Design Synthesis and Antimicrobial Evaluation of Fluoroquinolone Thiadiazole Hybride: Agents Against Antimicrobial Infection

Corresponding Author: Ayushi Patwari[1],

Co Author: Dr. Sudha Vengurlekar[2], Dr. Sachin K. Jain[3]

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Oriental University, Indore

[2]Department of Pharmaceutical Chemistry, Professor of Medicinal Chemistry, Faculty of Pharmacy, Oriental University, Indore

[3]Department of Pharmacy, Professor & Principal, Faculty of Pharmacy, Oriental University, Indore

ABSTRACT

Background: The increasing prevalence of antimicrobial resistance has heightened the need for novel therapeutic agents to treat infections effectively. Among various classes of antibiotics, fluoroquinolones have been widely used due to their broad-spectrum activity and ability to inhibit bacterial DNA gyrase and topoisomerase IV enzymes, which are essential for bacterial DNA replication. However, the efficacy of fluoroquinolones has been significantly compromised by emerging bacterial resistance. The design strategy involved molecular docking studies to optimize binding interactions of the fluoroquinolone-thiadiazole hybrids with bacterial enzymes, aiming to improve potency and spectrum of activity.

Result: The synthesis pathway was streamlined to ensure feasibility in a laboratory setting, with intermediates purified and characterized using advanced analytical techniques like NMR, MS, and IR spectroscopy. The synthesized compounds were subjected to in vitro antimicrobial evaluation against a panel of Gram-positive and Gram-negative bacteria, including drug-resistant strains. Minimum inhibitory concentration (MIC) values were determined to assess potency, and the fluoroquinolone-thiadiazole hybrids displayed significant antimicrobial activity compared to traditional fluoroquinolones. Furthermore, structure-activity relationship (SAR) analysis highlighted the importance of substitutions on the thiadiazole ring, revealing that electron-donating groups at specific positions contributed to increased antimicrobial activity.

Conclusion: The findings suggest that the fluoroquinolone-thiadiazole hybrid scaffold holds promise as an effective antimicrobial agent against multidrug-resistant infections, providing a novel direction for the development of future antibacterial agents.

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Keywords: Fluoroquinolone thiadiazole hybrid, antimicrobial resistance, bacterial DNA gyrase inhibition, structure-activity relationship (SAR), broad-spectrum antibiotics, antimicrobial evaluation

BACKGROUND

Antimicrobial resistance (AMR) is a critical global health issue that compromises the efficacy of existing antibiotics and jeopardizes the treatment of infectious diseases.[1] The rise in AMR is largely attributed to the extensive and sometimes indiscriminate use of antibiotics, leading to the emergence of multidrug-resistant (MDR) pathogens.[2] These pathogens are challenging to treat with conventional antibiotics, creating an urgent need for innovative therapeutic strategies and novel antimicrobial agents. In this scenario, drug design approaches that modify or hybridize existing antibiotic classes present a promising strategy to overcome resistance mechanisms.[3] One approach that has garnered significant interest is the development of fluoroquinolone-thiadiazole hybrids, a novel class of compounds that combine the potent antimicrobial activity of fluoroquinolones with the versatile pharmacological profile of thiadiazole rings.[4]

Fluoroquinolones are well-known for their broad-spectrum antimicrobial activity and their efficacy against various bacterial infections. They function by inhibiting bacterial DNA gyrase and topoisomerase IV, enzymes essential for DNA replication and transcription, leading to bacterial cell death.[5] However, despite their effectiveness, fluoroquinolones have encountered substantial resistance in clinical settings. Pathogens such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* have developed mechanisms to evade fluoroquinolone action through mutations in target enzymes, efflux pump overexpression, and other resistance pathways. As a result, the clinical effectiveness of fluoroquinolones is declining, prompting researchers to explore ways to enhance their efficacy and overcome resistance.[6, 7]

To address these challenges, researchers have explored combining fluoroquinolones with other pharmacologically active scaffolds to create hybrid molecules with enhanced antimicrobial potency.[8] One promising scaffold for this purpose is thiadiazole, a five-membered heterocyclic ring containing two nitrogen atoms and one sulfur atom. Thiadiazoles exhibit diverse biological activities, including antimicrobial, anti-inflammatory, and antitumor properties. The integration of a thiadiazole ring into fluoroquinolone structures offers the potential for synergistic effects, with the thiadiazole moiety contributing additional binding sites, unique pharmacodynamics, and improved efficacy against resistant strains.[9] The hybridization approach aims to improve the molecular interaction of fluoroquinolone-thiadiazole hybrids with bacterial targets, potentially reducing resistance development and broadening the spectrum of activity.[10]

This research contributes to the growing body of knowledge in drug design and synthesis, opening new avenues for combating MDR bacterial infections and improving public health outcomes.

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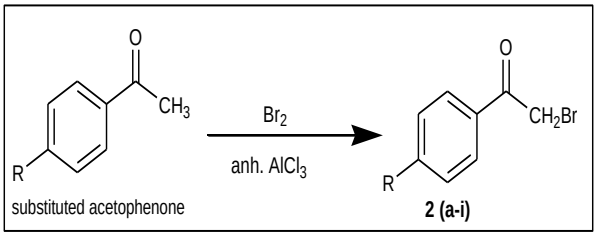
METHODS

All the chemicals used for synthesis were of Merck (Mumbai), Sigma, Loba-chemie (Mumbai), Rankem (Hariyana) and Avera laboratories (Hyderabad). All solvents, reagents and catalyst were of analytical grade and used directly. The purity of compounds was confirmed by thin layer chromatography using silica gel glass plates as the stationary phase and developed the solvent system as dichloromethane : methanol (10:1) for confirmed the reactions. The synthesized compounds were purified by recrystallisation through appropriate solvent. More precisely purification of the final compounds was done with column chromatography, in which silica was passed of 230-400 mesh through sintered glass column. The pure drug gatifloxacin procured as gift sample from Sunpharma Laboratories Ltd, Dewas (M.P.), India.
The final reaction was carried out by microwave irradiation method CEM, USA, model, Discover system, model no. 908010, serial no. DU9317, maximum power, 700 watt. Melting points were determined by using Analab scientific instrument (Thermocol- sr. no. 2010-11/1205) open capillary method and are uncorrected. The IR spectra were recorded by using KBr on FT-IR 8400S Shimadzu, Japan.

Step-I: Synthesis of Compound-I

- Chemicals used :-
  - ✓ Acetophenone
  - ✓ Acetone
  - ✓ Aluminium-tri-chloride
  - ✓ Bromine



General procedure of Compound-I[87]

0.1 mol substituted acetophenones were taken in two-necked RBF and introduced appropriate dry solvent. (Ether, chloroform, acetone or carbon tetrachloride) The reaction condition was maintained either in cold or at room temperature. Introduce anhydrous aluminium-tri-chloride as catalytic amount in the reaction flask. Stirred the mixture for 1-4 hour at room temperature or 5-10°C. After completion the stirring, bromine (0.1 mol) was gradually added with stirring the reaction mixture. Usually the addition of bromine was taken up to one and half hour. The temperature of the reaction mixture becomes rise up to 20°C. The reaction mixtures poured into ice water, separate the precipitate by evaporate the solvent under reduced pressure or filtered the

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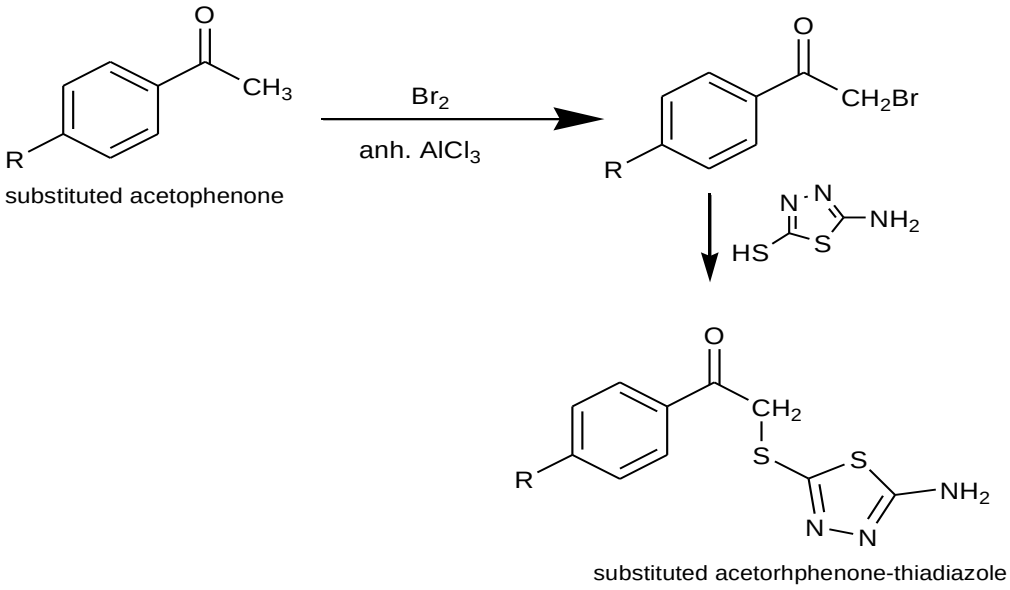
solution through vacuum pump. Recrystallized the crude substituted phenacyl bromide 2 (a-f) by rectified spirit. The pure 2 (a-f) was obtained as brownish yellow to colorless crystals.
Melting point: 48–50◦
Yield: 60–65%.

Step–II: Synthesis of Compound-II[88]

- Chemicals used:-
  - ✓ Potassiun hydroxide
  - ✓ Charcoal
  - ✓ Ether
  - ✓ Distilled water



Procedure: - General Procedure for Synthesis of 3(a-f). Add (0.1 mol) of 80% KOH to a suspension of (0.1 mol) of 2-amino-5- mercapto-1,3,4-thiadiazole, in 15 mL of water. Solution was clarified with activated charcoal and diluted with 32 mL of ethanol, 0.1 mol of 2(a-f) was added rapidly with stirring. Thick reaction mixture was formed, stirred vigorously and cooled for 30–45 minutes, and then diluted with 200 mL of cold water. The solid was obtained by filtration, washed with water and ether. 3(a-f) were obtained (Scheme 1)
Melting Point: 90–98◦ C;
Yield: 60–65%.

Step–III: - Synthesis of Compound-III

- Chemicals used: -
  - ✓ Sodiun nitrite
  - ✓ HCl
  - ✓ Chloroform

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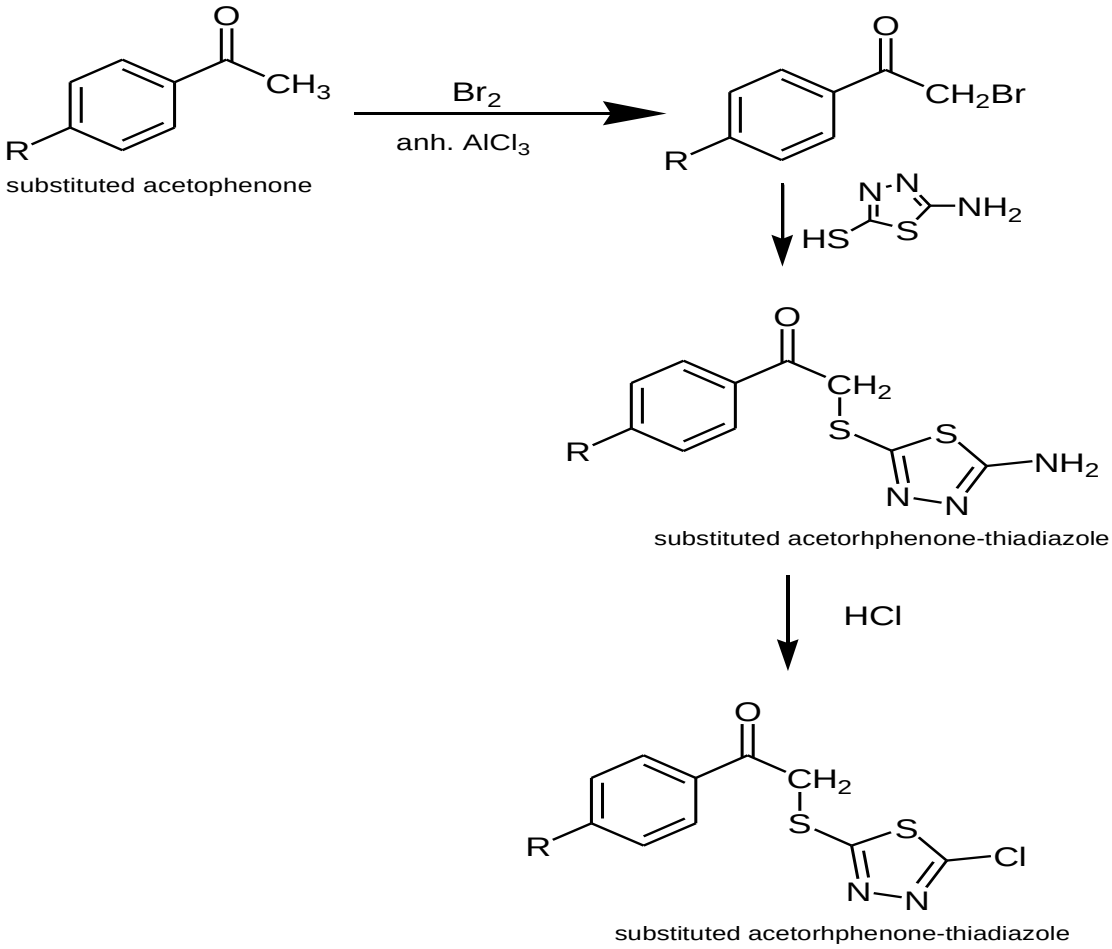
- ✓ Sodium bicarbonate
- ✓ Ethanol



General procedure for preparation of IV(a-f) [88-90]

Powder 3(a-f) (15 mmol) with an excess of sodium nitrite (30 mmol). Introduce the mixture slowly with constant stirring, into an ice-cooled solution of 30 mL conc. hydrochloric acid and 15 mL water, maintained at 0–5∘ C and heated up to 75∘ C for 1 hour. The reaction mixture was cooled and extracted with dry chloroform (75 mL × 3). The combined extracts were washed with sodium bicarbonate solution, and chloroform followed by evaporation under reduced pressure and finally recrystallized from ethanol to yield 2-chloro-5- benzoylmethylenethio-1,3,4-thiadiazole 4(a-f) (Scheme 1).

Melting Point:108–116◦C

Yield: 55–60%

Step–IV:- Synthesis of Compound-IV

- ➢ Chemicals used:-
  - ✓ DMF
  - ✓ Sodium bicarbonate

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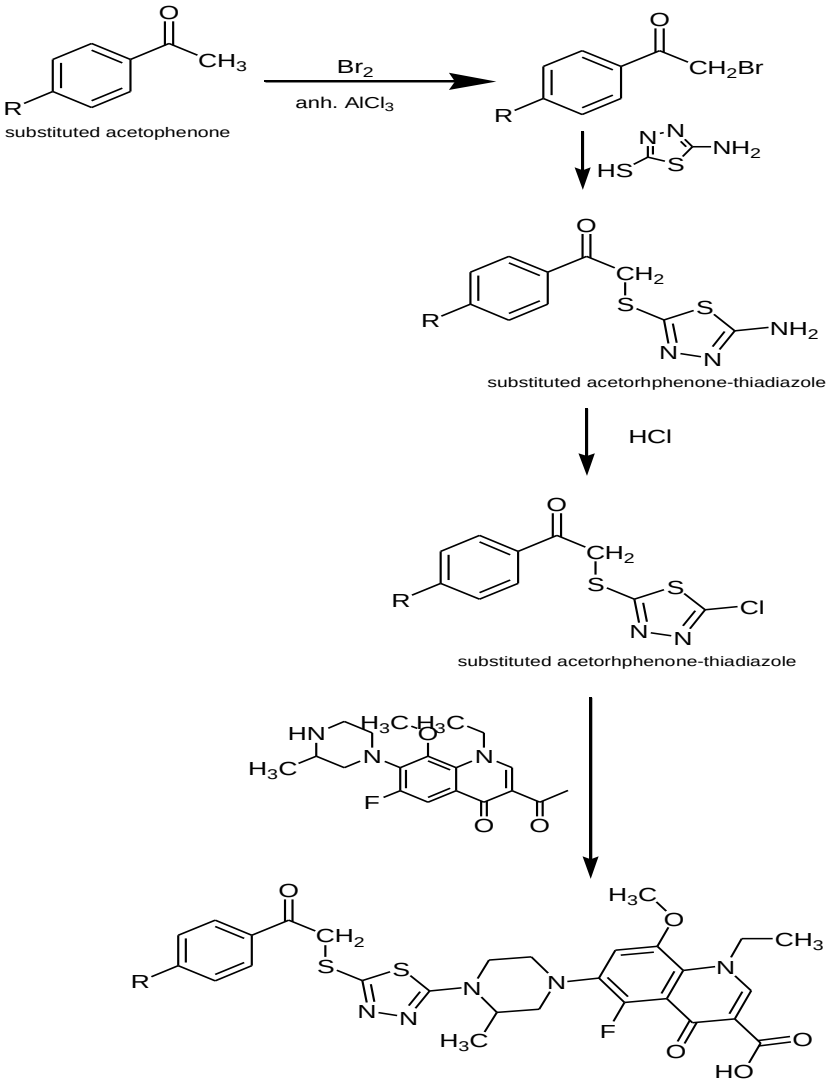
✓ Distilled water



General Procedure for Synthesis of 5(a-f)[91]

A mixture of equimolar quantities of 4(a-f), and piperazinyl fluoroquinolone such as gatifloxacin, along with sodium-bicarbonate in 10 mL dimethylformamide was heated at 118–140∘ C for 20–24 hrs. After cooling, 10 mL of cold water was added, and precipitate was filtered, recrystallized from DMF-H2O to yield the titled compounds (Scheme 1).

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Melting Point: 120–134◦C
Yield: 45-50%

Table 1: Physical Data of the Compound IV(a-f)

Compound	Molecular weight	Molecular formula	Melting Point	R_f value
IV(a)	598	$C_{28}H_{28}FN_5O_5S_2$	121-123°C	0.37
IV(b)	632	$C_{28}H_{27}ClFN_5O_5S_2$	127-130°C	0.39
IV(c)	677	$C_{28}H_{27}BrFN_5O_5S_2$	122-125°C	0.35
IV(d)	612	$C_{29}H_{30}FN_5O_5S_2$	137-140°C	0.41
IV(e)	628	$C_{29}H_{30}FN_5O_5S_2$	131-135°C	0.38
IV(f)	614	$C_{28}H_{28}FN_5O_6S_2$	127-130°C	0.42
IV(g)	615	$C_{28}H_{27}F_2N_5O_5S_2$	137-140°C	0.45
IV(h)	613	$C_{28}H_{29}FN_6O_5S_2$	128-131°C	0.48
IV(i)	613	$C_{28}H_{28}FN_5O_6S_2$	138-140°C	0.49
IV(j)	723	$C_{28}H_{27}FIN_5O_5S_2$	138-142°C	0.40

Table 1 represents Physical Data of the Compound IV(a-f)

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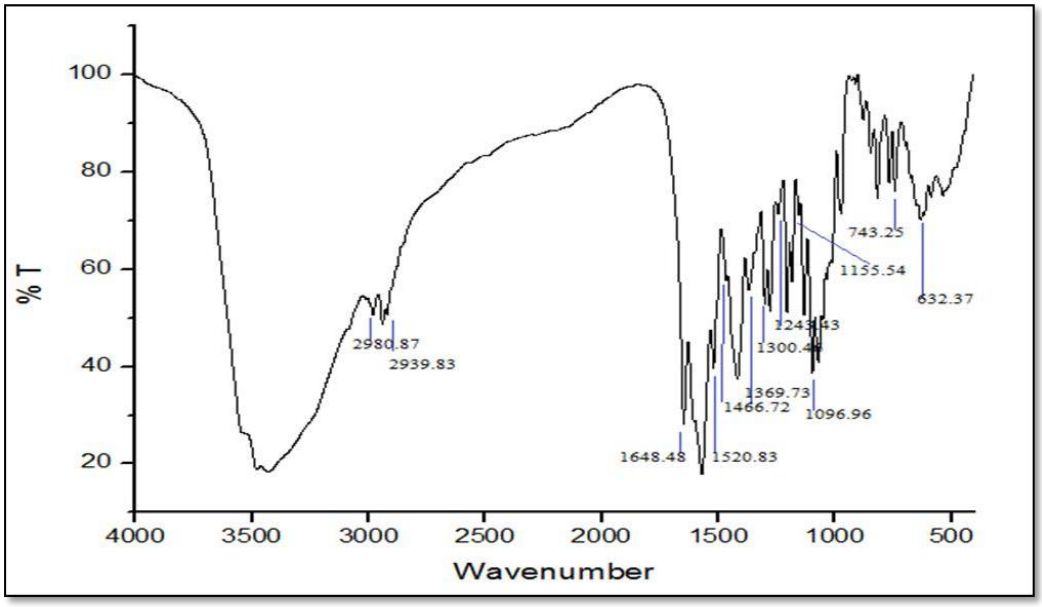
RESULT

Spectral presentation:

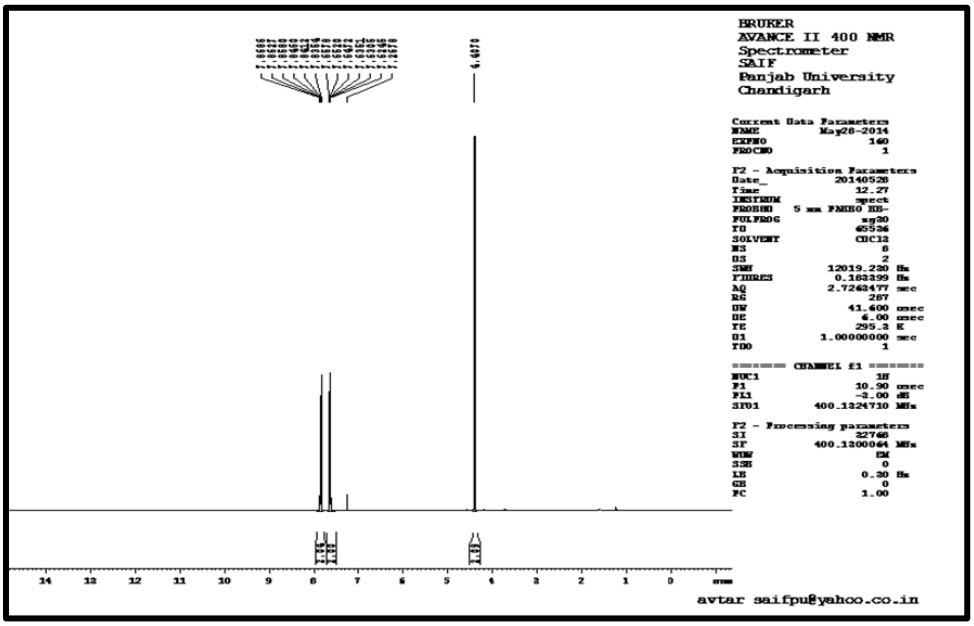
1. IR Spectra of Compound IV(a)



Infrared Spectrum Features (cm^{-1})

2980-2939 (C-H), 1300-1369 (-CH_3), 1243 (C-N)

1. NMR Spectra of Compound IV(a)



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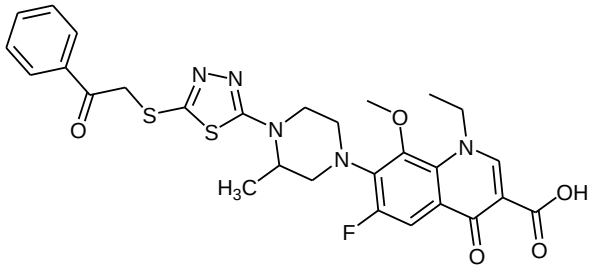
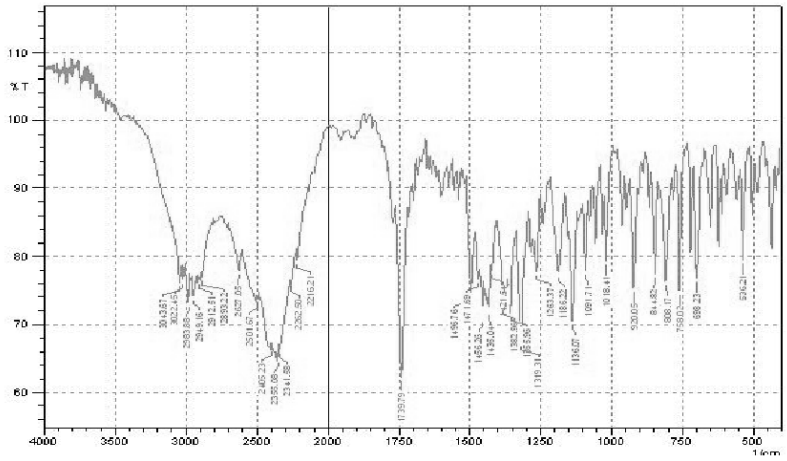
NMR Spectrum Features NMR(DMSO-$dd6$) $\delta\delta$ppm:13.50 (s, 1H, OH), 7.90 (s, 1H, H2-quinoline), 7.37–7.45 (m,5H, Ar.), 6.70 (d, 1H, H5-quinoline), 4.24 (s, 2H, CH2), 3.84(s, 3H, methoxyl), 3.24–3.52 (m, 7H, piperazinyl), 3.10 (q,2H, NCH2CH3), 1.34 (m, 3H, 3′-methylpiperazine), 1.14 (t,3H, NCH2CH3).



5(a),7-[4-{5-(2-Oxo-2-phenylethylthio)-1,3,4-thiadiazol-2yl}-3′-methylpiperazin-1yl]-1-ethyl-6-fluoro-8-methoxyl-4-oxo- 1,4-dihydroquinoline-3-carboxylic Acid

2. IR Spectra of Compound IV (b)



Infrared Spectrum Features (cm^{-1})

820-540(C-Cl), 1460-1340 (-CH_3), 1230 (C-N), 2970-2850 (C-H)

NMR Spectra of Compound IV(b)

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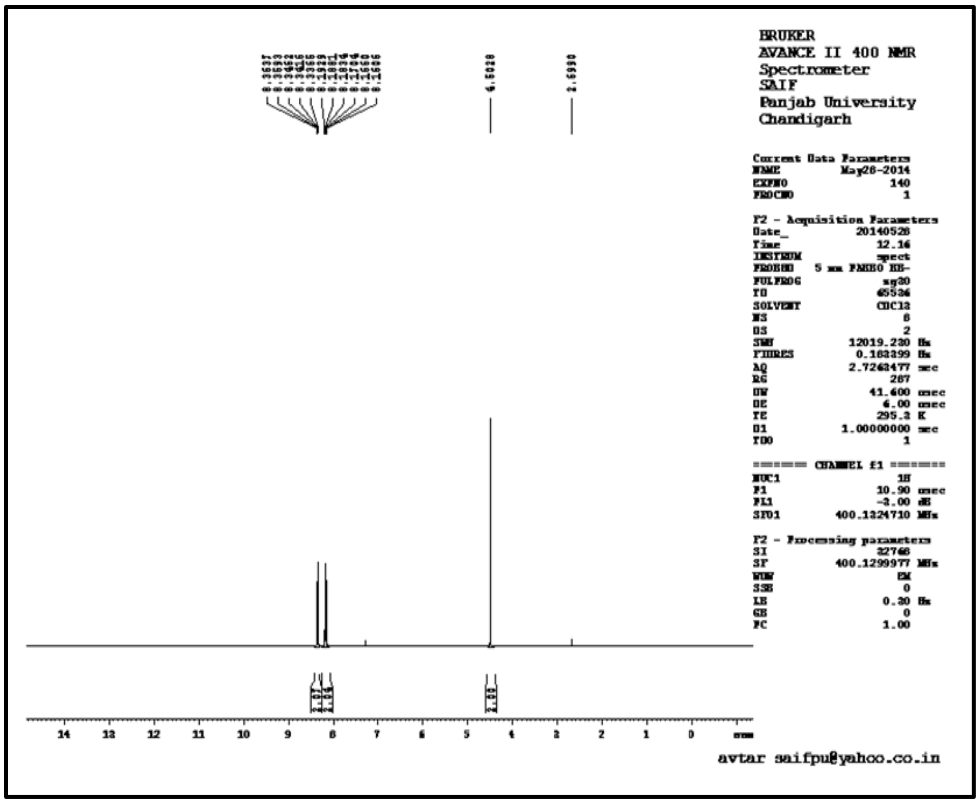
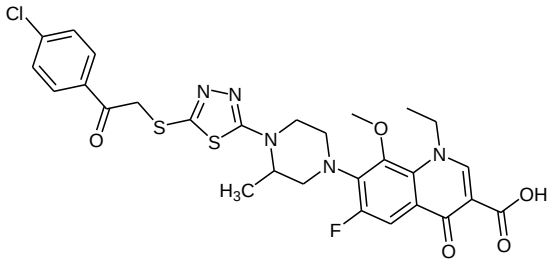


NMR Spectrum Features:NMR(DMSO-*dd*6) $\delta\delta$ppm: 13.68 (s, 1H, OH), 8.02 (s, 1H,H2-quinoline), 7.88 (m, 2H, Ar.) 7.40 (m, 2H, Ar.), 6.64 (d,1H, H5-quinoline), 4.30 (s, 2H, CH2), 3.88 (s, 3H, methoxyl),3.20–3.46 (m, 7H, piperazinyl), 3.20 (q, 2H, NCH2CH3), 1.24(m, 3H, 3′-methylpiperazine), 1.18 (t, 3H, NCH2CH3).



5(b),7-[4-{5-(2-Oxo-2-p-chlorophenylethylthio)-1,3,4-thiadiazol-2yl-}3′ methylpiperazin-1yl]-1-ethyl-6-fluoro-8-methoxyl-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid

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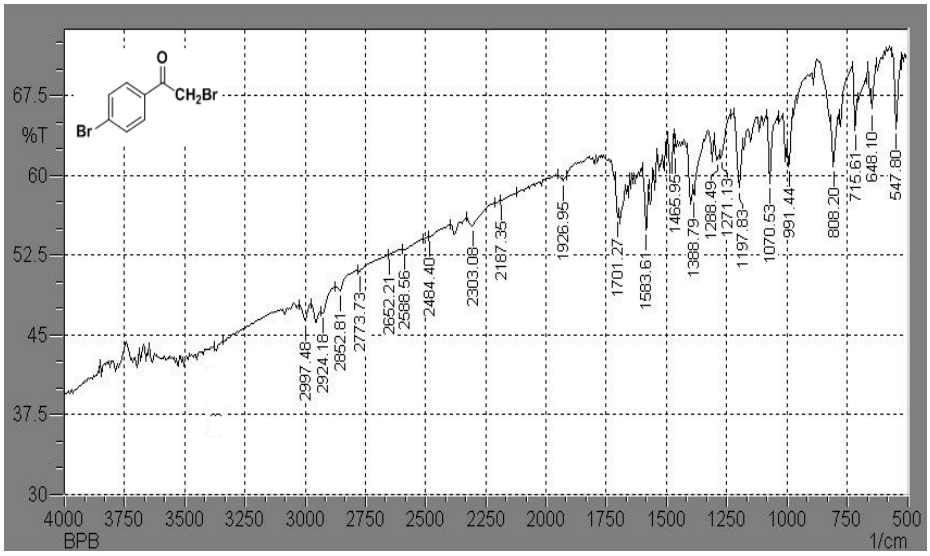
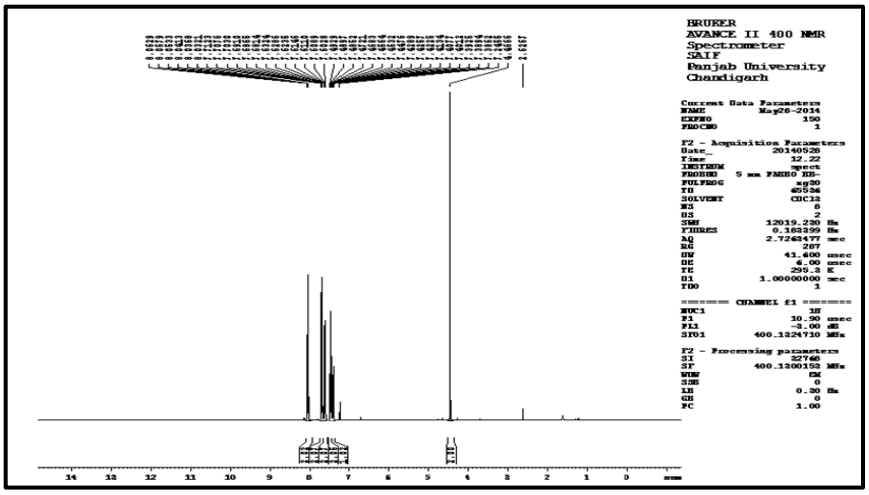
3. IR Spectra of Compound 5(c)



Infrared Spectrum Features (cm^{-1})

820-540(C-Br), 1470-1365 (-CH_3), 1230 (C-N), 2900-2855 (C-H)

NMR Spectra of Compound 5(c)



NMR Spectrum Features: NMR(DMSO-*dd*6) $\delta\delta$ppm: 14.06 (br, s, 1H, OH), 7.98 (s, 1H,H2-quinoline), 7.78 (m, 2H, Ar.) 7.34 (m, 2H, Ar.), 6.66 (d,1H, H5-quinoline), 4.24 (s, 2H, CH2), 3.94 (s, 3H, methoxyl),3.18–3.38 (m, 7H, piperazine), 3.10 (q, 2H, NCH2CH3), 1.20(m, 3H, 3′-methylpiperazine), 1.10 (t, 3H, NCH2CH3).

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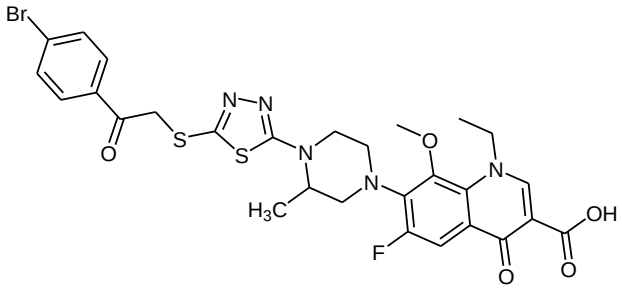
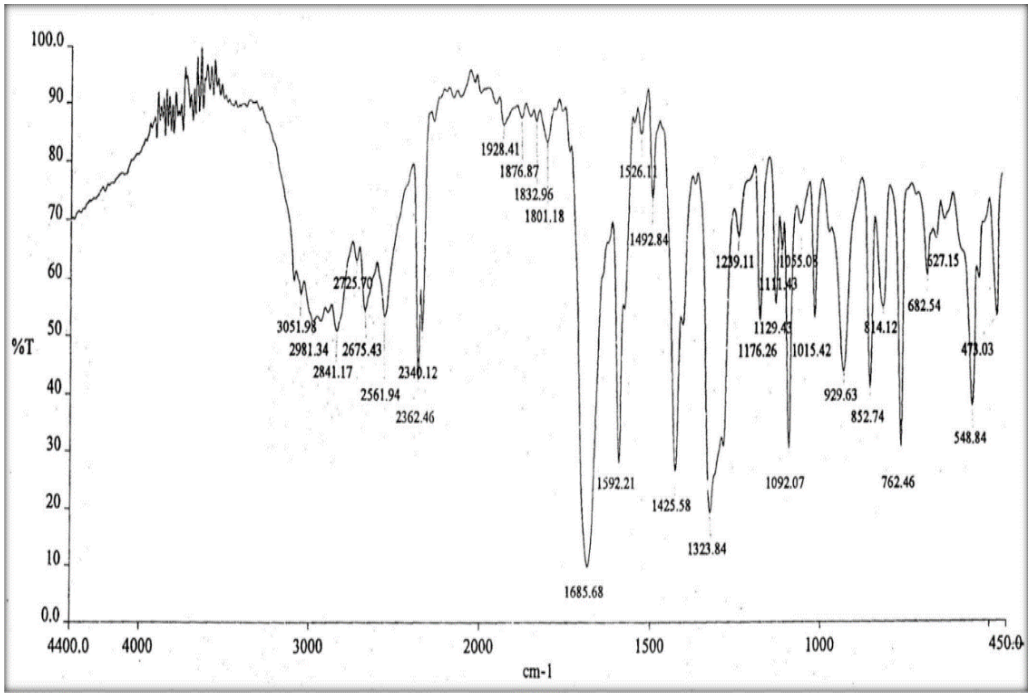


5(c),7-[4-{5-(2-Oxo-2-p-bromophenylethylthio)-1,3,4-thiadiazol-2yl-}3′methylpiperazin-1yl]-1-ethyl-6-fluoro-8-methoxyl-4-oxo-1,4-dihydroquinoline-3 carboxylic Acid

4. IR Spectra of Compound 5(d)



Infrared Spectrum Features (cm^{-1})

1480-1371 ($-CH_3$), 1100 (C-N), 2920-2880 (C-H)

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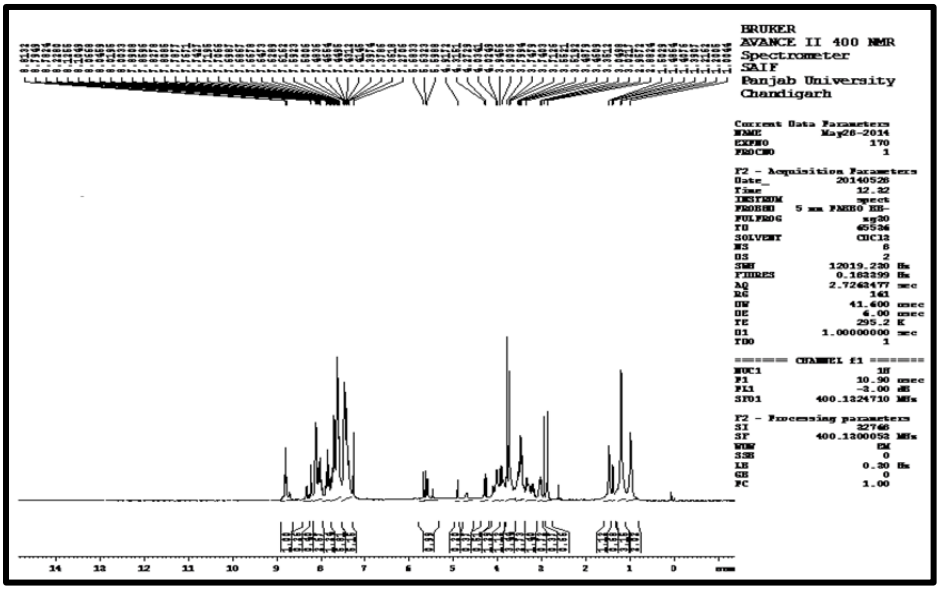
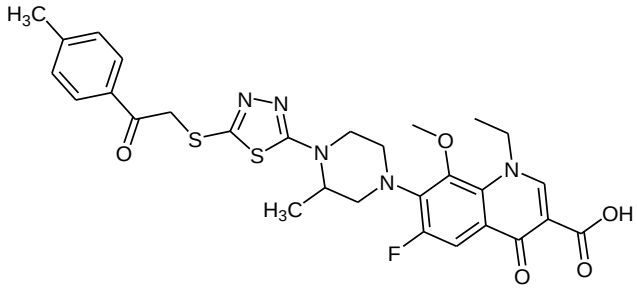
NMR Spectra of Compound 5(d)



NMR Spectral Features:NMR(DMSO-dd6) $\delta\delta$ppm: 14.70 (s, 1H, OH), 7.93 (s, 1H,H2-quinoline), 8.36 (m, 2H, Ar.) 8.20 (m, 2H, Ar.), 6.80 (d,1H, H5-quinoline), 4.32 (s, 2H, CH2), 3.96 (s, 3H, methoxyl),3.24–3.48 (m, 7H, piperazinyl), 3.20 (q, 2H, NCH2CH3), 1.40(m, 3H, 3′-methylpiperazine), 1.16 (t, 3H, NCH2CH3).



5(d),7-[4-{5-(2-Oxo-2-p-methylphenylethylthio)-1,3,4-thiadiazol-2yl-}3′methylpiperazin-1yl]-1-ethyl-6-fluoro-8-methoxyl-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid

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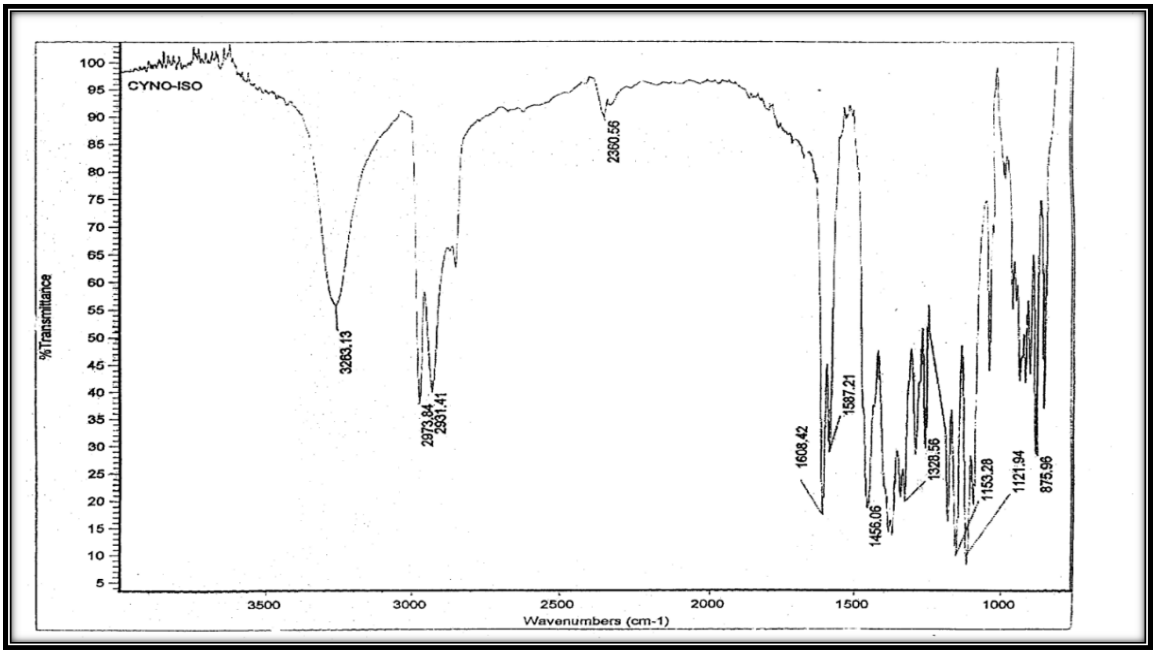
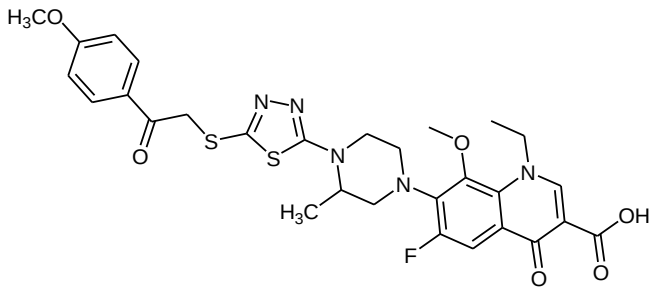
5. IR Spectra of Compound 5(e)



Infrared Spectrum Features (cm^{-1})

2865-2820(-OCH3), 1459-1311 (-CH_3), 1222 (C-N), 2855 (C-H)



5(e),7-[4-{5-(2-Oxo-2-p-methoxyphenylethylthio)-1,3,4-thiadiazol-2yl-}methylpiperazin-1yl]-1-ethyl-6-fluoro-8-methoxyl-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid

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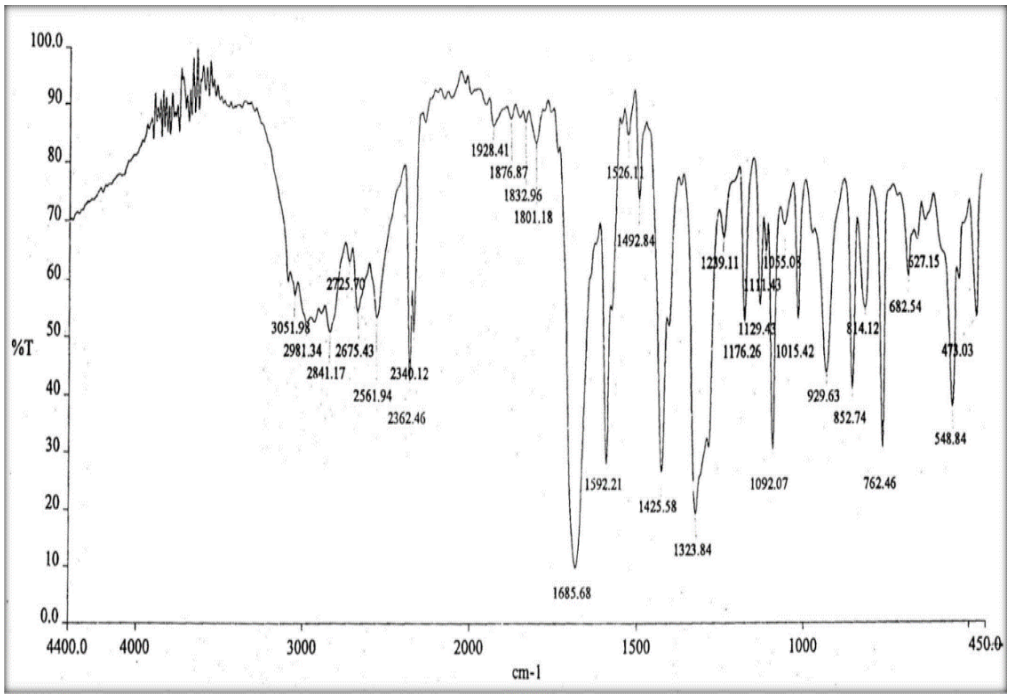
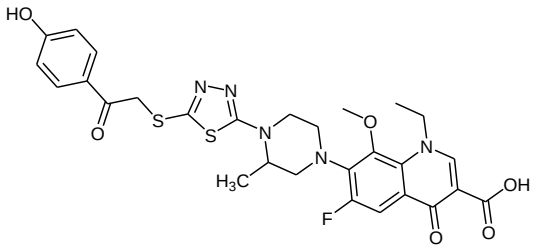
6. IR Spectra of Compound 5(f)



Infrared Spectrum Features (cm^{-1})

3540-3120(-OH), 1465-1340 ($-CH_3$), 1205 (C-N), 2950-2800 (C-H)



5(f),7-[4-{5-(2-Oxo-2-p-hydroxyphenylethylthio)-1,3,4-thiadiazol-2yl-}3methylpiperazin-1yl]-1-ethyl-6-fluoro-8-methoxyl-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid

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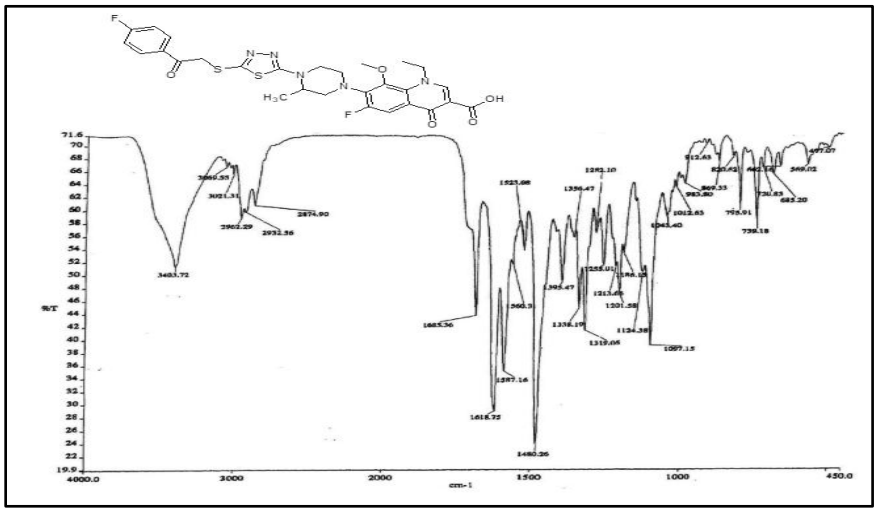
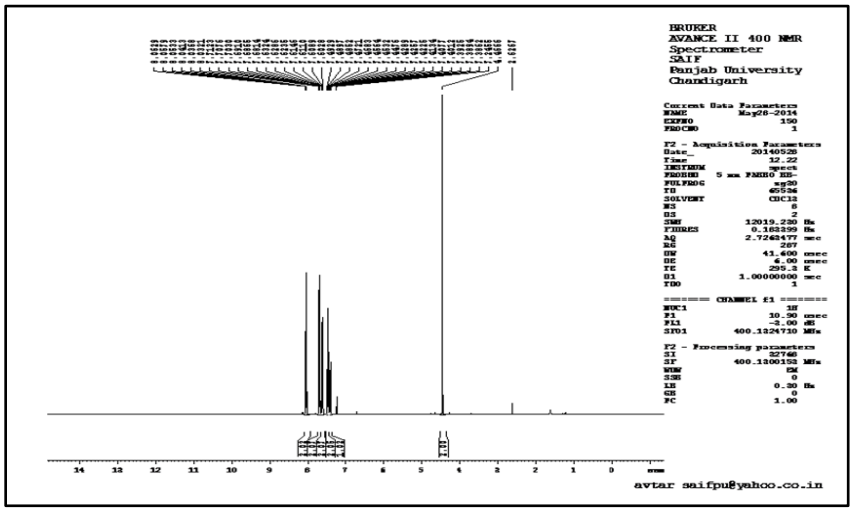
6. IR Spectra of Compound 5(g)



NMR Spectra of Compound 5(g)



NMR Spectral Feature:NMR(DMSO-dd6) $\delta\delta$ppm: 14.62 (s, 1H, OH), 8.12 (m, 2H,Ar.), 7.84 (s, 1H, H2-quinoline), 7.37 (m, 2H, Ar.), 6.50 (d,1H, H5-quinoline), 4.21 (s, 2H, CH2), 3.84 (s, 3H, methoxyl)3.10–3.30 (m, 7H, piperazinyl), 3.00 (q, 2H, NCH2CH3),2.85 (s, 3H, Ar. methyl), 1.30 (m, 3H, 3′-methylpiperazine),1.16 (t, 3H, NCH2CH3).

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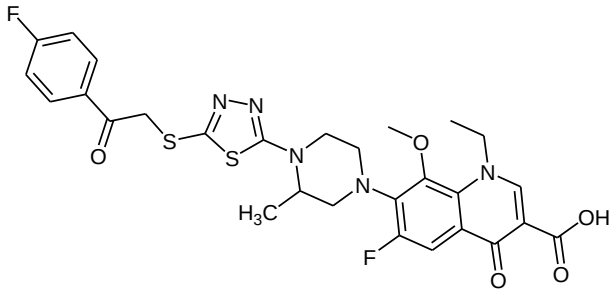
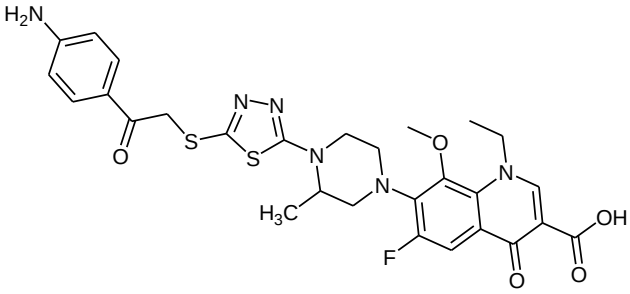
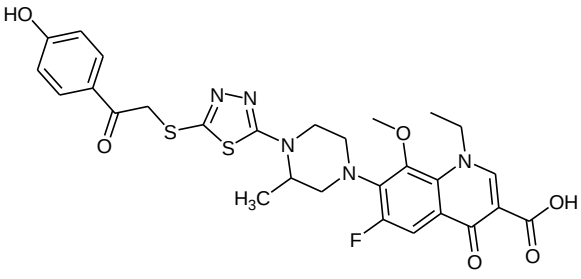


5(g) 7-[4-{5-(2-Oxo-2-p-fluorophenylethylthio)-1,3,4-thiadiazol-2yl-}3′ methylpiperazin-1yl]-1-ethyl-6-fluoro-8-methoxyl-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid



5(h) 7-[4-{5-(2-Oxo-2-p-aminophenylethylthio)-1,3,4-thiadiazol-2yl-}3′ methylpiperazin-1yl]-1-ethyl-6-fluoro-8-methoxyl-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid



5(i) 7-[4-{5-(2-Oxo-2-p-hydroxyphenylethylthio)-1,3,4-thiadiazol-2yl-}3′ methylpiperazin-1yl]-1-ethyl-6-fluoro-8-methoxyl-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid

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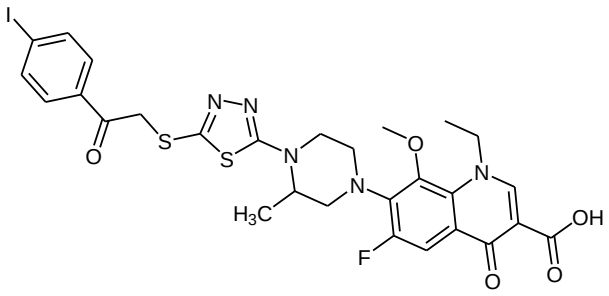

5(j) 7-[4-{5-(2-Oxo-2-p-iodophenylethylthio)-1,3,4-thiadiazol-2yl-}3′ methylpiperazin-1yl]-1-ethyl-6-fluoro-8-methoxyl-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid

6. PHYSICOCHEMICAL STUDIES

6.1 Melting point determination
6.2 Thin layer chromatography
6.3 Rotational and Vibrational absorption (IR)

6.1 Melting point determination:

Melting points of the synthesized compounds were determined in open capillary tubes using thiel's tube and liquid paraffin. All the melting point were measured in range. The temperature at which the compound starts to melt was taken as initial temperature while the temperature at which the whole compound melts taken as final temperature. The melting points were recorded in degree centigrade (^{0}C) and were reported in the section of experimental work and results, after the synthetic procedures of the individual derivatives.

6.2 Thin layer chromatography (TLC): The purity and homogeneity of the synthesized compounds was routinely ascertained by thin layer chromatography using glass plates. Silica gel G (silica gel) was used as an absorbent. TLC plates were prepared by spreading solution of silica with binder gypsum gel G on the glass plate and the plates were activated at 1100C in hot air oven. The solution of compound were prepared in methanol. The solvent system used for the compounds was Acetone : Alcohol (50:50v/v) . Spots were visualized by using iodine vapor chamber and occasionally by UV irradiation at 254nm.

Preparation of chromatoplate

For initial stage we were take cleaned and dried glass plate. Uniform slurry of silica gel G in water was prepared in the ratio 1:1. The slurry was then poured into the chamber of TLC applicator, which was fixed and the thickness was set to 0.5 mm glass plates were moved under the applicator smoothly to get a uniform coating of slurry on plate. The plates were dried first at room temperature and then kept for activation at 100^{0}C for 1 hour.

Preparation of solvent system and saturation of chamber

The solvent system used for the development of chromatogram was prepared carefully

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Acetone:Alcohol (50:50 v/v %)

Application of sample

The solution of the present compounds and its derivatives were taken in small bored capillary tube and spotted at 2 cm from the base end of the plate. After spotting the plate were allowed to dry at temperature and plates were transferred to chromatographic chamber containing solvent system for development.

Development of Chromatogram

Plates were developed by ascending technique when solvent front had reached a distance of 10-12 cm., they were taken out and dried at roomtemperatures.

Detection of spots

The developed spots were detected by exposing them to iodide vapours.

Calculation of Rf values

The Rf value is calculating by using for formula:

Rf value = Distance travelled by sample / Distance travelled by solvent front

In all the cases the distance travelled by the sample was found to be different from that of the parent compound spotted along with it. Thus, confirming the fact that the compounds formed were entirely different from that of the parent compound. Moreover since the entire sample spot, the compounds were taken to be free from impurities.

6.3 Rotational and vibrational absorption spectra (IR):

In order to identify the various functional groups present in the synthesized molecules IR spectroscopy was carried out. The infrared absorption spectra of the synthesized compound were recorded using ATR disc on 2017 Shimadzu model. The IR absorption stretching and binding shown by different function group were expressed in wave number/cm (v max cm^{-1}). The assignment of IR spectra of the compound are given after the synthetic procedure of the individual derivatives. The IR spectra are shown in the section of sexperimental work and results.

7. PHARMACOLOGICAL SCREENING

***In-vitro* antibacterial activity of title compound IV(a-j)**

All the compounds were evaluated for their *In-vitro* antimicrobial activity against two gram positive and two gram negative bacterial pathogen. Ciprofloxacin, gatifloxacin and streptomycin is potent antibacterial drugs were used as a standards. The gram positive organisms as *Staphylococcus aureus* (NCIM 2079), *Bacillus subtilis* (NCIM 2250) and gram negative organism as *Escherichia coli* (NCIM 2109), *Pseudomonas aeruginosa* (NCIM 2036) were used for the screening of *In-vitro* antibacterial activity. Antimicrobial evaluation was access from microbiology dept. of Maharaja Ranjeet Singh College, Indore, Madhya Pradesh, India. Microbiological media was used for above mentioned bacteria was nutrient agar (Hi-media).

Antibacterial activity

All the test compounds were evaluated for antibacterial activity against *S. aureus*, *B. subtilis* (gram-positive), *E. coli* & *P. aeruginosa* (gram-negative).

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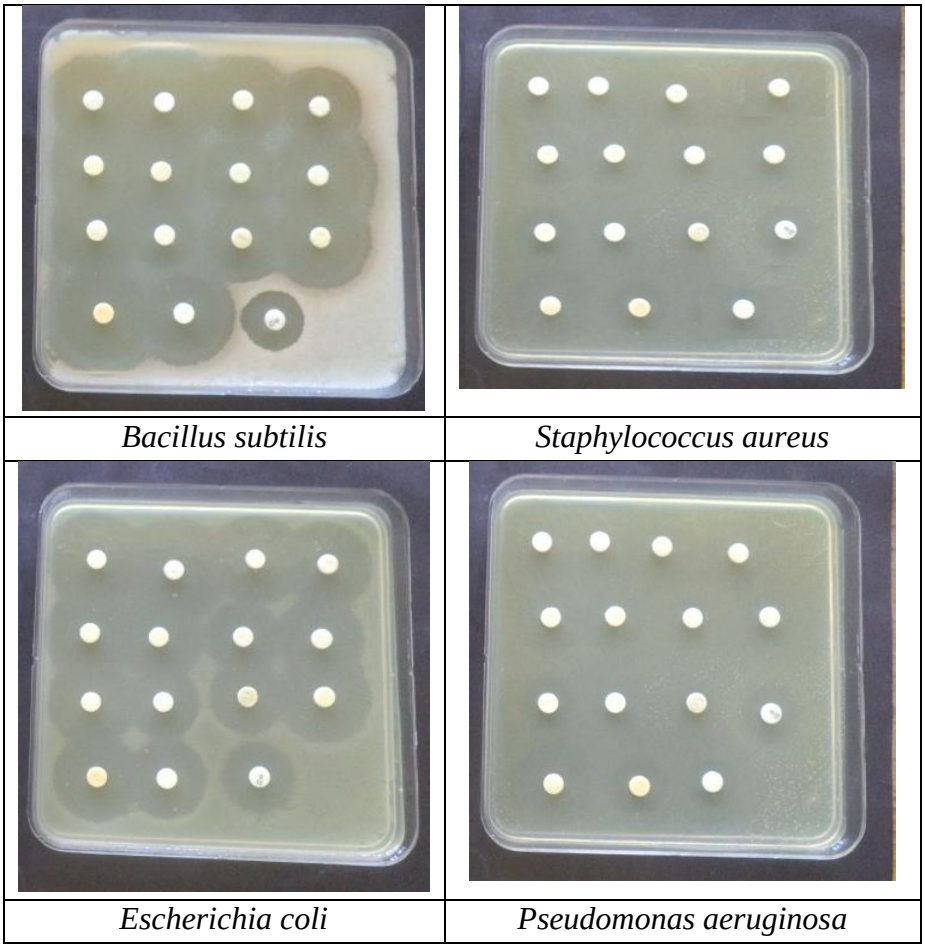
Generally, the antibacterial activity of a compound is expressed in terms of its ability to inhibit the growth of bacteria in nutrient broth. The bacterial inhibition can be measured by disk diffusion method. The disk diffusion method is very much useful for the determination of the antibacterial activity.

Culture MediumNutrient broth was used for the preparation of inoculums of the bacteria & nutrient agar was used for the screening method.

Solution of the test compounds were prepared by dissolving 10 mg each in Dimethylsulfoxide (10 ml; Annular grade). A reference standard for gram-positive & gram-negative bacteria, Ciprofloxacine, Gatifloxacinand Streptomycin (10 microgram/disk) moistened with DMSO.



Bacillus subtilis	*Staphylococcus aureus*
Escherichia coli	*Pseudomonas aeruginosa*

Figure 1: Zone of Inhibition

Table 2 and figure 1 represents a zone of inhibition

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Table 2: Zone of Inhibition (mm)

Zone of inhibition (mm)					
Sr. No.	**Compound**	***B. subtilis***	***S.aureus***	***E. coli***	***P. aeroginosa***
1	**IV(a)**	25.80	20.38	27.56	17.52
2	**IV(b)**	21.68	19.65	24.97	13.66
3	**IV(c)**	24.06	19.56	27.19	14.40
4	**IV(d)**	23.42	20.21	29.16	19.19
5	**IV(e)**	26.88	18.65	26.77	16.35
6	**IV(f)**	25.97	23.87	26.34	14.76
7	**IV(g)**	25.97	23.87	26.34	14.76
8	**IV(h)**	25.97	23.87	26.34	14.76
9	**IV(i)**	25.97	23.87	26.34	14.76
10	**IV(j)**	25.97	23.87	26.34	14.76
11	**Ciprofloxacin**	25.46	28.17	32.56	26.63
12	**Gatifloxacin**	34.72	27.22	35.12	30.64
13	**Streptomycin**	19.17	18.63	18.51	18.45

DISCUSSION

The general procedure for the preparation of compound I**V(a-j)** described in scheme. The compound **I(a-c)** synthesized from the substituted acetophenones. The reaction of compound **I(a-c)** was based on free radical reaction mechanism followed by side chain halogenations of alkyl benzene with bromide ion in presence of Lewis acid (anh. $AlCl_3$). The IR spectra of compound **I(a-c)** showed, Ar. C-H *str*. in the region of 2937.68 2922.28 cm^{-1}, Ali.C-H *str*. around 2852.81 cm^{-1}, C-Br *str*. near 651.96-648.10 cm^{-1} and C=O *str*. around 1685.84 cm^{-1}

The compound **III(a-c)** was synthesized from the treatment of gatifloxacin with compound **I(a-c)** and DMF. The reaction of compound **III(a-c)** was based on the necleophilic substitution

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mechanism. The IR spectrum of compound **III(a-c)** showed O-H *str*. vibration in the region of 3358-3015 cm^{-1}, Ar. C-H *str*. around 2970.48 cm^{-1}, ketonic C=O *str*.1740-1720 cm^{-1} and C-O *str*. 1068-60-1058.96 cm^{-1}.

The synthesis of substituted phenacyl bromide 2(a-f) was based on free radical reaction mechanism followed by side-chain halogenations of alkyl benzene with bromide ion in presence of Lewis acid (anhydrous AlCl3). The synthesis of 2-amino-5-benzoylmethylenethio 1,3,4-thiadiazole 3(a-f) was carried out by reacting 2(a-f) and 2-amino-5-mercapto-1,3,4-thiadiazole via dehydrobromination mechanisms. Compounds 3(a-f) were directly converted to 2-chloro-5-benzoylmethylenethio-1,3,4-thiadiazole 4(a-f) by diazotization of amines followed by chlorination. □e synthesis of 7-[4-{5-(2-oxo-2-p-substituted-phenylethylthio)-1,3,4-thiadiazol-2yl}-3-methylpiperazin-1yl]-1-ethyl-6-fluoro-8-methoxyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 4(a-f) was based on aromatic nucleophilic substitution mechanism with FQ.

Structure Activity Relationship for 4(a-f)

- Introduction of 1,3,4-thiadiazole carrying benzoylmethylenethio moiety at N-4 position on the piperazine ring was well tolerated in terms of antibacterial and antimycobacterial activity, as exemplied by gatioxacin and moxioxacin analogues. Compound 5a that is, unsubstituted analogue at R position did not produce enhanced activity.
- Halogenated analogues such as chloro, bromo and also the nitro substitution at 2-Oxo-2-p-phenylthylthio-1,3,4-thiadiazole linked to N-4-3 methyl piperazinyl quinolone, 4b, 4c, and 4d, respectively, resulted in comparable activity with MIC = 1.0–2.5 $\mu\mu$g/mL (gram positive and antitubercular). However, the fluoro analogue 5g showed moderate activity might be due to highly unstable behavior of fluorine atom.
- Presence of amino and hydroxyl substituent, such as 5h and 5i, showed moderate activity, while compounds having methyl and methoxyl substituent such as 5e and 5f showed weak activity.

Compounds 4(a-j) were synthesized by conventional synthetic route and these analogues were confirmed with various spectral techniques. Titled derivatives were screened for antibacterial and antimycobacterial activity which possess similar activity for 4b, 4c, and 4d compared to reference. But less activity than moxifloxacin, whereas other derivtives of the series showed moderate to weak activity. Results indicate that further exploration in this yield may lead to new synthetic derivatives and scope of other pharmacological and biological studies of the existing compounds.

CONCLUSION

The findings suggest that the fluoroquinolone-thiadiazole hybrid scaffold holds promise as an effective antimicrobial agent against multidrug-resistant infections, providing a novel direction for the development of future antibacterial agents.

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LIST OF ABBREVIATIONS

Not applicable

DECLARATION

We confirm that the study titled "Design Synthesis and Antimicrobial Evaluation of Fluoroquinolone Thiadiazole Hybrids: Agents Against Antimicrobial Infection" adheres to ethical guidelines, with no requirement for ethical approval or participant consent as it involves no human or animal subjects. Consent for publication is granted. All data supporting this work are available upon request. The authors declare no competing interests.

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Author contributions

All authors contributed to the research, analysis, and manuscript preparation, and have reviewed and approved the final version for publication.

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Availability of data and materials

Data will be made available on reasonable request.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
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Author details

1, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Oriental University, Indore

2, Department of Pharmaceutical Chemistry, Professor of Medicinal Chemistry, Faculty of Pharmacy, Oriental University, Indore

REFERENCES

1. V. Kumar, A.K. Abbas, N. Fausto, R. N. "Robinns basic pathology" *Saunders Elsevier*, 2007, 516.
2. K. Sravani., "Tuberculosis- A review of clinical features, differential diagnosis and treatments available" *International Journal of Pharmacy and Technology,* 2010, 2,206-207.
3. P. C. Sharma, M. Chaudhary, R. Pahwa, A. Sharma, M. Dhamija "Impact of stereochemical features on biological potential of fluoroquinolones" International Journal of Pharmaceutical Innovations" 2011, 1, 1-2.
4. M. I. Andersson, A. P. Mc Gowan, "Development of the quinolines" Journal of Antimicrobial Chemotherapy, 2003, 51, 1–2.
5. M. Negar, A. Zahra , E. Alipour, S. Emami, "Synthesis and antibacterial activity of novel levofloxacin derivatives containing a substituted thienylethyl moiety" Journal of Pharmaceutical Sciences, 2012, 20, 2-6.
6. Y. L. Chen, K. C. Fang, J. Y. Sheu, C. C. Tzeng, "Synthesis and antibacterial evaluation of certain quinolone derivatives" Journal of Medicinal Chemistry, 2001, 44, 2374-2377.
7. L. Saikia, J. M. Baruah, A. J. Thakur, "A rapid, convenient, solventless green approach for the synthesis of oximes using grindstone chemistry" Organic and Medicinal Chemistry Letters, 2011, 41, 1-2.
8. Z. Yue-Ling , C. Yeh-Long , S. Jia-Yuh , W. Tai-Chi , T. Cherng-Chyi , "Synthesis and antimycobacterial evaluation of certain fluoroquinolone derivatives" Bioorganic & Medicinal Chemistry, 2005, 13, 3921-3926.
9. S. Rajabalian, A. Foroumadi, A. Shafiee, S. Emami, "Functionalized N-(2-oxyiminoethyl) piperazinyl quinolones as new cytotoxic agents" Jouranal of Pharmacy and Pharmaceutical Sciences, 2007, 10,153-158.
10. A. Foroumadi, L. Firoozpour, S. Emami, "Synthesis and antibacterial activity of N-[5-(chlorobenzythio)-1,3,4-thiadiazole-2-yl] piperazinyl quinolone derivatives" Archives of Pharmacal Research, 2007, 43, 138-145.

 https://doi.org/10.5281/zenodo.14575679