Journal of Interdisciplinary and Multidisciplinary Research (JIMR)
E-ISSN:1936-6264| Impact Factor: 8.886| UGC CARE II
Vol. **20** Issue **02**, **Feb**- 2025
Available online at: https://livejimrjournal.in/
(An open access scholarly, peer-reviewed, interdisciplinary, monthly, and fully refereed journal.)

Star fruit juice catalysed synthesis of 5-(p-substituted phenyl)-N-[3-(5-nitrofur-2-yl) allydine)-1,3,4-thiazol-2-amine derivatives and their antimicrobial activity

AASTHA SINGH & VIPIN KUMAR SINGH

Department of Chemistry, T.D.P.G. College, Jaunpur U.P. (India).

Abstract

5-(p-substituted phenyl)-N-(3-(5-nitrofur-2-yl) allylydene-1,3,4-thiadiazol-2-amino were prepared in presence of star fruit juice using different p-substituted acids. Semicarbazide reacts with benzoic acid derivative in presence of star fruit juice and phosphorus oxychloride to give 2-amino-5-substituted 1,3,4-thiadiazoles (compound 1-9) when it reacted with 5-nitro-2-furan crolein desired product obtained. Structures of synthesized compounds were confirmed by m.p., elemental analysis and spectral analysis. Antimicrobial activity of synthesized compounds revealed that only few compounds exhibited antimicrobial activity.

Key words : 1, 3, 4-thiadiazole, antimicrobial activity, 5-nitro-2-furana crolein.

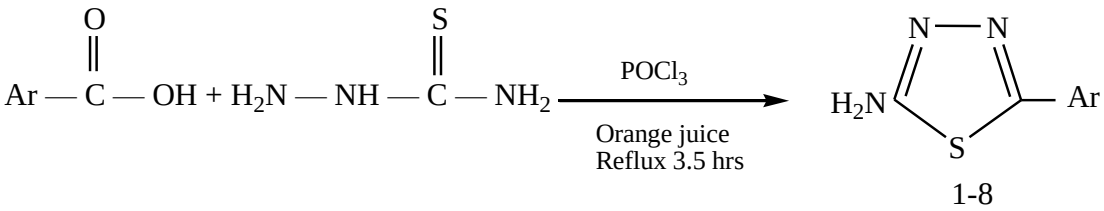
Introduction

Thiadiazole containing two nitrogen and one sulphur atom exist in different isomeric forms e.g. (a) 1,2,3-thiadiazole (b) 1,2,5-thiadiazole (c) 1,3,4-thiadiazole (d) 1,3,4-thiadiazole[1]. Among, 1,3,4-thiadiazoles having more applications and exhibiting potential biological activities like insecticidal[2], fungicidal[3], herbicidal activity[4], potent anti-cancer[5], anti-proliferative activity[6], Antiviral[7], inhibitors of acetyl cholinesterase (AChE) and butyrylcholinesterase (BuChE)[8], Alzheimer[9] and antimicrobial activities[10]. 1,3,4-thiadiazoles also used in electrical and optical[11], liquid crystal[12], corrosion inhibitors[13], in dye preparation[14]. The literature survey reveals that various thiadiazoles are the part of many potential drugs and exhibiting the wide spectrum of pharmacological activities and the biological activity of 1,3,4-thiadiazole moieties is may due to the presence of the =N–C–S moiety. Synthesis by either ferric chloride or acids catalyzed oxidative cyclization of thiosemicarbazide derivatives and biological studies of similar 5-[Aryl]-1, 3, 4-thiadiazol-2-amines were reported.

Padmavathi *et al.*[15] synthesized a few 2-(aryl-methanesulfonylmethyl) -5-aryl-1,3,4-thiadiazoles which showed enhanced activity with the presence of benzylsulfonyl group and chloro substituent. On the other hand, some of the novel methylene bridged benzisoxazolyl imidaozo [2,1-b] [1,3,4] thiadiazoles derivatives were synthesized by Lamani *et al.*[16] displayed very good antibacterial and/or antifungal activity. Furthermore, a number of new 5-(1*H*-indol-3-yl methyl)-*N*-(substituted phenyl)-1,2,4-thiadiazol-2-amine derivatives were synthesized and evaluated for their antibacterial and antifungal activity by Siddiqui and Alam[17]. The research study by Karegoudar *et al.*[18] reports the successful synthesis and antimicrobial activity of 1,2,4-triazolo [3,4- b] [1,3,4] thiadiazoles bearing 2,3,5-trichlorophenyl moiety. The antimicrobial activity study showed moderate to good antibacterial and antifungal activities against pathogenic strains. SAR of these compounds showed that presence of 2,3,5-trichloro, -OCH_3, 2,3-dichloro, 4-hydroxy-3-amido, 4-chloro, SCH_3 groups attached to phenyl ring as well as pyridyl and bromopyridyl groups attached to the thiadiazole ring are responsible for good antimicrobial activity.

In view of the above mentioned findings and as continuation of our effort[19] to identify new candidates that may be of value in designing new, potent, selective and less toxic antimicrobial agents, we report herein the synthesis of some heterocyclic derivatives starting from different substituted carboxylic acids in order to investigate their antimicrobial activity.

Present Work

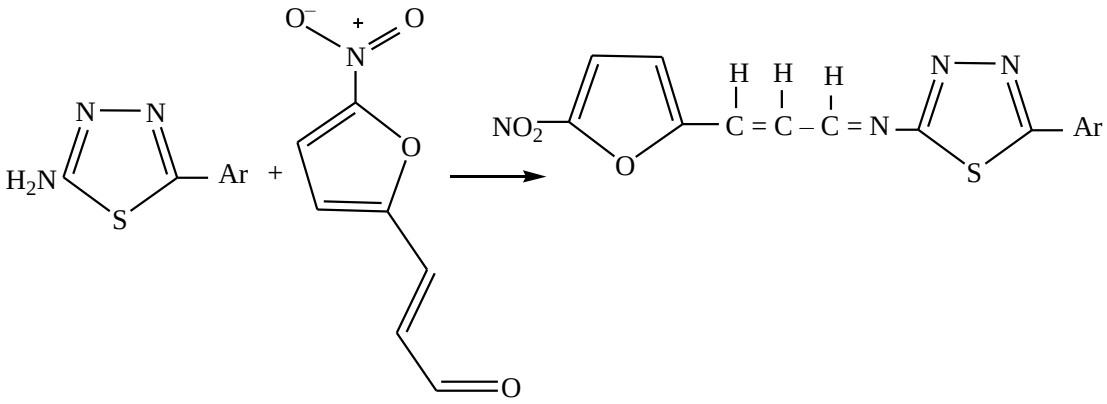


1-8

Ar–C_6H_5, p-$CH_3C_6H_4$, p-$OCH_3C_6H_4$, p-OHC_6H_4, p-$NO_2C_6H_4$, p-BrC_6H_4, p-IC_6H_4, p-ClC_6H_4

Journal of Interdisciplinary and Multidisciplinary Research (JIMR)
E-ISSN:1936-6264| Impact Factor: 8.886| UGC CARE II
Vol. **20** Issue **02**, **Feb**- 2025
Available online at: https://livejimrjournal.in/
(An open access scholarly, peer-reviewed, interdisciplinary, monthly, and fully refereed journal.)

Scheme-1 : Synthesis of 2-amino 5-substituted 1,3,4-thiazole



5-Nitro-2-furanacrotein

Ar–C_6H_5, p-$CH_3C_6H_4$, p-$OCH_3C_6H_4$, p-OHC_6H_4, p-$NO_2C_6H_4$, p-BrC_6H_4, p-IC_6H_4, p-ClC_6H_4

Scheme-2: Synthesis of 5-(p-substituted phenyl)-N-(3-(5-nitrofur-2yl)allylidene 1,3,4-thiadiazole-2-amine

Selection of Catalyst

Star fruits belong to the family oxilidaceae and known as Averrhoa carambola. The pH of star berry juice is 3.26-3.39. The synthesis of benzimidazole with fruit juice is ecofriendly and produced fewer amounts of toxic byproducts. It is tropical fruit and native to the Philippines, Indonesia, India, Nepal, Vietanam, Bangaladesh and Srilanka. It contains oxalic acid which characteristic of acidity. Approximately 74% of its total acid content vary on fruit maturity. Due to its low pH and easily libration of proton which suitable for synthesis of benzimidazole[20].

Preparation of fruit juice

Unriped mature green star fruit were purchased from Varanasi (U.P.) India. The fruits were cut into small pieces. The hard green piece of fruit (20g) was boiled in 100ml water. It was cooled and was centrifuged using micro-centrifuge. The clear aqueous extract of fruit was used as catalyst cum solvent for the synthesis.

4.2.6 Acid composition of star fruits

Major amount of oxalic acid present in fruits which compositions vary with maturity. Other acid as ascorbic acid, Gallic acids and caramboxin. Some other organic acids are acetic acid, citric acid, formic acid, lactic acid. It contains approximately 60% cellulose, 27% hemicelluloses and 13% of pectin.

MATERIAL AND METHODS

Measurements

Melting points were determined in open glass capillaries on a Gallenkamp apparatus and are uncorrected. The percentage compositions of the elements (CHNS) for the compounds were determined using an elemental analyzer CHNS Model Fison EA 1108. The infrared spectra were recorded as potassium bromide discs using a Perkin-Elmer spectrophotometer GX. The ^{1}H NMR spectra were recorded using the JEOL JNM-ECP 400 spectrometer in DMSO-d_6 as solvent, using TMS as an internal standard and chemical shifts are expressed as δ_{ppm}. The purities of the compounds were checked by thin layer chromatography (TLC) using Silica gel plates and benzene:methanol (8:2) as a solvent system. The spots were developed in an iodine chamber and visualized under ultraviolet (UV) lamp.

Synthesis of compounds

General procedure for the synthesis of 2-amino5-substituted-1,3,4-thiadiazole 2-9

A mixture of thiosemicarbazide (0.01 mol) and aryl substituted carboxylic acid (0.01 mol), and $POCl_3$ (5 mL) with 7.5ml star fruit juice was refluxed for 4 hrs. The resultant product was transferred into a beaker to cool to room temperature then poured onto crushed ice. The solid separated out was filtered, washed with cold water and recrystalized from ethanol[20] (Scheme-1).

General procedure for the synthesis of 5-(p-substituted phenyl)-N-(3-(5-nitrofur-2-yl)allylidene)-1,3,4-thiadiazol-2-amine 2-9

A mixture of 5-nitro-2-furanacrolein (0.01 mole) appropriate 2-amino-1,3,4-thiadiazole 2-9 (0.01 mole) and 25 mL ethanol was refluxed for 3 hrs with continuous stirring. After cooling to room temperature the precipitate was filtered and recrystalized from ethanol (Scheme-2).

Journal of Interdisciplinary and Multidisciplinary Research (JIMR)
E-ISSN:1936-6264| Impact Factor: 8.886| UGC CARE II
Vol. **20** Issue **02**, **Feb**- 2025
Available online at: https://livejimrjournal.in/
(An open access scholarly, peer-reviewed, interdisciplinary, monthly, and fully refereed journal.)

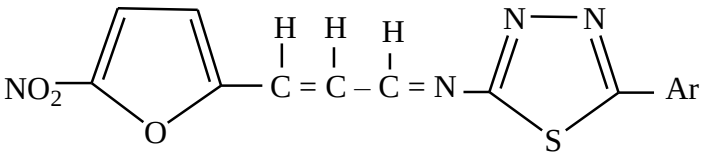
Melting point and elemental analysis of compounds

Table-1: 5-Phenyl-N-(3-(5-nitrofur-2-yl)allylidene)-1,3,4-thiadiazol-2-amine

S. No	Ar	M.P. °C Reported[21] (Found)	Yield %	Molecular Formula	Analysis (%)	
					S	N
					Calcd. (Found)	Calcd. (Found)
2	C_6H_5	96-98 (98.5)	78	$C_{10}H_{10}N_4O_3S$	9.83 (9.82)	17.17 (17.18)
3	p-$CH_3C_6H_4$	121-123 (124)	78	$C_{16}H_{12}N_4O_3S$	9.42 (9.43)	16.46 (16.47)
4	p-$OCH_3C_6H_4$	133-135 (136)	68	$C_{16}H_{12}N_4O_4S$	9.00 (9.01)	15.72 (15.73)
5	p-OHC_6H_4	200-202 (202)	73	$C_{15}H_{10}N_4O_4S$	9.37 (9.36)	16.38 (16.38)
6	p-$NO_2C_6H_4$	169-171 (171.5)	81	$C_{15}H_9N_5O_5S$	8.64 (8.65)	18.86 (18.87)
7	p-BrC_6H_4	110-112 (111.6)	83	$C_8H_6BrN_3S$	12.52 (12.51)	16.41 (16.40)
8	p-IC_6H_4	204-206 (206.5)	76	$C_8H_6IN_3S$	10.58 (10.59)	13.86 (13.87)
9	p-ClC_6H_4	134-136 (136.7)	76	$C_8H_6ClN_3S$	15.15 (15.16)	19.85 (19.86)

Journal of Interdisciplinary and Multidisciplinary Research (JIMR)
E-ISSN:1936-6264| Impact Factor: 8.886| UGC CARE II
Vol. **20** Issue **02**, **Feb**- 2025
Available online at: https://livejimrjournal.in/
(An open access scholarly, peer-reviewed, interdisciplinary, monthly, and fully refereed journal.)

Table-2: Characterization of synthesized compounds



S. No	Ar	IR (KBr) cm^{-1}	^{1}H-NMR (DMSO) □□ppm
2	C_6H_5	υ = 3069 (C-H aromatic), 1620 (C=N), 1554 (C=C), 669 (C-S).	δ = 5.52-5.54 (1H, d, - CH=C-), 5.68-5.70 (1H, d, -CH=C-), 5.76-5.78 (1H, d, -CH=N-), 8.03-8.05 (d, 1H, Ar-H), 8.12-8.14 (d, 1H, Ar-H), 8.18-8.20 (d, 1H, Ar-H), 8.24-8.26 (d, 1H, Ar-H), 8.73-8.75 (t, 1H, Ar-H), 8.80-8.82 (t, 1H, Ar-H), 8.87-8.90 (t, 1H, Ar-H)
3	p-$CH_3C_6H_4$	υ = 3090 (C-H aromatic), 2967, 2851 (C-H aliphatic), 1623 (C=N), 1560 (C=C), 637 (C-S).	δ = 2.56 (s, 3H, -CH3), 5.25-5.27 (1H, d, -CH=C-), 5.34-5.36 (1H, d, -CH=C-), 5.42-5.44 (1H, d, -CH=N-), 8.49-8.51 (d, 1H, Ar-H), 8.56-8.58 (d, 1H, Ar-H), 8.63-8.65 (d, 1H, Ar-H), 8.69-8.71 (d, 1H, Ar-H), 8.75-8.77 (t, 1H, Ar-H), 8.78-8.80 (t, 1H, Ar-H).
4	p-$OCH_3C_6H_4$	υ = 3045 (C-H aromatic), 2952, 2868 (C-H aliphatic), 1625 (C=N), 1565 (C=C), 640 (C-S).	δ = 3.10 (s, 3H, -OCH3), 5.22-5.24 (1H, d, -CH=C-), 5.30-5.32 (1H, d, -CH=C-), 5.36-5.38 (1H, d, -CH=N-), 8.45-8.47 (d, 1H, Ar-H), 8.51-8.53 (d, 1H, Ar-H), 8.59-8.61 (d, 1H, Ar-H), 8.64-8.66 (d, 1H, Ar-H), 8.70-8.72 (t,

			1H, Ar-H), 8.74-8.76 (t, 1H, Ar-H).
5	p-OHC_6H_4	υ = 3456 (O-H), 3086 (C-H aromatic), 1623 (C=N), 1550 (C=C), 638(C-S).	δ = 5.31-5.33 (1H, d, -CH=C-), 5.35-5.37 (1H, d, -CH=C-), 5.40-5.42 (1H, d, -CH=N-), 8.33-8.35 (d, 1H, Ar-H), 8.40- 8.42 (d, 1H, Ar-H), 8.47-8.49 (d, 1H, Ar-H), 8.55- 8.57 (d, 1H, Ar-H), 8.62-8.64 (t, 1H, Ar-H), 8.68- 8.70 (t, 1H, Ar-H), 9.67 (s, 1H, O-H).
6	p-$NO_2C_6H_4$	υ = 3065 (C-H aromatic), 1620 (C=N), 1567 (C=C), 1534, 1368 (NO2), 630 (C-S).	δ = 5.23-5.25 (1H, d, -CH=C-), 5.28-5.30 (1H, d, - CH=C-), 5.34-5.36 (1H, d, -CH=N-), 8.29-8.31 (d, 1H, Ar-H), 8.35-8.37 (d, 1H, Ar-H), 8.43-8.45 (d, 1H, Ar-H), 8.49-8.51 (d, 1H, Ar-H), 8.56-8.58 (t, 1H, Ar-H), 8.62-8.64 (t, 1H, Ar-H).
7	p-BrC_6H_4	υ = 3090 (C-H aromatic), 1627 (C=N), 1557 (C=C), 633 (C-S).	δ = 5.50-5.52 (1H, d, - CH=C-), 5.55-5.58 (1H, d, -CH=C-), 5.60-5.62 (1H, d, -CH=N-), 8.22-8.24 (d, 1H, Ar-H), 8.28-8.30 (d, 1H, Ar-H), 8.34-8.36 (d, 1H, Ar-H), 8.40-8.42 (d, 1H, Ar-H), 8.46-8.48 (t, 1H, Ar-H), 8.52-8.54 (t, 1H, Ar-H).

8	p-IC_6H_4	υ = 3045 (C-H aromatic), 1623 (C=N), 1550 (C=C), 631 (C-S).	δ = 5.41-5.43 (1H, d, - CH=C-), 5.49-5.51 (1H, d, -CH=C-), 5.55-5.57 (1H, d, -CH=N-), 8.11-8.12 (d, 1H, Ar-H), 8.18-8.20 (d, 1H, Ar-H), 8.24-8.26 (d, 1H, Ar-H), 8.29-8.31(d, 1H, Ar-H), 8.35-8.37 (t, 1H, Ar-H), 8.42-8.44 (t, 1H, ArH).
9	p-ClC_6H_4	υ = 3089 (C-H aromatic), 1620 (C=N), 1556 (C=C), 633 (C-S).	δ = 5.41-5.43 (1H, d, - CH=C-), 5.49-5.51 (1H, d, -CH=C-), 5.55-5.57 (1H, d, -CH=N-), 8.10-8.12 (d, 1H, Ar-H), 8.11-8.12 (d, 1H, Ar-H), 8.16-8.18 (d, 1H, Ar-H), 8.22-8.24(d, 1H, Ar-H), 8.31-8.33 (t, 1H, Ar-H), 8.38-8.40 (t, 1H, ArH).

Antimicrobial activity

The in vitro antimicrobial activities of synthesized compounds were carried out by cup-plate method[22]. Antibacterial activity was screened against two gram positive bacteria (*Staphylococcus aureus* and *Enterococcus faecalis*) and two gram negative bacteria (*Acinetobacterb baumannii* and *Escherichia coli*), whereas antifungal activity was screened against fungus *Candida albicans* by measuring the zone of inhibition on agar plates at two different concentrations 50 and 100 µg/mL. Ampicillin, Aztreonam and Amphotericin B were used as standard drugs for evaluation of antimicrobial activity.

RESULTS AND DISCUSSION

Chemistry

The designed compounds, 5-(p-substituted phenyl)-N-(3-(5-nitrofur-2-yl) allylidene)-1,3,4-thiadiazol-2-amine 1-9, were synthesized. Schiff bases under investigation were synthesized by condensation of compounds 2-9 with 5-nitro-2-furanacrolein in 1:1 molar proportion in ethanol. The reaction mixture was heated under reflux for about 3 hrs then cooled to room temperature and filtered off. The desired compounds were purified by repeated recrystalization from ethanol, dried to yield the final products. The purity of the synthesized compounds was checked by TLC, spectroscopic analysis and also by constancy of melting points.

Formation of the compounds 2-9 were confirmed by sharp bands around 3300 and 3200 cm^{-1} for NH_2 group along with a band at about 3100 and 630 cm^{-1} for aromatic C-H and C-S stretching vibrations, respectively, in IR spectra. The disappearance of NH_2 stretching band and the presence of sharp NO_2 bands at about 1534 and 1330 cm^{-1} together with bands about 1625 cm^{-1} due to Schiff bases azomethine group (–CH=N-) stretching vibration confirmed the formation of 5-(p-substituted phenyl)-N-(3-(5-nitrofur2-yl)allylidene)-1,3,4-thiadiazol-2-amines 10-17. ^1H NMR spectra showed three multiplt signals around d 5.55-5.43 ppm assigned for –CH=CH-CH=N- and the signals at about δ 8.38-8.33 ppm was due to furan ring hydrogen's.

Antimicrobial activity

Antibacterial activity

Generally bacteria may become resistant to antimicrobial agents through mutation or by acquiring from other bacteria the genetic information that encodes resistance. The antibacterial activities of synthesized compounds are reported in Table-3.

Table-3: Gram positive antibacterial activity of compounds 2-9

Comp.	Ar	*S. aureus*		Std: Ampicillin	
		Zone of inhibition			
		U_2 100 □g/ml	U_1 50 □g/ml	S_2 100 □g/ml	S_1 50 □g/ml
2	C_6H_5	3	2	12	8
3	p-$CH_3C_6H_4$	2	1	12	7
4	p-$OCH_3C_6H_4$	4	2	12	8
5	p-OHC_6H_4	3	3	12	8
6	p-$NO_2C_6H_4$	6	4	12	8
7	p-BrC_6H_4	6	4	12	8
8	p-IC_6H_4	6	4	12	8
9	p-ClC_6H_4	6	5	12	8

In this work, the results of antibacterial activity are shown in the Table-3 and Table-4 of inhibition zones measurements at conc. 50 and 100 µg/mL. Compounds 3 has the highest activity (80.39%) while compounds 6, 7, 8, exhibited good activities (51.78% - 49.88%) against gram positive bacteria *S. aureus*. Compounds 8 and 9 displayed highest activities (61.31% and 62.00%, respectively) against gram positive bacteria *E. faecalis*. On the other hand, compounds 6 and 7 have highest activities (63.90 and 75.03, respectively) while compounds 8, 9 showed good activities (62.50% - 57.63%) against gram negative bacteria *A. baumannii*. Compounds 6 and 7 showed good activities (55.66% and 63.29%, respectively) against gram negative bacteria *E. coli*. The remaining compounds possess moderate to poor activities as compared to Ampicillin and Aztreonam.

Journal of Interdisciplinary and Multidisciplinary Research (JIMR)
E-ISSN:1936-6264| Impact Factor: 8.886| UGC CARE II
Vol. **20** Issue **02**, **Feb**- 2025
Available online at: https://livejimrjournal.in/
(An open access scholarly, peer-reviewed, interdisciplinary, monthly, and fully refereed journal.)

Table-4: Gram negative antibacterial activity of compounds 2-9

Comp.	Ar	*E. coli*		Std: Aztreonam	
		Zone of inhibition			
		U_2 100 □g/ml	U_1 50 □g/ml	S_2 100 □g/ml	S_1 50 □g/ml
2	C_6H_5	2	2	14	8
3	p-$CH_3C_6H_4$	3	3	14	7
4	p-$OCH_3C_6H_4$	4	4	14	8
5	p-OHC_6H_4	3	3	14	8
6	p-$NO_2C_6H_4$	5	3	14	9
7	p-BrC_6H_4	6	5	14	9
8	p-IC_6H_4	8	6	14	9
9	p-ClC_6H_4	7	5	14	9

The results of antifungal activity are shown in the Table-5 of inhibition zones measurements at conc. 50 and 100 µg/mL. Compound 16 showed the highest activity (65.25%) while the other synthesized compounds possess moderate to poor activities against *C. albicans* as compared to Amphotercin B.

Antifungal activity

An antifungal drug is a medication used to treat fungal infections such as athlete's foot, ringworm, candidiasis (thrush), serious systemic infections such as cryptococcal meningitis. Antifungals work by exploiting differences between mammalian and fungal cells to kill the fungal organism without dangerous effects on the host. Unlike bacteria, both fungi and humans are eukaryotes. Thus fungal and human cells are similar at the molecular level. This makes it more difficult to find or design drugs that target fungi without affecting human cells. In general, fungi can be intrinsically resistant to antifungal drugs (primary resistance) or can develop resistance in response to exposure to the drug during treatment (secondary resistance).

Table-5: Antifungal activity of compounds 2-9

Comp.	Ar	*C. albicans*		Std: Amphotericin B	
		Zone of inhibition			
		U_2 100 □g/ml	U_1 50 □g/ml	S_2 100 □g/ml	S_1 50 □g/ml
2	C_6H_5	2	1	9	4
3	p-$CH_3C_6H_4$	0	0	9	4
4	p-$OCH_3C_6H_4$	1	0	9	4
5	p-OHC_6H_4	2	1	9	4
6	p-$NO_2C_6H_4$	4	2	9	4
7	p-BrC_6H_4	3	2	9	4
8	p-IC_6H_4	4	2	9	4
9	p-ClC_6H_4	3	1	9	4

CONCLUSIONS

The preparation procedures follow in this work offers reduction in the reaction time, operation simplicity, cleaner reaction and easy work-up. The antimicrobial data given for the compounds presented in this paper allowed us to state that the variation of antimicrobial activity may be associated with the nature of tested microorganisms and also is due to the chemical structure of the tested compounds.

References:

1. Demirbas, A., Sahin, D., Demirbas, N., & Karaoglu, S. A. (2009). Synthesis of some new 1, 3, 4- thiadiazol-2-ylmethyl-1, 2, 4-triazole derivatives and investigation of their antimicrobial activities. Eur. J Med. Chem., 44(7), 2896-2903.
2. Luo, Y. P., & Yang, G. F. (2007). Discovery of a new insecticide lead by optimizing a targetdiverse scaffold: tetrazolinone derivatives. Bioorg. Med. Chem., 15(4), 1716-1724.

3. Chen, H., Li, Z., & Han, Y. (2000). Synthesis and Fungicidal Activity against Rhizoctonia s olani of 2-Alkyl (Alkylthio)-5-pyrazolyl-1, 3, 4-oxadiazoles (Thiadiazoles). J. Agric. Food Chem., 48(11), 5312-5315.
4. Li, Z. S., Wang, W. M., Lu, W., Niu, C. W., Li, Y. H., Li, Z. M., & Wang, J. G. (2013). Synthesis and biological evaluation of nonsymmetrical aromatic disulfides as novel inhibitors of acetohydroxyacid synthase. Bioorg. Med. Chem. Lett., 23(13), 3723-3727.
5. Polkam, N., Rayam, P., Anireddy, J. S., Yennam, S., Anantaraju, H. S., Dharmarajan, S., ... & Balasubramanian, S. (2015). Synthesis, in vitro anticancer and antimycobacterial evaluation of new 5-(2, 5-dimethoxyphenyl)-1, 3, 4-thiadiazole-2-amino derivatives. Bioorg. Med. Chem. Lett., 25(7), 1398-1402.
6. Jakovljević, K., Matić, I. Z., Stanojković, T., Krivokuća, A., Marković, V., Joksović, M. D., ... & Joksović, L. (2017). Synthesis, antioxidant and antiproliferative activities of 1, 3, 4-thiadiazoles derived from phenolic acids. Bioorg. Med. Chem. Lett., 27(16), 3709-3715.
7. Gan, X., Hu, D., Chen, Z., Wang, Y., & Song, B. (2017). Synthesis and antiviral evaluation of novel 1, 3, 4-oxadiazole/thiadiazole-chalcone conjugates. Bioorg. Med. Chem. Lett., 27(18), 4298- 4301.
8. Skrzypek, A., Matysiak, J., Niewiadomy, A., Bajda, M., & Szymański, P. (2013). Synthesis and biological evaluation of 1, 3, 4-thiadiazole analogues as novel AChE and BuChE inhibitors. Eur. J. Med. Chem., 62, 311-319.
9. Wang, J., Zhang, H. Y., & Tang, X. C. (2009). Cholinergic deficiency involved in vascular dementia: possible mechanism and strategy of treatment. Acta Pharmacol. Sin., 30(7), 879.
10. Reddy, K. R., Mamatha, R., Babu, M. S., Shiva Kumar, K., Jayaveera, K. N., & Narayanaswamy, G. (2014). Synthesis and antimicrobial activities of some triazole, thiadiazole, and oxadiazole substituted coumarins. J. Heterocycl. Chem., 51(1), 132-137.

11. Wang, G., Jin, L., Ye, J., & Li, X. (2010). Electrical and electrochemical properties of poly (2, 5- dimercapto-1, 3, 4-thiadiazole)-polyaniline adduct intercalated graphite oxide composites. Mater. Chem. Phy., 122(1), 224-229.
12. Tomi, I. H. R., Al-Heetimi, D. T., & Jaffer, H. J. (2017). Asymmetric 1, 3, 4-thiadiazole derivatives: synthesis, characterization and studying their liquid crystalline properties. J. Mol. Stru., 1141, 176-185.
13. Solmaz, R., Kardaş, G., Yazıcı, B., & Erbil, M. (2008). Adsorption and corrosion inhibitive properties of 2-amino-5-mercapto-1, 3, 4-thiadiazole on mild steel in hydrochloric acid media. Colloids and Surf., 312(1), 7-17.
14. Gowramma, B., Kulkarni, A., Gomathy, S., & Kandula, R. (2012). Synthesis And Anticonvul sant Screening Of Some Novel 1, 3, 4-Thiadiazole Derivatives. J. Pharma. Res., 5(1), 58-60.
15. Padmavathi, V., Reddy, G.S., Padmaja, A., Kondaiah, P., Shazia, A. (2008). Synthesis, antimicrobial and cytotoxic activities of 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles. Eur. J. Med. Chem. 44, 2106-2112.
16. Lamani, R.S., Shetty, N.S., Kamble, R.R., Khazi, I.A. (2009). Synthesis and antimicrobial studies of novel methylene bridged benzisoxazolyl imidazo[2,1-b][1,3,4] thiadiazole derivatives. Eur. J. Med. Chem. 44: 2828-2833.
17. Siddiqui, N., Alam, M.S. (2009). 5-(1H-Indol-3-ylmethyl)-N-(substituted phenyl)-1,2,4-thiadiazol-2-amine derivatives: synthesis and biological screening. Biosci. Biotech. Res. Asia. 6(1): 261-264.
18. Karegoudar, P., Prasad, D.J., Ashok, M., Mahalinga, M., Poojary, B., Holla, B.S. (2008). Synthesis, antimicrobial and anti-inflammatory activities of some 1,2,4-triazolo[3,4-b]thiadiazoles and 1,2,4-triazolo[3,4-b][1,3,4]thiadiazines bearing trichlorophenyl moiety. Eur. J. Med. Chem. 43, 808-815.

19. Salimon, J., Salih, N., Yousif, E., Hameed, A., Ibraheem, H. (2010b). Synthesis Characterization and Biological Activity of Schiff Bases of 2,5-Dimercapto-1,3,4-thiadiazole. Aust. J. Basic Appl. Sci. 4, 2016-2021.
20. Kusun, L., Pamodh, Y., Umesh, J., Suranjith (2021). Nutritional and Medicinal properties of star fruit (*Averrhoa carambola*): A review food Sci. Nutr. 9(3): 1810-1823.
21. Nadia Salih, Jumat Salimon and Emad Yousif (2011). Synthesis and antimicrobial evaluation of 5-(p-substituted phenyl)-N-(3-(5-nitrofur-2-yl)allylidene)-1,3,4-thiadiazol-2-amine derivatives, Oriental Journal of Chemistry, 27(2), 373-383.
22. Barry, A.L. (1976). The antimicrobial susceptibility test, principles and practices. Philadelphia, USA.