

Original Article

Synthesis and Evaluation of Substituted 1, 3, 4-Thiadiazole as Potential Antimicrobial Agent

Anuj Singhai^{a,b,*}, Shankar Kumar^b, Rajeev Saxena^c, Anindya Goswami^c, Hemant Nagar^c

^aDepartment of Pharmaceutical Chemistry, Truba Institute of Pharmacy, Bhopal, Madhya Pradesh, India.

^bDepartment of Pharmaceutical Chemistry, K.L.E.U's College of Pharmacy, Vidyanagar, Hubli, Karnataka, India.

^cTruba Institute of Pharmacy, Bhopal, Madhya Pradesh, India.

*Corresponding Author. Tel.: +91 9424454220, E-mail address: anujsinghai1989@gmail.com

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ABSTRACT

New series of N-(substituted phenyl)-2-[(5-substituted)-1,3,4-thiazol-2-yl]acetamide (IVa-l) were synthesized by condensation of N-(substituted phenyl)-2-(5-sulfanyl-1,3,4-thiadiazol-2-yl) acetamide (IIIa-d) with different 2° amines. The structure of the synthesized compounds were characterized on the basis of physicochemical and spectral analysis (IR, and ¹H-NMR). All these newly synthesized compounds (IVa-l) were screened for their antimicrobial and antifungal activity. The compounds IVc, IVf, IVg, IVj, IVl showed the good antibacterial activity and IVc and IVj showed the moderate antifungal activity.

1. INTRODUCTION

Infectious diseases are remaining a serious threat to public health, rapid resistance development by the microorganisms is recognized from the beginning. The resistance development among major pathogens makes antimicrobials more and more ineffective. The resistance is developed by bacteria due to bacterial enzymes, transfer of genetic material, acquired resistance and poor prescribing and utilization of antimicrobial in practice [1,2].

The incidence of multidrug-resistant pathogenic bacteria is increasing. One additional reason for developing new antibiotics is related to their own toxicity. As with other therapeutic agents, the use of antibiotics may also cause side effects in patients. These include mild reactions such as upset stomach, vomiting, and diarrhoea (cephalosporins, macrolides, penicillins and tetracyclines), rash, other mild and severe allergic reactions (cephalosporins and penicillins), sensitivity to sunlight (tetracyclines), nervousness, tremors and seizures (quinolones). Some side effects are more severe and depending on the antibiotic, may disrupt the hearing function (aminoglycosides), kidneys (aminoglycosides and polypeptides) or liver (rifampin). To counteract the resistance produced by microbes there is a need to invent new drugs, which are more safe and effective [3,4].

A large number of medicines which have been discovered belong to a major class of heterocycles containing nitrogen, oxygen and sulphur. Biological activities of these heterocycles has helped the medicinal chemist to plan, organize and implement newer approaches towards the discovery of new drugs.[5,6]

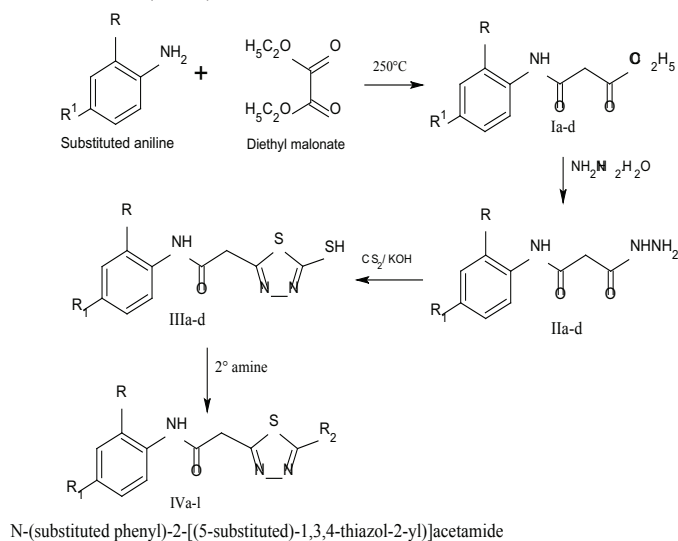
In view of the general observation that pharmacological activity is invariably associated with a large variety of heterocyclic compounds, the investigation of some heterocyclic such as substituted 1,3,4 thiadiazole derivatives has been undertaken. Derivatives of these compounds are reported to possess a wide spectrum of biological activities such as antimicrobial, anti-inflammatory, anticonvulsant, antitumor, antitubercular, Antidiuretics activities. [7-12]

2. MATERIALS AND METHODS

2.1. Chemistry

The synthetic route used to synthesize title compounds is outlined in Scheme 1. Substituted anilines were condensed with diethylmalonate to give ethyl-2-[substituted anilido] ethanoate. This on treating with hydrazine hydrate (99%) resulted in the synthesis of the ethyl-2-[substituted anilido] actohydrazide. When this hydrazide stirring with carbondisulphide and KOH in

the presence of ethanol to give N-(substituted phenyl)-2-(1,3,4-thiadiazol-2-yl) acetamide. These thiadiazoles when treated with piperidine, diethylamine and morpholine to give derivatives of thiadiazoles (IVa-1).



Scheme 1

2.2 Antimicrobial Activity

2.2.1 Antibacterial Activity

All the newly synthesized compounds were screened for the antibacterial activity by agar-diffusion method (filter paper disc technique) using Muller Hinton agar. Ciprofloxacin was used as standard drug and activity of all newly synthesized compounds was measured against it. The zone of inhibition (in mm) was measured and compared against Ciprofloxacin.

2.2.2 Anti-fungal activity

All the newly synthesized compounds were screened for the antifungal activity by agar-diffusion method (filter paper disc technique) using Sabouraud Dextrose Agar. Fluconazole was used as standard drug and activity of all newly synthesized compounds was measured against it.

3. EXPERIMENTAL

Chemicals used in this synthetic work were purchased from S.D. Fine Chem. Ltd. Mumbai, and Sigma Aldrich (St. Louis, Missouri, USA). Solvents except laboratory reagent grade were dried and purified according to the literature when necessary. Purity of the compounds was checked on TLC plates using silica gel G as stationary phase and iodine vapors as visualizing agent. Melting points of synthesized compounds were determined using ThermoNik melting point apparatus and are uncorrected, IR spectra were recorded on Thermo Nicolet Spectrophotometer by using KBr pellets. The ¹H NMR was recorded on Bruker Avance II NMR 300 MHz instruments using appropriated solvent and TMS as internal standard, chemical shifts are expressed as δ values (ppm).

3.1.0 Synthesis of Ethyl-3[(substituted phenyl)amino]-3-oxo propanoate (Ia-d).

A mixture of substituted aniline (10ml) and diethylmalonate (20 ml) was refluxed for 1 hr in a round bottomed flask fitted with an air condenser of such length (14") that ethanol formed escaped and diethylmalonate flowed back into the flask. Contents were cooled, ethanol (30 ml) was added, when malon-substituted anilide separated out. It was filtered under suction. The filtrate was poured on to crushed ice and stirred when ethyl-3[(substituted phenyl) amino]-3-oxo propanoate precipitated as green mass. On recrystallization from aqueous ethanol (50%), ester was obtained as white crystals. The Physico-chemical data of ethyl 3-[(substituted phenyl)amino]-3-oxo propanoate (Ia-d) are given in Tables 1 and 2 respectively.

Table 1. The Physico-chemical data of ethyl 3-[(substituted phenyl) amino] -3-oxo propanoate (Ia-d)

Compound	R	R ₁	Yield (%)	M.P. (°C)	Rf*	Molecular Formula
I a	Cl	H	88	62-64	0.86	C ₁₁ H ₁₂ NO ₃ Cl
I b	Cl	Cl	79	68-70	0.72	C ₁₁ H ₁₁ NO ₃ Cl ₂
I c	H	F	82	72-74	0.69	C ₁₁ H ₁₂ NO ₃ F
I d	F	F	86	78-80	0.76	C ₁₁ H ₁₁ NO ₃ F ₂

*n-Hexane and Ethyl acetate (9:1) as a mobile phase, silica gel G as a stationary phase and iodine vapors as visualizing agent.

Table 2. Spectral data of ethyl 3-[(substituted phenyl)amino]-3-oxo propanoate (Ia-d)

Compound	R	R ₁	IR (KBr, cm ⁻¹)
I a	Cl	H	3255.79(N-H), 783.56 (C-Cl), 1726(C=O).
I b	Cl	Cl	3375.53(N-H), 740.17(C-Cl), 1723.23(C=O).
I c	F	H	3304.37(N-H), 767.59(C-F), 1693.32(C=O).
I d	F	F	3289.40(N-H), 840.72(C-Cl), 1697.93(C=O).

3.1.1 Synthesis of 3-(substituted phenyl)-3-oxopropanehydrazide (II a-d).

Ethyl 3-[(substituted phenyl) amino]-3-oxo propanoate (10.98 gm; 0.03 mol), ethanol (8 ml) and hydrazine hydrate (15 ml; 98%) were mixed together and stirred 3 hrs. Then cooled into freezer 3-4 hrs and poured into crushed ice. Ethyl-3 (substituted phenyl)-3-oxopropanehydrazide was filtered under suction and recrystallised from ethanol in white crystals. The physical and spectral data of synthesized compounds (IIa-d) are given in Tables 3 and 4 respectively.

Table 3. Physicochemical data of 3-(substituted phenyl)-3-oxopropanehydrazide (IIa-d)

Compound	R	R1	Yield (%)	M.P. (°C)	Rf*	Molecular-formula
II a	Cl	H	75	98-100	0.67	C ₉ H ₁₀ N ₃ O ₂ Cl
II b	Cl	Cl	74	95-97	0.58	C ₉ H ₉ N ₃ O ₂ Cl ₂
II c	H	F	72	87-89	0.67	C ₉ H ₁₀ N ₃ O ₂ F
II d	F	F	80	101-103	0.66	C ₉ H ₁₀ N ₃ O ₂ F ₂

*n-Hexane and Ethyl acetate (9:1) as a mobile phase, silica gel G as a stationary phase and iodine vapors as visualizing agent.

Table 4. Spectral data of 3-(substituted phenyl)-3-oxopropanehydrazide (IIa-d)

Compound	R	R1	IR(KBr, cm ⁻¹)
II a	Cl	H	3427.67(N-H), 827.16(C-Cl), 1711(C=O).
II b	Cl	Cl	3305.63(N-H), 751.14(C-Cl), 1647.71(C=O).
II c	F	H	3264.22(N-H), 756.98(C-F), 1690.37(C=O).
II d	F	F	3255.79(NH), 751.14(CI), 1681.58(C=O).

3.1.2 Preparation of N(substituted phenyl)-2-(5-sulfanyl-1,3,4 thiadiazol-2-yl) acetamide (IIIa-d):

A mixture of 3-(substituted phenyl)-3-oxopropanehydrazide (14.6gm, 0.09 mol) (IIa-d), KOH (0.005 mol, 0.28 g) and carbon disulphide (5 ml) in anhydrous ethanol (50 ml) was refluxed on a steam bath for 12 h (monitored by TLC). The solution was then concentrated, cooled and acidified with dil. HCl. The solid mass that separated out was filtered, washed with water and recrystallized from ethanol. The physico-chemical and spectral data of synthesized compound (IIIa-d) are given in Tables 5 and 6 respectively.

Table 5. Physicochemical data of N-(substituted phenyl)-2-(5-sulfanyl-1,3,4 thiadiazol-2-yl) acetamide (IIIa-d).

Compound	R	R1	Yield (%)	M.P. (°C)	Rf*	Molecular Formula
III a	Cl	H	74.66%	180-182	0.53	C ₁₀ H ₈ N ₃ O ClS ₂
III b	Cl	Cl	72.55%	193-195	0.44	C ₁₀ H ₇ N ₃ OCl ₂ S ₂
III c	F	H	65.63%	183-185	0.35	C ₁₀ H ₈ N ₃ O FS ₂
III d	F	F	64.34	174-176	0.47	C ₁₀ H ₇ N ₃ O F ₂ S ₂

*n-Hexane and Ethyl acetate (9:1) as a mobile phase, silica gel G as a stationary phase and iodine vapors as visualizing agent.

Table 6. Spectral data of N-(substituted phenyl)-2-(5-sulfanyl-1,3,4-thiadiazol-2 yl) acetamide (IIIa-d)

Compound	R	R ₁	IR (KBr,cm)	HNMR spectra (δ,ppm)
III a	Cl	H	3383.95 (N-H), 797.26 (C-Cl), 1724.87(C=O).	14.44(s, 1H,SH), 8.24(s, 1H,NH), 7.30-7.55 (m, 4H,Ar-H), 4.12 (s, 2H,CH ₂).
III b	Cl	Cl	3375.53(N-H), 1724.87(C=O), 797.26(C-Cl).	14.18(s, 1H,SH), 8.32(s, 1H,NH), 7.20-7.35(m, 3H,Ar-H), 4.20(s, 2H,CH ₂).
III c	F	H	3376.62(N-H), 727.79(C-Cl), 1721.91(C=O).	14.10(s, 1H,SH), 8.10(s, 1H,NH), 7.10-7.75(m, 4H,Ar-H), 4.32(s, 2H,CH ₂).
III d	F	F	3375.49(N-H), 836.75(C-F), 1722.99(C=O).	14.20(s, 1H,SH), 8.15(s, 1H,NH), 7.20-7.75(m, 3H,Ar-H), 4.40(s, 2H,CH ₂).

3.1.3 Preparation of derivative of N-(substituted phenyl)-2-(5-substituted-1,3,4 thiadiazol-2-yl) acetamide (IVa-d)

These obtained N-(substituted phenyl)-2-(5-sulfanyl-1,3,4 thiadiazol-2-yl) acetamide compound (0.005 mol) were treated with equimolar quantity of 2° amine (0.005mole) in the presence of ethanol (50ml). Refluxed for 8 hrs on oil bath to give the different derivatives of 1,3,4-thiadiazoles. The physico-chemical and spectral data of synthesized compound (IVa-l) are given in Table no. 7 and 8 respectively.

Table 7. Physio-chemical data of title compounds (IVa-l)

Compound	R	R ₁	R ₂	Yield (%)	M.P. (°C)	Rf*	Molecular Formula
IV a	Cl	H	C ₅ H ₁₀ N	66%	200-202	0.37	C ₁₅ H ₁₆ N ₃ OClS
IVb	Cl	Cl	C ₅ H ₁₀ N	59%	210-212	0.44	C ₁₅ H ₁₅ N ₃ OCl ₂ S
IV c	F	H	C ₅ H ₁₀ N	54%	230-232	0.27	C ₁₅ H ₁₆ N ₃ OFS
IV d	F	F	C ₅ H ₁₀ N	43%	221-223	0.35	C ₁₅ H ₁₅ N ₃ O F ₂ S
IV e	Cl	H	C ₄ H ₁₁ N	53%	224-226	0.51	C ₁₄ H ₁₆ N ₃ OClS
IV f	Cl	Cl	C ₄ H ₁₁ N	55%	235-237	0.46	C ₁₄ H ₁₅ N ₃ OCl ₂ S
IV g	F	H	C ₄ H ₁₁ N	56%	211-213	0.44	C ₁₄ H ₁₆ N ₃ OFS
IV h	F	F	C ₄ H ₁₁ N	45%	232-234	0.44	C ₁₄ H ₁₅ N ₃ O F ₂ S
IV i	Cl	H	C ₄ H ₉ NO	52%	194-196	0.33	C ₁₄ H ₁₄ N ₃ O ₂ ClS
IV j	Cl	Cl	C ₄ H ₉ NO	51%	195-197	0.35	C ₁₄ H ₁₃ N ₃ O ₂ Cl ₂ S
IV k	F	H	C ₄ H ₉ NO	53%	202-204	0.41	C ₁₄ H ₁₄ N ₃ O ₂ FS
IV l	F	F	C ₄ H ₉ NO	51%	207-209	0.44	C ₁₄ H ₁₃ N ₃ O ₂ F ₂ S

*n-Hexane and Ethyl acetate (9:1) as a mobile phase, silica gel G as a stationary phase and iodine vapors as visualizing agent.

Table 8. Spectral data of title compounds (IVa-l)

Compound	R	R ₁	R ₂	IR (KBr,cm ⁻¹)	¹ HNMR spectra (δ, ppm)
IV a	Cl	H	C ₅ H ₁₀ N	3370.27(N-H), 2918.91(C-H), 1724.53(C=O), 732.31(C-Cl),	7.95(s,1H,NH), 7.22-7.78 (m,4H,Ar-H), 4.32 (s,2H,CH ₂), 3.33-3.48 (m,4H, piperidine), 1.32-1.79 (m, 6H, piperi- dine)
IV b	Cl	Cl	C ₅ H ₁₀ N	3359.90(N-H), 2923.57(C-H), 764.29(C-F), 1686.10(C=O),	8.10(s,1H,NH), 7.24-7.72 (m,3H,Ar-H), 4.22(s,2H, CH ₂), 3.36-3.48 (m,4H, piperidine), 1.31-1.70 (m, 6H, piperi- dine)
IV c	F	H	C ₅ H ₁₀ N	3377.30(NH), 2850.66(C-H), 728.94(C-F), 1722.77(C=O)	8.14(s,1H,NH), 7.20-7.77 (m,4H,Ar-H), 4.22(s,2H,CH ₂), 3.32-3.48 (m,4H, piperidine), 1.32-1.69 (m, 6H, piperi- dine)
IV d	F	F	C ₅ H ₁₀ N	3370.20(NH), 2367.15(C-H), 732.60(C-Cl), 1719.99(C=O)	8.18(s,1H,NH), 7.50-7.82 (m,3H,Ar-H), 4.22 (s,2H,CH ₂), 3.40-3.50 (m,4H, piperidine), 1.32-1.72 (m, 6H, piperi- dine)
IV e	Cl	H	C ₄ H ₁₁ N	3370.64(N-H), 2922.77(C-H), 739.29(C-Cl), 1725.91(C=O),	8.22 (s,1H,NH), 7.30-7.50 (m,4H,Ar-H), 4.20 (s,2H,CH ₂), 2.40-2.56 (m,4H, diethylamine), 1.18-1.60 (m,6H,diethylamine)
IV f	Cl	Cl	C ₄ H ₁₁ N	3370.54(N-H), 2923.27(C-H), 732.34(C-Cl), 1733.39(C=O)	8.14 (s,1H,NH), 7.02-7.31(m,3H, Ar-H), 4.25 (s,2H,CH ₂), 2.40-2.55(m,4H,diethylamine), 1.18-1.70(m,6H,diethylamine)
IV g	F	H	C ₄ H ₁₁ N	3361.75(N-H), 2923.79(C-H), 763.98(C-F), 1733.26(C=O),	8.28(s,1H,NH), 7.35-7.55(m,4H, Ar-H), 4.26(s,2H,CH ₂), 2.45-2.56 (m,4H,diethylamine), 1.16-1.60(m,6H,diethylamine)
IV h	F	F	C ₄ H ₁₁ N	3370.46(N-H) 2923.01(C-H), 732.28(C-F), 1720.07(C=O).	8.25(s,1H,NH), 7.30-7.60 (m,3H,Ar-H), 4.20 (s,2H,CH ₂), 2.51-2.62 (m,4H,diethylamine), 1.20-1.72(m,6H,diethylamine)
IV i	Cl	H	C ₄ H ₉ NO	3328.76(N-H), 2918.37(CH ₂), 732.98(C-Cl), 1724.53(C=O),	7.15 (s,1H,NH), 6.10-7.25 (m,4H,Ar-H), 4.55 (s,2H,CH ₂), 2.75-3.45 (m,4H, morpholine), 2.35-2.45(m,4H,morpholine)
IV j	Cl	Cl	C ₄ H ₉ NO	3359.90(N-H), 2923.57(C-H), 764.29(C-Cl), 1701.54(C=O),	7.75 (s,1H,NH), 6.62-7.25 (m,3H, Ar-H), 4.25(s,2H, CH ₂), 2.95-3.40 (m,4H, morpholine), 2.40-2.65(m,4H,morpholine)
IV k	F	H	C ₄ H ₉ NO	3010.64(N-H), 2854.66(C-H), 728.94(C-F), 1722.77(C=O),	7.10(s, 1H,NH), 6.10-7.20(m, 4H,Ar-H), 4.50(s, 2H, CH ₂), 2.95-3.41(m,4H,morpholine), 2.30-2.55(m,4H,morpholine)
IV l	F	F	C ₄ H ₉ NO	3471.15(N-H), 2922.77(C-H), 792.68(C-F), 1719.99(C=O),	7.85(s,1H,NH), 6.62-7.01(m,3H,Ar-H), 4.15(s,2H,CH ₂), 2.95-3.31(m, 4H, morpholine), 2.40-2.55(m,4H,morpholine)

3.2.0 Antimicrobial activity

3.2.1 Anti bacterial activity

All the newly synthesized compounds were screened for the antibacterial activity by agar-diffusion method (filter paper disc technique) using Muller Hinton agar. Ciprofloxacin was used as standard drug and activity of all newly synthesized compounds was measured against it. The zone of inhibition (in mm) was measured and compared against Ciprofloxacin. Table No. 09 reveals the antibacterial activity (zone of inhibition) of title compounds (IVa-l). Among the series, tested, compound IVc,

IVf, IVg, IVj and IVl exhibited good antibacterial activity with zone of inhibition 20,19,20,24,19 mm respectively.

3.2.2 Antifungal activity

All the newly synthesized compounds were screened for the antifungal activity by agar-diffusion method (filter paper disc technique) using Sabouraud Dextrose Agar. Fluconazole was used as standard drug and activity of all newly synthesized compounds was measured against it. The zone of inhibition (in mm) was measured and compared against Ciprofloxacin. Table 10 reveals the antifungal activity (zone of inhibition) of

title compounds (IVa-l). Among the series compounds IVc and IVj showed good antifungal activity.

Table 9. Antibacterial screening of (IVa-l) at Concentration of 100 µg/ml by Agar Diffusion method (filter paper disc technique)

Compound	E. Coli	S.aureus	P.aeruginosa
Ciprofloxacin	26	23	25
IV a	13	11	14
IV b	10	12	16
IV c	20	13	13
IV d	11	18	15
IV e	13	15	21
IV f	12	13	19
IV g	20	17	15
IV h	18	17	21
IV i	16	18	20
IV j	20	24	15
IV k	12	16	18
IV l	18	19	18

Abbreviations; E.coli- Escherischia coli, P. aeruginosa- Pseudomonas aeruginosa, S.aureus- Staphylococcus aureus.

Table 10. Antifungal screening of title compounds at concentration of 100 µg by filter paper disc method

Compound Name	Penicillium notatum	Candida albicans
Fluconazole	22	23
IV a	10	12
IV b	13	14
IV c	16	21
IV d	12	10
IV e	13	13
IV f	11	12
IV g	11	16
IV h	10	12
IV i	10	14
IV j	18	17
IV k	13	14
IV l	11	12

4. RESULT AND DISCUSSION

Ethyl 3-[(2,4 disubstituted phenyl) amino]-3-oxo propanoate (Ia-d) were synthesized by the reaction of appropriate substituted anilines and diethylmalonate. The purity of these compounds was confirmed by TLC and the melting point. The structures of these compounds were confirmed by spectral studies. IR spectrum of these compound showed characteristic peaks at 3255-3375 (NH stretching), 1693-1723 (C=O) and 740-840 (C-Cl). These ester undergo hydrolysis with hydrazine hydrate (98%) in the presence of dry ethanol to give N-(substituted phenyl)-3-hydrazinyl-3-oxo propanamide (IIa-d). The purity of

these compounds was confirmed by TLC and the melting point. The structures of these compounds were confirmed by spectral studies. IR spectrum of these compounds showed characteristic peaks at 3427-3355. (NH stretching), 1647-1711(C=O), 751-827(C-Cl). These hydrazide on treating with carbon disulphide (CS₂) in the presence of KOH and ethanol gave N-(substituted phenyl)-2-(5-sulfanyl-1,3,4 thiadiazole-2-yl) acetamide (III a-d). The purity of the compounds were confirmed by TLC and the melting point. The structures of these compounds were confirmed by spectral studies. IR spectrum of these compounds showed characteristic peaks at 3375-3383 (NH stretching), 1721-1727(C=O), 727-836(C-Cl). These substituted-1,3,4-thiadiazole treated with various 2° amine in presence of ethanol yielded title compounds (IVa-l). The purity of these compounds was confirmed by TLC and the melting point. The structures of these compounds were confirmed by spectral studies. The IR spectra showed characteristic peak of N-H at 3328-3483, C=O at 1686-1725 and C-Cl at 723-764 cm⁻¹. These structure were further supported by ¹HNMR spectral data. The presence of singlet between 8.14 to 7.85 of N-H, multiplet between 7.77 to 6.62 of Ar-H, singlet between 4.25 to 4.15 of CH₂ and 3.48-1.18 of various amines reveals confirmation of structures. All these newly synthesized compounds (IVa-l) were screened for their antimicrobial activity and the compounds IVc, IVf, IVg, IVj, IVl showed the good antibacterial activity and IVc and IVj showed the moderate antifungal activity.

5. CONCLUSION

Series of Substituted 1,3,4-Thiadiazole were synthesized according to scheme 1 and the identity of the compounds were confirmed on the basis of their Melting point, TLC, IR and ¹H-NMR data. Preliminary antibacterial activity was carried out for all the synthesized compounds using disc-diffusion method against S.aureus, P.aeruginosa, E.coli bacterial strains and Ciprofloxacin was used as standard. Compounds IVc, IVf, IVg, IVj and IVl showed good antibacterial activity with zone of inhibition of 20, 19, 20, 24, 19 mm respectively. The compounds were screened for their antifungal activity using disc diffusion method against C. albicans and P. notatum fungal strains and Fluconazole was employed as the standard for antifungal activity. From the screening studies it is evident that IVc, and IVj of the synthesized compounds showed moderate antifungal activity against all tested organisms.

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