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Synthesis and Biological Activities of Some New Derivatives Based on 5-Styryl-2-amino-1,3,4-thiadiazole

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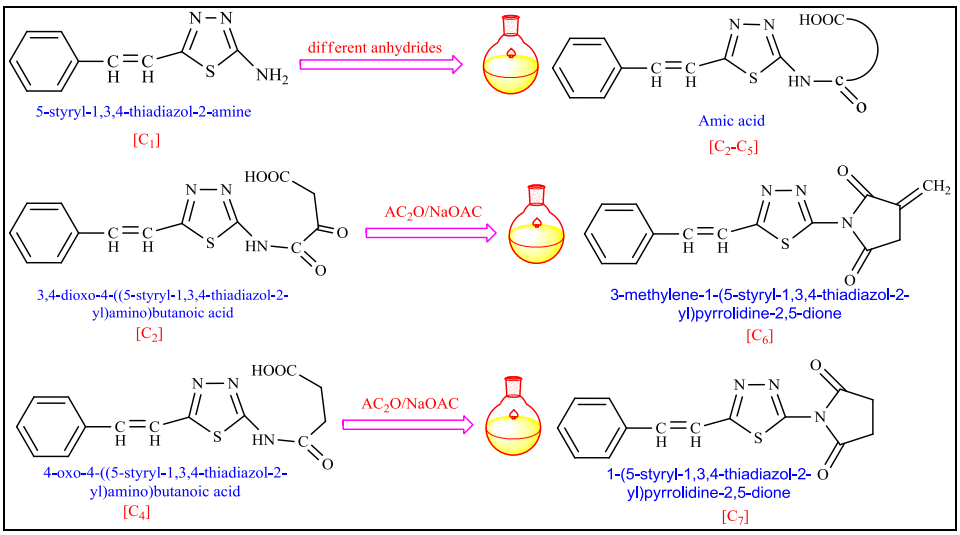
ABSTRACT

In this research, 5-Styryli-2-amino-1, 3, 4-thiadiazole [C_1] was prepared from the reaction of acid 3-phenyl propenoic acid with thiosemicarbazide. Amic acids [C_2-C_5] were synthesized by reactive compound [C_1] with different types of hydrides, then [C_2, C_4] were treated with AC_2O in the presence of NaOAC as a catalyst giving Imide compounds [C_6, C_7]. The structure of the new derivatives was confirmed *via* FT-IR spectroscopy, some of which were confirmed *via* ^{1}H-NMR spectroscopy. Three of these new derivatives were evaluated by their Esherichiacoli, Staphylococcus, and Rhizopus emporium.

GRAPHICAL ABSTRACT



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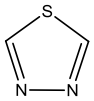
Introduction

The development of synthetic routes to widely used organic compound by using readily available reagents is one of the major objectives of organic synthesis. The 1,3,4-thiadiazole compound is a five-membered heterocyclic scaffold including diverse physicochemical properties, as shown in structure, which refers to the general structure of 1,3,4-thiadiazole [1].



Scheme 1: General structure of 1,3,4-thiadiazole

It is a mesoionic system associated with the discrete regions of positive and negative charges leading to electrons and highly polarizable derivatives [2]. This distinguishing feature allows mesoionic compounds to effectively cross cellular membranes and interact with biological molecules in unique ways, which is considered as the high potential of this ring system in medicinal chemistry [3]. 1,3,4-thiadiazole derivatives are known as compounds having significant and diverse biological activities such as antimicrobial [4], anti-Alzheimer agents [5], anticancer agents [6], antimycobacterial agents [7], antitubercular [8], kinesin inhibitors [9] etc. The 1,3,4-thiadiazole ring is also found in several medicines such as acetazolamide, methazolamide, cefazolin, cefazedone, sulfamethizole or megazol[8,10-12]. Amic acids are organic compounds containing both carboxyl and amide groups in their molecules and can be prepared easily with excellent yields *via* the reaction of cyclic anhydrides with different aliphatic or aromatic amines [13]. Numerous derivatives have been extensively studied and many of these compounds have proved to be active as antibacterial, anti-fungal, anti-cancer, and anti-inflammatory agents, and some of them are expansively used as an analgesic and anti-nociceptive agent [14].

Imides are diacyl derivatives of ammonia or primary amine. Among imides, cyclic imides and their N-derivatives containing bisamide linkages with a general structure of [-CO-N(R)-CO-] are the most important representatives of this class. These compounds are structurally related to acid anhydrides. The presence of oxygen and nitrogen atoms as co-ordination sites can attach these ligands with the biological system and cause various pharmacological effects [15, 16]. Due to hydrophobicity and neutral structures, these compounds can easily cross biological membranes in vivo [17-19]. In view of the favourable pharmacokinetic properties, derivatives of cyclic imides have been found to exhibit a wide range of biological activities such as antibacterial [20-22], antifungal [23, 24], antiviral [25, 26], analgesic [27, 28], antiangiogenic [18], anti-HIV [19], antimalarial [20], anticancer [21], androgen receptor antagonistic [22], anti-inflammatory [23], anxiolytic [24], anti-depressive [25], anticonvulsant [26], hypolipidemic [27] and muscle-relaxant activities [28]. As a very important cyclic imide moiety, Isoindoline-1, 3-dione commonly known as phthalimide, is the key structural unit of a variety of biologically active molecules which are of pharmaceutical significance. Various drugs such as lenalidomide, pomalidomide, etc., contain isoindoline structure that have been used for the treatment of multiple myeloma [29]. Various other isoindoline structures containing drugs are also known to be used for the treatment of certain types of diseases [30].

Material and methods

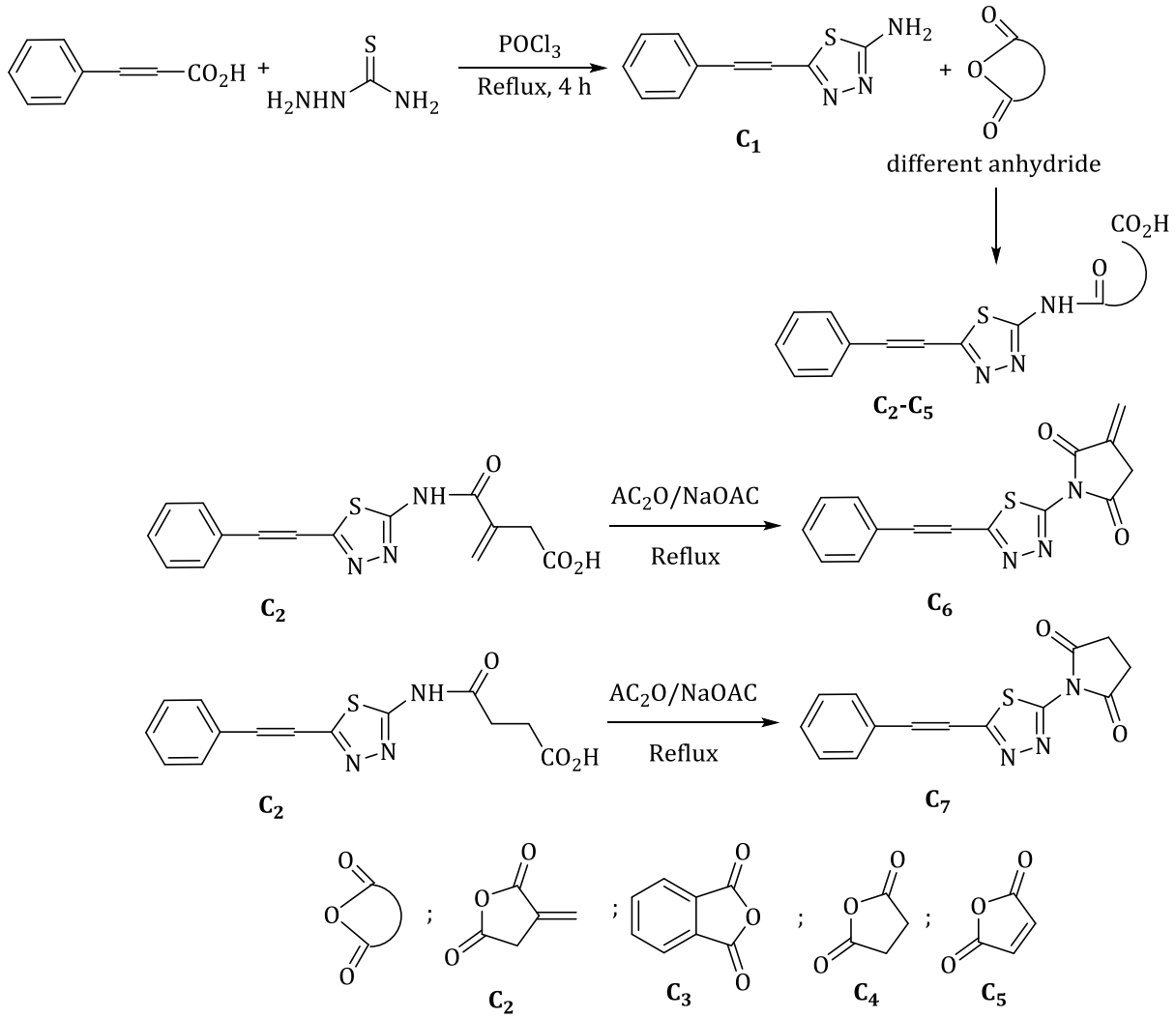
All chemicals were supplied from diverse corporations such as Thomas baker, Merck, BDH, GCC, and Scharlau and used without further purification. Melting points were determined on an electrothermal melting point apparatus (Stuart Germany), and they were uncorrected. End of purity and reaction of all compounds were checked on aluminum-coated TLC plates 60 F245 (E. Merck) by using ethanol as the mobile phase and imagined under iodine vapor. Resolves of infrared spectra were done and recorded as a KBr disk in the range of (400 -4000 cm^{-1}) using FTIR Shimadzu (Japan). The proton ^{1}H-NMR spectra were tested for the synthesized compounds using Bruker DMX-500 spectrophotometer (500 MHZ, solvent DMSO-d_6).

Synthesis 5-styryl-2-amino -1, 3, 4-thiadiazole [C_1]
The mixture (0.01 mol, 1.4 g) of 3-phenyl propenoic acid with (0.01 mol, 0.9 g) thiosemicarbazide in (10 ml) of $POCl_3$ was refluxed 4 hours, the excess of $POCl_3$ was removed and the residue was dissolved in distilled water (50 ml) then heated for 1 h. After that, the resulting product was cooled, filtered, and neutralized with KOH. The precipitate was filtered, dried, and recrystallized in ethanol (MP 238 - 240 °C).

Synthesis of Amic Acid compounds [C_2-C_5]
A solution of (0.0016 mol, 0.4 g) of compound [C_1] dissolved in (10ml) of absolute ethanol was added dropwise to the solution of (0.0032mol) of different anhydrides {maleic anhydride, phthalic anhydride, succinic anhydride, itaconic anhydride} and dissolved in (10 ml) of absolute ethanol with stirring and cooling stirring was continued for 4 hrs. Then, the formed amic acid was filtered, washed with diethyl ether, dried, and purified from absolute ethanol.

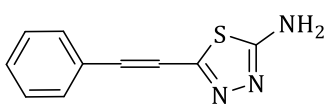
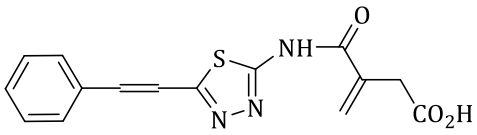
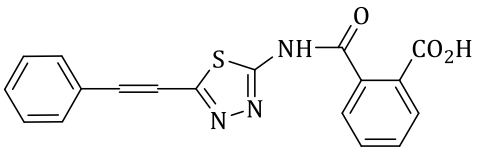
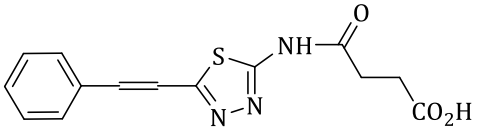
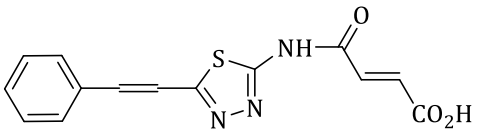
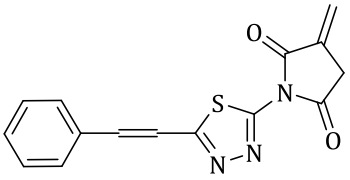
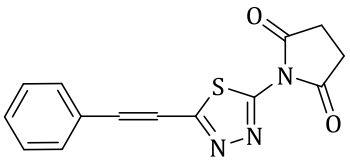
Synthesis of Imide compounds [C_6,C_7]
The compound [C_2, C_4] was the treatment of compounds (0.01 mole, 1 gm) with acetic anhydride (25 ml) and anhydrous sodium acetate (0.125 g) under reflux followed by pouring in excess cold water. The resulting solid was recrystallized from cyclohexane.

Result and Dissection
In general, the reaction is illustrated in Scheme 2.

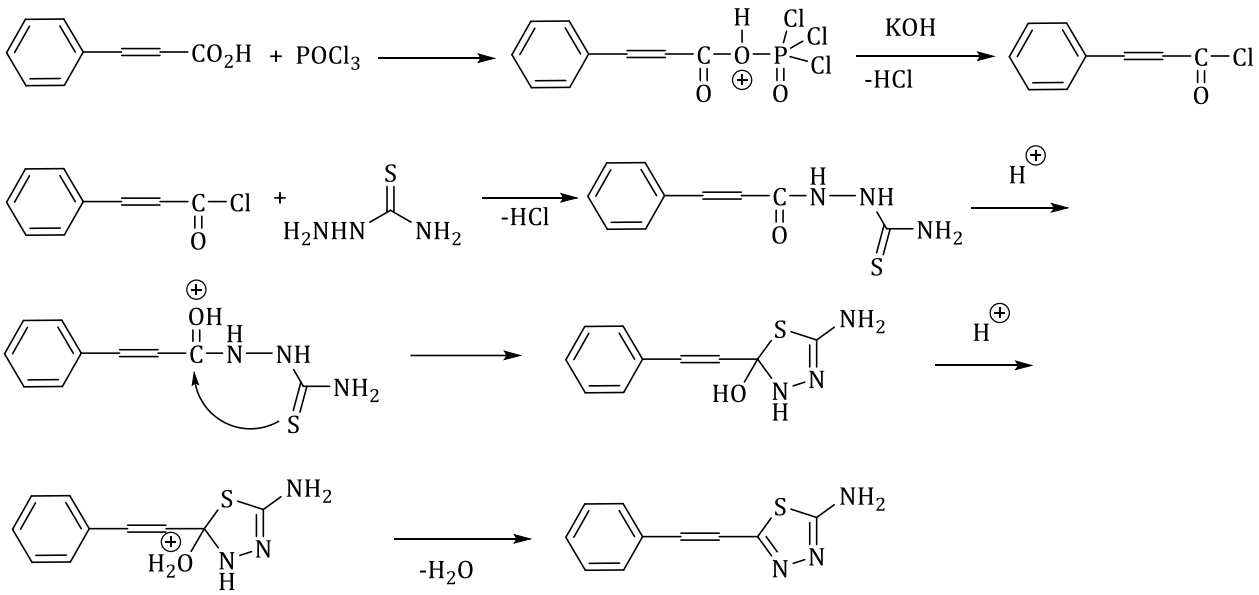


Scheme 2: Pathway for Synthesis [C_1-C_7] compounds

Table 1: Physical Properties of Synthesized Compounds [C_1-C_7]

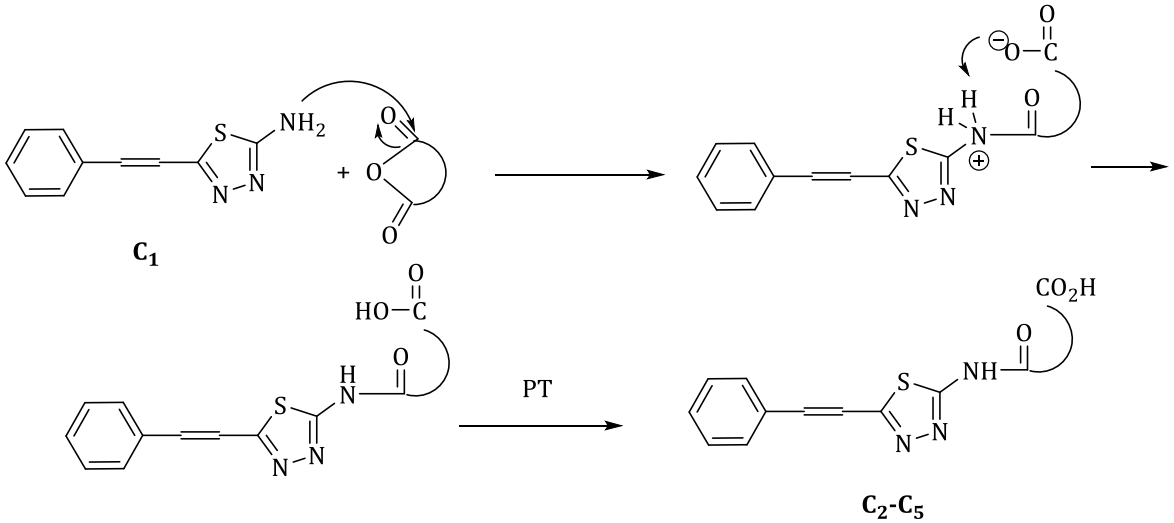
Comp. No	Structure of compound	Yield %	Color[i]	M.P (^oC)
C_1		90	white	238- 240
C_2		92	White	156-158
C_3		89	white	150-152
C_4		95	white	118-120
C_5		92	white	184-186
C_6		88	pale Yellow	174-176
C_7		89	White	194-196

In the Scheme 2 the general reaction is summarized. The Compound [C_1] was obtained from the reaction of 3-phenyl propenoic acid with thiosemicarbazide in the presence of $POCl_3$. The reaction mixture was refluxed for 4hrs. The Compound [C_1] was diagnosed by FT-IR spectrum. Absorption band at (3433-3379 cm^{-1}) belongs to ν (NH_2) asymmetric and symmetric, ν (=CH) olefin at (3078), ν(C=C) olefin at (1543 cm^{-1}), ν (C=N) at (1662 cm^{-1}), ν(N-N) at (1438 cm^{-1}), ν(C-S) at (937 cm^{-1}), and ν(C-O) at (1253 cm^{-1}) . The characterization of compound [C_1] was also performed by ^{1}H-NMR spectra which gave [C_1] the following signals: δ (7.0-7.5) ppm due to (m, 5H, Ar-H δ (6.5) ppm due to (d, 2H, CH=CH), δ (5.13) ppm due to (s, 2 H, NH_2), and δ (2.50) ppm due to (DMSO). The mechanism or the reaction can be outlined in the scheme 3.



Scheme 3: Mechanism steps of 5-styryl-2-amino 1, 3, 4-thiadiazole

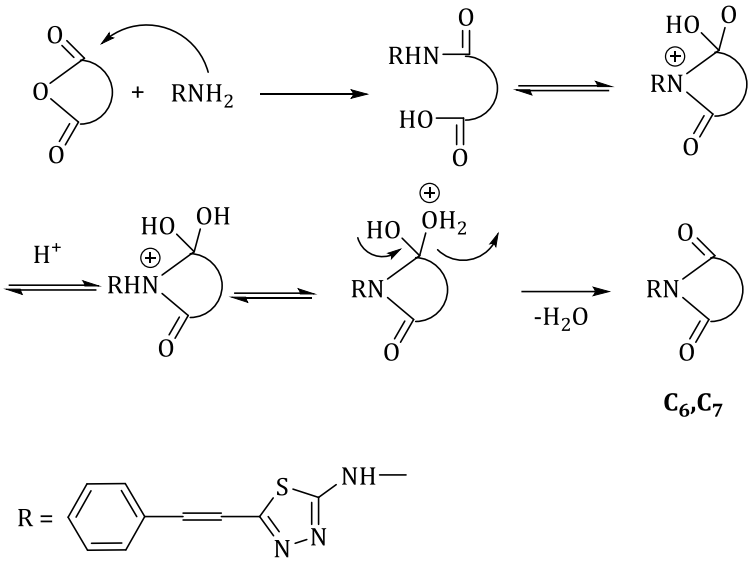
The amic acid compounds [C_2-C_5] are prepared from one mole of compound [C_1] with two moles of different anhydrides in the presence of ethanol as a solvent and stirring of the mixture for 4 hrs. Amic acid compound from [C_2-C_5] have been characterized by (FT-IR). These spectra determined the disappearance of bands due to NH_2 symmetric and asymmetric at (3433-3379 cm^{-1}) and the appearance of bands due to υ (C=O) groups. FTIR spectrum of compound [C_2] showed absorption band at (1728 cm^{-1}) belonged to υ (C=O carboxylic) and appearance of the (C=O amide) at (1693 cm^{-1}) and υ (NH) at (3267 cm^{-1}). The FTIR spectrum of compound [C_3] showed absorption band at (1725 cm^{-1}) belonged to υ (C=O carboxylic) and the appearance of the (C=O amide) at (1631 cm^{-1}) and υ (NH) at (3263 cm^{-1}). Other absorptions amic acids compounds are found in Table 2. The mechanism or the reaction can be outlined in the scheme 4.



Scheme 4: The mechanism steps for the synthesis of amic acids compounds

The Imide compounds were synthesized by the reaction among the substances [C_2, C_4] and many anhydrides (phthalic, Itaconic) are in the presence of acetic anhydride as a catalyst for the production of these compounds; with tetrahydrofuran as the solvent using the FT-IR spectrum, the structure of the prepared compounds was characterized and confirmed. The disappearance of the absorption tape at (3417 cm^{-1}) of [C_1] is due to NH_2 and the presence of the bands of NH at *ν* (3275 cm^{-1}) as well as the carbonyl group at *ν* (1708) cm^{-1} in the

compounds [C_6, C_7]. The mechanism or the reaction can be outlined in the scheme 5.



Scheme 5: Mechanism steps of Imides synthesis

Table 2: Spectral Data of Compounds [C_1-C_7]

Comp NO.	ν(N-H)	ν(=CH) Olefin	ν(C=C) aromatic	ν(C=O) Carboxylic	ν(C=O) amide	ν(N-N)	others
[C_1]	-	3078	1534	-	-	1438	ν(NH_2) 3433,3379, ν (C-S)937 ν(N-N)1438 ν(C-O)1253 ν(C=N) 1662
[C_2]	3267	3059	1523	1728	1693	1419	ν (C-S)891 ν(C-N)1311 ν(C-O)1203 ν(C=C)olefin(1570)
[C_3]	3263	3035	1504	1725	1631	1435	ν(C=C) olefin(1566) ν(C-S)925 ν(C-N)1384 ν(C-O)1219
[C_4]	3263	3082	1523	1720	1639	1419	ν (C-S)910 ν(C-N)1400 ν(C-O)1288 ν(C=C)olefin(1558)
[C_5]	3363	3012	1520	1724	1693	1419	ν(C-Br)748 ν (C-S)914 ν(C-N)1307 ν(C-O)1242 ν(C=C)olefin(1555)
[C_6]	3275	3095	1522	1708	-	1420	ν(O-H)taut 3417 ν(C-H)Aliph 2916,2850 ν(C-N)1373 ν(C=S)1319
[C_7]	3295	3066	1525	1720	-	1422	ν(O-H)taut 3407 ν(C- H)Aliph 2935,2900 ν(C -N)1373 ν(C =S)1319

Biological Part

The biological activates of some prepared compounds (C_1, C_2, C_6) were tested against bacterial strains and fungi. Escherichia coli, staphylococcus aureus, and Rhizopus emporium using agar well diffusion method.

Table 3 shows anti-bacterial and anti-fungal results which were interpreted in terms of the

diameter of inhibition zone for antibacterial activity.

Compounds (C_1, C_2, and C_6) showed a medium biological effect against *Staphylococcus aureus* and against *E.coli* because these compounds contain (oxadiazole, imide) rings.

Table 3: biological activity for some synthesized compounds

	Inhibition zone (6mm.)			
Gram negative		***Gram positive***	***Fungi (yeast***	
Compound No.1000 ppm	***E.coli***	***Staphylococcus aureus***	*Rhizopus emporium*	
C_1	12	11	-	
C_2	13	11	-	
C_6	12	12	-	
DMSO	-	-	-	

Conclusion

In this work, we have succeeded in synthesizing new 5-Styryl-2-amino-1,3,4-thiadiazole derivatives bearing amic acid and imide moiety at the position, which gave highly biological activity agreement with the proposed structure, so the compounds [C_1, C_2, C_6] were evaluated for their anti-bacterial, anti-fungal, and rhizosphere emporium using agar diffusion method. Compounds (C_1, C_2, and C_6) showed high biological effects against Staphylococcus aureus and E. coli. The structure of these compounds was confirmed with FT-IR and some of them by ^{1}HNMR.

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Authors' contributions

All authors contributed toward data analysis, drafting and revising the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

We have no conflicts of interest to disclose.

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