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Synthesis of (Z)-2-((5-(2-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)butanoic Acid as Antimicrobial Agent

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Abstract: Rhodanine and substituted aromatic aldehydes prompted via knoevenagel condensation in the presence of sodium acetate and glacial acetic acid to give an excellent yield of thioxothiazolidin-4-one derivatives. Synthesis of (Z)-2-((5-(2-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)butanoic acid as an antimicrobial agent (6a-l). All these synthesized compounds were characterized and screened for their antimicrobial activity. According to the results obtained, most compounds showed good to moderate antimicrobial activity. Among these compounds (6d) shows very good and moderate activity compared to standard drugs against bacteria *B. subtilis*, *S. aureus*, and *E. Coli*. Some of the most potent compounds, namely (6a, 6c, and 6d), possessed selectively antibacterial activity. Also, some compounds (6f, 6j, and 6k) show very good and moderate activity compared to standard drugs against *C. albicans*, *A. flavus*, and *A. niger*.

Keywords: Rhodanine; aromatic aldehydes; knoevenagel condensation; antimicrobial.

1. Introduction

Antimicrobial Infections caused by various microbes are among the leading causes of death worldwide. Currently available, a limited number of antibiotics for the treatment of infection and the constant development of resistance to the recently used antimicrobial agents posture a serious challenge [1]. Thiazole and thiazolidinones scaffolds containing carbonyl group are known for their significant biological activities, which are clear in these compounds present in the chemical structure of many approved marketed drugs. Thiazole and thiazolidinones derivatives have been reported to have anticonvulsant [2,3], antimicrobial [4-7], anti-inflammatory [8,9], anticancer [10], antidiabetic [11-13], antiviral, and anti-HIV [14-17], antihyperlipidemic [18-20], antioxidant [21] and antihypertensive [22].

The substituted thiazole and thiazolidinones moiety has attracted considerable interest in developing biologically active compounds. In the present study, substituted thiazolidinones were synthesized and evaluated as antimicrobial agents from the heterocyclic scaffold.

Continuing our previous work on thiazole, thiazolidinones, and biological activity [23-31]. In the present work, we report the synthesis and screening of the antimicrobial activity of

synthesized compounds. All the synthesized compounds (6a-l) have been characterized by physical data and spectral analysis.

2. Materials and Methods

2-chlorobenzaldehyde, 2-thioxothiazolidin-4-one, and various solvents were commercially available in the market. The major chemicals were purchased from Merck and Avra labs. IR spectra were recorded on an FT-IR (Bruker). Melting points were recorded on SRS Optimelt, melting point apparatus, which are uncorrected. ^{1}H NMR spectra were recorded on a 400 MHz Bruker spectrometer and reported as parts per million (ppm) downfield from a tetramethylsilane internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Mass spectra were taken with Micromass-QUATTRO-II of WATER mass spectrometer.

2.2. Spectral characterization.

2.2.1. (Z)-2-((5-(2-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)propanoic acid (6a).

Yellow solid. Yield: 98%. mp 180–182 ºC; ES-MS m/z: 310.85, IR νmax/cm^{-1}: 3397 (OH), 2850 (CH–Ar), 1734 (C=O), 1649 (C=C), 1486 (C=N), 1280 (C-S), 1013 (C–N). ^{1}H NMR (400 MHz, DMSO): δppm = 1.40–1.42 (d, 3H, CH_3), 4.60–4.62 (m, 1H, CH), 7.35–7.40 (m, 4H, ArH), 7.70 (s, 1H, =CH), 10.20 (s, 1H, NH), 12.65 (s, 1H, OH). Molecular formula $C_{13}H_{11}ClN_2O_3S$.

2.2.2. (Z)-2-((5-(2-chlorobenzylidene) -4-oxo- 4,5-dihydrothiazol -2-yl)amino)-3-methyl butanoic acid (6b**).**

Yellow solid. Yield: 96%. mp 170–172 ºC; ES-MS m/z: 339.00, IR νmax/cm^{-1}: 3463 (OH), 2969 (CH–Ar), 1730 (C=O), 1641 (C=C), 1490 (C=N), 1183 (C-S), 1093 (C–N). ^{1}H NMR (400 MHz, DMSO): δppm= 0.80–0.82 (d, 6H, CH_3), 1.40–1.42 (m, 1H, CH), 3.30–3.32 (d, 1H, CH), 7.30–7.30-5.50 (m, 4H, ArH), 7.65 (s, 1H, =CH), 9.85 (s, 1H, NH), 11.02 (s, 1H, OH). Molecular formula $C_{15}H_{15}ClN_2O_3S$.

2.2.3. (Z)-2-((5-(2-chlorobenzylidene) -4-oxo- 4,5-dihydrothiazol -2-yl) amino) -3-methylpentanoic acid (6c).

Yellow solid. Yield: 92%. mp 160–162 ºC; ES-MS m/z: 353.10, IR νmax/cm^{-1}: 3463 (OH), 2959 (CH–Ar), 1712 (C=O), 1642 (C=C), 1486 (C=N), 1198 (C-S), 1003 (C–N). ^{1}H NMR (400 MHz, DMSO): δ ppm= 1.01–1.03 (t, 3H, CH_3), 1.21–1.23 (d, 3H, CH_3), 1.83–1.85 (m, 3H, CH_2, CH), 3.42–3.44 (d, 1H, CH), 7.40–7.60 (m, 4H, ArH), 7.80 (s, 1H, =CH), 9.04 (s, 1H, NH), 11.75 (s, 1H, OH). Molecular formula $C_{16}H_{17}ClN_2O_3S$.

2.2.4. (Z)-2-((5-(2-chlorobenzylidene)-4- oxo-4,5-dihydrothiazol -2-yl) amino)-3-phenylpropanoic acid (6d).

Yellow solid. Yield: 96%. mp 145–147 ºC; ES-MS m/z: 387.20, IR νmax/cm^{-1}: 3397 (OH), 2959 (CH–Ar), 1694 (C=O), 1611 (C=C), 1488 (C=N), 1196 (C-S), 1089 (C–N). ^{1}H NMR (400 MHz, DMSO): δ ppm= 2.40–2.42 (d, 2H, CH_2), 3.32–3.34 (t, 1H, CH), 7.40–7.70

(m, 9H, ArH), 7.75 (s, 1H, =CH), 9.02 (s, 1H, NH), 11.70 (s, 1H, OH). Molecular formula $C_{19}H_{15}ClN_2O_3S$.

2.2.5. (Z)-2-((5-(2-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)pentanedioic acid (6e).

Yellow solid. Yield: 94%. mp 133–135 ºC; ES-MS m/z: 369.20, IR νmax/cm^{-1}: 3227 (OH), 2989 (CH–Ar), 1693 (C=O), 1612 (C=C), 1488 (C=N), 1231 (C-S), 1006 (C–N). ^{1}H NMR (400 MHz, DMSO): δ ppm= 1.25–1.27 (m, 2H, CH_2), 2.25–2.27 (t, 2H, CH_2), 2.55–2.57 (t, 1H, CH), 7.20–7.60 (m, 4H, ArH), 7.70 (s, 1H, =CH), 9.04 (s, 1H, NH), 11.80 (s, 2H, OH). Molecular formula $C_{15}H_{13}ClN_2O_5S$.

2.2.6. (Z)-2-((5-(2-chlorobenzylidene) -4-oxo-4,5 -dihydrothiazol -2-yl)amino) -4-methylpentanoic acid (6f).

Yellow solid. Yield: 96%. mp 166–168 ºC; ES-MS m/z: 353.00, IR νmax/cm^{-1}: 3396 (OH), 2989 (CH–Ar), 1748 (C=O), 1680 (C=C), 1486 (C=N), 1192 (C-S), 1000 (C–N). ^{1}H NMR (400 MHz, DMSO): δ ppm= 1.00–1.10 (d, 6H, CH_3), 1.60–1.62 (m, 1H, CH), 1.90–1.92 (t, 2H, CH_2), 2.20 (s, 1H, NH), 3.30–3.32 (t, 1H, CH), 7.30–7.50 (m, 4H, ArH). 7.70 (s, 1H, =CH), 9.90 (s, 1H, NH), 11.10 (s, 1H, COOH). Molecular formula $C_{16}H_{17}ClN_2O_3S$.

2.2.7. (Z)-2-((5-(2-chlorobenzylidene) -4-oxo-4,5- dihydrothiazol-2-yl) amino)-3 -hydroxypropanoic acid (6g).

Yellow solid. Yield: 94%. mp 198–200 ºC; ES-MS m/z: 403.85.20, IR νmax/cm^{-1}: 3398 (OH), 2963 (CH–Ar), 1738 (C=O), 1610 (C=C), 1481 (C=N), 1173 (C-S), 1011 (C–N). ^{1}H NMR (400 MHz, DMSO): δ ppm= 11.82 (s, 1H,). 7.92 (s, 1H), 7.80 (dd, J = 7.7, 1.5 Hz, 1H), 7.51 (ddd, J = 8.1, 6.8, 1.3 Hz, 1H), 7.48 – 7.39 (m, 4H), 6.97 (dt, J = 8.6, 0.9 Hz, 2H), 6.76 – 6.70 (m, 2H), 4.57 (dt, J = 7.3, 6.5 Hz, 1H), 3.20 – 3.12 (m, 1H), 2.95 (ddt, J = 13.9, 6.6, 0.9 Hz, 1H).Molecular formula $C_{19}H_{15}ClN_2O_4S$.

2.2.8. (Z)-2-((5-(2-chlorobenzylidene) -4-oxo-4,5-dihydrothiazol -2-yl)amino) -3-mercaptopropanoic acid (6h).

Yellow solid. Yield: 95%. mp 195–197 ºC; ES-MS m/z: 342.30, IR νmax/cm^{-1}: 3397 (OH), 2952 (CH–Ar), 1714 (C=O), 1607 (C=C), 1487 (C=N), 1147 (C-S), 1033 (C–N). ^{1}H NMR (400 MHz, DMSO): δ ppm= 1.10 (s, 1H, SH), 2.15–2.17 (d, 2H, CH_2), 2.18–2.19 (t, 1H, CH), 5.70–5.72 (t, 2H, CH_2), 7.00–7.30 (m, 4H, ArH), 8.50 (s, 1H, =CH), 9.10 (s, 1H, NH), 10.90 (s, 1H, OH). Molecular formula $C_{13}H_{11}ClN_2O_3S_2$.

2.2.9. (Z)-2-((5-(2-chlorobenzylidene) -4-oxo-4,5-dihydrothiazol -2-yl)amino) -4-(methylthio)butanoic acid (6i).

Yellow solid. Yield: 97%. mp 202–204 ºC; ES-MS m/z: 371.30, IR νmax/cm^{-1}: 3497 (OH), 3031 (CH–Ar), 1713 (C=O), 1610 (C=C), 1551 (C=N), 1177 (C-S), 1007 (C–N). ^{1}H NMR (400 MHz, DMSO): δ ppm= 2.10 (s, 2H, CH_3), 2.15–2.17 (m, 2H, CH_2), 2.60–2.62 (t, 2H, CH_2), 3.60–3.62 (t, 1H, CH), 7.35–7.70 (m, 4H, ArH), 8.12 (s, 1H, =CH), 9.90 (s, 1H, NH), 10.90 (s, 1H, OH). Molecular formula $C_{15}H_{15}ClN_2O_3S_2$.

2.2.10. (Z)-2-((5-(2-chlorobenzylidene)-4- oxo-4,5- dihydrothiazol-2 -yl)amino) -3-(1H-imidazol-2-yl)propanoic acid (6j).

Yellow solid. Yield: 98%. mp 140–142 ºC; ES-MS m/z: 378.00, IR νmax/cm^{-1}: 3455 (OH), 3031 (CH–Ar), 1713 (C=O), 1610 (C=C), 1551 (C=N), 1488 (C-S), 1089 (C–N). ^{1}H NMR (400 MHz, DMSO): δ ppm= 1.25–1.27 (d, 2H, CH_2), 4.15–4.17 (d, 2H, CH_2), 5.30–5.32 (d, 2H, CH=CH), 6.95–6.97 (t, 1H, CH), 8.10–8.40 (m, 4H, ArH), 8.68 (s, 1H, =CH), 8.70 (s, 2H, NH), 10.90 (s, 1H, OH). Molecular formula $C_{16}H_{13}ClN_4O_3S$.

2.2.11. (Z)-2-((5-(2-chlorobenzylidene) -4-oxo- 4,5-dihydrothiazol- 2-yl)amino)-3-hydroxypropanoic acid (6k).

Yellow solid. Yield: 94%. mp 198–200 ºC; ES-MS m/z: 327.20, IR νmax/cm^{-1}: 3455 (OH), 3398 (OH), 2963 (CH–Ar), 1738 (C=O), 1610 (C=C), 1481 (C=N), 1173 (C-S), 1011 (C–N). ^{1}H NMR (400 MHz, DMSO): δ ppm= 2.05 (s, 1H, NH), 3.10–3.22 (t, 1H, CH), 3.60 (s, 1H, OH), 4.50–4.67 (d, 2H, CH_2), 7.40–7.55 (m, 4H, ArH), 7.82 (s, 1H, =CH), 10.82 (s, 1H, OH). Molecular formula $C_{13}H_{11}ClN_2O_4S$.

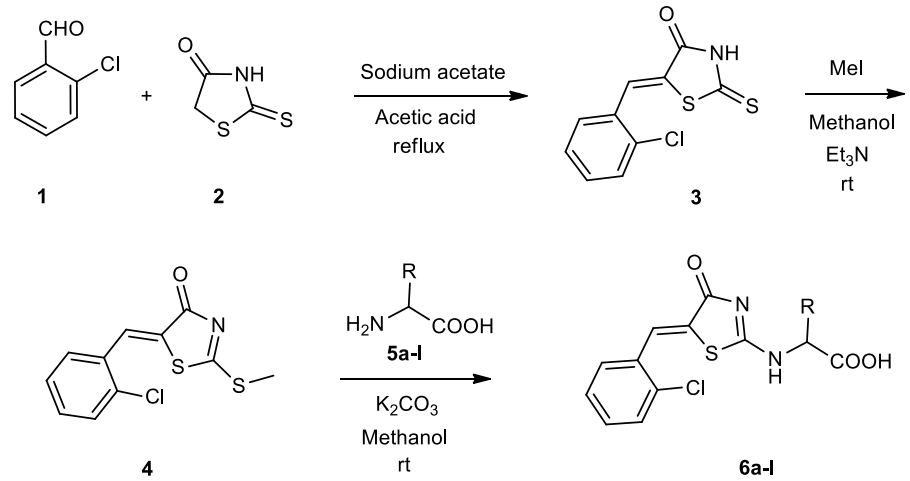
2.2.12. (Z)-2-((5-(2-chlorobenzylidene) -4-oxo- 4,5-dihydrothiazol -2-yl)amino) -3-hydroxybutanoic acid (6l).

Yellow solid. Yield: 96%. mp 163–165 ºC; ES-MS m/z: 341. IR νmax/cm^{-1}: 3396 (OH), 3031 (CH–Ar), 1714 (C=O), 1607 (C=C), 1486 (C=N), 1156 (C-S), 1033 (C–N). ^{1}H NMR (400 MHz, DMSO): δ ppm= 1.10–1.22 (d, 3H, CH_3), 3.40–3.55 (d, 1H, CH), 3.81–3.98 (m, 1H, CH), 5.04 (s, 1H, OH), 7.42–7.62 (m, 4H, ArH), 7.82 (s, 1H, =CH), 9.20 (s, 1H, NH), 10.52 (s, 1H, OH). Molecular formula $C_{14}H_{13}ClN_2O_4S$.

3. Results and Discussion

The synthesis of new protocols employed for the synthesis of thiazolidinone derivatives is presented in Scheme 1. The compound (Z)-5-(2-chlorobenzylidene)-2-thioxothiazolidin-4-one (3) was prepared by knoevenagel condensation between 2-chlorobenzaldehyde and 2-thioxothiazolidin-4-one in the presence of acetic acid and sodium carbonate at reflux condition. After that, this compound (3) was treated with iodomethane in the presence of trimethylamine and methanol as a solvent and stirred at room temperature to give (Z)-5-(2-chlorobenzylidene)-2-(methylthio)thiazol-4(5H)-one (4) excellent product yield. After that, this compound (4) was treated with various amino acids in the presence of base as potassium carbonate and methanol as a solvent and stirred at room temperature to give (Z)-2-((5-(2-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl) amino) substituted acid (6a-l) excellent product yield.

The physical parameters of the synthesized compounds (6a-l) are presented in Table 1. The reaction was completed in 25-120 min. to give the product a very good yield (92-98). Melting points were recorded on SRS Optimelt, melting point apparatus and are uncorrected, and TLC checked the purity of the synthesized compounds on silica gel pre-coated F254 Merck plates The structure of the synthesized compounds was confirmed by IR, ^{1}H NMR, ^{13}C NMR, and Mass spectral analysis.



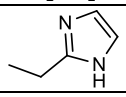
Scheme 1. Synthesis of (Z)-2-((5-(2-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino) substituted acid.

3.1. Biological evaluation.

3.1.1. Antimicrobial activity.

The antibacterial activity was evaluated against two Gram-positive bacteria, namely, *Bacillus subtilis* (NCIM-2063)and *Staphylococcus aureus* (NCIM-2901), and one Gram-negative bacterium *Escherichia coli* (NCIM-2256). The antibacterial activity of compounds was monitored by observing their Minimum Inhibitory Concentration (MIC, µg/mL) as previously mentioned [32] by broth dilution method using Ciprofloxacin and Ampicillin as standard drugs. The antifungal activity was evaluated against three fungal strains; *Candida albicans* (NCIM-3471), *Aspergillus flavus* (NCIM-539), and *Aspergillus niger* (NCIM-1196)using Fluconazole and Miconazole as standard drugs. Minimum inhibitory concentration (MIC, µg/mL) values for antifungal were determined using the standard agar dilution method [33,34]. Methanol was used as solvent control for both antibacterial and antifungal testing. MIC values of the tested compounds are presented in Table 2. From the antibacterial activity data (Table 2), the synthesized compounds of the present series showed better antimicrobial activity.

Table 1. Physical data of the synthesized compounds 3, 4, and 6a-l[a].

Compounds	Substituent (R)	Time (min)	Yield[b] (%)	Melting point (°C)
3	-	120	98	180-182
4	-	30	96	170-172
6a	$-CH_3$	25	92	160-162
6b	$-CH(CH_3)_2$	25	96	177-179
6c	$-CH(CH_3)CH_2CH_3$	30	96	145-147
6d	$-CH_2C_6H_5$	30	94	158-160
6e	$-CH_2-CH_2-COOH$	25	94	133-135
6f	$-CH_2CH(CH_3)_2$	35	96	166-168
6g	$-CH_2C_6H_4OH$	30	94	198-200
6h	$-CH_2SH$	30	95	195-197
6i	$-CH_2CH_2SCH_3$	30	97	202-204
6j		25	98	140-142
6k	$-CH_2OH$	25	96	184-186
6l	$-CH(OH)CH_3$	25	96	152-154

[a]Reaction condition (6a-l): Compound (4) (1 mmol), Amino acid (5a-l) (1.1 mmol), K_2CO_3 (1.1 mmol), 2 ml methanol at room temperature.
[b]Isolated yields

Compound 6a shows better antibacterial activity, MIC values 18.23, 16.21, and 16.11 µg/mL against *B. substilis*, *S. aureus*, and *E. coli*, respectively. Compound 6c shows better antibacterial activity, MIC values 20.23, 16.34, and 18.32 µg/mL against *B. substilis*, *S. aureus* and *E. coli*, respectively. The compound 6d shows better antibacterial activity, MIC values 15.34, 15.55, and 18.57 µg/mL against *B. substilis*, *S. aureus*, and *E. coli*, respectively.

Compound 6f shows moderate antifungal activity, MIC values are 15.32, 12.22, and 15.33 µg/mL against *C. albicans*, *A. flavus*, and *A. niger*, respectively. Compound 6j shows moderate antifungal activity, MIC values are 16.34, 13.14, and 14.11 µg/mL against *C. albicans*, *A. flavus*, and *A. niger*, respectively. Compound 6k shows moderate antifungal activity, MIC values are 16.55, 14.12, and 15.44 µg/mL against *C. albicans*, *A. flavus*, and *A. niger*, respectively. Compound 6l shows better antifungal activity, MIC values are 14.64 µg/mL against *C. albicans.* From the above data, our aim has been confirmed by synthesizing thiazolidinone derivatives are effective for enhanced antimicrobial activity.

Table 2. Antimicrobial activity of the synthesized compounds (**3, 4,** and **6a-l)** (MIC/MBC Values (µg/mL)).

Entry	Antibacterial activity (MIC values in µg/mL)			Antifungal activity (MIC values in µg/mL)		
	B. subtilis	*S. aureus*	*E. coli*	*C. albicans*	*A. flavus*	*A. niger*
3	70.24	55.12	70.24	70.12	88.23	75.44
4	70.25	36.23	66.56	12.23	95.23	95.23
6a	**18.23**	**16.21**	**18.57**	78.34	47.34	75.56
6b	70.12	68.23	68.32	75.55	55.56	65.67
6c	**20.23**	**16.34**	**18.32**	65.55	75.64	65.54
6d	**15.34**	**15.55**	**16.11**	65.44	50.22	60.55
6e	55.64	30.56	75.12	50.32	65.11	60.78
6f	20.33	67.56	70.13	**15.32**	**12.22**	**15.33**
6g	70.23	36.45	68.23	65.11	75.44	65.12
6h	50.23	80.54	70.34	65.23	50.33	60.24
6i	75.45	36.33	68.55	50.21	65.13	60.44
6j	60.45	40.22	70.32	**16.34**	**13.14**	**14.11**
6k	75.54	50.33	60.12	**16.55**	**14.12**	**15.44**
6l	40.33	45.33	70.24	**14.64**	25.21	30.23
Ciprofloxacin	8.50	8.50	7.05	-	-	-
Ampicillin	13.50	13.50	14.50	-	-	-
Fluconazole	-	-	-	6.25	6.25	6.25
Miconazole	-	-	-	14.12	9.25	9.25

10% of the mean; (-) denotes not tested.
The data represents the mean values of three replicates; Standard errors were all within

4. Conclusions

In summary, we have developed a new methodology for synthesizing thiazolidinone derivatives by coupling substituted aldehyde and rhodanine. This is an efficient and convenient synthesis and investigation of the potent antimicrobial activities of some new thiazolidinone derivatives (3, 4, 6a-l), discovering new structures that can be used as potent antimicrobial agents. The process also exhibits good to excellent yield. This method offers advantages such as chief starting materials and amino acids with mild reaction conditions, excellent yield, best conversion, and short reaction time. According to the results obtained, most compounds showed good to moderate antimicrobial activity. Among these compounds (6d) shows moderate activity compared to standard drugs against bacteria *B. subtilis*, *S. aureus*, and *E. Coli*. Some of the most potent compounds, namely (6a, 6c, and 6d), possessed selectively antibacterial activity. Also, compounds (6f, 6j, 6k, and 6l) show best activity compared to standard drugs against *C. albicans*, *A. flavus*, and *A. niger*.

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Conflicts of Interest

The authors declare no conflict of interest.

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Supplementary materials

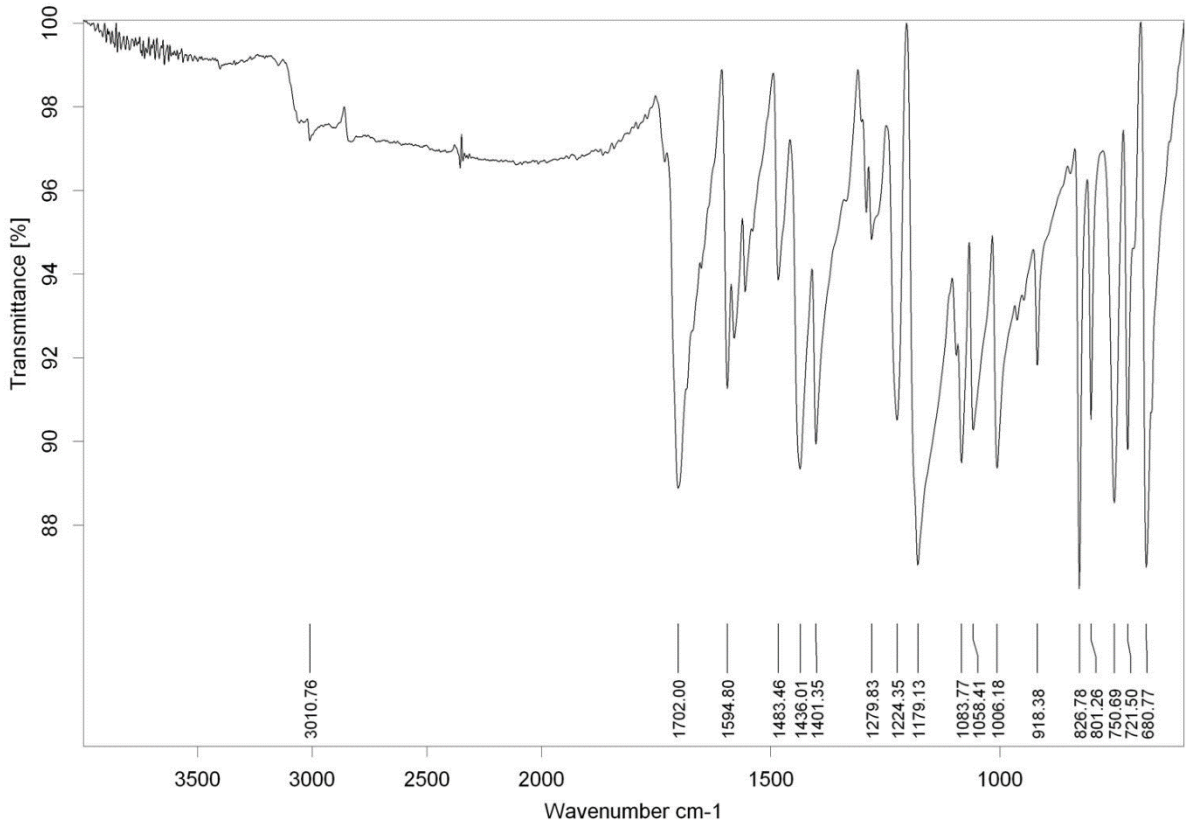


Figure S1. IR of (Z)-5-(2-chlorobenzylidene)-2-thioxothiazolidin-4-one (**3**).

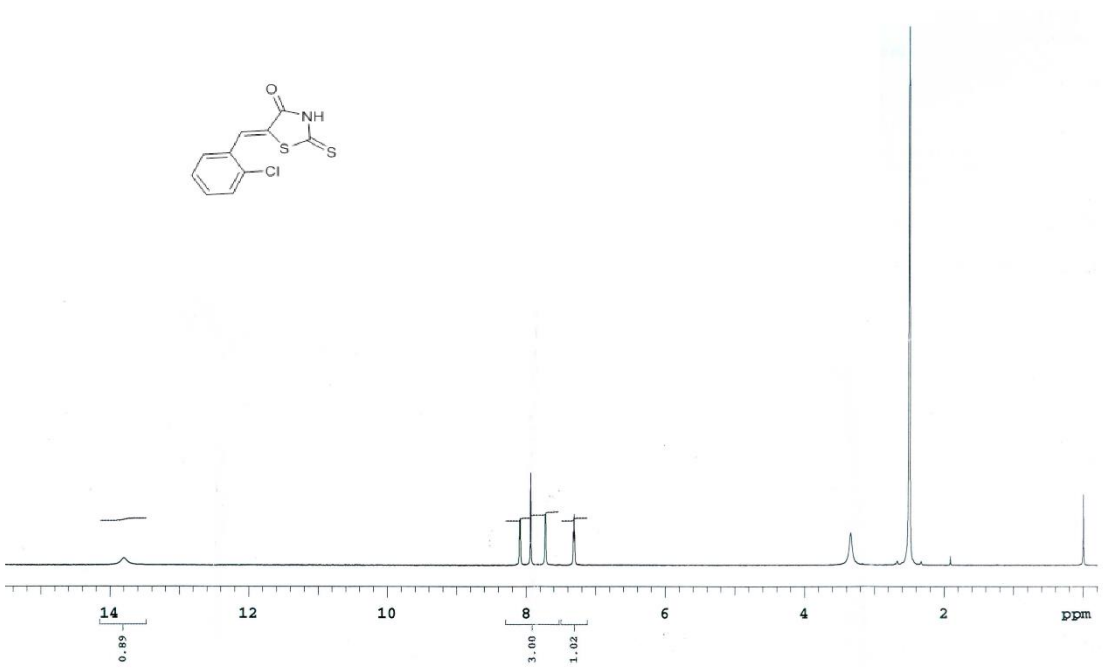


Figure S2. [1]H NMR of (Z)-5-(2-chlorobenzylidene)-2-thioxothiazolidin-4-one (**3**).

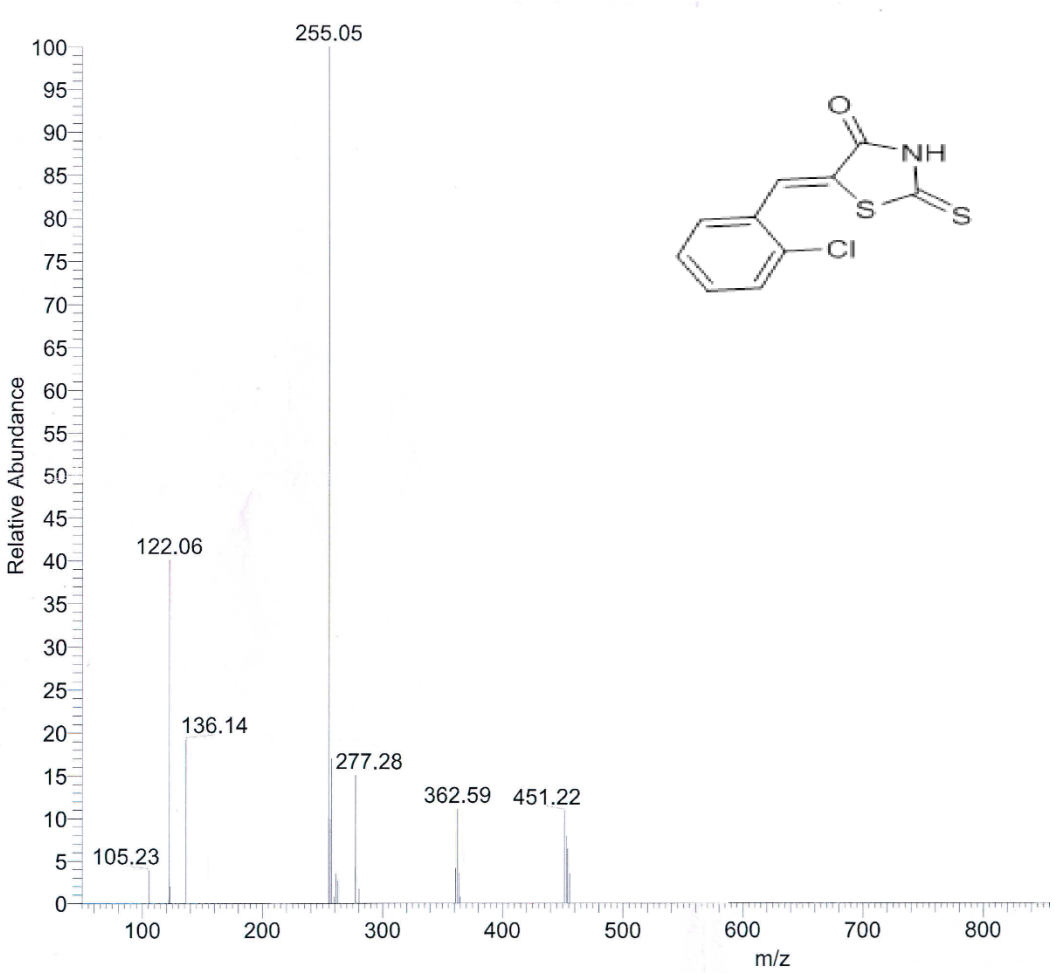


Figure S3. Mass of (Z)-5-(2-chlorobenzylidene)-2-thioxothiazolidin-4-one (**3**).

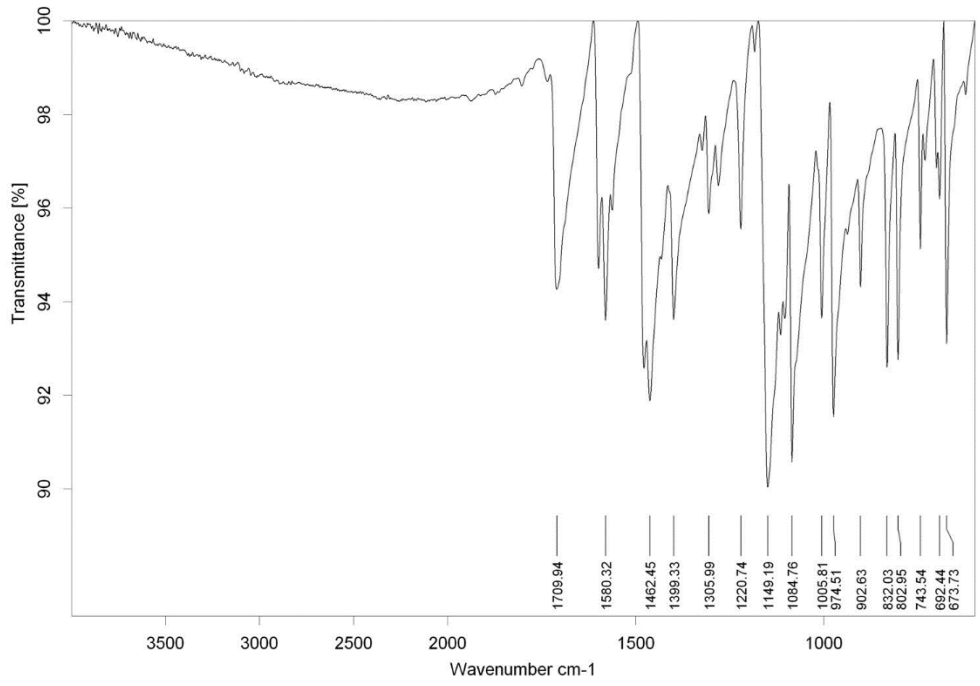


Figure S4. IR of (*Z*)-5-(2-chlorobenzylidene)-2-(methylthio)thiazol-4(5H)-one (**5**)

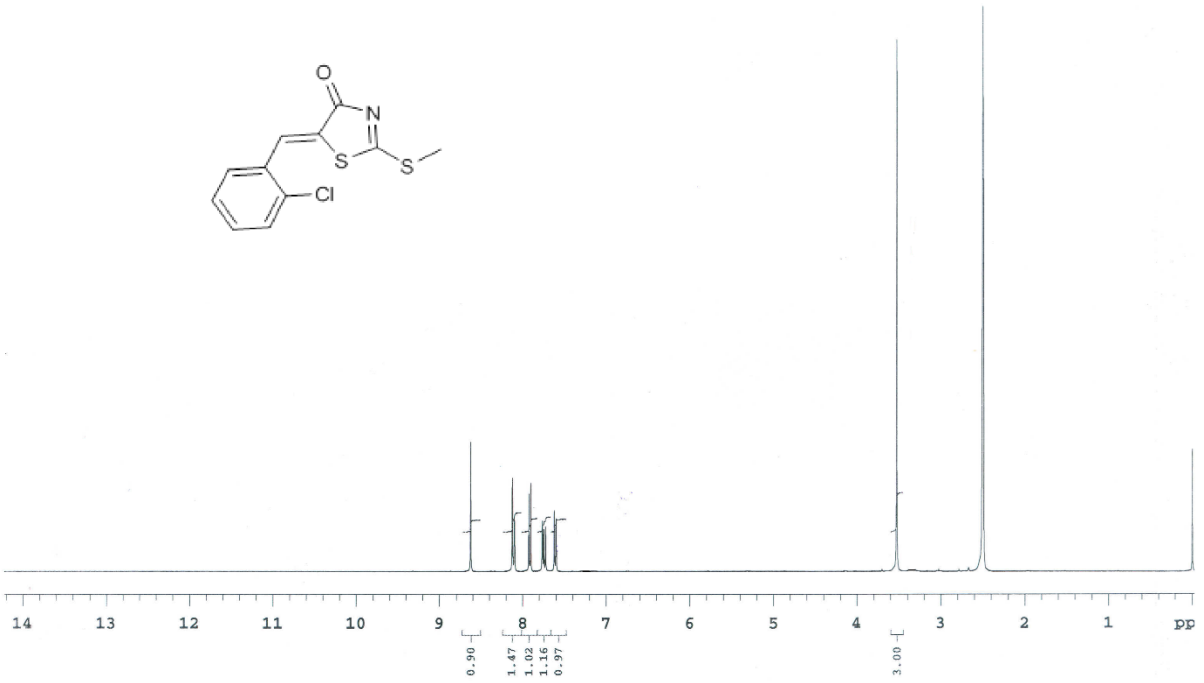
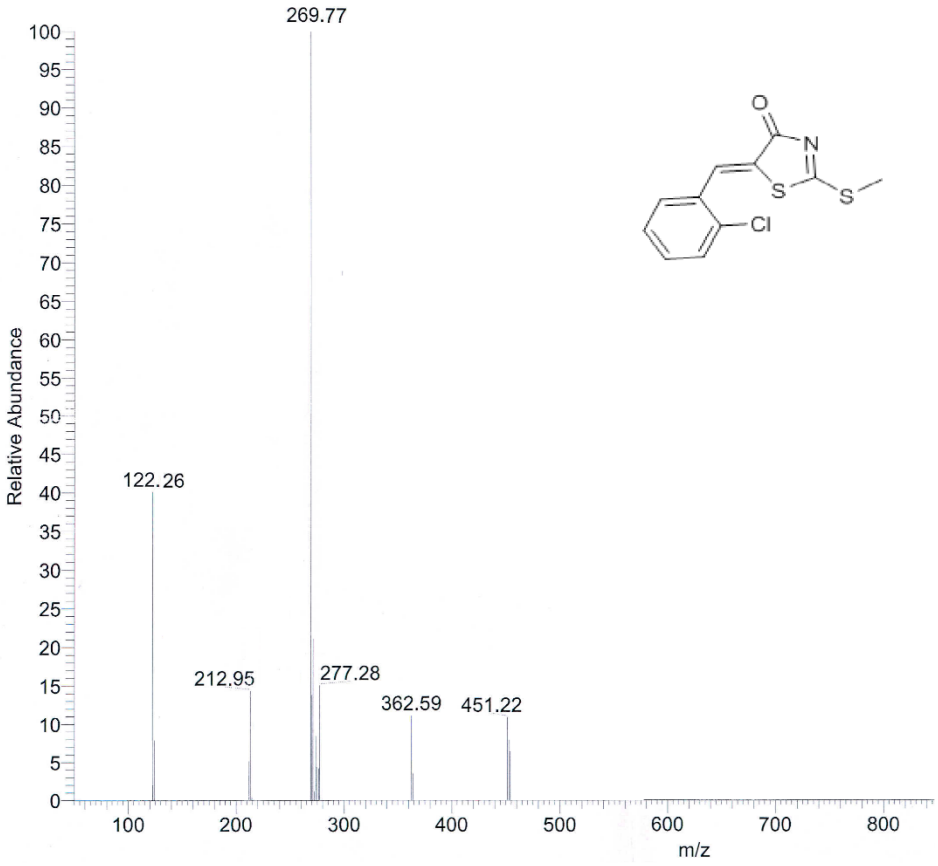


Figure S5. [1]H NMR of (*Z*)-5-(2-chlorobenzylidene)-2-(methylthio)thiazol-4(5H)-one (**5**).



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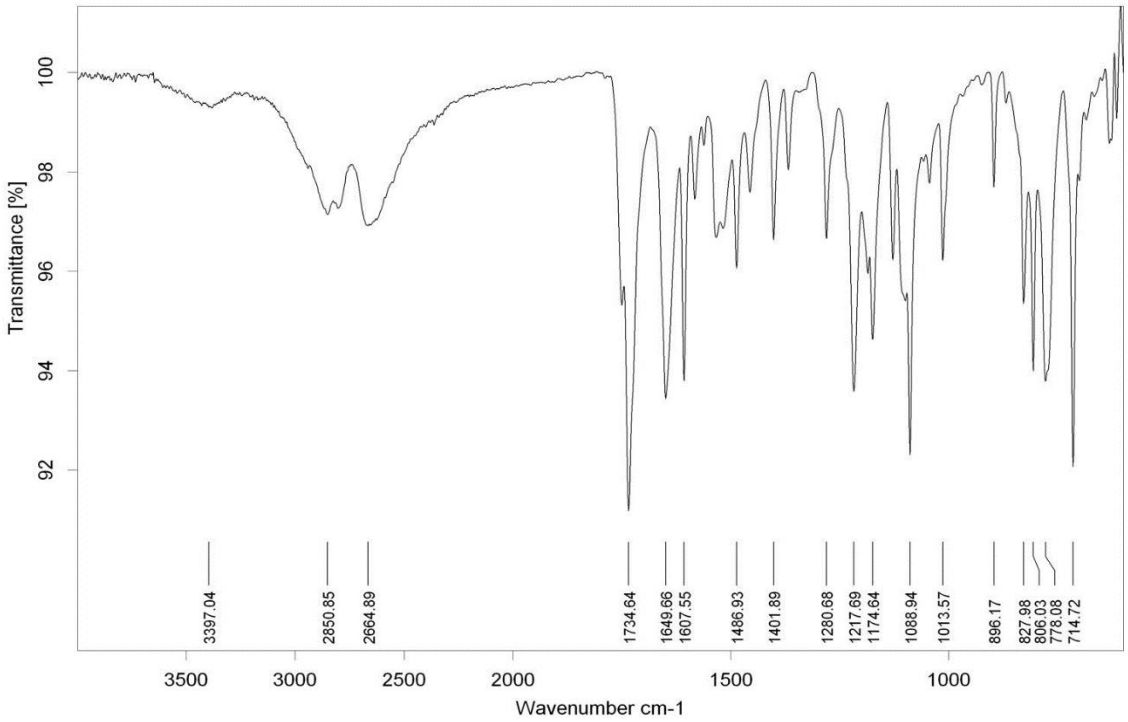

Figure S7. IR of (Z)-2-((5-(2-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)propanoic acid (**6a**).

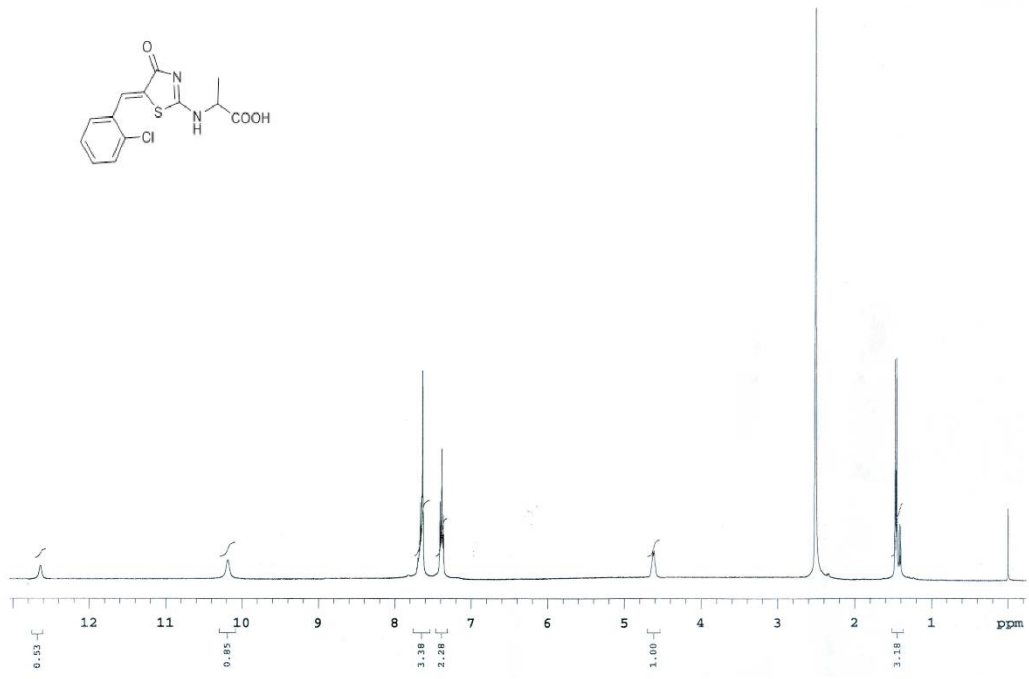

Figure S8. [1]H NMR (Z)-2-((5-(2-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)propanoic acid (**6a**).

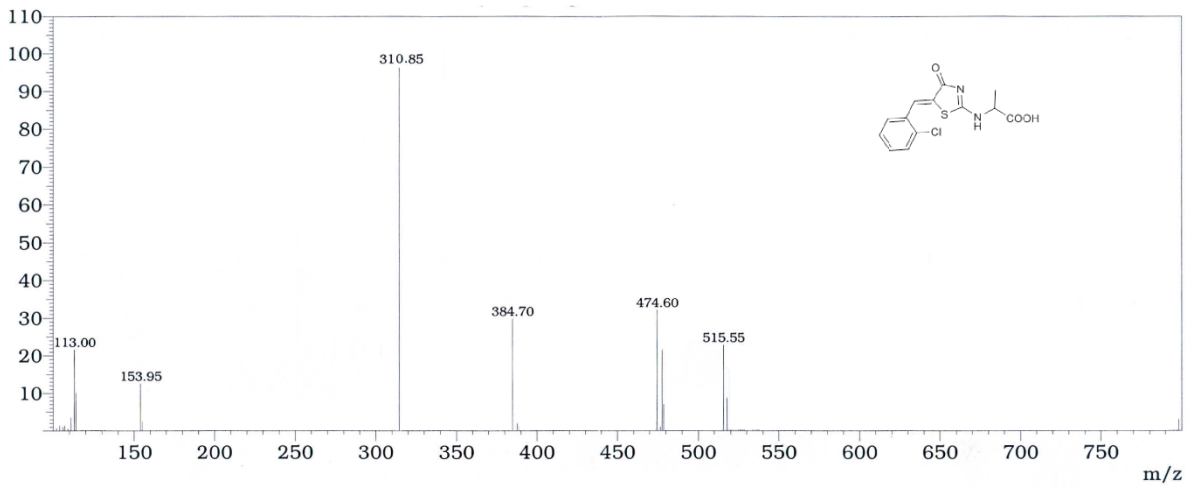

Figure S9. Mass of (Z)-2-((5-(2-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)propanoic acid (**6a**).

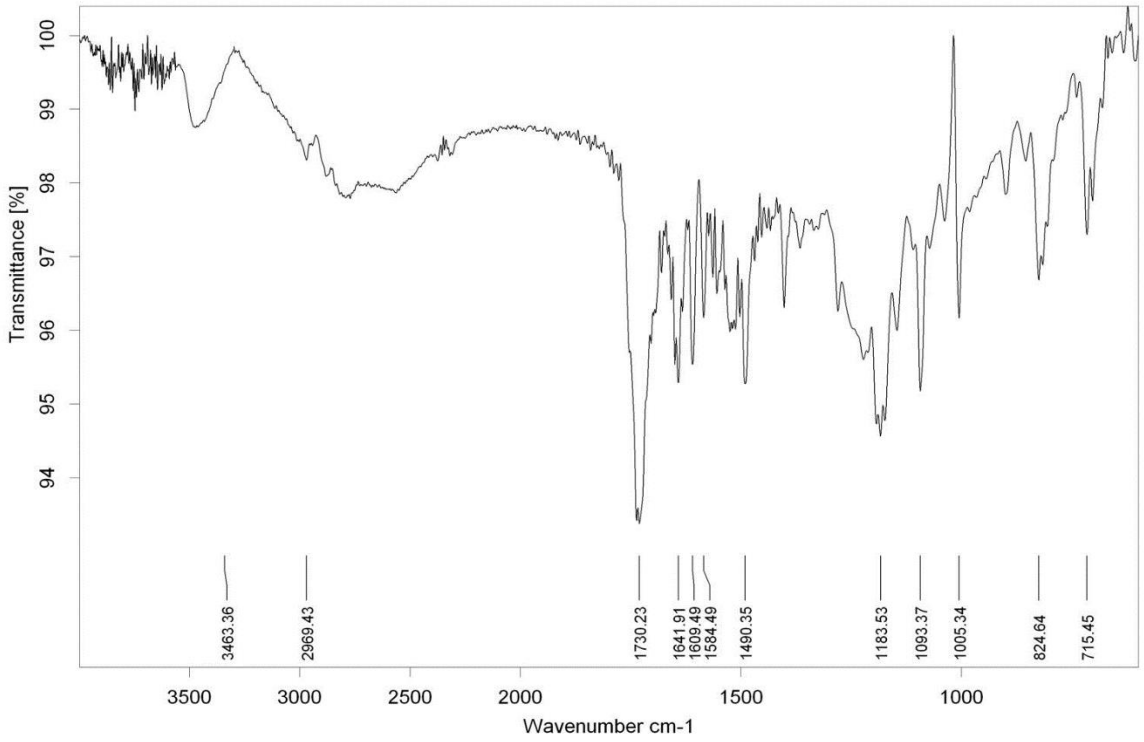

Figure S10. IR of (Z)-2-((5-(2-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-methyl butanoic acid (**6b**).

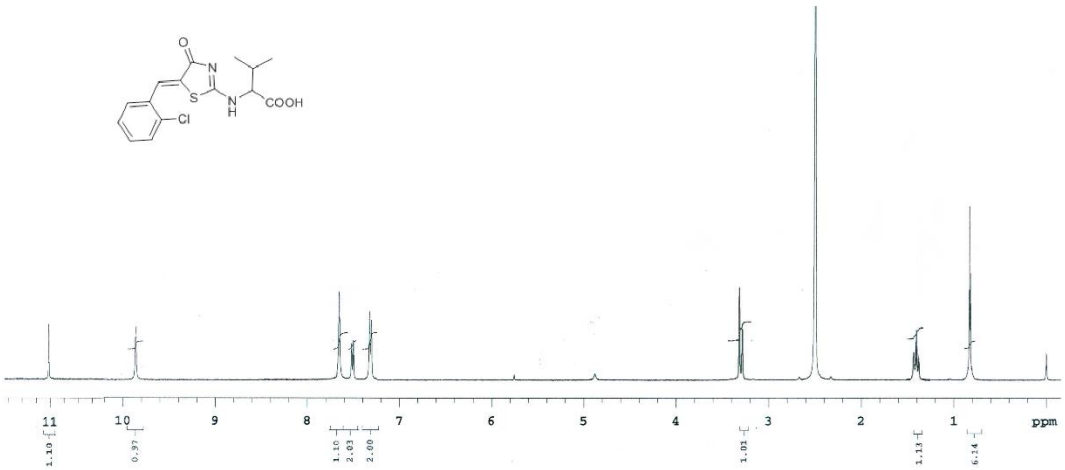

Figure S11. [1]H NMR of (Z)-2-((5-(2-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-methylbutanoic acid (**6b**).

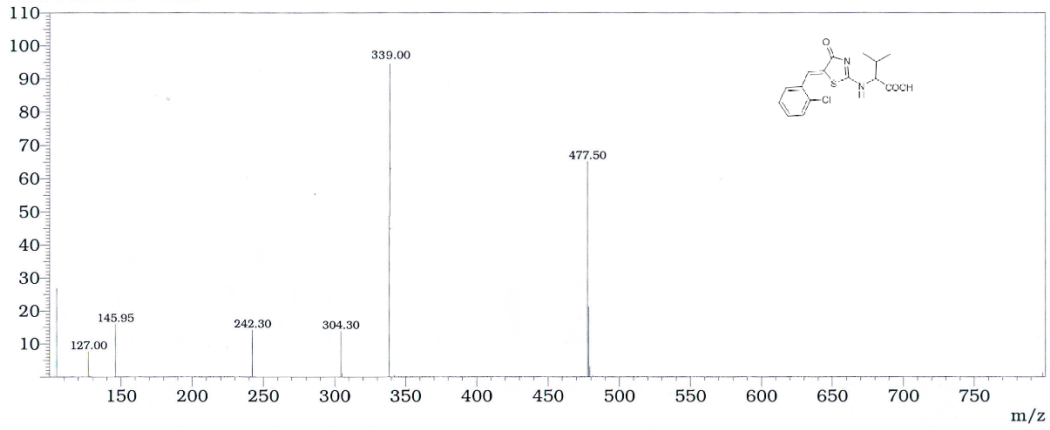

Figure S12. Mass of (Z)-2-((5-(2-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-methylbutanoic acid (**6b**).

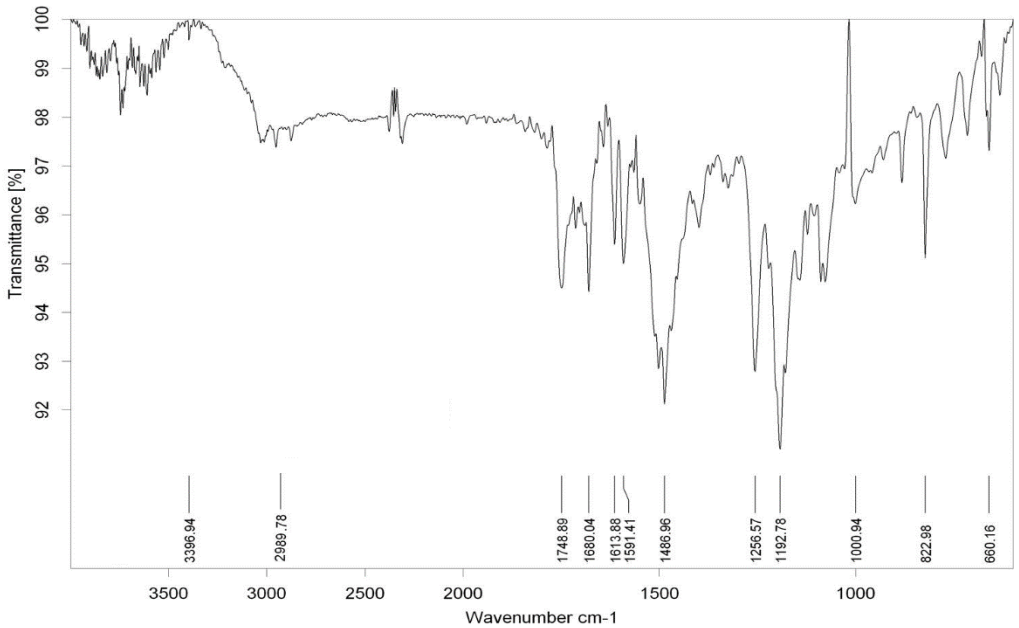

Figure S13. IR of (Z)-2-((5-(2-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-4-methylpentanoic acid (**6f**).

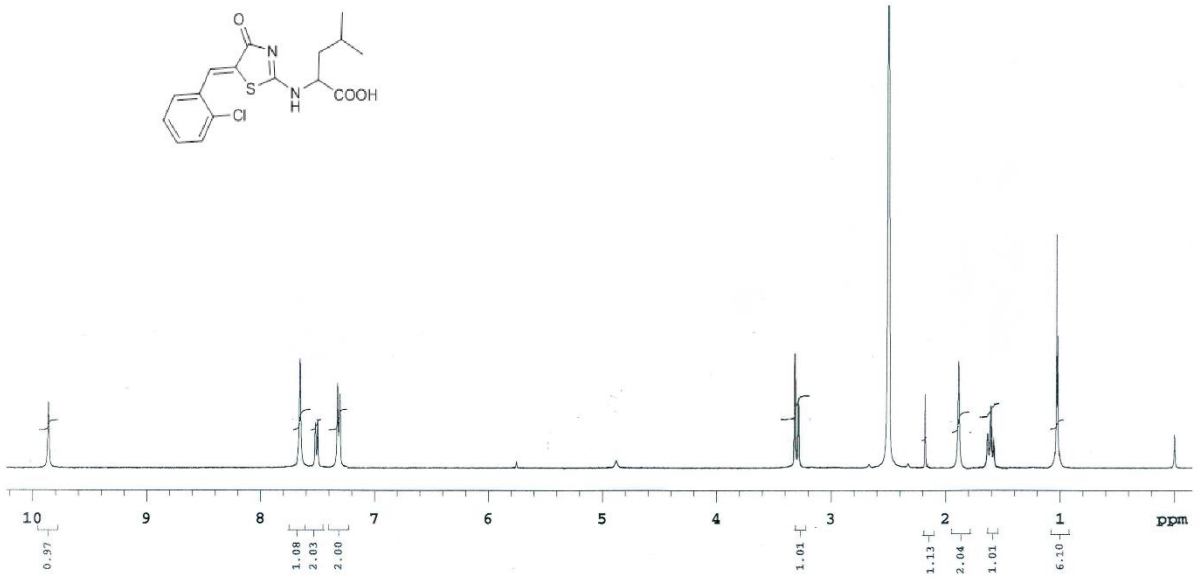

Figure S14. [1]H NMR of (Z)-2-((5-(2-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-4-methylpentanoic acid (**6f**).

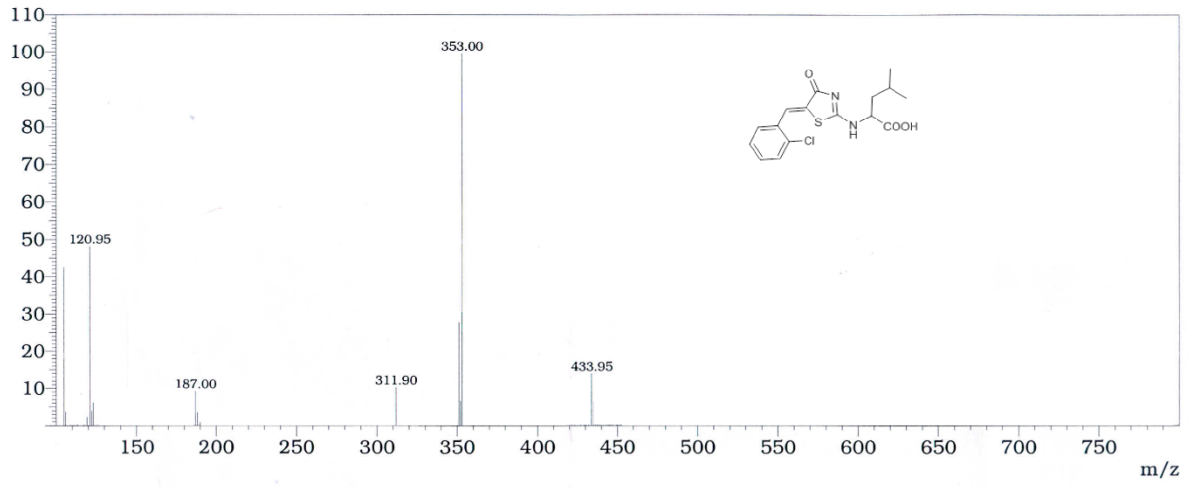

Figure S15. Mass of (Z)-2-((5-(2-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-4-methylpentanoic acid (**6f**).

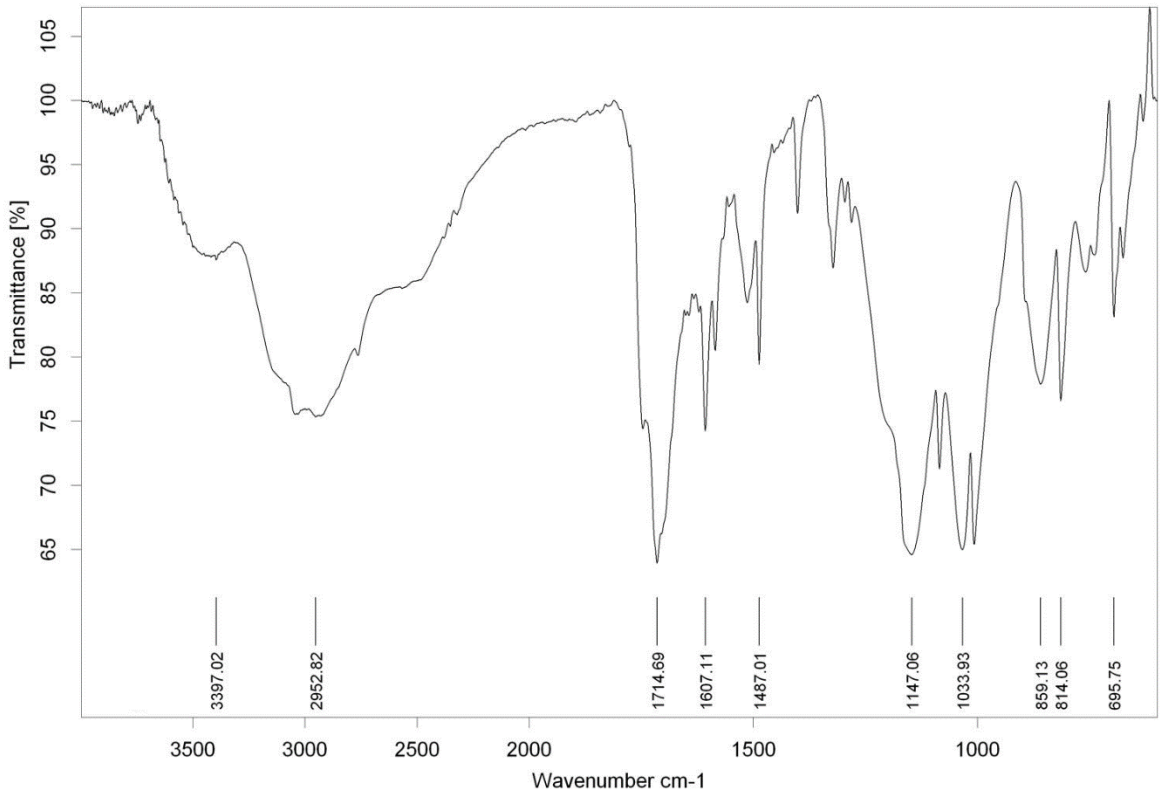

Figure S16. IR of (Z)-2-((5-(2-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-mercapto propanoic acid (**6h**).

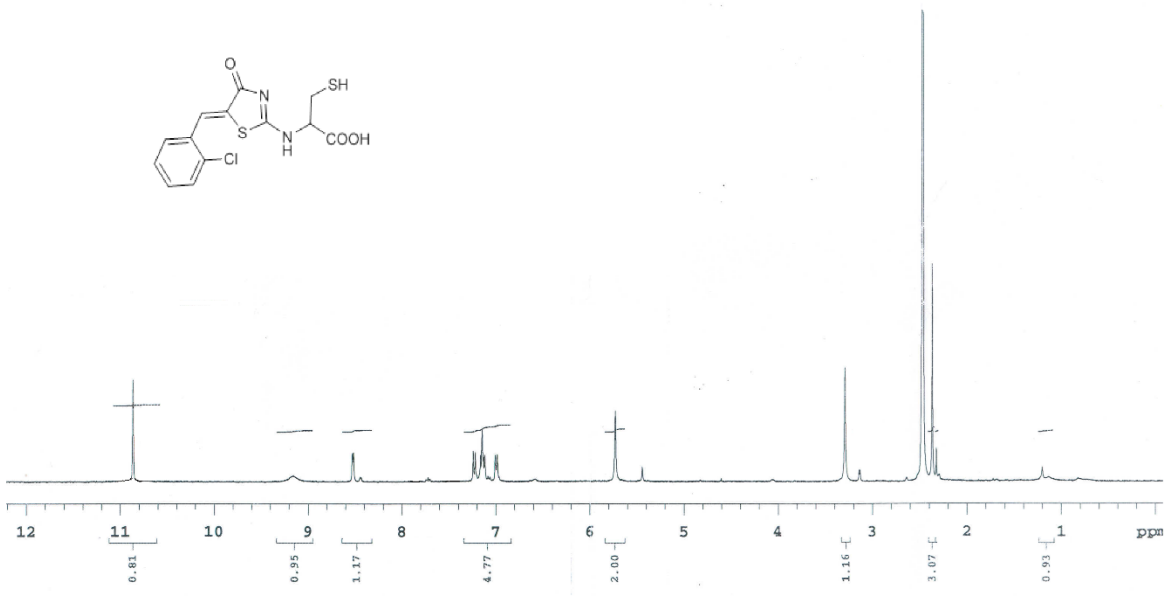

Figure S17. ^{1}H NMR of (Z)-2-((5-(2-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-mercapto propanoic acid (**6h**).

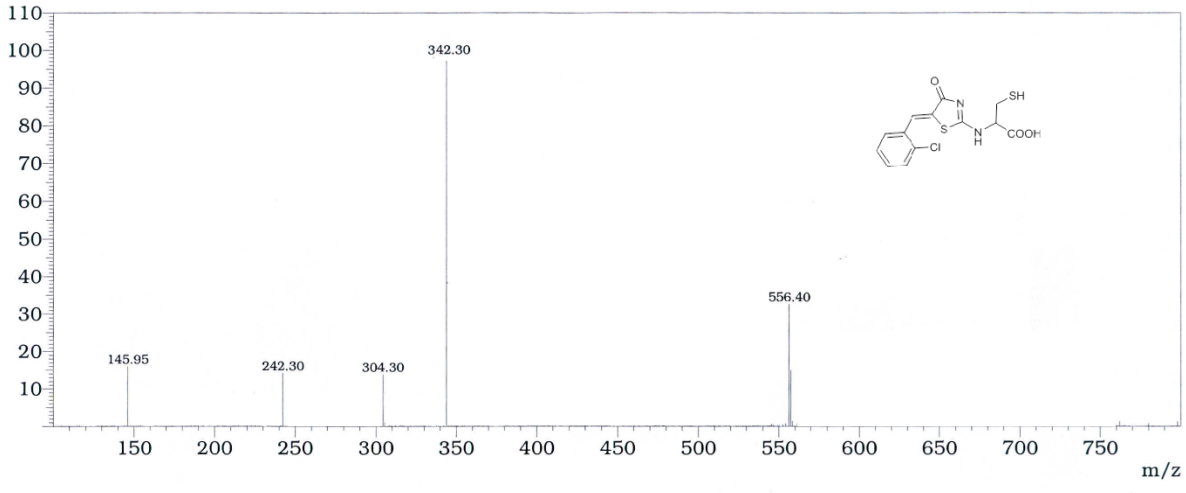

Figure S18. Mass of (Z)-2-((5-(2-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-mercapto propanoic acid (**6h**).

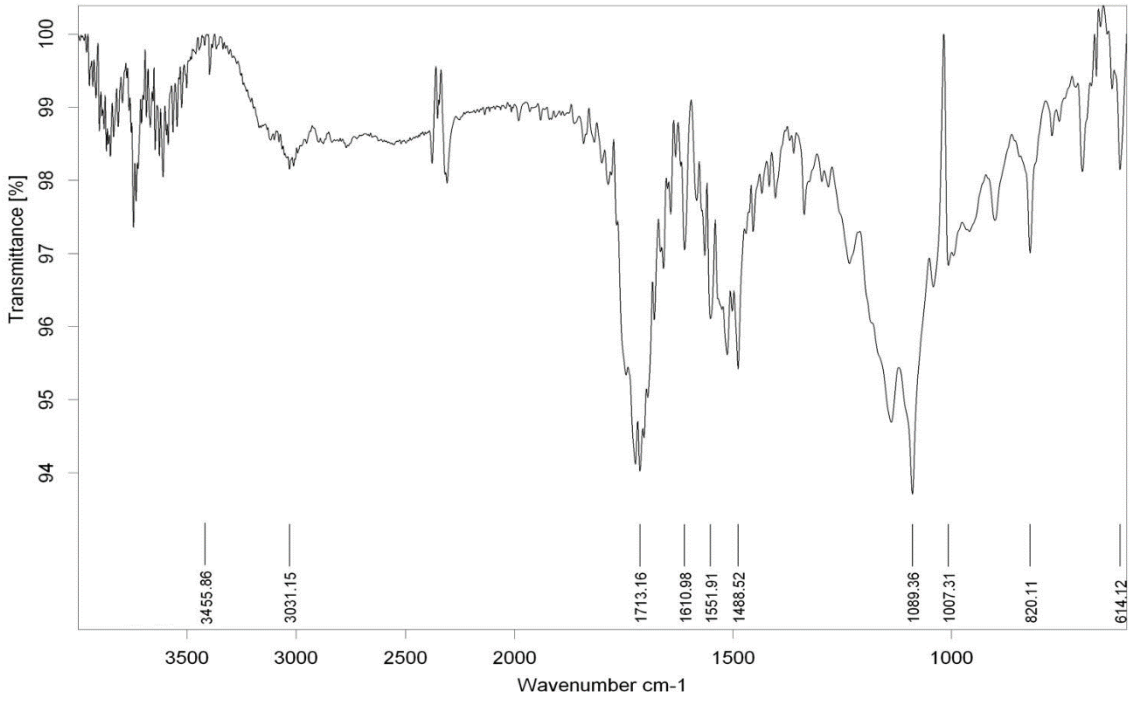

Figure S19. IR of (Z)-2-((5-(2-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-(1H-imidazol-2-yl)propanoic acid (**6j**).

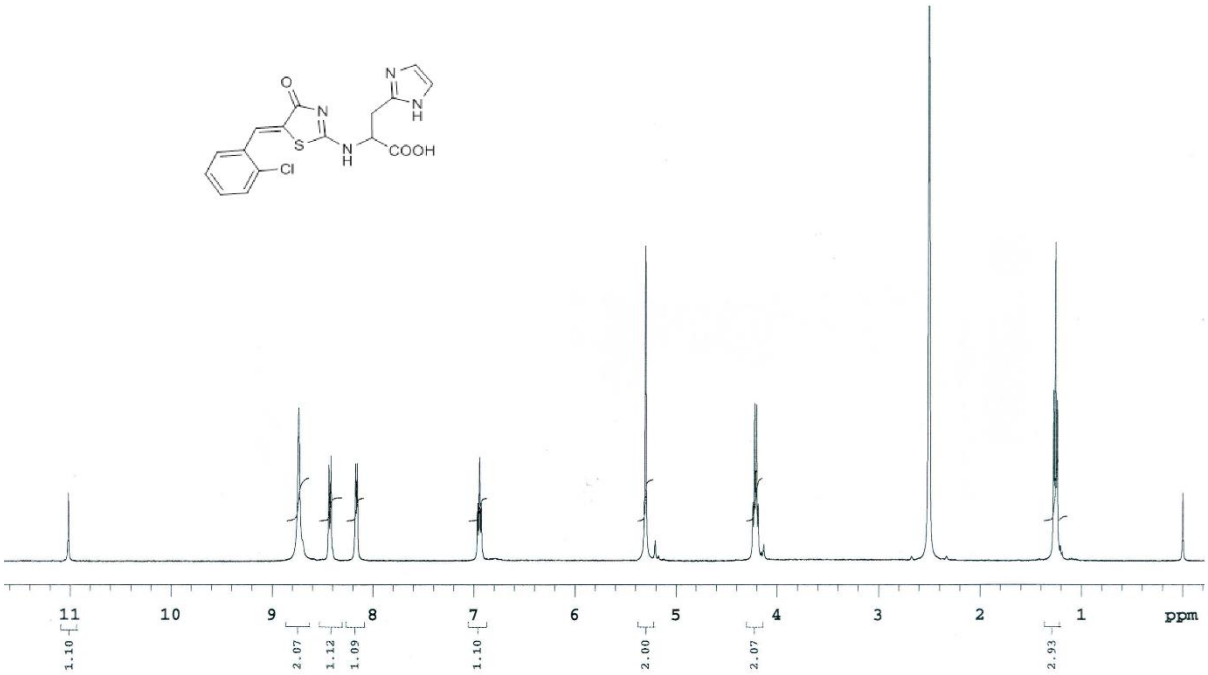

Figure S20. [1]H NMR of (Z)-2-((5-(2-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-(1H-imidazol-2-yl)propanoic acid (**6j**).

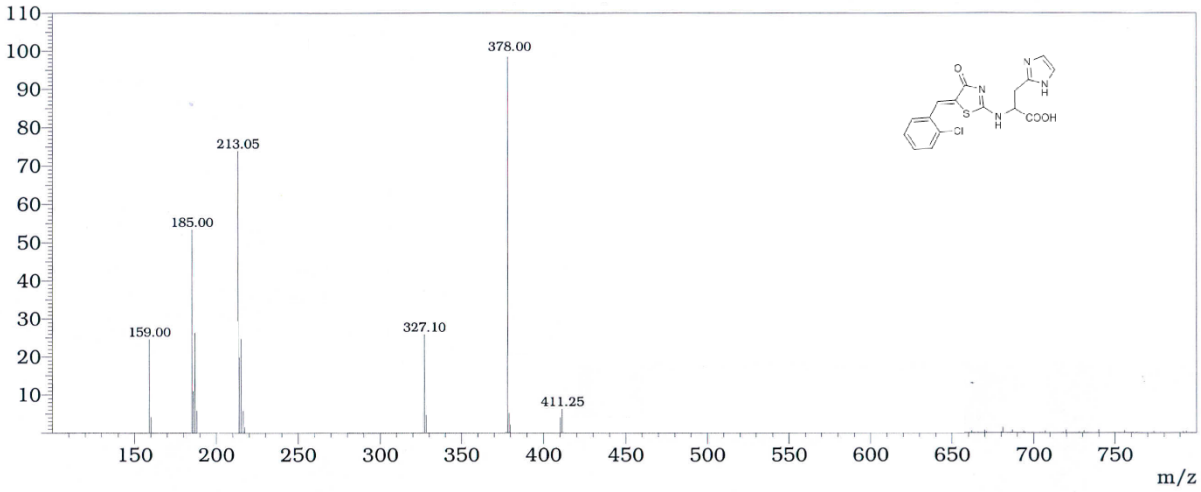

Figure S21. Mass of (Z)-2-((5-(2-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-3-(1H-imidazol-2-yl)propanoic acid (**6j**).