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Microwave Assisted Multicomponent Design of Methyl 2-(3-alkyl-4-oxo-2-(pyridin-3-ylimino)thiazolidin-5-ylidene) Acetate as Antimicrobial Agents

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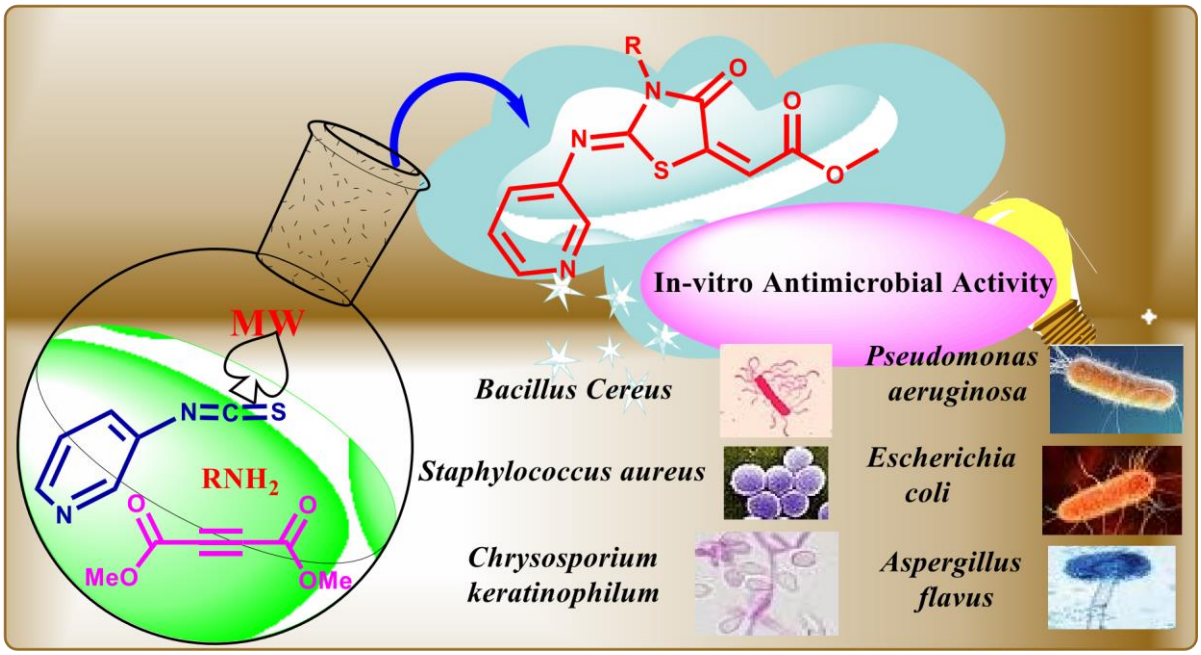
Abstract:

An effective and simple designing of methyl 2-(3-alkyl-4-oxo-2-(pyridin-3ylimino)thiazolidin-5-ylidene)acetate **4-8** *via* three-components reaction of 3-pyridyl isothiocyanate, primary aliphatic amines namely: methanamine **2a**, ethanamine **2b**, propan-1amine **2c**, 2-aminoethanol **2d**, 1-aminopropan-2-ol **2e** and dimethyl acetylenedicarboxylate under microwave reaction conditions to afforded methyl 2-(3-alkyl-4-oxo-2-(pyridin-3ylimino)thiazolidin-5-ylidene)acetate **4-8**, respectively. Furthermore, the novel 1,3thiazolidin-4-one derivatives were screened against six microorganisms. The pathogenic microorganisms that were selected included *Aspergillus flavus* and *Chrysosporium keratinophilum* as fungus, *Pseudomonas aeruginosa and Escherichia coli as* Gram-negative bacteria, & *Staphylococcus aureus* and *Bacillus cereus* as Gram-positive bacteria. Compounds **7** and **8** was the greatest promising antibacterial & antifungal agent may be due to the increase by the long aliphatic chain and the presence of the hydroxyl group.

Keywords: Microwave; 1,3-Thiazolidin-4-one; Dimethyl acetylenedicarboxylate; Multicomponent reaction, Antimicrobial



Introduction:

These days, most harmful microbial have become resistant to widely used antibiotics and anti-infective medications, which directly affects every individual. Additionally, in bacterial consortiums, multidrug-resistant (MDR) microorganisms have developed crossresistances, hence a research for novel potent antimicrobial and antibacterial agents is required. Therefore, employing the mainstream medicinal chemistry approach, structural alteration must be used to generate a new potential candidate or candidates in order to battle the wide range of antibacterial resistance [1, 2]. The enhancement of synthetic method for thiazolidinone is a significant work field in heterocyclic products owed their noteworthy pharmaceutical properties [3,4]. Their analogues are significant in many biological products such as antiinflammatory [5], anticancer [5, 6], anti-HIV [7], Antitubercular [8, 9], antifungal [10], antidiabetic [11], anticonvulsant [12], analgesic [13, 14], anaesthetic [15, 16], amoebicidal[17], antioxidant[18], antimalarial [19] and antimicrobial [20-22] agents. Similarly, thiazolidinone frameworks contain EGFR and HER-2 kinase inhibitor [23]. It is well known that microwave irradiation has become an important method that can be used successfully in several fields of designing of heterocyclic compounds [24-29]. Not only decreasing the times of chemical reaction from hours to seconds but the decomposition or polymerization of the reactants and the reversibility of the reaction have been avoided, i.e. it can diminish side reactions and increase yields, a situation not accessible in conventional methods [30]. The multi-component reactions (MCRs) has an effectual technique in arena of heterocyclic design because their straightforwardness, excellent selectivity, condensed reaction time, easy work-

up, egofriendly, and high yielding [31-35]. According to this perspective, we herein demand to report a novelty enhanced technique for the design of biologically motivating poly-functionalized 1,3thiazolidin-4-one compounds using three multi-components reaction under microwave irradiation and assess their antimicrobial activities.

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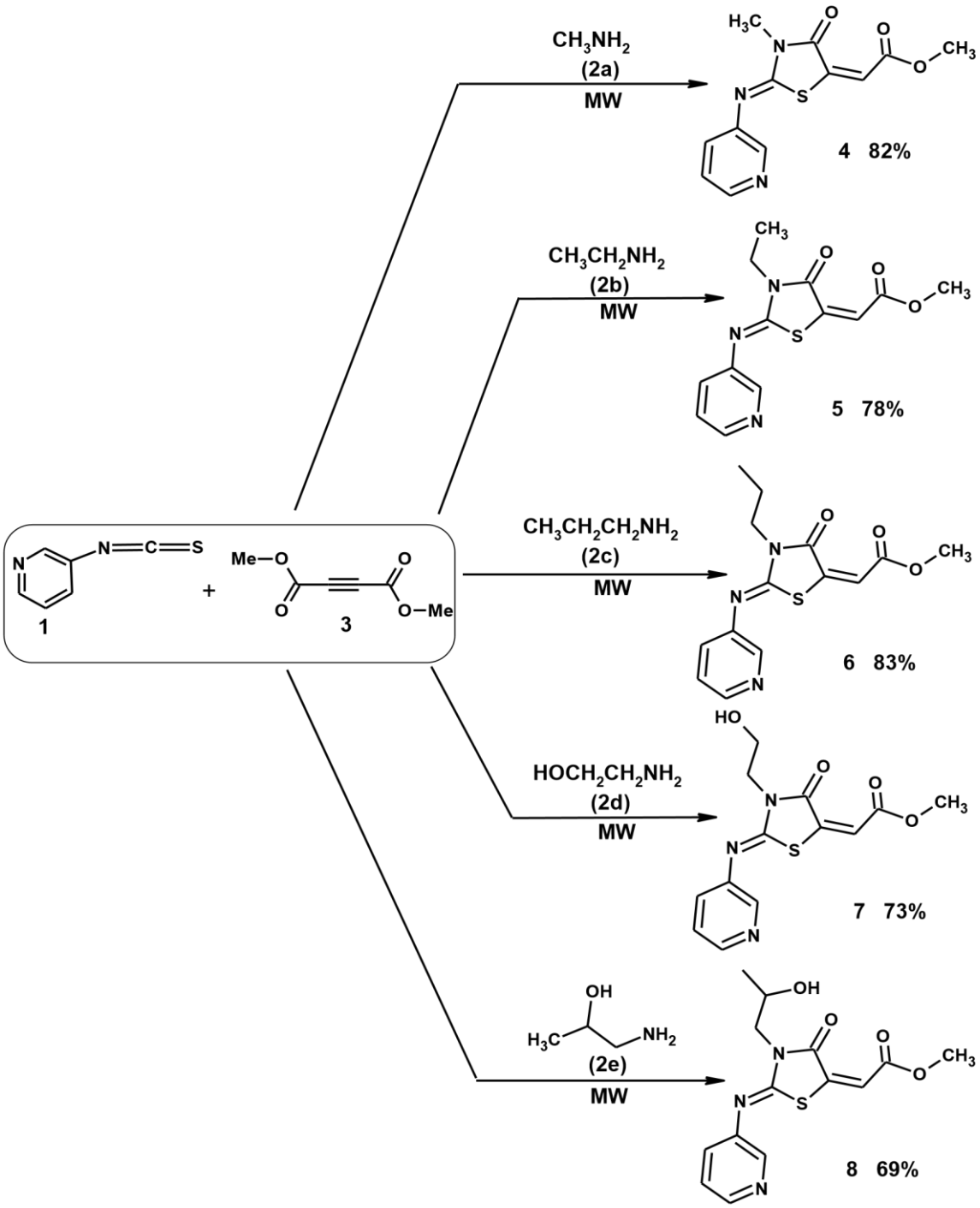
Results and discussion

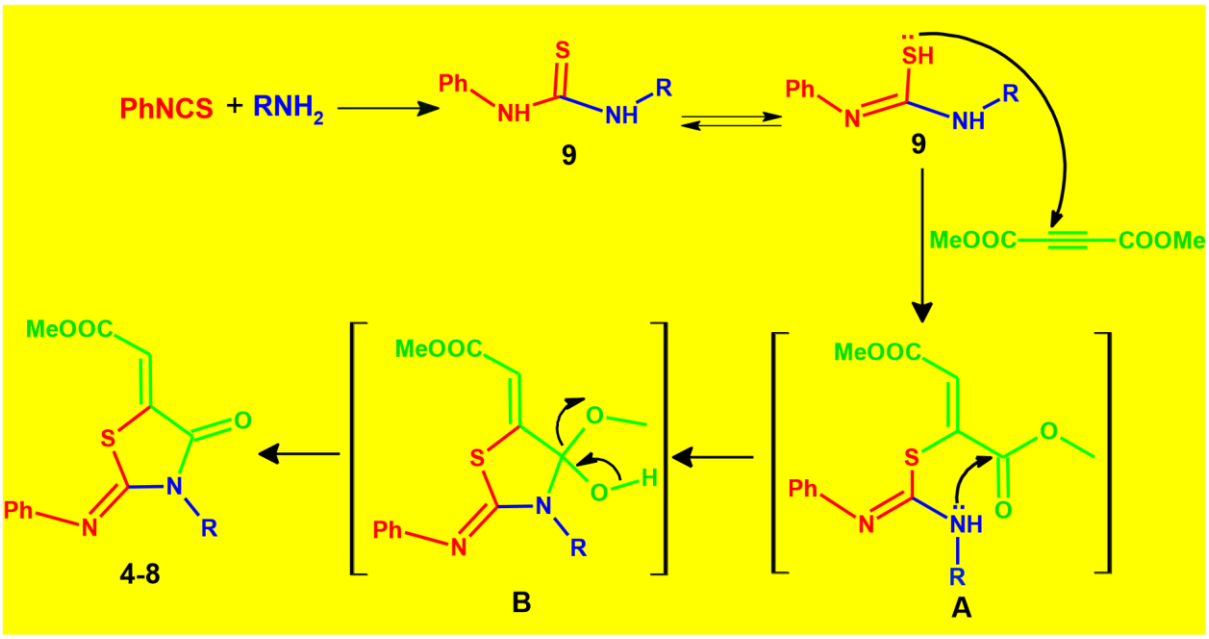
In this research, we hope to describe a new operative & simple method of design of 1,3thiazolidin-4-one compounds through three-components reaction of 3-pyridyl isothiocyanate, primary aliphatic amine derivatives & dimethyl acetylenedicarboxylate in ethyl alcohol via microwave irradiation. 1,3-thiazolidin-4-one derivatives 4-8 were obtained (Scheme 1) within a limited time irradiation (60-100 sec) in very good to excellent yields simply by filtration and recrystallization, and were avoiding of using toxic solvent. As an initial experimental was achieved by heating an equimolecular amounts of 3-pyridyl isothiocyanate **1**, methylamine **2a** & dimethyl acetylenedicarboxylate **3** in 20 ml ethyl alcohol under MW conditions for about 58 sec. After optimization of the technique, the possibility of the method were examined with a sequence of primary amine derivatives to yielded the equivalent 1,3-thiazolidin-4-one **4-8** (Scheme 1).



Scheme 1: Designing of 1,3-thiazolidin-4-one **4-8**

The formation of 1,3-thiazolidin-4-one **4-8** may be begins by the formation of thiourea **9** by reaction between pyridylisothiocyanate and primary amine followed by the sulfur atom of thiourea attacking the C≡C bond of dimethyl acetylenedicarboxylate **3** nucleophilically to produce intermediate **A**. This intermediate then goes through intramolecular cyclization by nucleophilically attacking the NH group onto the carbonyl group, and finally, methanol is

eliminated to produce methyl 2-(3-alkyl-4-oxo-2-(pyridin-3-ylimino)thiazolidin-5ylidene)acetate **4-8** (Scheme 2).



Scheme 2: Reaction mechanism for the formation of methyl 2-(3-alkyl-4-oxo-2-(pyridin-3-ylimino)thiazolidin-5-ylidene)acetate **4-8.**

The chemical structures of methyl 2-(3-alkyl-4-oxo-2-(pyridin-3-ylimino)thiazolidin5-ylidene)acetate **4-8** were proved based on their spectral (IR, NMR) and elemental analysis results. For instance, the IR spectrum of **4** displayed an absorption peaks at 1714, 1683 cm^{-1} caused by the 2 carbonyl groups. Its ^{1}H NMR spectrum displayed the occurrence of 2 singlet signal at δ 3.74, 3.32 ppm, distinguishing of OCH_3 and CH_3 protons, respectively; it also exhibited a singlet signal at δ 6.79 ppm outstanding to the vinylic proton; furthermore, it displayed two triplet signals and one singlet signal at 7.47-7.00 ppm distinguishing the aromatic protons. The ^{13}C NMR spectrum of **5** displayed two signals at 166.20 and 164.83 ppm caused by two carbonyl groups C=O and COOMe, respectively; while the pyridyl carbons appears at 147.84, 129.91, 125.54, 121.40; beside two signal at 151.94 and 141.75 ppm characterized of the C-2 and C-5 of thiazole ring, respectively; it also exhibited a signal at δ 115.58 ppm outstanding to the vinylic carbon, in the other hand O C H_3 is described by signal at 51.98 ppm, finally the methyl carbon appear at 29.77 ppm.

4. Antimicrobial effectiveness

Using the agar plate disc-diffusion method, the novel synthetic compounds' primary antimicrobial screening was evaluated against six microorganisms. The pathogenic microorganisms that were selected included *Aspergillus flavus* and *Chrysosporium keratinophilum* as fungus, *Pseudomonas aeruginosa* and *Escherichia coli* as Gram-negative bacteria, and *Staphylococcus aureus* and *Bacillus cereus* as Gram-positive bacteria. Ketoconazole and Ciprofloxacin were used as standard reference antifungal and antibacterial compound, respectively. The data shown in Table 1 establish that products **4**-**6** have weak effectiveness on Gram-negative bacteria, but they were supplementary effectiveness on Grampositive bacteria based on antimicrobial testing. Compounds **7** and **8** demonstrated strong action agains *B. Cereus* and *S. aureus*, while compound **8** outperformed the standard (Ciprofloxacin) against *E. coli* at all concentrations. While all of the compounds showed a mild inhibitory effect against *P. aeruginosa* at low doses; however, the inhibitory effect increased with concentration.

Regarding the antifungal activity, only compound **8** exhibited a highly potent activity against *A. flavus*, while compounds **7** had strong activities against *C. keratinophilum*. The activity of the other examined substances was minimal. According to Tables 1 and 2, Compounds **7** and **8** is the most promising antibacterial and antifungal agent may be due to the increase in the aliphatic chain and the presence of the hydroxyl group.

Table 1: Antibacterial effectiveness of products **4-8** by measuring inhibition zone (mm).

Type / Comp.	*Gram positive*						*Gram negative*					
	Bacillus Cereus			*Staphylococcus aureus*			*Pseudomonas aeruginosa*			*Escherichia coli*		
	A	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*
4	15	19	23	15	21	28	11	19	22	5	16	21
5	16	20	22	18	25	32	10	15	18	14	16	24
6	14	19	22	19	26	31	19	25	29	15	18	22
7	20	26	36	19	25	36	13	19	22	29	35	48
8	19	25	37	24	32	41	11	22	27	30	39	56
Control	0	0	0	0	0	0	0	0	0	0	0	0
Cip.	25	28	40	31	39	46	24	29	46	29	37	51

A = concentration of compound = 10,000 ppm, **B** = concentration of compound = 30.000 ppm.
C= concentration of compound = 50,000 ppm

Table 2: Antifungal activity of compounds **4-8** by measuring inhibition zone (mm).

Fungi / *Compound*	*A. flavus*			*C. keratinophilum.*		
	A	*B*	*C*	*A*	*B*	*C*
4	10	15	18	10	14	18
5	10	17	20	11	16	19
6	9	15	19	17	20	22
7	18	24	29	23	30	37
8	21	28	34	21	28	34
Control	0	0	0	0	0	0
Ketoconazole	25	32	39	27	33	41

A = concentration of compound = 10,000 ppm, **B** = concentration of compound = 30.000 ppm.
C= concentration of compound = 50,000 ppm

Experimental

General procedure for designing of components 4-8:

A mixture of 3-pyridyl isothiocyanate **1**(1.36 gram, 0.01 mol), primary amine **2**(10 mmol) namely: methanamine **2a** (0.31g, 10 mmol), ethanamine **2b** (0.45g, 10 mmol), propan1-amine **2c** (0.59g, 10 mmol), 2-aminoethanol **2d** (0.39g, 10 mmol), 1-aminopropan-2-ol **2e** (0.75g, 10 mol) and dimethyl acetylenedicarboxylate (1.42g, 10 mmol) **3** in 20 ml ethanol was irradiated in a microwave oven about 80 sec. The reaction mixture cooled at 25 ^{0}C, the precipitated compounds were filtered & recrystallized according to suitable solvent to give methyl 2-(3-alkyl-4-oxo-2-(pyridin-3-ylimino)thiazolidin-5-ylidene)acetate **4-8**.

Methyl 2-(3-methyl-4-oxo-2-(pyridin-3-ylimino)thiazolidin-5-ylidene)acetate (4):

Yield 82 %, m.p.:137-138 °C; ν_{max}(ATR) 3054, 2972, 2887, 1714, 1683 cm^{-1}. ^{1}H-NMR (400 MHz,DMSO-d_6) δ 7.45-7.41(t, *J*= 8Hz, 2H,CH_{arom}), 7.24-7.21(t, *J*= 8 Hz, 1H,CH_{arom}), 7.00(s, 1H, $CH_{arom.}$), 6.79(s, 1H, CH_{vinyl}), 3.74 (s, 3H, OMe), 3.32 (s, 3H, Me). ^{13}C-NMR(100 MHz, DMSO-d_6) δ 166.20, 164.83, 151.94, 147.84, 141.75, 129.91, 125.54, 121.40, 115.58, 52.98, 29.77. Anal. Calcd. for $C_{12}H_{11}N_3O_3S$ (277.30): C, 51.98; H, 4.00; N, 15.15. Found: C, 52.08; H, 3.85; N, 15.23.

Methyl 2-(3-ethyl-4-oxo-2-(pyridin-3-ylimino)thiazolidin-5-ylidene)acetate (5):

Yield 78%, m.p.:148-150 °C; ν_{max} (ATR) 3071, 2950, 2864, 1711, 1676 cm-1. ^{1}H-NMR (400 MHz, DMSO-d6) δ 7.47-7.43(m, 2H, CH_{arom}), 7.41-7.33(m, 1H, CH_{arom}), 7.22(s, 1H, $CH_{arom.}$), 6.04 (s, 1H, CH_{vinyl}), 3.77 (s, 3H, OMe), 2.98-2.92 (q, 2H, *J*= 8 Hz, CH_2) 1.18-1.15(t, 3H, *J*= 8 Hz, Me). ^{13}C-NMR (100 MHz, DMSO-d6) δ 167.72, 163.74, 146.89, 145.66, 145.34, 141.68, 125.22, 120.90, 115.64, 51.91, 41.16, 19.68. Anal. Calcd. for $C_{13}H_{13}N_3O_3S$ (291.33): C, 53.60; H, 4.50; N, 14.52. Found: C, 53.84; H, 4.38; N, 14.40.

Methyl 2-(4-oxo-3-propyl-2-(pyridin-3-ylimino)thiazolidin-5-ylidene)acetate (6):

Yield 83%, m.p.: 98-99 °C; □$_{max}$ (ATR) 3068, 2957, 2876, 1719, 1686 cm-1. ^{1}H-NMR (400 MHz, DMSO-d6) δ 7.46-6.99(m, 5H, 4CH$_{arom}$+1CH$_{vinyl}$), 3.75 (s, 3H, OMe), 2.56-2.54 (t, *J* = 4 Hz, 2H,CH$_2$), 1.71-167 (t, *J* = 8 Hz, 2H,CH$_2$), 0.95-.93(t, *J* = 8Hz, 3H,CH$_3$). Anal. Calcd.for $C_{14}H_{15}N_3O_3S$ (305.35): C, 55.07; H, 4.95; N, 13.76. Found: C, 55.25; H, 4.81; N, 13.67.

Methyl 2-(3-(2-hydroxyethyl)-4-oxo-2-(pyridin-3-ylimino)thiazolidin-5-ylidene)acetate (7):

Yield 73 %; m.p.: 146-148 °C; □$_{max}$ (ATR) 3075, 2966, 2882, 1724, 16775 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d6) δ 7.47-7.43(m, 2H, CH$_{arom}$), 7.23-7.17(m, 2H, CH$_{arom}$), 7.05(s, 1H, CH$_{vinyl}$), 4.54 (br. s, 1H, HO-), 4.44-4.41 (t, *J* = 8 Hz, 2H, CH$_2$), 4.01-3.99 (t, *J* = 8 Hz, 2H, CH$_2$), 3.85 (s, 3H, OCH$_3$). ^{13}C-NMR (100 MHz, DMSO-d6) δ 166.14, 165.21, 141.03, 129.49, 125.80, 121.38, 121.01, 116.77, 60.98, 52.52, 45.97. Anal. Calcd.for $C_{13}H_{13}N_3O_4S$ (307.32): C, 50.81; H, 4.26; N, 13.67. Found: C, 50.98; H, 4.08; N 13.80.

Methyl 2-(3-(2-hydroxypropyl)-4-oxo-2-(pyridin-3-ylimino)thiazolidin-5-ylidene)acetate (8):

Yield 69 %; 115-117 °C; □$_{max}$ (ATR) 3081, 2964, 2861, 1708, 1690 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d6) δ 7.47-7.42(m, 2H, CH$_{arom}$), 7.21-7.15(m, 2H, CH$_{arom}$), 7.04(s, 1H, CH$_{vinyl}$), 4.39-4.32(m, 1H, CH), 4.24-4.22(d, *J* = 8 Hz, 2H, CH$_2$), 3.85 (s, 3H, OCH$_3$), 3.83 (br. s, 1H, OH),1.38(d, *J* = 6 Hz, 3H, CH$_3$). Anal. Calcd. for $C_{14}H_{15}N_3O_4S$ (321.35): C, 52.33; H, 4.71; N, 13.08. Found: C, 52.75; H, 4.59; N, 13.27.

Antimicrobial Activity:

(Methanesulfinyl)methane (DMSO) was used to dissolve the compounds. To make sure the solvent had no impact on enzyme activity or microbial growth, negative control experiments with identical amounts of DMSO were carried out. Via the agar diffusion technique (cup &

plate technique) [36], the inhibitory impact of compounds **4–8** was assessed *in vitro* growth of a comprehensive spectrum of bacteria and fungi via estimating the zone of inhibition on agar plates at three different concentrations: 10 ppm, 30ppm, & 50 ppm. The solvent control was DMSO. Every plate was incubated for 48 hours for bacteria and 72 hours for fungus at 37±0.5 °C. Using a millimeter scale, the compounds' zone of inhibition was determined.

Conclusion

Finally, methyl 2-(3-alkyl-4-oxo-2-(pyridin-3-ylimino)thiazolidin-5-ylidene)acetates were designing *via* three-components reaction of 3-pyridyl isothiocyanate, primary aliphatic amines & dimethyl acetylenedicarboxylate under both microwave reaction conditions was introduced. In the other hand, the novel 1,3-thiazolidin-4-on derivatives were screened against six microorganisms. The pathogenic microorganisms that were selected included *Aspergillus flavus* and *Chrysosporium keratinophilum* as fungus, *Pseudomonas aeruginosa and Escherichia coli as* Gram-negative bacteria, & *Staphylococcus aureus* and *Bacillus cereus* as Gram-positive bacteria. Methyl 2-(3-(2-hydroxyethyl)-4-oxo-2-(pyridin-3 ylimino) thiazolidine -5- ylidene) acetate)7(, Methyl 2-(3-(2-hydroxypropyl)-4-oxo-2-(pyridin-3ylimino)thiazolidin-5-ylidene)acetate (8) are the greatest promising antibacterial & antifungal agent may be due to the increase in the aliphatic chain and the presence of the hydroxyl group.

Conflict of Interest

The author confirmed that there is no any conflict of interest.

Supporting Information

Experimental methods & characterization results for products **4-8** associated with this manuscript are found in the Supporting Information file.

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