Synthesis, Characterization, ADME Study and Antimicrobial Evaluation of New 1,2,3-triazole Derivatives of 2-phenyl benzimidazole.

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Abstract :

Novel 2-amino benzimidazole derivatives containing amide, azide and 1,2,3-triazole moieties have been synthesized. Compound **3** was synthesized by reaction of o-phenylenediamine with p-aminobenzoic acid. Compound **3** was converted into amide by treatment with chloroacetyl chloride to get compound **4**. Compound **4** and sodium azide were combined to create compound which has an azide group. Compound **5** was converted into 1,2,3-triazole derivatives by treatment with acetylene derivatives. FTIR, ^{1}H-NMR, and Mass spectra have been used to confirm the chemical structures of various substances. By using a technique called well diffusion agar, the final products were examined *in vitro* to predict activity against two kinds of gram-positive bacteria and two kinds of gram-negative bacteria as well as the antifungal activity against *Candida albicans* fungus. All the final products exhibited moderate to potent activity compared to Trimethoprim and Fluconazole as reference antibacterial and antifungal drugs respectively. Swiss ADME was also used to undertake ADME tests to determine the bioavailability, drug-likeness and topological polar surface area of the synthesized molecule. The results showed that every chemical tested was absorbed orally and followed the Lipinski rule.

Keywords: azide, amide, 1,2,3-triazole, acetylene derivatives, ADME.

تحضير، تشخيص، دراسة الحركية الدوائية وتقييم مضادات الميكروبات لمشتقات جديدة من ٢-فينيل بنزاميدازول تحتوي ١,٢,٣ - تريازول

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الخلاصة:

تم تصنيع مشتقات 2-أمينو بنزاميدازول تحتوي على معوضات أمايد، أزايد و ٣,٢,١-تريازول. تم تصنيع مركب ٣ من تفاعل فنيلين ثنائي الأمين مع حامض ٤-أمينوبنزويك.تم تحويل مركب ٣ الى أمايد بتفاعله مع كلوريد كلوروالأسيتيل للحصول على مركب ٤. مركب ٥ الذي يحتوي على مجموعة أزايد تم تحويله الى مشتقات ٣,٢,١-تريازول بتفاعله مع مشتقات الأسيتيلين الطرفية. تم توصيف المركبات من خلال قياس أطياف الأشعة تحت الحمراء وطيف الرنين البروتوني وطيف الكتلة. تم فحص النشاط المضاد للبكتريا والفطريات في المركب عن طريق تقنية اكار جيد الانتشار على البكتريا الموجبة للغرام والبكتيريا سلبية الغرام وفطر الكانديدا وقد أظهرت النتائج نشاطا جيدا مقارنة مع دواء الترايميثوبريم المضاد للبكتريا ودواء الفلوكانازول المضاد للفطريات. إضافة لذلك تم دراسة حركية الدواء للتنبؤ هل المركبات المصنعة ممكن اعطاؤها عن طريق الفم، وموقع الامتصاص، التوافر الحيوي، ومساحة سطح القطب القطبية، شبه الدوائية. أظهرت النتائج إن جميع المركبات يمكن امتصاصها عن طريق الجهاز الهضمي وأنها مستوفية لشروط قاعدة ليبينسكي.

الكلمات المفتاحية: ٣,٢,١-تريازول، أزايد، أمايد، مشتقات الأسيتيلين، الحركة الدوائية.

Introduction

Every day, infectious diseases brought on by microbes threaten human health and cause enormous economic loss.[1] Because of bacterial resistance to drugs and adverse effects on human health, the therapy for bacterial and fungal illnesses is not sufficient.[2] A new generation of antibiotics and antimicrobial agents must be created due to growing awareness of human health issues and microorganisms.[3] Since benzimidazole is an important pharmacophore in medicinal chemistry and pharmacology, pharmacists have been interested in the synthesizing of polyheterocycles based on these chemicals for a few decades.[4] The 1,2,3-triazole is a solely synthesized five–membered nitrogenated aromatic heterocyclic molecule.[5][6] The 1,2,3-triazole units plays a crucial role in a variety of medications and drug development candidates.[7] With its characteristics of structural stability and metabolic resistance, the 1,2,3-triazole molecule is a crucial pharmacophore in current medicinal chemistry research and is frequently employed in drug discovery. The 1,2,3-triazole ring is an important pharmacophore in a number of medicinal medications approved by the US Food and Drug Administration ,including the anti-epileptic drug rufinamide and antibacterial treatments tazobactam and cefatrizine.[8][9] This heterocyclic moiety enhances solubility and binding to biomolecular targets by participating in hydrogen bonds and dipole interactions.[10] The triazole ring is resistant to hydrolysis, oxidative, reductive, and enzymatic destruction.[11] In addition, medicinal benefits such as antibacterial[12], anticancer[13], and anti-inflammatory properties[14], among others, have been documented for 1,2,3-triazole hybrids.[15] By using the click chemistry method developed by Sharpless, a copper (I)-catalyzed version of the alkyne-azide cycloaddition reaction (CuAAC), a significant number of 1,2,3-triazole which are 1.4-disubstituted were produced in extremely high yields (Figure 1).[16][17]

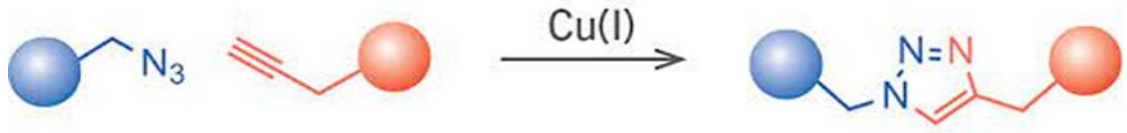
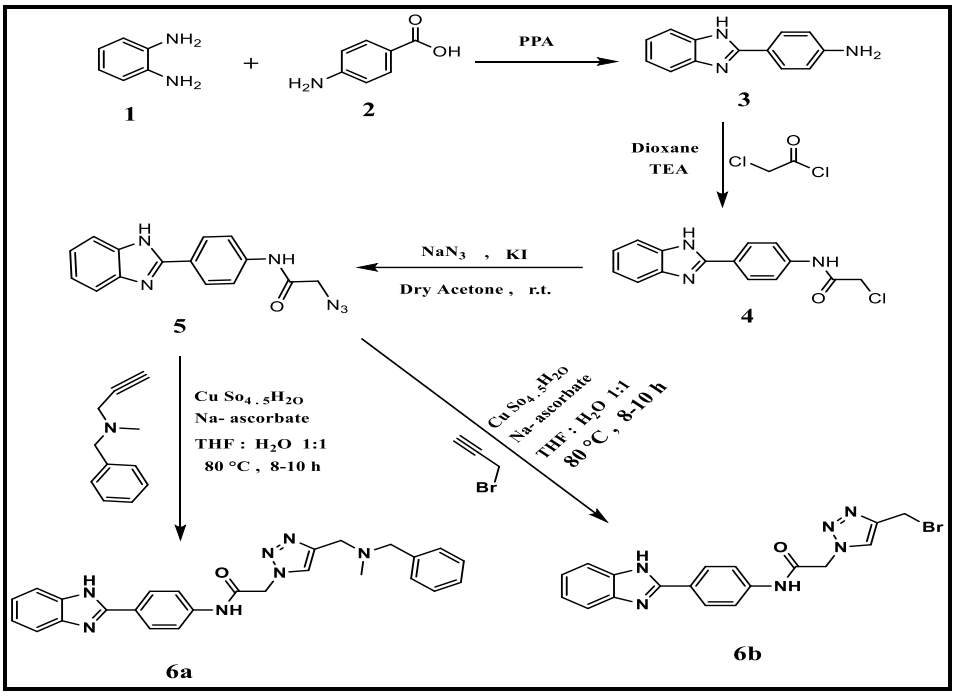


Figure (1): Scheme represents the common reaction that lead to the formation of 1,2,3-triazole-linked chemicals.

Materials and Methods:

Commercial sources provided the synthetic chemicals employed in the synthesis as well as the solvents needed in the purification, recrystallization, and analysis of generated products (BDH-England, Himedia-India, CDH-India, HyperChem-China and Sigma Aldrich-Germany).The melting point of the synthesized compounds were determined using the (Digital Stuart scientific SMP30) and was uncorrected. The infrared spectrum (IR) was measured by using a (SHIMADZU FT-IR 8400S spectrophotometer) within the range (4000-600 cm^{-1}), at Department of Chemistry/College of science/ University of Mustansiriyah /Iraq. The ^{1}H-NMR spectra were measured on (Bruker DMX-500 NMR spectrophotometer) 500MHz, using DMSO- d_6 solution with TMS (tetramethylsilane) as an internal standard reference, at Sharif University of Technology-Iran. Mass spectra were recorded on (VARIAN 3900, 5793 Network Mass Selective Detector), at Tehran University-Iran.

Chemical synthesis:



Scheme (1): The synthesis of the final products and intermediates.

Synthesis of 4-(1H-benzo[d]imidazole-2-yl) aniline (3):

A suitable amount of polyphosphoric acid (PPA) was mixed with equimolar amounts of o-phenylenediamine **1** (1.08g, 10mmol) and 4-aminobenzoic acid **2** (1.37g, 10 mmol) to give a stirrable paste. After being gradually heated to 160°C, then the resulting mixture was agitated at that temperature for four hours and allowed to cool to room temperature, and then poured in a thin stream into ١٥٠ ml of rapidly stirring water. Then neutralized with a solution of 40% NaOH. The precipitated chemical compound was filtered, collected, and then dried before being recrystallized from ethanol.[18][19] (Light brown powder), yield = 82.9%, m.p.= 235–236°C, FTIR υ (cm^{-1}), 3330 (N-H of secondary amine), 3280, 3205 (N-H Asymmetric, symmetric primary amine), 3043 (C-H of aromatic ring), 1616 (C=N of imidazole ring). ^{1}H-NMR (DMSO- d_6, 500MHz) (ppm), 3.56(2H, singlet, NH_2), 7.20 -7.24 (2H,doublet, CH of the benzene ring), 7.26 – 7.70 (4H, multiplet, benzimidazole ring), 7.72 – 7.76 (2H,doublet, CH of the benzene ring), 12.47 (1H, singlet, NH proton). Mass, molecular ion (m/z, 209.00) calculated M.W (209.25 g/mol).

Synthesis of N-(4-(1H-benzo[d]imidazole-2-yl) phenyl)-2-chloroacetamide (4):

Triethylamine (0.5 ml) and compound **3** (2.09 g, 10 mmol) were dissolved in dioxane (30 ml) and agitated for 15 minutes. Then, chloroacetyl chloride (10 mmol, 0.79 ml) was gradually added to the solution of reaction and stirred for two hours. After the reaction was finished, the fluid was poured, while being constantly stirred, onto crushed ice. The resulting solid was filtered out, washed with water, and recrystallized from ethanol to produce the pure chemical compound.[19] (Light green powder), yield = 79 %, m.p. = 284-286 °C, FTIR υ (cm^{-}1), 3267 (N-H secondary amide), 3174 (N-H of secondary amine), 3078 (C-H of aromatic ring), 2929, 2854 (C-H alkane, Asymmetric, symmetric), 1668 (C=O, amide). ^{1}H-NMR (DMSO-d_6, 500MHz) (ppm), 4.19 (2H,singlet , CH_2 of amide) , 7.46 – 7.78 (8H, multiplet, for aromatic ring protons), 9.66 (1H , singlet, for NH amide) , 12.66 (1H , singlet, for NH

benzimidazole). Mass, molecular ion (m/z, 285.00), calculated M.W (285.73 g/mol).

Synthesis of N- (4-(1H-benzo[d]imidazole-2-yl) phenyl)-2-azidoacetamide (5):

Potassium iodide (1.6g, 10 mmol), compound **4** (2.8g), and 15 ml dry acetone were stirred for two hours. The residue was added to the sodium azide solution (0.6g, 10mmol) in (10 ml) water, and the resulting mixture was also stirred for a further hour. Once the reaction was complete, the mixture was poured onto crushed ice while being continuously stirred. Filtration was used to collect the generated solid that then recrystallized by using ethanol to give a pure compound.[20] Light pink powder, yield = 83.4 %, m.p. = 305 -307°C , FTIR υ (cm^{-1}), 3240 (N-H of secondary amide) , 3207(N-H secondary amine), 3064 (of C-H of aromatic ring), 2953, 2879 (C-H alkane, Asymmetric ,symmetric), 2207 (N=N=N-, azide group), 1661 (C=O, carbonyl amide) , 1637 (C=N). ^{1}H-NMR (DMSO- d_6, 500MHz) (ppm), 4.22 (2H, singlet, for CH_2 of amide) , 6.72 – 6.75(2H, doublet, aromatic ring protons near NH group) , 7.22 – 7.25 (2H, doublet, aromatic ring protons far NH group), 7.52 – 7.75 (4H, multiplet, benzimidazole ring), 9.82 (1H, singlet, for NH amide) ,12.52 (1H , singlet, benzimidazole ring). Mass, molecular ion (m/z, 292.00), calculated M.W (292.30 g/mol).

Synthesis of 1,2,3-triazole derivatives (6a, b):

To a solution of a terminal alkyne derivative (1 mmol) (Table 1) in a 1:1 combination of tetrahydrofuran (THF) and water (20 ml), Copper (II) sulfate pentahydrate (0.٠٥g), sodium ascorbate (0.٠٧٩g), and azide compound (1 mmol) were added with stirring. For 8-10 hrs. , the resultant mixture was stirred at 80 °C. After the addition of distilled water, the reaction mixture had been quenched. The solid that had been produced as a result of this process was then filtered, washed with a saturated sodium chloride solution, and dried. The required 1,2,3-triazoles were produced by recrystallizing the reaction mixture from ethanol.[21]

Table 1: The amount of terminal alkynes used in the preparation of (6a, b) derivatives.

R	Terminal alkynes	The amount used in gram
a	N-Methyl-N-propargylbenzylamine.	0.159 g
b	Propargyl bromide.	0.118 g

Compound 6a : N-(4-(1H-benzo[d]imidazole-2-yl)phenyl)-2-(4-((benzyl(methyl)amino) methyl)-1H-1,2,3-triazole-1-yl)acetamide.

Light brown powder, yield = 70.4 %, m.p. = 198-200°C, FTIR υ (cm^{-1}), 3158 (N-H for secondary amide), 3122 (N-H for secondary amine), 3061 (C-H for aromatic ring), 2958, 2833 (C-H of alkane, asymmetric and symmetric), 1651 (C=O of carbonyl amide), 1595, 1556 (C=C of aromatic ring) 1585 (N=N of triazole ring). ^{1}H-NMR (DMSO-d_6, 500MHz) (ppm), 2.90 (3H, singlet, for CH_3), 3.58 (2H, singlet for CH_2 near phenyl group), 3.78 (2H, singlet for CH_2 of amide), 4.21 (2H, singlet, for CH_2 between the carbonyl and the triazole ring), 7.40 – 7.52 (5H, multiplet, for phenyl group), 7.56 (1H, singlet, for CH proton of triazole ring), 7.58 – 7.97 (4H, multiplet, for benzimidazole ring), 7.98 – 8.20 (2H, doublet, for aromatic ring protons near NH), 8.20 – 8.22 (2H, doublet, for aromatic ring protons far NH), 9.81 (1H, singlet, for NH amide), 12.46 (1H, singlet, for NH of benzimidazole). Mass, molecular ion (m/z, 451.00), calculated M.W (451.53 g/mol).

Compound 6b : N- (4- (1H-benzo[d]imidazole-2-yl) phenyl)-2-(4-(bromomethyl)-1H-1,2,3-triazole-1-yl)acetamide.

Off white powder, yield = 88 %, m.p.= 267-268°C, FTIR υ (cm^{-1}), 3211 (N-H of secondary amide), 3164 (N-H of secondary amine), 3030 (C-H of aromatic ring), 2976, 2876 (C-H of alkane, asymmetric, symmetric), 1666 (C=O , of carbonyl amide),1602, 1525 (C=C of aromatic ring) 1585 (N=N of triazole ring). ^{1}H-NMR (DMSO-d_6,500MHz) (ppm), 4.24 (2H, singlet, for CH_2 between the carbonyl and the triazole ring), 5.24 (2H, singlet, CH_2-Br), 7.10 (1H, singlet, for CH proton of triazole ring), 7.21 – 7.42 (4H, multiplet, of benzimidazole ring), 7.44 – 7.75 (2H, doublet, for aromatic ring protons near NH), 7.78 – 7.81 (2H, doublet, for aromatic ring protons far NH), 9.85 (1H, singlet for NH amide), 12.44 (1H, singlet for NH of benzimidazole). Mass, molecular ion (m/z, 411.00), calculated M.W (411.26 g/mol).

Computational procedure:

With the use of Swiss ADME, absorption, distribution, metabolism, and excretion (ADME) of the prepared chemical compounds have been anticipated.

Procedure of ADME:

Swiss ADME (Server) was used to carry out the pharmacokinetic profile (ADME) Study. Chem. Sketch (v. 12) was used to draw the products (6a, b), which were changed to the term SMILE by the Swiss ADME tool to evaluate physicochemical and pharmacokinetic parameters. BOILED EGG was used to determine the tiny molecule's polarity and lipophilicity.[22]

Antimicrobial screening:

The antibacterial and antifungal activities of the final products under test were performed at the Department of biology – Science College –Mustansiriyah University –Iraq. The synthesized products were tested for their activity against four bacterial species *in vitro*, *Staphylococcus aureus*, *Staphylococcus epidermidis* as gram-positive bacteria, and *Escherichia coli*, *Klebsiella pneumonia* as gram-negative bacteria. Also, the products tested against *Candida albicans* fungus to evaluate its antifungal activity. The well Diffusion Method was used to carry out these antibacterial and antifungal tests. The isolates were obtained from several clinical sources. Trimethoprim and fluconazole were the reference drugs for their antibacterial and antifungal effects, respectively. 70 % of DMSO was used as a negative control.

Sequential dilution preparation of the newly synthesized compounds:

- To create the stock solution (1000 µg/ml), 5 mg from each chemical was dissolved in 5 ml of dimethyl sulfoxide (70%).
- The first dilution (500 µg/ml) was made by mixing DMSO (2.5 ml) with 2.5 ml of the stock solution.
- The second dilution (250 µg/ml) was prepared by mixing 2.5 ml of DMSO with 2.5 ml of the first dilution.
- The third dilution (125 µg/ml) was prepared by mixing 2.5 ml of DMSO with 2.5 ml of the second dilution.
- The fourth dilution (62.5 µg/ml) was prepared by mixing 2.5 ml of DMSO with 2.5 ml of the third dilution.

These steps are performed for compounds (**6a, b**) and standard drugs.

Sensitivity Assay:

The antifungal and antibacterial activities of each derivative were evaluated using well diffusion agar method on pure cultures of all types of bacteria and fungi. The inoculum of fungus had been incubated at 37°C for 72 hours, whereas the inoculum of bacteria was initially subcultured in brain heart infusion broth and incubated at that temperature for a period of range from 18 to 24 hours. After incubation, a loopful of each species was added to a tube with a vortex well and 3 ml of normal saline. The concentration of 1.5 ×108 CFU/ml was

achieved by employing the McFarland turbidity standard of number 0.5 for each bacterium that was injected using a glass spreader on the surface of previously prepared plates of Mueller Hinton Agar (MHA). Three wells with 6 mm diameter were punched into the agar after the plate had dried. Then, three wells were created in each of the tested bacteria and fungus' agar plates, and 100 µl of the products' concentrations (500,250,125 and 62.5µg/ml) were added to the wells on the plate MHA. The negative controller used was dimethyl sulfoxide. By measuring the inhibition zone diameter, the antimicrobial effect of the plates was evaluated after being maintained warm at 37°C for 24 hours.[23] Additionally, the plates were kept warm at 37°C for 72 hours, and the antifungal effect was evaluated by measuring the diameter of the inhibitory zone. Based on the measurement of inhibition zone in diameter created across the well, as shown in (Table 2), the antibacterial and antifungal actions were assessed.

Result and Discussion

Chemical synthesis:

The synthesis of the target compounds (**6a, b**) through their intermediates was achieved successfully. In the current work, we predict the synthesis of new 1,2,3-triazole derivatives.

The target compounds were derived from 4-(1H-benzo[d]imidazole-2-yl) aniline, which were obtained by the reaction between o-phenylenediamine **1** and p-amino benzoic acid **2**. Chloroacetyl chloride was used to transform compound **3** into an amide to create compound **4**. A compound with an azide group was created by combining compound **4** and sodium azide. Compound **5** was treated with acetylene derivatives to create 1,2,3-triazole derivatives as shown in (scheme 1).

The FT-IR spectrum of compound **3** showed the disappearance of the broad band of OH group on carboxylic acid at (3200-2545 cm^{-1}) and C=O band of carboxylic acid at (1658 cm^{-1}) that are present in the starting compound (p-amino benzoic acid). The ^1H -NMR spectra of compound **3** showed the appearance of singlet for terminal NH_2 at 3.56 (δ, ppm), multiplet for aromatic ring protons at 7.26 – 7.70 (δ, ppm) and singlet for NH proton at 12.47(δ, ppm).

The FT-IR spectrum of compound **4** showed the appearance of a band of NH secondary amide at (3267 $cm^{-1)}$, band of CH alkane at (2929- 2854 cm^{-1}), and a band of carbonyl amide at (1668 cm^{-1}).The ^1H -NMR spectra of compound **4** showed the appearance of singlet for CH_2 of side chain at 4.19 (δ, ppm), multiplet for aromatic ring protons at 7.46 – 7.78 (δ, ppm) and singlet for NH amide at 9.66 (δ, ppm).

Compound **5** was characterized by the appearance of the FT-IR absorption band of the azide group at (2207 cm^{-1}) as displayed in figure (2).

The ^1H -NMR spectra of compound **5** showed the appearance of singlet for CH_2 of side chain at 4.22 (δ, ppm), multiplet for aromatic ring protons at 7.52 – 7.75 (δ, ppm) and singlet for NH amide at 9.82 (δ, ppm).

Compound **6a** was characterized by the disappearance of the FT-IR characteristic absorption band of azide group at (2207 cm^{-1}) that present in compound **5** and the appearance of peak of C-H alkane (Asymmetric and symmetric) at (2958-2833 cm^{-1}) as shown in figure (3).

The ^1H -NMR spectra of compound **6a** showed the appearance of singlet for CH_3 at 2.90 (δ, ppm), singlet for CH_2 at 3.58-3.78 (δ, ppm), singlet for CH_2 between the carbonyl and the triazole ring at 4.21 (δ, ppm), multiplet for aromatic ring protons at 7.40 – 7.52 (δ, ppm), singlet for CH proton of triazole ring at 7.56 (δ, ppm) and singlet for NH amide at 9.81 (δ, ppm) as shown in figure (4).

The Mass spectra of the synthesized compound **6a** as displayed in figure (5) gave a signal at (451 m/z), representing the molecular ion and this corresponds to the calculated molecular weight of N-(4-(1H-

benzo[d]imidazole-2-yl)phenyl)-2-(4-((benzyl(methyl)amino)methyl)-1H-1,2,3-triazole-1-yl)acetamide.

The compound **6b** was characterized by the disappearance of the FT-IR absorption band of the azide group at (2207 cm^{-1}) that present in compound **5,** and the appearance of a band of NH of secondary amide at (3211 cm^{-1}), band of C-H alkane (Asymmetric and symmetric) at (2976-2876 cm^{-1}), band of N=N of triazole ring at (1585 cm^{-1}), and a band of C-Br at 667 cm^{-1}. The ^{1}H -NMR spectra showed the appearance of for CH_2 of side chain at 4.24(δ, ppm), singlet for CH_2 protons between the carbonyl and the triazole ring at 5.24 (δ, ppm), singlet for CH proton of triazole ring at 7.10 (δ, ppm) multiplet for aromatic ring protons at 7.21 – 7.42 (δ, ppm) and singlet for NH amide at 9.85 (δ, ppm).

The Mass spectra of the synthesized compound **6b** gave a signal at (411 m/z) representing the molecular ion and this corresponds to the calculated molecular weight of N-(4-(1H-benzo[d]imidazol-2-yl)phenyl)-2-(4-(bromomethyl)-1H-1,2,3-triazol-1-yl)acetamide.

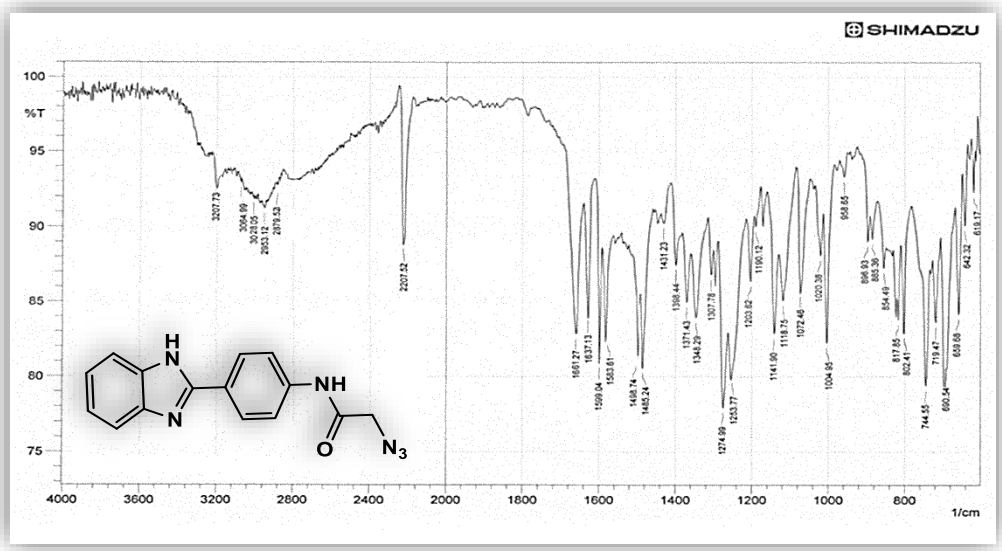


Figure (2): FT-IR Spectrum of Compound (5)

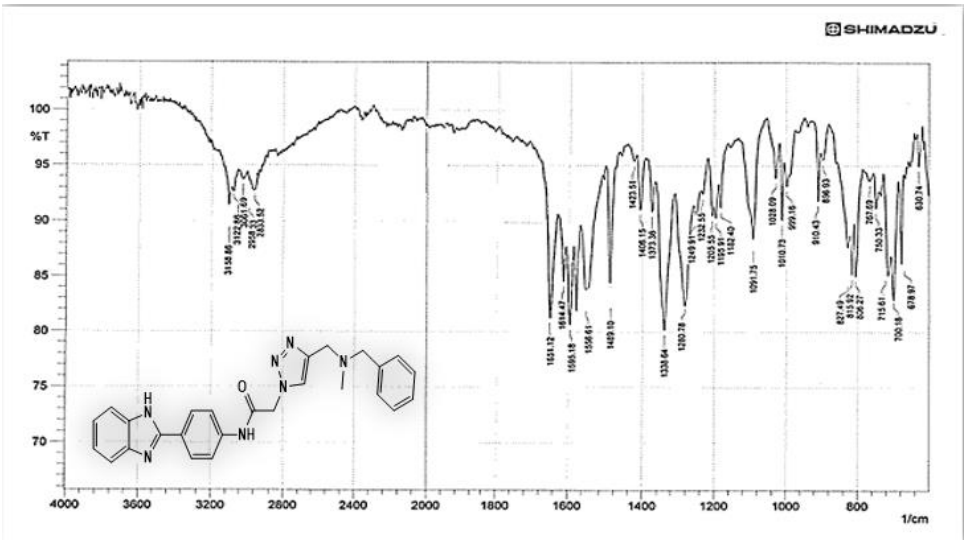


Figure (3): FT-IR Spectrum of Compound (6a)

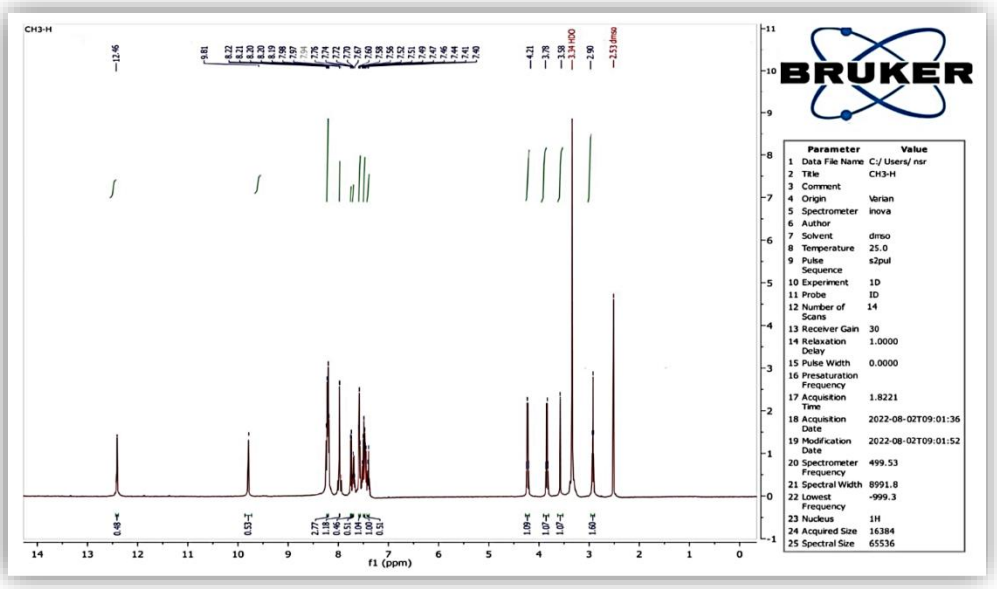


Figure (4): ^{1}H -NMR Spectrum of compound (6a).

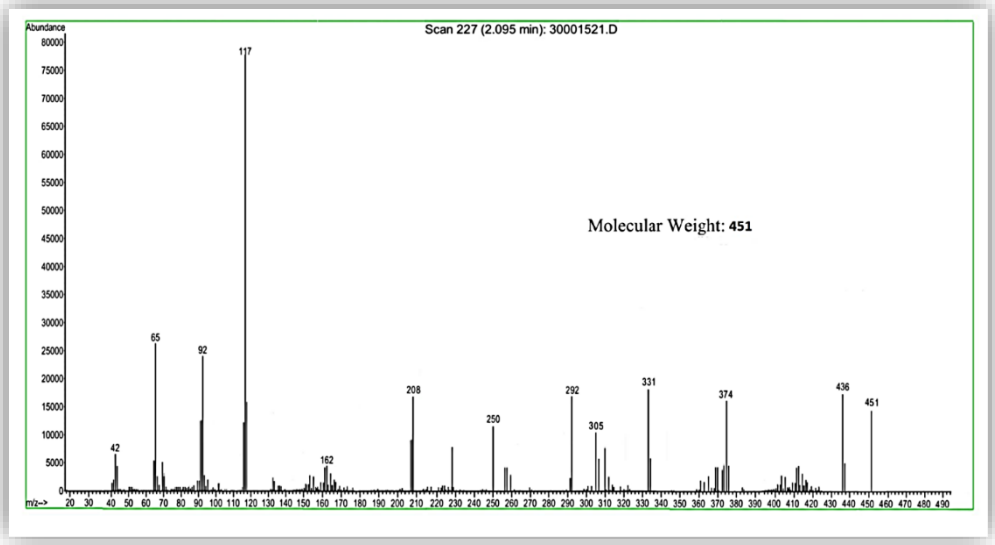


Figure (5): Mass Spectrum of Compound (6a)

Antimicrobial assay:

Candida albicans were utilized to assess the antifungal activity of the produced compounds (**6a, b**) at concentrations of (500,250,125, and 62.5 µg/ml), while DMSO was employed as the control at a concentration of 70%. Fluconazole served as a standard medication and the zone of inhibition in (mm) for each investigated chemical concentration is illustrated in the table (2).The tested compounds (**6a, b**) exert significant antifungal activity and compound **6b** showed better antifungal activity than the reference drug and other compounds at 125 µg/ml concentration.

Two gram-negative bacteria (Escherichia coli, Klebsiella pneumonia) and two gram-positive bacteria (Staphylococcus aureus, Staphylococcus epidermidis) were used in the antibacterial assay and Trimethoprim was used as a reference drug. The synthesized chemical (**6a, b**) was evaluated for its antibacterial activity at concentrations of (500,250,125, and 62.5 µg/mL), whereas DMSO was employed as a control at a concentration of 70%. The

zone of inhibition in millimeters for each measured concentration of the compounds tested was shown in table (2).When compared with DMSO as a control group, the tested derivative exerted moderate to potent antibacterial activity against four bacterial species, which were used in this assay. Compound **6a** displayed the same antibacterial activity as the reference drug Trimethoprim against Staphylococcus aureus at 250 µg/ml concentration while compound **6b** exhibited better antibacterial activity than Trimethoprim and **6a** at the same concentration. Compound **6a** was exhibited nearly the same activity as Trimethoprim against both gram-negative bacteria (Escherichia coli, Klebsiella pneumonia) at 250 µg/ml concentration, but compound **6b** displayed more potent antibacterial activity than both compound **6a** and reference medication at the same concentration.

Table 2: Antimicrobial activity of compounds (6a, b), Fluconazole and Trimethoprim against tested fungi and bacteria.

Compound	Conc. (µg/ml)	Inhibition zone (mm)				
		Fungi	Gram-positive bacteria		Gram-negative bacteria	
		Candida albicans	*Staphylococcus aureus*	*Staphylococcus epidermidis*	*E. coli*	*Klebsiella pneumonia*
Fluconazole	**500**	34	-	-	-	-
	250	26	-	-	-	-
	125	16	-	-	-	-
	62.5	13	-	-	-	-
Trimethoprim	**500**	-	٢٠	٣٣	٢٢	٢١
	250	-	١٧	٣٠	١٥	١٢
	125	-	١٥	٢٩	١٠	١٠
	62.5	-	١٠	٢٦	٠	٩
DMSO	**70%**	-	-	-	-	-
6a	**500**	21	١٩	١5	17	١٥
	250	19	١٧	١4	١٦	1٣
	125	17	٠	١2	٠	٩
	62.5	0	٠	١0	٠	٠
6b	**500**	25	2٠	٢١	20	1٨
	250	2٣	19	٢٠	18	١٥
	125	2١	١٠	1٠	١٢	٨
	62.5	12	٠	٠	0	٠

Note: − = no inhibition zone observed. Inhibition zones 15 mm or more was declared as strong, from 8 to 15 mm as moderate and from 1 to 8 mm as weak activities.

Interpretation of ADME results:

Swiss ADME investigated the ADME properties of the desired substances (**6a, b**). We evaluated the ADME (absorption, distribution, metabolism, and excretion) approach for analyzing substances. In addition, the (TPSA) topological polar surface area, which is a significant quality that has been linked to how well drugs are absorbed by the body, was calculated. Because of this, it is thought that drugs with a topological polar surface area greater than 140 and passive absorption have a low oral bioavailability.[24] According to the data of ADME prediction, all of the final chemicals were within the acceptable range, had a

topological polar surface area less than 140 and had a bioavailability of 0.55, indicating that they enter the systemic circulation. The ligands also adhere to fingerprints of the molecular drug-likeness structure keys, LogP and LogS, Lipinski's Rule of five and the topological descriptors (table 3).All substances had excellent absorption rates, which was to be expected given their strong intestinal absorption

Table 3: Results of the final derivatives' ADME study.

Comp.	Formula	M.W	H-bond acceptor	H-bond donor	MR	TPSA	GIT Abs.	BBB permeate	Bio Availability	Lipinski violation
6a	$C_{26}H_{25}N_7O$	451.52	5	2	132.17	91.73	High	No	0.55	0 violation
6b	$C_{18}H_{15}BrN_6$	411.26	4	2	103.04	88.49	High	No	0.55	0 violation

Conclusion

1,2,3-triazole moiety remains one of the most frequently studied fields in medicinal chemistry. The ADME analyses revealed that the newly synthesized chemicals (**6a** and **6b**) satisfied the requirements of Lipinski rule, and these compounds were absorbed from GIT. The proposed triazole derivatives were successfully synthesized, and their structural formula was established by using Infrared spectroscopy, ^{1}H-NMR and Mass spectroscopy. The results of antibacterial and antifungal examination reveal that 1,2,3-triazole pharmacophore exhibit moderate to potent antibacterial and antifungal activities.

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