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Review Article

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The Study of Chemical and Biological Behaviour of Novel 2-Ammino-5-(Substituted)-1,3,4-Thiadiazole

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ABSTRACT

Due to biological and pharmacological properties, heterocyclic compounds and their derivatives have attracted strong interest in medicinal chemistry. The series of 2amino-5-(substituted phenyl)-1,3,4-thiadiazole was prepared in the laboratory via $POCl_3$-promoted cyclization reaction, and it is characterized by UV, FT-IR, and 1HNMR. Thiadiazoles have a heterocyclic nucleus that contains a five-member ring and nitrogen & sulfur. Thiadiazoleheterocyclic nucleus is an important class for new biologically active drug development. Thiadiazoles have unique chemical properties and biological characteristics. Thiadiazole & its derivatives have shown several pharmacological activities as antimicrobial, anti-inflammatory activity, antitubercular activity, antidiabetic activity, diuretic, antidepressant, and cytotoxic activity. Thiadiazole shows high energy against E. coli, gram-negative bacteria. It shows good antifungal activity against Aspergillus and Candida. However, the wide range of therapeutic values of 1,3,4-thiadiazole has encouraged us to do advanced research on it. This article is a review of the series of 2-amino-5-(substituted phenyl)-1,3,4thiadiazole.

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Keywords: Thiadiazole, Heterocyclic Compound, Anti-Microbial, Anti-Inflammatory, Anti Tubercular, Antidiabetic, Antidepressant

Introduction

Thiadiazole is a heterocyclic compound featuring two nitrogen atoms and one sulfur atom as part of the aromatic five-membered ring. Thiadiazole and related compounds are called 1, 3,4-thiadiazole (two nitrogen and one other hetero atom in a five-membered ring). The other four isomeric forms of thiadiazole occur in nature as 1,2,3-thiadiazole, 1,2,5-thiadiazole, and 1,2,4-thiadiazole. 1,3,4-thiadiazoles are important compounds in medicine. 1,3,4Thiadiazoles and some of their derivatives are extensively studied because of their broad spectrum of pharmacological activities. The literature review showed that the thiadiazole nuclei have anticonvulsant activity, antimicrobial, anti-inflammatory, anticancer, antitubercular, antifungal, etc [1-4].

Review

Preparation of 2-Amino-5-(Substituted Phenyl) 1, 3, 4-Thiadiazole The commercially purchased reagents and solvents of analytical grade were used without any purification.2- Amino-5-(substituted phenyl)-1,3,4-thiadiazole was prepared by alkanoylation of thiosemicarbazide followed by dehydration in the laboratory [5-7]. The reaction progress was screened by thin-layer chromatography (TLC). The molecular structure of the derived moiety is shown in Figure 1.

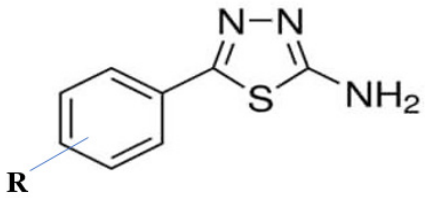


Figure 1: 2-Ammino-5(Substituted Phenyl)1,3,4-Thiadiazole

Synthesis of 2-Amino-5-(Substituted Phenyl)-1, 3, 4-Thiadiazole

A mixture of appropriate substituted benzoic acid (0.01mol) and (0.91g,0.01 mol) of thiosemicarbazide with 5mL of phosphorus oxychloride was refluxed gently for 5 h. After cooling, 50mL of water was added, and the mixture was then refluxed for 7h and filtered, neutralized with potassium hydroxide. The precipitate was washed with water and recrystallized from (ethanol-water) to give the titled compounds.

Experimental Part

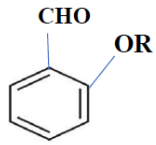
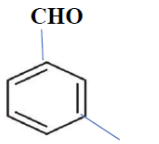
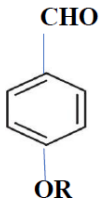
Melting points were determined using an electro-thermal melting point apparatus, and sonication was applied by using an ultrasonic cleaner Buehler Ltd, 50/60Hz). IR spectra were recorded on a Bio-Rad Merlin FT-IR spectroscopy Mod FTS 3000 using a KBr disc of 12 mm in diameter from each compound and were made by the pressing method (PyeUnicam, England) at the Department of Chemistry, College of Science. On Bruker 300MHz with TMS, 1H-NMR spectra were recorded as an internal reference, and the elemental analysis was obtained using Carlo Erba 1106in Al-Bayt

central lab (Jordan)I 1H-NMR spectra were recorded.

Experimental Procedure by Sonication Route for the Preparation of: A: Starting Material, Benzyloxy Benzaldehydes(1a-1c) (Sybo et al,2007)

In a 50ml round bottom flask a mixture of 0.015mol of benzyl bromide 0.01mole, (1m) hydroxyl benzaldehyde, and then 0.03mol, 4.2g anhydrous potassium carbonate in 40ml Absolute ethanol was placed, then submerged in the sonic bath at room temperature for 40, 54, and 15min for (1a-1c) respectively until the starting materials have been reacted through the applying TLC, after cooling, it was poured into water, the obtained crystals were separated by filtration then rinsed with cold ethanol. The products were recrystallized with ethanol to obtain white crystals of benzyloxy benzaldehyde(1a-1c) Table 1).

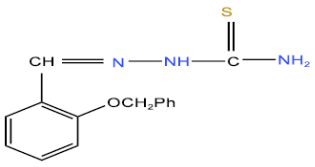
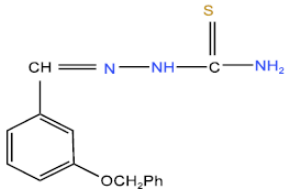
Table 1: Yield Percentage, M.P., and Reaction Time of Compounds(1a-1c)

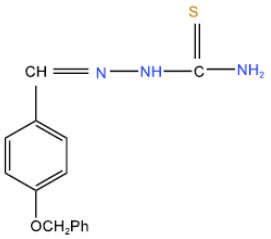
Compound	M.P.°C	Time min	Yield %
 1a	49-51	40	89
 1b	42-44	54	73
 1c	72-73	15	82

B: Intermediate Compounds Thiosemicarbazone(2a-2c) (Syboetal,2007)

The reaction was carried out between (0.01) mol for each of the compound (1a1c)with (0.01) mol thiosemicarbazidein the presence of 4 drops glacial acetic acid in75 ml ethanol, after sonication of an appropriate time, the resulting precipitates were produced during cooling, the compounds (2a-2c) were isolated by suction filtration after washing with water and ethanol, then recrystallized from the ethanol and dried [8].The reaction time, melting point, and yield percentage of semicarbazonee intermediate(2a-2c) are shown in Table (2).

Table 2: Yield Percentage, M.P. and Reaction Time of Compounds(2a-2c)

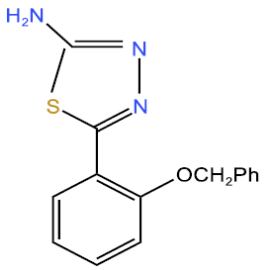
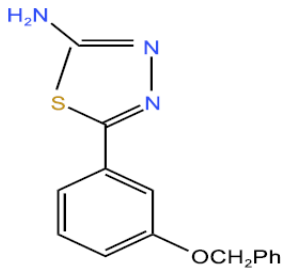
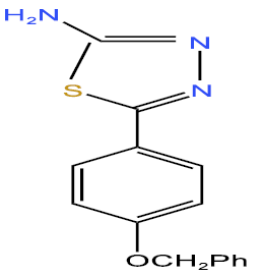
Compound	M.P.°C	Time min	Yield%
 2a	92-94	48	80
 2b	118-119	34	87

 2c	144-146	27	92

C: 2-Amino-1,3,4-Thiadiazolederivatives(3a-3c) (Syboetal,2007)

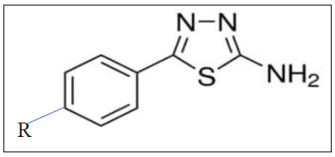
0.002molofeachcompound(2a-2c) with 0.002 mol,1g Iron (III) ammonium sulfate. $12H_2O$ was dissolved in 20 ml of distilled water, then sonicated for 1h, above amount of Fe (III) $NH_4(SO_4)_2.12H_2O$ was added to it with continuous sonication for a definite time. The products (3a-3c) were collected after cooling and recrystallization from ethanol in a high yield, and light yellowish, white-yellowish to corn color were obtained [9]. The M.P. and yield percent determined by their reaction time are seen in Table 3).

Table 3: Yield Percentage, M.P., and Reaction Time of Compounds (3a-3c)

Compound	M.P.°C	Time hr	Yield%	Colour
 **3a**	193-195	1.5	89	Lightyellowish
 **3b**	246-247	1.45	91	White– yellowish
 **3c**	144-146	1.0	96	Corn

3.1 Synthesis of [2-Amino 5-(4-Substituted Phenyl) Thiadiazoles] (7)

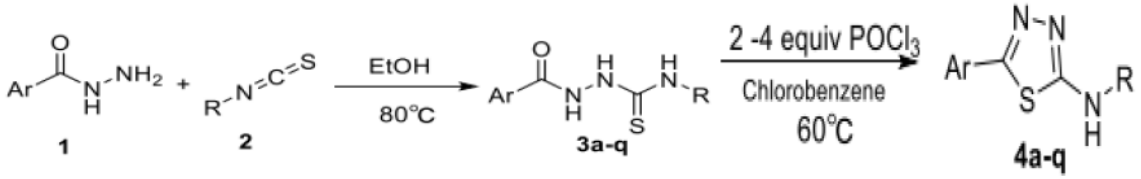
The mixture of 0.01 mole of substituted benzoic acid, 0.01mole thiosemicarbazide and 3.5ml of $POCl_3$(phosphorous oxychloride) was refluxed gently for 30 minutes, cooled to room temperature, then10 ml of water was added drop by drop and refluxed for 4 hours, cooled and the precipitate was filtered washed with 5% Na_2CO_3, H_2O recrystallized in DMSO, water. The yields, melting points, and IR data were summarized in Table 1[10].



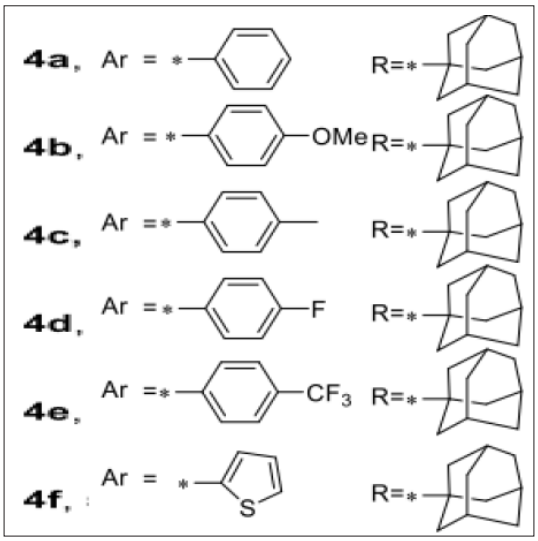
Comp.	formula	R	Yield%	M.P. °C	NH str	cyclicC=N	C=C str
7a	$C_8H_7SN_3$	4-H	40.5	174-176	3261,3108	1662	1608
7b	$C_9H_9SN_3$	4-CH_3	82	214-216	3278,3094	1634	1609
7c	$C_9H_9SN_3O$	4- OCH_3	56.5	228-230	3250,3190	1645	1612
7d	$C_{10}H_{11}SN_3O$	4-OC_2H_5	62	238-240	3240,3180	1675	1608
7e	$C_8H_6SN_4O_2$	4-NO_2	55	226-228	3430,3230	1626	1595
7f	$C_8H_6SN_4O_2$	3- NO_2	62.2	220-222	3283,3153	1614	1594
7g	$C_8H_6SN_3Cl$	4-Cl	80	180-182	3397,3273	1682	1620
7h	$C_8H_6SN_3Cl$	2-Cl	58	220-222	3340,3260	1646	1623
7i	$C_8H_6SN_3Br$	4-Br	84	231-233	3272,3128	1680	1618
7j	$C_8H_7SN_3O$	4-OH	50	232-234	3264,3067	1634	1604

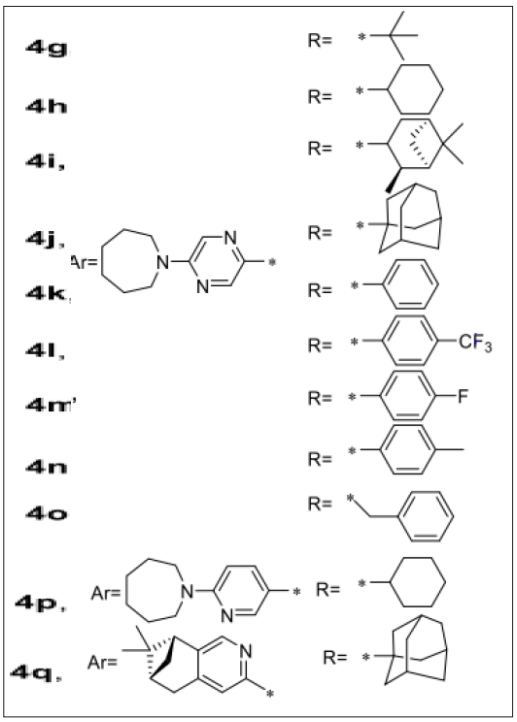
4.1 Optimized POCl3-Assisted Synthesis of 2-Amino-1,3,4-Thiadiazolederivatives

The route for the preparation of 2-amino-1,3,4-thiadiazole is illustrated in Scheme 1. The key starting acyl hydrazides 1 were purchased or prepared as per the literature, which underwent the nucleophilic addition reaction with the isothiocyanate 2 to generate the corresponding thiosemicarbazides 3a-q. The dehydrative cyclization of the thiosemicarbazide intermediates 3 occurred to provide the 1,3,4-thiadiazoles 4a-q under optimized reaction conditions, namely, stirring the thiosemicarbazide and 2-4 equivalents. $POCl_3$ in chlorobenzene at 60 °C for 2h [11]. The process of optimization conditions for the preparation of 2-amino-1,3,4-thiadiazole derivatives 4a-q was presented in detail as follows. All final products 4a-q were characterized by IR, 1H NMR, 13C NMR, and HRMS spectra. Among them, the structure of compound 4j was also further confirmed by 2D ^{1}H-^{1}H COSY and HSQC NMR spectroscopy.



Scheme 1: Synthesis of 2-Amino-1,3,4-Thiadiazole Derivatives

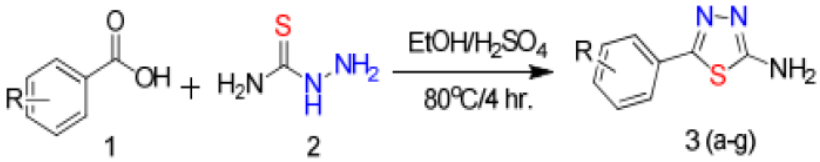




5.1 Synthetic Methods of 2-Amino-1,3,4-Thiadiazole

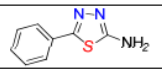
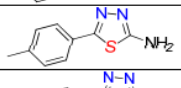
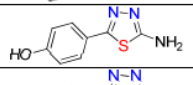
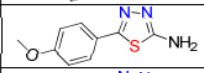
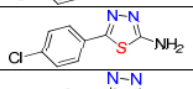
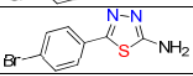
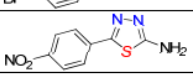
The melting points of all the compounds were determined in open-head capillary and are uncorrected. The IR spectra of the compounds were recorded in the region of 4000-400 cm-1 by using a KBr pellet on an FT-IR Perkin-Elmer spectrophotometer. H1 NMR spectra were recorded on a Bruker FT-NMR spectrophotometer with TMS as the internal standard. values of the chemical shift values are expressed in δ ppm as a unit. All the compounds were checked for purity by thin-layer chromatography (TLC).

Reaction Scheme: 1.



Reaction Scheme 1. Selection of appropriate substituted aromatic carboxylic acid for the comparative study of the synthesis of 2-amino-1, 3, 4-thiadiazole by conventional method using ethanol and catalytic conc. Sulfuric acid.

Table 5

Comp.	Structure of Product	Molecular Formula	Molecular Weight	Melting point (°C)	Yield of product	IR (KBr) cm^{-1}	Elemental Analysis Found %
3a		$C_8H_7N_3S$	177	226-231°C	77%	3403,1514, 1057,680	C= 53.22;H=2.99 ,N=22.90 S=18.01
3b		$C_9H_9N_3S$	191	218-222°C	81%	3214,1500, 1180 1054, 693,	C=56.51;H=4.75; N=21.98;S=16.71
3c		$C_8H_7N_3OS$	193	138-142°C	74%	3394,3140,1480 1449,1051,704.	C=49.71;H3.63; N=21.74; O=8.214 S=16.58
3d		$C_9H_9N_3OS$	207	192-195°C	94%	3406,1525,1402, 1053.	C=52.14;H=4.29 N=20.26;O=7.73 S=15.45
3e		$C_8H_6ClN_3S$	211	229-232°C	79%	3340,1520,1050, 678	C=45.40;H=2.84;N=19.83 S=15.14; Cl=16.74
3f		$C_8H_6BrN_3S$	256	228-231°C	90%	3350,1531,1052, 688	C=37.52;H=2.37;N=16.41 S=12.51; Br=31.19
3g		$C_8H_6N_4O_2S$	222	258-261°C	74%	3410,1512, 1022,621	C=43.23;H=2.71;N=25.19 O=14.42;S=14.43

Synthesis of 5-(4-Methoxyphenyl)-1, 3, 4-Thiadiazol-2-Amine by Conventional Method using Conc. Sulphuric Acid

An ethanolic solution of aromatic carboxylic acid (0.05mol) was added to an aqueous solution of Thiosemicarbazide (0.05mole) with constant stirring, a few drops of conc. Sulphuric acid was added and heated for 4 hours at 80-90 °C, after completion of the reaction (TLC), cooled and poured into ice-cold water, basified with 10% Na2CO3 solution, filtered, dried, and recrystallized from a suitable solvent. NMR (δ ppm) (DMSO-D6): 7.11 (2H, s), 3.96 (3H, s), 6.87-6.92 (4H, m). IR (KBr, cm-1): 3406 (NH stretching), 1525 (C-N stretch), 1053 (C-O stretch). MS: (m/z): 209, 208, 207(bp) [12].

Synthesis of 5-(4-Methoxyphenyl)-1, 3, 4-Thiadiazol-2-Amine by Conventional Method by using $POCl_3$

An equimolar amount of mixture of aromatic carboxylic acid (0.1mole) and thiosemicarbazide (0.1mole), in POCl3 (excess), was heated for half an hour, water (90ml) was added and reaction mixture was reflux for another 3 hour, on completion of reaction (TLC), cool to room temperature and poured in ice-cold water, neutralized by saturated KOH solution, filter, dried and recrystalised from suitable solvent [13].

Synthesis of 5-(4-Methoxyphenyl)-1, 3, 4-Thiadiazol-2-Amine by Conventional Method using $SOCl_2$

Aromatic carboxylic acid (0.01mole) and thionyl chloride (0.012 mole) were heated for 1 hour at 70 ^{0}C with a calcium chloride guard tube. Thiosemicarbazide (0.012mole) was added to this hot reaction mixture and heated for another 4 hours at the same temperature. On completion of reaction (TLC), basify with aqueous NaHCO3, filter, dry, and recrystallize from a suitable solvent [14].

Synthesis of 5-(4-Methoxyphenyl)-1, 3, 4-Thiadiazol-2-Amine by Microwave
Method using Conc. Sulfuric Acid

A mixture of aromatic carboxylic acid (0.05mole) and thiosemicarbazide (0.05mole) was dissolved in DMF (10ml) to this added conc. sulfuric acid (10 drops) and irradiated in a microwave oven (480 watts) for 5 minutes. On completion of reaction (TLC), pour to ice-cold water, filter, dry, and recrystallize from a suitable solvent [15].

Synthesis of 5-(4-Methoxyphenyl)-1, 3, 4-Thiadiazol-2-Amine by Microwave Method using $POCl_3$

An aromatic carboxylic acid (0.01mole), thiosemicarbazide (0.012mole), and catalytic amount of $POCl_3$ were mixed thoroughly and irradiated in microwave oven (600 Watt) for 5 minute on completion of reaction (TLC) pour to crushed ice and pH was adjust to alkaline, filter, dried and recrystalised from suitable solvent [16].

Synthesis of 5-(4-Methoxyphenyl)-1, 3, 4-Thiadiazol-2-Amine by Microwave Method using $SOCl_2$

Mixture of aromatic carboxylic acid (0.01mole) and thionyl chloride (0.012mole) was irradiated at 300 watt for 1 minutes, upon cooling thiosemicarbazide (0.012 mole) was added and irradiated (480 watt) for 3 minute, on completion of reaction (TLC) poured to ice cold water, filter, dried and recrystalised from suitable solvent [17].

Synthesis of 5-(4-Methoxyphenyl)-1, 3, 4-Thiadiazol-2-Amine by Microwave Method using $MgSO_4$ as a Catalyst

Mixture of aromatic carboxylic acid (0.01mole) and thiosemicarbazide (0.01mole) was irradiated in the presence of magnesium sulphate (2 g) for 5 minutes (250 watts) (TLC), poured into ice-cold water neutralized by sodium carbonate solution. Obtained solid was filtered, dried, and recrystallized from a suitable solvent [18].

Synthesis of 5-(4-Methoxyphenyl)-1, 3, 4-Thiadiazol-2-amine neat Reaction Condition

Mixture of aromatic carboxylic acid (0.1mole) and Thiosemicarbazide (0.1mole) was heated under solvent-free conditions for 3 hours, then the reaction mixture was cooled at room temperature. Water was added, filters, dried and recrystallized from a suitable solvent [19].

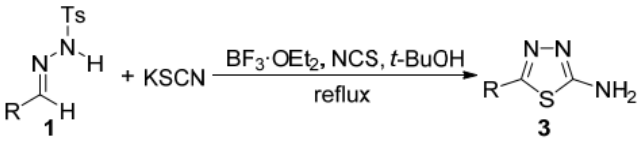
Synthesis of 5-(4-Methoxyphenyl)-1, 3, 4-Thiadiazol-2-Amine by Ultrasonic Irradiation

The equimolar quantity of aromatic carboxylic acid (0.1 mol), thiosemicarbazide (0.1 mol) in 15ml of ethanol was added conc. Sulphuric acid (10 drops) and the reaction mixture were subjected to Ultrasonic irradiation for 30 minutes at 80 °C. On completion of the reaction (TLC) solid obtained was poured into ice-cold water, filtered, dried, and recrystallized from a suitable solvent [20].

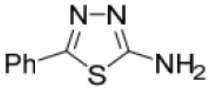
Synthesis of 5-(4-Methoxyphenyl)-1, 3, 4-Thiadiazol-2-Amine by Simple Grinding Method

Aromatic carboxylic acid (0.01mole), Thiosemicarbazide (0.01 mole), and a catalytic amount of H2SO4, grind in a mortar and pestle for one and a half hours, then stand at room temperature for another 4 hours with occasional grinding. On completion of reaction (TLC) cold water was added, basified with sodium hydroxide (10%), obtained solid was filtered, dried and recrystalised from suitable solvent.

General Procedure for the Synthesis of 1,3,4-Thiadiazol-2-Amines 3a-3k [21-28].

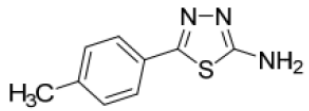


Under an argon atmosphere, a mixture of N-tosylhydrazones 1 (0.2 mmol), KSCN (0.4 mmol), NCS (0.4 mmol), and BF3·OEt2 (0.1 mmol) in t-BuOH (3 mL). The reaction mixture was heated in an oil bath and stirred at reflux temperature for 0.5-4 hours. After quenching with water, the product was extracted with ethyl acetate, and the organic layer was washed with saturated Na_2CO_3 solution and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel afforded the products 3.



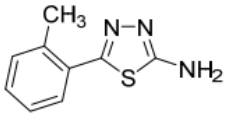
3a

3a was prepared according to the general procedure and purified by chromatography on silica gel using petroleum ether/ethyl acetate (petroleum ether/ethyl acetate = 1:1) as eluent as a white solid (15.5 mg, 87% yield). The spectral data is in agreement with the literature values.2a 1 H NMR (400 MHz, DMSO-d6) δ = 7.72-7.70 (m, 2H), 7.457.37 (m, 5H); 13C NMR (100 MHz, DMSO-d6) δ = 168.5, 156.4, 131.0, 129.6, 129.1, 126.3 ppm.



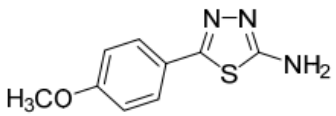
3b

3b was prepared according to the general procedure and purified by chromatography on silica gel using petroleum ether/ethyl acetate (petroleum ether/ethyl acetate = 1:1) as eluent as a white solid (31.0 mg, 81% yield). The spectral data is in agreement with the literature values.2a 1 H NMR (400 MHz, DMSO-d6) δ = 7.66-7.63 (m, 2H), 7.40 (brs, 2H), 7.28 (d, J = 8.0 Hz, 2H), 2.34 (s, 3H); 13C NMR (100 MHz, DMSO-d6) δ = 168.2, 156.5, 139.3, 129.7, 128.3, 126.3, 20.9 ppm.



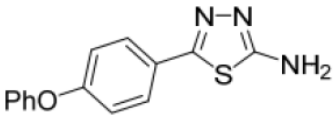
3c

3c was prepared according to the general procedure and purified by chromatography on silica gel using petroleum ether/ethyl acetate (petroleum ether/ethyl acetate = 1:1) as eluent as a white solid (23.4 mg, 61% yield). The spectral data is in agreement with the literature values.2b 1 H NMR (400 MHz, DMSO-d6) δ = 7.53 (d, J = 7.2 Hz, 1H), 7.40-7.27 (m, 5H), 2.48 (s, 3H); 13C NMR (100 MHz, DMSO-d6) δ = 168.8, 155.7, 135.9, 131.4, 130.0, 129.8, 129.1, 126.3, 21.2 ppm.



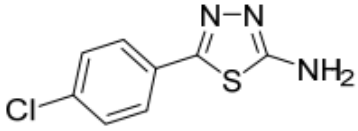
3d

3d was prepared according to the general procedure and purified by chromatography on silica gel using petroleum ether/ethyl acetate (petroleum ether/ethyl acetate = 1:1) as eluent as a white solid (20.3 mg, 49% yield). The spectral data is in agreement with the literature values.2b 1 H NMR (400 MHz, DMSO-d6) δ = 7.69 (dd, J = 6.8, 2.0 Hz, 2H), 7.32 (brs, 2H), 7.03 (dd, J = 6.8, 2.0 Hz, 2H), 3.81 (s, 3H); 13C NMR (100 MHz, DMSO-d6) δ = 167.9, 160.3, 156.3, 127.8, 123.6, 114.5, 55.3 ppm.



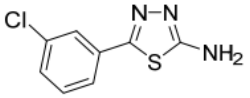
3e

3e was prepared according to the general procedure and purified by chromatography on silica gel using petroleum ether/ethyl acetate (petroleum ether/ethyl acetate = 1:1) as eluent as a white solid (32.9 mg, 61% yield). 1 H NMR (400 MHz, DMSO-d6) δ = 7.79-7.76 (m, 2H), 7.47-7.41 (m, 4H), 7.21 (dd, J = 7.6, 7.6 Hz, 1H), 7.11-7.05 (m, 4H); 13C NMR (100 MHz, DMSO-d6) δ = 168.3, 158.0, 155.8, 130.2, 128.2, 126.1, 124.1, 119.3, 118.6 ppm; HRMS (ESI) m/z: [M + Na]+Calcd for C14H11N3OSNa 292.0515; Found 292.0509.



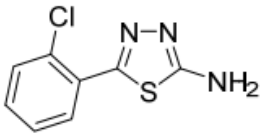
3f

3f was prepared according to the general procedure and purified by chromatography on silica gel using petroleum ether/ethyl acetate (petroleum ether/ethyl acetate = 1:1) as eluent as a white solid (29.6 mg, 70% yield). The spectral data is in agreement with the literature values.2b 1 H NMR (400MHz, DMSO-d6) δ = 7.80-7.77 (m, 2H), 7.557.51 (m, 4H); 13C NMR (100 MHz, DMSO-d6) δ = 168.9, 155.1, 134.0, 129.8, 129.2, 127.9 ppm.



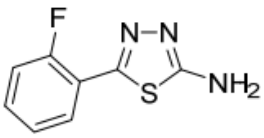
3g

3g was prepared according to the general procedure and purified by chromatography on silica gel using petroleum ether/ethyl acetate (petroleum ether/ethyl acetate = 1:1) as eluent as a white solid (27.1 mg, 64% yield). The spectral data is in agreement with the literature values.2b 1 H NMR (400MHz, DMSO-d6) δ = 7.81 (dd, J = 2.0, 1.2 Hz 1H), 7.73-7.69 (m, 1H), 7.56 (brs, 2H), 7.53-7.48 (m, 2H); 13C NMR (100 MHz, DMSO-d6) δ = 169.1, 154.7, 133.8, 132.9, 131.1, 129.3, 125.4, 125.1 ppm



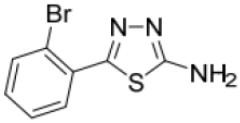
3h

3h was prepared according to the general procedure and purified by chromatography on silica gel using petroleum ether/ethyl acetate (petroleum ether/ethyl acetate = 1:1) as eluent as a white solid (35.1 mg, 83% yield). The spectral data is in agreement with the literature values.2b 1 H NMR (400MHz, DMSO-d6) δ = 8.02-7.99 (m, 1H), 7.637.60 (m, 1H), 7.50-7.46 (m, 4H); 13C NMR (100 MHz, DMSO-d6) δ = 170.1, 151.6, 131.0, 130.5, 130.4, 130.3, 129.6, 127.7 ppm.



3i

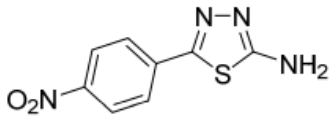
3i was prepared according to the general procedure and purified by chromatography on silica gel using petroleum ether/ethyl acetate (petroleum ether/ethyl acetate = 1:1) as eluent as a white solid (19.9 mg, 51% yield). The spectral data is in agreement with the literature values.2b 1 H NMR (400 MHz, DMSO-d6) δ = 8.12-8.08 (m, 1H), 7.547.49 (m, 3H), 7.42-7.32 (m, 2H); 13C NMR (100 MHz, DMSO-d6) δ = 170.0, 159.1, 156.6, 148.5, 131.4, 131.3, 127.7, 125.19, 125.16, 118.8, 118.6, 116.5, 116.2 ppm.



3j

3j was prepared according to the general procedure and purified by chromatography on silica gel using petroleum ether/ethyl acetate (petroleum ether/ethyl acetate = 1:1) as eluent as a white solid (29.2 mg, 57% yield). The spectral data is in agreement with the literature values.2b 1 H NMR (400 MHz, DMSO-d6) δ = 7.88 (dd, J = 8.0, 1.2 Hz, 1H), 7.78 (dd, J = 8.0, 1.2 Hz, 1H), 7.53-7.38 (m, 4H); 13C NMR (100 MHz, DMSOd6) δ = 170.0,

153.1, 133.8, 131.6, 131.2, 128.1, 120.9 ppm.



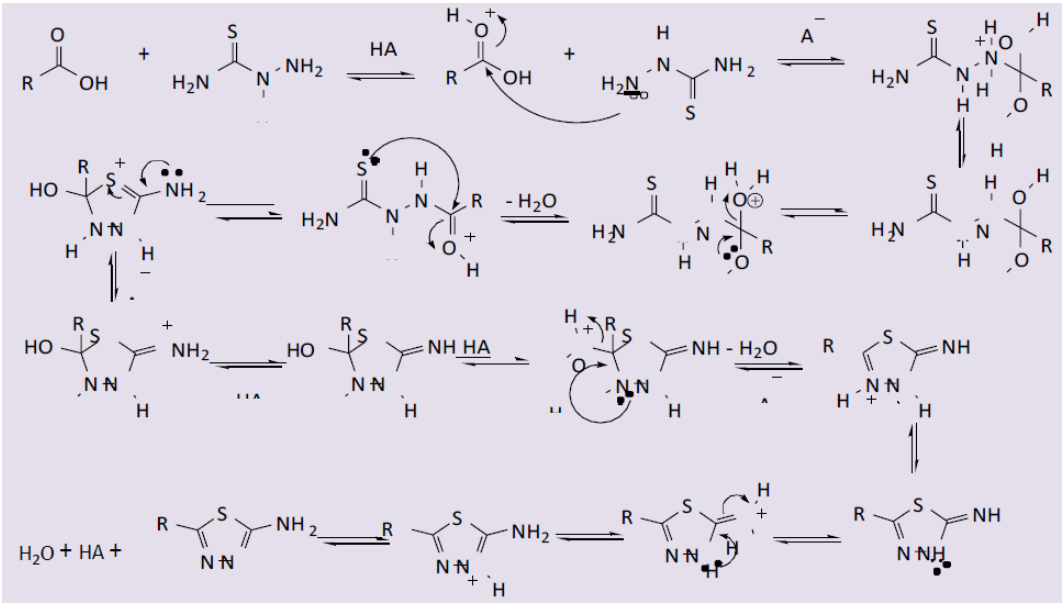
3k

3k was prepared according to the general procedure and purified by chromatography on silica gel using petroleum ether/ethyl acetate (petroleum ether/ethyl acetate = 1:2) as eluent as a yellow solid (30.2 mg, 68% yield). The spectral data is in agreement with the literature values.2b 1 H NMR (400 MHz, DMSO-d6) δ = 8.28 (d, J = 8.8 Hz, 2H), 8.01 (d, J = 9.2 Hz, 2H), 7.75 (brs, 2H); 13C NMR (100 MHz, DMSO-d6) δ = 170.0, 154.1, 147.4, 136.8, 127.1, 124.4 ppm.

Procedure for Synthesize of 3a on Large-scale. Under an argon atmosphere, a mixture of N-tosyl hydrazones 1a (100 mmol), KSCN (200 mmol), NCS (200 mmol), and BF3·OEt2 (50 mmol) in t-BuOH (250 mL). The reaction mixture was heated in an oil bath and stirred at reflux temperature for 3 hours. After quenching by water, the product was extracted with ethyl acetate and the organic layer was washed with saturated Na_2CO_3 solution and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by recrystallization from n-hexane and EtOAc afforded product 3a (10.8 g) in 61% yield.

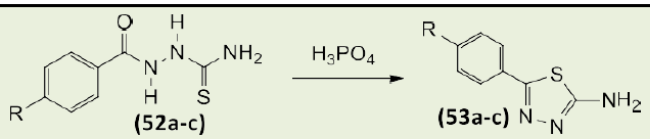
Syntheses of 1,3,4-Thiadiazoles from Thiosemicarbazides

Many syntheses of 1,3,4-thiadiazoles proceed from thiosemicarbazide cyclization, which has been widely used and is efficient in the formation of thiadiazoles. This reaction occurs according to the mechanism presented in Scheme 12 [29]. The proposed mechanism starts with a nucleophilic attack of the nitrogen electron pair of thiosemicarbazide to the carboxylic acid sp^2 carbon, followed by dehydration of the intermediate. The sulfur atom electron pair attacks the carbonyl, causing cyclization, and the intermediate formed is then dehydrated. Finally, an electron migration produces the aromatic heterocycle.



The procedure performed by Hoggarth (1949) involved the treatment of thiosemicarbazide derivatives (52a-c) with phosphoric acid to form the thiadiazoles (53a-c) with yields of 3050 % (Table 6) [30].

Table 1. Synthesis of thiadiazoles from the cyclization of thiosemicarbazide derivatives



Compound (**53**)	R	Yields (%)
a	H	40
b	-OCH_3	30
c	Cl	50

2-Amino-1,3,4-thiadiazole as a potential scaffold for promising antimicrobial agents:Antimicrobial activities associated with 2-amino-1,3,4-thiadiazole system

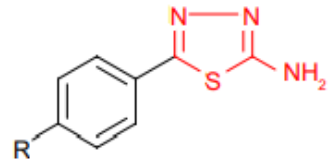
Pathogenic microorganisms are causative agents for different types of diseases such as upper and lower respiratory tract infections, typhoid fever, gastrointestinal infections, gynecological infections, sexually transmitted diseases, urinary tract infections, bacterial meningitis, osteomyelitis and malaria, and also for severe diseases such as tuberculosis, influenza, syphilis and acquired immunodeficiency syndrome (AIDS). Taking into account thatmillions of people affected by infectious diseases and cause many deaths worldwide, it can be said that anti-infective agents have saved more lives than other classes of drugs [31].

Antibacterial and Antifungal Activities

Antimicrobial Chemotherapy is the way to combat infections through the pharmacological effects of the drugs used. Antimicrobial agents have specific toxic action on pathogenic organisms. Since the introduction of the first antibiotic (penicillin, 1942) into medical practice, there has been an ongoing race between scientists and pathogenic bacteria. 56 In the struggle for existence, the microorganisms constantly adapt by selecting higher invasive and more resistant strains. Despite a large number of antibiotics and chemotherapeutics available for medical use, bacterial infections have dramatically increased due to bacterial resistance to antimicrobial drugs. On the other hand, the spread of HIV infection combined with the increased use of powerful immunosuppressive drugs for cancer therapy and organ transplants led to an increased incidence of fungal infections among immunocompromised patients. Although most fungal infections were superficial in the past, the incidence of systemic fungal infections has currently increased [31,33]. The gravity of bacterial and fungal infections became a major worldwide problem, and the World Health Organization chose antimicrobial resistance as the theme of the 2011 World Health Day. Due to the occurrence of bacterial resistance (eg, MRSA is resistant to many antibiotics), researchers are in a continuous effort to counteract infections by synthesizing new effective antibacterial and antifungal agents [32,34-36].

The thiazole ring acts as a pharmacophore. It is a bioisostere of the thiazole ring included in the third- and fourth-generation cephalosporins, and this observation makes it possible to use it in the synthesis of antimicrobial agents [37].

Upadhyay and Mishra synthesized the 5-(4-substituted phenyl)-1,3,4thiadiazol-2-amine derivatives 8 and performed in vitro antibacterial activity against S [38]. aureus, Bacillus subtilis, Escherichia coli, and Pseudomonas aeruginosa and antifungal activity against Aspergillus niger and Candida albicans by the disk diffusion technique. Fluorinated and chlorinated compounds 8a and 8b showed good inhibitory effects (inhibition between 81% and 91%) with Minimum Inhibitory Concentration (MIC) values of 20–28μg/mL (controlled to ciprofloxacin, MIC =18–20 μg/mL) for S. aureus and B. subtilis. In addition, halogenated compounds 8a-c and hydroxyl derivative 8d showed moderate inhibitory effects (inhibition between 58% and 79%) with MIC values of 24–40 μg/mL (controlled to ciprofloxacin, MIC =20–24 μg/mL) for E. coli and P. aeruginosa. Significant antifungal activity against A. niger and C. Albicans was exhibited by derivatives 8d and 8e bearing oxygenated substituents at the phenyl ring (inhibition between 58% and 66% and MIC =32–42 μg/mL compared to fluconazole, MIC =24–26 μg/mL). It appears that the halogen attached to the phenyl-1,3,4-thiadiazol moieties increases the antibacterial activity with a preference against Gram-positive bacteria, while the oxygenated substituents impart antifungal activity.



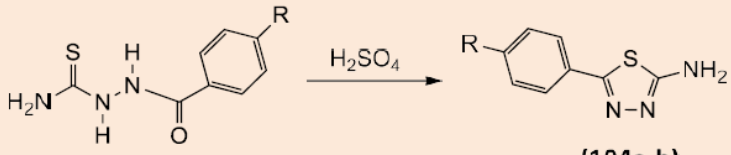
R = F (a); Cl (b); Br (c);
OH (d); OCH_3 (e)

8

1,3,4-Thiadiazoles: Microbiological Activities

Upadhyay and Mishra (2017) performed microbial studies of 1,3,4-thiadiazoles(104a-h) by the disc diffusion technique and minimum inhibitory concentration (MIC) [39]. The compounds were tested against Gram-negative bacteria, *Escherichia coli, Bacillus subtilis*, and *Pseudomonas aeruginosa*, Gram-positive bacteria, Staphylococcus aureus, and the fungi *Aspergillus niger* and *Candida albicans*. Ciprofloxacin and fluconazole were used as standards for antibacterial and antifungal studies, and the results are summarized in Tables 7 and 8 [39].

Table 7: Data for Antimicrobial Activity of Compounds (104a-h)



(104a-h)

Compound (**104**)	R	%inhibition					
		Antibacterial activity				Antifungal activity	
		S. aureus	*B. substilis*	*E. coli*	*P. aeruginosa*	*A. niger*	*C. albicans*
a	F	90.9	85.4	79.1	70.5	51.1	51.2
b	Cl	85.1	81.5	75.4	67.2	43.6	49.6
c	Br	70.3	71.5	66.4	59.9	51.9	49.6
d	I	62.8	63.8	52.3	54.1	44.3	46.3
e	CH_3	45.5	44.6	41.8	45.9	52.6	56.1
f	OH	57.0	54.6	60.5	58.2	58.6	65.9
g	OCH_3	56.2	53.1	47.0	53.3	57.9	65.0
Ciprofloxacin[a]		100	100	100	100	NT	NT
Fluconazole[a]		NT	NT	NT	NT	100	100

concentration - 20 µg/mL; NT = not tested

Results presented in Table 7 showed that 104a and 104b presented a high degree of activity against *Staphylococcus aureus* and *Bacillus subtilis* (inhibitionbetween80%and 91%), which are close to the standard drugs. The compounds 104a, 104b, 104c, and 104f showed moderate antibacterial activity when compared to ciprofloxacin against *Escherichia coli* and *Pseudomonas aeruginosa* (59 % to 80%). Compounds 104e and 104 g exhibited mild inhibitory activity [39].

The study showed that 104a (4 fluorophenylon C-5ofthiadiazole nucleus) produced the highest antimicrobial activity against all bacterial strains, while 104 b-c) activity [39]. In contrast,104f (R=4-hydroxy) and 104 g (R = 4-methoxy) showed better fungal activities when compared to results against bacteria. The antibacterial activities of compounds104e(R=methyl) and104g (R= methoxy) werethelowest [39].

Some of the compounds in the series were modified in their action against *Aspergillus niger* and *Candida albicans*. Compounds (104f-h) showed better inhibitory action (57% to 66 % inhibition), while the other compounds showed mild antifungal activities (Table 7) [39]. Table 23 shows the MIC values for the most potent compounds.

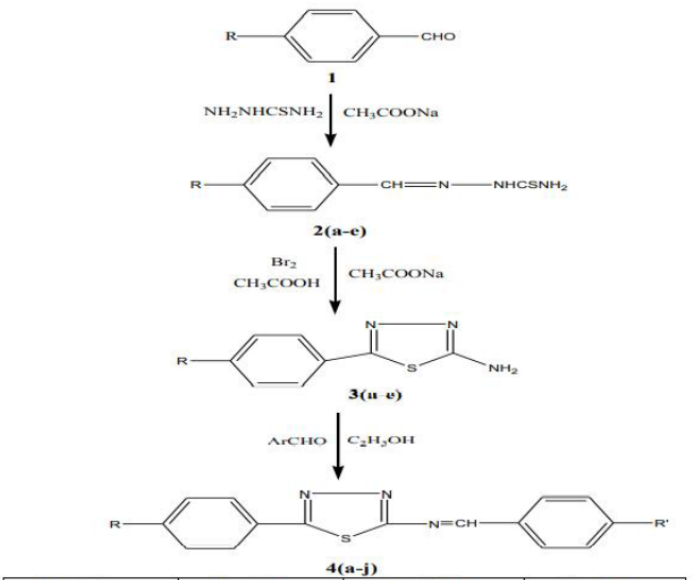
Table 8: Minimum inhibitory concentrations of the compounds with the higher percentages of inhibition reported by UP Adhyay and Mishra

Compound (**104**)	R	Minimum Inhibitory Concentrations (MICs) - µg/mL					
		Antibacterialactivity				Antifungal activity	
		S. aureus	*B. substilis*	*E. coli*	*P. aeruginosa*	*A. niger*	*C. albicans*
a	F	20	22	24	32	44	48
b	Cl	28	26	30	36	NT	NT
c	Br	34	36	38	38	NT	NT
f	OH	36	38	40	40	34	32
g	OCH_3	NT	NT	NT	NT	42	36
Ciprofloxacin		18	20	20	24	NT	NT
Fluconazole		NT	NT	NT	NT	26	24

NT = not tested

Synthesis of 2-Amino-5-aryl-1,3,4- Thiadiazole& Its Derivatives and Study of Analgesic, Anti-Inflammatory and Anti-Bacterial Activity [40-54].

Against a panel of 3 cell lines i.e., lung, breast, and CNS cancer the derivatives of 1,3,4-thiadiazoles are active. They also showed good cytotoxicity against SI leukemia and SF268 CNS cancer. 2-5-Dimercapto-1,3,4-thiadiazoles such as corrosion inhibition,vulcanization acceleration, prevention of sunburn, and darkening of photographic developers are recorded in the patient literature. The derivatives of 1,3,4-thiadiazoles were tested for their cytotoxic potential using A549 (lung adenocarcinoma) cells in the presence of fetal bovine serum. 1,3,4-thiadiazoles also show mild antihistaminic activity. In the control of fluid secretion (glaucoma)N[5-(aminosulphonyl)-1,3,4-thiadiazole- 2-yl] acetamide is effective, in the treatment of the convulsive disorder (epilepsy) and in the promotion of diuresis in the instances of abnormal fluid retention (cardiac edema). In view of the above-mentioned fact, we synthesized biologically important heterocyclic compounds. We are describing the synthesis of Schiff bases of 1,3,4-thiadiazoles derivatives and evaluating its analgesic, anti-inflammatory, and antibacterial activity. Their synthesis is outlined in scheme 1. On the basis of their IR and 1H NMR spectral data, the structures of the compounds were established.



R = OCH_3	R' = OH	R = OCH_3	R' = NO_2
R = OH	R' = OH	R = OH	R' = NO_2
R = Cl	R' = OH	R = Cl	R' = NO_2
R = NO_2	R' = OH	R = NO_2	R' = NO_2
R = $N(CH_3)_2$	R' = OH	R = $N(CH_3)_2$	R' = NO_2

Experimental

In open capillary tubes, melting points were determined. By TLC (Thin layer Chromatography) on silica gel plates the purity of the compounds was checked and spots were visualized by exposure to iodine vapors. On Perkins Elmer Infrared-283 FTIRIR spectra (KBr, cm-1) were recorded. 1H NMR ($CDCl_3$) on a Bruker 300MHz spectrometer using TMS as an internal reference (chemical shift in δ ppm). The physical data of the compounds prepared are presented in Table 1. In Table 1.

Table 1. Characterization data of Compounds

Comp.	R	R'	Mol. Formula	M.P. (°C)	Yield %	N % Found	S % Found
4A	OCH_3	OH	$C_{16}H_{16}N_3O_2S$	155	62 %	13.37	10.19
4B	OH	OH	$C_{15}H_{14}N_3O_2S$	214	58 %	14	10.66
4C	Cl	OH	$C_{15}H_{13}N_3OSCl$	188	45 %	13.20	10.06
4D	NO_2	OH	$C_{15}H_{13}N_4O_3S$	170	48 %	17.02	9.72
4E	$N(CH_3)_2$	OH	$C_{17}H_{19}N_4OS$	185	51 %	17.12	9.78
4F	OCH_3	NO_2	$C_{16}H_{15}N_4O_3S$	138	54 %	16.32	9.32
4G	OH	NO_2	$C_{15}H_{13}N_4O_3S$	194	38 %	17.02	9.72
4H	Cl	NO_2	$C_{15}H_{12}N_4O_2SCl$	205	43 %	16.13	9.22
4I	NO_2	NO_2	$C_{15}H_{12}N_5O_4S$	148	54 %	19.55	8.93
4J	$N(CH_3)_2$	NO_2	$C_{17}H_{18}N_5O_2S$	197	36 %	19.66	8.98

Synthesis of Thiosemicarbazone 2(a)

In RB, thiosemicarbazide (0.01м m) and Crystalline sodium acetate (0.02 м) were taken,8-10 ml of water and 0.5 g of aldehyde were added slowly with continuous stirring. The mixture was turbid, so I added methanol until a clear solution was obtained, shaking the mixture for a few minutes and allowing it to stand. Thiosemicarbazone precipitated from the cold solution. Filter off the precipitate and recrystallize with ethanol. 2a IR (KBr) 3290(C-H), 1157(C-C),1691(C=N), 1249 (C=S), 3070.78 (N-H). 2a 1H NMR (CDCl3), □ 6.8-7.5 (m, 4H, Ar-H), □ 3.73(t, 3H of OCH3), □ 5.0 (s, 1H of OH), □ 2.85 (t, 3H of CH3), □ 2.0(t, 2H, NH2). Other compounds 2(a-e) were prepared similarly and their characterization data are recorded in Table 1

Synthesis of 2-Amino-5-aryl-1, 3, 4-Thiadiazole 3(a)

Thiosemicarbazone 2a (0.01 м) and Sodium acetate (0.02 м) were dissolved in 30-40 ml of glacial acetic acid taken in a roundbottom flask equipped with a separating funnel for the addition of bromine. Bromine (0.7 ml in 5 ml of glacial acetic acid) was added slowly to it while stirring magnetically. After half an hour of stirring, the solution was poured on crushed ice. The resulting solid was separated, dried, and recrystallized from ethanol. 3a IR (KBr) 3201(C-H), 1170(C-C), 1624(C=N), 1567(N=C), 949(C-S), 3385(O-H), 1096(C-O), 1674(N=O). 3a 1H NMR (CDCl3), □ 6.797.31(m, 4H, Ar-H), □ 4.0(t, 2H, NH2), □ 5.0 (s, 1H, OH). Other compounds 3(a-e) were prepared similarly, and their characterization data are recorded in Table 1.

Synthesis of Schiff bases of 2-Amino-5-aryl-1, 3, 4-Thiadiazole 4(a)

A solution of 3a (0.01 м) was prepared in 20 mL of alcohol in a round-bottom flask. The required aldehyde (0.01 м) dissolved in 15 ml of alcohol was then added to it. The mixture was refluxed for 5-6 hr. By distillation, under reduced pressure, the volume of alcohol was reduced to half. The resulting solution was poured on crushed ice. The precipitate, which had been separated, was dried and recrystallized from ethanol. 4a IR (KBr) 3385(C-H), 1157(C-C), 1691(C=N), 1567(N=C), 949 (C-S), 3201(O-H), 1096(C-O), 1674(N=O). 4a 1H NMR (CDCl3), □ 6.83-7.37(m, 4H, Ar-H), □ 6.8-7.4 (m, 4H, C6H5CH=N), □ 5.0 (s, 1H, OH), □ 8.1(s, 1H, C6H5CH=N), □ 3.73 (t, 3H, OCH3). Other compounds 4(a-j) were prepared similarly, and their characterization data are recorded in Table 1.

Antimicrobial Activity

The synthesized compounds were evaluated for their antibacterial activity against bacterial strains S. aureus (Gram +ve) and E. coli (Gram -ve) by cup plate diffusion method at 1000, 500, and 250 µg/mL concentrations. Ofloxacin was used as a standard drug for

antibacterial activity. The minimal inhibitory concentration (MICs, µg/mL) of the tested compounds is recorded in Tables 2 and 3.

Table 2. Anti –Bacterial Activity of 1, 3, 4-thiadiazole derivatives against *S. aureus.*

S. No.	Comp.	*S. aureus* (+ve) Zone of inhibition (mm)			
		1000µg/ml	500µg/ml	250µg/ml	Ofloxacin (Std. drug) 1000µg/ml
1	**4a**	18	14	11	22
2	**4b**	16	13	10	20
3	**4c**	19	13	9	22
4	**4d**	18	14	11	22
5	**4e**	19	16	10	22
6	**4f**	17	15	9	21
7	**4g**	16	15	7	22
8	**4h**	16	13	7	22
9	**4i**	17	15	9	22
10	**4j**	19	15	12	21

Analgesic Activity

The synthesized compounds were evaluated for their analgesic activity in Swiss albino mice by using the hot plate method, using Pentazocine as the standard drug.

Anti-Inflammatory Activity

The synthesized compounds were evaluated for their antiinflammatory activity in Wister albino rats by the Carrageenan-induced paw edema method using Indomethacin as the standard drug.

Table 3. Anti –Bacterial Activity of 1, 3, 4-thiadiazole derivatives against *E.coli.*

S. No.	Comp.	*E. coli* (-ve) Zone of inhibition (mm)			
		1000µg/ml	500µg/ml	250µg/ml	Ofloxacin (Std. drug) 1000µg/ml
1	**4a**	16	13	9	22
2	**4b**	18	15	12	20
3	**4c**	17	13	11	22
4	**4d**	16	15	11	22
5	**4e**	17	16	10	22
6	**4f**	18	13	10	21
7	**4g**	16	15	7	22
8	**4h**	18	13	8	22
9	**4i**	17	13	9	22
10	**4j**	18	15	10	21

Table 4

Treatment Group	Dose mg/kg)	Reaction time (sec)				
		15 (min)	30 (min)	45 (min)	60 (min)	90 (min)
Control (vehicle)	10	2.0 ±0.3	2.6 ± 0.4	2.3 ± 0.2	1.7 ± 0.2	1.3 ± 0.2
Pentazocine	30	4.6 ±0.5	6.0 ± 0.3	6.3 ± 0.7	8.6 ± 0.7	10.6 ±0.2
4a	30	2.1 ±0.4	3.3 ± 0.4	4.4 ± 0.2	3.7 ± 0.8	3.9 ± 0.4
4b	30	2.2 ±0.4	3.0 ± 0.3	2.7 ± 0.2	3.4 ± 0.3	3.2 ± 1.7
4c	30	2.3 ±0.3	3.47 ±0.2	4.32 ±0.4	3.22 ±0.5	4.9 ± 0.1
4d	30	1.7 ±0.1	2.5 ± 0.4	2.67 ±0.2	3.34 ±0.4	3.90 ±0.3
4e	30	2.4 ±0.3	3.77 ±0.3	3.8 ± 0.1	3.2 ± 0.4	3.7 ± 0.2
4f	30	1.5 ±0.2	2.1 ± 0.1	1.8 ± 0.3	2.4 ± 0.5	2.3 ± 0.1
4g	30	2.5 ±0.6	2.2 ± 0.2	2.4 ± 0.5	2.7 ± 0.7	2.9 ± 0.6
4h	30	2.6 ±0.4	2.4 ± 0.3	2.8 ± 0.3	3.1 ± 0.4	2.9 ± 0.3
4i	30	2.1 ±0.3	2.6 ± 0.5	3.2 ± 0.2	3.1 ± 0.2	2.9 ± 0.4
4j	30	1.9 ±0.5	2.5 ± 0.6	2.9 ± 0.8	3.2 ± 0.1	2.7 ± 0.2

Table 5

Groups	Dosemg/kg	Paw diameter (mm)						% of inhibition
		0 hr	1hr	2hr	3hr	4hr	5hr	
Control	--	0.79±0.0423	0.925±0.0223	1.3±0.018	2.062±0.033	2.358±0.042	2.568±0.020	--
Std	10	0.810±0.014	0.978±0.012	1.10±0.011	0.978±0.014	0.952±0.011	0.951±0.06	72.55
4a	30	0.775±0.013	0.915±0.025	1.240±0.038	1.523±0.033	1.830±0.015	1.638±0.038	23
4b	30	0.801±0.012	0.925±0.014	1.095±0.022	1.19±0.09	1.395±0.013	1.330±0.042	48
4c	30	0.682±0.020	0.855±0.0150	0.922±0.011	1.252±0.034	1.401±0.038	1.502±0.042	31
4d	30	0.725±0.025	1.425±0.0485	1.655±0.032	1.757±0.089	1.548±0.0455	1.422±0.035	29
4e	30	0.621±0.032	0.952±0.0425	1.28±0.018	2.238±0.033	2.445±0.0252	2.728±0.021	14
4f	30	0.752±0.014	1.102±0.0121	1.225±0.041	1.445±0.014	1.278±0.0128	1.052±0.072	43
4g	30	0.87±0.32	1.11±0.0152	1.205±0.62	1.523±0.015	1.728±0.0128	1.875±0.045	16
4h	30	0.628±0.045	0.952±0.0548	1.221±0.035	1.542±0.012	1.667±0.0212	1.438±0.055	24
4i	30	0.722±0.082	1.208±0.0221	1.432±0.052	1.566±0.043	1.732±0.0368	1.652±0.025	20
4j	30	0.998±0.528	1.118±0.0485	1.332±0.042	1.654±0.011	1.55±0.0445	1.477±0.078	35

Conclusion

With good yields, a total of compounds were synthesized. All synthesized compounds exhibit analgesic, anti-inflammatory, and antibacterial activity. The compounds 4a, 4b, 4c, and 4e showed significant analgesic activity against Swiss albino mice. The compounds that showed good anti-inflammatory activity against Wister albino rats were compounds 4b, 4c, 4f, and 4j. The synthesized compounds were screened in vitro for antibacterial activity against S. aureus Gram (+ve) and E. coli Gram (-ve) bacteria, which are common to most of the diseases. A few compounds, like compounds 4a, 4d, 4e, and 4j show good antibacterial activity against S. aureus Gram (+ve), and compounds 4b, 4d, 4e, and 4j show good antibacterial activity against E. coli Gram (-ve) bacteria. Further exploration of all the compounds 4c, 4e, and 4j showed comparatively significant activity.

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