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Synthesis, Characterization and Molecular Docking of Drug Sulfonylhydrazide Derivatives

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Abstract
New Indomethacin derivatives, Aryl sulfonyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl) acetohydrazide. The indomethacin hydrazide derivatives (3a, 3b and 3c) were synthesised using different sulfonylchlorides in dichloromethane and triethylamine. The antibacterial activity of the new compounds was evaluated by molecular docking against gram-positive bacteria. The compounds (3b and 3c) showed the highest anti-microbial efficacy against Bacillus subtilis ATCC 6633. The structures of the target sulfonyl-hydrazide derivatives were confirmed by their synthesis and spectroscopic and analytical data. The target compounds were isolated and characterised by melting point, thin layer chromatography, FT-IR and ^{1}HNMR.

Keywords
Indomethacin,
Hydrazine Hydrate,
Sulfonylchlorides,
Molecular Docking

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INTRODUCTION

Nevertheless, there is a growing demand for the synthesis of compounds with promise effectiveness as therapeutic agents with reduced toxicity [1]. However, antibiotic resistance is still among the top causes of mortality owing to the increasing resistance of bacteria to the available therapies. Any drug that has the molecular functional group R-SO2-NH2 is called a sulfonamide [2, 3]. They work against both gram-negative and gram-positive bacteria. This means that they can prevent the spread of illness [4, 5]. The antibiotics are used to treat a range of bacterial infections [6, 7] such as the respiratory system, skin and the malaria parasite [8] etc. Sulfonamides because of the wide range of bioactivities that can be exhibited by this class of chemicals, including antiviral [9], antibacterial [10-12], antifungal [13, 14], anticancer [15-17], anti-depressant properties (18), activity against Alzheimer disease [19, 20] and ability to inhibit the activity of enzymes [21, 22]. Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) which has a number of various therapeutic uses [23]. Generally, nonsteroidal anti-inflammatory medications (NSAIDs) have a broad range of antimicrobial tendency [24]. The indomethacin sulfonyl-hydrazide derivatives synthesised in the current work were produced by the reaction of indomethacin hydrazide with three distinct sulfonyl chlorides to yield the final compounds.

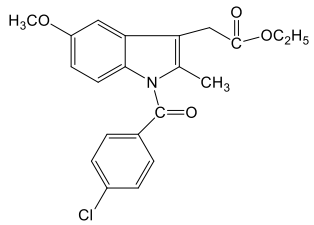
THE MATERIALS AND METHODS Used in This Experiment

In this synthesis, only substances of the highest analytical purity were used. Final synthesised derivatives' melting points were measured (uncorrected). All reported melting points were measured with a Thomas Hoover Apparatus. Using thin layer chromatography (TLC) on aluminium precoated silica gel 60 F254 sheets (Merck), the purity and successful completion of the reactions were validated, and the Rf values of the intermediates and final products were determined, which revealed single round spots after exposing the chromatograms to iodine vapour. The infrared spectrum of a KBr disc was measured with a Shimadzu FT-IR spectrophotometer. The ^{1}HNMR spectra were acquired in DMSO-d_6 using a BRUKER type Ultrashield spectrophotometer (500 MHz).

Indomethacin ethyl ester synthesis [25, 26](compound 2)

Thionyl chloride (0.02 mol, 2 mL) was added drop by drop to indomethacin (0.02 mol, 7.2 gm) in a separatory funnel under stirring until the vigorous evolution of gas has nearly ceased. The mixture was then refluxed for 3 hours, and its completion was confirmed by thin layer chromatography (TLC). Once the reaction was complete, the mixture was allowed to cool to room temperature. The yield was high and the result was a liquid yellow colour. This yellow result was added (0.01 mol, 25 mL) of 100% ethanol, and the mixture was stirred while refluxing at 70-80 degrees Celsius for 6-7 hours. Washing the acquired off-white crystals in Na_2CO_3 solution and then distilled water yielded the desired result. The product was ester. Re-crystallized from ethanol. M.p. = 88-90 ^0C .

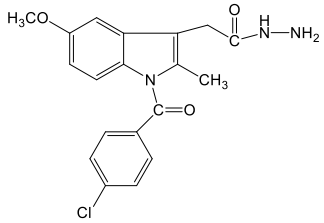
The infrared spectrum (KBr disc, cm^{-1}) shows the following: 3101.54 aromatic (C-H) str., 2985.81, 2924 (C-H) asymm. str. of CH_3 and CH_2, 2835 (C-H) symm. str. of CH_3 and CH_2, 1728.22 (C=O) str. ester, 1180.44 (C=O) str. ether.



Synthesis of indomethacin hydrazide 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetohydrazide (compound 3)[27-30]

Compound1 (0.015 mol, 5.5 g) was dissolved in abs. To EtOH (70 mL) was added 80% hydrazine hydrate (7 mL), and the liquid was refluxed at 80 °C for 6 hours.

The reaction mixture was cooled to room temperature after the reflux period, and distilled water was added, giving a light precipitate, which was left to stand overnight. After filtering, washing several times with cold distilled water, air-drying and recrystallising from ethanol, a light yellow precipitate was obtained. Yield 86%, m.p. (142-144 °C). Rf= 0.71 (acetone: petroleum ether (1:1)). The infrared spectrum (KBr disc, cm^{-1}) shows the following: (ú cm^{-1}): 3305.99, 3205.69 and 3194)str. NH and NH_2 in hydrazide group, 3008 (C-H)str. of aromatic ring, 2935asym. and 2810 sym. of (C-H) str. aliphatic ring, 1662 (C=O)str. amide and 1095(C-O-C)str. of ether. ^{1}HNMR-(δppm): 9.91 (s, 1H, NH), 7.85-7.50 (m, 7H, Ar-H), 4.57 (s, 2H, NH_2), 3.36 (s, 3H, OCH_3), 2.47 (s, 3H, CH_3).

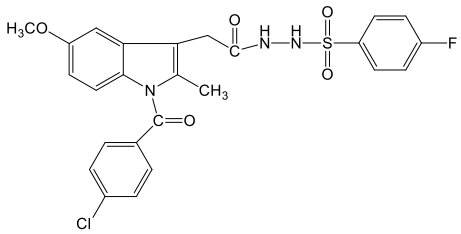


Synthesis of aryl sulfonyl 2-(1-(4-chloro benzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetohydrazide deriva-tivees (compound 4, 5 and 6)[31, 32]

Compound 2 (0.65g, 0.001mol) was dissolved in 20 mL dichloromethane with benzene sulfonylchloride (0.35g, 0.001), p-toluenesulfonyl chloride (0.3g, 0.001 mol) and p-chlorobenzenesulfonyl chloride (0.45g, 0.001 mol) in the presence of triethylamine (0.003, 1mL). The solution was transferred to a separatory funnel and rinsed with 100 mL of distilled water. The organic layer was dried with anhydrous sodium sulphate and the solvent was removed at reduced pressure using a rotary evaporator to provide products.

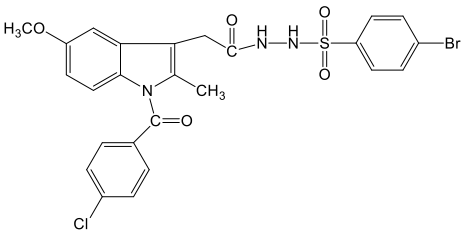
(4)N'-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetyl)-4-fluorobenzenesulfonohydrazide

Brown Powder, Yield= 63%, m.p.(157-159). Rf = 0.60 (Ethyl acetate 4: n-Hexane). The infrared spectrum (KBr disc, cm^{-1}) shows the following: 3410.15, 3240.41 (NH) str., 3062.96 aromatic (C-H) str., (2924.09 asym. and 2834 sym.) aliphatic (C-H) str., 1654.92 (C=O) str. of amide, 1597.06 and 1485.19 (C=C) ring str., 1342.46 asym. and 1161 sym. of (S=O) str., 1219 (C-O-C) str. of ether. ^{1}HNMR-(δppm): 9.84 (s, 1H, O=C-NH), 7.82-7.50 (m, 11H, Ar-H), 4.92 (s, 3H, OCH_3), 3.80 (s, 1H, NH-SO_2), 2.47 (s, 2H, CH_2), 1.20 (s, 3H, CH_3).



(5) 4-Bromo-N'-(2-(1-(4-chlorobenzo-yl)-5-methoxy-2-methyl-1H-indol-3-yl)acetyl)-benzenesulfonohydrazide

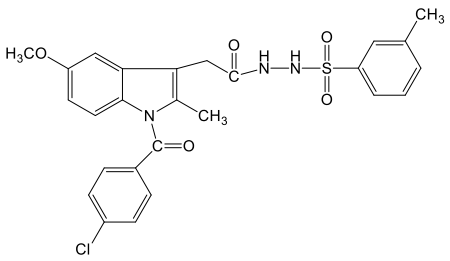
Brown Powder, Yield= 51%, m.p.(112-114). Rf = 0.74 (Ethyl acetate 4: n-Hexane). The infrared spectrum (KBr disc, cm^{-1}) shows the following: 3410.15, 3194.12 (NH) str., 3070.68 aromatic (C-H) str., (2927.94 asym. and 2854.65 sym.) aliphatic (C-H) str., 1662.64 (C=O) str. of amide, 1600.92 and 1477.47 (C=C) ring str., 1269.16 asym. and 1161.15 sym. of (S=O) str., 1091.71 (C-O-C) str. of ether. ^{1}HNMR-(δppm): 9.83 (s, 1H, O=C-NH), 7.80-7.51 (m, 11H, Ar-H), 3.74 (s, 3H, OCH_3), 1.89 (s, 1H, NH-SO_2), 1.13 (s, 3H, CH_3).



(6) N'-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetyl)-3-methylbenzenesulfonohydrazide

Brown Powder, Yield= 58%, m.p.(98-100). Rf = 0.68 (Ethyl acetate 4: n-Hexane). The infrared spectrum (KBr disc, cm^{-1}) shows the following: 3305.99, 3194.12 (NH) str., 3059.10 aromatic (C-H) str., (2927.94 asym. and 2858.51 sym.) aliphatic (C-H) str., 1654.92 (C=O) str. of amide, 1597.06 and 1481.33 (C=C) ring str., 1265.30 asym. and 1145 sym. of (S=O) str., 1091.71 (C-O-C) str. of ether. ^{1}HNMR-

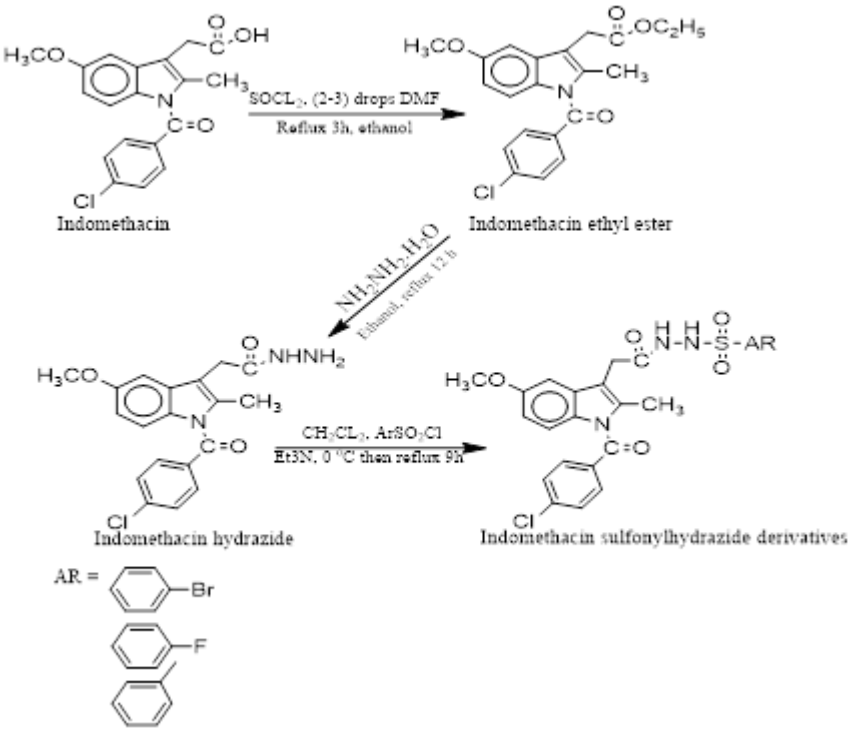
(δppm): 9.85 (s, 1H, O=C-NH), 7.50-7.07 (m, 11H, Ar-H), 3.73 (s, 2H, CH_2), 3 (s, 3H, OCH_3), 2.26 (s, 3H, CH_3), 1.87 (s, 1H, NH-SO_2), 1.10 (s, 3H, CH_3)



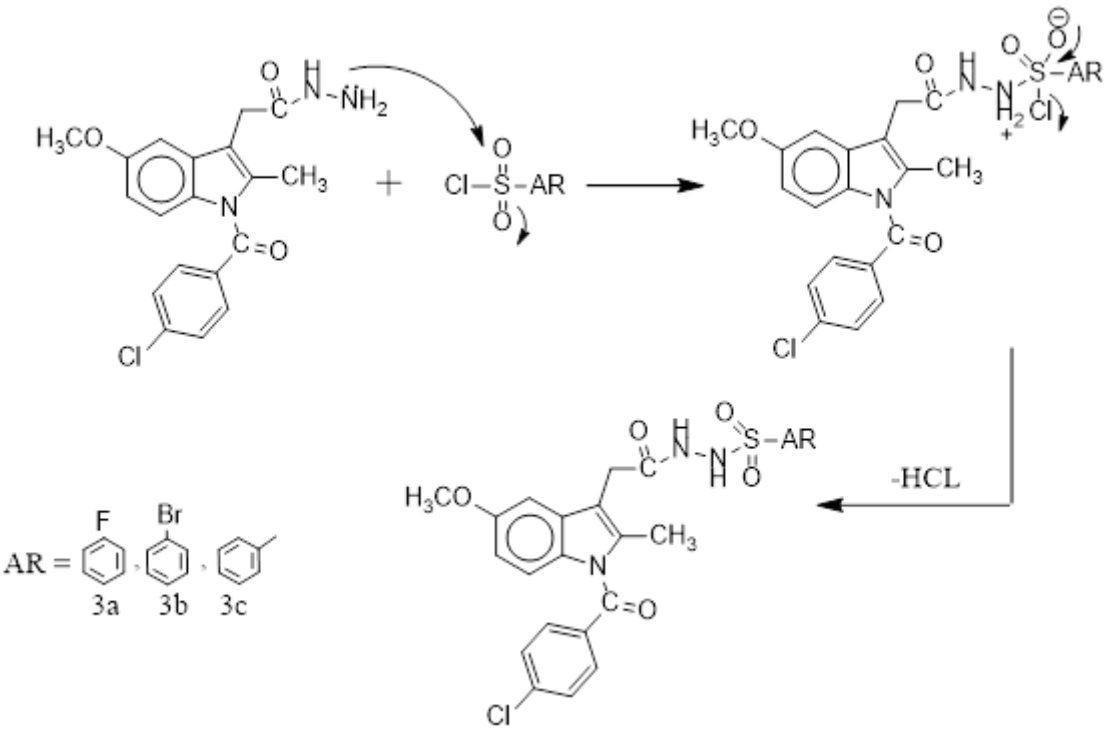
RESULTS AND DISCUSSION

Chemistry

Scheme1: Overall synthesis of Indomethacin sulfonyl hydrazide derivatives (3a, 3b and 3c) The reaction of indomethacin with thionyl chloride to form the ethyl ester product (1) used DMF. Compound 2 was prepared via the reaction of indomethacin ethyl ester with hydrazine hydrate. The final indomethacin sulfonyl-hydrazide derivatives were synthesised by reacting indomethacin hydrazide in dichloro-methane with benzene-sulfonyl chloride, para-toluenesulfonyl chloride and para-chlorobenzenesulfonyl chloride correspondingly, in presence of triethylamine as a base. Scheme 2 shows the nucleophilic attack of the amine on the sulphur atom of the sulfonyl-chloride with the release of HCl.



Scheme1: The synthesis of target compound (3a, 3b and 3c)



Scheme2: Mechanism of sulfonamide formation

Molecular docking study

The molecular docking study of the prepared organic derivatives revealed the number and types of bonds through which these prepared derivatives are linked with the active site amino acid residues, as the study revealed that the compound (3a) reacted with the active site amino acid residues by forming three bonds. Among the many different types of bonds present in the active site are carbon hydrogen bonds between the amino acid LEU22 residues and the oxygen atom of the sulfamide group, Pi-cation bonds between the amino acid LYS3 residues and the electronic pairs of the aromatic ring, and bonds between the amino acid ALA97 residues and a pi-alkyl residue of the aromatic ring. Compound (3b) forms two distinct types of bonds with the active site amino acid residues: a hydrogen bond between the active site SER146 residue and the hydrogen atom of the amine of the sulfamide group, and four bonds of the Pi-Alkyl type between the active site TYR157, ALA149, PRO14, and CYS143 acid residues and aromatic ring electron pairs. Compound (3c) forms two distinct types of bonds with the active site amino acid residues: a carbon hydrogen bond between the active site LEU22 residues and the sulfamide group's oxygen atom, and three Pi-alkyl bonds between the active site LYS3, ALA21, and ALA97 residues and the aromatic ring.

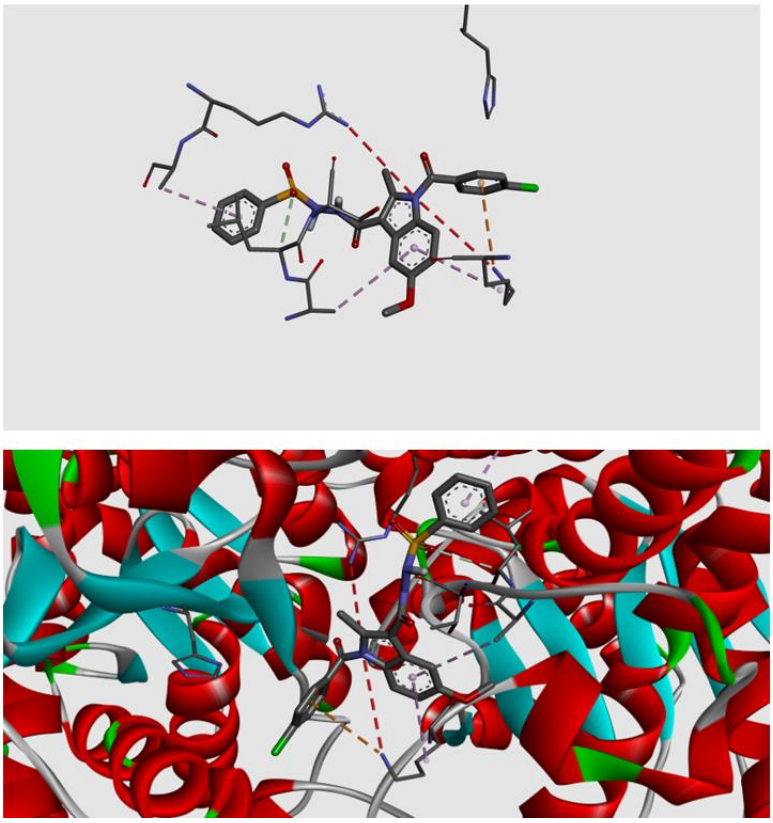


Fig (1): reaction between compound 3a and enzyme *Bacillus subtilis* ATCC 6633 dimensions 2D and 3D

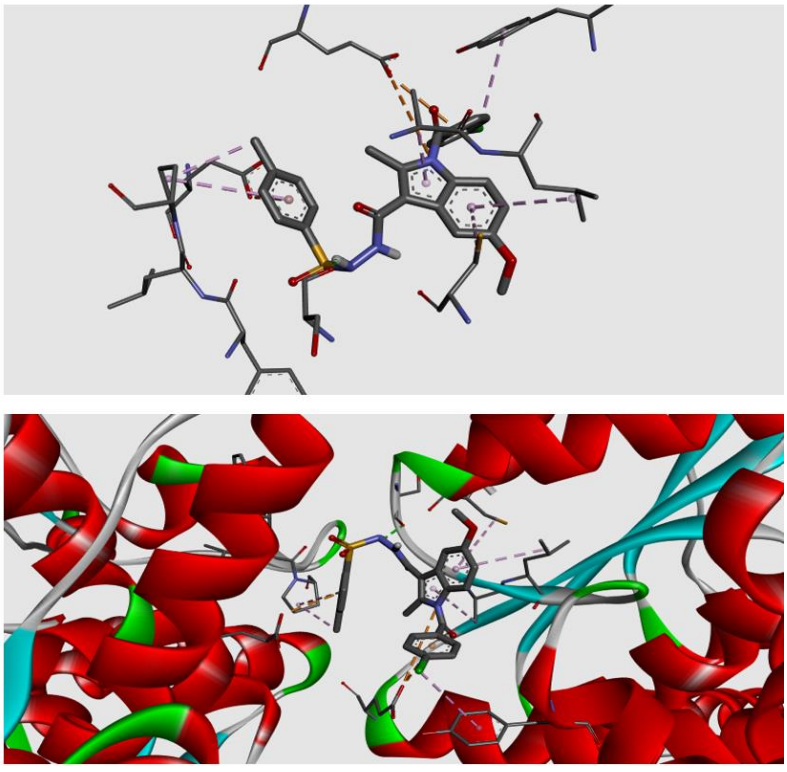


Fig (2): reaction between compound 3b and enzyme *Bacillus subtilis* ATCC 6633 dimensions 2D and 3D

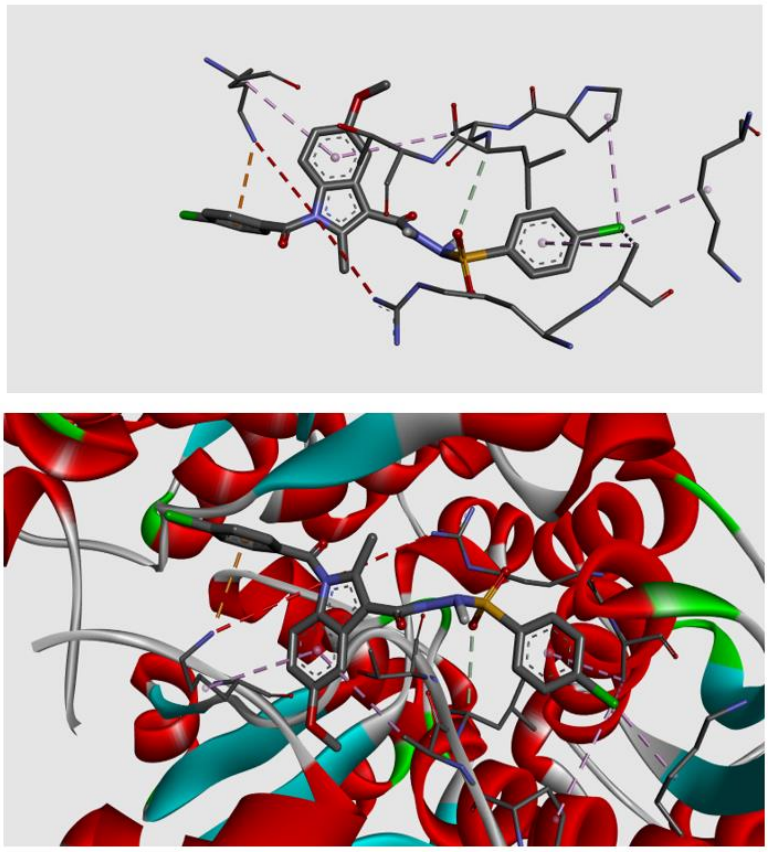


Fig (3): reaction between compound 3c and enzyme *Bacillus subtilis* ATCC 6633 dimensions 2D and 3D

Table (1) values of correlation energy for derivatives prepared

Compound Symble	RMSD	Docking Score
3a	0.025	-9.1
3b	0.028	-9.3
3c	0.022	-9.3

CONCLUSION

These suggested compounds were synthesised using the techniques described above. The findings of physical and chemical investigation (TLC, melting point, FT-IR, ^{1}HNMR, ^{13}CNMR) demonstrated that the synthesised compounds conformed to the design, showing that the method chosen for the synthesis of the planned derivatives was effective. These compounds have shown antibacterial activity that is competitive with commercially available medicines.

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