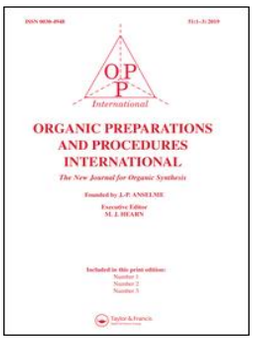

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EXPERIMENTAL PAPER

Synthesis of Terminal Thiazoles from *N*-Protected Amino Acids and a Study of Their Antibacterial Activities

H. S. Lalithamba[a], K. Uma[a], T. S. Gowthami[a], and G. Nagendra[b]

[a]Department of Chemistry, Siddaganga Institute of Technology, Tumakuru, India; [b]Department of Chemistry, School of Applied Sciences, REVA University, Bengaluru, India

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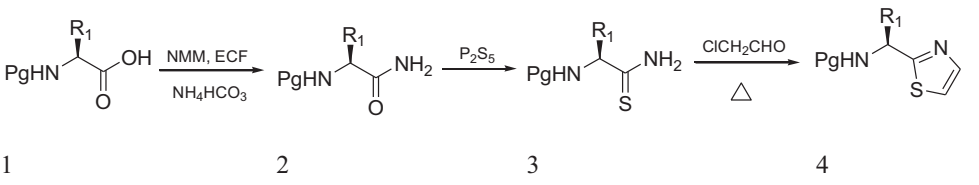
Thiazoles have gained a particular significance in the field of organic chemistry. Amino acid derived thiazoles comprise a common motif in biologically active substances such as the thiopeptide antibiotics.[1–8] Hence, the preparation and reactions of thiazoles are important for the synthesis of pharmaceuticals and fine chemicals. A sequential procedure for the preparation of 2,5-disubstituted thiazoles from sulfonyl azides, terminal alkynes and thionoesters, by the elimination of the sulfonyl group, was reported.[9] Cyclization reactions of thiosemicarbazide derivatives yielding thiazoles have also been explored.[10] In particular, we may note the production of thiazole esters from the cyclization reaction of 4-substituted benzenenitriles and L-cysteine, followed by the esterification with selected alcohols and oxidation of thiazoline esters mediated by $BrCCl_3$/DBU.[11] Thiazole and its derivatives were efficiently prepared through a gold-catalyzed oxidation at room temperature.[12] Besides, the reaction of 11-bromo-10-oxoundecanoic acid with acetamide and thiourea yielded the terminally located thiazole derivatives.[13]

Several methods for the synthesis of thiazoles have been reported as follows: (i) thiazole-containing amino acids were synthesized by condensation-cyclization,[14] (ii) Ling and his group prepared 1,2,4-triazole-linked thiazole derivatives from the reaction of α-bromo substituted acetophenones and thiourea,[15] (iii) Wardakhan and his co-workers synthesized several thiazole derivatives from pyridazin-3-hydrazidic acids,[16] and (iv) Khazi *et al.*, have reported a preparation of thiazole-fused diazepinones by the application of intramolecular hydrazinolysis.[17] Thiazoles were also synthesized by an alternative substitution method using MnO_2.[18] Notwithstanding the ground that has been broken by these methods, some disadvantages remain. In this context, we have developed a simple, well-ordered and practical method of synthesis of terminal thiazoles in good isolated yields.

In our work, we proceeded with the elaboration of Fmoc/Cbz-amino acids to yield the required terminal thiazoles. The necessary thioamides were prepared by the reaction of *N*-protected α-amino acid amides with the thionating agent P_2S_5 through an ultrasonication mediated protocol. The thioamides were then refluxed with chloroacetaldehyde to obtain the thiazole-linked molecules. *N*-Protected amino acid **1** was dissolved in tetrahydrofuran (THF), followed by the addition of *N*-methyl morpholine (NMM) and ethyl chloroformate (ECF) at -15 °C. The reaction mixture was stirred for 15 minutes at the same temperature

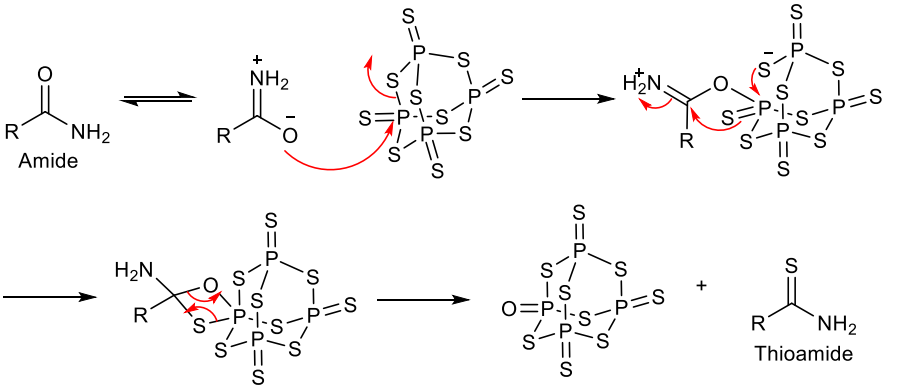
CONTACT H. S. Lalithamba lalithambasit@yahoo.co.in Department of Chemistry, Siddaganga Institute of Technology, B.H. Road, Tumakuru-572 103, Karnataka, India



1 2 3 4

Pg = Fmoc/Cbz group; R = Amino acid side chains

Scheme 1. Synthesis of N^{α}-protected terminal thiazoles.



Scheme 2. Mechanism for the formation of thioamide from amide and P_4S_{10}.

and ammonium bicarbonate (NH_4HCO_3) was added to obtain the corresponding amide **2**. Simple work-up was done to yield the amide. The amide was then dissolved in THF and treated with P_2S_5 to form the thioamide under ultrasonic conditions.[19,20] The resulting thioamide **3** was reacted with chloroacetaldehyde ($ClCH_2CHO$) under reflux to afford the target *N*-protected thiazole **4** (Scheme 1). Using this procedure several terminal thiazoles were synthesized from *N*-protected amino acids as shown in Table 1. The synthesized compounds were fully characterized by ^{1}H NMR, ^{13}C NMR and HRMS techniques.

N^{α}-Protected peptidyl thiazoles were also prepared (Scheme 3) starting from Fmoc-peptide acids. The synthesized peptidyl thiazoles (Table 2, **8a-d**) were also fully characterized.

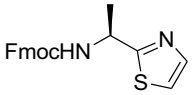
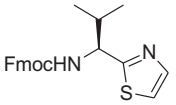
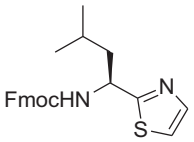
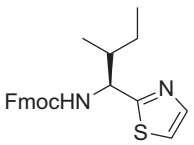
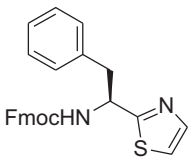
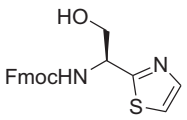
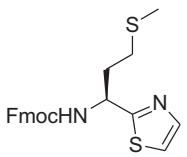
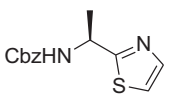
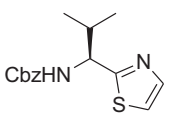
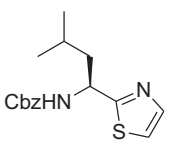
The newly-synthesized compounds Fmoc-Val-Thiazole **(4b)** and Fmoc-Leu-Thiazole **(4c)** were subjected to antibacterial studies. Compound **4c** showed significant inhibitory activity against *Staphylococcus aureus*.

In conclusion, we have developed an efficient protocol for the synthesis of terminal thiazoles from the corresponding thioamides derived from protected amino acids. All the synthesized terminal thiazoles were isolated after simple work up and were fully characterized. We hope that our method of preparation of terminal thiazoles will stimulate further research into the chemistry and biological activity of these unique compounds.

Experimental section

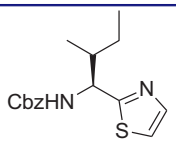
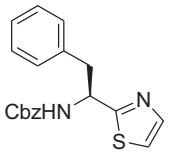
All the chemicals were purchased from Sigma-Aldrich and Merck and were used without purification except that solvents were freshly distilled before use. Melting points

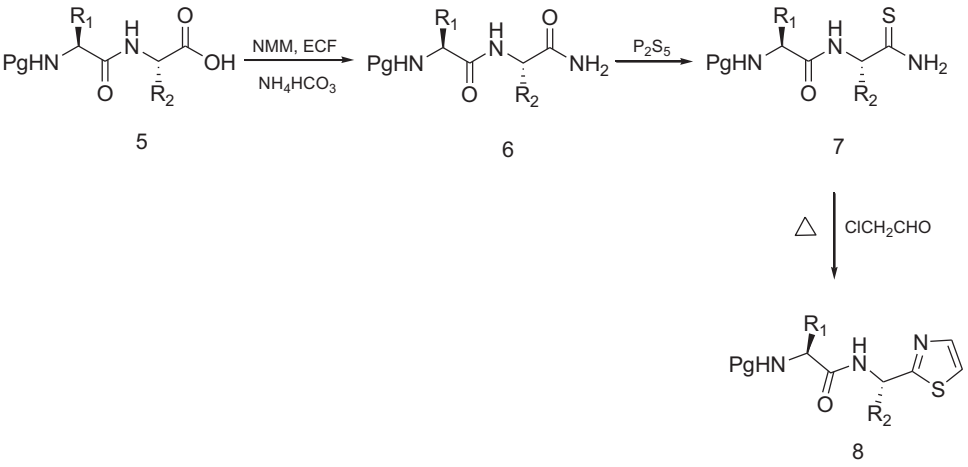
Table 1. N^{α}-Protected terminal thiazoles.

Entry	N^{α}-protected terminal thiazole	Yield (%)	Mp °C
4a		89	121
4b		90	130
4c		86	135
4d		83	Gum
4e		88	140
4f		85	Gum
4g		85	Gum
4h		80	118
4i		86	122
4j		84	Gum

(*continued*)

Table 1. Continued.

Entry	N^{α}-protected terminal thiazole	Yield (%)	Mp °C
4k		90	Gum
4l		88	128



Pg = Fmoc/Cbz group; R_1, R_2 = Amino acid side chains

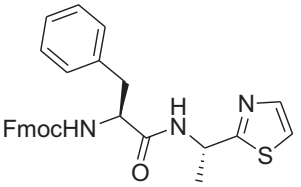
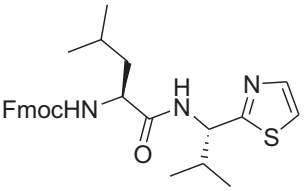
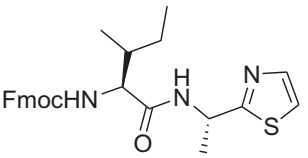
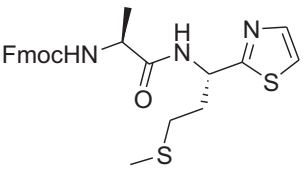
Scheme 3. Synthesis of N^{α}-protected terminal peptide thiazoles.

were taken in open capillaries and are uncorrected. TLC analysis was carried out using plates precoated with silica gel F_{254} (solvent system-EtOAc:hexane). ^{1}H NMR and ^{13}C NMR spectra were done on a Bruker AMX 400 MHz spectrometer using Me_4Si as an internal standard and DMSO-d_6 as the solvent. Elemental analyses were obtained using a Vario Microselect CHNS analyzer. Mass spectra were recorded on a Micromass Q-ToF Micro mass Spectrometer. The pathogenic bacterial strains were purchased from the National Chemical Laboratory (NCL) Pune, India.

Synthesis of N^{α}-protected amino/peptidyl terminal thiazoles from protected amino acids

The appropriate *N*-protected amino/peptide acid (1.0 mmol) was dissolved in THF, to which NMM (1.5 mmol) and ECF (1.5 mmol) were added at -15 °C, followed by the addition of NH_4HCO_3 (1.5 mmol) to obtain the corresponding amide. The reaction

Table 2. N^{α}-Protected terminal thiazoles from peptide acids.

Entry	N^{α}-protected terminal thiazoles	Yield (%)	Mp °C
8a		90	Gum
8b		88	Gum
8c		85	Gum
8d		85	Gum

mixture was stirred until the completion of the reaction and the progress of the reaction was checked by TLC. After the removal of THF, the product was extracted into ethyl acetate (15 mL) and the organic layer was washed with dilute HCl solution (10 mL) or citric acid solution (10 mL) in the case of the Boc-protected compounds, then with Na_2CO_3 solution (15 mL x 2), water (15 mL) and brine (15 mL). The organic extract was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The amide thus formed was then treated with P_2S_5 (0.5 mmol) to form the thioamide under ultrasonic conditions for 2-3 hrs. The resulting thioamide in dry THF was reacted with chloroacetaldehyde (1.0 mmol) under reflux conditions for 2 hrs. *N*-Protected thiazoles were obtained in good yield after simple acid-base work up and purified through column chromatography using EtOAc:hexane (3:7) as an eluent.

(S)-(9H-Fluoren-9-yl) methyl 1-(thiazol-2-yl) ethylcarbamate (4a)

Yield 89%; Solid; Melting Point 121 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.45 (d, J=8.0 Hz, 3H), 4.36 (t, J=6.8 Hz, 1H), 4.70 (d, J=8.0 Hz, 2H), 4.95 (m, 1H), 6.0 (s, 1H), 7.12 (d, J=8.0 Hz, 1H), 7.28-7.60 (m, 8H), 7.73 (d, J=8.0 Hz,1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 20.4, 46.7, 48.5 66.3 116.2, 126.4 128.0, 128.4, 128.6

140.8, 142.0, 143.4, 156.0, 168.8. MS: Calcd. for $C_{20}H_{18}N_2O_2S$ *m/z*: 373.11 (M^+ +Na), Found: 373.1098.

Anal. Calcd. for $C_{20}H_{18}N_2O_2S$: C, 68.55; H, 5.18; N, 7.99. Found: C, 68.30; H, 5.11; N, 7.85.

(S)-(9H-Fluoren-9-yl)methyl 2- methyl 1-(thiazol-2-yl) propylcarbamate (4b)

Yield 90%, Solid, Melting Point 130 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.92 (m, 2H), 4.4 (m, 1H), 4.65 (d, *J*=8.0 Hz, 2H), 5.26 (t, *J*=6.8 Hz, 1H), 6.0 (s, 1H), 7.07-7.68 (m, 15H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 40.7, 46.5, 54.2, 66.9, 118.0, 126.2, 126.8, 127.6, 128.0, 128.4, 128.6, 128.8, 139.0, 140.8, 142.0, 143.5, 155.3, 170.2. MS: Calcd. for $C_{22}H_{22}N_2O_4S$ *m/z*: 401.14 (M^+ +Na), Found: 401.1402.

Anal. Calcd. for $C_{22}H_{22}N_2O_4S$: C, 69.81; H, 5.86; N, 7.40. Found: C, 69.68; H, 5.47; N, 7.22.

(S)-(9H-Fluoren-9-yl)methyl 3- methyl 1-(thiazol-2-yl) butylcarbamate (4c)

Yield 86%, Solid, Melting Point 135 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.98 (t, *J*=6.8 Hz, 3H), 1.12 (d, *J*=8.0 Hz, 3H),1.26 (m, 2H), 2.08 (m, 1H), 4.38 (t, *J* = 6.8 Hz, 1H), 4.70 (d, *J*=8.0 Hz, 2H), 4.83 (d, *J*=8.0 Hz, 1H), 6.0 (s, 1H), 7.12-7.84 (m, 10H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 16.8, 32.5, 46.4, 57.2, 66.3, 118.0, 126.3, 128.0, 128.3, 128.6, 141.0, 141.9, 143.1, 155.8, 170.4. MS: Calcd. for $C_{23}H_{24}N_2O_2S$ *m/z*: 415.16 (M^+ +Na), Found: 415.1600.

Anal. Calcd. for $C_{23}H_{24}N_2O_2S$: C, 70.38; H, 6.16; N, 7.14. Found: C, 70.00; H, 6.03; N, 7.11.

(S)-(9H-Fluoren-9-yl)methyl (1S, 2R)-2- methyl 1-(thiazol-2-yl) butylcarbamate (4d)

Yield 83%, Gum; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.96 (d, *J* = 8.0 Hz, 6H), 1.80 (s, 2H), 1.83 (br, 1H), 4.4 (t, *J* = 6.8 Hz, 1H), 4.73 (d, *J* = 8.0 Hz, 2H), 4.82 (t, *J* = 6.8 Hz, 1H), 6.0 (s, 1H), 7.10-7.82 (m, 10H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 22.5, 23.2, 46.0, 47.1, 51.8, 67.3, 118.0, 126.8, 128.1, 128.4, 128.7, 141.0, 142.2, 143.4, 155.8, 170.6. MS: Calcd. for $C_{23}H_{24}N_2O_2S$ *m/z*: 415.16 (M^+ +Na), Found: 415.1558.

Anal. Calcd. for $C_{23}H_{24}N_2O_2S$: C, 70.38; H, 6.16; N, 7.14. Found: C, 70.25; H, 6.00; N, 7.12.

(S)-(9H-Fluoren-9-yl)methyl 2-phenyl- 1-(thiazol-2-yl) ethylcarbamate (4e)

Yield 88%, Solid, Melting Point 140 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.96 (d, *J* = 8.0 Hz, 2H), 4.42 (t, *J* = 6.8 Hz, 1H), 4.68 (d, *J* = 8.0 Hz, 2H), 4.83 (t, *J* = 6.8 Hz, 1H), 6.0 (s, 1H), 7.08-7.78 (m, 15H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 11.6, 15.0, 25.4, 41.2, 46.9, 55.1, 67.2, 118.5, 126.8, 128.0, 128.4, 128.7, 141.0, 142.1, 143.5, 156.0, 170.4. MS: Calcd. for $C_{26}H_{22}N_2O_2S$ *m/z*: 449.14 (M^+ +Na), Found: 449.1404.

Anal. Calcd. for $C_{26}H_{22}N_2O_2S$: C, 73.21; H, 5.20; N, 6.57. Found: C, 73.12; H, 5.26; N, 6.65.

(S)-(9H-Fluoren-9-yl) methyl 2-hydroxy-1-(thiazol-2-yl) ethylcarbamate (4f)

Yield 85%, Gum; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.96 (s, 1H), 3.85 (m, 2H), 4.42 (t, *J*=6.8 Hz, 1H), 4.7 (d, *J* = *8*.0 Hz, 2H), 4.96 (d, *J*=6.8 Hz, 1H), 6.0 (s, 1H), 7.12-7.80 (m, 10H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 46.9, 58.5, 64.2, 67.7, 118.7, 126.8, 128.1, 128.6, 128.8, 141.0, 142.0, 143.6, 156.1, 170.6. MS: Calcd. for $C_{20}H_{18}N_2O_3S$ *m/z*: 389.10 (M^+ +Na), Found: 389.1007 .

Anal. Calcd. for $C_{20}H_{18}N_2O_3$s: C, 65.55; H, 4.95; N, 7.64. Found: C, 65.72; H, 4.79; N, 7.60.

(S)-(9H-Fluoren-9-yl) methyl 3-(methylthio)-1-(thiazol-2-yl) propylcarbamate (4g)

Yield 85%, Gum; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.04 (s, 3H), 2.18 (t, *J*=6.8 Hz, 2H), 2.44 (t, *J*=6.8 Hz, 2H), 4.4 (t, *J*=6.8 Hz, 1H), 4.74 (d, *J*=8.0 Hz, 2H), 4.81 (t, *J*=6.8 Hz, 1H), 6.0 (s, 1H), 7.05-7.72 (m, 10H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 17.4, 29.9, 37.7, 47.0, 54.2, 67.4, 118.7, 126.8, 128.2, 128.4, 128.8, 140.8, 142.2, 143.6, 156.0, 170.2. MS: Calcd. for $C_{22}H_{22}N_2O_2S_2$ *m/z*: 433.11 (M^+ +Na), Found: 433.1099.

Anal. Calcd. for $C_{22}H_{22}N_2O_2S_2$: C, 64.36; H, 5.40; N, 6.82. Found: C, 64.31; H, 5.28; N, 6.92.

(S)-Benzyl 1-(thiazol-2-yl) ethylcarbamate (4h)

Yield 80%, Solid, Melting Point 118 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.52 (d, *J*=8.0 Hz, 3H), 5.0 (m, 1H), 5.32 (s, 2H), 6.0 (s, 1H) 7.11 - 7.70 (m, 7H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 21.2, 48.7, 65.3, 118.4, 127.1, 127.6, 129.0, 141.2, 156.0, 170.7. MS: Calcd. for $C_{13}H_{14}N_2O_2S$ *m/z*: 285.08 (M^+ +Na), Found: 285.0801.

Anal. Calcd. for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38; N, 10.68. Found: C, 59.29; H, 5.18; N, 10.82.

(S)-Benzyl 2-methyl-1-(thiazol-2-yl) propylcarbamate (4i)

Yield 86%, Solid, Melting Point 122 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.01 (d, *J*=8.0 Hz, 6H), 2.82 (m, 1H), 4.83 (d, *J*=8.0 Hz, 1H), 5.18 (s, 2H), 6.0 (s, 1H), 7.08 - 7.68 (m, 7H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 17.7, 33.4, 57.2, 68.9, 118.5, 127.0, 127.9, 129.1, 141.4, 142.2, 156.0, 170.3. MS: Calcd. for $C_{15}H_{18}N_2O_2S$ *m/z*: 313.11 (M^+ +Na), Found: 313.1102.

Anal. Calcd. for $C_{15}H_{18}N_2O_2S$: C, 62.04; H, 6.25; N, 9.65. Found: C, 62.13; H, 6.09; N, 9.80.

(S)-Benzyl 3-methyl-1-(thiazol-2-yl) butylcarbamate (4j)

Yield 84%, Gum; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.0 (d, *J*=8.0 Hz, 6H), 1.78 (d, *J*=8.0 Hz, 2H), 1.80 (m, 1H), 4.8 (t, *J*=6.8 Hz, 1H), 5.27 (s, 2H), 6.0 (s, 1H), 7.11-7.72 (m, 7H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 22.7, 23.0, 45.9, 52.1, 65.5,

118.3, 127.1, 127.7, 129.0, 141.2, 142.2, 156.0, 170.3. MS: Calcd. for $C_{16}H_{20}N_2O_2S$ *m/z*: 327.12 (M^+ +Na), Found: 327.1198 .

Anal. Calcd. for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62; N, 9.20. Found: C, 63.35; H, 6.51; N, 9.17.

Benzyl (1S, 2R)-2-methyl-1-(thiazol-2-yl) butylcarbamate (4k)

Yield 90%, Gum; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.92 (t, *J*=6.8 Hz, 3H), 1.03 (d, *J*=8.0 Hz, 3H), 1.27 (m, 2H), 2.62 (m, 1H), 4.86 (d, *J*=8.0 Hz, 1H), 5.28 (s, 2H), 6.0 (s, 1H), 7.0-7.68 (m, 7H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 11.6, 14.8, 24.9, 40.8, 55.0, 65.4, 118.5, 127.1, 127.8, 129.0, 141.0, 142.6, 156.0, 170.1. MS: Calcd. for $C_{16}H_{20}N_2O_2S$ *m/z*: 327.12 (M^+ +Na), Found: 327.1203.

Anal. Calcd. for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62; N, 9.20. Found: C, 63.22; H, 6.38; N, 9.18.

(S)-Benzyl 2-phenyl-1-(thiazol-2-yl) ethylcarbamate (4l)

Yield 88%, Solid, Melting Point 128 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.92 (d, *J*=8.0 Hz, 2H), 5.25 (t, *J*=6.8 Hz, 1H), 5.31 (s, 2H), 6.0 (s, 1H), 7.05-7.73 (m, 12H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 41.6, 53.8, 65.3, 118.3, 126.0, 127.3, 127.7, 127.9, 128.6, 129.0, 139.1, 141.9, 170.4. MS: Calcd. for $C_{19}H_{18}N_2O_2S$ *m/z*: 361.11 (M^+ +Na), Found: 361.1107.

Anal. Calcd. for $C_{19}H_{18}N_2O_2S$: C, 67.43; H, 5.36; N, 8.28. Found: C, 67.06; H, 5.31; N, 8.22.

(9H-Fluoren-9-yl) methyl (S)-1-oxo-3-phenyl-1-((S)-1-(thiazol-2-yl) ethyylamino) propan-2-ylcarbamate (8a)

Yield 90%, Gum; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.55 (s, 3H), 2.90 (m, 2H), 4.43 (t, *J*=6.8 Hz, 1H), 4.72 (d, *J*=8.0 Hz, 2H), 4.97 (m,1H), 5.09 (m,1H), 6.0 (s,2H), 7.10-7.78 (m, 15H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 20.9, 36.4, 46.5, 47.3, 55.4, 66.8, 118.0, 126.2, 126.8, 127.6, 128.0, 128.2, 128.4, 128.8, 139.5, 141.0, 142.2, 143.5, 156.0, 170.4, 171.2. MS: Calcd. for $C_{29}H_{27}N_3O_3S$ *m/z*: 520.18 (M^+ +Na), Found: 520.1797.

Anal. Calcd. for $C_{29}H_{27}N_3O_3S$: C, 70.00; H, 5.47; N, 8.44. Found: C, 70.08; H, 5.46; N, 8.36.

(9H-Fluoren-9-yl) methyl (S)-4-methyl-1-((S)-2-methyl-1-(thiazol-2-yl) propylamino)-1-oxopentan-2-ylcarbamate (8b)

Yield 88%, Gum; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.05 (d, *J*=8.0 Hz, 12H), 1.62 (d, *J*=8.0 Hz, 2H), 1.80 (m, 1H), 2.82 (m, 1H), 4.43 (m, 1H), 4.5 (d, *J*=8.0 Hz, 1H), 4.70 (d, *J*=8.0 Hz, 2H), 4.83 (d, *J*=8.0 Hz, 1H), 6.0 (s, 2H), 7.1-7.84 (m, 10H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 17.4, 22.0, 22.5, 33.4, 41.0, 46.8, 53.1, 56.0, 67.3, 118.5,

126.8, 128.0, 128.4, 128.6, 141.0, 142.3, 143.6, 156.0, 170.7, 171.0. MS: Calcd. for $C_{28}H_{33}N_3O_3S$ *m/z*: 514.22 (M^+ +Na), Found: 514.2200.

Anal. Calcd. for $C_{28}H_{33}N_3O_3S$: C, 68.40; H, 6.77; N, 8.55. Found: C, 68.29; H, 6.52; N, 8.50.

(9H-Fluoren-9-yl) methyl (2S, 3R)-3-methyl-1-oxo-1-((S)-1-(thiazol-2-yl) ethylamino) pentan-2-ylcarbamate (8c)

Yield 85%, Gum; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.92 (t, *J*=6.8 Hz, 3H), 1.06 (d, *J*=8.0 Hz, 3H), 1.20 (m, 2H), 1.58 (d, *J*=8.0 Hz, 3H), 2.48 (d, *J*=8.0 Hz, 1H), 4.46 (m, 1H), 4.52 (d, *J*=8.0 Hz, 1H), 4.65 (d, *J*=8.0 Hz, 2H), 5.0 (m, 1H), 6.0 (s, 2H), 7.12-7.84 (m, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 10.4, 14.2, 21.3, 24.8, 36.6, 47.0, 47.5, 57.8, 67.4, 118.6, 126.8, 128.2, 128.4, 128.8, 141.0, 142.1, 143.5, 156.0, 170.5, 171.0. MS: Calcd. for $C_{26}H_{29}N_3O_3S$ *m/z*: 486.19 (M^+ +Na), Found: 486.1897.

Anal. Calcd. for $C_{26}H_{29}N_3O_3S$: C, 67.36; H, 6.31; N, 9.06. Found: C, 67.32; H, 6.28; N, 9.00.

(9H-Fluoren-9-yl) methyl (S)-1-((S)-3-methylthio-1-(thiazol-2-yl) propylamino)-1-oxopropan-2-ylcarbamate (8d)

Yield 85%, Gum; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.45 (d, *J*=8.0 Hz, 3H), 2.04 (s, 3H), 2.21 (m, 2H), 2.40 (m, 2H), 4.45 (t, *J*=6.8 Hz, 1H), 4.68 (d, *J*=8.0 Hz, 2H), 4.70 (m, 1H), 4.85 (t, *J*=6.8 Hz, 1H), 6.0 (s, 1H), 7.08-7.74 (m, 10H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 17.0, 17.6, 29.7, 37.6, 47.0, 51.1, 52.5, 67.4, 118.7, 126.8, 128.0, 128.3, 128.8, 141.0, 142.2, 143.4, 156.0, 170.5, 171.7. MS: Calcd. for $C_{25}H_{27}N_3O_3S_2$ *m/z*: 514.22 (M^+ +Na), Found: 514.2201.

Anal. Calcd. for $C_{25}H_{27}N_3O_3S_2$: C, 62.34; H, 5.65; N, 8.72. Found: C, 62.40; H, 5.59; N, 8.64.

In vitro antibacterial activity

Preparation of Bacterial Suspension

For each test, 2 ml normal saline (0.85% w/v) was taken in a test tube, plugged with cotton, and wrapped with a newspaper. The test tubes were put in an autoclave for sterilization at 15 lbs for 20 min. After autoclaving, a loop was used to take 1-2 colonies of bacteria from a sub-cultured bacterial plate. Colonies were dissolved in the normal saline with rubbing and stirring.

Preparation of Mueller Hinton Agar Plates

Mueller Hinton agar medium (3.0 mg) was dissolved properly in 80 mL distilled water in a 250 mL conical flask with stirring. The mouth of the conical flask was plugged with cotton, wrapped with a newspaper and put in an autoclave for sterilization at 15 lbs for 20 min. After autoclaving, 20-25 mL of the warm medium was poured onto a petri dish and left until it solidified.

Table 3. Antibacterial testing of the new thiazoles.

		Inhibition zone (mm)				
		Sample Concentration				
Organisms	Compound	50 µl	100 µl	150 µl	200 µl	Time (hrs)
E.coli	**4b**	–	–	10 mm	12 mm	24
S.aureus	**4c**	14 mm	17 mm	15 mm	18 mm	24

Preparation of sample solution

The test compound (5 mg) was dissolved in 1 mL of DMSO: PEG (1:10) in a test tube with vertex stirring. The prepared plate was divided into four quadrants. One plate was swabbed from one bacterial suspension with the use of a cotton swab. With the help of a micro pipette, 50-200 µl sample solution was dropped per quadrant. All the plates were put in an incubator for 18-24 hrs.

Agar well diffusion method

The bacterial strains (*Escherichia coli* and *Staphylococcus aureus*) were maintained on the nutrient agar medium by sub culturing them at regular intervals. Nutrient broth cultures of organisms, designated as inocula, were obtained after incubation for 24 hrs at 37 °C. The well was made using a 5 mm cork borer sterilized using flame and alcohol. A sterile swab was dipped into the nutrient broth culture and was rotated firmly against upper inside wall of the tube to expel the excess fluid. The entire surface of the Mueller Hinton agar medium (MHA) was swabbed with the inoculum. As soon as the MHA was partly solidified, the plates were inverted and left for 2 hrs. Samples (100 µl) dissolved in DMSO were introduced into the wells. The plates were incubated overnight at 37 °C. Microbial growth was determined by measuring the diameter of the zone of inhibition and compared with those of standard antibiotics (Table 3).

The synthesized compounds Fmoc-Val-Thiazole **(4b)** and Fmoc-Leu-Thiazole **(4c)** were subjected to antibacterial studies against *E. coli* and *S. aureus* respectively. The inhibition zones were recorded for different concentrations of the samples. In case of *E. coli*, the synthesized terminal thiazole, **4b** showed a moderate zone of inhibition of 12 mm at 200 µl sample concentration, whereas compound **4c** showed significant activity of 18 mm against *S. aureus* at 200 µl.

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