WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.63
Volume 15, Issue 5, 780-792. Research Article ISSN 2277–7105

NEW PIPERAZINE DERIVATIVES: DESIGN, SYNTHESIS, AND MOLECULAR DOCKING ANALYSIS AS POSSIBLE ANTIMICROBIAL DRUGS

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Article Received on 27 Jan. 2026,
Article Revised on 18 Feb. 2026,
Article Published on 01 March 2026,

https://doi.org/10.5281/zenodo.18802000

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How to cite this Article: Md. Afaque[1]*, Kuldeep Singh[2], Syed Misbahul Hasan[3], Saddam Hussain[4], Md. Rahat Raza[5], Md Quamar Niyaz[6]. (2026). New Piperazine Derivatives: Design, Synthesis, and Molecular Docking Analysis As Possible Antimicrobial Drugs. World Journal of Pharmaceutical Research, 15(5), 780–792.

ABSTRACT

Purpose: Formulation and analysis of antimicrobial effectiveness of new heterocyclic compounds containing 1-(4-fluorophenyl) piperazine derivatives. **Aim:** The piperazine moiety is an important nucleus for several biological functions, particularly against microbes, the research is envisaged to synthesize some novel piperazine derivatives and carry out their antimicrobial activity. Therefore, the purpose of this research is to design a novel piperazine derivatives as antimicrobial agents. **Methods:** Piperazine derivatives synthesized by the reaction of of When ethylenediamine and bromo-phenyl acetic acid ethyl ester react, 2-phenyl piperazine is produced. Intermediate compound of 3-phenyl-piperazin-2-one. This intermediate compound further reduction in thepresence of lithium Aluminum hydride to obtained 2-phenylpiperazine. The intermediate compounds 1a were produced through the 1-(4-fluorophenyl) piperazine reaction with bromoacetyl acetyl chloride in the presence of potassium carbonate and intermediate compounds 1b, 1c & 1d were synthesized by the reaction of different sulfonamide derivatives. Intermediate 1a react with Sulfanilic acid to form Benzenesulfonic acid The amino acid Piperazin-1-yl)-2-oxoethyl 4-((2-(4-(4-fluorophenyl)) (A2). Where intermediate 1b, 1c & 1d react with 1-(4-fluorophenyl)

piperazine to form A1, A3 & A4. They were then pharmacologically evaluated for the antimicrobial activity by cup-plate method.

KEYWORDS: Piperazine, Sulphonamide, Antibacterial, *Escherichia Coli*, *Bacillus subtilis* and *Staphylococcus aureus.*

A Brief Introduction

The organic molecule Piperazine is a heterocyclic compound containing six members. Component with two atoms of nitrogen in opposition positions in the ring and four carbon atoms attached.[1]

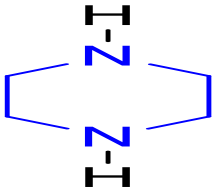


Figure 1: Piperazine.

Piperazine Along with its derivatives have a broad variety of biological effects, consisting of antibacterial, antimalarial, antineoplastic, anti-inflammatory, antimicrobial, and antifungal drugs.[2] Because of their acceptable pka, the piperazine moiety has two main nitrogen molecules that are used in the pharmacokinetic features of drugs application.[3] These nitrogen moieties cause a significant increase in the drug's water solubility, and they play an essential role in bioavailability. The shape of a drug, similar moiety, is an important component in the design and formation of new agents in order to maintain a balance between pharmacokinetic and pharmacodynamics. The aim of these synthesised drugs is to produce compounds with strong affection for their target.[4] Every year, Cancer kills 8.2 million individuals annually, making up 13% of all deaths worldwide. It is common for cancer rates to rise by 70% among more than 100 cancer types.[5] Relevant WHO advice 20% to 30% of kids and 5%–10% of adults have an infection with the influenza virus worldwide, leading in 3 to 5 million new cases and over 2500000 to 500000 deaths.[6] Antifungal.[7] Anticancer.[8] Antimalarial.[9] Antibacterial.[10] Anticonvulsant.[11] Oxazolidinones are a new class of antibacterials. Linezolid was the first of the oxazolidinones to obtain approval for clinical use, and it works very well against drug-resistant Gram-positive bacteria, such as enterococci, streptococci, and staphylococci.[12] The outer bacterial envelope effectively prevents the entry of new therapeutic medicines, preventing them from displaying their antimicrobial properties

to cellular targets.[13,14] A large number of infections obtained in hospitals are caused by ESKAPE, that signifies Staphylococcus aureus, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species, and Enterococcus fecium and drug resistance incidents are rising yearly globally. Bacteria.[15,17] In order to find synthetic antimicrobial scaffolds that could potentially prevent drugs resistance, drug design experts have been employing the hybrid drug technique. Biologically active heteromeric molecules are created when various chemical fragments fuse together using tether that is cleavable or not via a covalent connection. In contrast to noncleavable linker techniques, cleavable linkers are pro-drug. By carrying out its antibacterial function, conventional drug hybrids may employ use of both pharmacophoric domains or only one of them action.[18,20] For the design and discovery of tiny molecule drugs, nitrogen heterocycles continue to be an appealing topic. Piperazines, which are heterocyclic rings with six members that include nitrogen, are undoubtedly one of the most well-known and significant pharmacophores in medicinal chemistry.[21,22] Many significant Fluoroquinoline antibiotics marketed commercially, including Levofloxacin, norfloxacin, ciprofloxacin, gatifloxacin, grepafloxacin, and sparfloxacin, for instance, have their main structure's piperazine moiety. (Fig.2). Thousands of After the structure of pleuromutilin was clarified, semisynthetic pleuromutilin analogues were created and assessed to increase the antibacterial activity and in vivo efficacy.[23,25] In 2007, retapamulin it has been approved for use as a topical antibiotic to treat impetigo in humans.[26]

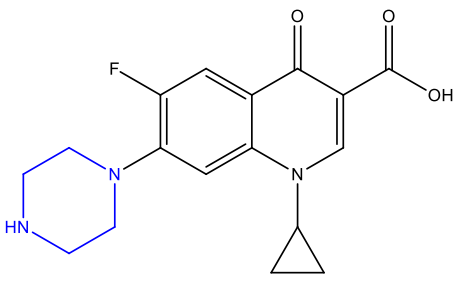


Figure:- 2 Ciprofloxacin

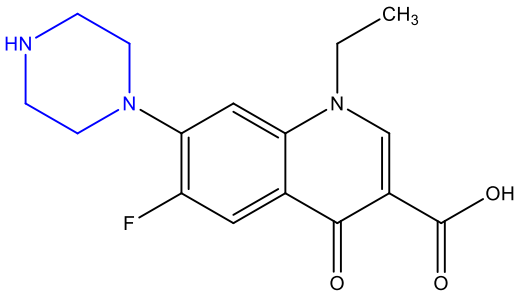


Figure:-3 Norfloxacin

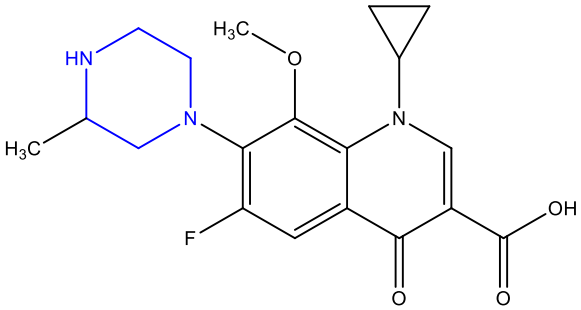


Figure:-4 Gatifloxacin

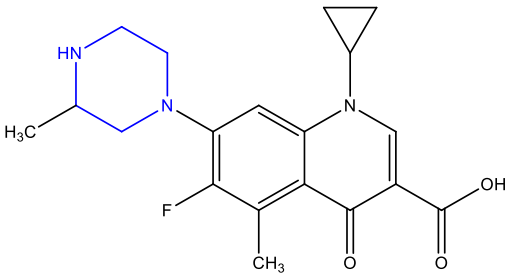


Figure:-5 Grepafloxacin

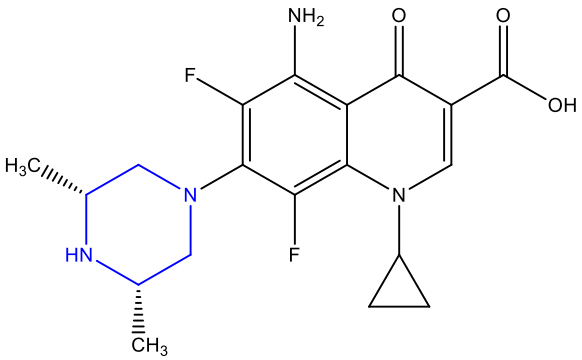


Figure:-6 Sparfloxacin

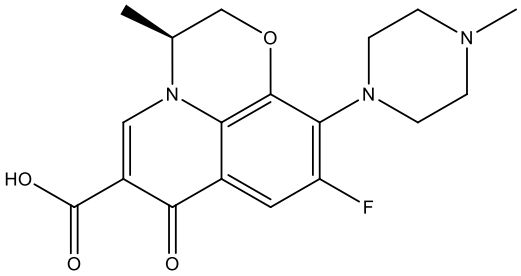


Figure:-7 Levofloxacin

MATERIALS AND METHODS

Chemicals

1-(4-Fluorophenyl) piperazine, (Alfa Aesar), Sulphanilamide, 3-aminomethane sulphonamide, 4-nitrobenzene sulphonamide, 2-nitrobenzene sulphonamide (Sigma), Bromoacetyl chloride (Others), 3-bromopropionyl chloride (Sigma), Benzene (Sdfine), Acetone (Sdfine), Chloroform (Sdfine), Cyclohexane (Sdfine), Dichloromethane (Sdfine), Potassium carbonate, Nutrient agar was obtained from Acros organics, India. Sodium sulphate, Silica gel-G, Methanol (Sdfine), Dimethylsulfoxide (Sdfine).

Various types of bacteria

Escherichia coli, S. aureus, and Bacillus subtilis.

Analytical Work

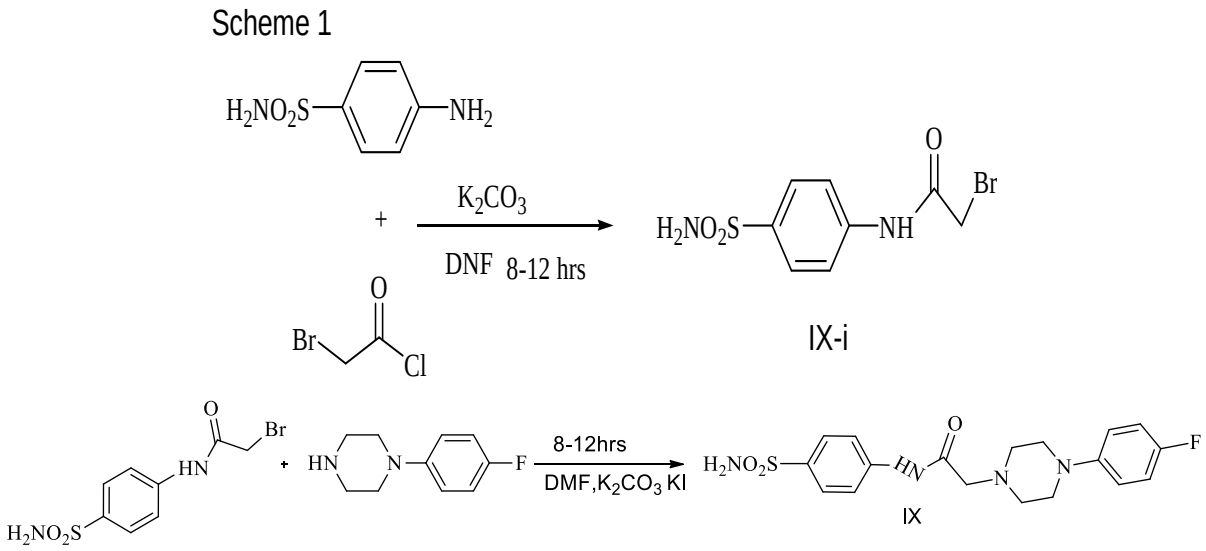
The melting points are corrected and were measured in a naked glass capillary using a melting point device (Veego, Bombay, India). Employing iodine fumes and ultraviolet radiation, thin layer chromatography was used to observe actions on silica gel G plates. visible light as visualizing agent. ES-MS mass spectra were obtained and Spectra of infrared light were obtained using a Perkin Elmer FTIR model. ^{1}H nuclear magnetic resonance Spectra were recorded using the Bruker DRX-300 and chemical shifts. (δ, ppm) are observed relative to tetra methyl silane as an internal standard.

Synthesis of compounds Scheme:-1

2-N-(4-sulfamoylphenyl) acetamide-(4-(4-Fluorophenyl) piperazin-1-yl): (XI)

Synthesis of Synthesis of N-((4-aminophenyl) sulfonyl)-2-bromoacetamide (IXi): Bromoacetyl chloride (0.01mol) was mixed with an equimolar amount of sulfanilamide. Dissolved in 10 mL of DM. Equimolar amounts of potassium iodide and carbonate were added to this solution is added and the reaction stirred the mixture 4-5 hrs at 0-10 ℃. Thin

layer chromatography was utilized to monitor the reaction. (Acetone: Methanol = 7:3). The yield was found to be 53.5% with melting point of 210℃. 1-yl 2-(4-(4-Fluorophenyl) piperazin) I:N-((4-aminophenyl) sulfonyl-2-bromoacetamide (IXi) (0.01 mol) was added to the solution of 1-(4-fluorophenyl) piperazine (0.01 mol) in DMF 10 ml. Equimolar amounts of potassium iodide and carbonate were added to this solution, and Heat was applied to the reaction mixture to 70°C for eight to twelve hours. Following the conclusion of the reaction, the mixture was submerged the precipitate was filtered in cold water off, and recrystallization was used to extract the pure products from water and ethanol. Melting point: 210-212℃. The reaction was mentioned by Chromatography using thin layer. (Hexane: Methanol = 7:3). The yield was found to be 70%.

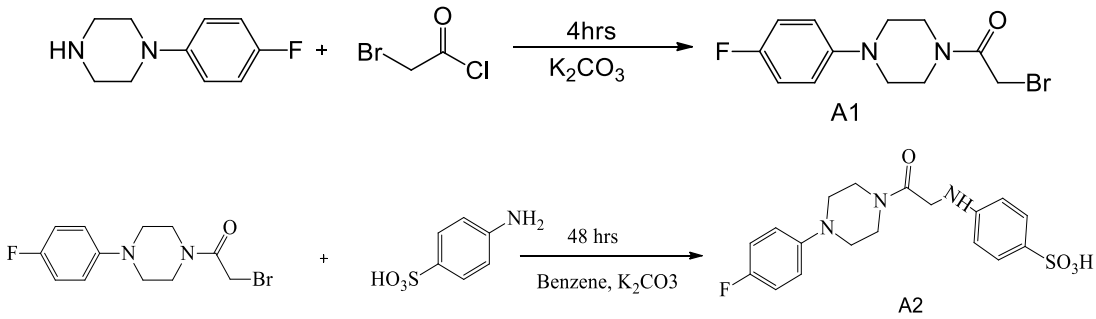


The synthesis of 4-((2-(4-(4-fluorophenyl) piperazin-1-yl)-2-oxoethylamino)

benzenesulfonic acid (A2)

2-bromo-Piperazin-1-yl) 1-(4-(4-fluorophenyl) ethanone (A1) synthesis involves: An equimolar amount of Piperazine 1-(4-fluorophenyl) (0.01mol) dissolved in 10 milliliters of benzene was mixed with bromoacetyl chloride (0.01mol). An equimolar amount of Included was potassium carbonate to this solution, and the reaction mixture was agitated for four hours at a temperature between 0 and 10 °C. After washing the layer of benzene with water and drying it In contrast to sodium sulfate, the solvent was removed, leaving behind solid material that was gathered. (hexane: acetone, 8 : 2). Thin chromatography was used to track the reaction. The yield was found to be 65% with melting point of 180℃. Synthesis of 4-((2-(4-(4-fluorophenyl) piperazin-1-yl)-2-oxoethyl) amino) benzenesulfonic acid (A2): A mixture of 2-bromo-1-(4-(4-fluorophenyl) piperazine-1-yl) ethanone (A1) (0.01 mol) and sulphanilic

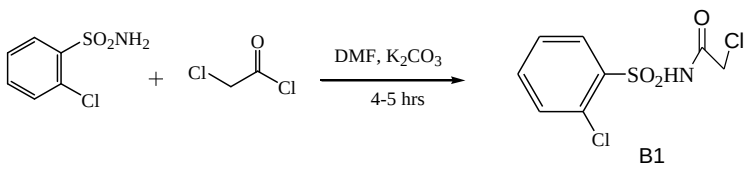
acid (0.01 mol) in benzene 10 ml. Equimolar insertion of potassium carbonate to this solution, and For 48 hours, The mixture was mixed at room temperature. To monitor the reaction, thin layer chromatography was employed. (Hexane: Methanol = 7: 3). The mixture was put into cold water once the reaction was finished, the precipitate was removed by filtering and the pure product was recovered by recrystallization from water. The yield product was found to be 87% with melting point of 180-182℃.

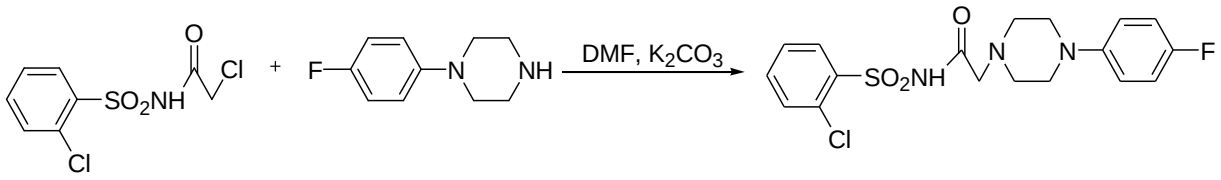


N-((2-Chlorophenyl) sulfonyl)-2-(4-(4-fluorophenylphenyl) piperazin-1-yl) acetamide (A3)

Synthesis of 2-Chloro-N-((2-chlorophenyl)sulfonyl)acetamide (B1): Chloroacetyl chloride An equimolar amount of (0.01mol) was added of 2-chlorobenzene sulfonamide (0.01mol) dissolved in 10 ml of DMF. Equimolar potassium carbonate was added to this solution, and the reaction mixture was agitated for four to five hours at 0 to 10 °C. To observe the reaction, thin layer chromatography was employed. (Acetone: Methanol, 7 : 5). The yield product was found to be 48% with melting point of 210℃.

Synthesis of N- ((2-Chlorophenyl) sulfonyl)-2-(4-(4-fluorophenyl) piperazine-1-yl) acetamide (A3): 2-Chloro-N-((2-Chlorophenyl) sulfonyl) acetamide (B1) (0.01 mol) was added to the solution of 1-(4-fluorophenyl) piperazine (0.01 mol) in DMF 5 ml. To this solution equimolar quantity of potassium carbonate and potassium iodide was added and the reaction mixture was heat at 70℃ for 8-12 hrs after completion of the reaction the mixture was poured in cold water filter off and the pure product were obtained by recrystallization from water and methanol. The yield was found to be 56% with melting point of 220-222℃.

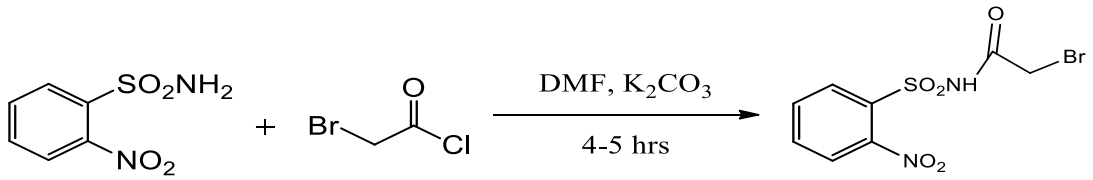




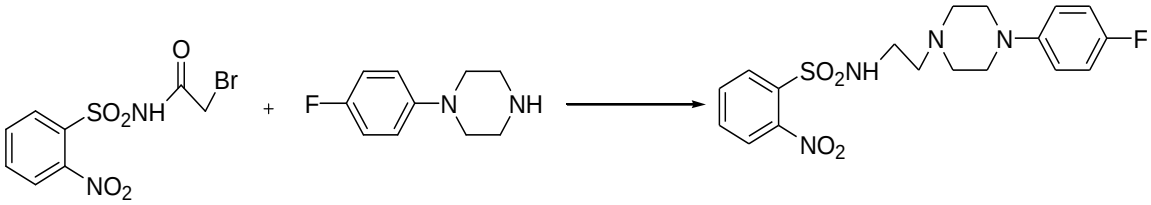
Synthesis of 2-(4-(4-fluorophenyl) piperazin-1-yl)-N-((2-nitrophenyl) sulfonyl) acetamide (A4)

Synthesis of 2-bromo-N-((2-nitrophenyl) sulfonyl) acetamide (C1):- Bromoacetyl chloride an equimolar amount of (0.01mol) was added 2-Nitrobenzene sulfonamide (0.01 mol) in DMF 10 ml. An equimolar amount of potassium carbonate was added to this solution, and the reaction mixture was agitated. 4-5 hrs at 0-10℃. Thin layer chromatography was utilized to monitor the reaction.(Chloroform: Methanol, 2: 8).

Synthesis of 1-yl)-N 2-(4-(4-fluorophenyl) piperazin-((2-nitrophenyl) sulfonyl) acetamide (A4):-2-Bromo-N-((2-nitrophenyl)sulfonylacetamide (C1) was introduced to the 1-(4-Fluorophenyl) piperazine solution (0.01 mol) in DMF 5 ml. Equimolar amounts of potassium carbonate were added to this solution and potassium iodide was added and the reaction mixture was heat at 70℃ for 8-12 hrs after completion of the reaction after the mixture was added in cold water and the precipitated was filter off and the pure product obtained through the process of recrystallization from water and methanol. The yield was found to be 78% with melting point 195-197℃. (Hexane: Methanol = 7:3).



(C1)



(A4)

RESULT

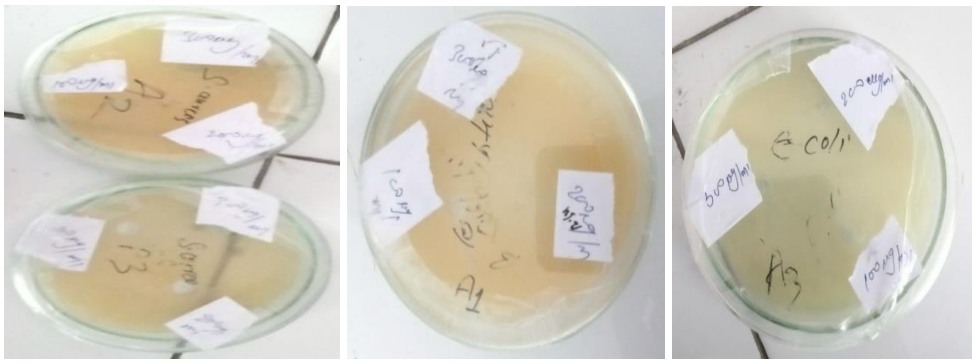
Among all the synthesized compounds (at conc. 100 µg/ml, 200µg/ml and 300 µg/ml) compound A2 showed the higher zone of inhibition (20 mm, 25 mm and 28 mm diameter

respectively), but lesser than the standard drug i.e. Norfloxacin (ZOI-25 mm, 30 mm and 35 mm diameter) against *Escherichia coli* (gram negative bacteria).

Among all the synthesized compounds (at conc. 100 µg/ml, 200 µg/ml and 300 µg/ml) A2 displayed the higher zone of inhibition (no zone, 22 mm and 25 mm and 28 mm diameter respectively), but lesser than the standard drug i.e. Norfloxacin (ZOI-32 mm, 37 mm and 40 mm diameter) against *Staphylococcus aureus* (gram-positive bacteria).

Among all the synthesized compounds (at conc. 100 µg/ml, 200 µg/ml and 300 µg/ml) compound A3 showed the higher zone of inhibition (20 mm, 24 mm and 30 mm diameter) but lesser than standard drug i.e. Norfloxacin (ZOI- 30 mm, 35 mm and 40 mm diameter) *Escherichia coli* against (gram-negative bacteria).

Among all the synthesized compounds (at conc. 100µg/ml, 200µg/ml and 300 µg/ml) A1 displayed the most inhibition zone (18 mm,22mm, and 30 mm diameter), but lesser than the standard drug i.e. Norfloxacin (ZOI-35 mm, 38 mm 42 mm diameter) *Bacillus subtilis* (gram positive bacteria).



A **B** **C**

Figure 8: Antimicrobial activity of tested compounds (A) *Staphylococcus aureus* (B) *B. subtilis* (C) *Escherichia coli.*

Table 1: Antimicrobial data of synthesized compounds.

Compounds	Dilutions (µg/ml)	Zone of inhibition (mm)	
		Escherichia coli.	*Staphylococuus aureus*
(IX)	100	25	20
	200	20	25
	300	28	30
(A2)	100	20	20
	200	25	25
	300	28	30

A3	100	20	20
	200	24	24
	300	30	30

Compounds	Dilutions (µg/ml)	Zone of inhibition (mm)
		Bacilus subtilis
A1	100	18
	200	22
	300	30
Norfloxacin	100	30
	200	36
	300	40

Table 2: Antimicrobial data of synthesized compounds.

Compounds	Dilutions (µg/ml)	Zone of inhibition (mm)	
		Escherichia coli.	***Staphylococuus aureus***
A1	100	28	30
	200	25	20
	300	20	25
A2	100	20	20
	200	25	25
	300	28	30
A3	100	20	20
	200	24	24
	300	30	30

Table 3

Compounds	Dilutions (µg/ml)	Zone of inhibition (mm)
		Bacilus subtilis
A1	100	18
	200	22
	300	30
Norfloxacin	100	30
	200	36
	300	40

Table 4: Physical data of synthesized compounds (A1-A2).

S.NO.	**1**	**2**
Compounds	**A1**	**A2**
Molecular formula	$C_{18}H_{21}FN_4O_3S$	$C_{18}H_{20}FN_3O_4S$
Molecular weight	392.43 g/mol	393.43 g/mol
Yield	70%	87%
R_f Value	0.7	0.5
Melting point	210-212^{O}C	180-182^{O}C
Solvent System	(acetone : methanol, 5 : 5)	(acetone : methanol, 7 : 3)
Appearance	White colourless cystaline	*Pale yellow precipitate*

DISCUSSION

The intermediate compound N-((4-aminophenyl) sulfonyl)-2-bromoacetamide was produced by the reaction of Bromoacetyl chloride with sulfanilamide in the presence of DMF as a solvent and potassium carbonate as a catalyst.

The final 2-(4-(4-Fluorophenyl) compound piperazine-1-yl)-N-(4-sulfomomylphenyl) acetamide **(Compound A1)** was synthesized by the stirring of (**Intermediate 1a,** N-((4-aminophenyl) sulfonyl)-2-bromoacetamide and sulphanilamide (both are dissolved in methanol) in the presence of potassium carbonate about 10-12 hr. 70℃.

The compound 4-((2-(4-(4-fluorophenyl)piperazine-1-yl)-2-oxoethyl)amino)benzene sulfonic acid **(Compound A2)** was synthesized by the stirring of **(Intermediate 1b**, Bromo-1-(4-(4-fluorophenyl)piperazine-1-yl) ethanone and sulfanilic acid (both are dissolved in Acetone and DMSO) in the presence of potassium carbonate about 8-12 hr. at ℃.

TLC observed the reaction's progress, and their structures have been confirmed by ^{1}HNMR and Mass spectroscopy. The proposed structures and the spectral data are totally similar.

Figure: 9 Comppound A2.

CONCLUSION

The thesis titled "Biological and Synthesis screening of piperazine derivatives" had been separated into five sections. **Chapter 1:** Introduction of piperazine, This chapter represents the physical, chemical properties, Mechanism action of piperazine, synthetic derivatives of piperazine and some biological activity of piperazine derivatives uses of piperazine etc. **Chapter 2:** Summarizes the literature review. **Chapter 3:** Summarizes the all plan of work as first of some important compound was designed and synthesize and then after characterization was carried out. Pharmacological activities were seen of final compound. **Chapter 4:** This chapter deals with the experimental protocol of ll synthesized compounds its

pharmacology and chemistry. Total two reaction scheme were taken for the synthesis of compounds and after synthesizing each intermediate and final compound have been characterized through 1HNMR, MASS and purified either through crystallization Experimental Design (Synthesis): The compounds (A1) were produced via the synthetic the strategy presented in scheme 1. The compound (A2) were manufactured following the synthetic route presented in Scheme 2. The compound (A3 and A4) were produced in accordance with the synthesis the strategy presented in Scheme 3. In Scheme 1 the 1-(4-fluorophenyl) piperazine reacts with Bromoacetyl chloride in presence of benzene and potassium carbonate to form intermediate 1a this is further reacted with Sulfanilic acid to form final compound A2.

ACKNOWLEDGEMENT

Md Afaque is a M. Pharm (Pharmaceutical Chemistry) student at department of Pharmacy. Authors are grateful to an eminent and honorable Chancellor of Integral University in Lucknow, Prof. S. W. Akhtar, for supplying the required facilities for carrying out this work.

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