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Synthesis And Biological Screening Of Quinoline-Linked Oxadiazole Derivatives As Potent Antibacterial Agents

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Abstract **- Ten derivatives of quinolin-8-yl[(5-aryl-1,3,4-oxadiazol-2-yl)sulfanyl] acetate were synthesized using a range of methods. The structures of the generated compounds were determined using IR, 1H NMR, and mass spectroscopy examinations. The antibacterial efficacy of the chemicals generated was evaluated using the bacterial strains Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa, and Escherichia coli. The study's findings suggest that a number of the chemicals exhibit promising antibacterial properties.**

Key Words**: acetamide, quinoline, oxadiazole, and biological evaluation.**

I. INTRODUCTION

Heterocyclic chemistry is an essential part of organic chemistry, accounting for more than half of the literature. It involves the study of numerous novel compounds that contain different types of atoms in their ring structures. Oxadiazole is a notable heterocyclic structure formed by the presence of nitrogen and oxygen heteroatoms in a five-membered ring. This oxadiazole nucleus has multiple biological applications, such as being anti-tubercular15 & 16, anti-inflammatory13, antioxidant6–9, anticancer10–12, analgesic14, anti-convulsant17–18,Alzheimer19, antiallergic20, and more. We have synthesized a collection of compounds derived from the 1,3,4-oxadiazole core, which exhibit promising antibacterial properties.

II. MATERIAL AND METHODS

The production of the derivatives involved the use of laboratory and analytical grade chemicals. The open capillary method was employed to determine the melting points of the derivatives, which exhibit no correlation. The Thin Layer Chromatography (TLC) method was selected to ascertain the purity of the substances. The mobile phase was accurately sprayed onto silica gel-coated metal plates (Merk), and the resultant spots were examined using a UV chamber. The NMR spectra were recorded using the Bruker AM-400 instrument, with DMSO serving as the solvent and TMS as the internal standards. The Perkin-Elmer 237 spectrophotometer was utilized to capture infrared spectra by employing a KBr pellet. The JMS 600-H equipment from the MS route was utilized for the purpose of capturing mass spectra.

The overall technique for preparing quinolin-8-yl[(5-aryl-1,3,4-oxadiazol-2-yl)sulfanyl]acetate is as follows:

Step 1: Synthesis of aryl enoates (2) The process entailed combining 6.0 ml of concentrated H2SO4 with different substituted aromatic acid (0.1 mol) in the presence of 80 ml of methanol, followed by refluxing the mixture for a duration of 12 to 14 hours. After introducing the reaction mass to crushed ice and thoroughly agitating it, the resulting products were extracted from the reaction mass. The products were purified using ethyl alcohol. The TLC method was utilized to monitor the development of the reaction, using an eluent mixture consisting of toluene and acetone in a ratio of 8:2.

Step II: Synthesis of Aryl Hydrazides (3) -In this experiment, a solution containing 0.1 mol of aryl enoate and 0.2 mol of hydrazine hydrate was prepared in 80 ml of methyl alcohol. The solution was then heated under reflux for a period of 12 to 15 hours to synthesize several substituted benzohydrazides. After undergoing the process of chilling and thorough mixing in crushed ice, the reaction mixture was then separated into its individual constituent components. The products were recrystallized using ethyl alcohol. The TLC method was employed to monitor the course of the reaction using a toluene:acetone (8:2) eluent.

Step III involves the synthesis of 5-aryl-1,3,4-oxadiazole-2-thiol.

(4) - A solution containing aryl hydrazide (0.1 mol), CS2 (0.1 mol), and alcoholic KOH (0.05 mol) was heated under reflux

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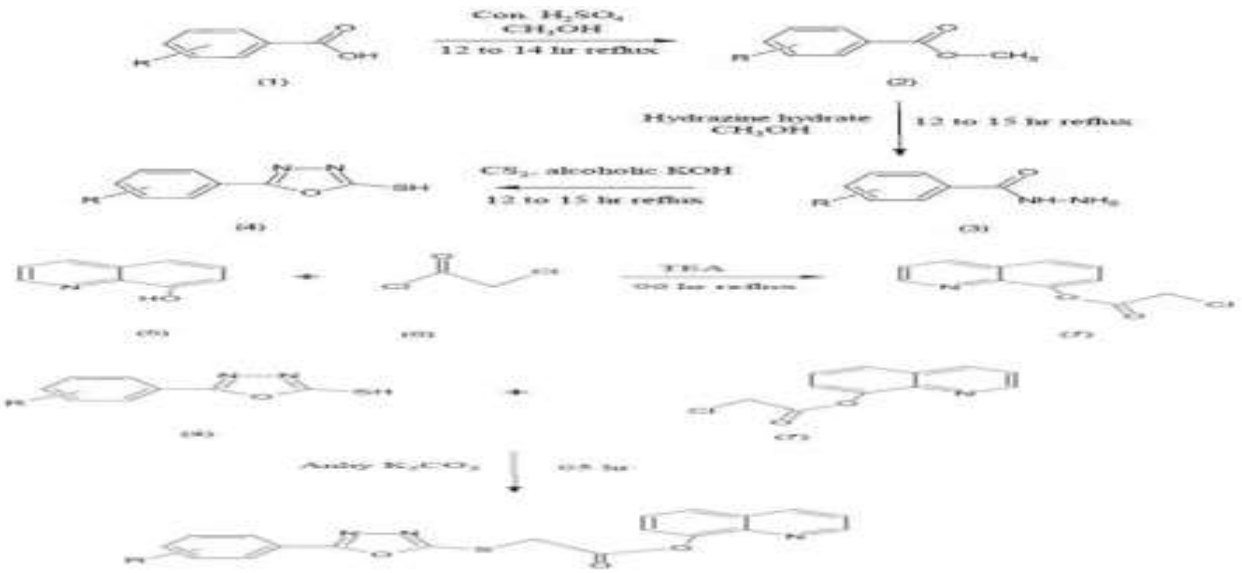
in methyl alcohol (80 ml) for a period of 12 to 15 hours to synthesize 5-aryl-1,3,4-oxadiazole-2-thiol. The resulting substance was neutralized by adding 2N HCl to crushed ice. In order to segregate the products, the bulk was subjected to filtration followed by rinsing with chilled water. Ethyl alcohol has the property of causing the products to undergo recrystallization. Using a mixture of toluene and acetone in a ratio of 8:2 as the solvent, thin-layer chromatography (TLC) was employed to monitor the progress of the reaction.

Step IV involves the synthesis of quinolin-8-yl chloroacetate (7).

The solution containing 0.1 mol of quiniol-8-ol, 2-4 drops of TEA, and 0.1 mol of chloro acetyl chloride in 70 ml of toluene was heated under reflux for 6 hours. Employing a separation process, the product was extracted from the reaction mixture and subsequently rinsed with 25 milliliters of toluene. The product's purification process involved the use of ethyl alcohol. In order to observe the advancement of the reaction, a thin-layer chromatography (TLC) technique was utilized using a toluene:acetone (8:2) mixture as the solvent.

The synthesis of quinolin-8-yl [(5-aryl-1,3,4-oxadiazol-2-yl)sulfanyl] is carried out in step V.Acetate (8) - A total of five hours were dedicated to stirring a mixture consisting of varying quantities of 5-aryl-1,3,4-oxadiazole-2-thiol (0.1 mol), quinolin-8-yl chloroacetate (0.1 mol), and anhydrous K2CO3 (0.2 mol) in 50 milliliters of dry acetone. Subsequently, the reaction mixture was placed on top of crushed ice, completely blended, filtered, and subjected to a cold water rinse. The presence of ethyl alcohol induced the recrystallization of the products. The reaction's progress was monitored using thin-layer chromatography (TLC) with a toluene:acetone (8:2) mixture as the solvent.

[Course of Action]



R represents a list of substituents: 2-Br, 4-F, c, 3,4,5-OCH3, d, 4-NO2, e, 4-Br, g, 4-CH3, h, 2-NO2, i, 4-Cl, j, 2-CH3.

III RESULTS AND REMARKS

Characterization refers to the process of creating and developing a character in a story or play. 8(a).The compound 5-(2-bromophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl acetate, quinolin-8-yl was obtained with a yield of 56%. It has a melting point of 170-172˚C. The FT-IR spectrum (KBr) showed peaks at 659 cm-1 (C-Br), 1141 cm-1 (C-O-C), 1469 cm-1 (-C=C-), 1568 cm-1 (-C=N), 1769 cm-1 (-C=O), and 2916 cm-1 (-CH2-). The 1H NMR spectrum (400 MHz, DMSO-d6) displayed a singlet at 4.54 ppm (2H, -CH2-) and peaks at δ 7.21-7.25 ppm (2H, Ar-H), δ 7.35-7.39 ppm (2H, Ar-H), δ 7.46-7.47 ppm (1H, Ar-H), 7.63-7.65 ppm (1H, Ar-H), δ 7.91-7.95 ppm (2H, Ar-H), δ 7.99-8.01 ppm (1H, Ar-H), and δ 8.39-8.41 ppm (1H, Ar-H). The compound has a molecular ion peak at m/z 443 in the mass spectrum. The determined elemental composition of C19H12BrN3O3S is as follows: carbon (C) - 51.60%, hydrogen (H) - 2.73%, nitrogen (N) - 9.50%, and sulfur (S) - 7.25%. The percentages of sulfur, hydrogen, nitrogen, and carbon in the sample are 7.21%, 2.69%, 9.48%, and 51.57%, respectively.

5-(4-fluorophenyl)-1,3,4-oxadiazol-2-ylSulfanyl acetate, also known as quinolin-8-yl: The FT-IR spectrum (KBr) of the compound shows absorption peaks at 1138 cm-1 (C-O-C), 1374 cm-1 (C-F), 1465 cm-1 (-C=C-), 1595 cm-1 (-C=N), 1764 cm-1 (-C=O), and 2935 cm-1 (-CH2-). The 1H NMR spectrum (400 MHz, DMSO-d6) displays a singlet at 4.77 ppm corresponding to 2 hydrogen atoms (-CH2-), and several signals in the aromatic region: a singlet at δ 7.44-7.48 ppm (2H, Ar-H), a multiplet at δ 7.55-7.59 ppm (2H, Ar-H), a multiplet at δ 7.65-7.66 ppm (1H, Ar-H), a multiplet at 7.93-7.95 ppm (1H, Ar-H), a singlet at δ 8.05-8.09 ppm (2H, Ar-H), a multiplet at δ 8.43-8.45 ppm (1H, Ar-H), and a multiplet at δ 8.76-8.77 ppm (1H, Ar-H). The compound has a molecular ion peak at m/z 382 in the mass spectrum. The calculated empirical formula is C19H12FN3O3S. The analysis results are as follows: Carbon (C) content is 59.84%, Hydrogen (H) content is 3.17%, Nitrogen (N) content is

11.02%, and Sulfur (S) content is 8.41%. Additionally, there is another sulfur component with a content of 8.39%. The hydrogen content is 3.16%, nitrogen content is 11.01%, and carbon content is 59.83%.

The compound is 5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazol-2-ylSulfanyl acetate, also known as quinolin-8-yl: The compound was obtained with a yield of 76% and had a melting point of 182-184˚C. The FT-IR spectrum (KBr) showed peaks at 1084 cm-1 (C-O-C al-kanyl), 1157 cm-1 (C-O-C), 1473 cm-1 (-C=C-), 1588 cm-1 (-C=N), 1779 cm-1 (-C=O), and 2921 cm-1 (-CH2-). The 1H NMR spectrum (400 MHz, DMSO-d6) displayed signals at δ 3.49 (singlet, 6H, -OCH3), δ 3.56 (singlet, 3H, -OCH3), 4.53 (singlet, 2H, -CH2-), δ 7.19-7.23 (singlet, 2H, Ar-H), δ 7.43-7.47 (multiplet, 2H, Ar-H), δ 7.59-7.61 (multiplet, 1H, Ar-H), 7.88-7.90 (multiplet, 1H, Ar-H), δ 8.13-8.15 (singlet, 2H, Ar-H), δ 8.39-8.41 (multiplet, 1H, Ar-H), and δ 8.62-8.64 (multiplet, 1H, Ar-H). The mass spectrum (MS) showed a peak at m/z 455. The calculated elemental analysis for C22H19N3O6S was C-58.27, H-4.22, N-9.27, S-7.07, and the found values were not provided. The composition of the substance is as follows: 4.19% hydrogen (H), 9.24% nitrogen (N), 7.04% sulfur (S), and 58.24% carbon (C).

The compound 5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]sulfanylacetate, quinolin-8-yl was obtained with a yield of 69% and a melting point of 177-179˚C. The compound was characterized by various spectroscopic techniques. The FT-IR spectrum showed peaks at 1163 cm-1 (C-O-C), 1482 cm-1 (-C=C-), 1601 cm-1 (-C=N), 1786 cm-1 (-C=O), and 2898 cm-1 (-CH2-). The 1HNMR spectrum (400 MHz, DMSO-d6) displayed signals at δ 4.37 (s, 2H, -CH2-), δ7.22-7.26 (s. 2H, Ar-H), δ 7.49-7.53 (m, 2H, Ar-H), δ7.64-7.68 (m, 1H, Ar-H), 7.93-7.97 (m, 1H, Ar-H), δ8.19-8.21 (s, 2H, Ar-H), δ 8.45-8.47 (m, 1H, Ar-H), and δ8.69-8.71 (m, 1H, Ar-H). The compound was also analyzed by mass spectrometry, which gave a molecular ion peak at m/z 409. The calculated elemental composition for C19H12N4O5S is C-55.88, H-2.96, N-13.72, and S-7.85, which is consistent with the experimental data. The composition of the substance is as follows: 55.86% carbon, 13.68% nitrogen, 2.94% hydrogen, and 7.83% sulfur.

5-(4-bromophenyl)-1,3,4-oxadiazol-2-ylSulfanylacetate, also known as quinolin-8-yl: The compound was obtained with a yield of 69% and has a melting point of 183-185˚C. The FT-IR spectrum (measured in KBr) showed peaks at 673 cm-1 (C-Br), 1157 cm-1 (C-O-C), 1469 cm-1 (-C=C-), 1608 cm-1 (-C=N), 1698 cm-1 (-C=O), and 2893 cm-1 (-CH2-). The 1H NMR spectrum (measured at 400 MHz in DMSO-d6) exhibited a singlet at 4.47 ppm (2H, -CH2-) and signals in the range of δ 7.13-7.17 ppm (2H, Ar-H), δ 7.32-7.36 ppm (2H, Ar-H), δ 7.48-7.50 ppm (1H, Ar-H), 7.67-7.69 ppm (1H, Ar-H), δ 7.99-8.01 ppm (2H, Ar-H), δ 8.12-8.14 ppm (1H, Ar-H), and δ 8.45-8.47 ppm (1H, Ar-H). The compound's mass spectrum showed a peak at m/z 443. The calculated molecular formula for the compound is C19H12BrN3O3S. The analysis results are as follows: Carbon (C) content is 51.60%, Hydrogen (H) content is 2.73%, Nitrogen (N) content is 9.50%, and Sulfur (S) content is 7.25%.

5-(2-chlorophenyl)-1,3,4-oxadiazol-2-ylSulfanyl acetate, also known as quinolin-8-yl: The FT-IR spectrum (KBr) shows absorption peaks at 659 cm^-1 (C-Cl), 1160 cm^-1 (C-O-C), 1463 cm^-1 (-C=C-), 1598 cm^-1 (-C=N), 1776 cm^-1 (-C=O), and 2903 cm^-1 (-CH2-). The 1H NMR spectrum (400 MHz, DMSO-d6) exhibits a singlet at 4.38 ppm (2H, -CH2-) and signals in the range of δ 7.12-7.16 ppm (singlet, 2H, Ar-H), δ 7.29-7.33 ppm (multiplet, 2H, Ar-H), δ 7.51-7.53 ppm (multiplet, 1H, Ar-H), 7.69-7.71 ppm (multiplet, 1H, Ar-H), δ 7.86-7.90 ppm (singlet, 2H, Ar-H), δ 7.96-7.98 ppm (multiplet, 1H, Ar-H), and δ 8.22-8.24 ppm (multiplet, 1H, Ar-H). The mass spectrum shows a peak at m/z 398. Analytical calculations were performed for the compound with the molecular formula C19H12ClN3O3S. The analysis revealed the following composition: Carbon (C) - 57.36%, Hydrogen (H) - 3.04%, Nitrogen (N) - 10.56%, Sulfur (S) - 8.06%. Additionally, there were traces of Hydrogen (H) - 3.01%, Nitrogen (N) - 10.52%, and Sulfur (S) - 8.02%. The majority of the composition consisted of Carbon (C) - 5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl]sulfanylacetate,
quinolin-8-yl: The FT-IR spectrum of the compound shows absorption peaks at 1182 cm-1 (C-O-C), 1479 cm-1 (-C=C-), 1609 cm-1 (-C=N), 1798 cm-1 (-C=O), and 2872 cm-1 (-CH2-). The 1H NMR spectrum (400 MHz, DMSO-d6) reveals peaks at δ 2.41 (singlet, 3H, -CH3), δ 4.60 (singlet, 2H, -CH2-), δ 7.04-7.08 (singlet, 2H, Ar-H), δ 7.23-7.27 (multiplet, 2H, Ar-H), δ 7.57-7.59 (multiplet, 1H, Ar-H), 7.73-7.76 (multiplet, 1H, Ar-H), δ 7.89-7.93 (singlet, 2H, Ar-H), δ 8.04-8.06 (multiplet, 1H, Ar-H), and δ 8.43-8.45 (multiplet, 1H, Ar-H). The compound has a molecular ion peak at m/z 378 in the mass spectrum. Calculation of the compound Anal. C20H15N3O3S: The analysis revealed the following composition: Carbon (C) - 63.65%, Hydrogen (H) - 4.01%, Nitrogen (N) - 11.13%, Sulfur (S) - 8.49%. Additionally, there were traces of Hydrogen (H) - 3.99%, Nitrogen (N) - 11.12%, and Sulfur (S) - 8.47%. The predominant element was Carbon (C) with a concentration of

The compound 5-(2-nitrophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl acetate, quinolin-8-yl was obtained with a yield of 59% and has a melting point of 157-159˚C. The compound was characterized using various spectroscopic techniques. The FT-IR spectrum (KBr) showed absorption peaks at 1149 cm-1 (C-O-C), 1456 cm-1 (-C=C-), 1586 cm-1 (-C=N), 1768 cm-1 (-C=O), and 2893 cm-1 (-CH2-). The 1H NMR spectrum (400 MHz, DMSO-d6) displayed signals at 4.26 ppm (singlet, 2H, -CH2-), δ7.18-7.22 ppm (singlet, 2H, Ar-H), δ7.33-7.37 ppm (multiplet, 2H, Ar-H), δ7.56-7.58 ppm (multiplet, 1H, Ar-H), 7.67-7.71 ppm (multiplet, 1H, Ar-H), δ7.82-7.86 ppm (singlet, 2H, Ar-H), δ7.99-8.03 ppm (multiplet, 1H, Ar-H), and δ8.32-8.36 ppm (multiplet, 1H, Ar-H). The compound was also analyzed by mass spectrometry, which showed a molecular ion peak at m/z 409. Elemental analysis revealed the following composition: N-13.71%, C-55.85%, H-2.92%, S-7.81%.

5-(4-chlorophenyl)-1,3,4-oxadiazol-2-ylSulfanyl acetate,

also known as quinolin-8-yl: The compound was obtained with a yield of 72% and has a melting point of 181-183˚ C. The FT-IR spectrum (measured using KBr) showed peaks at 659 cm-1 (C-Cl), 1178 cm-1 (C-O-C), 1474 cm-1 (-C=C-), 1583 cm-1 (-C=N), 1772 cm-1 (-C=O), and 2843 cm-1 (-CH2-). The 1H NMR spectrum (measured at 400 MHz in DMSO-d6) displayed a singlet at 4.27 ppm (2H, -CH2-) and signals in the range of δ 7.15-7.19 ppm (2H, Ar-H), δ 7.31-7.35 ppm (2H, Ar-H), δ 7.54-7.55 ppm (1H, Ar-H), δ 7.67-7.69 ppm (1H, Ar-H), δ 8.13-8.15 ppm (1H, Ar-H), and δ 8.47-8.49 ppm (1H, Ar-H). The compound's mass spectrum showed a peak at m/z 398. Analytical calculation performed for the compound C19H12ClN3O3S: The analysis revealed the following composition: Carbon (C) - 57.36%, Hydrogen (H) - 3.04%, Nitrogen (N) - 10.56%, Sulfur (S) - 8.06%, and an additional 8.04% of Sulfur (S), Hydrogen (H) - 3.03%, Nitrogen (N) - 10.53%, and Carbon (C) - 57.35%.

The compound is 5-(2-methylphenyl)-1,3,4-oxadiazol-2-yl]sulfanylacetate, quinolin-8-yl FT-IR analysis using KBr reveals the following peaks: 1196 cm-1 (C-O-C), 1484 cm-1 (-C=C-), 1602 cm-1 (-C=N), 1787 cm-1 (-C=O), and 2891 cm-1 (-CH2-). The 1H NMR spectrum, recorded at 400 MHz in DMSO-d6, shows the following chemical shifts: δ 2.37 (singlet, 3H, -CH3), δ 4.51 (singlet, 2H, -CH2-), δ 7.11-7.15 (singlet, 2H, Ar-H), δ 7.29-7.33 (multiplet, 2H, Ar-H), δ 7.59-7.61 (multiplet, 1H, Ar-H), δ 7.70-7.72 (multiplet, 1H, Ar-H), δ 7.91-7.95 (singlet, 2H, Ar-H), δ 8.11-8.13 (multiplet, 1H, Ar-H), and δ 8.34-8.38 (multiplet, 1H, Ar-H). The mass spectrometry (MS) analysis shows a peak at m/z 378. Analytical calculations were performed for the compound with the molecular formula C20H15N3O3S. The analysis results are as follows: Carbon (C) - 63.65%, Hydrogen (H) - 4.01%, Nitrogen (N) - 11.13%, Sulfur (S) - 8.49%. Additionally, there is Hydrogen (H) - 3.97%, Nitrogen (N) - 11.10%, Sulfur (S) - 8.45%, and Carbon (C) - 63.61%.

The antibacterial activity of the produced compounds was assessed using the effective disc diffusion technique on four bacterial strains: Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa, and Escherichia coli. The culture medium employed was nutrient agar, while the solvent selected was DMSO. The experiment involved determining the zone of inhibition after incubating for 24 hours at 37°C. This was done at different concentrations. The study employed streptomycin, a very effective antibacterial medication, as a benchmark for comparison. The table below presents the antibacterial characteristics of the synthesized compounds.

Based on the antibacterial study findings, compounds 8a, 8b, 8f, and 8i exhibited significant antibacterial efficacy against all bacterial strains included in the study, surpassing the reference chemical. In contrast, the remaining compounds had only moderate to poor activity. Compounds 8d, 8e, and 8h exhibited ineffectiveness against multiple bacterial strains non this study.

Table 1: Antibacterial data of synthesized compounds.

Comp. Code	Gram Positive Bacteria				Gram Negative Bacteria			
	Staphylococcus aureus		*Bacillus subtilis*		*Pseudomonas aeruginosa*		*E. coli*	
	Zone of Inhibition (mm)	MIC (µg/ml)	Zone of Inhibition (mm)	MIC (µg/ml)	Zone of Inhibition (mm)	MIC (µg/ml)	Zone of Inhibition (mm)	MIC (µg/ml)
8a	9	>12.5	5	12.5	6	25	7	12.5
8b	8	12.5	11	>12.5	8	12.5	8	12.5
8c	8	25	16	50	8	25	7	25
8d	16	12.5	19	12.5	--	12.5	18	50
8e	8	12.5	--	--	8	12.5	31	100
8f	8	12.5	5	12.5	7	50	12	50
8g	13	25	9	12.5	16	12.5	14	12.5
8h	15	50	14	25	18	100	--	--
8i	10	>12.5	8	12.5	7	12.5	9	>12.5
8j	15	50	12	12.5	16	12.5	19	100
Reference drug	12	>12.5	13	>12.5	16	>12.5	13	>12.5

CONCLUSION: The synthetic derivatives were produced by diverse methodologies, and the structures of the synthetic compounds are substantiated by a range of spectroscopic analyses. An evaluation was conducted to determine the powerful antibacterial properties of the synthesized compounds.

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