

2,4-Substituted diphenyl-5-imino- Δ^2 -1,3,4-thiadiazole derivatives: synthesis and evaluation of antimicrobial properties

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Abstract

Some new substituted-2,4-diphenyl-5-imino-1,3,4-thiadiazole derivatives were synthesized and studied for their antibacterial activity. These compounds were prepared from reaction of benzoyl chloride and phenyl hydrazine in pyridine yielded the corresponding substituted hydrazone derivatives (1a-h) which were chlorinated to the corresponding α -chlorobenzal phenylhydrazone derivatives (2a-h). Reaction of Compounds (2a-h) with potassium thiocyanate yielded the targeted compound 2,4-diphenyl-5-imino- Δ^2 -1,3,4-thiadiazole derivatives (3a-h). These compounds were characterized by CHN analyses, IR, mass and ¹H NMR spectral data. All the compounds were evaluated for their *in vitro* antibacterial activity against two Gram negative strains (*Escherichia coli* and *Pseudomonas aeruginosa*) and two Gram positive strains (*Bacillus cereus* and *Staphylococcus aureus*) and their minimum inhibitory concentration (MIC) were determined. The newly synthesized compounds exhibited promising antimicrobial activities.

Keywords: antibacterial activity, hydrazone, 1,3,4-thiadiazole derivatives, minimum inhibitory concentration.

Introduction

There are numbers of five member heterocycles containing nitrogen and sulphur atom, have treatment to be potential chemotherapeutics and pharmacotherapeutics agents. The biological profile of thiadiazoles is very extensive (Zaidi et al. 1977, Antonardi et al. 1992, Kulkarni et al. 1992, Thomas 1996, Arun et al. 1999). It is well documented that 1,2,3-thiadiazoles undergo multiple transformations into a wide variety of products like, antitubercular (Forumadi et al. 2004), anticancer (Holla et al. 2006), anthelmintic (Nadkarni et al. 2001), anti-inflammatory (Adnan et al. 2007) and antimicrobial (Holla et al. 2006, Adnan et al. 2007) antiviral (Holla et al. 2001, Marina et al. 2002), antifungal (Holla et al. 2006) activities etc. On the other hand, a considerable number of 1,3,4-thiadiazole derivatives endowed with antimicrobial property have been reported (Sakata et al. 2000, Holla et al. 2001 and 2006, Forumadi et al. 2004, Gülgün et al. 2005, Hui et al. 2005, Onkol et al. 2008, Adnan et al. 2007).

Hydrazone intermediates were prepared in the synthesis of thiadiazole derivatives. Hydrazone intermediates are highly versatile intermediates for synthesis of a variety heterocyclic

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compounds (Shawali 1993). 1,3,4-Thiadiazoles represent an important heterocyclic system due to their pharmacological activity. They were found to have antihypertensive, anticonvulsive activities (Chapleo et al. 1988), antimicrobial (Gulerman et al. 2001), and biological activities (Andotra et al. 1993), also some 1,3,4-thiadiazole have industrial importance (Miyake et al. 1970), act as semiconductors. As a part of a program directed for developing new biologically active compounds (Shawali et al. 2004), it is reported here on the utility of hydrazonoyl halides as a candidates for a facile synthetic route to substituted 1,3,4 thiadiazoles.

The development of resistance to current antibacterial therapy continues to drive the search for more effective agents. In addition, primary and opportunistic microbial infections continue to increase the number of immunocompromised patients, those suffering from such as AIDS or cancer or who have undergone organ transplantation. We designed and prepared a series of thiadiazole in an effort to investigate their antimicrobial activities. These above observations promoted us to synthesis of the title compounds for antimicrobial activity (Fig. 1).

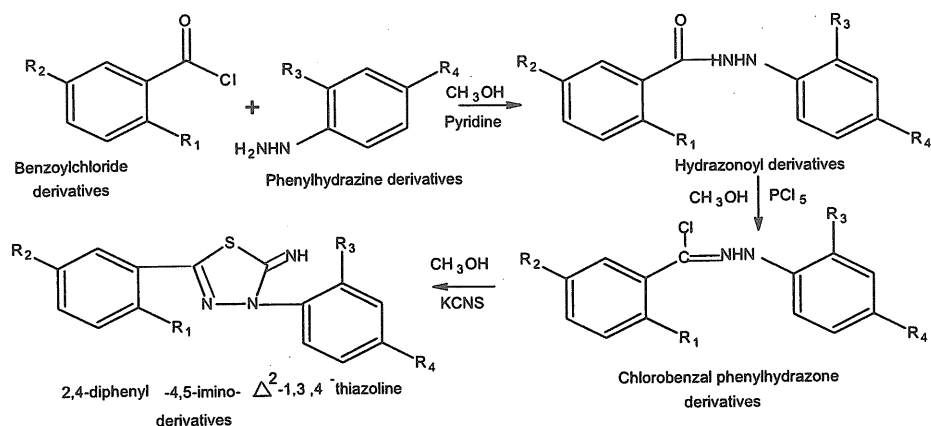


Figure 1. Synthesis of 2,4-Substituted diphenyl-5-imino- Δ^2 -1,3,4-thiadiazole derivatives

compounds	R ₁	R ₂	R ₃	R ₄
(3a)	H	H	H	H
(3b)	H	H	NO ₂	NO ₂
(3c)	Cl	H	H	H
(3d)	Cl	H	NO ₂	NO ₂
(3e)	H	Cl	H	H
(3f)	H	Cl	NO ₂	NO ₂
(3g)	H	NH ₂	H	H
(3h)	H	NH ₂	NO ₂	NO ₂

Materials and Methods

Experimental

The purity of the synthesized compounds were ascertained by thin layer chromatography on silica gel G in various solvent systems, the most common solvent system used were toluene, ethyl acetate, and formic acid in the ratio of 5:4:1 and benzene and acetone in two ratios 5:1 and 4:1 and using iodine vapors as detecting agent. Melting points were determined by open capillary boiling point determination method and are uncorrected. Elemental analyses were done using CHN analyzer. Infra-red spectra were recorded on Perkin Elmer Spectrophotometer in KBr Phase. Proton NMR spectra were recorded in deuterated

chloroform (CDCl₃) on Bruker Avance 400-NMR Spectrometer using tetramethyl silane as internal standard.

General procedure of Synthesis of substituted hydrazoneyl (1a-1h)

The first step of the synthesis was commenced with the reaction between benzoyl chloride (0.01M) or its derivatives were dissolved in methanol and ethanol (10 to 25mL) and then pyridine (0.005M) was added along with of phenyl hydrazine (0.01M) or its derivatives and then the reaction mixture was refluxed at 50-60°C for 2 to 15 hours depends on derivatives used in the reaction mixture. The reaction time was monitored by TLC. Then we get different hydrazoneyl derivatives (1a-1h) as the product. These products were recrystallized by ethanol.

General procedure of Synthesis of substituted α -chlorobenzal phenylhydrazone derivatives (2a-2h)

The substituted hydrazoneyl (0.01M) and its derivatives (1a-1h) is chlorinated using (0.01M) PCl₅ in methanol and ethanol used as solvent and then refluxed for 5- 12 hours at 40-60°C depend on the different derivatives used in this reaction. The reaction time was monitored by TLC, different α - chlorobenzal Hydrazone derivatives (2a-2h) was obtained after keeping the mixture overnight. The recrystallization of these compounds from ethanol.

General procedure of Synthesis of substituted 2,4-diphenyl-5-imino- Δ^2 -1,3,4- thiadiazole derivatives (3a-3h): (Cyclization)

Cyclization of substituted α -chlorobenzal phenylhydrazone (0.003M) derivatives with potassium thiocyanate (0.005M) in ethanol and methanol used as solvent. The reaction mixture was refluxed 50-70°C for 3-10 h. The reaction time was monitored by TLC, and when the reaction completes the reaction mixture was kept overnight to get the crystals of products (3a-3h).The recrystallization of these compounds from ethanol.

Synthesis of 2,4-diphenyl-5-imino- Δ^2 -1,3,4-thiadiazole (1a-3a)

Compound (1a)- m.p 188°C, molecular formula C₁₃H₁₂ON₂, molecular weight 212, recrystallization solvent ethanol, yield 76%, IR cm⁻¹ 1645(C=O), 3208(NH). Compound (2a)- M.P 192°C, molecular formula C₁₃H₁₁N₂Cl, molecular weight 230.5, recrystallization solvent ethanol, yield 47%, IR cm⁻¹ 1682(C=N), 582(C-Cl), 3206(NH). Compound (3a)-M.P 200°C, molecular formula C₁₄H₁₁N₃S, molecular weight 253, recrystallization solvent ethanol, Yield 38%, elemental analysis (%)- found- H (4.37), 66.37), N(16.58), S(12.65), calculated H (4.31), C(66.42), N(16.49), S(12.58). IR spectra cm⁻¹: 1645cm⁻¹(C=O), 3208 cm⁻¹ (NH), 1599 cm⁻¹ (C-C,Ar), 582 cm⁻¹ (C-Cl), 1682 cm⁻¹ (C=N), 3201 cm⁻¹ (NH), 692 cm⁻¹ (C-S-C), 1601 cm⁻¹ (C=N), 3391 cm⁻¹ (NH). ¹H NMR spectra (DMSO-d₆) ppm: 6.8-7.34 (10H, m, Ar-H), 8.32 (1H, s, NH imine).

Synthesis of 2-phenyl-2-(2',4'-dinitrophenyl)-5-imino- Δ^2 -1,3,4-thiadiazole(1b-3b)

Compound 1b- M.p.130°C, Molecular Formula C₁₃H₁₀N₄O₅, Molecular weight 302, recrystallization solvent ethanol, Yield 67%, IR cm⁻¹ 1418(NO₂), 1619(C=O), 281(NH). Compound (2b)- m.p 208°C, molecular formula C₁₃H₉N₄O₄Cl, molecular weight 320.5, recrystallization solvent ethanol, yield 73%, IR cm⁻¹ 1521(NO₂), 1621(C=N), 599(C-Cl), 3375(NH). Compound (3b)- m.p. 202°C, molecular formula C₁₄H₉N₅O₄S, molecular weight 343, recrystallization solvent ethanol, yield 75%. elemental analysis (%), found H (2.64), C (48.97), N (20.39), S (9.33) calculated H(2.61), C(48.93), N(20.38), S (9.40). IR spectra cm⁻¹: 1519 cm⁻¹(NO₂), 661 cm⁻¹ (C-S-C), 1661 cm⁻¹ (C=N), 3374 cm⁻¹ (NH). ¹H NMR spectra (DMSO-d₆) ppm: 7.3-8.2(5H, m, Ar) 10.9 (1H, s, NH), 8.3-9.14(3H, m, Ar- NO₂).

Synthesis of 2-(2'-chlorophenyl)-4-phenyl-5-imino- Δ^2 -1,3,4-thiadiazole (1c-3c)

Compound (1c)- m.p 186°C, molecular formula $C_{13}H_{11}N_2OCl$, molecular weight 246.5, recrystallization solvent ethanol, yield 45 %, IR cm^{-1} 1590 (C=O), 735(C-Cl), 3430(NH). Compound (2c)- m.p 190°C, molecular formula $C_{13}H_{10}N_2Cl_2$, molecular weight 265, recrystallization solvent ethanol, yield 79%, IR cm^{-1} 573(C-Cl), 769(Ar-Cl), 1596(C=N), 3419(NH). Compound (3c)- m.p 198°C, molecular formula $C_{14}H_{10}N_3S$, molecular weight 287.5, recrystallization solvent ethanol, yield 57 %, elemental analysis(%)- found H(3.50), C(58.43), N(14.60), S(11.14) calculated H(3.52), C(58.37), N(14.67), S(11.21). IR cm^{-1} spectra 670 cm^{-1} (C-S-C), 1595 cm^{-1} (C=N), 3440 cm^{-1} (NH). 1H NMR spectra (DMSO- d_6) ppm: 7.1-7.8 (9H,m,Ar), 3.7 (1H,s,NH).

Synthesis of 2-[2'-chlorophenyl]-4-(2'',4''-dinitro-phenyl)-5-imino- Δ^2 -1,3,4-thiadiazole (1d-3d)

Compound (1d)- m.p 210°C, molecular formula $C_{13}H_9O_5N_4Cl$, molecular weight 336.5, recrystallization solvent ethanol, yield 66%, IR cm^{-1} 1590 (C=O), 735(C-Cl), 3430(NH). Compound (2d)- m.p 182°C, molecular formula $C_{13}H_8O_4N_4Cl_2$, molecular weight 335, recrystallization solvent ethanol, yield 56%, IR cm^{-1} 1596(C=N), 1350(NO_2), 3444(NH), 752 (CCl). Compound (3d)- m.p 164°C, molecular formula $C_{14}H_8O_4N_5S$, molecular weight 377.5, recrystallization solvent ethanol, yield 53%. elemental analysis (%) - found H(2.13), C(44.51), N(18.53), S(8.48) calculated H(2.16), C(44.43), N(18.48), S(8.52). IR spectra cm^{-1} : 672 cm^{-1} (C-S-C), 1524 cm^{-1} (C=N), 1340 cm^{-1} (NO_2), 3450 cm^{-1} (NH). 1H NMR (DMSO- d_6) ppm: 8.2-9.0 (4H,m, Ar-Cl), 9.3 (1H,s,NH), 8.3-9.14 (3H,m,Ar- NO_2).

Synthesis of 2-(4'-chlorophenyl)-4-phenyl-5-imino- Δ^2 -1,3,4-thiadiazole (1e-3e)

Compound (1e)- m.p 120°C, molecular formula $C_{13}H_{11}N_2OCl$, molecular weight 246.5, recrystallization solvent ethanol, yield 62%, IR cm^{-1} 1630(C=O), 850(Ar-Cl), 3400(NH). Compound (2e)-m.p 195°C, molecular formula $C_{13}H_{10}N_2Cl_2$, molecular weight 265, recrystallization solvent ethanol, yield 47%, IR cm^{-1} 820(Ar-Cl), 570(C-Cl), 1520(C=N), 3600(NH). Compound (3e)- m.p 147°C, molecular formula $C_{14}H_{10}N_3S$, molecular weight 287.5, recrystallization solvent ethanol, yield 62%. elemental analysis(%)- found H(3.50), C(58.43), N(14.60), S(11.14) calculated H(3.45), C(58.35), N(14.54), S(11.17). IR spectra cm^{-1} 1630 cm^{-1} (C=O), 850 cm^{-1} (Ar-Cl), 3400 cm^{-1} (NH), 820 cm^{-1} (Ar-Cl), 570 cm^{-1} (C-Cl), 1520 cm^{-1} (C=N), 3600 cm^{-1} (NH). 1H NMR (DMSO- d_6) ppm 7.2-7.9 (9H, m, Ar), 3.9 (1H,s,NH).

Synthesis of 2-(4'-chlorophenyl)-4-(2'',4''-dinitrophenyl)-5-imino- Δ^2 -1,3,4-thiadiazole (1f-3f)

Compound (1f)- m.p 228°C, molecular formula $C_{13}H_9O_5N_4Cl$, molecular weight 336.5, recrystallization solvent ethanol, yield 65 %, IR cm^{-1} 1592(C=O), 850(Ar-Cl), 3431(NH). Compound (2f)- m.p 232°C, molecular formula $C_{13}H_8O_4N_4Cl_2$, molecular weight 355, recrystallization solvent ethanol, yield 63%, IR cm^{-1} 764(Ar-Cl),545(C-Cl),1595(C=N), 1425 (NO_2),3427(NH). Compound (3f)- m.p. 210°C, molecular formula $C_{14}H_8O_4N_5S$, molecular weight 377.5, recrystallization solvent ethanol, yield 66%, elemental analysis(%)- Found H(2.13), C(44.51), N(18.53), S(8.48) calculated H(2.15), C(44.47), N(18.57), S(8.43). IR spectra cm^{-1} : 672 cm^{-1} (C-S-C), 1351 cm^{-1} (NO_2), 1595 cm^{-1} (C=N), 769 cm^{-1} (Ar-Cl), 3433 cm^{-1} (NH). 1H NMR (DMSO- d_6) ppm : 7.1-7.8 (4H,m,Ar-Cl), 8.2-8.9 (3H,m,Ar- NO_2).

Synthesis of 2-p-aminophenyl-4-phenyl-5-imino- Δ^2 -1,3,4-thiadiazole (1g-3g)

Compound (3g)- m.p 238°C, molecular formula $C_{14}H_{12}N_4S$, molecular weight 268, recrystallization solvent ethanol, yield 61%, elemental analysis (%) - found H(4.50), C(62.66), N(20.87), S(11.94) calculated H(4.53), C(62.61), N(20.83), S(11.87). IR spectra cm^{-1} :1398 cm^{-1} (Ar- NH_2), 1631 cm^{-1} (C=N), 3442 cm^{-1} (NH), 692 cm^{-1} (C-S-C).

Synthesis of 2-(p-aminophenyl)-4-(2'',4''-dinitrophenyl)-5-imino-Δ²-1,3,4-thiadiazole (1h-3h)

compound (1h)- m.p 194°C, molecular formula C₁₃H₁₁N₅O₅, molecular weight 317, recrystallization solvent ethanol, yield 59%, IR cm⁻¹ 1496(NO₂), 1618(C=O), 3418(NH). Compound (2h)- m.p 182°C, molecular formula C₁₃H₁₀N₅O₄Cl, molecular weight 335.5, recrystallization solvent ethanol, yield 71%, IR cm⁻¹ 1349(NO₂), 1594(C=N), 3442(NH). Compound (3h)- m.p 252°C, molecular Formula C₁₄H₁₀N₆O₄S, molecular weight 294, recrystallization solvent ethanol, yield 56%, elemental analysis (%)- found H(2.81), (46.92), N(23.45), S(8.94) calculated H(2.76), C(46.84), N(23.54), S(8.98). IR spectra cm⁻¹: 1350 cm⁻¹(NO₂), 1595 cm⁻¹(C=N), 671 cm⁻¹(C-S-C), 3443 cm⁻¹(NH). ¹H NMR (DMSO-d₆) ppm: 7.3-7.6 (4H,m,Ar- NH₂), 7.7-7.9 (3H,m, Ar- NO₂), 8.7(1H,s,NH), 4.3(1H,s,NH₂).

Antimicrobial Activity

Organisms

The microorganisms were collected from the department of biochemistry, Bundelkhand University, Jhansi, U.P. India. The fungal cultures were *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus cereus* and *Escherichia coli*. All the organisms were maintained on specified media slants at 4°C and reviewed prior to use.

Antimicrobial assay

All the compounds were screened for their *in vitro* antibacterial activity against two Gram negative strains, *i.e.*, *Escherichia coli* and *Pseudomonas aeruginosa*, and two Gram positive strains, *i.e.*, *Bacillus cereus* and *Staphylococcus aureus*. The disc diffusion method was performed to determine *in vitro* antimicrobial activity of the different synthetic thiadiazole derivatives (Olukoya et al. 1986). Ciprofloxacin was used as a standard drug. All the compounds were dissolved in dimethyl sulfoxide. The cultures were subculture in agar medium and incubated at 27°C for 72-120 h and from this, the spore suspension was prepared containing 10⁵ cell/mL. Turbidity of the organism suspension was adjusted to the Mc-Farland standard (0.5) and 100μL of suspension was plated on agar medium. Sterile empty discs (Hi-media) were allowed to soak and absorb the different synthetic thiadiazole derivatives for 24 h before draining off the excess and drying in the oven at 60°C (Sakata et al. 2000). These discs were placed on the agar plates against the control (solvents). Plates were incubated at 25-27°C for 72-120 h and observed for the zone of inhibition. Disc diameter (6 mm) was deducted while recording the zone size. The tests were conducted in triplicate (Table 1).

Table 1. Antimicrobial activity of different Thiadiazole derivatives.

Compounds	<i>P.aeruginosa</i> (μg/mL)			<i>S.aureus</i> (μg/mL)			<i>B.cereus</i> (μg/mL)			<i>E.coli</i> (μg/mL)		
	50	100	200	50	100	200	50	100	200	50	100	200
3a	10	10	12	11	14	18	06	8	10	10	10	14
3b	10	13	17	10	14	16	11	11	13	10	11	12
3c	13	15	17	10	12	15	10	10	11	09	13	14
3d	10	11	11	10	10	13	10	12	15	07	07	08
3e	09	09	12	12	13	14	09	11	12	06	08	07
3f	07	13	14	10	15	16	07	12	14	08	07	07
3g	06	08	08	12	12	14	09	13	17	08	08	11
3h	11	12	12	07	06	07	10	12	14	07	10	12

SEM ± 02, Note: Standard drug-Ciprofloxacin (dose: 10 μg/mL).zone of inhibition: 12-16 mm. Control-Dimethyl formamide (DMF)

Minimum inhibitory concentration

Minimum inhibitory concentration (MIC) was evaluated by tube dilution method against selected cultures only that was inhibited by synthetic thiadiazole derivative(s). MIC was determined by dilution of the different derivatives to various concentrations (0.0488-50 mg/mL) and compared with a standard (Ciprofloxacin, Cipla Ltd. Mumbai, India). All the tubes were incubated at suitable temperature for 72-120 h. The tubes were observed for the appearance of any growth. The MIC was interpreted as the lowest concentration of the different derivatives that did not permit any visible growth when compared with control tubes (Fig. 1).

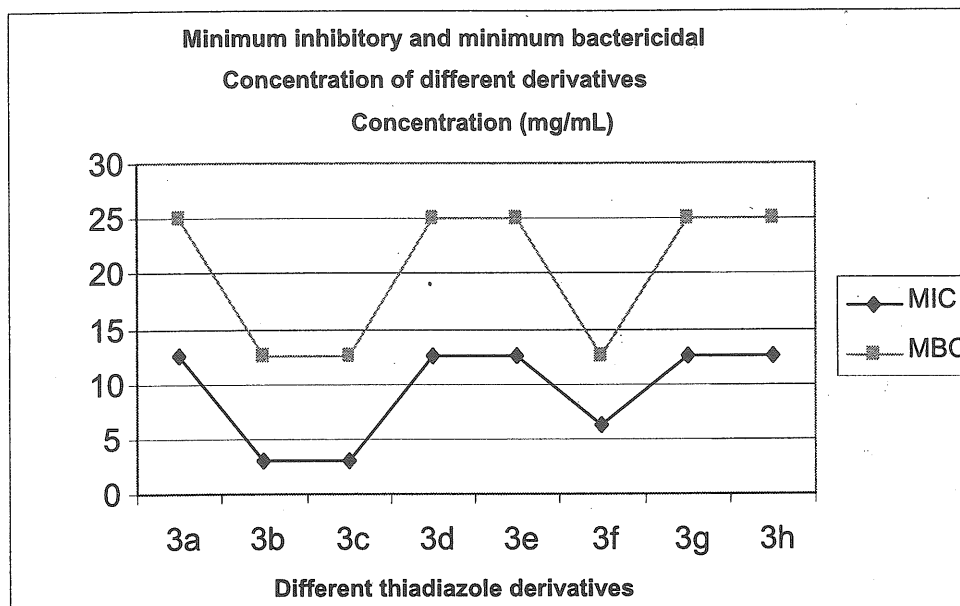


Figure 1. Determination of Minimum inhibitory and minimum bactericidal concentrations against *S. aureus*

Minimum bactericidal concentration

Minimum bactericidal Concentration (MBC) was determined by sub culturing methods. Subcultures made from samples obtained from those test tubes which showed no visible turbidity or growth in MIC assays, were made on freshly prepared agar plates. After 72 h incubation, the MBC was regarded as the lowest concentration of the different synthetic thiadiazole derivatives that did not permit any growth on the agar plate surface used. (Fig. 2)

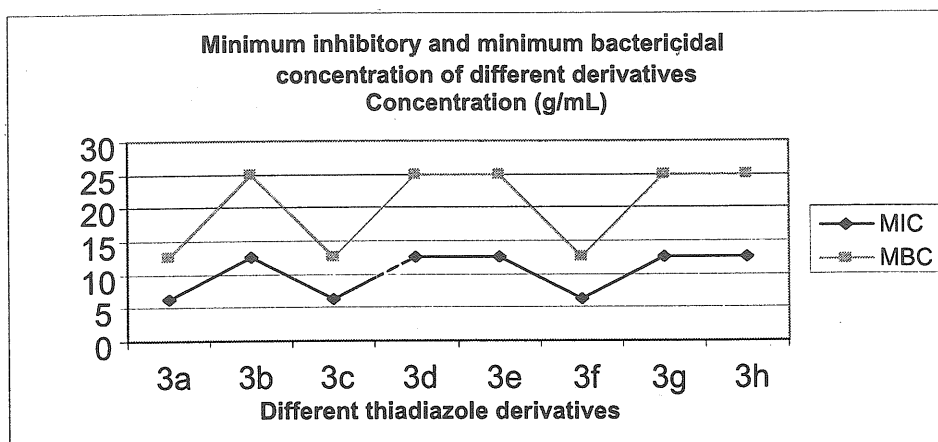


Figure 2. Determination of Minimum inhibitory and minimum bactericidal concentrations against *E. coli*.

Results and discussion

Chemistry & Spectral characterization of the compounds

In this study, some 2,4-diphenyl-5-imino- Δ^2 -1,3,4-thiadiazole derivatives were synthesized compounds (3a-h). All derivatives were prepared in moderate to good yield (38%-76%). The rate of reaction is affected by the solvent used because of the varying abilities of solvents to solvate reagents and transition state. Solvation refers to specific interactions between solvent molecules and dissolved reagents and or transition state. These interactions are hydrogen bonding, dipole-dipole and ion-dipole interactions. Hence the products formed and the rate of reaction is however affected by the solvent used. The target compounds were synthesized by reaction of substituted benzoyl chloride with phenyl hydrazine derivative in the presence of pyridine and methanol to obtain substituted hydrazonoyl (1a-h). Chlorination of hydrazonoyl yields substituted α -chlorobenzal phenylhydrazone derivatives (2a-h) and then reaction with potassium thiocyanate yields compounds (3a-h). All derivatives were prepared in moderate to good yield (38%-76%). The rate of reaction is affected by the solvent used because of the varying abilities of solvents to solvate reagents and transition state. Solvation refers to specific interactions between solvent molecules and dissolved reagents and or transition state. These interactions are hydrogen bonding, dipole-dipole and ion-dipole interactions. Hence the products formed and the rate of reaction is however affected by the solvent used. The compounds were characterized on the basis of IR, ^1H NMR spectral data and elemental analysis and physical characteristic data. IR spectrum showed the characteristics bonds at 670, 1600 and 3400 cm^{-1} for -C-S-C-, -C=N-, and NH (imino) groups. The ^1H NMR spectrum showed the multiplet signal at 6.8-8.0, for aryl hydrogen's and singlet at 8.0-9.0 for amino NH at C-5 position of the ring.

Antimicrobial assessment

All the compounds were evaluated for antimicrobial activity. After the careful perusal from table1. All the synthetic derivatives of thiadiazole (3a-3h) were showing inhibitory potential at different concentration levels. In the case of *Staphylococcus aureus* at the higher concentration level, 5a were showing maximum zone of inhibition (18), similarly 5b and 5f derivatives were also showing the remarkable potential data, clearly indicating that responses dose dependent. In case of 3h, 3d, 3e and 5g were showed the moderate inhibition. Antimicrobial activity against *Escherichia coli* at the higher concentration level 3a, 3c were showing maximum zone of inhibition (14), similarly 5b and 5h derivatives were also showing the remarkable potential data clearly indicating that response is dose dependent. In case of 3g, 3d, 3e and 3f were showed the moderate inhibition. All the derivatives were showing inhibitory potential against tested micro organisms.

Among all the different synthetic thiadiazole derivatives, revealed remarkable effect on bacteria like *Pseudomonas aroginosa* (17mm 3b, 3c), *Staphylococcus aureus* (18mm 3a), *Bacillus cereus* (17mm 3g) & *Escherichia coli* (14mm 3a, 3c) respectively in terms of zone of inhibition (Table-1). The MIC and MBC of thiadiazole derivatives was found between the range 6.25 and 12.5 mg/mL compared (Graph-1). Results revealed that synthesized thiadiazole derivatives exerted inhibitory effects against certain pathogenic bacteria associated with severe infections

justify the reasoning behind the use of these thiadiazoles against bacterial diseases. Further research is expected to boost the use of thiadiazole in the nearby future against bacterial infections.

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