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DESIGN, SYNTHESIS, AND MOLECULAR DOCKING STUDY OF NEW ARYLTHIOETHER-AMIDE LINKED SULFONYL PIPERAZINE HYBRIDS AS ANTIBACTERIAL AGENTS

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ABSTRACT

Antibiotic resistance is a significant global health concern, and innovative antimicrobial agents are needed to combat this. A study aimed to synthesize and assess the antibacterial activity of sulfonyl piperazine hybrids linked by arylthioether-amide. Nine derivatives were evaluated against Gram-positive and Gram-negative bacteria. Compounds 9b, 9e, and 9i showed significant antibacterial effectiveness, surpassing conventional medications. Molecular docking studies revealed strong binding affinities of these compounds to the DNA gyrase A binding pocket, highlighting their potential as antibacterial agents. The findings suggest that further research is warranted to explore the therapeutic potential, safety profile, and mechanistic insights of these compounds, particularly 9b and 9i, which show promise for future development as novel antibacterial agents.

Keywords: Antibiotic Resistance, Anti-bacterial, Molecular Docking, Aryl thioether-amide, piperazineamide, DNA GyrA.

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INTRODUCTION

Antibiotic resistance is a global concern, causing 17 million fatalities annually due to bacterial infections. The growth of drug-resistant bacteria makes traditional antibiotic treatments ineffective, and the CDC has designated several bacteria as urgent and alarming concerns. As resistance to commercially available antibiotics increases, there is a need to investigate novel routes for creating antibacterial medicines with improved efficacy. This preventative approach is critical for successfully combating drug-resistant diseases. The development of novel and effective antimicrobial medications has grown in response to multidrug resistance, as microbial infections are often treated with protracted therapy using powerful medicines, fostering the growth of drug-resistant strains. The incidence of undetected but potentially lethal infections while hospitalized exacerbates the situation, leading to a constant demand for antimicrobial agents that exhibit a wide range of activities while maintaining excellent safety and potency.[1-3] Organosulfur compounds have been used as medicinal agents since ancient Egypt, with sulfuric ointments being discovered in ancient Greek mythology. In the Victorian era, "brimstone and treacle" was popular for

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children's laxatives and tonics. In the 1920s, "colloidal" sulfur was given to rheumatoid arthritis patients. Modern medicinal applications include antibacterials, anti-inflammatory drugs, dermatologics, and cancer therapies. As drug resistance increases, existing sulfur-containing compounds may serve as potential pharmaceutical products.[4] Aryl thioethers are crucial building blocks for various biological and therapeutic molecules. Diphenyl sulfides, found in many pharmaceutical drugs, play a significant role in the structure of bioactive proteins. Examples include major depressive disorder (Vortioxetine), cancer kinase inhibitor (Inlyta), antibacterial, anthelmintic, and algaecide (Bithinol), antitubercular agent, antibacterial, antifungal, ADAM, FOBM, IDAM, and ADM, which are used as serotonin transporter (SERT) and norepinephrine transporter (NET) inhibitors, combustion retarding agents, and treatments for cancer, Parkinson's, and Alzheimer's diseases.[5-12] Meanwhile, Piperazine templates are a valuable moiety with diverse biological activities, serving as key building blocks in drug discovery. They have shown positive results in various biological screens,[13] like antibacterial,[14] anticonvulsant,[15] antituberculosis,[16] antiviral,[17] anticancer,[18] and acetylcholinesterase inhibition,[19-20] antimicrobial,[21] anti-inflammatory,[22] antimycobacterial,[23] antiischemic,[24] and antiparasitic [25] activity studies. Sulfonamide derivatives are used in various medicinal applications due to their antibacterial, antiviral, antimalarial, antifungal, anticancer, and antidepressant properties. They have gained popularity due to their broad bioactivity and versatile structure, making them ideal for repurposing old drugs or developing new multi-target agents for diseases like Alzheimer's, diabetes, psychosis, cancers, tumors, antidiabetic, and antibacterial. The sulfonamide group can also be added to biologically relevant scaffolds, producing potent antibacterial agents by synthesizing sulfonyl piperazine analogs of previously discovered drugs.[26-29]

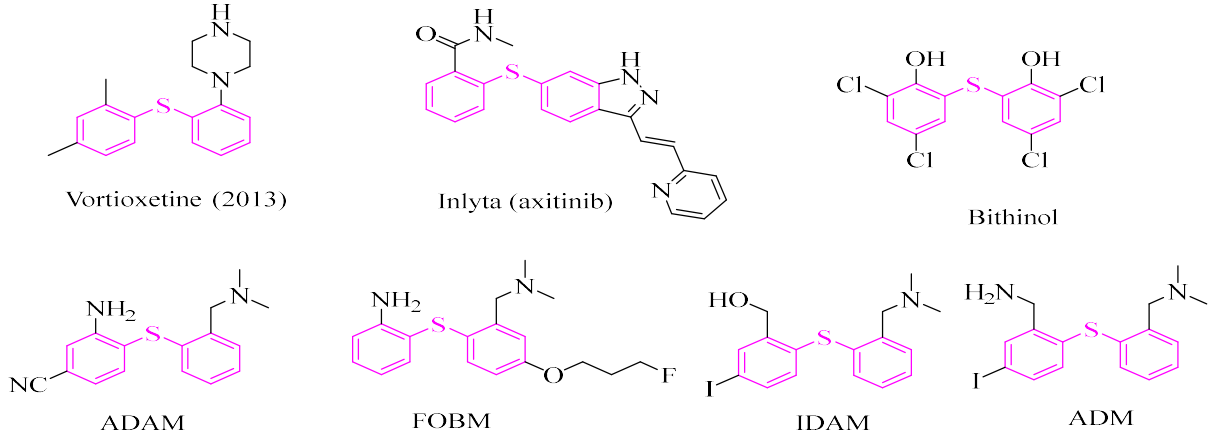

Fig.-1: Aryl Thioethers as Building Blocks Various Biological Drugs

DNA gyrase, a crucial enzyme in DNA transcription, replication, and chromosome segregation, is divided into two subunits: Gyrase A and Gyrase B. These subunits are essential for DNA breakage and re-joining, which is necessary for negative supercoiling. The antibiotics that have been validated target the bacterial topoisomerases DNA gyrase and topoisomerase IV, which govern DNA topology. Inhibiting either activity in bacteria disrupts DNA synthesis and causes cell death. This makes them an attractive target for developing new antibacterial drugs. This paper proposes derivatives of aryl thioether-amide linked sulfonyl piperazine hybrids, a new class of topoisomerase inhibitors discovered through computational analysis.[30-32] Hybrid molecules combine multiple pharmacophoric sections into a single substance capable of interacting with various targets. A series of arylthioether-amide linked sulfonyl piperazine hybrids were designed using a linking strategy. Eleven hybrids were produced, described, and evaluated for in vitro activities, including antibacterial studies. Optimized compounds were also investigated for molecular docking to determine their mode of inhibition and binding to DNA gyr A via molecular interactions.

EXPERIMENITAL

Chemistry

The chemicals were directly from sourced from commercial suppliers without undergoing any purification. All reactions underwent monitoring through TLC, and compounds were purified through column chromatography over silica gel (60–120). IR spectra were recorded using a SHIMDZU-8400 spectrometer.

For both intermediates and target compounds, ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker spectrometer operating at 400 MHz, utilizing $CDCl_3$/DMSO-d_6 solvents. Tetramethyl silane served as an internal standard, with measurements reported in δ parts per million (ppm) and J in hertz (Hz). HR–MS analysis was conducted on an Xevo TQD Quadrupole (XVEO-TQD-QCA583) mass spectrometer.

General Procedure of Synthesis of 2-(phenylthio)aniline (3)
Diphenyl disulfide (1, 0.5 mmol) and bromobenzene (2, 1.0 mmol) in DMSO (1 mL) were then added to the flask. KO^{t}Bu (1.25 mmol) was added gradually, and the resulting mixture was stirred at 40-45 °C for 15 minutes, followed by heating at 80 °C. The reaction progress was tracked by TLC. After completion (2-4 h), the mixture was cooled, poured into water, and extracted four times with 10 mL of ethyl acetate. The collective organic layers were dried Na_2SO_4, filtered, evaporated. The residue was purified by column chromatography (20% ethylacetate/hexane) to get final product.

Synthetic Procedure of 2-chloro-*N*-(2-(phenylthio)phenyl)acetamide (4)
To a solution of 2-(phenylthio)aniline (**3**, 10 mmol) in THF (20 mL) cooled at 0 ºC was added chloroacetylchloride (12 mmol) dropwise and stirred at room temperature for 1.5 hours. Then residue was concentrated and separated with EtOAc and water. Organic layer washed with satd. $NaHCO_3$ followed by brine, then dried over Na_2SO_4. Subsequently, concentrated furtherly purified by column chromatography (12% EtOAc+Hexane) to afford **2-chloro-*N*-(2-(phenylthio)phenyl)acetamide (4)** as a off-white crystalline solid.

Synthetic Procedure of tert-butyl 4-(2-oxo-2-((2 (phenylthio)phenyl)amino)ethyl) piperazine-1-carboxylate (6)
A mixture of 2-chloro-*N*-(2-(phenylthio)phenyl)acetamide (4, 1 mmol), *N*-Boc-piperazine (5, 1.5 mmol), K_2CO_3 (2 mmol), KI (0.01 mmol), and CH_3CN (30 mL) was heated at 80 °C for 2 hours. After completion, the mixture was diluted with water and extracted with ethyl acetate (3 x 15 mL). The combined organic layer was washed with water, saturated NH_4Cl solution (20 mL) (to remove unreacted Boc-piperazine), and brine, then dried with anhydrous Na_2SO_4. Concentration under vacuum yielded tert-butyl 4-(2-oxo-2-((2 (phenylthio)phenyl) amino)ethyl)piperazine-1-carboxylate (6).

2Synthetic Procedure of *N*-(2-(phenylthio)phenyl)-2-(piperazin-1-yl)acetamide (7)
Compound **6** (10 mmol) was suspended in methanolic HCl (20 mL, 10-12% w/v) at room temperature, stirred for 1-2 hours. After completion, MTBE (15 mL) was added, stirred for 30 minutes, and the solid separated was filtered and washed with MTBE (5 mL). The solid was dissolved in water (5 mL), and *p*H was adjusted to 8–9 with saturated Na_2CO_3 solution. The aqueous layer was extracted with DCM (3 x 15 mL). Combined organic layer was washed with water (2 x 15 mL until get neutral *p*H), followed by brine, and dried with anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure to yield residue **7** as a pale-yellow solid.

Synthetic Procedure of 2-(4-(phenylsulfonyl)piperazin-1-yl)-*N*-(2-(phenylthio) phenyl) acetamide (9 a-i)
Compound **7** (10 mmol), various substituted benzene sulfonyl chlorides (**8a-i**, 10 mmol), and TEA (20 mmol) were dissolved in DCM (10 mL) and stirred at 40 °C for 3-4 hours. Residue was then extracted with DCM (3 x 15 mL), and organic phase was washed with satd $NaHCO_3$ solution (3 x15 mL), and brine. After drying with anhydrous Na_2SO_4, filtration, and vacuum concentration, the crude product was purified by column chromatography using 5% (MeOH + DCM) as an eluent, yielding compound **7a** as a pale brown solid with a 92% yield.

***N*-(2-(phenylthio)phenyl)-2-(4-tosylpiperazin-1-yl)acetamide (9a) :** White solid, Yield: 68%; mp: 164-168 ºC, IR (KBr, υ cm $^{-1}$): 3236, 2998, 1698, 1523, 1309, 1262, 1213, 1155, ^{1}H-NMR ($CDCl_3$, δ): δ 7.70 – 7.64 (m, 1H), δ 7.57 (dd, J = 7.6, 1.4 Hz, 0H), δ 7.46 – 7.40 (m, 1H), δ 7.40 – 7.29 (m, 2H), δ 7.26 – 7.15 (m, 1H), δ 7.13 – 7.06 (m, 0H), δ 3.36 (s, 1H), δ 3.21 – 3.15 (m, 2H), δ 2.90 – 2.79 (m, 2H). ^{13}C-NMR ($CDCl_3$, δ): 170.06, 142.40, 140.33, 135.67, 134.19, 132.29, 129.73, 129.36, 129.08, 128.77, 128.13, 127.70, 124.55, 123.08, 121.01, 59.79, 53.09, 46.08, 21.55. Chemical Formula: $C_{25}H_{27}N_3O_3S_2$. HRMS: 481.63 $[M+H]^+$.

2-(4-((4-nitrophenyl)sulfonyl)piperazin-1-yl)-N-(2-(phenylthio)phenyl)acetamide (9b): Pale-Yellow solid, Yield: 73%; mp: 184-186 ºC, IR (KBr, υ cm $^{-1}$): 3240, 2990, 1694, 1523, 1313, 1268, 1213, 1155, ^{1}H-NMR ($CDCl_3$, δ): 8.17 – 8.11 (m, 1H), 7.95 – 7.88 (m, 1H), 7.57 (dd, J = 7.5, 1.4 Hz, 0H), 7.40 – 7.29 (m, 2H), 7.26 – 7.15 (m, 1H), 7.13 – 7.06 (m, 0H), 3.36 (s, 1H), 3.21 – 3.15 (m, 2H), 2.90 – 2.79 (m, 2H); ^{13}C-NMR ($CDCl_3$, δ): 170.06, 150.02, 142.04, 140.33, 135.67, 134.19, 129.36, 129.08, 128.77, 128.19, 127.70, 124.55, 124.52, 123.08, 121.01, 59.79, 53.09, 46.10; Chemical Formula: $C_{24}H_{24}N_4O_5S_2$; HRMS: 512.60 $[M+H]^+$.

2-(4-((4-(tert-butyl)phenyl)sulfonyl)piperazin-1-yl)-N-(2-(phenylthio)phenyl) acetamide (9c)
Brown solid, Yield: 64%; mp: 153-156 ºC, IR (KBr, υ cm $^{-1}$): 3235, 2994, 1692, 1523, 1309, 1266, 1213, 1155, ^{1}H-NMR ($CDCl_3$, δ):7.70 – 7.64 (m, 1H), δ 7.57 (dd, J = 7.5, 1.4 Hz, 0H), δ 7.41 – 7.29 (m, 2H), δ 7.26 – 7.15 (m, 1H), δ 7.13 – 7.06 (m, 2H), δ 3.36 (s, 1H), δ 3.21 – 3.15 (m, 2H), δ 2.90 – 2.79 (m, 2H); ^{13}C-NMR ($CDCl_3$, δ): 170.06, 156.56, 140.33, 138.07, 135.67, 134.19, 129.36, 129.08, 128.77, 127.73, 127.70, 126.17, 124.55, 123.08, 121.01, 59.79, 53.09, 46.08, 34.76, 31.17. Chemical Formula: $C_{28}H_{33}N_3O_3S_2$; HRMS: 523.71 $[M+H]^+$.

N-(2-(phenylthio)phenyl)-2-(4-((2,4,6-triisopropylphenyl)sulfonyl)piperazin-1-yl)acetamide (9d)
White solid, Yield: 69%; mp: 168-170 ºC, IR (KBr, υ cm $^{-1}$): 3232, 2990, 1695, 1523, 1313, 1262, 1213, 1155, ^{1}H-NMR ($CDCl_3$, δ): 7.40 – 7.29 (m, 2H), 7.26 – 7.15 (m, 1H), 4.05 (heptd, J = 6.6, 0.9 Hz, 1H), 3.36 (s, 1H), 3.30 – 3.25 (m, 2H), 2.98 – 2.83 (m, 1H), 2.87 – 2.80 (m, 1H), 1.22 (dd, J = 6.5, 1.9 Hz, 7H) ; ^{13}C-NMR ($CDCl_3$, δ): 170.06, 152.78, 149.21, 140.33, 135.67, 134.19, 133.30, 129.36, 129.08, 128.77, 127.70, 124.55, 123.97, 123.08, 121.01, 59.79, 53.08, 46.18, 34.44, 29.12, 24.81, 23.77 ; Chemical Formula: $C_{33}H_{43}N_3O_3S_2$; HRMS: 593.27 $[M+H]^+$.

2-(4-((3-nitrophenyl)sulfonyl)piperazin-1-yl)-N-(2-(phenylthio)phenyl)acetamide (9e)
Pale-Yellow solid, Yield: 59%; mp: 183-185 ºC, IR (KBr, υ cm $^{-1}$): 3236, 2998, 1698, 1523, 1309, 1262, 1213, 1155, ^{1}H-NMR ($CDCl_3$, δ): δ 9.48 (s, 1H), δ 8.51 (ddd, J = 8.6, 2.2, 1.2 Hz, 1H), δ 8.43 (t, J = 2.2 Hz, 1H), δ 8.18 (ddd, J = 9.0, 2.2, 1.3 Hz, 1H), δ 7.95 (t, J = 8.7 Hz, 1H), δ 7.57 (dd, J = 7.5, 1.4 Hz, 1H), δ 7.40 – 7.29 (m, 4H), δ 7.26 – 7.15 (m, 1H), δ 7.13 – 7.06 (m, 1H), δ 3.36 (s, 1H), δ 3.21 – 3.15 (m, 3H), δ 2.90 – 2.79 (m, 3H) ; ^{13}C-NMR ($CDCl_3$, δ): 170.06, 147.29, 140.33, 138.28, 135.67, 134.19, 133.13, 132.68, 129.36, 129.08, 129.04, 128.77, 127.70, 124.90, 124.55, 123.08, 121.01, 59.79, 53.08, 46.15 ; Chemical Formula: $C_{24}H_{24}N_4O_5S_2$; HRMS: 512.60 $[M+H]^+$.

2-(4-(cyclopropylsulfonyl)piperazin-1-yl)-N-(2-(phenylthio)phenyl)acetamide (9f)
Pale reddish solid, Yield: 71%; MP: 153-156 ºC, IR (KBr, υ cm $^{-1}$): 3233, 2988, 1692, 1523, 1309, 1262, 1213, 1155, ^{1}H-NMR ($CDCl_3$, δ): ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.48 (s, 1H), 7.57 (dd, J = 7.5, 1.4 Hz, 1H), 7.40 – 7.29 (m, 5H), 7.26 – 7.15 (m, 2H), 7.13 – 7.06 (m, 1H), 3.36 (s, 2H), 3.31 – 3.25 (m, 4H), 2.91 – 2.80 (m, 4H), 2.01 (p, J = 8.0 Hz, 1H), 1.75 – 1.66 (m, 2H), 1.50 – 1.41 (m, 2H) ; ^{13}C-NMR ($CDCl_3$, δ): 170.06, 140.33, 135.67, 134.19, 129.36, 129.08, 128.77, 127.70, 124.55, 123.08, 121.01, 59.79, 53.16, 46.21, 38.33, 10.29 ; Chemical Formula: $C_{21}H25N_3O_3S_2$; HRMS: 431.57 $[M+H]^+$.

2-(4-(phenylsulfonyl)piperazin-1-yl)-N-(2-(phenylthio)phenyl)acetamide (9g)
White solid, Yield: 64%; mp: 159-163 ºC, IR (KBr, υ cm $^{-1}$): 3236, 2994, 1695, 1523, 1309, 1262, 1213, 1155, ^{1}H-NMR ($CDCl_3$, δ): ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.93 (tt, J = 7.5, 1.5 Hz, 0H), 7.79 – 7.72 (m, 1H), 7.68 – 7.60 (m, 1H), 7.57 (dd, J = 7.5, 1.4 Hz, 0H), 7.40 – 7.29 (m, 2H), 7.26 – 7.15 (m, 1H), 7.13 – 7.06 (m, 0H), 3.36 (s, 1H), 3.21 – 3.15 (m, 2H), 2.90 – 2.79 (m, 2H) ; ^{13}C-NMR ($CDCl_3$, δ): 170.06, 140.33, 137.82, 135.67, 134.19, 133.72, 129.36, 129.32, 129.08, 128.77, 127.92, 127.70, 124.55, 123.08, 121.01, 59.79, 53.09, 46.08 ; Chemical Formula: $C_{24}H_{25}N_3O_3S_2$; HRMS: 467.60 $[M+H]^+$.

2-(4-((4-methoxyphenyl)sulfonyl)piperazin-1-yl)-N-(2-(phenylthio)phenyl) acetamide (9h)
White solid, Yield: 74%; mp: 174-176 ºC, IR (KBr, υ cm $^{-1}$): 3236, 2998, 1698, 1523, 1309, 1262, 1213, 1155, ^{1}H-NMR ($CDCl_3$, δ): ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.66 – 7.55 (m, 1H), 7.40 – 7.29 (m, 2H), 7.26 – 7.15 (m, 1H), 7.13 – 7.01 (m, 1H), 3.80 (s, 1H), 3.36 (s, 1H), 3.21 – 3.15 (m, 2H), 2.90 – 2.79 (m, 2H) ; ^{13}C-NMR ($CDCl_3$, δ): 170.06, 163.98, 140.33, 135.67, 134.19, 132.85, 129.36, 129.33, 129.08, 128.77, 127.70, 124.55, 123.08, 121.01, 115.23, 59.79, 55.34, 53.09, 46.08 ; Chemical Formula: $C_{25}H_{27}N_3O_4S_2$; HRMS: 497.63 $[M+H]^+$.

2-(4-((4-(methylsulfonyl)phenyl)sulfonyl)piperazin-1-yl)-N-(2-(phenylthio) phenyl) acetamide (9i) Pale-Brown, Yield: 64%; mp: 169-173 ºC, IR (KBr, υ cm $^{-1}$): 3236, 2998, 1698, 1523, 1309, 1262, 1213, 1155, ^{1}H-NMR ($CDCl_3$, δ): ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.14 – 8.08 (m, 1H), 8.01 – 7.95 (m, 1H), 7.57 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.40 – 7.29 (m, 2H), 7.26 – 7.15 (m, 1H), 7.13 – 7.06 (m, 0H), 3.36 (s, 1H), 3.24 (s, 1H), 3.21 – 3.15 (m, 2H), 2.90 – 2.79 (m, 2H) ; ^{13}C-NMR ($CDCl_3$, δ): 170.06, 144.67, 142.03, 140.33, 135.67, 134.19, 129.36, 129.08, 128.77, 128.17, 128.00, 127.70, 124.55, 123.08, 121.01, 59.79, 53.09, 46.08, 44.44 ; Chemical Formula: $C_{25}H_{27}N_3O_5S_3$; HRMS: 545.69 $[M+H]^+$.

Biological Assays

The chemicals, buffer solutions, and agarose gel utilized in the study were procured from Thermo Fischer Scientific and Sigma Aldrich. Electrophoresis was conducted in agarose gels containing 4% Tris-Borate-EDTA (TBE). Fluorescence emissions were examined and quantified using a double fluorescence FMYG100 microscope, while cytofluorometric analysis was performed on Beckman Coulter's Gallio 10/3 Cytofluorometer.

Anti-Bacterial Activity

The in-vitro antimicrobial activity was evaluated using a standard protocol of aga well diffusion method on Muller-Hinton agar (MHA), the synthesized derivatives 9 (a-i) were tested against a couple of gram-negative bacterial strain *Escherichia Coli* and gram-positive bacterial strain *Corynebacterium* against *Streptomycin*, *chloramphenicol* and *Tetracyclin* as standard at 25, 50, 75 and 100 μg/mL concentrations. For the purpose of getting 104-106 colony forming units (CFU) in median, Merk's nutritional agar and agar plates containing bacterial strains cultured for 24 hours were utilized. These species were often cultivated over the entire surface of agar plates. A sterile cork borer was used to punch an aseptic hole with a diameter of 6-8 mm, spaced 25 mm apart. A volume of 10 μL of the tested compounds in DMSO was then added to each well. After that, the plates were incubated for 24 hours at 37 ^{O}C. Additionally, a DMSO control (5 % v/v) was screened to make sure the solvent did not prevent the growth of bacteria. Visible inhibition zones around the wells indicated antibacterial activity, with the diameter of the zones (mm) representing the degree of bacterial growth inhibition. Using a meter ruler, the inhibitory zones were measured to the closest whole millimeter. Agar dilution was also used to calculate the zone of inhibition (DIZ) values which indicate the lowest concentration at which bacterial growth is inhibited. Minimal Inhibition Zone (MIZ) for antibacterial activity were reported in Table-1, revealing significant activity of the compounds against the tested bacterial and fungal strains, with all molecules exhibiting superior antibacterial effects.[33-34]

Table-1: Antibacterial Activity of Compounds 9(a-i), Minimal Inhibition Zone (MIZ) (in mm)

Strains	Gram Positive Bacteria (Corynebacterium)					Gram Negative Bacteria (E. coli)				
Compound	25 μL	50 μL	75 μL	100 μL	Standard Drug	25 μL	50 μL	75 μL	100 μL	Standard Drug
9a	13	13	17	17	23	12	13	16	16	22
9b	17	19	21	26	23	15	17	20	24	22
9c	7	7	9	11	23	14	18	21	23	22
9d	6	7	9	10	23	-	12	13	13	22
9e	14	16	18	22	24	15	16	19	22	21
9f	14	15	16	18	24	13	16	18	19	21
9g	11	13	14	15	23	14	19	16	16	22
9h	13	16	17	21	23	14	16	18	20	22
9i	21	19	26	25	18	16	17	21	23	17

Standard Drug: Streptomycin antibiotic for 9a, 9b, 9c, 9d, 9g, 9h, Tetracyclin antibiotic for 9e and 9f, hloromphenicol antibiotic for 9i.

Molecular Docking

Molecular docking experiments were carried out to better understand the mechanism of antibacterial activity and the detailed intermolecular interactions between the produced compounds (9a-9h). Docking investigations were carried out using the 2015 Molecular Operating Environment (MOE) software package,[35] utilizing the DNA gyrase A PDB ID: 1AB4, to explore the antibacterial mode of action of small

molecule compounds. The crystal structure, 59KDA Fragment of Gyrase A from *Escherichia Coli*, was sourced from the Protein Data Bank (https://www.rcsb.org/). Compounds were drawn with ChemDraw, imported into MOE, and underwent 3D protonation and energy minimization (0.01 gradient), saved as an MDB file for docking calculations. The protein structure in MOE underwent correction using the structure preparation wizard, adding hydrogen atoms in standard geometry, removing solvent molecules, and undergoing energy minimization,[36] The finalized structures were saved, and program specifications were configured with dummy atoms as the docking site, triangle matcher for placement, London dG for scoring, rigid receptor for refinement, and GBVI/WSA dG for pose selection. The MDB file of three ligands was loaded, and general dock calculations were executed automatically.[37] Following the docking processes, the obtained poses were analyzed.[38,39]

RESULTS AND DISCUSSION

Chemistry

The procedure for synthesizing new analogs, 2-(4-(phenylsulfonyl)piperazin-1-yl)-*N*-(2-(phenylthio)phenyl)acetamide 9(a-i), is described in Scheme-1, which consists of five sequential steps. 2-Phenylthioaniline (3) was first made from 2-Aminophenyl disulfide (1) and bromobenzene (2) with minor adjustments.[40] Chloroacetylchloride was used to produce chloro-*N*-(2-(phenylthio)phenyl)acetamide (4) in subsequent processes. Compound 4 was subjected to piperazination using Boc-protected piperazine, resulting in the formation of tert-butyl 4-(2-oxo-2-((2-(phenylthio)phenyl)amino)ethyl)piperazine-1-carboxylate (6). The removal of the Boc protecting group with methanolic 2N HCl resulted in the formation of *N*-(2-(phenylthio)phenyl)-2-(piperazin-1-yl)acetamide (7).[41] Compound 7 was reacted with several substituted benzenesulfonylchlorides (8a-i) and yielded phenylsulfanyl-piperazine sulfonamide analogues (9a-i).[42] The target compounds were characterized through study of FT-IR, ^{1}H-NMR, ^{13}C-NMR, and HR-MS data.

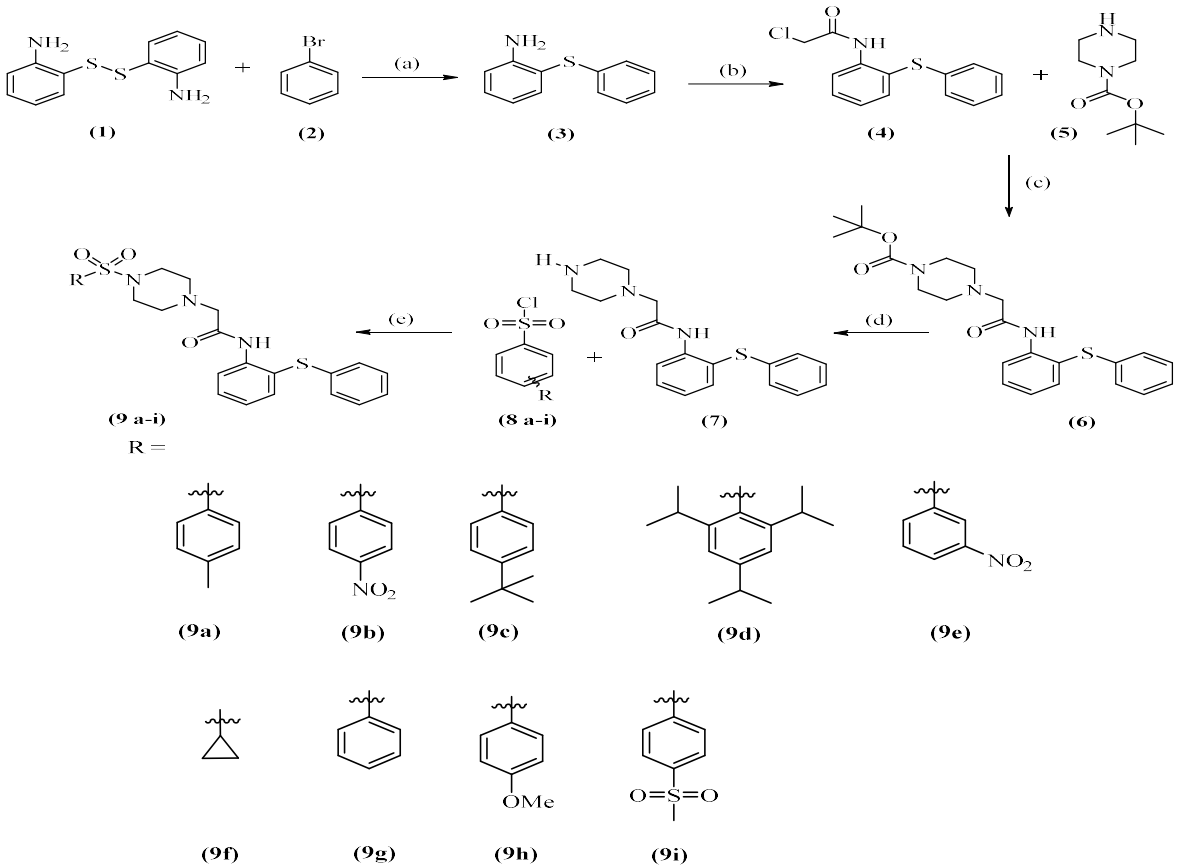

Fig.-2: Synthesis of New Phenylsulfanyl-Piperazine Derivatives 9 (a-i) (Scheme-1)
Reagents and Conditions: (a). KO^{t}Bu (2.5 eq), DMSO, 80 ^{o}C, (b). Chloroacetylchloride, TEA, THF, (c) K_2CO_3, KI, CH_3CN, (d) 2N HCl, (e) TEA, DCM.

Anti-Bacterial Activity

The study evaluated the antimicrobial activity of new derivatives 9(a-i) against *Escherichia Coli* and *Corynebacterium* using the agar well diffusion technique. Bacterial strains were cultured on a nutrient agar medium, and wells were created in the agar plates using a metallic borer. Visible inhibition zones around the wells indicated antibacterial activity, with the diameter of the zones representing the degree of bacterial growth inhibition. The Minimal Inhibition Zone (MIZ) assay was used to examine the antibacterial effects of the compounds at different concentrations compared to standard drugs. The study examined the antibacterial activity of synthesized compounds 9(a-i) against Gram-positive and Gram-negative bacteria using the Minimal Inhibition Zone (MIZ) assay. The results showed that compound 9b showed significant antibacterial efficacy against Gram-positive bacteria, with inhibition zones ranging from 17 mm to 26 mm, surpassing the standard drug streptomycin. Compound 9i also showed significant activity against Gram-positive bacteria, with inhibition zones ranging from 21 mm to 26 mm. Compound 9e showed significant antibacterial properties against Gram-negative bacteria, with inhibition zones ranging from 14 mm to 22 mm. Compounds 9d and 9f showed selective activity against either Gram-positive or Gram-negative bacteria. The study highlights the potential of these compounds in treating various bacteria. Certain derivatives 9b, 9e, and 9i showed superior antibacterial activity compared to standard drugs, indicating their potential for further development. These variations may be due to differences in chemical structures, suggesting structure-activity relationships that could guide optimization. Synthesized derivatives 9(a-i) showed promising antibacterial activity against both Gram-positive and Gram-negative bacteria. Further investigations, including microbial strains, toxicity assessments, and mechanistic studies, are needed to evaluate their therapeutic potential and safety profile, potentially leading to the development of novel antibacterial agents.

Molecular Docking

The molecular docking study aimed to elucidate the binding interactions of synthesized derivatives 9(a -i) within the binding pockets of DNA gyrase A (gyr A), a crucial enzyme involved in DNA replication and repair. Additionally, two standard drugs, streptomycin and ciprofloxacin, and two antibiotics, tetracycline and chloramphenicol, were included for comparative analysis. The calculated parameters, encompassing docking scores, rmsd_refine values, and interacting residues with their respective distances, are presented in Table-2. Additionally, the interactions with specific residues were examined to understand the molecular basis of the observed docking scores. In silico results revealed that all screened compounds exhibited superior docking scores compared to Ciprofloxacin, Tetracycline, and Chloramphenicol, 9b and 9i exhibited particularly noteworthy docking scores, indicating strong binding affinities to the DNA gyrase A binding pocket. Compound 9b displayed an impressive docking score of -7.7795, showcasing its robust interaction with the target protein. The rmsd_refine value of 0.9507 suggests a close structural alignment with the crystal structure. Notably, interactions with key residues, such as ALA 117 (3.11 Å), ASN 269 (3.02 Å), and HOH 523 (2.03 Å), further support the strong binding potential of 9b. Similarly, compound 9i demonstrated a remarkable docking score of -7.0934, indicating a high binding affinity. The low rmsd_refine value of 0.9301 suggests a close structural alignment with the crystal structure. Interactions with ASN 269 (3.03 Å) and ALA 117 (3.00 Å) highlight the specific binding interactions of 9i within the DNA gyrase A binding pocket. In brief, the molecular docking results highlight the exceptional binding affinities of synthesized derivatives, particularly compounds 9b and 9i, to the DNA gyrase A binding pocket.

The specific interactions with key residues provide insights into the molecular mechanisms underlying their potential antibacterial activities. The comprehensive investigation into the antibacterial activity and molecular docking of synthesized compounds 9(a-i) aimed to evaluate their potential as novel antibacterial agents. The Minimal Inhibition Zone (MIZ) assay against both Gram-positive bacteria (*Corynebacterium*) and Gram-negative bacteria (*Escherichia Coli*) provided valuable insights into the inhibitory effects of the compounds at varying concentrations compared to standard drugs. Simultaneously, the molecular docking study focused on elucidating the binding interactions of these compounds within the DNA gyrase A binding pockets.

Table-2: Calculated Parameters Obtained from Docking of Derivatives and Standard in the Binding Pockets of DNA Gyrase A

Compound	Docking Score	rmsd_refine	Residue (Distance Å)
9b	-7.7795	0.9507	ALA 117 (3.11), ASN 269 (3.02), HOH 523 (2.03)
9c	-7.6696	1.1502	HOH 524 (2.96), GLN 94 (3.11)
9d	-6.7396	1.6471	ARG 91 (3.70)
9f	-6.7348	1.2893	GLY 114 (3.83)
9g	-6.9540	1.6575	ARG 91 (3.13), ASN 269 (4.40)
9h	-7.7071	2.0538	GLN 94 (3.35), ALA 117 (4.18)
9i	-7.0934	0.9301	ASN 269 (3.03), ALA 117 (3.00)
Streptomycin	-7.3795	1.3066	GLY 114 (2.72), ASP 87 (2.93), SER 111 (2.81) ASP 115 (3.17), PHE 96 (2.93), GLN 94 (2.97)
Ciprofloxacin	-5.1042	1.1013	ARG 91 (3.49)
Tetracycline	-5.8023	1.3439	PHE 96 (3.40), GLN 94 (3.09), ARG 91 (2.86)
Chloramphenicol	-5.7324	1.1725	ALA 117 (3.01), ARG 91 (3.12)

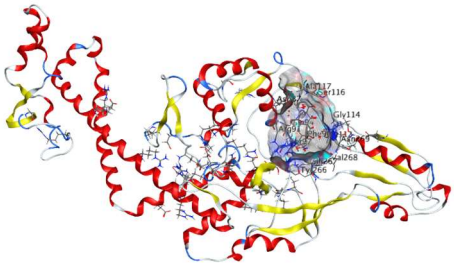

Fig.-3: The Monomeric form of E. Coli DNA Gyrase A

In conclusion, the synthesized derivatives 9(a-i) demonstrated promising antibacterial activity against both Gram-positive and Gram-negative bacteria. The integration of molecular docking results highlighted specific compounds, particularly 9b and 9i, with exceptional binding affinities to DNA gyrase A.

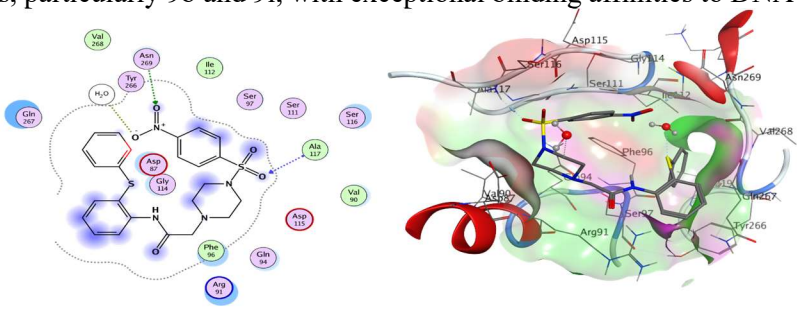

Fig.-4: The 2D and 3D Binding Modes of 9b in the Active Site of DNA Gyrase

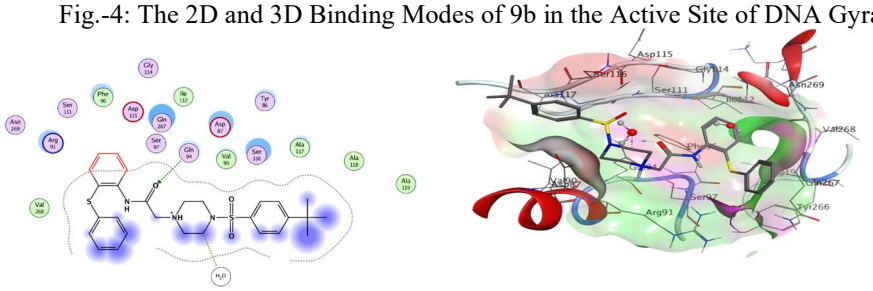

Fig.-5: The 2D and 3D Binding Modes of 9c in the Active Site of DNA Gyrase

These findings provide a solid foundation for further research, emphasizing the need for additional investigations, including toxicity assessments, mechanistic studies, and in vivo evaluations. The identified

candidates, 9b and 9i, hold potential for development as novel antibacterial agents, contributing to the ongoing efforts in combating bacterial infections.

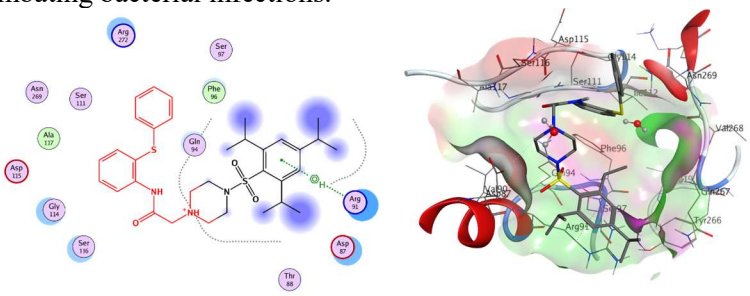

Fig.-6: The 2D and 3D Binding Modes of 9d in the Active Site of DNA Gyrase

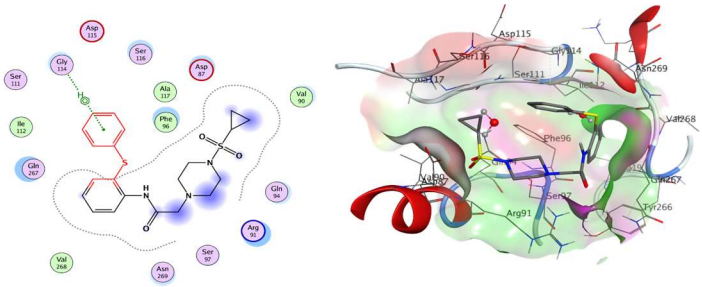

Fig.-7: The 2D and 3D Binding Modes of 9f in the Active Site of DNA Gyrase

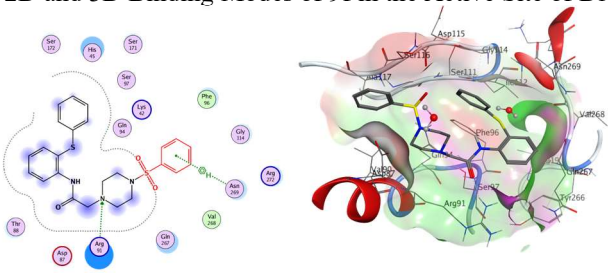

Fig.-8: The 2D and 3D Binding Modes of 9g in the Active Site of DNA Gyrase

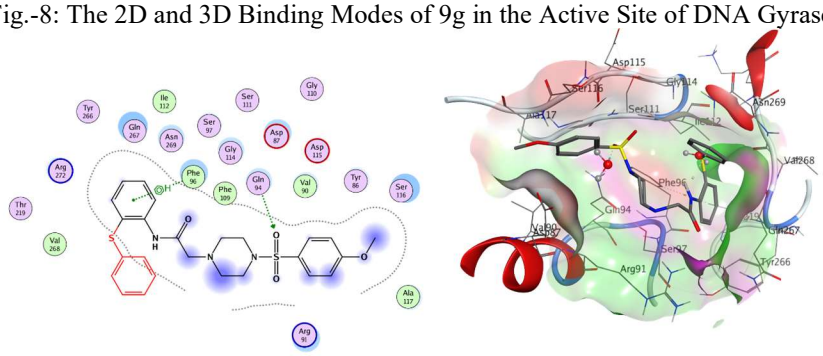

Fig.-9: The 2D and 3D Binding Modes 9h in the Active Site of DNA Gyrase

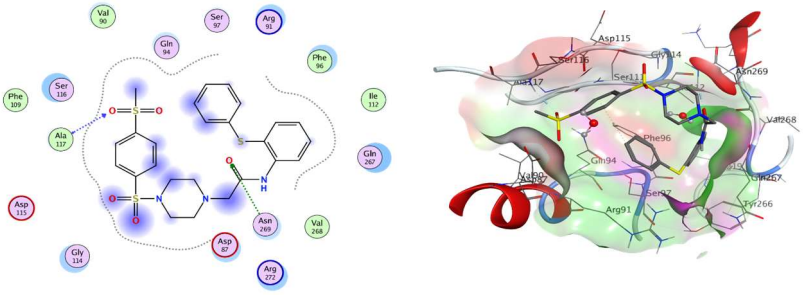

Fig.-10: The 2D and 3D Binding Modes of 9i in the Active Site of DNA Gyrase

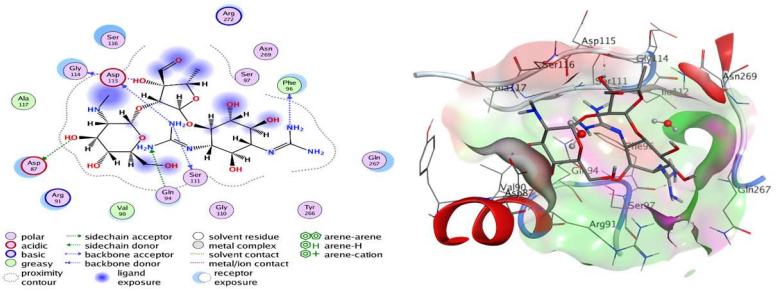

Fig.-11: The 2D and 3D Binding Modes of Streptomycin in the Active Site of DNA Gyrase

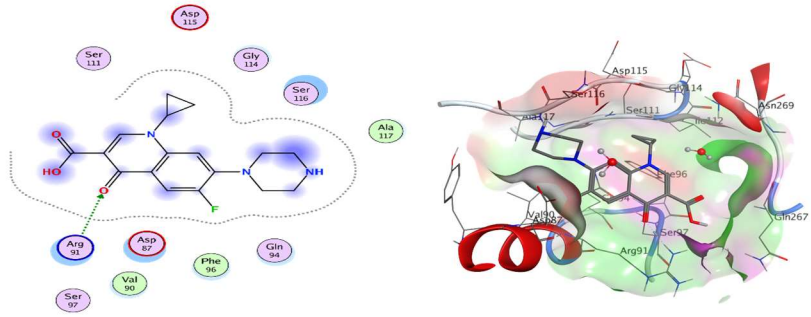

Fig.-12: The 2D and 3D Binding Modes of Ciprofloxacin in the Active Site of DNA Gyrase

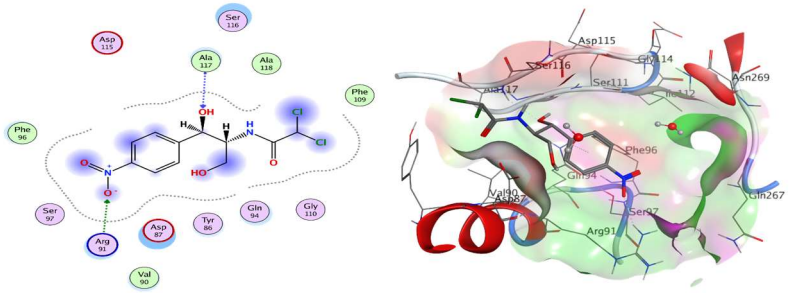

Fig.-13: The 2D and 3D Binding Modes of Chloramphenicol in the Active Site of DNA Gyrase

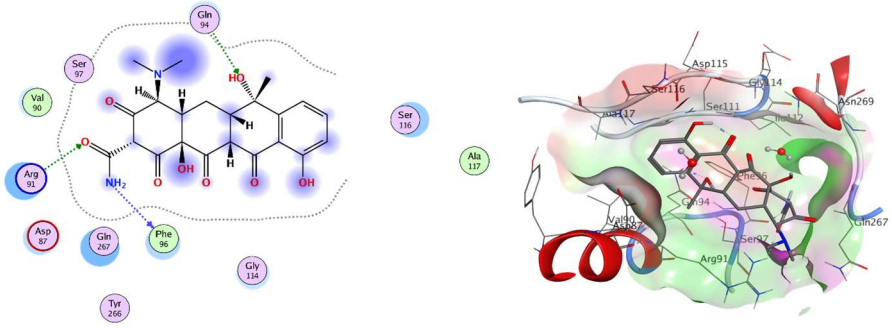

Fig.-14: The 2D and 3D Binding Modes of Tetracycline in the Active Site of DNA Gyrase

CONCLUSION

The synthesis of new analogs, 2-(4-(phenylsulfonyl)piperazin-1-yl)-*N*-(2-(phenylthio)phenyl)acetamide 9(a-i), involves five steps. The compounds are prepared from 2-Aminophenyl disulfide and bromobenzene, chloroacetyl chloride is used to produce chloro-*N*-(2-(phenylthio)phenyl)acetamide, compound 4 is subjected to piperazination using Boc-protected piperazine, and compound 7 is reacted with substituted benzene sulfonyl chlorides to yield phenylsulfanyl-piperazine sulfonamide analogues. Antimicrobial activity was evaluated using the aga well diffusion method on Muller-Hinton agar (MHA). Compounds 9b, 9i, and 9i exhibited notable antibacterial efficacy against Gram-positive and Gram-negative bacteria. The observed variations in activity among the derivatives may be attributed to differences in their chemical structures, suggesting structure-activity relationships that could guide future optimization for enhanced

efficacy. In conclusion, the synthesized derivatives 9(a-i) demonstrated promising antibacterial activity against both Gram-positive and Gram-negative bacteria. Further investigations, including additional microbial strains, toxicity assessments, and mechanistic studies, are essential to comprehensively evaluate the therapeutic potential and safety profile of these compounds. A molecular docking study was conducted to understand the binding interactions of synthesized derivatives within the binding pockets of DNA gyrase A, a crucial enzyme in DNA replication and repair. The identified candidates, 9b and 9i, hold potential for development as novel antibacterial agents, contributing to ongoing efforts in combating bacterial infections.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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