Original Article

Synthesis, Characterization and Pharmacological Evaluation of Biphenyl Based 4-Thiazolidinones

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ABSTRACT

Background: Biphenyl based 4-thiazolidinones are found to possess a wide range of activities resulting in their synthesis. **Methods:** Eight molecules (VIIa-VIIh) were profoundly synthesized using four step procedures. These 4-thiazolidinone derivatives were characterized by elemental analysis (CHN) and spectral (IR and ^{1}H NMR) analysis. All the compounds were evaluated for their *in vitro* antimicrobial activity against one Gram negative strain (*Escherichia coli*) and two Gram positive strains (*Bacillus subtilis* and *Staphylococcus aureus*) and two fungal strains (*Candida albicans* and *Aspergillus niger*). **Results:** The results of antimicrobial studies revealed that compounds (VIIg) possessed moderate antifungal activity and compounds (VIIc and VIIe) showed good antibacterial activity against fungal and bacterial strain respectively. **Conclusion:** Compounds containing electron withdrawing groups (-NO_2, -Cl, -Br) on the aromatic ring showed improved antimicrobial activity.

Key words: Biphenyl based 4-thiazolidinone, Antimicrobial, Antibacterial, Antifungal, Schiff's bases.

INTRODUCTION

Until the seventies of the 20th century, microbial infections were rather easily cured and the need for new antimicrobial drugs was low. Choice of antimicrobial was preparations, toxicity and limited spectrum of action and the risk of resistant strains proved the need of new effective medicines for systemic microbial diseases. The incidences of microbial infections have increased over the last two decades leading to superficial illness to life threatening diseases.[1]

If atleast one atom other than carbon forming the part of a ring system is replaced by other atom, then it is designated as a heterocyclic compound. Of the various divisions of organic chemistry which are assumed to have immense biological and industrial importance, heterocyclic chemistry has a major share. There are many heterocycles of natural origin *e.g.* reserpine, theophylline, *etc.*[2] Even biological processes which are essentially chemical reactions, utilize various heterocycles such as vitamins, 90-cnzymes, ATP, serotonin, *etc.* for their completion. Also, these exhibit a striking structural feature which is inherent to all heterocycles *viz.* ability to manifest substituents around the core scaffold in a defined manner.[3] Hence, heterocycles are of great interest in organic synthesis. Heterocyclic compounds containing nitrogen, sulphur and oxygen, have been explored widely for application in drug industry.[4]

The need of new compounds is satisfied by searching leads through different sources hike natural, marine, synthetic route, *etc.* Amongst the synthetic routes, heterocyclic compounds represents one of the most active classes of compounds possessing a wide spectrum of biological activities,[5] including antibacterial,[6,7] antimicrobial,[8] anti-HIV,[9] *etc.* However, nitrogen and sulphur containing compounds like biphenyl

Submission Date: 10-06-2020;
Revision Date: 18-09-2020;
Accepted Date: 13-03-2021

DOI: 10.5530/ijper.55.2.74

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based 4-thiazolidinones[10] are well famed for their broad spectrum of biological activities.4-thiazolidinone is a derivative of thiazolidine with a carbonyl group at 4th position heterocyclic compounds. The methylene carbon an important group of atom at fifth position possesses nucleophilic activity and attacks on electrophilic centre. The reaction loses water by forming 5 membered unsaturated derivatives 4-thiazolidinone. The Instrument facility reaction occurs in presence of a base and the anion of the 4-thiazolidinone is the attacking species.[11] The ease of formation of the anion and hence the degree of the nucleophilic activity is dependent not only on the electron withdrawing effect of the adjacent carbonyl group, but also on the presence of other electron withdrawing groups such as those attached to the second carbon atom.[12]

MATERIALS AND METHODS

Materials

All the chemicals like thioglycollic acid, hydrazine hydrate, thionyl chloride and solvents were purchased from Loba Chem, Mumbai. 1,1-Biphenyl 4-carboxylic acid was purchased from Sigma Aldrich, Mumbai. The identity of all the compounds was confirmed by taking the melting point and the purity by TLC where a single spot was observed. Solvents were used after distillation throughout the course of the work. Melting points of all the intermediates and the final products were recorded using open capillary tube method on Veego-VMP-D apparatus. Purity of the compounds and reaction progress was monitored by TLC, using silica gel G plates of size 3 x 8 cm (Sigma Aldrich) using suitable solvent system and was visualized under UV radiation. The FTIR spectra were recorded in the 4000-400 cm^{-1} range using Shimadzu FTIR Infinity Spectrometer. ^{1}H-NMR spectra were recorded on Varian Mercury (600 mHz) and Bruker Avance II (400 mHz) using DMSO-d_6 and $CDCl_3$, as solvents and TMS was internal standard. ^{1}H NMR and Mass spectra studies was outsourced from Sophisticated Analytical Instrument facility (SAIF), Punjab. Purification of intermediate and final products was performed by techniques such as re-crystallization or column chromatography using appropriate solvents and solvent systems as per requirements.

Methods for synthesis of title compounds (VIIa-VIIh)

Step 1: General procedure for synthesis of 1,1-Biphenyl 4-carbonyl chloride (II)

1,1-Biphenyl 4-carboxylic acid (I) (1.98 g, 0.01 mol) was taken in a 250 ml round bottom flask. Thionyl chloride (1.45 mL, 0.02 mol) was added drop wise within a period of 1 h. The mixture then refluxed with continuous stirring for 3 to 4 h. The progress of the reaction was monitored by TLC at regular intervals using ethyl acetate and hexane (1:1) as a solvent system. Single spot indicated the completion of step 1 reaction and formation of a brown coloured 1,1-Biphenyl-4-carbonyl chloride (II). The crude product was then recrystallized with ethanol.

Step 2: Synthesis of 1,1-Biphenyl 4-carboxylic acid hydrazide (III)

1,1-Biphenyl-4-carbonyl chloride (II) (1.75 g, 0.008 mol) was treated with hydrazine hydrate (3 mL, 0.024 mol). The mixture was then refluxed for 2-3 h and the progress of reaction was monitored by TLC at regular interval using ethyl acetate and hexane (1:1) as a solvent system. After completion of the reaction, the reaction mixture was cooled to room temperature and was then poured in a beaker containing 50 mL ice cold water and was kept for stirring for 1-2 h. The solid thus obtained was separated, filtered and washed with water to yield 1,1-Biphenyl 4-carboxylic acid hydrazide (III). The crude product was then recrystallized with ethanol.

Step 3: Synthesis of 1,1-Biphenyl 4-carboxylic acid hydrazone (Schiff's Bases) (Va-Vh)

A mixture of 1,1-Biphenyl 4-carboxylic acid hydrazide (III) (0.55 g, 0.002 mol) and the corresponding aromatic aldehyde (IV) (0.003 mol) was dissolve in 10 mL ethanol. Glacial acetic acid was added to the reaction mixture in catalytic amount and it was refluxed for 5-7 h. The reaction was monitored to completion by TLC using ethyl acetate and hexane (1:1) as solvent system. The compounds (Va-Vh) were obtained by pouring the reaction mixture into a beaker containing ice cold water. The solid, thus obtained was separated by filtration and dried at room temperature. The crude product was then recrystallized using ethanol.

Step 4: Synthesis of 4-Thiazolidinone derivatives (VIIa-VIIh)

1,1-Biphenyl 4-carboxylic acid hydrazide hydrazine (Schiff's bases) (Va-Vh) (0.001 mol) was dissolved in ethanol. Thioglycolic acid (VI) (0.11 mL, 0.009 mol) and zinc chloride was added to the reaction mixture in catalytic amount and refluxed for 6-7 h. The reaction was monitored to completion by TLC using ethyl acetate and hexane (1:1) as solvent system. The compound (VIIa-VIIh) were obtained by pouring the reaction mixture into a beaker containing ice cold water. The solid, compound obtained was separated by filtration

and dried at room temperature. The crude product was then recrystallized with ethanol.

By adopting similar type of procedures and employing equimolar quantities of reactants, eight compounds were synthesized. Synthetic pathway for preparation of title compounds is Scheme 1.

Spectral analysis of title compounds (VIIa-VIIh).

The structures of the synthesized compounds (VIIa-VIIh) were confirmed by elemental analysis and IR spectra (KBr pellet technique). ^{1}H NMR (DMSO-d_6 and $CDCl_3$ as solvents and TMS was internal standard), Mass spectral analysis and elemental analysis (carbon, hydrogen, nitrogen) was carried out for representative compounds.

Antimicrobial evaluation of title compounds (VIIa-VIIh)

The synthesized compounds **(VIIa-VIIh)** were evaluated for their antimicrobial method by disc diffusion method.[13,14] The antibacterial activity was screened against *Staphylococcus aureus*, *Escherichia coli* and *Bacillus subtilis* and antifungal activity against *Aspergillus niger* and *Candida albicans* by using Ciprofloxacin and Fluconazole as standard drugs respectively.

Media Used – Brain Heart Infusion agar media was used for antibacterial activity. In the anti-fungal disc diffusion method, the Sabouraud agar medium was used.

Temperature – Brought agar plates to room temperature before used.

Inoculum preparation – A loop or swab was used to transfer the colonies to the plates. The turbidity was adjusted visually with the broth equal to that of a 0.5 McFarland turbidity standard that has been vortexed. Alternatively, it the suspension was standardized with a photometric device.

Inoculation of Agar plate – Within 15 min of inoculum adjustment to McFarland 0.5 turbidity standard, sterile cotton swab was dipped into the inoculum and rotated against the wall of the tube above the liquid to remove excess inoculum. The entire surface of agar plate was swabbed three times and the plates were rotated to approximately 60° between streaking to ensure even distribution, avoiding hitting the sides of the Petri plate and aerosols were created. The inoculated plates were allowed to stand for at least 3 min but no longer than 15 min before made wells.

Stock solution preparation – The stock solution was prepared by dissolving 10 mg of compound in 1 mL of DMSO.

Addition of compound into plate – A hollow tube of 5 mm diameter was heated and was pressed above inoculated Agar plate to remove it immediately by making a well in the plate. Likewise, five wells were made on each plate. With the help of micropipette 75 µl, 50 µl, 25 µl, 10 µl and 5 µl sample was added in each well.

Incubation – The plates were incubated within 15 min of compound application. The plates were inverted and were incubated for 18-24 h at 37°C in an incubator.

Reading plates – The plates were read only if the lawn of growth was confluent or nearly confluent. The diameter of inhibition zone was measured to the nearest whole millimeter by holding the measuring device.

RESULTS AND DISCUSSION

Synthesis of title compounds (VIIa-VIIh)

Physical data of the intermediates and the title compounds are given in Table 1.

Spectral analysis of intermediates (II, III, Va-Vh) and the title compounds (VIIa-VIIh)

The intermediates and the title compounds were characterised by IR (KBr, cm^{-1}) which showed the presence of prominent peaks in all the molecules. The data is represented in Figures 1-3.

(II): 3126.74, 2938.68 (Ar C-H stretch), 1684.89 (C=O stretch), 790.85 (C-Cl stretch)

(III): 3309.99 (N-H stretch), 2946.39 (Ar C-H stretch), 1708.04 (C=O stretch), 1604.84 (N-H bend)

(Va): 3024.38 (N-H stretch), 2912.51 (Ar C-H stretch), 1645.28 (C=O stretch), 1600.92 (N-H bend), 1548.84 (C=N stretch), 844.82 (Ar C-H bend)

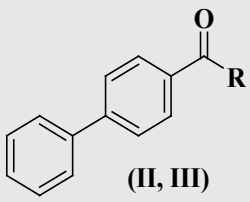
(Vb): 3058.27 (N-H stretch), 2860.56 (Ar C-H stretch), 1682.96 (C=O stretch), 1607.74 (N-H bend), 1529.62 (C=N stretch), 1482.36 (N-CH_3 stretch), 1004.96 (C-N stretch), 844.86 (Ar C-H bend)

(Vc): 3255.98 (N-H stretch), 2828.73 (Ar C-H stretch), 1682.00 (C=O stretch), 1646.32 (N-H bend), 1524.79 (C=N stretch), 844.86 (Ar C-H bend), 794.71 (C-Cl stretch)

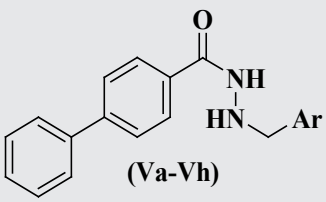
(Vd): 3396.64 (-OH stretch), 3196.05 (N-H stretch), 2887.44 (Ar C-H stretch), 1681.93 (C=O stretch), 1600.92 (N-H bend), 1546.91 (C=N stretch), 1263.37 (OH bend), 837.11 (Ar C-H bend)

(Ve): 3228.84 (N-H stretch), 3030.17 (Ar C-H stretch), 1647.21 (C=O stretch), 1608.63 (N-H bend), 1544.96 (C=N stretch), 850.61 (Ar C-H bend), 744.52 (C-Br stretch)

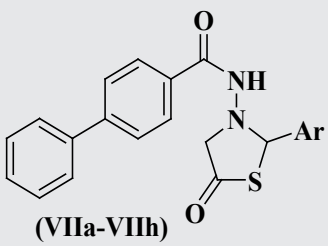
Table 1: Physical data of intermediates (II, III, Va-Vh) and title compounds (VIIa-VIIh).



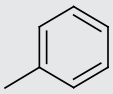
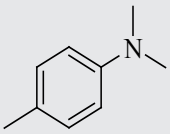
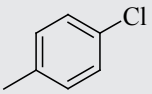
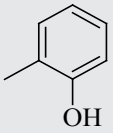
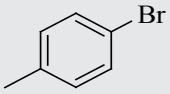
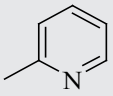
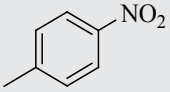
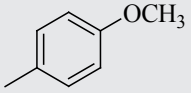
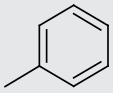
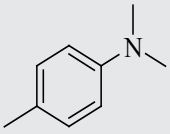
(II, III)

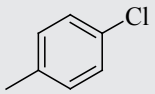
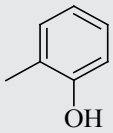
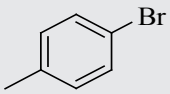
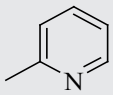
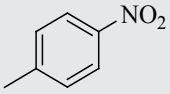
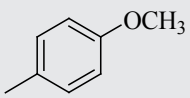


(Va-Vh)



(VIIa-VIIh)

Comp. No.	– R / – Ar	Molecular formula	Molecular weight	Yield (%)	Melting point (°C)	Rf (TLC)	Log P
II	-Cl	$C_{13}H_9ClO$	216.66	70.83	112-114	0.62	3.45
III	-NH-NH_2	$C_{13}H_{12}N_2O$	212.25	78.83	180-182	0.69	2.15
Va		$C_{20}H_{18}N_2O$	302.37	70.02	200-202	0.60	3.83
Vb		$C_{22}H_{23}N_3O$	345.44	74.08	198-200	0.62	3.99
Vc		$C_{20}H_{17}ClN_2O$	336.81	64.00	220-222	0.68	4.54
Vd		$C_{20}H_{18}N_2O_2$	318.37	69.02	210-212	0.57	3.11
Ve		$C_{20}H_{17}BrN_2O$	381.27	62.00	280-282	0.70	4.69
Vf		$C_{19}H_{17}N_3O$	303.36	50.04	218-220	0.56	2.33
Vg		$C_{20}H_{17}N_3O_3$	347.37	72.32	210-212	0.62	3.57
Vh		$C_{21}H_{20}N_2O_2$	332.4	66.06	216-218	0.65	3.75
VIIa		$C_{22}H_{18}N_2O_2S$	374.46	65.55	210-212	0.70	4.74
VIIb		$C_{24}H_{23}N_3O_2S$	417.52	52.08	216-218	0.58	4.90

VIIc		$C_{22}H_{17}ClN_2O_2S$	408.9	55.00	230-232	0.76	5.45
VIId		$C_{22}H_{18}N_2O_3S$	390.45	62.87	200-202	0.65	4.03
VIIe		$C_{22}H_{17}BrN_2O_2S$	453.35	56.03	240-242	0.76	5.61
VIIf		$C_{21}H_{17}N_3O_2S$	375.44	56.00	214-216	0.68	3.25
VIIg		$C_{22}H_{17}N_3O_4S$	419.45	67.32	218-220	0.72	4.49
VIIh		$C_{23}H_{20}N_2O_3S$	404.48	56.09	232-234	0.67	4.66

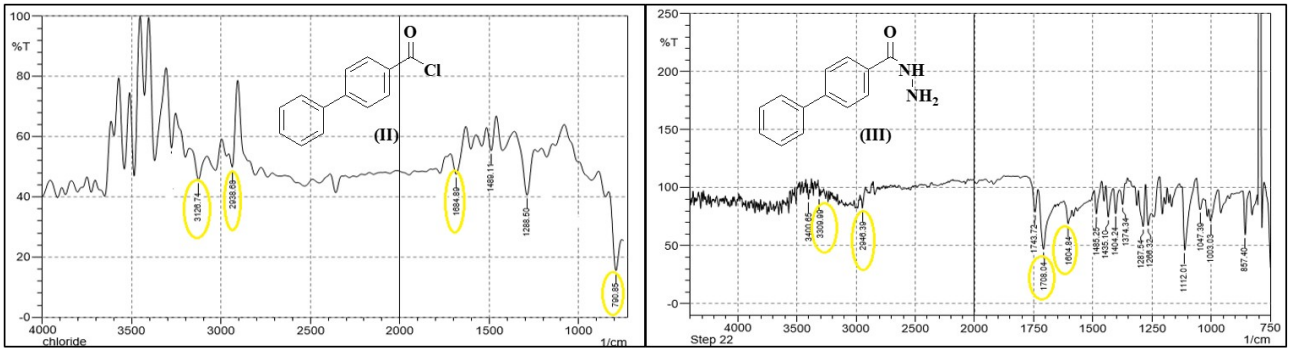


Figure 1: IR (KBr, cm^{-1}) spectrum of 1,1-Biphenyl 4-carbonyl chloride (II) and 1,1-Biphenyl 4-carboxylic acid hydrazide (III).

(Vf): 3203.90 (N-H stretch), 2986.90 (Ar C-H stretch), 1716.72 (C=O stretch), 1631.85 (N-H bend), 1545.05 (Ar C=N stretch), 846.79 (Ar C-H bend)

(Vg): 2945.43 (N-H stretch), 2845.13 (Ar C-H stretch), 1709.00 (C=O stretch), 1603.88 (N-H bend), 1580.73 (Ar –NO2 stretch), 1549.87 (Ar C=N stretch), 856.43 (Ar C-H bend)

(Vh): 2946.39 (N-H stretch), 2845.13 (Ar C-H stretch), 1709.00 (C=O stretch), 1604.84 (N-H bend), 1485.25 (Ar C=N stretch), 1287.29 (C-H bend), 856.43 (Ar C-H bend)

(VIIa): 3233.80 (N-H stretch), 2992.69 (Ar C-H stretch), 1816.06, 1690.68 (C=O stretch), 1601.95 (N-H bend), 1538.30 (Ar C=C stretch), 856.43 (Ar C-H bend), 674.15 (C-S stretch)

(VIIb): 3373.64 (N-H stretch), 2902.03 (Ar C-H stretch), 1705.15, 1652.10 (C=O stretch), 1591.34 (N-H bend), 1422.56 (N-CH3 stretch), 1098.51 (C-N stretch), 824.60 (Ar C-H bend), 738.77 (C-S stretch)

(VIIc): 3006.19 (N-H Stretch), 2884.67 (Ar C-H stretch), 1732.15, 1669.46 (C=O stretch), 1614.49 (N-H bend), 1527.69 (Ar C=C stretch), 829.43 (Ar C-H bend), 758.06 (C-Cl stretch), 688.62 (C-S stretch)

(VIId): 3491.31 (OH stretch), 3298.42 (N-H stretch), 3090.10 (Ar C-H stretch), 1811.24, 1682.96 (C=O stretch), 1600.99 (N-H bend), 1445.71 (Ar C=C stretch), 1295.28 (OH bend), 851.81 (Ar C-H, bend), 681.87 (C-S stretch)

(VIIe): 3153.75 (N-H stretch), 2886.60 (Ar C-H stretch), 1811.24, 1742.76 (C=O stretch), 1676.21 (N-H bend), 665.47 (C-S stretch), 526.59 (C-Br stretch)

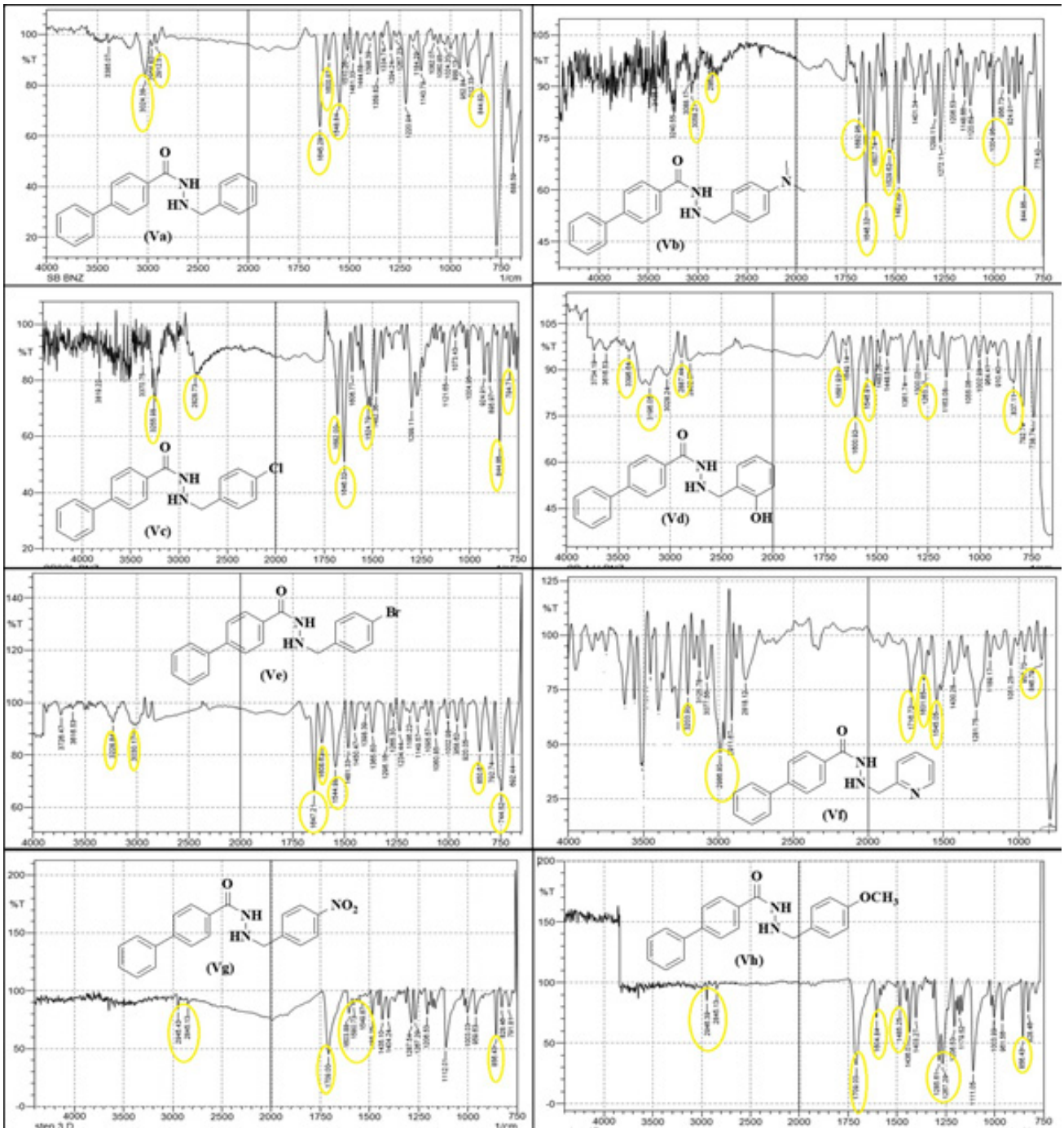


Figure 2: IR (KBr, cm^{-1}) spectrum of 1,1-Biphenyl 4-carboxylic acid hydrazone (Schiff's Bases) (Va - Vh).

(VIIf): 3219.33 (N-H stretch), 2985.94 (Ar C-H stretch), 1727.33 (C=O stretch), 1623.17 (N-H bend), 1533.47 (Ar C=N stretch), 840.04 (Ar C-H bend), 666.43 (C-S stretch)

(VIIg): 3248.27 (N-H Stretch), 3002.33 (Ar C-H stretch), 1731.19, 1668.50 (C=O stretch), 1589.41 (N-H bend), 1521.90 (Ar –NO2 stretch), 830.39 (Ar C-H bend), 678.01 (C-S stretch)

(VIIh): 3251.16 (N-H stretch), 3086.24 (Ar C-H stretch), 1812.20, 1709.97 (C=O stretch), 1548.91 (N-H bend), 1229.67 (C-H bend), 837.14 (Ar C-H bend), 683.79 (C-S stretch)

The results for ^{1}H NMR (DMSO-d_6 and $CDCl_3$ as solvents and TMS was internal standard), Mass spectral analysis and elemental analysis (carbon, hydrogen, nitrogen) for representative compounds are depicted in Figures 4-13.

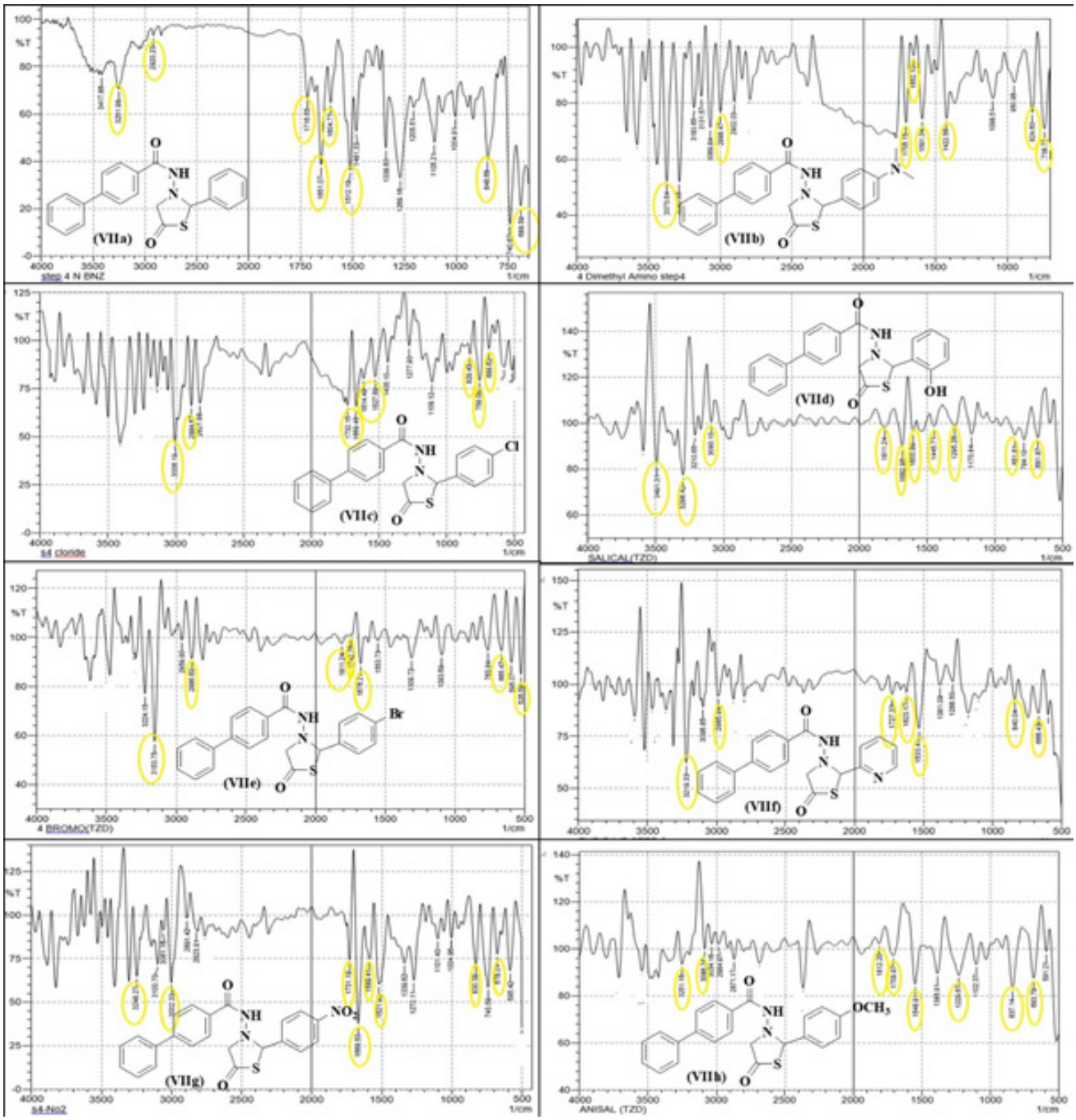


Figure 3: IR (KBr, cm^{-1}) spectrum of 4-Thiazolidinone derivatives (VIIa - VIIh).

Antimicrobial evaluation of title compounds (VIIa-VIIh)

Figures 14 and 15 confirmed that all the tested compounds possess antibacterial and antifungal activity against the tested bacterial and fungal strains. However, the antimicrobial activity of the synthesized compounds against the tested organisms was found to be less than that of the standard antibacterial drug Ciprofloxacin and standard antifungal drug Fluconazole at their tested dose levels.

CONCLUSION

Novel 4-thiazolidinone derivatives were synthesized and subjected to spectroscopic analysis which confirmed the proposed structure of these compounds. IR, ^{1}H NMR, mass and elemental analysis confirmed the molecular structures of these compounds. These compounds were further evaluated for antimicrobial activities, the results of which revealed that some compounds possessed moderate antifungal activity and good antibacterial activity against fungal and bacterial strain respectively. It

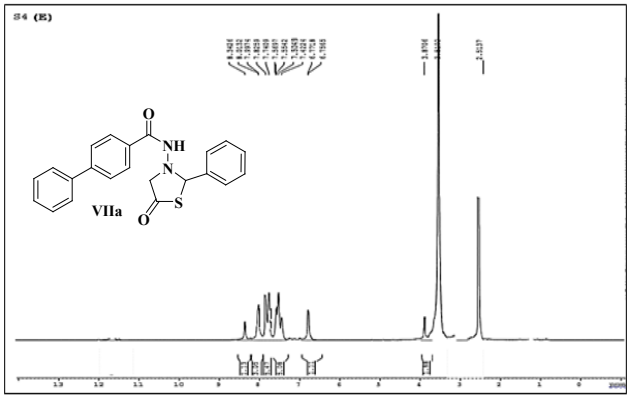


Figure 4: ^{1}H NMR (DMSO-d6, δ, ppm) spectrum of 3-((1,1-Biphenyl 4-ylcarbonyl)-amino)-2-phenyl-1,3-thiazolidin-4-one (VIIa); 8.3 (^{1}H, s, -NH), 8.01-7.4 (14H, m, Ar-H), 6.7 (^{1}H, s, -NCH), 3.8 (^{1}H, s, -SCH2).

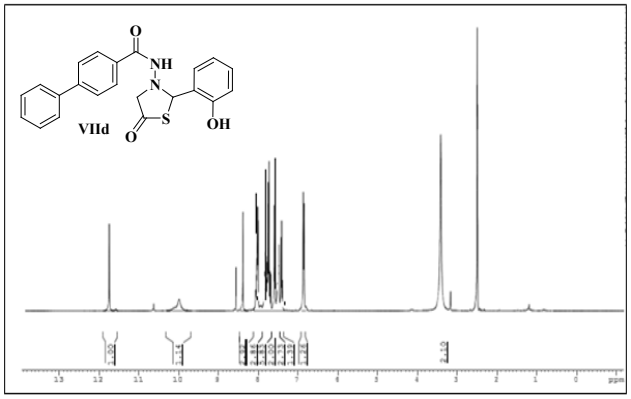


Figure 7: ^{1}H NMR (DMSO-d6, δ, ppm) spectrum of 3-((1,1-Biphenyl-4ylcarbonyl)-amino)-2-(2-hydroxyphenyl)-1,3-thiazolidin-4-one (VIId); 11.7 (s, ^{1}H, -OH), 8.5-7.4 (m, 14H, ArH), 9.9 (s, ^{1}H, -NH), 6.8 (s, ^{1}H, -NH), 6.8 (s, ^{1}H, -NCH), 3.4-3.1 (s, ^{1}H, -SCH2).

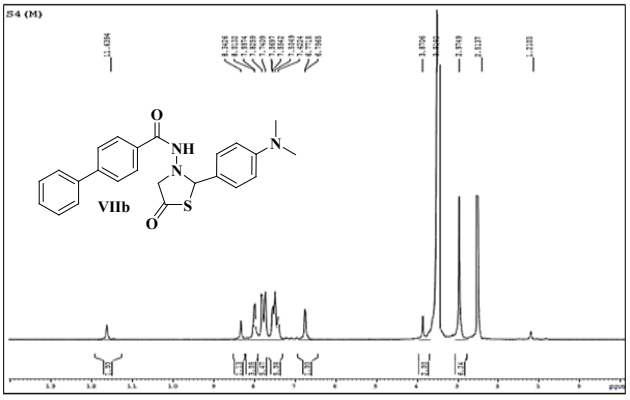


Figure 5: ^{1}H NMR (DMSO-d6, δ, ppm) spectrum of 3-((1,1-Biphenyl 4-ylcarbonyl)-amino)-2-(4-(dimethylamino) phenyl)-1,3-thiazolidin-4-one (VIIb); 11.6 (1H, s, -NH), 8.3-7.4 (14H, m, Ar-H), 6.7 (1H, s, -NCH), 3.8 (1H, s, -SCH2), 2.9 (6H, s, (-CH3)2).

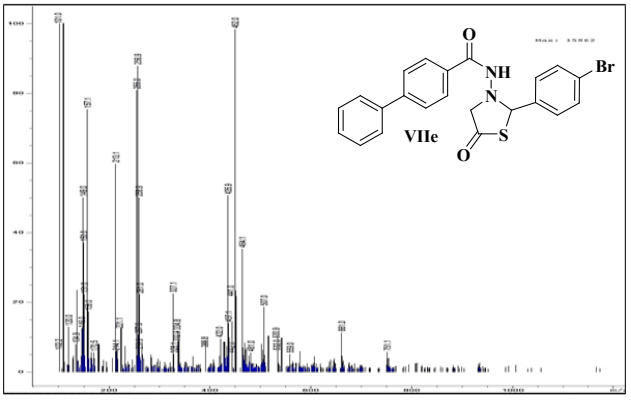


Figure 8: Mass spectrum (*m/z*) of 3-((1,1-Biphenyl-4ylcarbonyl)amino)-2-(4-bromophenyl)-1,3-thiazolidin-4-one (VIIe); 452 (100%), 255 (56.41%), 213 (47.12%), 157 (34.73%).

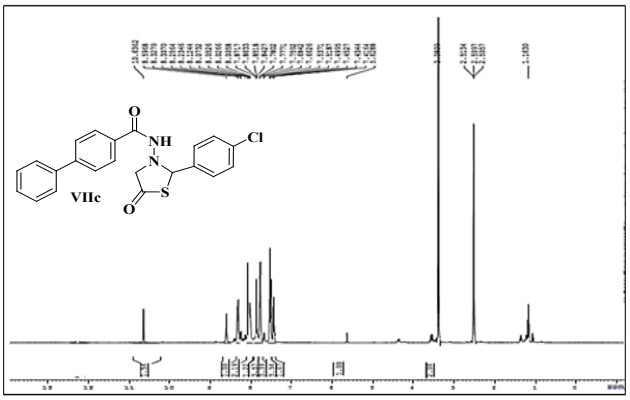


Figure 6: ^{1}H NMR (DMSO-d6, δ, ppm) spectrum of 3-((1,1-Biphenyl 4-ylcarbonyl)-amino)-2-(4-chlorophenyl)-1,3-thiazolidin-4-one (VIIc); 10.6 (^{1}H, s, -NH), 8.5-7.4 (14H, m, ArH), 5.6 (^{1}H, s, -NCH), 3.3 (^{1}H, s, -SCH2).

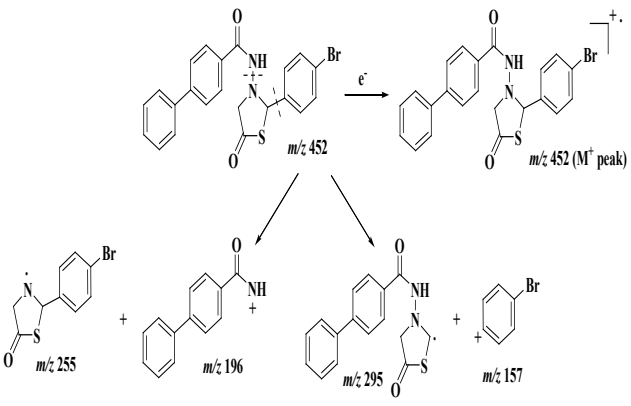


Figure 9: Fragmentation pattern for 3-((1,1-Biphenyl-4ylcarbonyl)amino)-2-(4-bromophenyl)-1,3-thiazolidin-4-one (VIIe).

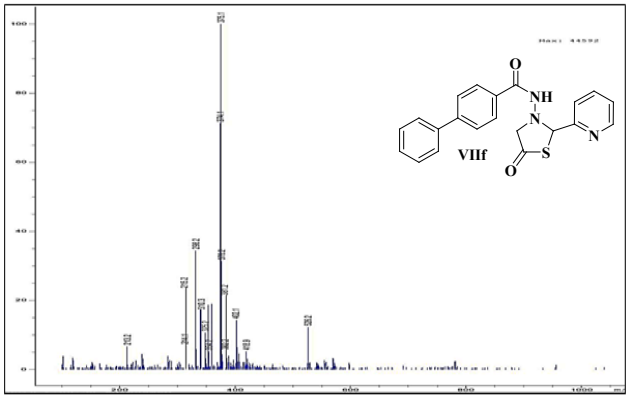


Figure 10: Mass spectrum (*m/z*) of 3-((1,1-Biphenyl-4 ylcarbonyl)amino)-2-(pyridin-2-yl)-1,3-thiazolidin-4-one (VIIf); 375 (100%), 374 (99.73%), 298 (79.46%).

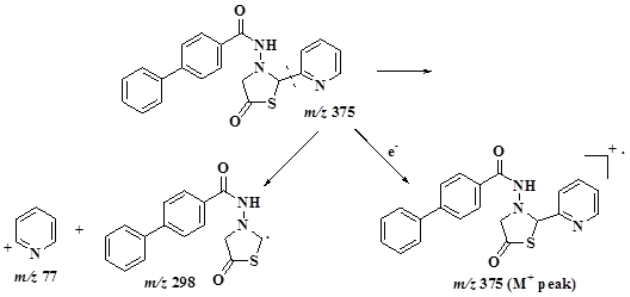


Figure 11: Fragmentation pattern for 3-((1,1-Biphenyl-4 ylcarbonyl)amino)-2-(pyridin-2-yl)-1,3-thiazolidin-4-one (VIIf).

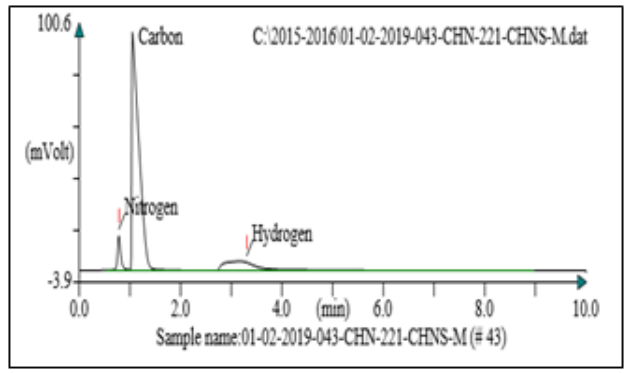


Figure 12: CHN Spectrum of 3-((1,1-Biphenyl-4-ylcarbonyl) amino)-2-(4-nitrophenyl)-1,3-thiazolidin-4-one (VIIg); Calculated Value – N (10.02%), C (63.00%), H (4.0%), Obtained Value – N (10.08%), C (62.60%), H (4.02%).

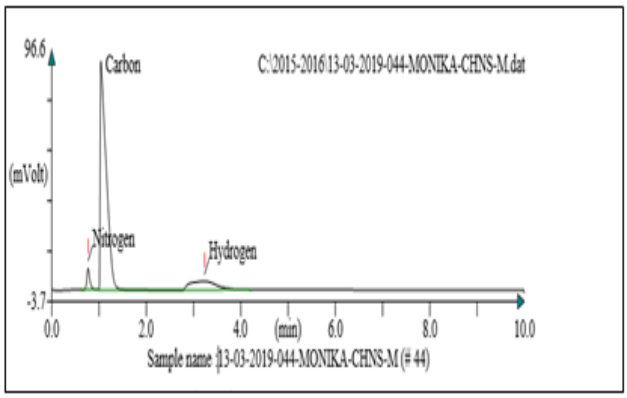


Figure 13: CHN Spectrum of 3-((1,1-Biphenyl-4-ylcarbonyl) amino)-2-(4-methoxy-phenyl)-1,3-thiazolidin-4-one (VIIh); Calculated Value – N (6.93%), C (68.31%), H (4.9%), Obtained Value – N (6.10%), C (68.00%), H (4.06%).

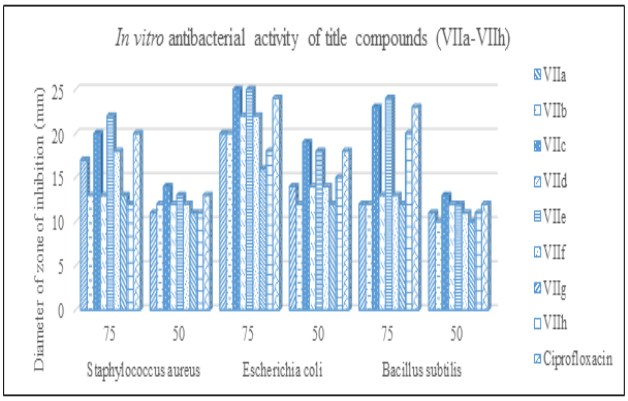


Figure 14: *In vitro* antibacterial activity of title compounds (VIIa-VIIh).

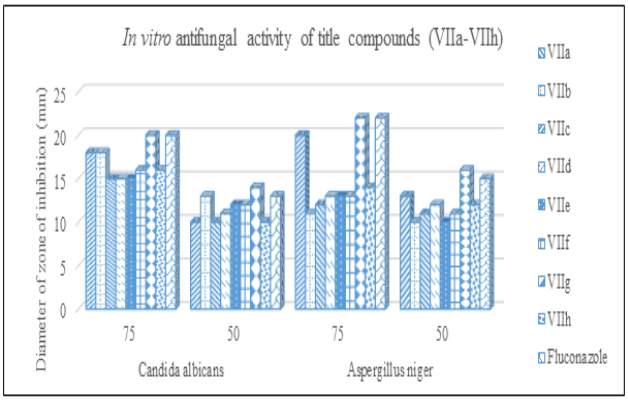


Figure 15: *In vitro* antifungal activity of title compounds (VIIa-VIIh).

was concluded that the compounds containing electron withdrawing groups (-NO_2, -CI, -Br) on the aromatic ring showed improved antimicrobial activity. The results of antimicrobial study indicated that the presence of halogen moiety in VIIc and VIIe on the aromatic ring showed improved antibacterial activity, whereas the presence of nitro group in VIIg on the aromatic ring showed improved antifungal activity of substituted 4-thiazolidinone.

ACKNOWLEDGEMENT

The authors thank the college management who provided all the facilities for carrying out the research work. The authors also acknowledge Sophisticated Analytical Instrument facility (SAIF), Punjab for NMR and Mass spectra studies.

CONFLICT OF INTEREST

Th authors declare no Conflict of Interest.

ABBREVIATIONS

TLC: Thin Layer Chromatography; **UV:** Ultraviolet; **FTIR:** Fourier Transform Infrared; **NMR:** Nuclear Magnetic Resonance; **TMS:** Tetramethylsilane; **KBr:** Potassium bromide; **DMSO:** Dimethyl sulfoxide; **$CDCl_3$:** Deuterated chloroform.

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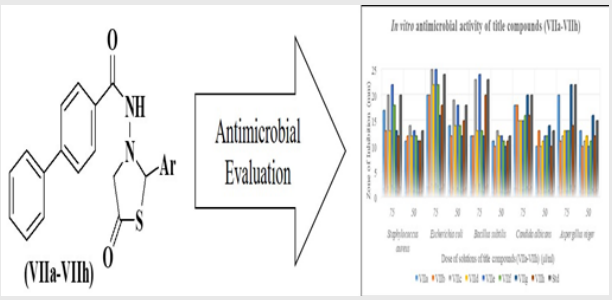
PICTORIAL ABSTRACT



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Cite this article: Shirke M, Gangthade M, Chaskar P, Somani R. Synthesis, Characterization and Pharmacological Evaluation of Biphenyl Based 4-Thiazolidinones. Indian J of Pharmaceutical Education and Research. 2021;55(2):363-73.