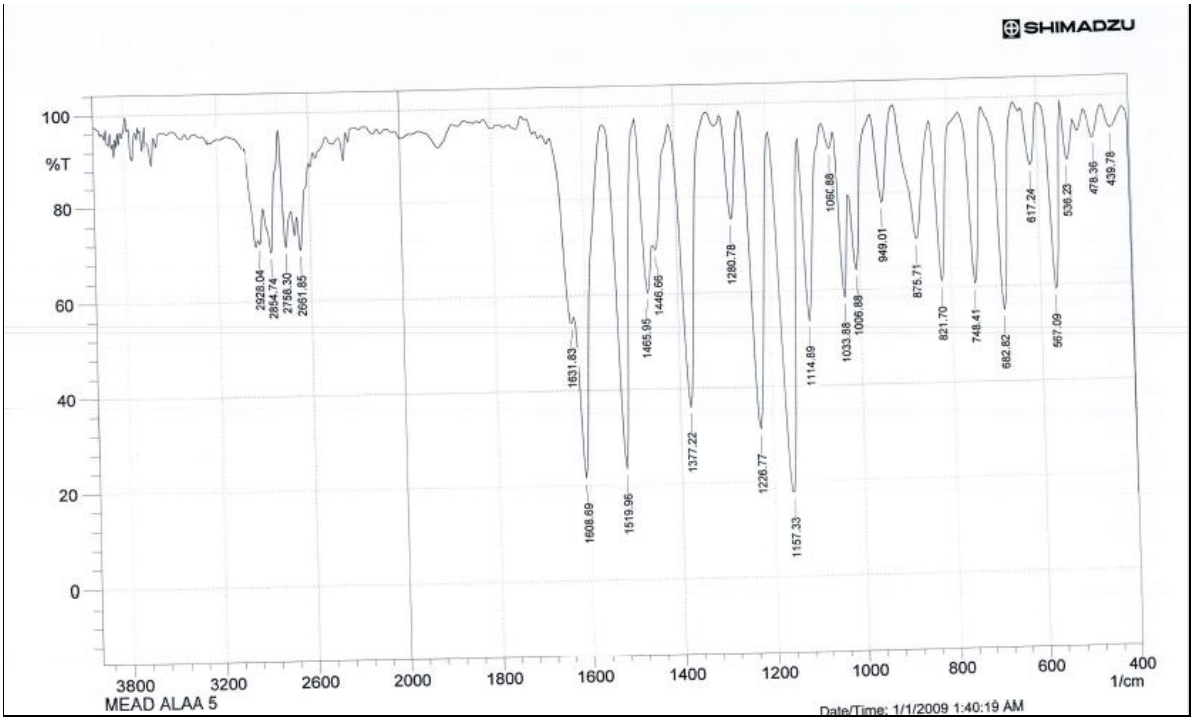


Figure (4): The infra-red Spectrum for the comp. 5

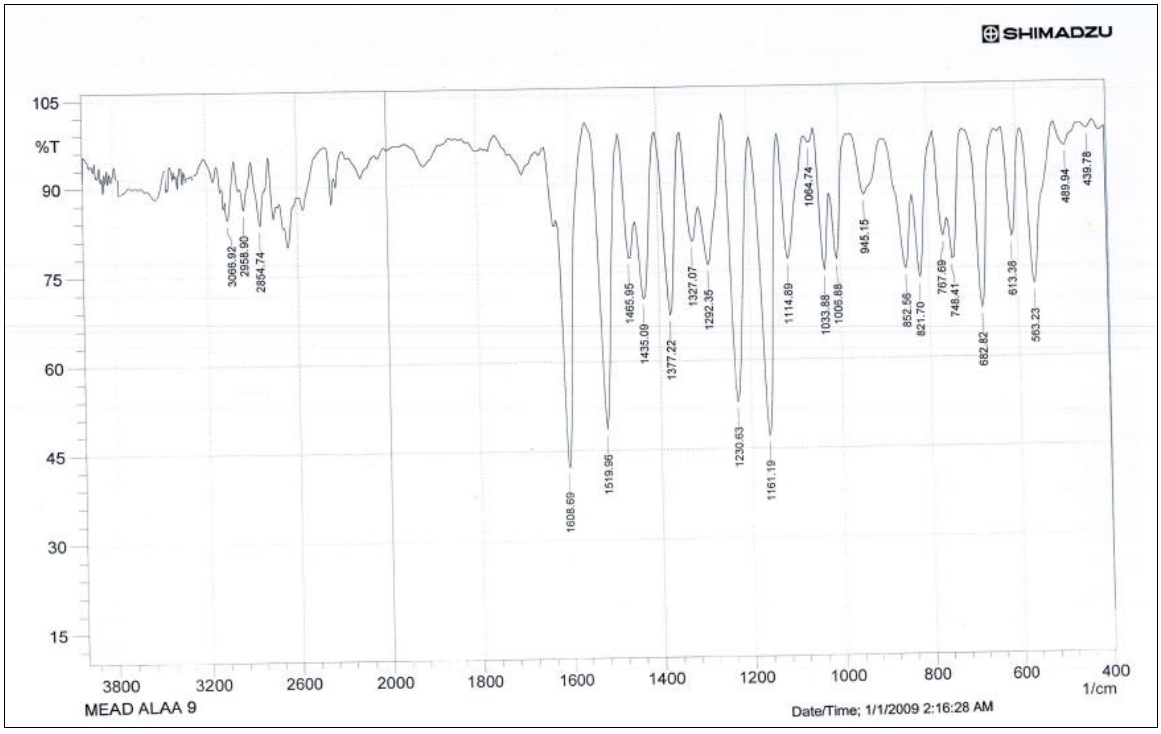


Figure (5): The infra-red Spectrum for the comp. 9

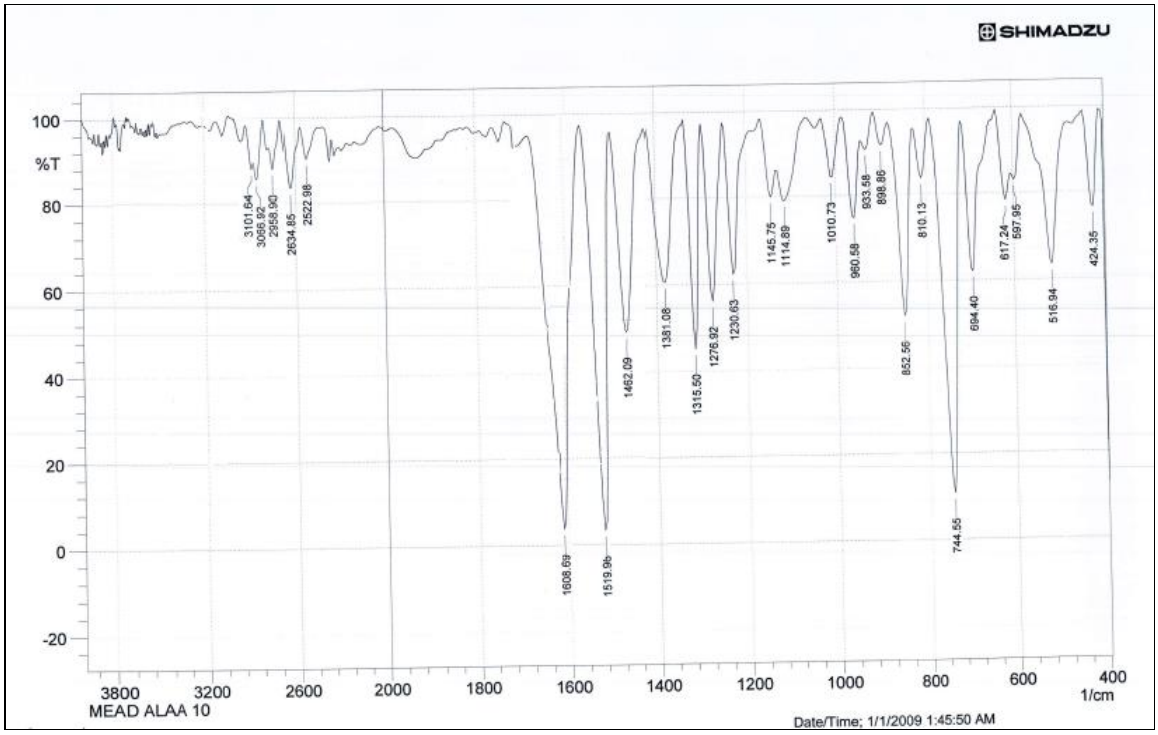


Figure (6): The infra-red Spectrum for the comp.10

Proton Nuclear Magnetic Resonance (H^1 NMR)

The H^1-NMR spectra of benzimidazole-ketonitrone derivatives compounds showed a singlet signal in δ (2.30) ppm due to the aliphatic methyl of nitrone group. double signals in the region δ (7.5-7.53) ppm, (7.12-7.14) ppm and (8.03-8.06) ppm foe the aromatic protons of benzimidazole rings, **d** and **a** respectively.

A Multiplet singles appear at δ (6.96-6.99) ppm belong to **b , H** protons and in the region δ (7.73-7.77)ppm for the aromatic protons **c** (as appears in the Figure(7)), also it was observed that bundles of dimethyl sulfoxide DMSO-d^6 solvent in their specific locations upon displacement (2.50-2.53) ppm, and for the H_2O at (3.10-3.30)ppm.

The chemical shifts of H^1-NMR spectra for the synthesized compounds are shown in Table 3, and the H^1-NMR spectea of the compounds were shown in the Figures 8-12

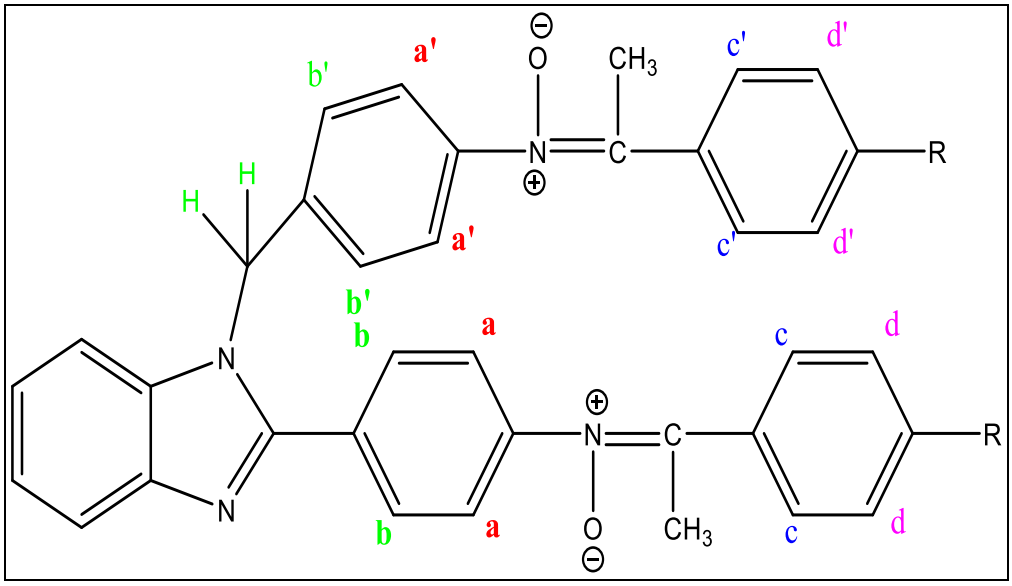


Figure (7): The chemical structure for the synthesized compounds

Table (3): Chemical Shifts H^1-NMR Spectra for the synthesized compounds.

Comp.	a	b	c	d	CH_3	Benzimidazole ring	Others
3	8.03-8.07	6.96-6.99	7.73-7.77	7.12-7.14	2.30	7.49-7.53	
4	8.03-8.06	6.96-6.99	7.73-7.77	7.12-7.14	2.30	7.49-7.53	14.52 OH
5	8.03-8.06	6.67-6.99	7.73-7.75	7.12-7.14	2.30	7.48-7.52	
9	8.03-8.06	6.96-6.99	7.73-7.77	7.12-7.14	2.30	7.50-7.53	
10	8.03-8.06	6.96-6.99	7.73-7.77	7.12-7.14	2.30	7.49-7.53	

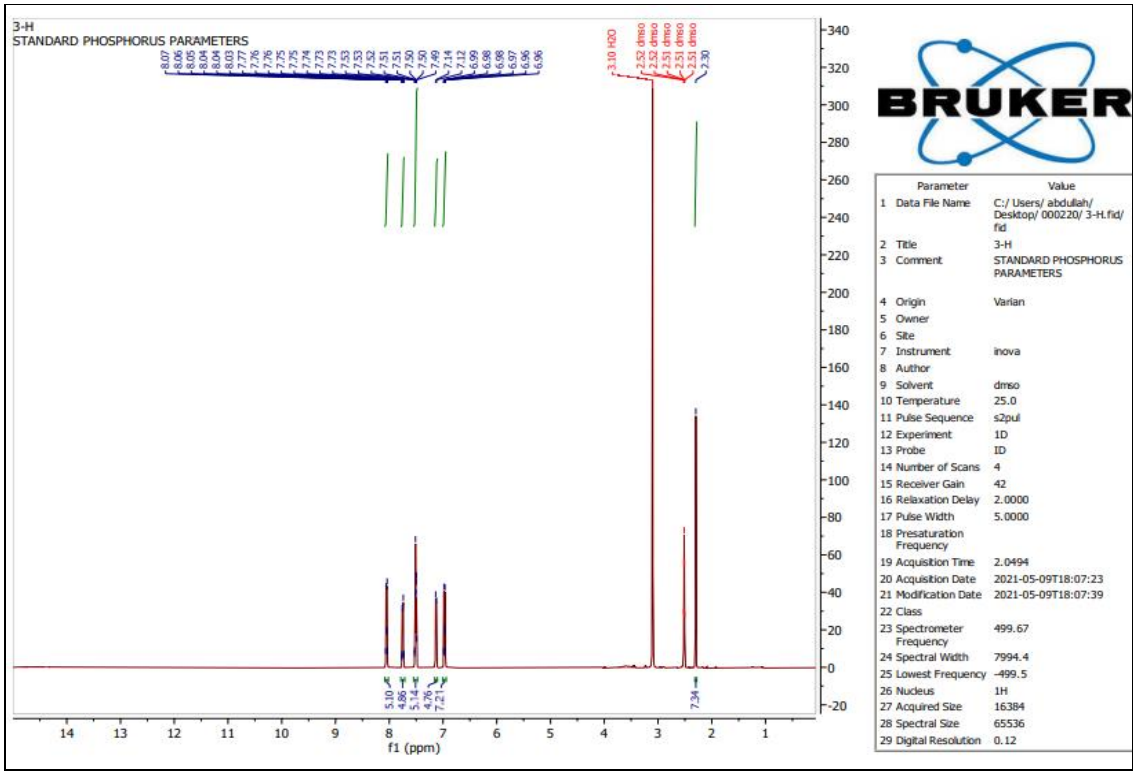


Figure (8): H^1-NMR spectra for comp. 3

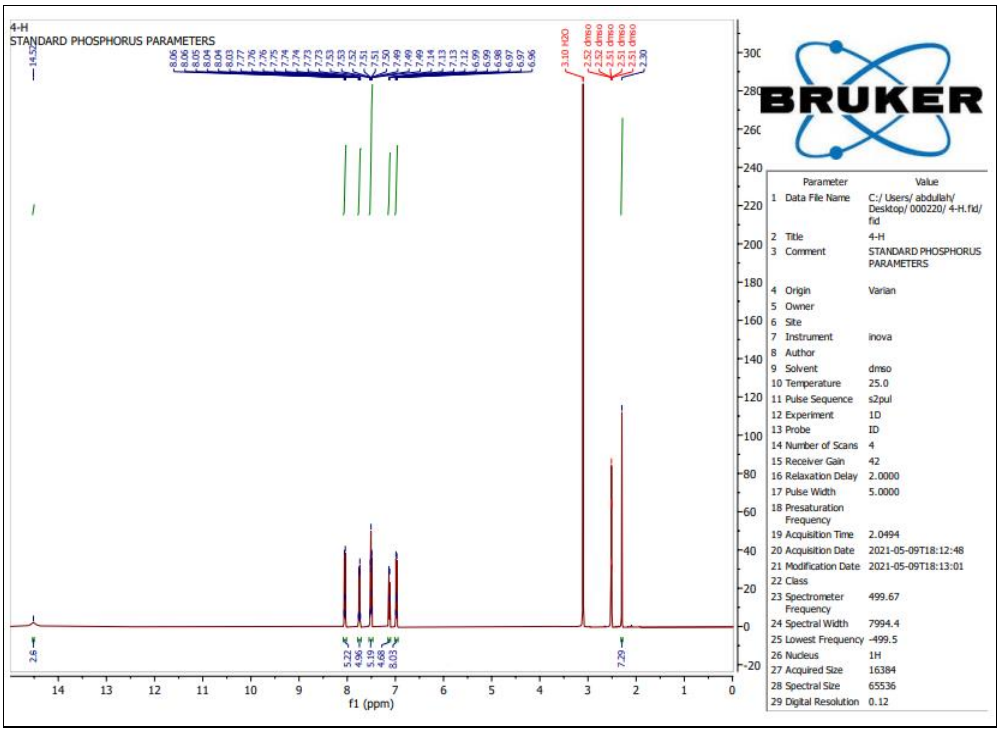


Figure (9): H[1]-NMR spectra for comp. 4

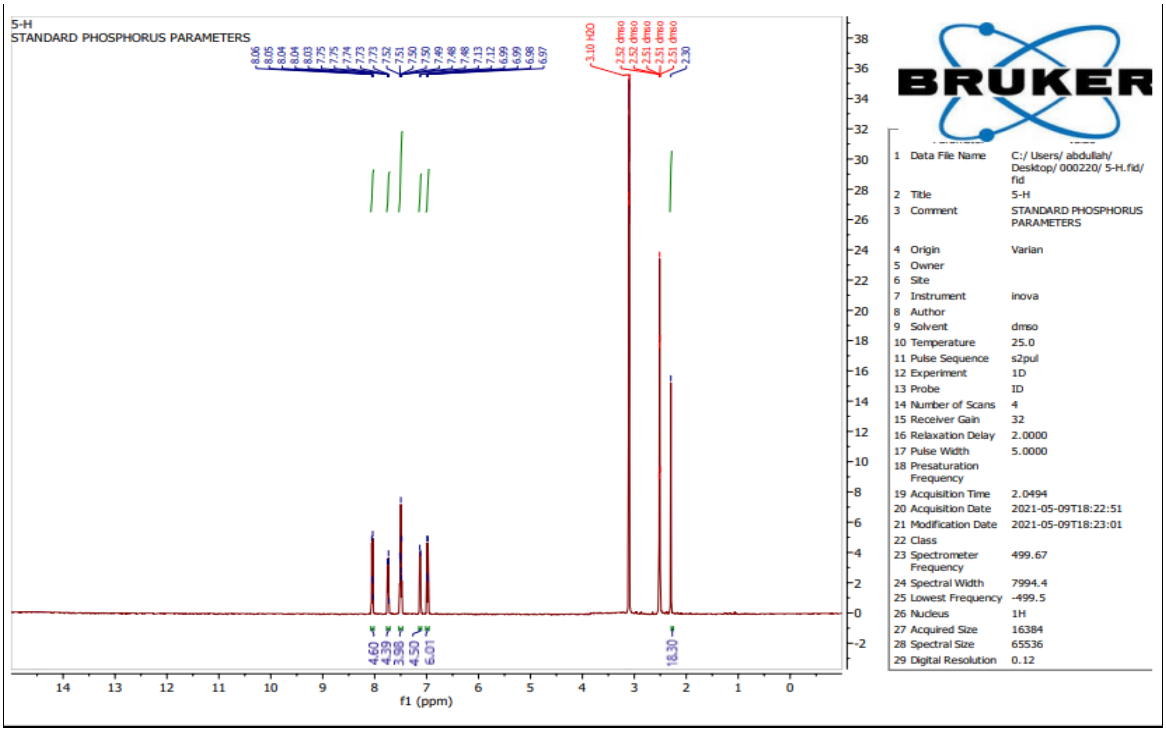


Figure (10): H[1]-NMR spectra for comp. 5

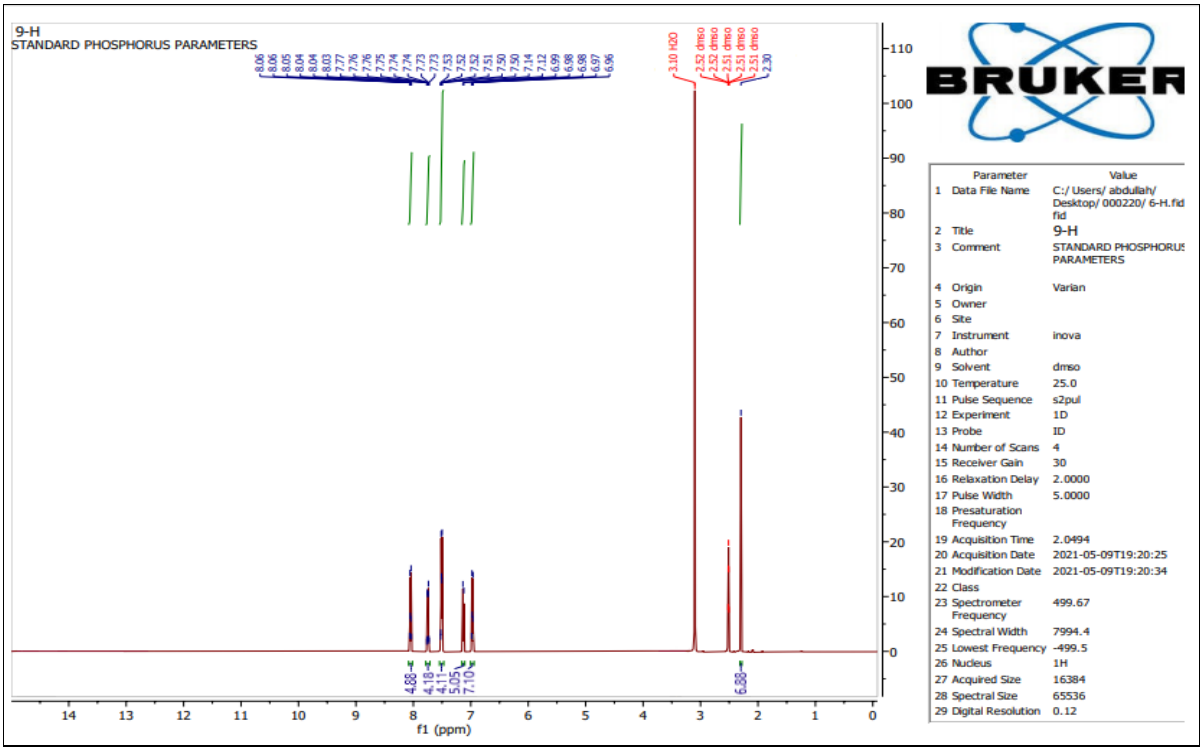


Figure (11): H^1-NMR spectra for comp. 9

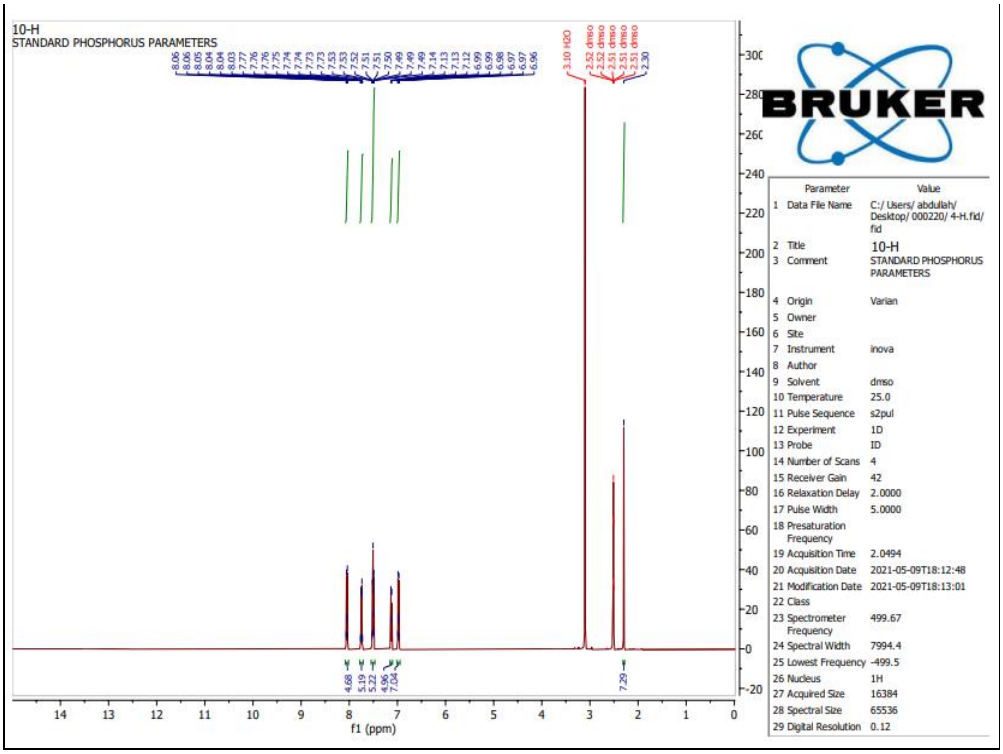


Figure (12): H^1-NMR spectra for comp.10

The elemental analysis (C, H, N)

An elemental analysis have carried out for the synthesized compounds and the table (4) shows the extent of congruence between the practical percentages of the elements (C H N)and the calculated theoretical ratios for these prepared compounds.

Table (4): Elemental Analysis of the prepared Compounds

Comp.	Calculated			Observed		
	%C	%H	%N	%C	%H	%N
3	78.52	5.49	10.17	78.56	5.52	10.18
4	74.21	5.19	9.62	74.19	5.21	9.65
5	75.45	6.33	13.20	75.47	6.30	13.22
9	73.71	4.81	9.55	73.69	4.85	9.50
10	69.79	4.56	9.04	69.81	4.52	9.07

Result of Anti-fungi activity:

Heterocyclic compounds were excessive importance in medicinal chemistry, as they were used as probable goals in contradiction of several fungi pathogens [39].

There were several types of fungi, but the most common fungal was Candida albicans and aspergillus[40]. In our study, anti-fungal was studied using 1000 ppm concentration for all the compounds.

Table (5) appears the inhibition zone of all synthesized compounds towards the candida albicans and aspergillus fungal.

Comp.	Candida	Aspergillus
3	11mm	-

4	12mm	25mm
5	10mm	-
9	-	-
10	-	-

From the table (5), The compounds 3,4,5 were showed reactivity that due to Ph, OH and $N(CH_3)_2$ groups as substituted in synthesized benzimidazole derivatives

References

[1] Keshav A, Sharad W.Development of drugs based on Benzimidazole Heterocycle: recent advancement and insights, IJCS 5 (2) (2017) 350–362.

[2] Yadav G, Ganguly S. Structure activity relation_ship (SAR) study of benzimidazole scaffold for different biological activities: A mini-review. Eur J Med Chem. 2015 Jun 5;97:419–443.

[3] Pathan S, Singh GP. Synthesis of novel tetrazole tetrahydrobenzo[b]thiophene via UgiMCR: as new antileishmanial prototype. J Saudi Chem Soc. 2021;25(8):101295.

[4] Kamanna K. Synthesis and Pharmacological Profile of Benzimidazoles. Chemistry and Applications of Benzimidazole and Its Derivatives. 2019. DOI:10.5772/intechopen.85229

[5] Boschelli DH, Connor DT, Bornemeier DA, et al. 1,3,4-Oxadiazole, 1,3,4-thiadiazole, and 1,2,4-triazole analogs of the fenamates: in vitro inhibition of cyclooxygenase and 5-lipoxygenase activities. J Med Chem. 1993;36(13):1802–1810.

[6] Sondhi SM, Rajvanshi S, Johar M, et al. Anti-inflammatory, analgesic and antiamoe_bic activity evaluation of pyrimido[1,6-a] benzimidazole derivatives synthesized by the reaction of ketoisothiocyanates with mono and diamines. European Journal of Medicinal Chemistry. 2002 Oct;37(10):835– 843.

[7] Eswayah A, Saad SA, Khaliel S, et al. Evaluation of antioxidant, analgesic and anti-inflammatory activity of 2-(4-aminophenyl) benzimidazole-- based Schiff bases. IOSR J Pharm. 2020;10(10– 1):48–56. Journal; Online Computer File 2020, CODEN:IJPOCY,2250-3013.

[8] Habib NS, Abdel-Hamid S, el-Hawash M. Synthesis of benzimidazole derivatives as potential antimicrobial agents. Farmaco. 1989 Dec;44 (12):1225–1232.

[9] Antoci V, Cucu D, Zbancioc G, et al. Bis-(imida_zole/benzimidazole)-pyridine derivatives: synthesis, structure and antimycobacterial activity. Future Med Chem. 2020;12(3):207–222.

[10] Singhal S, Khanna P, Khanna L. Synthesis, DFT studies, molecular docking, antimicrobial screening and UV fluorescence studies on ct-DNA for novel Schiff bases of 2-(1-aminobenzyl) benzimidazole. Heliyon. 2019;5(10): e02596.

[11] Ozkay Y, Tunalı Y, Karaca H, et al. Antimicrobial activity of a new series of benzimidazole derivatives. Arch Pharm Res. 2011;34 (9):1427–1435.

[12] Krishnanjaneyulu I, Saravanan G, Sunil Kumar M, et al. Synthesis, characterization and antimicrobial activity of some novel benzimidazole derivatives. Adv Pharm Technol Res. 2014;5(1):21–27.

[13] Francesconi V, Cichero E, Schenone S, et al. Synthesis and Biological Evaluation of Novel (thio)semicarbazone-Based Benzimidazoles as Antiviral Agents against Human Respiratory Viruses. Molecules. 2020;25(7):1487.

[14] Kanwal A, Ahmad M, Aslam S, et al. Recent Advances in Antiviral Benzimidazole Derivatives: a Mini Review. Pharm Chem J. 2019;53(3):179–187.

[15] Perin N, Alić J, Liekens S, et al. Different positions of amide side chains on the benzimidazo[1,2-a] quinoline skeleton strongly influence biological activity. New J Chem. 2018;42(9):7096–7104.

[16] Picanço GA, Lima NF, Alves DS, et al. Partial inhibition of the tricarboxylic acid cycle in Taenia crassiceps cysticerci after the in vitro exposure to a benzimidazole derivative (RCB15). Acta Trop. 2020;202:105254.

[17] Andreadou I, Tasouli A, Bofilis E, et al. Antioxidant Activity of Novel Indole Derivatives and Protection of the Myocardial Damage in Rabbits. Chem Pharm Bull. 2002;50(2):165–168.

[18] Salahuddin, Shaharyar M, Mazumder A. Benzimidazoles: a biologically active com_pounds. Arabian J Chem. 2017;10:S157–S173.

[19] Wei Y, Wang N, Li D, et al. Study on the fluorescence modulation of benzimidazole through energy transfer and photochromic isomerization in the pillar(5)arene-based supermolecular system. React Funct Polym. 2019;144:104351.

[20] Palit R, Kumar R, Saraswat N, et al. Benzimidazole: an overview. Int J Res Ayurveda Pharm. 2017;7(6):68–73.

[21] Prasad PMK, S AK, S R. Potent biological agent benzimidazole–a review. Int J Pharm Pharm Sci. 2016;8(12):22.

[22] Racané L, Zlatar I, Perin N, et al. Biological Activity of Newly Synthesized Benzimidazole and Benzothizole 2,5-Disubstituted Furane Derivatives. Molecules. 2021;26(16):4935. Published 2021 Aug 14. DOI:10.3390/molecules26164935. [23] Dziwornu, G. A., Coertzen, D., Leshabane, M., Korkor, C. M., Cloete, C. K., Njoroge, M., . . . Chibale, K. (2021). Antimalarial Benzimidazole Derivatives Incorporating Phenolic Mannich Base Side Chains Inhibit Microtubule and Hemozoin Formation: Structure–Activity Relationship and In Vivo Oral Efficacy Studies. Journal of Medicinal Chemistry, 64(8), 5198–5215.

[24] Bansal Y, Minhas R, Singhal A, et al. Benzimidazole: a Multifacted Nucleus for Anticancer Agents. Curr Org Chem. 2021;25 (6):669–694.

[25] Refaat HM. Synthesis and anticancer activity of some novel 2-substituted benzimidazole derivatives. Eur J Med Chem. 2010;45 (7):2949–2956.

[26] Navarrete-Vázquez G, Cedillo R, HernándezCampos A, et al. Synthesis and antiparasitic activity of 2-(Trifluoromethyl)benzimidazole derivatives. Bioorganic Med Chem Lett. 2001;11(2):187–190.

[27] Pathan SI, Chundawat NS, Chauhan NPS, et al. A review on synthetic approaches of heterocycles via insertion-cyclization reaction. Synth Commun. 2020;1–35. DOI:10.1080/00397911.2020.1712609

[28] Pardeshi VAS, Chundawat NS, Pathan SI, et al. A review on synthetic approaches of benzimidazoles. Synthetic Communications. 2020;1– 29. DOI:10.1080/00397911.2020.1841239

[29] Christopher R. Plant Health Instructor. (2012).

[30] https://www.cdc.gov/fungal/images/Fungal-environmental.

[31] Joon Kim, Peter Sudbery. J Microbiol. 49(2):171-7. (2011).

[32] Jadhav, G. R., Shaikh, M.U., Kale, R.P., Gill, C.H., 1-Heptanesulfonic acid sodium salt: One pot efficient synthesis of 2-aryl-1-arylmethyl-1H-1,3-benzo[d]imidazole. Chinese Chemical Letters 2009, 20, 535-538.

[33] Heba H. Sabah Der Pharma Chemica, Synthesis, spectroscopic characterization of schiff bases derived from 4,4'-methylen di aniline, 2014, 6(2):38-41.

[34] Ippolito A, Francesco C, Gloria C, Palmarisa F, Mario G,Sante M.

J.Med. chem., 1981, 24,1181.

[35] Matheus H, Tejashree A, Badveti S. Open Journal of Medical Microbiology, V (11), 129-143, (2021).

[36] Pawar, S. S., Dekhane, D.V., Shingare, M.S., Thore, S.N., Glyoxylic acid as catalyst: A simple selective synthesis of 1,2-disubstituted benzimidazoles in aqueous media. Chinese Chemical Letters 2008, 19, 1055-1058.

[37] Azman, A.; Koller, J.; Plenicar, B.J. Am. Chem.Soc.1979,101, 1107.

[38] Brennan, NF. [2006]: Infra-Red and Raman spectroscopy. Chapter 3. The University of Pretoria.

[39] Mossaraf Hossain, Ashis Kumar Nanda . Science Journal of Chemistry. 6(5): 83-94.(2018).

[40] Li Sun, Jie Wu, Lingzi Zhang, Min Luo and Dequn Sun. Molecules, V.16.(2011).