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Synthesis and antimycobacterial screening of a novel series of α-amino acids containing thiazole linker

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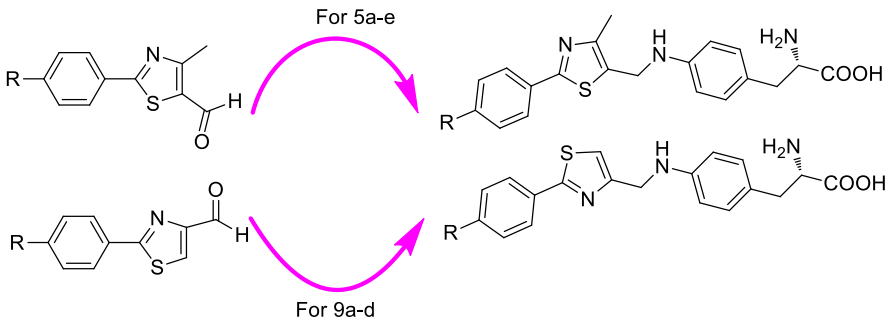
Abstract

A small focused library of uncommon (S)-2-amino-3-(4-(((4-methyl-2-arylthiazol-5-yl)methyl)amino)phenyl) propanoic acid (**5a-e**) and (S)-2-amino-3-(4-(((2-arylthiazol-4-yl)methyl)amino)phenyl)propanoic acid (**9a-d**) derivatives have been efficiently synthesized by employing molecular simplification. The title compounds were screened for inhibitory activity against *Mycobacterium tuberculosis* H37Ra (MTB) and *Mycobacterium bovis* (BCG) strains. The cytotoxicity study was conducted against primary Human Umbilical Vein Endothelial Cells (HUVECs), on two different human tumor cells HeLa, and HCT 116 and was observed non-toxic to host cells.



Keywords: Thiazole, amino acid, synthesis, *Mycobacterium tuberculosis,* antibacterial activity, cytotoxicity

Introduction

Tuberculosis (TB) is one of the top causes of death worldwide.[1] The unusual cell wall barrier, ability to remain dormant, and the emergence of multidrug (MDR) as well as extensively drug-resistant (XDR) Mtb strains, demand the development of a library of novel entities having various biodynamic heteroaryl scaffolds and active pharmacophores for treatment of TB.[2-4]

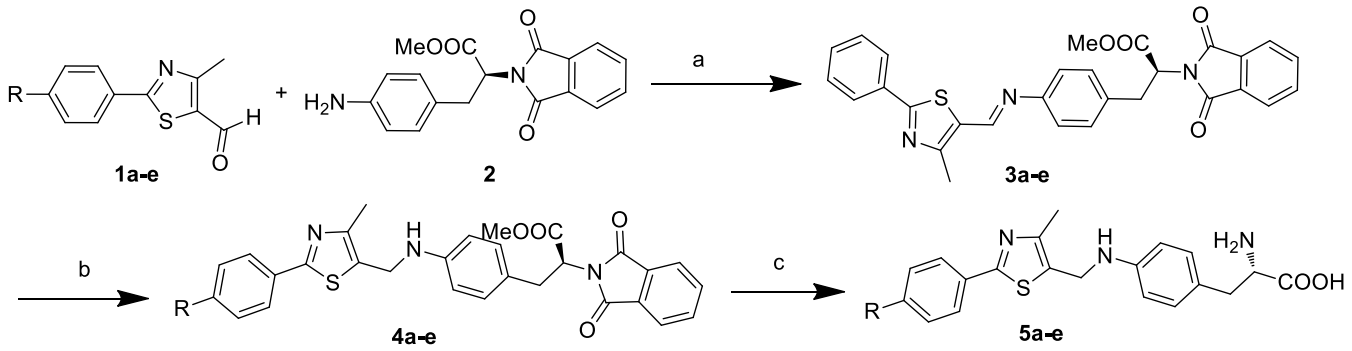
Thiazole is an important nucleus of several bioactive natural products,[5-9] which has been reported for a wide range of antimycobacterial activity.[10-15] Due to its appreciable diversity in biological actions, thiazole is one of the influential scaffolds in drug discovery and development processes.

Cyclic peptides containing thiazole nuclei have been continuously isolated from marine organisms and attracted significant interest in drug discovery and development.[16-26] The design and synthesis of peptidomimetics containing various heterocycles such as tetrazoles,[27] triazole,[28] oxadiazole,[29,30] and thiazole[31] have received attention due to their potent biological significance. Researchers believed that these heterocyclic pharmacophores played vital roles in favoring bioactive conformation with decreased flexibility, inclining the lipophilicity of the whole molecule, serving as recognition targets, and even tuning the binding properties of biomolecules such as RNAs, DNAs, and proteins. Among them, thiazoles have been studied extensively as a number of peptide-based natural products and drugs such as melenocortical receptor ligands, which contain the thiazole motif as a pharmacophore.[32-35] Therefore, to carry out investigations towards the synthesis of various thiazole-containing amino acids in order to exploit their antimycobacterial potential were determined. In the present investigation we report on the synthesis of uncommon S)-2-amino-3-(4-(((4-methyl-2-arylthiazol-5-yl)methyl)amino)phenyl)propanoic acid (**5a-e**) and (S)-2-amino-3-(4-(((2-arylthiazol-4-yl)methyl)amino)phenyl)propanoic acid (**9a-d**) derivatives employing molecular simplification.

Results and Discussion

Synthesis of target amino acids

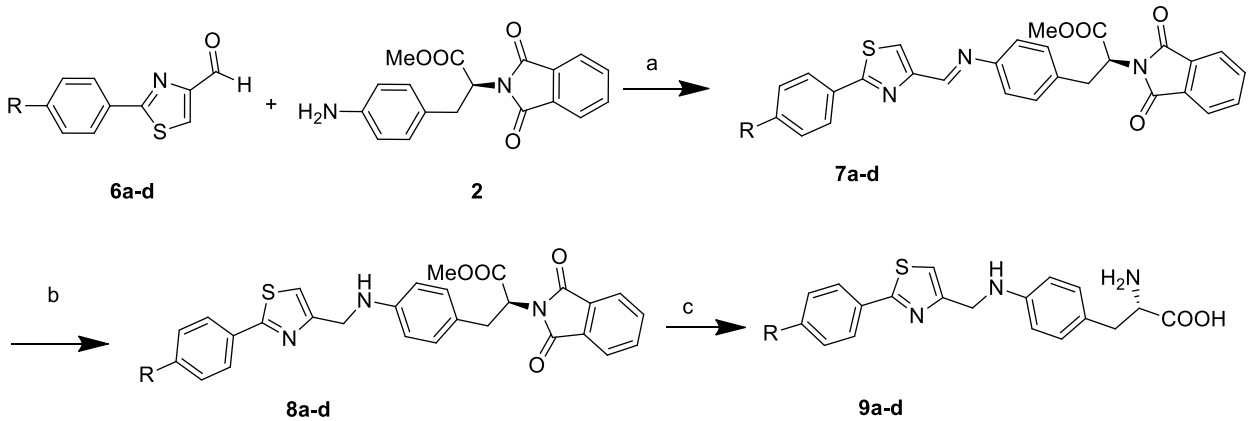
The synthetic strategies adopted for the synthesis of titled compounds **5a**-**e** and **9a-d** are depicted in Schemes 1 and 2, respectively. The 4-methyl-2-arylthiazole-5-carbaldehyde **1a-e** on condensation with (S)-methyl 3-(4-aminophenyl)-2-(1,3-dioxoisoindolin-2-yl)propanoate **2** gave (S)-methyl 2-(1,3-dioxoisoindolin-2-yl)- 3-(4-(((4-methyl-2-phenylthiazol-5-yl)methylene)amino)phenyl)propanoate **3a-e**. Compounds **3a-e** on selective reduction with $NaBH_3CN$ gave (S)-methyl 2-(1,3-dioxoisoindolin-2-yl)-3- (4-(((4-methyl-2-phenylthiazol-5-yl)methyl)amino)phenyl)propanoate **4a-e** which on acid hydrolysis furnished target compounds **5a-e**.



Compound: **3a 3b 3c 3d 3e 4a 4b 4c 4d 4e 5a 5b 5c 5d 5e**
R H Br Cl F CH_3 H Br Cl F CH_3 H Br Cl F CH_3

Scheme 1. Synthesis of (S)-2-amino-3-(4-(((4-methyl-2-arylthiazol-5-yl)methyl)amino)phenyl)propanoic acid **5a-e.** Reagents and conditions: a) EtOH, reflux, 2h, 80-88%; b) $NaBH_3CN$, MeOH, 0 °C – r.t., 24 hr, 85-90%; c) Conc. HCl, reflux, 8 h, 70-75%.

For the synthesis of (S)-methyl 2-amino-3-(4-(((2-arylthiazol-4-yl)methyl)amino)phenyl)propanoate **9a-d** similar strategy was adopted starting from 2-arylthiazole-4-carbaldehyde (**6a-d**). The structure of the synthesized compounds, **5a-e** and **9a-d** was confirmed by spectral analysis. The synthesized compounds were screened for antimycobacterial activity.



Compound: **7a 7b 7c 7d 8a 8b 8c 8d 9a 9b 9c 9d**
R: H Cl F CH_3 H Cl F CH_3 H Cl F CH_3

Scheme 2. Synthesis of (S)-2-amino-3-(4-(((2-arylthiazol-4-yl)methyl)amino)phenyl)propanoic acid **9a-d.** Reagents and conditions: a) EtOH, reflux, 2h, 75-80%; b) $NaBH_3CN$, MeOH, 0 °C – r.t., 24 hr, 90%; c) Conc. HCl, reflux, 8 h, 75-80%.

Biological evaluation

The *in vitro* anti-tubercular activity against *M. tuberculosis* H37Ra (Dormant stage) and *M. bovis* (Dormant stage) revealed that most of the screened compounds showed moderate to good anti-tubercular activity against both strains. (Table 1) The compound **5c** exhibited good anti-tubercular activity against *M. bovis*. The preliminary structure-activity relationship study revealed that the replacement of hydrogen atoms of phenyl ring by substituents like Cl, F, and CH_3 significantly affects the anti-tubercular activity.

Table 1. Anti-mycobacterial activity in IC_{50} of the compounds **5a-e** and **9a-d**

Comp	*M. tuberculosis* H37Ra	*M. bovis* BCG	*E. coli*	*P. flurescnce*	*S. aureus*	*B. subtilis*
5a	3.20	2.43	>30	>30	>30	>30
5b	3.22	>30	2.37	2.41	2.45	2.43
5c	3.18	~ 2.34	2.40	2.41	2.40	~ 2.36
5d	~ 2.56	>30	2.97	2.43	3.21	3.01
5e	8.60	6.82	2.40	2.41	2.50	2.48
9a	>30	>30	>30	>30	>30	>30
9b	>30	11.86	>30	>30	>30	>30
9c	12.59	>30	>30	>30	>30	>30
9d	>30	8.09	2.40	2.41	~ 2.38	~ 2.38

The antibacterial activity of synthesized compounds was determined against the standard Gram-negative bacteria, *E. coli* (NCIM 2576), *P. flurescence* (NCIM 2059) and Gram-positive bacteria, *S. aureus* (NCIM 2602), *B. subtilis* (NCIM 2162). (Table 2) Unsubstituted phenyl at 2-position and methyl amino group at 5-position of thiazole ring showed good activity against both tubercular strains but found inactive against bacterial strains. The Br/Cl/F/CH_3 substituted phenyl and methyl amino group at 5-position of thiazole ring at 2-position of thiazole showed good activity against *M. tuberculosis* H37Ra and all bacterial strains. The phenyl or substituted phenyl group at 2-position of thiazole and methyl amino group at 4-position found less active. From the antibacterial activity data, it is concluded that compounds **5c** and **5e** showed good activity against all tested strains.

To evaluate the cytotoxicity, the synthesized compounds **5a-e** and **9a-d** were further assayed for their cytotoxic activity in exponentially dividing primary (HUVECs) and human cancer cells (HeLa and HCT 116), the cells were treated with increasing concentrations of compounds, and cell viability was measured over time by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide MTT assay.[32,33] Paclitaxel was used as a positive control. The cytotoxic effect of these compounds was checked on cancer cell lines using the concentration range between 30, 10, and 3 μg mL^{-1} to determine the growth inhibition. The results indicated that, in MTT cytotoxicity studies, most active compounds are leads as antimicrobials owing to no significant cell toxicity against HeLa, HCT 116 and HUVEC cell lines at the maximum concentration evaluated. It is noteworthy that compounds did not demonstrate cell toxicity towards HUVEC cells (>100 μg mL^{-1}), implying its non-toxicity toward normal cells.

Conclusions

Two series of uncommon (S)-3-(4-((4-methyl-2-p-tolylthiazol-5-yl)methylamino)phenyl)-2-aminopropanoic acid derivatives were synthesized. The antimycobacterial activities studies were undertaken to evaluate the effects of substituent/group on the antitubercular and antimicrobial activities. From the SAR, it is concluded that (S)-2-amino-3-(4-(((2-(4-chlorophenyl)-4-methylthiazol-5-yl)methyl)amino)phenyl)propanoic acid **5c** and (S)-2-amino-3-(4-(((2-(p-tolyl)thiazol-4-yl)methyl)amino)phenyl)propanoic acid **9d** displayed excellent antibacterial activity at 3 μg mL^{-1} concentration against all tested strains. The compound (S)-2-amino-3-(4-(((2-(4-chlorophenyl)-4-methylthiazol-5-yl)methyl)amino)phenyl)propanoic acid (**5c**) showed good antitubercular

activity against *M. bovis*. Compounds significantly not inhibited the survival of two cell lines HeLa and HCT 116 and were found to be non-toxic towards normal human umbilical vein endothelial cells (HUVEC) even at high concentrations.

Experimental Section

General. All the reactions were monitored by thin layer chromatography (TLC). TLC was performed on Merck 60 F-254 silica gel plates. Melting points were determined in capillary tubes in a silicon oil bath using a Veego melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian mercury XL-300 and Bruker at either 400/500 MHz (^{1}H NMR) or 100/126 MHz (^{13}C NMR), spectrometer instruments. Chemical shifts are reported from the internal tetramethylsilane standards and are given in δ units. Infrared spectra were recorded on Shimadzu FTIR (KBr) - 408 in KBr. The chemicals and solvents used were laboratory grade and were purified as per literature methods. The starting compounds 4-methyl-2-arylthiazole-5-carbaldehyde (**1a-e**) and 2-arylthiazole-4-carbaldehyde (**6a-d**) were synthesized by our previous methods.[34]

General procedure for synthesis of methyl 3-(4-((4-methyl-2-arylthiazole-5-yl) methyl eneamino) phenyl) 2-(1, 3 dioxoisoindolin-2yl) propanoate (**3a-e**)**.** To a solution of 4-methyl 2-arylthiazole-5-caraldehyde **1a-e** (4.60 mmol) in methanol (10mL), methyl 3-(4-aminophenyl) 2-(1,3 dioxoisoindolin-2-yl) propionate (4.60 mmol) was added. The reaction mixture was stirred for 8 hours. After completion of reaction (TLC), the solid was filtered under vacuum and dried, furnished methyl 3-(4-((4-methyl-2-arylthiazole-5-yl) methyleneamino) phenyl) 2-(1, 3 dioxoisoindolin-2yl) propanoate. Compounds **7a-d** were synthesized by applying similar experimental conditions.

General procedure for synthesis of methyl 3-(4-((4-methyl-2-arylthiazole-5-yl) methyl amino) phenyl) 2-(1, 3 dioxoisoindolin-2yl)propanoate (**4a-e**). To the ice-cold solution of methyl 3-(4-((4-methyl-2-arylthiazole-5-yl) methyleneamino) phenyl) 2-(1, 3 dioxoisoindolin-2yl) propanoate (0.9 mmol) in dry methanol (5mL), acetic acid (0.5mL) was added and stirred for 10 min. The reaction mixture was cooled at 0-5 °C and sodium cyanoborohydride (1.84 mmol) was added portion-wise at 0-5 °C and the reaction mixture was further stirred for 12 hours. After completion of the reaction (TLC), solvent was removed under reduced pressure. The residue was dissolved in water (30mL) and the pH was adjusted to neutral using a saturated $NaHCO_3$ solution. The aqueous layer was extracted with DCM (15mL x 2), and the organic layer was dried over anhydrous Na_2SO_4 and distilled under vacuum gave a crude product, which was purified by column chromatography, using ethyl acetate: hexane (3:7) as eluent. Compounds **8a-d** were synthesized by applying similar experimental conditions.

General procedure for synthesis of (S)-2-amino-3-(4-(((4-methyl-2-arylthiazol-5-yl)methyl)amino)phenyl)propanoic acid (**5a-e**). The solution of methyl 3-(4-((4-methyl-2-arylthiazole-5-yl)methylamino)phenyl)2-(1,3 dioxoisoindolin-2yl)propanoate (0.8 mmole), in conc. HCl (8N) was refluxed for about 8-12 h. The reaction mass was cooled and phthalic acid was removed by filtration. The filtrate was diluted with 25mL water and the reaction mixture was extracted with 10 mL diethyl ether. The pH of the aqueous layer was adjusted to 6-7 by using ammonia solution. The precipitated mass was stirred for 2 hours at room temperature. The product was filtered on a Buckner funnel, and washed with distilled water followed by acetone (10 mL). The product was dried in a vacuum drier. Compounds **9a-d** were synthesized by using similar reaction conditions.

(*S*)-2-Amino-3-(4-(((4-methyl-2-phenylthiazol-5-yl)methyl)amino)phenyl)propanoic acid (5a). Yield 55%. mp 215 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.42 (s, 3H, Thiazole-C$\underline{H}_3$), 2.62-2.72 (m, 1H, Ar-C$\underline{H}_2$-CH), 2.98 (dd, *J* 4.12 and 14.68 Hz, 1H, Ar-C$\underline{H}_2$-CH), 4.38 (d, *J* 5.92 Hz, 2H, Thiazole-C$\underline{H}_2$-NH), 6.18-6.24 (m, 1H, H_2N-C$\underline{H}$-COOH), 6.54 (d, *J* 8.28, 2H, Ar-H), 6.98 (d, *J* 8.28 Hz, 2H, Ar-H), 7.42-7.45 (m, 3H, Ar-H), 7.82-7.85 (m, 2H, Ar-H). ^{13}C NMR (126 MHz, DMSO-d_6): δ_C 15.6 (CH_3, Thiazole-CH_3), 36.5 (CH_2, Ar-$\underline{C}H_2$-CH), 40.0 (CH_2, Thiazole-CH_2-N), 56.2 (CH_2, CH_2-$\underline{C}$H-(-NH_2, -COOH)), 113.0 (CH, C-2′, C-6′), 125.5 (C, C-4′), 126.1 (CH, C-3′, C-5′), 129.6 (CH, C-3, C-5), 130.3 (CH, C-4), 130.4 (CH, C-2, C-6), 133.3 (C, Thiazole-C-5), 133.7 (C, C-1), 147.1 (C, N-C-1′), 149.2 (C, Thiazole-C-2), 163.8 (C, Thiazole-C-2), 170.5 (C, COOH). HRMS: *m/z* 368.1450 $[M+H]^+$ (calcd. for $C_{20}H_{22}N_3O_2S$, 368.1433).

(*S*)-2-Amino-3-(4-(((2-(4-bromophenyl)-4-methylthiazol-5-yl)methyl)amino)phenyl)propanoic acid (5b). Yield 60%. mp 214 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.43 (s, 3H, Thiazole-CH_3), 2.68 (dd, *J* 14.60 and 14.68 Hz, 1H, Ar-C$\underline{H}_2$-CH), 2.98 (dd, *J* 4.12 and 14.64 Hz, 1H, Ar-C$\underline{H}_2$-CH), 4.38 (d, *J* 4.56 Hz, 2H, Thiazole-C$\underline{H}_2$-NH), 6.18-6.24 (m, 1H, H_2N-C$\underline{H}$-COOH), 6.54 (d, *J* 8.24, 2H, Ar-H), 6.98 (d, *J* 8.24 Hz, 2H, Ar-H), 7.43 (d, *J* 8.42 Hz, 2H, Ar-H), 7.77 (d, *J* 8.42 Hz, 2H, Ar-H). ^{13}C NMR (126 MHz, DMSO-d_6): δ_C 15.6 (CH_3, Thiazole-CH_3), 36.5 (CH_2, Ar-$\underline{C}H_2$-CH), 40.1 (CH_2, Thiazole-CH_2-N), 56.2 (CH_2, CH_2-$\underline{C}$H-(-NH_2, -COOH)), 113.0 (CH, C-2′, C-6′), 123.5 (C, C-4), 125.5 (C, C-4′), 126.1 (CH, C-3′, C-5′), 130.4 (CH, C-2, C-6), 132.6 (CH, C-3, C-5), 133.3 (C, Thiazole-C-5), 133.7 (C, C-1), 147.1 (C, N-C-1′), 149.2 (C, Thiazole-C-2), 163.8 (C, Thiazole-C-2), 170.5 (C, COOH), HRMS: *m/z* 446.0515 [M+H]+ (calcd. for $C_{20}H_{21}N_3O_2SBr$, 446.0538).

(*S*)-2-Amino-3-(4-(((2-(4-chlorophenyl)-4-methylthiazol-5-yl)methyl)amino)phenyl)propanoic acid (5c). Yield 62%. mp 214 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.27 (s, 3H, Thiazole-CH_3), 2.61 (dd, *J* 14.2 and 14.3 Hz 1H, Ar-C$\underline{H}_2$-CH), 2.92 (dd, *J* 3.6 and 14.3 Hz, 1H, Ar-C$\underline{H}_2$-CH), 4.32 (d, *J* 5.4 Hz, 2H, Thiazole-C$\underline{H}_2$-NH), 6.12-6.14 (m, 1H, H_2N-C$\underline{H}$-COOH), 6.47 (d, *J* 8.32, 2H, Ar-H), 6.91 (d, *J* 8.32 Hz, 2H, Ar-H), 7.43 (d, *J* 8.52 Hz, 2H, Ar-H), 7.78 (d, *J* 8.52 Hz, 2H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 15.0 (CH_3, Thiazole-CH_3), 37.4 (CH_2, Ar-$\underline{C}H_2$-CH), 40.2 (CH_2, Thiazole-CH_2-N), 56.8 (CH_2, CH_2-$\underline{C}$H-(-NH_2, -COOH)), 112.5 (CH, C-2′, C-6′), 125.5 (C, C-4′), 127.3 (CH, C-3′, C-5′), 129.2 (CH, C-2, C-6), 129.9 (CH, C-3, C-5), 132.1 (C, C-1), 133.5 (C, Thiazole-C-5), 134.2 (C, C-4), 146.7 (C, N-C-1′), 149.1 (C, Thiazole-C-2), 162.1 (C, Thiazole-C-2), 172.5 (C, COOH). HRMS: *m/z* = 402.1013 [M+H]+ (calcd. for $C_{20}H_{21}N_3O_2SCl$, 402.1043).

(*S*)-2-Amino-3-(4-(((2-(4-fluorophenyl)-4-methylthiazol-5-yl)methyl)amino)phenyl)propanoic acid (5d). Yield 55%. mp 208 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.27 (s, 3H, Thiazole-CH_3), 2.61 (dd, *J* 14.2 and 14.3 Hz 1H, Ar-C$\underline{H}_2$-CH), 2.92 (dd, *J* 3.6 and 14.3 Hz, 1H, Ar-C$\underline{H}_2$-CH), 4.38 (d, *J* 4.56 Hz, 2H, Thiazole-C$\underline{H}_2$-NH), 6.19-6.21 (m, 1H, H_2N-C$\underline{H}$-COOH), 6.54 (d, *J* 8.24, 2H, Ar-H), 6.97 (d, *J* 8.24 Hz, 2H, Ar-H), 7.27-7.30 (m, 2H, Ar-H), 7.87-7.90 (m, 2H, Ar-H). ^{13}C NMR (126 MHz, DMSO): δ_C 15.6 (CH_3, Thiazole-CH_3), 36.6 (CH_2, Ar-$\underline{C}H_2$-CH), 40.1 (CH_2, Thiazole-CH_2-N), 55.7 (CH_2, CH_2-$\underline{C}$H-(-NH_2, -COOH)), 113.0 (CH, C-2′, C-6′), 116.6 (CH, C-3, C-5), 125.6 (C, C-4′), 128.3 (CH, C-3′, C-5′), 128.4 (CH, C-2, C-6), 130.5 (C, C-1), 133.4 (C, Thiazole-C-5), 147.1 (C, N-C-1′), 149.2 (C, Thiazole-C-4), 162.7 (C, Thiazole-C-2), 163.4 (C, C-4), 170.2 (C, COOH). HRMS: *m/z* 386.1366 [M+H]+ (calcd. for $C_{20}H_{21}N_3O_2SF$, 386.1339).

(*S*)-2-Amino-3-(4-(((4-methyl-2-(p-tolyl)thiazol-5-yl)methyl)amino)phenyl)propanoic acid (5e). Yield 65%. mp 218 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.32 (s, 3H, Thiazole-CH_3), 2.41 (s, 3H, Ar-CH_3), 2.77 (dd, *J* 7.72 and 14.64 Hz, 1H, Ar-C$\underline{H}_2$-CH), 2.98 (dd, *J* 4.56 and 14.64 Hz, 1H, Ar-C$\underline{H}_2$-CH), 4.37 (s, 2H, Thiazole-C$\underline{H}_2$-NH), 6.22-6.24 (m, 1H, H_2N-C$\underline{H}$-COOH), 6.55 (d, *J* 8.72, 2H, Ar-H), 6.99 (d, *J* 8.72Hz, 2H, Ar-H), 7.25 (d, *J* 8.24, 2H, Ar-H), 7.72 (d, *J* 8.24, 2H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 15.1 (CH_3, Thiazole-CH_3), 20.9 (CH_3, Ar-CH_3), 35.8 (CH_2, Ar-$\underline{C}H_2$-CH), 40.1 (CH_2, Thiazole-CH_2-N), 55.1 (CH_2, CH_2-$\underline{C}$H-(-NH_2, -COOH)), 112.5 (CH, C-2′, C-6′), 124.2 (CH, C-2, C-6), 125.6 (C, C-4′), 129.7 (CH, C-3′, C-5′), 130.0 (CH, C-3, C-5), 130.7 (C, C-1), 132.1 (C, Thiazole-C-5),

139.6 (C, C-4), 146.9 (C, N-C-1'), 148.6 (C, Thiazole-C-4), 163.5 (C, Thiazole-C-2), 170.1 (C, COOH). HRMS: *m/z* 382.1579 $[M+H]^+$ (calcd. For $C_{21}H_{24}N_3O_2S$, 382.1589).

(*S*)-2-Amino-3-(4-(((2-phenylthiazol-4-yl)methyl)amino)phenyl)propanoic acid (9a). Yield 60%. mp 210 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.66 (dd, *J* 8.5 and 14.64 Hz, 1H, Ar-C$\underline{H}_2$-CH), 2.98 (dd, *J* 4.16 and 14.64 Hz, 1H, Ar-C$\underline{H}_2$-CH), 4.38 (d, *J* 5.48 Hz, 2H, Thiazole-C$\underline{H}_2$-NH), 6.12-6.15 (m, 1H, H_2N-C$\underline{H}$-COOH), 6.58 (d, *J* 8.68, 2H, Ar-H), 6.97 (d, *J* 8.68 Hz, 2H, Ar-H), 7.44 (s, 1H, Thiazole-H), 7.47-7.50 (m, 3H, Ar-H), 7.92-7.94 (m, 2H, Ar-H). ^{13}C NMR (126 MHz, DMSO-d_6): δ_C 36.6 (CH_2, Ar-$\underline{C}H_2$-CH), 44.1 (CH_2, Thiazole-CH_2-N), 56.3 (CH_2, CH_2-$\underline{C}$H-(-NH_2, -COOH)), 112.9 (CH, C-2', C-6'), 116.0 (CH, Thiazole C-5), 125.0 (C, C-4'), 126.5 (CH, C-3, C-5), 129.7 (CH, C-3', C-5'), 130.3 (CH, C-2, C-6), 130.6 (CH, C-4), 133.6 (C, C-1), 147.6 (C, N-C-1'), 157.1 (C, Thiazole-C-4), 167.36 (C, Thiazole-C-2), 170.2 (C, COOH). HRMS: *m/z* 376.1077 $[M+Na]^+$ (calcd. For $C_{19}H_{19}N_3O_2SNa$, 376.1096).

(*S*)-2-Amino-3-(4-(((2-(4-chlorophenyl)thiazol-4-yl)methyl)amino)phenyl)propanoic acid (9b). Yield 62%. mp 212 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ_H 2.67 (dd, *J* 8.58 and 14.46 Hz, 1H, Ar-C$\underline{H}_2$-CH), 2.98 (dd, *J* 4.08 and 14.46 Hz, 1H, Ar-C$\underline{H}_2$-CH), 3.25-3.27 (m, 1H, NH), 4.38 (d, *J* 6.24 Hz, 2H, Thiazole-C$\underline{H}_2$-NH), 6.14 (m, 1H, H_2N-C$\underline{H}$-COOH), 6.58 (d, J 8.22 Hz, 2H, Ar-H), 6.97 (d, *J* 8.22 Hz, 2H, Ar-H), 7.48 (s, 1H, Thiazole-H), 7.57 (d, *J* 8.28 Hz, 2H, Ar-H), 7.95 (d, *J* 8.28 Hz, 2H, Ar-H). ^{13}C NMR (126 MHz, DMSO-d_6): δ_C 36.6 (CH_2, Ar-$\underline{C}H_2$-CH), 44.0 (CH_2, Thiazole-CH_2-N), 56.3 (CH_2, CH_2-$\underline{C}$H-(-NH_2, -COOH)), 112.8 (CH, C-2', C-6'), 116.5 (CH, Thiazole C-5), 125.2 (C, C-4'), 128.2 (CH, C-3', C-5'), 129.8 (CH, C-2, C-6), 130.3 (CH, C-3, C-5), 132.4 (C, C-1), 135.1 (C, C-4), 147.5 (C, N-C-1'), 157.2 (C, Thiazole-C-4), 166.0 (C, Thiazole-C-2), 170.1 (C, COOH). HRMS: *m/z* 388.0917 [M+H]+ (calcd. For $C_{19}H_{19}N_3O_2SCl$, 388.0887).

(*S*)-2-Amino-3-(4-(((2-(4-fluorophenyl)thiazol-4-yl)methyl)amino)phenyl)propanoic acid (9c).Yield 56%. mp 218 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.66 (dd, *J* 13.72 and 14.64 Hz, 1H, Ar-C$\underline{H}_2$-CH), 2.98 (dd, *J* 4.12 and 14.64 Hz, 1H, Ar-C$\underline{H}_2$-CH), 4.38 (d, *J* 5.04 Hz, 2H, Thiazole-C$\underline{H}_2$-NH), 6.12-6.16 (m, 1H, H_2N-C$\underline{H}$-COOH), 6.58 (d, *J* 8.24, Ar-H), 6.97 (d, *J* 8.24 Hz, 2H, Ar-H), 7.34 (t, *J* 8.72 Hz, 2H, Ar-H), 7.44 (s, 1H, Thiazole-H), 7.96-7.99 (m, 2H, Ar-H). ^{13}C NMR (126 MHz, DMSO-d_6): δ_C 36.6 (CH_2, Ar-$\underline{C}H_2$-CH), 44.1 (CH_2, Thiazole-CH_2-N), 56.4 (CH_2, CH_2-$\underline{C}$H-(-NH_2, -COOH)), 112.9 (CH, C-2', C-6'), 116.1 (CH, Thiazole C-5), 116.7 (CH, C-3, C-5), 125.2 (C, C-4'), 128.8 (CH, C-3', C-5'), 128.8 (CH, C-2, C-6), 130.3 (C, C-1), 147.5 (C, N-C-1'), 157.0 (C, Thiazole-C-4), 163.6 (C, C-4), 166.2 (C, Thiazole-C-2), 172.4 (C, COOH). HRMS: *m/z* 372.1176 $[M+H]^+$ (calcd. For $C_{19}H_{19}N_3O_2SF$, 372.1182).

(*S*)-2-Amino-3-(4-(((2-(p-tolyl)thiazol-4-yl)methyl)amino)phenyl)propanoic acid (9d). Yield 66%. mp 216 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.35 (s, 3H, Ar-CH_3), 2.66 (dd, *J* 14.2 and 14.68 Hz 1H, Ar-C$\underline{H}_2$-CH), 2.92 (dd, *J* 4.12 and 14.68 Hz, 1H, Ar-C$\underline{H}_2$-CH), 4.37 (d, *J* 5.52 Hz, 2H, Thiazole-C$\underline{H}_2$-NH), 6.10-6.14 (m, 1H, H_2N-C$\underline{H}$-COOH), 6.58 (d, *J* 8.24, 2H, , Ar-H), 6.97 (d, *J* 8.24 Hz, 2H, Ar-H), 7.30 (d, *J* 8.24 Hz, 2H, Ar-H), 7.39 (s, 1H, Thiazole-H), 7.82 (d, *J* 8.24 Hz, 2H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 15.0 (CH_3, Ar-$\underline{C}H_3$), 37.4 (CH_2, Ar-$\underline{C}H_2$-CH), 49.2 (CH_2, Thiazole-CH_2-N), 56.8 (CH_2, CH_2-$\underline{C}$H-(-NH_2, -COOH)), 112.5 (CH, C-2', C-6'), 116.1 (CH, Thiazole C-5), 125.1 (C, C-4'), 127.3 (CH, C-2, C-6), 128.9 (CH, C-3', C-5'), 129.2 (CH, C-3, C-5), 132.1 (C, C-1), 138.2 (C, C-4), 146.7 (C, N-C-1'), 156.2 (C, Thiazole-C-4), 166.15 (C, Thiazole-C-2), 172.1 (C, COOH). HRMS: *m/z* 368.1452 $[M+H]^+$ (calcd. For $C_{20}H_{22}N_3O_2S$, 368.1433).

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Supplementary Material

NMR spectra for all new compounds and bioassay protocols and data are provided in the Supporting Information file.

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