

Research Article

Synthesis, Identification, and In-vitro Antidiabetic Evaluation of 2,4,5-Trisubstituted Imidazole Derivatives

Sawsan K Abbas*, Narjis Hadi Al-Saadi* H. D. Hanoon*

*Department of Chemistry, College of Science, University of Kerbala, Kerbala, Iraq

Article Info

Article history:

Received 6-3-2023

Received in revised form

7-4-2023

Accepted 10-4-2023

Available online 23-7 -2023

Keywords: trisubstituted imidazole, Radziszewski reaction, hyperglycemia, inhibitory activity.

Abstract

To offer new imidazole compounds powerful to reduce hyperglycemia by inhibiting the enzymes δ -amylase and α -glucosidase, a new series of trisubstituted imidazole derivatives 4(a-d) were prepared by using the Radziszewski reaction of 4,4'-dimethoxybenzil, different aromatic aldehydes and ammonium acetate in glacial acetic acid as a catalyst. All newly synthesized compounds were identified by various spectral data and were examined for purity by thin-layer chromatography. Then all prepared compounds were screened for them in *in vitro* α -amylase and α -glucosidase inhibitory activities using acarbose as a standard reference at different concentrations (50-250 μ g/mL). The findings showed that all the synthesized derivatives have good to excellent inhibitory potential against α -amylase ranging between 51% to 90% compared with the reference drug acarbose ranging from 32% to 63%. Among the series compounds, 4f was the most potent. The α -glucosidase inhibition assay showed the reference drug acarbose exhibited the highest α -glucosidase inhibition (66%) followed by compounds 4b, 4d, and 4a (55%), (52%) and (51%) respectively at their highest concentrations (250 μ g/mL). Therefore, these new imidazole derivatives have the potential to develop a new inhibitory activity.

Introduction

Diabetes mellitus, a chronic endocrine disease, affects protein, lipid, carbohydrate, electrolyte, and water metabolism. It describes hyperglycemic metabolic disorders, which occurs when the level of blood sugar rises due to either a lack of insulin production by the pancreas or a failure of cells to respond to the insulin produced. As a result, decreasing postprandial hyperglycemia is a therapeutic approach for diabetes [1]. This is achieved by inhibiting carbohydrate hydrolyzing enzymes such as α -amylase and α -glucosidase which are important in carbohydrates metabolism [2]. Long-chain carbohydrates are broken down by α -amylase, while starch and disaccharides are converted to glucose by α -glucosidase. In diabetic patients, pancreatic α -amylase inhibitors retard carbohydrate digestion, reducing glucose absorption and lowering postprandial blood glucose levels [3]. As a result, inhibiting α -amylase and α -glucosidase and noteworthy substances has been established as a beneficial and practical approach to decreasing postprandial hyperglycemia levels. Miglitol, Voglibose, and acarbose are a few antidiabetics commercial drugs now available for treating α -glucosidase and α -amylase catalyst restraint in diabetes mellitus [4]. As an all-inclusive answer, no one therapy is feasible. Anyway, these drugs are not recommended for long-term usage due to their side effects. So, scientists are searching for more secure, single, and ordinary

Experimental section

Materials and instrumentation

Chemicals and solvents that were used in this work were purchased from different manufacturers, such as Aldrich, Hi-Media and directly used without extra purification. All reactions were monitored by (TLC) thin-layer chromatography. Visualization of spots on TLC plates was done by heating plates coated with KMnO_4 stain. FT-IR spectra were

inhibitors with fewer side effects that can be used to treat diabetes. [5]. Some medicinal compounds' antidiabetic efficacy has been documented *in vitro* and *in vivo* [6].

Heterocyclic compounds containing imidazole moieties play a vital role in biological processes and are widespread as natural products due to its presence in bioactive compounds, synthetic intermediates, and pharmaceuticals; thus, researchers have focused on the methods for their synthesis and applications. Their derivatives are involved in a variety of vital natural products like alkaloids nucleic acid bases (RNA) and DNA [7], hormones [8], and vitamins [9]. They also have antiviral [10], antifungal [11], antibacterial [12], antioxidant [13], anticonvulsant [14], anti-inflammatory [15], and anticancer properties [16], as well as inhibitors of mammalian 15-LOX, [17], and B-Raf kinase [18], β -lactamase inhibitors, heme oxygenase inhibitors, and antiaging agents [19- 21]. Various methods for their synthesis have been used, including a typical one-pot synthesis from a 1,2-dione, an aromatic aldehyde, and NH_4OAc using zeolites HY/silica gel [22], ionic liquids [23], catalyst-free under microwave irradiation [24], and traditional refluxing in AcOH which is a good confirmed approach for the preparation of imidazole derivatives [25] generally, all of the above methods have their own advantages. The current study involved the synthesis, and characterization of new tri-imidazole and the study of their effect to reduce hyperglycemia.

registered as KBr disk using SHIMADZU FTIR-8400S. Melting points were measured by using Stuart SMP 30 capillary melting Electro thermal analyzer. ^1H NMR spectra was measured in deuterated dimethyl sulfoxide (DMSO-d_6) with Bruker Bio Spin at 500 MHz. Mass spectra were measured by Agilent technology (HP) instrument (EI, 70 eV).

preparation of 2,4,5- trisubstituted imidazole derivatives 4a–d

A mixture of 4,4'-dimethoxybenzil (1mmol), aromatic aldehyde (1mmol), NH_4OAC , (4mmol) with glacial acetic acid (15 mL) as solvent and catalyst in 50 mL round-bottom flask, the mixture was reflux at 120°C for 6–h until the reaction was completed. The progress of the reaction was monitored by TLC. A sufficient amount of cold water is added to the reaction vessel, followed by the addition of ammonium hydroxide solution drop by drop with stirring to obtain the solid, then the product was filtered and washed well with deionized water to remove any remnants of base and salts, the product was dried, and recrystallized from hot ethanol. Confirmation of all structures was done by mass and NMR spectra, as explained below:

3-[(4,5-bis(4-methoxyphenyl)-1H-imidazol-2-yl)] phenol (4a): $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_3$. Color: off-white powder, yield 80 %. m.p.; $110\text{--}111^\circ\text{C}$; FT-IR $\nu_{\text{max}} \text{ cm}^{-1} = 3302(\text{N-H}), 3055(\text{C-H, arom.}), 1654(\text{C=N})$. $^1\text{H NMR}$ (500 MHz, DMSO- d_6) δ ppm: 12.43 (s, 1H, NH), 9.54 (s, 1H, OH), 7.55 – 7.48 (m, 2H), 7.45 (d, $J = 8.2$ Hz, 4H), 7.26 (t, $J = 7.9$ Hz, 1H), 6.96 (d, $J = 7.7$ Hz, 4H), 6.79 (dd, $J = 7.9, 2.5$ Hz, 1H), 3.79 (s, 6H). MS(EI) (m/z) = $372[\text{M}]^+$.

2-[(4-chlorophenyl)-4,5-bis(4-methoxyphenyl)-1H-imidazole (4b): $\text{C}_{23}\text{H}_{19}\text{ClN}_2\text{O}_2$ White powder, yield 82 %.

Enzymatic evaluation

Anti- α -amylase assay

The inhibitory activity of the α -Amylase enzyme was determined using the reference method [26]. A test tube containing (250 μL) of tested compound solution with various concentrations (50 - 250 $\mu\text{g/mL}$), (250 μL) of [1% (w/v)] starch solution and (250 μL) of (1U/mL) α -amylase solution. A (500 μL) of dinitro salicylic acid (color reagent) was added to the mixture after it had been incubated at 20°C for 3 minutes to stop the enzymatic process. A (250 μL) of α -amylase was added immediately to the mixture after it had been kept in hot water. The mixture was

m.p.; $116\text{--}118^\circ\text{C}$; FT-IR $\nu_{\text{max}} \text{ cm}^{-1} = 3398(\text{N-H}), 3097(\text{C-H, arom.}), 1654(\text{C=N}), 640(\text{C-Cl})$. $^1\text{H NMR}$ (500 MHz, DMSO- d_6) δ ppm; 12.61 (bs, 1H, NH), 8.09 (d, $J = 8.6$ Hz, 2H), 7.96 (d, $J = 8.5$ Hz, 1H), 7.88 (d, $J = 8.9$ Hz, 1H), 7.57 (d, $J = 8.6$ Hz, 1H), 7.54 (d, $J = 8.7$ Hz, 2H), 7.46 (d, $J = 8.2$ Hz, 3H), 7.14 (d, $J = 9.0$ Hz, 2H), 3.88 (s, 6H). MS(EI) (m/z) = $390[\text{M}]^+$.

4-[(4,5-bis(4-methoxyphenyl)-1H-imidazol-2-yl)]-3-methoxyphenol (4c): $\text{C}_{24}\text{H}_{22}\text{N}_2\text{O}_4$ yellow colored powder, yield 85 %. m.p.; $123\text{--}125^\circ\text{C}$; FT-IR $\nu_{\text{max}} \text{ cm}^{-1} = 3448(\text{N-H}), 3088(\text{C-H, arom.}), 1651(\text{C=N}), 1245(\text{C-O})$. $^1\text{H NMR}$ (500 MHz, DMSO- d_6) δ ppm; 12.28 (bs, 1H, NH), 9.25 (bs, 1H, OH), 7.87 (d, $J = 8.8$ Hz, 1H), 7.61 (d, $J = 2.0$ Hz, 1H), 7.50 (dd, $J = 8.2, 2.0$ Hz, 1H), 7.43 (d, $J = 8.4$ Hz, 3H), 7.14 (d, $J = 6.8$ Hz, 1H), 6.94 (d, $J = 8.1$ Hz, 3H), 6.85 (d, $J = 8.2$ Hz, 1H), 3.86 (s, 3H), 3.77 (s, 6H). MS(EI) (m/z) = $402[\text{M}]^+$.

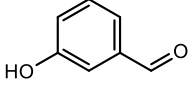
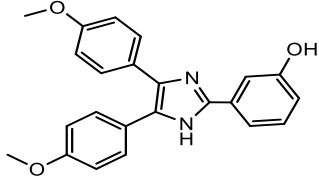
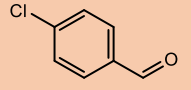
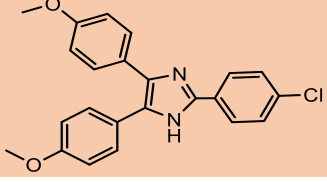
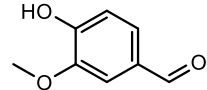
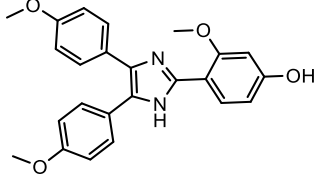
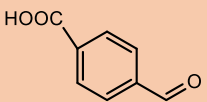
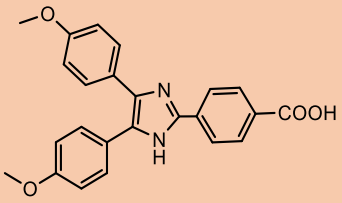
4-[(4,5-bis(4-methoxyphenyl)-1H-imidazol-2-yl)] benzoic acid (4d): $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_4$ Color: pale yellow colored powder, yield 79 %. m.p.; $220\text{--}222^\circ\text{C}$; FT-IR $\nu_{\text{max}} \text{ cm}^{-1} = 3483(\text{N-H}), 3005(\text{C-H, arom.}), 1647(\text{C=N}), 1253(\text{C-O})$. $^1\text{H NMR}$ (500 MHz, DMSO- d_6) δ ppm: 12.77 (s, 1H, COOH), 12.48 (bs, 1H, NH), 8.21 (d, $J = 8.3$ Hz, 3H), 8.05 (d, $J = 8.3$ Hz, 3H), 7.48 (d, $J = 8.3$ Hz, 6H), 3.79 (s, 6H). MS(EI) (m/z) = $400[\text{M}]^+$.

heated at 85°C for 15 minutes. Then, the solution was removed from the heating process and allowed to incubation for 5 minutes at room temperature. A (4500 μL) of distilled water was added to give a total volume of (6000 μL). The absorbance was determined at 540 nm using spectrophotometry. The control was prepared without test sample. Acarbose was utilized as reference drug, and the % inhibition was determined by equation (1)

$$\% \text{ inhibition} = [(\text{Abs control} - \text{Abs sample}) / \text{Abs control}] \times 100 \dots \dots \dots \text{eq. (1)}$$

where Abs mean the absorbance.

Table 1 Synthesis of 2,4,5-trisubstituted imidazole 4(a-d) by using glacial acetic acid.

Entry	Aldehyde	Product 4(a-d)	Time (h.)	Yield (%)
4a			6	80
4b			7	82
4c			6	85
4d			8	79

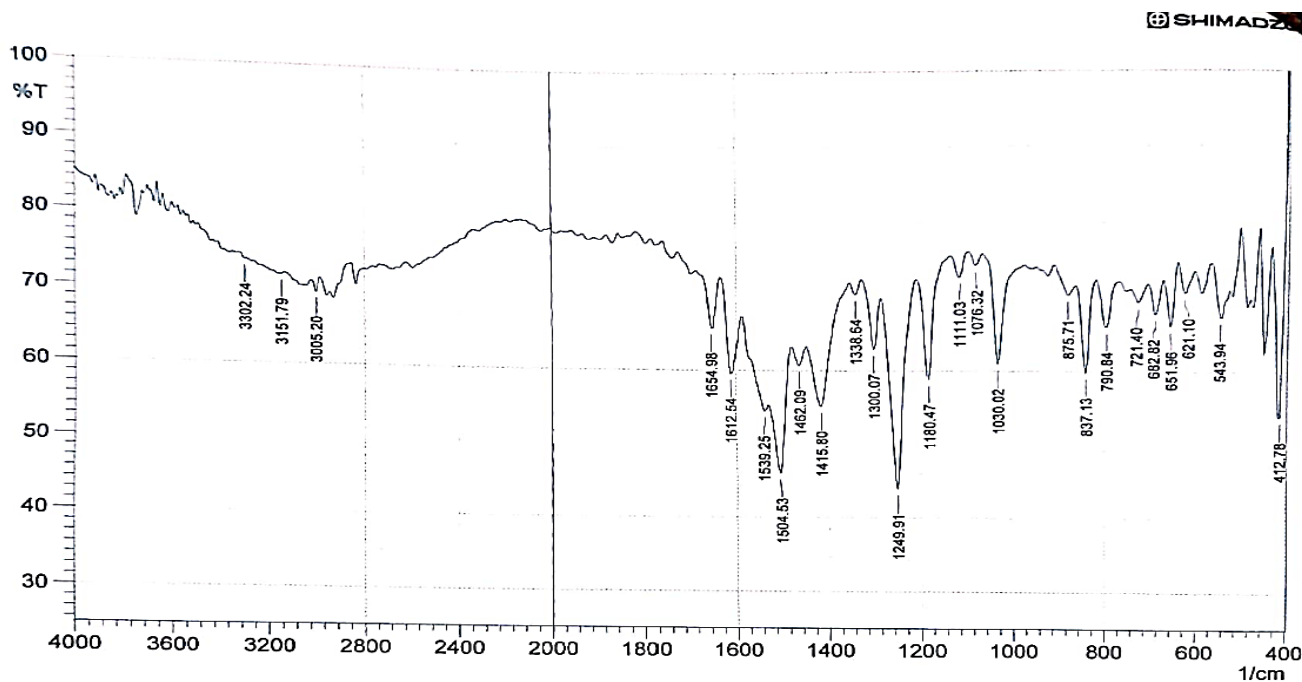


Figure (1): FT-IR spectrum of derivative (4c)

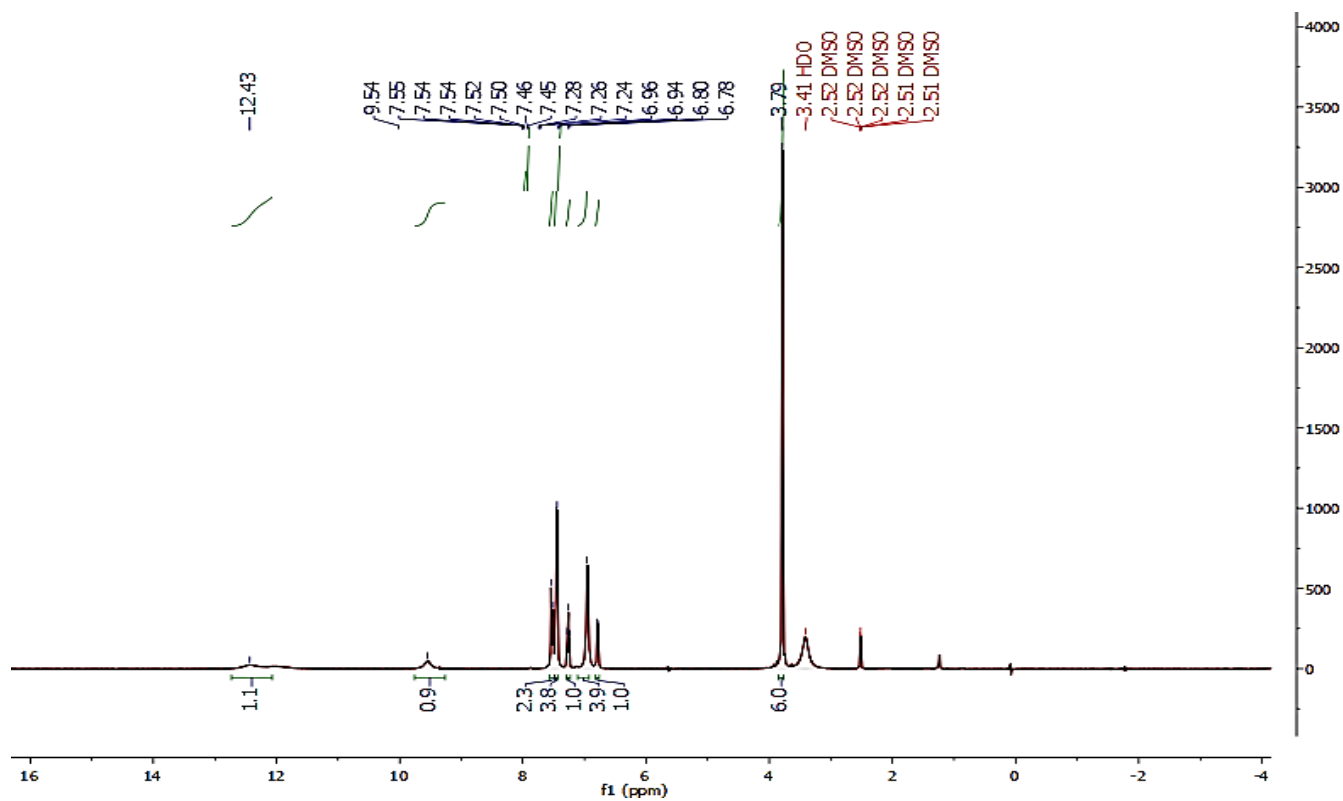


Figure (2): ¹H NMR (500 MHz, DMSO-d₆) spectrum of derivative 4a

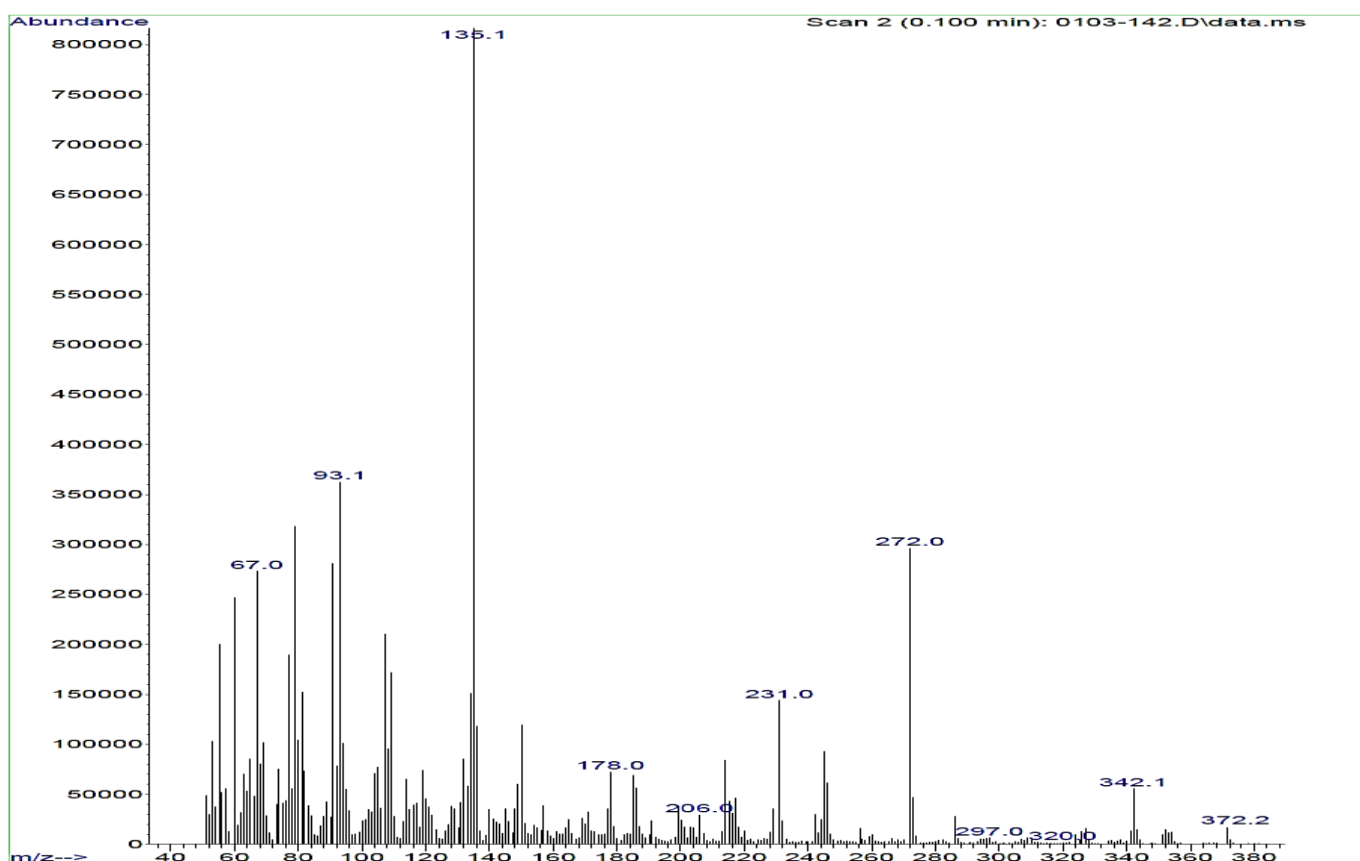


Figure (3): Mass spectrum of derivative 4a

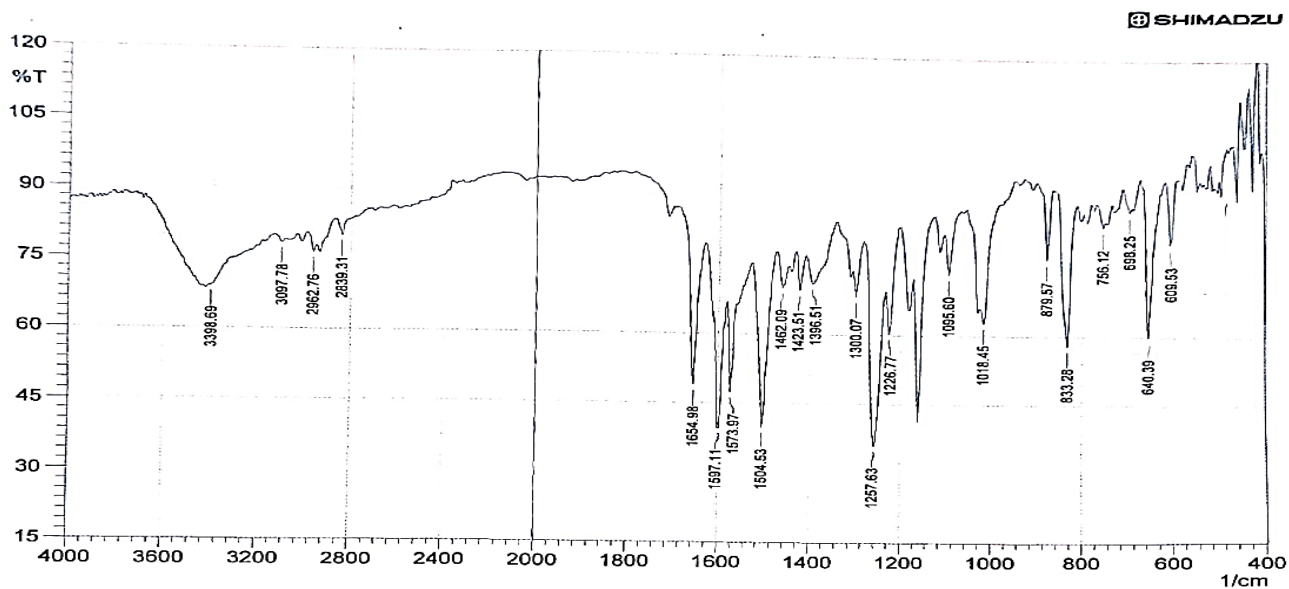


Figure (4): FT-IR spectrum of derivative 4b

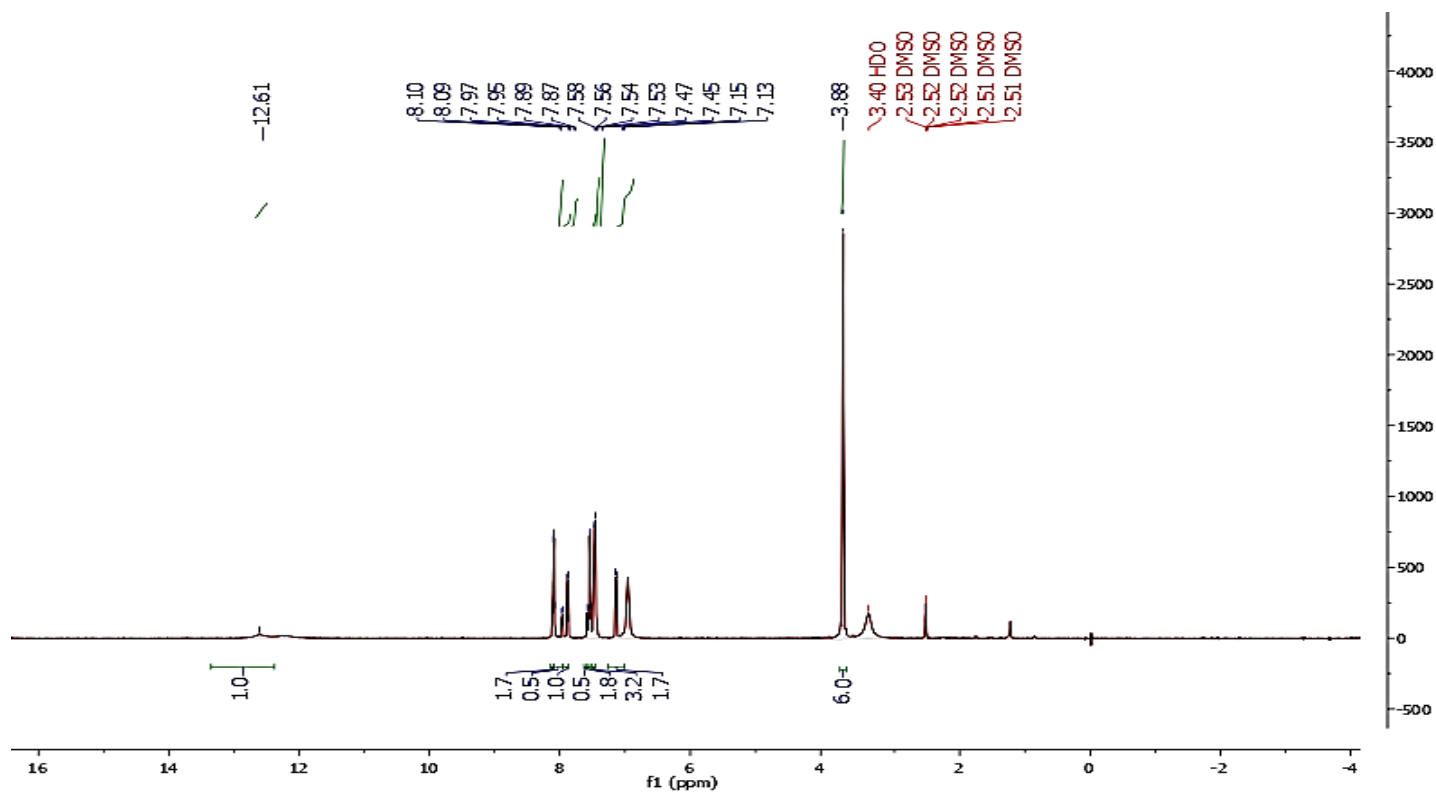


Figure (5): ¹H NMR (500 MHz, DMSO-d₆) spectrum of derivative 4b

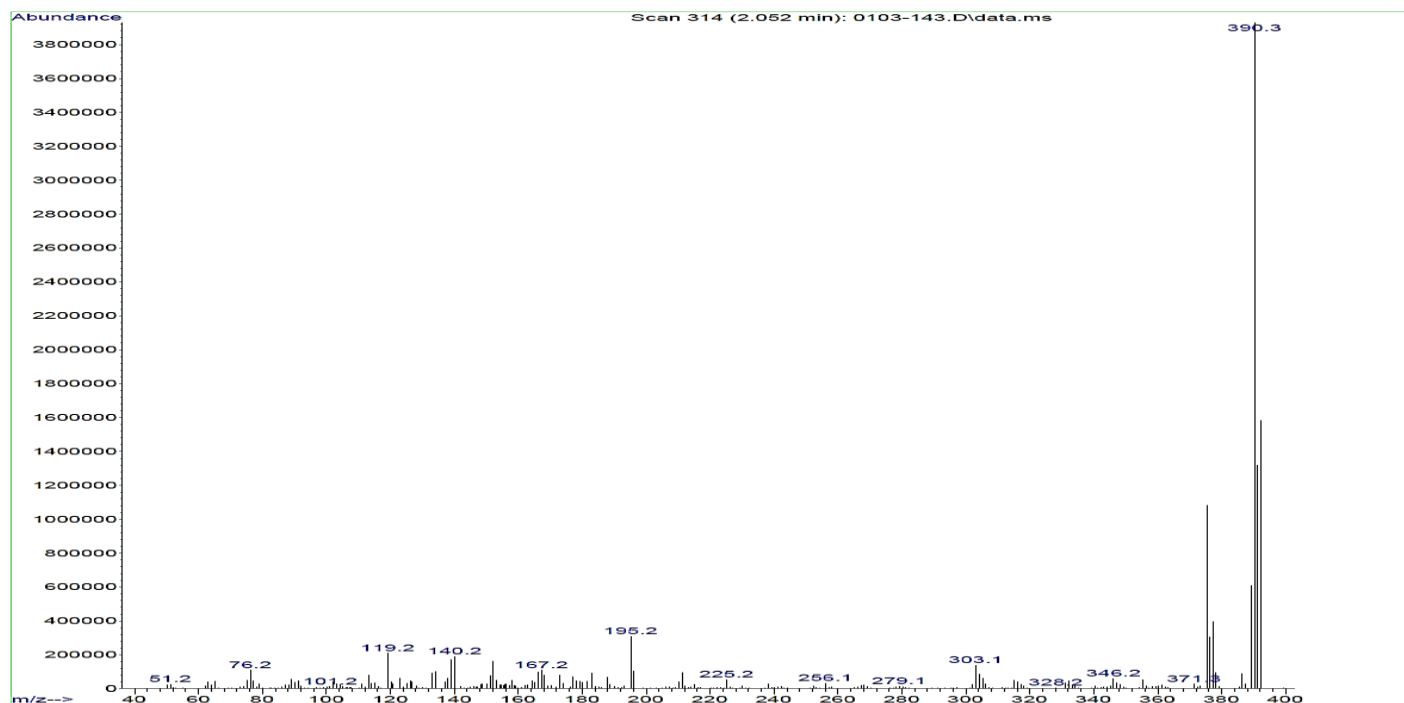


Figure (6): Mass spectrum of derivative 4b

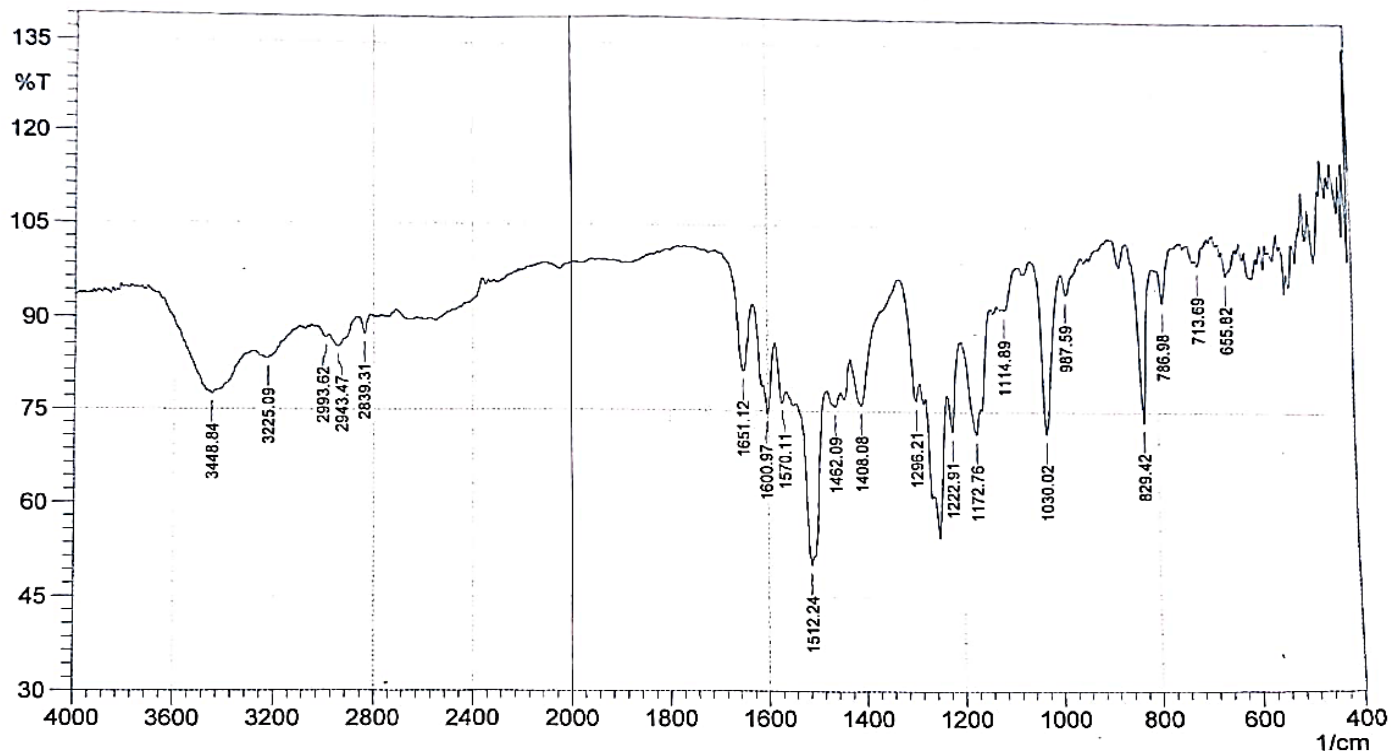


Figure (7): FT-IR spectrum of derivative 4c

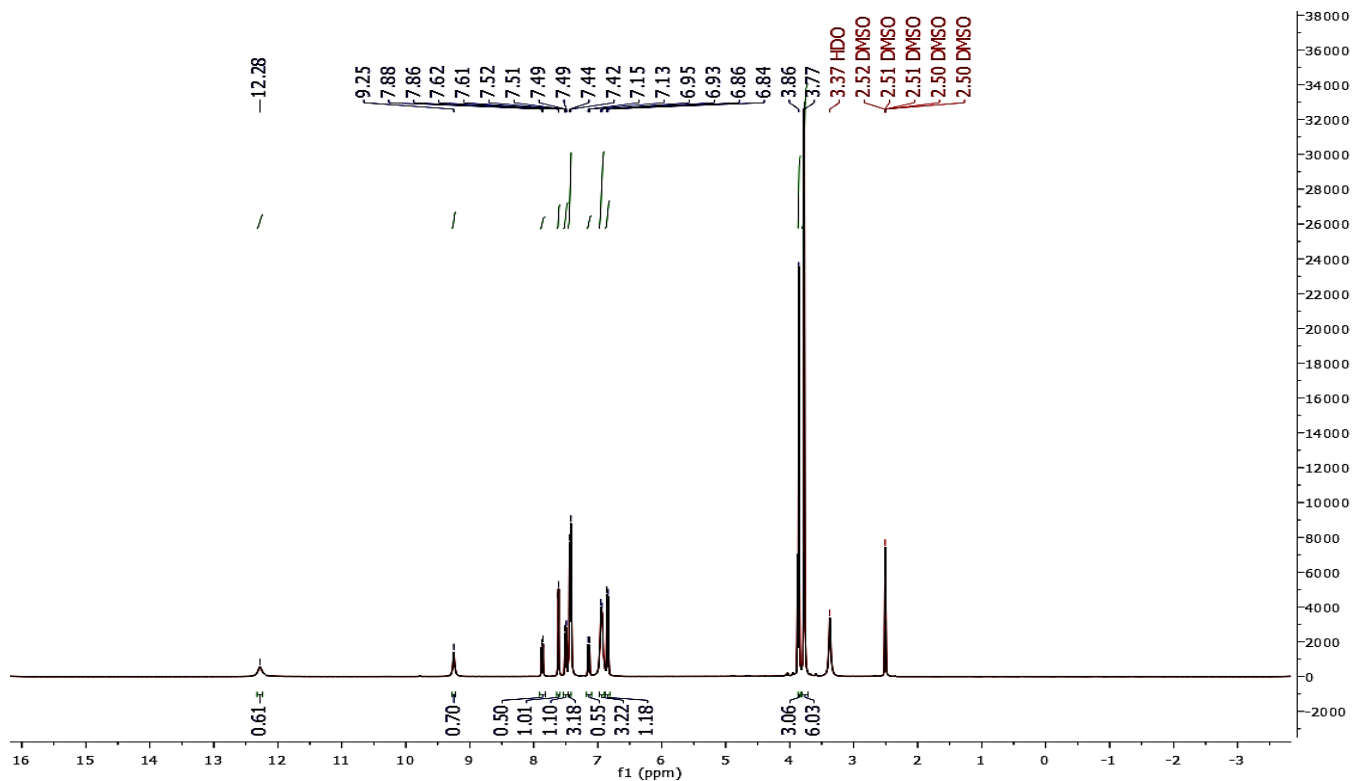


Figure (8): ¹H NMR (500 MHz, DMSO-d₆) spectrum of derivative 4c

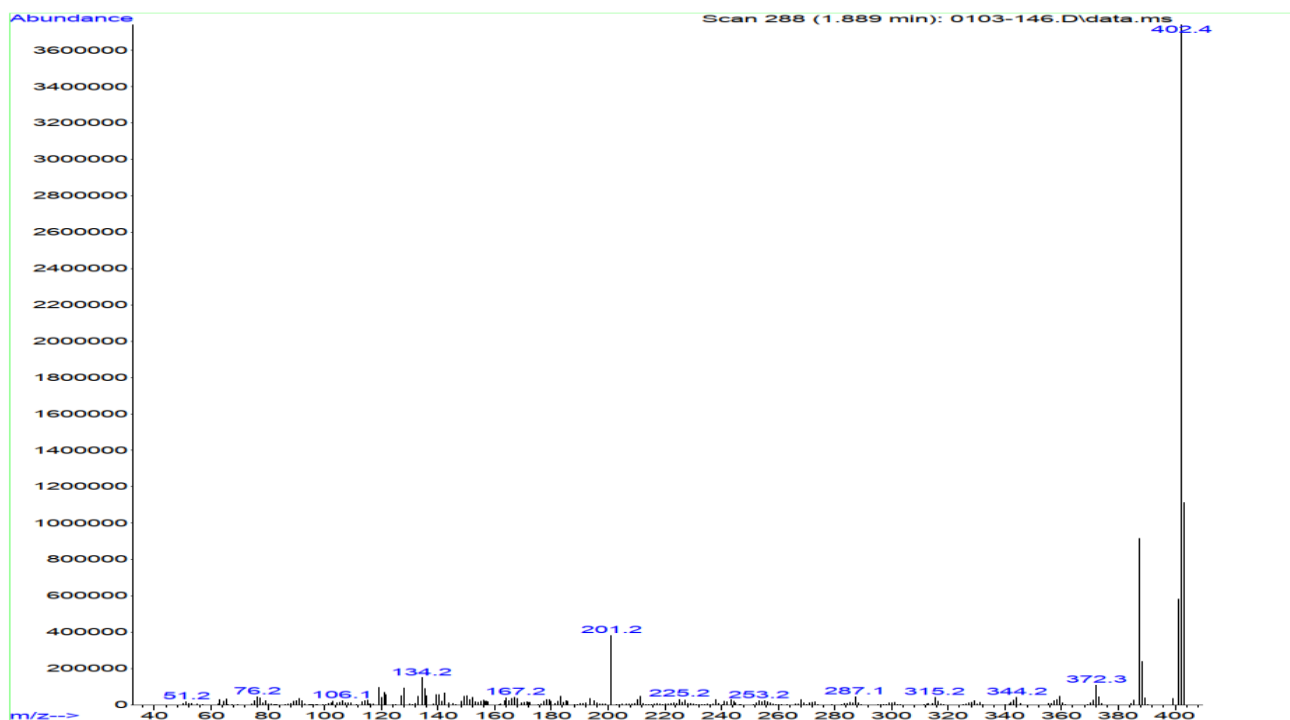


Figure (9): Mass spectrum of derivative 4c

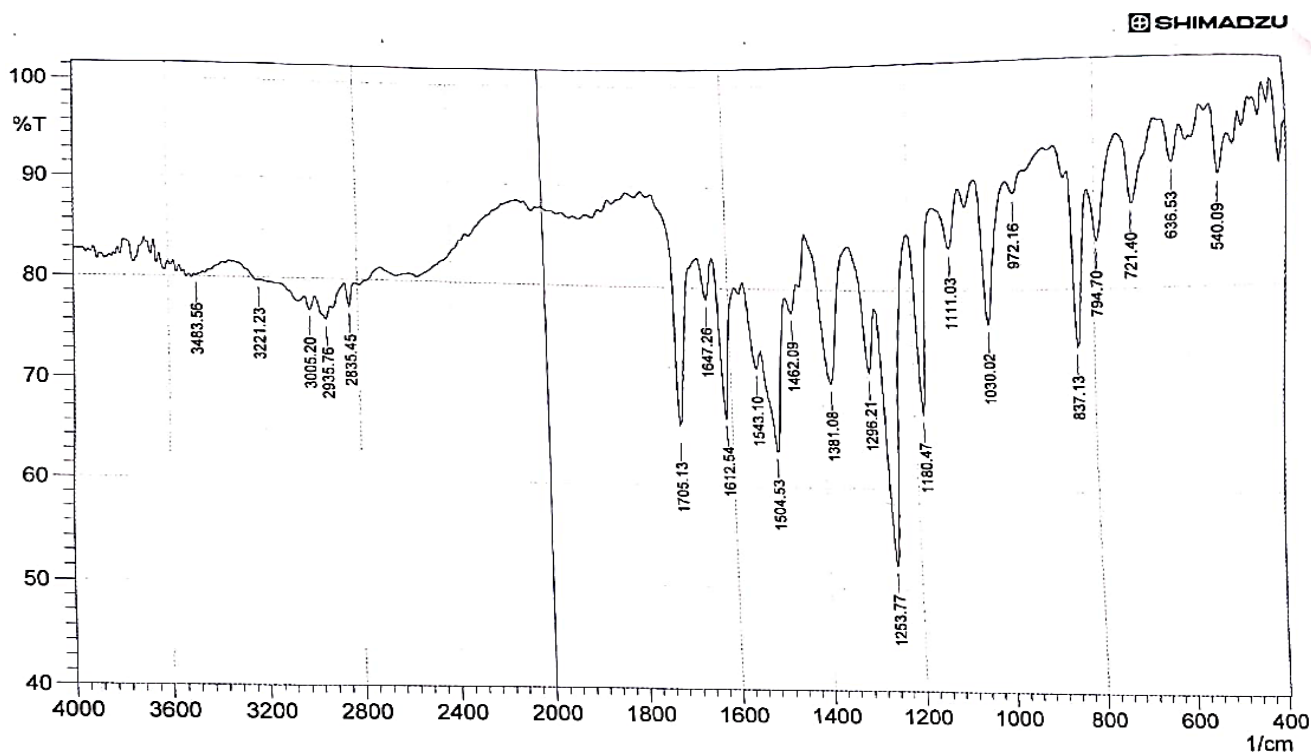


Figure (10): FT-IR spectrum of derivative 4d

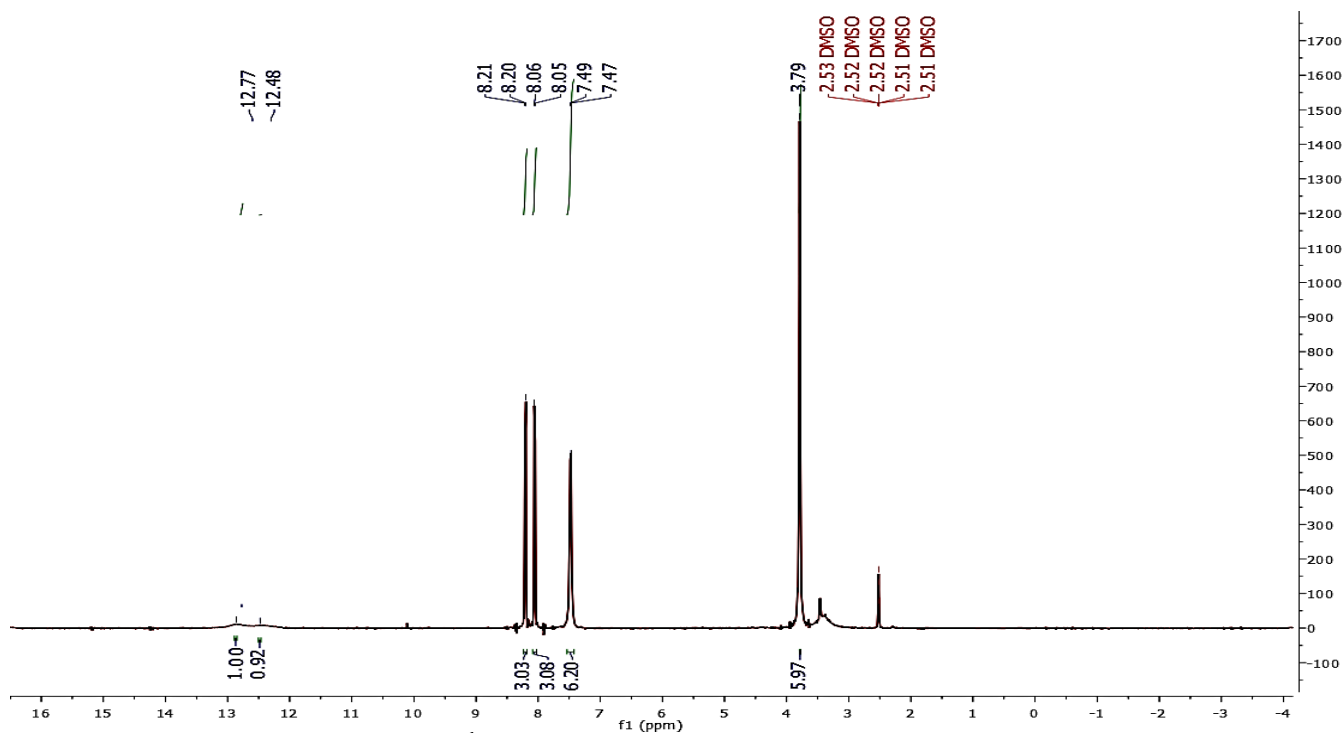


Figure (11): $^1\text{H NMR}$ (500 MHz, DMSO- d_6) spectrum of derivative 4d

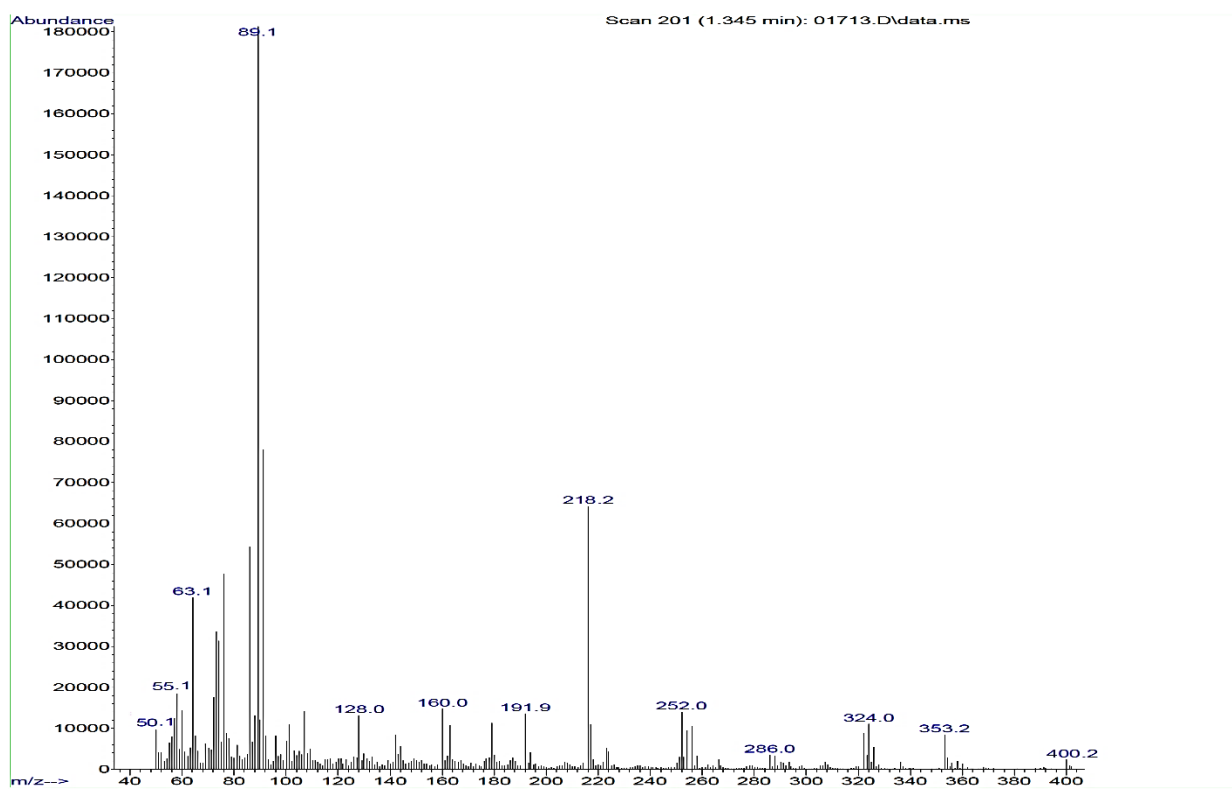


Figure (12): Mass spectrum of compound 4d

Evaluation of α -amylase and α -glucosidase Assay

The *in vitro* inhibitory activity of compounds (4a, 4b, 4c and 4d) was evaluated spectrophotometrically at 540 nm for α -amylase and 410 nm for α -glucosidase. The aim of diabetes therapy is to decrease postprandial hyperglycemia by inhibiting the digestive enzymes responsible for carbohydrate hydrolysis (alpha-amylase and alpha -glucosidase), glucose absorption is reduced. Inhibitors of these enzymes slow and prolong the digestion of carbohydrates, which in turn reduces the rate of glucose absorption and, as a result, reduces the increase in plasma glucose levels that occurs after a meal. In this study, inhibitory activity of tested compounds for α -amylase and α -glucosidase was examined and the findings are shown in Tables (2) and (3), α -amylase inhibitory studies demonstrated that all

samples have excellent to good inhibitory activity between 51% to 90% compared with the acarbose as a standard drug Table (1). The most potent active compound was 4d with 90% at highest concentration (250 mg/mL), which has substituent 4-COOH, while compounds 4a,4b and 4c with substituents 4-OH, 4-Cl and 4-OH,₃OCH₃, respectively exhibited 64% ,75% and 70% inhibitory activity.

In α -glucosidase assay, the results showed the reference drug acarbose exhibited the highest α -glucosidase inhibition (66%) followed by compounds 4b, 4d and 4a (55%), (52%) and (51%) respectively at their highest concentrations. Figures 1 and 2 show the percentage of α -amylase and α -glucosidase inhibition of the four tested compounds as a function of concentration compared with the acarbose.

Table 2: The percentage of inhibition for α -amylase using of 4a, 4b, 4c and 4d at different concentrations

Concentration ($\mu\text{g/ml}$)	% Inhibition 4a	% Inhibition 4b	% Inhibition 4c	% Inhibition 4d	% Inhibition acarbose
50	53	55	51	54	32
100	55	66	54	59	42
150	59	67	60	80	55
200	61	69	61	87	59
250	64	75	70	90	63

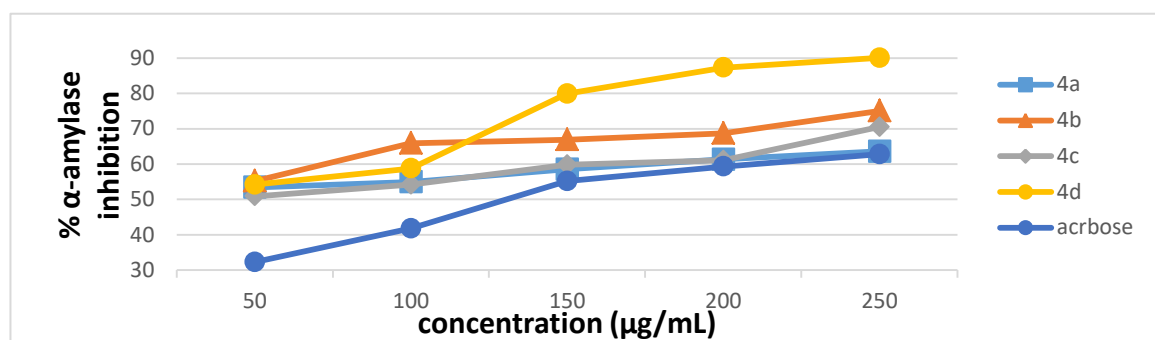
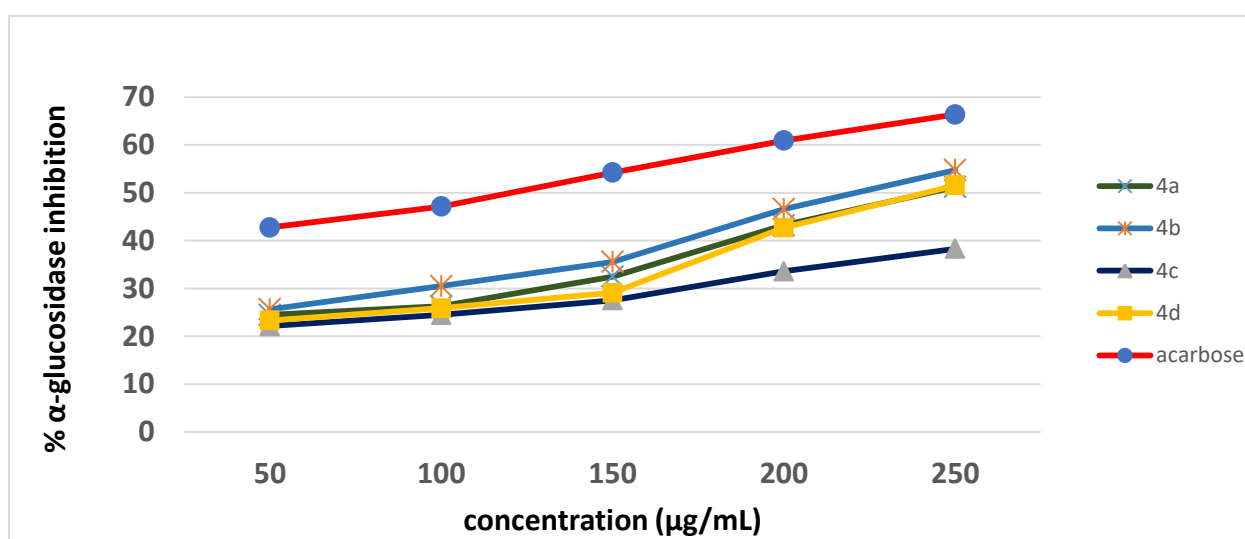


Figure (1) The % inhibition of the α -amylase enzyme by 4a-d and acarbose as a positive standard drug

Table 3: The percentage of inhibition for α -glucosidase using 4a, 4b, 4c and 4d at different concentrations

Concentration ($\mu\text{g/ml}$)	% Inhibition 4a	% Inhibition 4b	% Inhibition 4c	% Inhibition 4d	% Inhibition acarbose
50	24	26	22	23	43
100	26	31	24	26	47
150	32	36	28	29	54
200	43	47	34	43	61
250	51	55	38	52	66

Figure (2) The % inhibition of the α -glucosidase enzyme by 4(a-d) and acarbose as a positive standard drug

The current investigation indicates that 4b and 4d may be effectively treat postprandial hyperglycemia. The tested compounds showed a slightly lower inhibition of α -glucosidase enzyme as compared to α -amylase enzyme. The activity of examined compounds against these enzymes may be

because of the presence of free imino hydrogen inside imidazole ring [28] also, may be due to different substituent found in various position of imidazole derivatives are responsible for the antidiabetic inhibition activity[29]

Conclusion

In summary, a total of four new imidazole derivatives were prepared with good to excellent yields. Spectral analysis by Fourier - transform infrared spectroscopy (FT-IR), nuclear magnetic resonance (¹HNMR), and mass, among the tested compounds 4d showed the strongest effectiveness against α -amylase and α -glucosidase activity when

compared to the other compounds in the presence of the reference drug spectrometry (EI) were used to characterize them. All of synthesized compounds were evaluated for anti-hyperglycemic activity by α -amylase and α -glucosidase inhibition using the *in vitro* method.

Reference

- [1] R. T. Dewi *et al.*, "Inhibitory effect of Koji *Aspergillus terreus* on α -glucosidase activity and postprandial hyperglycemia," *Pakistan J. Biol. Sci.*, vol. 10, no. 18, pp. 3131–3135, 2007, doi: 10.3923/pjbs.2007.3131.3135.
- [2] S. S. Nair, V. Kavrekar, and A. Mishra, "In vitro studies on alpha amylase and alpha glucosidase inhibitory activities of selected plant extracts," *Eur. J. Exp. Biol.*, vol. 3, no. 1, pp. 128–132, 2013.
- [3] E. Onah, " α - amylase and α - glucosidase antidiabetic potential of ten essential oils from *Calophyllum inophyllum* Linn," vol. 04, pp. 253–260, 2020.
- [4] S. Wang, J. Yan, X. Wang, Z. Yang, F. Lin, and T. Zhang, "Synthesis and evaluation of the α -glucosidase inhibitory activity of 3-[4-(phenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one derivatives," *Eur. J. Med. Chem.*, vol. 45, no. 3, pp. 1250–1255, 2010, doi: 10.1016/j.ejmech.2009.12.031.
- [5] R. Tundis, M. R. Loizzo, and F. Menichini, "Natural Products as α -Amylase and α -Glucosidase Inhibitors and their Hypoglycaemic Potential in the Treatment of Diabetes: An Update," *Mini-Reviews Med. Chem.*, vol. 10, no. 4, pp. 315–331, 2010, doi: 10.2174/138955710791331007.
- [6] L. Narayanaswamy, S. Yarrappagaari, S. Cheemanapallia, and R. R. Saddala, "Synthesis , characterization , and hypoglycemic efficacy of nitro and amino acridines and 4-phenylquinoline on starch hydrolyzing compounds : an in silico and in vitro study," 2020.
- [7] E. Vessally, S. Soleimani-Amiri, A. Hosseinian, L. Edjlali, and A. Bekhradnia, "New protocols to access imidazoles and their ring fused analogues: Synthesis from: N - propargylamines," *RSC Adv.*, vol. 7, no. 12, pp. 7079–7091, 2017, doi: 10.1039/c6ra25816f.
- [8] A. Mermer, T. Keles, and Y. Sirin, "Recent studies of nitrogen containing heterocyclic compounds as novel antiviral agents: A review," *Bioorg. Chem.*, vol. 114, no. May, p. 105076, 2021, doi: 10.1016/j.bioorg.2021.105076.
- [9] I. Mohammadpoor-Baltork *et al.*, "Silica sulfuric acid: A versatile and reusable heterogeneous catalyst for the synthesis of oxazolines and imidazolines under various reaction conditions," *Catal. Commun.*, vol. 9, no. 5, pp. 894–901, 2008, doi: 10.1016/j.catcom.2007.09.017.
- [10] O. M. P. F. Luís, N. L. P. Ramos, S. P. G. Costa, and M. M. M. Raposo, "Synthesis, Characterization, and Preliminary Chemosensory Ability of a Novel 2,4,5-Tri(Hetero)Arylimidazole Based on an 8-Hydroxy-Quinoline Group," p. 15, 2022, doi: 10.3390/ecsoc-25-11748.
- [11] X. Moreira *et al.*, "An insight into the synthesis of cationic porphyrin-imidazole derivatives and their photodynamic inactivation efficiency against *Escherichia coli*," *Dye. Pigment.*, vol. 178, p. 108330, 2020, doi: 10.1016/j.dyepig.2020.108330.

- [12] F. Bellina, S. Cauteruccio, and R. Rossi, "Synthesis and biological activity of vicinal diaryl-substituted 1H-imidazoles," *Tetrahedron*, vol. 63, no. 22, pp. 4571–4624, 2007, doi: 10.1016/j.tet.2007.02.075.
- [13] S. R. Patel, R. V. Patil, J. U. Chavan, and A. G. Beldar, "Polymer based advanced recipes for imidazoles: a review," *Turkish J. Chem.*, vol. 46, no. 3, pp. 624–664, 2022, doi: 10.55730/1300-0527.3357.
- [14] A. A. Marzouk, A. M. Abu-Dief, and A. A. Abdelhamid, "Hydrothermal preparation and characterization of ZnFe₂O₄ magnetic nanoparticles as an efficient heterogeneous catalyst for the synthesis of multi-substituted imidazoles and study of their anti-inflammatory activity," *Appl. Organomet. Chem.*, vol. 32, no. 1, pp. 1–15, 2018, doi: 10.1002/aoc.3794.
- [15] Ö. Demirci *et al.*, "Acetylphenyl-substituted imidazolium salts: synthesis, characterization, in silico studies and inhibitory properties against some metabolic enzymes," *Mol. Divers.*, pp. 1–24, 2022, doi: 10.1007/s11030-022-10578-3.
- [16] Y. G. Zheng *et al.*, "Design, synthesis, and cytotoxic activity of novel 2H-imidazo[1,2-c]pyrazolo[3,4-e]pyrimidine derivatives," *Bioorg. Chem.*, vol. 109, no. November 2020, p. 104711, 2021, doi: 10.1016/j.bioorg.2021.104711.
- [17] D. S. Weinstein *et al.*, "Discovery of selective imidazole-based inhibitors of mammalian 15-lipoxygenase: Highly potent against human enzyme within a cellular environment," *Bioorganic Med. Chem. Lett.*, vol. 17, no. 18, pp. 5115–5120, 2007, doi: 10.1016/j.bmcl.2007.07.011.
- [18] H. D. Hanoon, E. Kowsari, M. Abdouss, M. H. Ghasemi, and H. Zandi, "Highly efficient and simple protocol for synthesis of 2,4,5-triarylimidazole derivatives from benzil using fluorinated graphene oxide as effective and reusable catalyst," *Res. Chem. Intermed.*, vol. 43, no. 7, pp. 4023–4041, 2017, doi: 10.1007/s11164-016-2847-6.
- [19] A. M. Venkatesan *et al.*, "5,5,6-Fused tricycles bearing imidazole and pyrazole 6-methylidene penems as broad-spectrum inhibitors of β -lactamases," *Bioorganic Med. Chem.*, vol. 16, no. 4, pp. 1890–1902, 2008, doi: 10.1016/j.bmc.2007.11.006.
- [20] G. Roman *et al.*, "Heme oxygenase inhibition by 2-oxy-substituted 1-(1H-imidazol-1-yl)-4-phenylbutanes: Effect of halogen substitution in the phenyl ring," *Bioorganic Med. Chem.*, vol. 15, no. 9, pp. 3225–3234, 2007, doi: 10.1016/j.bmc.2007.02.034.
- [21] B. Narasimhan, D. Sharma, and P. Kumar, "Biological importance of imidazole nucleus in the new millennium," *Med. Chem. Res.*, vol. 20, no. 8, pp. 1119–1140, 2011, doi: 10.1007/s00044-010-9472-5.
- [22] S. Balalaie and A. Arabanian, "One-pot synthesis of tetrasubstituted imidazoles catalyzed by zeolite HY and silica gel under microwave irradiation," *Green Chem.*, vol. 2, no. 6, pp. 274–276, 2000, doi: 10.1039/b006201o.
- [23] A. A. Marzouk, V. M. Abbasov, A. H. Talybov, and S. K. Mohamed, "Synthesis of 2,4,5-Triphenyl Imidazole Derivatives Using Diethyl Ammonium Hydrogen Phosphate as Green, Fast and Reusable Catalyst," *World J. Org. Chem.*, vol. 1, no. 1, pp. 6–10, 2013, doi: 10.12691/wjoc-1-1-2.
- [24] J. F. Zhou, G. X. Gong, X. J. Sun, and Y. L. Zhu, "Facile method for one-step synthesis of 2,4,5-triarylimidazoles under catalyst-free, solvent-free, and microwave-irradiation conditions," *Synth. Commun.*, vol. 40, no. 8, pp. 1134–1141, 2010, doi: 10.1080/00397910903043025.
- [25] J. Wang, R. Mason, D. VanDerveer, K. Feng, and X. R. Bu, "Convenient preparation of a novel class of imidazo[1,5-a]pyridines: Decisive role by ammonium acetate in chemoselectivity," *J. Org. Chem.*, vol.

- 68, no. 13, pp. 5415–5418, 2003, doi: 10.1021/jo0342020.
- [26] H. Ali, P. J. Houghton, and A. Soumyanath, “ α -Amylase inhibitory activity of some Malaysian plants used to treat diabetes; with particular reference to *Phyllanthus amarus*,” vol. 107, pp. 449–455, 2006, doi: 10.1016/j.jep.2006.04.004.
- [27] M. Govindappa, B. Hemashekhar, M. Arthikala, V. R. Rai, and Y. L. Ramachandra, “Results in Physics anti-inflammatory and antityrosinase activity of green synthesized silver nanoparticles using *Calophyllum tomentosum* leaves extract,” vol. 9, pp. 400–408, 2018.
- [28] N. Lohitha and V. Vijayakumar, “Imidazole Appended Novel Phenoxyquinolines as New Inhibitors of α -Amylase and α -Glucosidase Evidenced with Molecular Docking Studies,” *Polycycl. Aromat. Compd.*, vol. 42, no. 8, pp. 5521–5533, 2022, doi: 10.1080/10406638.2021.1939069.
- [29] D. Dahal, A. Subedee, K. Khanal, R. C. Basnyat, A. Campus, and T. M. Campus, “In Vitro Studies on Alpha-amylase Inhibitory Activities of,” *Amrit Res. J.*, vol. 2, no. 1, pp. 28–36, 2021.