Synthesis and antibacterial and antifungal activity of \(N\)-(4-fluorophenyl)-\(N\)-carboxyethylaminothiazole derivatives

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Abstract

A series of novel \(N\)-(4-fluorophenyl)-\(N\)-carboxyethylaminothiazoles and thiazolones with aliphatic, aromatic and heterocyclic substituents were obtained in good to excellent overall yields. The synthesized compounds were screened for their antimicrobial and antifungal activity. The antibacterial tests indicated that the functionalized aminothiazole derivatives exhibit a higher activity as compared with thiazolone derivatives.

Keywords: Amino acids, aminothiazoles, Hantzsch reaction, condensation, chalcones, antimicrobial agents

Introduction

The thiazole ring is integral in the structure of many biologically active compounds. Thiazoles are found to be associated with various biological activities such as antiviral, antimicrobial, antifungal, anticancer, anti-inflammatory, antihypertensive, anti-HIV, anticoagulant and antiarrhythmic, antidepressant, antidiabetic, etc. Chalcones have been shown to exhibit diverse biological activity, including antibacterial, antileishmanial, antimalarial, antifungal, antiviral, antifilarial, anti-inflammatory activities. In most of our previous works, \(N\)-aryl-\(N\)-thiocarbamoyl-\(\beta\)-amino acids were used for the synthesis of 1-substituted dihydropyrimidinediones and 1-substituted dihydropyrimidine-2-thiones. Part of our program is to synthesize new antimicrobial compounds. In a previous paper, a synthesis of \(N\)-phenyl-\(N\)-carboxyethylaminothiazoles with antibacterial properties was reported. Also, it was found that 3-[(4-oxo-4,5-dihydro-1,3-thiazol-2-yl)(phenyl)amino]propanoic acid promotes rapeseed growth, increases seed yield and oil content.
Results and Discussion

To find more potent antimicrobial agents, we report here the synthesis of new \(N,N\)-disubstituted aminothiazoles from \(N-(4\text{-fluorophenyl})-N\text{-thiocarbamoyl-\(\beta\)}}\text{-alanine (1)}. For the formation of the thiazole ring we used the Hantzsch method – reactions of thioamides with the \(\alpha\)-halocarbonyl compounds. It is known that the introduction of the halogen atom into a structure often increases its biological activity. In this part of the work, thiazolone 2 was synthesized, and some of its chemical transformations were investigated (Scheme 1). Compound 2 was synthesized from 3-[(4-fluorophenyl)carbamothioylamino]propanoic acid (1) and monochloroacetic acid. The reaction was carried out in water in the presence of a base such as sodium carbonate. In the \(^1H\) NMR spectrum of this compound, the methylene proton signals of the thiazolone ring were observed as a singlet at 3.93 ppm and the corresponding \(^{13}C\) signal at 40.58. Bromination of compound 2, performed in acetic acid at room temperature, gave the expected product, 3-[(5,5-dibromo-4-oxo-4,5-dihydro-1,3-thiazol-2-yl)(4-fluorophenyl)amino]propanoic acid (3). The methylene group in the five-membered heterocyclic ring easily participates in condensation reactions with carbaldehydes. All these reactions were carried out in water in the presence of sodium carbonate and glycine as a bifunctional catalyst which gave a single isomer (\(Z\)). The formed sodium salts were converted into acids by acidifying the reaction mixture with acetic acid to pH 6. The structures of the synthesized compounds were confirmed on the basis of their IR, \(^1H\), \(^{13}C\) NMR spectra and by elemental analysis data. A detailed analysis of the \(^1H\) and \(^{13}C\) NMR spectra of compounds 4–16 revealed new additional signals in the aromatic region of the spectra that were assigned to the incorporated benzylidene fragment. An intense molecular \([M+H]^+\) ion at \(m/z\) 663.75 in the mass spectrum of 16 confirmed the structure.

The second stage of this work was a synthesis of new substituted thiazoles \(17–29\). 3-[(4-Fluorophenyl)(1,3-thiazol-2-yl)amino]propanoic acid (17) was obtained from compound 1 and 50% aqueous chloroacetaldehyde in refluxing water. The obtained water-soluble amino acid hydrochloride was transformed into amino acid by adding sodium acetate to the reaction mixture. The structure of compound 17 was confirmed by IR, NMR spectral and elemental analysis data. In the \(^1H\) NMR spectrum, two triplets at 2.61 and 4.07 ppm were assigned to the CH\(_2\)CO and NCH\(_2\) group protons, two doublets at 6.72 and 7.18 ppm belonged to the thiazole ring SCH and NCH group protons, respectively, and a broad one-proton singlet for the carboxyl group was observed at 12.29 ppm. Also, new resonances at 108.23 and 139.19 ppm in the \(^{13}C\) NMR spectrum were detected, which are characteristic of carbon atoms of the NCH and SCH fragments of a thiazole ring. Reactions of thioureido acid 1 with various haloketones were also performed, and a number of new thiazole derivatives 18–21, 23 with aliphatic, aromatic, or heterocyclic substituents were synthesized. The reactions were carried out in refluxing acetone, and the pure products from the reaction mixture were separated by adding aqueous sodium acetate. An attempt at cyclization of compound 18 using acetic anhydride was unsuccessful. The reaction gave \(N\text{-}(4\text{-fluorophenyl})-N\text{-}(4\text{-phenylthiazol-2-yl})\)acetamide (22). By taking advantage
**Reagents:** i: ClCH\textsubscript{2}COOH, Na\textsubscript{2}CO\textsubscript{3}, H\textsubscript{2}O, t\textdegree, 4.5 h, CH\textsubscript{3}COOH to pH 6; ii: CH\textsubscript{3}COONa, CH\textsubscript{3}COOH, Br\textsubscript{2}, r.t., 1.5 h, H\textsubscript{2}O; iii: RCHO, NH\textsubscript{2}CH\textsubscript{2}COOH, Na\textsubscript{2}CO\textsubscript{3}, water, 80 °C, 8 h (11 – 21 h), CH\textsubscript{3}COOH to pH 6; iv: OHC-C\textsubscript{6}H\textsubscript{4}-CHO, NH\textsubscript{2}CH\textsubscript{2}COOH, Na\textsubscript{2}CO\textsubscript{3}, water, 80 °C, 6 h, CH\textsubscript{3}COOH to pH 6; v: HalCH\textsubscript{2}COR\textsuperscript{1}, acetone (17 – water), t\textdegree, 4 h, water, CH\textsubscript{3}COONa; vi: (CH\textsubscript{3}CO)\textsubscript{2}O, t\textdegree, 2 h, NH\textsubscript{3}; vii: CH\textsubscript{3}COCH\textsubscript{2}C\textsubscript{6}H\textsubscript{4}CH\textsubscript{3}, acetone, t\textdegree, 4 h, water, CH\textsubscript{3}COONa; viii: methanol, ArCHO+10% NaOH, 0 °C, 1.5 h, r.t., 22 h, water, CH\textsubscript{3}COOH to pH 6; ix: N\textsubscript{2}H\textsubscript{4}H\textsubscript{2}O, CH\textsubscript{3}COOH, methanol, t\textdegree, 5.5 h.

**Scheme 1.** Synthesis of N,N-disubstituted aminothiazolones 2–16 and N,N-disubstituted aminothiazoles 17–29.
of the well known aldol (Claisen–Schmidt) condensation reaction, chalcones 24–28 were synthesized from 5-acetyl-4-methylthiazole derivative 23 and corresponding aldehydes by the reported procedure, and products with the (E) configuration were obtained. Finally 3-[(5-{1-[(1-{2-[2-carboxyethyl]4-fluorophenyl]amino)-5-y1}ethylidene)hydrazono]ethyl]-4-methylthiazol-2-yl(4-fluorophenyl)amino)propanoic acid (29) was synthesized from compound 23 and hydrazine monohydrate in refluxing methanol. An intense molecular [M+H] + ion at m/z 641.80 was observed in the mass spectrum of compound 29.

Antibacterial and antifungal evaluation of synthesized compounds

The synthesized compounds 2–28 were evaluated for their antibacterial and antifungal activity against strains of Escherichia coli B-906, Staphylococcus aureus 209-P, Mycobacterium luteum B-917 (as a nonpathogenic test bacteria culture representative of the genus Mycobacterium), Candida tenuis VKM Y-70, and Aspergillus niger VKM F-1119 by the diffusion technique and by the serial dilution technique (determination of minimal inhibition concentrations MIC). Their activities were compared with those of the known antibacterial agent Vancomycin and antifungal agent Nystatin (control C).

Test-cultures of Escherichia coli appeared not to be sensitive to the tested compounds 2–28 investigated by the diffusion technique at concentrations of 0.1 and 0.5%. Staphylococcus aureus was highly sensitive to compounds 3, 20 and 21 at a concentration of 0.5% and slightly-sensitive to compounds 5, 19 and 23 at the same concentration. Other compounds were not active against this strain of bacteria. The Mycobacterium luteum strain was moderately sensitive to compounds 20 and 21 at a concentration of 0.5% (the diameter of the inhibition zone was 15.4 and 16.0 mm, respectively).

Compounds 3 and 19 were found to exhibit a low antibacterial activity against this strain in comparison with the control evaluated by the diffusion method. The biological characteristics of the compounds, obtained using the serial dilution technique, were classified as follows: the antibacterial activity was considered as significant when the MIC was 100 μg/mL or less, moderate, when the MIC was 100–500 μg/mL, weak, when the MIC was 500–1,000 μg/mL, and inactive, when the MIC was above 1,000 μg/mL. All the synthesized compounds, except 11 (MIC 500 μg/ml) and 12 (MIC 250 μg/ml), had no inhibitory effect at the studied concentrations against Escherichia coli. The evaluation of the antibacterial activity of these compounds showed that 3, 20 and 21 have MIC 125 μg/mL, 5, 11, 19 – 500 μg/mL against test-culture Staphylococcus aureus. The MIC of 20, 21 was observed at 31.2 μg/mL, 27 – at 62.5 μg/mL, 19, 24, 25 – at 125 μg/mL, 3 – at 250 μg/mL and 4, 13 – at 500 μg/mL against the test-culture Mycobacterium luteum. The growth of the bacteria S. aureus and M. luteum was observed for other compounds.

The evaluation of antifungal activity of the synthesized compounds showed that the strain Candida tenuis was slightly-sensitive (fungistatic action) to compounds 5 and 18 at a concentration of 0.5% (the diameter of the inhibition zone was 13.0 and 10.0 mm, respectively).
The MIC of 4 and 19 was observed at 125 μg/mL, of 5, 12, 17 – at 250 μg/mL, of 23 – at 500 μg/mL.

Compounds 5 and 10 showed a low fungistatic action against Aspergillus niger cultures at 0.5% concentrations (the diameter of the inhibition zone was 7.0 mm). A. niger was moderately sensitive to compounds 9 and 18 (the diameter of the inhibition zone was 13.7 and 14.0 mm, respectively). The MIC of 3 and 19 was observed at 125 μg/mL against A. niger. The growth of the fungi Candida tenuis and Aspergillus niger was observed for other compounds.

Conclusions

N,N-Disubstituted aminothiazole derivatives with a carboxyethyl moiety can be easily synthesized from N-aryl-N-thiocarbamoyl-β-alanines and α-halocarboxyl compounds by the Hantzsch method. Studies of antimicrobial activity of the synthesized compounds have revealed potentially new compounds with antibacterial activity against Staphylococcus aureus (3, 20, 21) and against Mycobacterium luteum (20 and 21). The antibacterial tests have indicated the functionalized aminothiazole derivatives to exhibit a higher activity as compared with thiazolone derivatives. The evaluation of the antifungal activity of the synthesized compounds showed them to be slightly-sensitive.

Experimental Section

General. The starting materials and solvents were obtained from Sigma-Aldrich Chemie GmbH (Munich, Germany) and Fluka (Buchs, Switzerland) and were used without further purification. The methods used to follow the reactions were TLC and NMR. The NMR spectra were recorded on a Bruker Avance III/400 (400 MHz). Chemical shifts are expressed as δ, ppm relative to TMS. The J constants are given in Hz. The IR spectra (v, cm⁻¹) were recorded on a Perkin–Elmer BX FT–IR spectrometer (Perkin–Elmer Inc., Waltham, MA, USA) using KBr tablets. The mass spectra were obtained on a Waters ZQ 2000 spectrometer (Waters, Germany) using the electrospray ionization (ESI) mode and operating at 25 V. Elemental analyses were performed with a CE-440 elemental analyzer (Exeter Analytical Inc., Chelmsford, MA, USA). Melting points were determined with a B-540 Melting Point Analyzer (Büchi Corporation, New Castle, DE, USA) and are uncorrected. TLC was performed using Merck, Silica gel 60 F254 (Kieselgel 60 F254) plates.

3-[(4-Fluorophenyl)(4-oxo-4,5-dihydro-1,3-thiazol-2-yl)amino]propanoic acid (2). A mixture of the 3-[(4-fluorophenyl)carbamothiolamino]propanoic acid (1) (1.21 g, 5 mmol), monochloroacetic acid (0.57 g, 6 mmol), sodium carbonate (0.64 g, 6 mmol) and water (15 mL) was refluxed for 4.5 h, cooled down to r.t. and acidified with acetic acid to pH 6. The precipitate
was filtered off, washed with water, dried. Purification was performed by dissolving crystals in 5% aqueous sodium carbonate, filtering, and acidifying the filtrate with acetic acid to pH 6 to give 2 as a white solid, yield 59%, 0.83 g, mp 190-191 °C; IR (νmax, cm⁻¹): 3419 (OH), 1720 and 1662 (C=O), 1521 (C=N). 1H NMR (400 MHz, DMSO-d6): δH 2.58 (2H, t, J 7.3 Hz, CH₂COO), 3.93 (2H, s, CH₂S), 4.15 (2H, t, J 7.3 Hz, NCH₂), 7.38 (2Hₐrom, t, J 8.7 Hz, 2CH), 7.51-7.59 (2Hₐrom, m, 2CH), 12.42 (1H, s, OH). 13C NMR (100 MHz, DMSO-d6): δC 31.8 (CH₂COO), 40.6 (CH₂S), 50.0 (NCH₂), 116.7 (d, 2JCF 23.0 Hz), 113.3 (d, 3JCF 9.3 Hz), 134.6 (d, 4JCF 2.8 Hz) and 162.0 (d, 1JCF 247.2 Hz) (6C, benzene), 171.9 (COOH), 183.3 (C=O), 186.9 (C=N); Anal. Calcd for C₁₂H₁₁FN₂O₃S (282.30): C, 51.06, H, 3.93, N, 9.92%. Found: C, 51.26, H, 3.90, N, 9.73%.

3-(5,5-Dibromo-4-oxo-4,5-dihydro-1,3-thiazol-2-yl)(4-fluorophenyl)amino)propanoic acid (3). To a solution of compound 2 (1.41 g, 5.00 mmol) and sodium acetate (1.23 g, 15 mmol) in acetic acid (15 mL), bromine (2.0 g, 0.64 ml, 12.5 mmol) was added dropwise. The solution was allowed to stir for 1.5 h. at r.t. Upon completion of the reaction (TLC), the reaction mixture was diluted with water (50 mL). The solid was filtered off, washed with water, dried and recrystallized to give the brominated product 3 as a white solid, yield 59.5%, 1.31 g, mp 163-164 °C (2-PrOH); IR (νmax, cm⁻¹): 3438 (OH), 1738 and 1692 (C=O), 1540 (C=N). 1H NMR (400 MHz, DMSO-d6): δH 2.61 (2H, t, J 7.2 Hz, CH₂COO), 4.27 (2H, t, J 7.2 Hz, NCH₂), 7.35-7.48 (2Hₐrom, m, 2CH), 7.56-7.70 (2Hₐrom, m, 2CH), 12.44 (1H, b s, OH). 13C NMR (100 MHz, DMSO-d6): δC 31.6 (CH₂COO), 50.1 (NCH₂), 51.9 (C-Br₂), 117.2 (d, 2JCF 23.1 Hz), 130.6 (d, 3JCF 9.4 Hz), 134.6 (d, 4JCF 2.8 Hz) and 162.7 (d, 1JCF 248.6 Hz) (6C, benzene), 171.8 (COOH), 175.6 (C=O), 180.0 (C=N); Anal. Calcd for C₁₂H₉Br₂FN₂O₃S (440.09): C, 32.75, H, 2.06, N, 6.37%. Found: C, 32.61, H, 2.16, N, 6.45%.

General synthetic procedure for 5-substituted thiazolones 4–15. A mixture of the compound 2 (1.41 g, 5 mmol), the corresponding aldehyde (5.5 mmol), sodium carbonate (1.59 g, 15 mmol), glycine (0.38 g, 5 mmol), and water (25 ml) was heated at 80 °C under stirring for 8 h (11 – for 21 h). Upon completion of the reaction (TLC), the reaction mixture was cooled to r.t. and acidified with acetic acid to pH 6. The precipitate was filtered off and washed with water. Purification was performed by dissolving crystals in 5% aqueous sodium carbonate, filtering, and acidifying the filtrate with acetic acid to pH 6 to give 4–15.

3-[5-(Benzylidene-4-oxo-4,5-dihydro-1,3-thiazol-2-yl)(4-fluorophenyl)amino]propanoic acid (4). Yellowish solid, yield 76%, 1.41 g, mp 129-130 °C; IR (νmax, cm⁻¹): 3369 (OH), 1768 and 1686 (C=O), 1541 (C=N). 1H NMR (400 MHz, DMSO-d6): δH 2.56 (2H, t, J 6.9 Hz, CH₂COO), 4.24 (2H, t, J 7.2 Hz, NCH₂), 7.28-7.60 (7Hₐrom, m, 7CH), 7.63 (1H, s, S-C=CH), 7.64-7.70 (2Hₐrom, m, 2CH). 13C NMR (100 MHz, DMSO-d6): δC 32.6 (CH₂COO), 50.6 (NCH₂), 117.0 (d, 2JCF 23.1 Hz), 129.1, 129.3, 129.5, 129.9, 130.5, 130.9 (d, 3JCF 9.3 Hz), 133.6, 136.3 (d, 4JCF 2.8 Hz), 162.3 (d, 1JCF 247.5 Hz) (14C, benzene, S-C=CH), 172.4-172.6 (COOH), 176.4 (C=O), 179.6 (C=N); Anal. Calcd for C₁₉H₁₅FN₂O₃S (370.41): C, 61.61, H, 4.08, N, 7.56%. Found: C, 61.85, H, 4.12, N, 7.34%.
3-[[5-(4-Chlorobenzylidene)(4-fluorophenyl)-4-oxo-4,5-dihydro-1,3-thiazol-2-yl]amino]-propanoic acid (5). Light brown solid, yield 80%, 1.62 g, mp 227-228 °C; IR (ν_max, cm⁻¹): 3400 (OH), 1723 and 1694 (C=O), 1538 (C=N). ¹H NMR (400 MHz, DMSO-d₆): δ_H 2.60 (2H, t, J 7.3 Hz, CH₂COO), 4.24 (2H, t, J 7.3 Hz, NCH₂), 7.40-7.51 (6_H arom, m, 6CH), 7.63 (1H, s, S-C=CH), 7.64-7.69 (2_H arom, q, J 5.0 Hz, 2CH), 12.24 (1H, s, OH). ¹³C NMR (100 MHz, DMSO-d₆): δ_C 32.3 (CH₂COO), 50.4 (NCH₂), 117.0 (d, Ĵ_{CF 22.9 Hz}), 129.2, 129.3, 129.8, 130.8 (d, Ĵ_{CF 9.3 Hz}), 131.1, 132.6, 134.4, 136.2 (d, Ĵ_{CF 2.9 Hz}), 162.3 (d, Ĵ_{CF 247.8 Hz}) (14C, benzene, S-C=CH), 172.1 (COOH), 176.2 (C=O), 179.4 (C=N); Anal. Calcd for C₁₉H₁₄ClFN₂O₄S (404.45): C, 56.37, H, 3.49, N, 6.92%. Found: C, 56.58, H, 3.43, N, 6.81%.

3-[[5-(4-Fluorophenyl)(4-methoxybenzylidene)-4-oxo-4,5-dihydro-1,3-thiazol-2-yl]amino]-propanoic acid (6). Light brown solid, yield 80%, 1.59 g, mp 225-226 °C; IR (ν_max, cm⁻¹): 3438 (OH), 1728 and 1649 (C=O), 1532 (C=N). ¹H NMR (400 MHz, DMSO-d₆): δ_H 2.63 (2H, t, J 7.1 Hz, CH₂COO), 3.76 (3H, s, OCH₃), 4.25 (2H, t, J 7.0 Hz, NCH₂), 6.93-7.08 (2_H arom, m, 2CH), 7.35-7.51 (4_H arom, m, 4CH), 7.61 (1H, s, S-C=CH), 7.63-7.71 (2_H arom, m, 2CH), 12.52 (1H, s, OH). ¹³C NMR (100 MHz, DMSO-d₆): δ_C 31.9 (CH₂COO), 49.9 (NCH₂), 55.4 (OCH₃). 114.9, 117.1 (d, Ĵ_{CF 23.1 Hz}), 126.1 (d, J 3.5 Hz), 130.7, 130.9 (d, Ĵ_{CF 9.2 Hz}), 131.5, 136.4 (d, Ĵ_{CF 2.5 Hz}), 160.6, 162.2 (d, Ĵ_{CF 247.6 Hz}) (14C, benzene, S-C=CH), 172.0 (COOH), 176.3 (C=O), 179.8 (C=N); Anal. Calcd for C₂₀H₁₇FN₂O₄S (400.43): C, 59.99, H, 4.28, N, 7.00%. Found: C, 59.79, H, 4.38, N, 6.87%.

3-[[5-(4-Fluorophenyl)(4-dimethylaminobenzylidene)-4-oxo-4,5-dihydro-1,3-thiazol-2-yl]amino]propanoic acid (7). Orange solid, yield 77.5%, 1.60 g, mp 247-248 °C; IR (ν_max, cm⁻¹): 3423 (OH), 1721 and 1639 (C=O), 1523 (C=N). ¹H NMR (400 MHz, DMSO-d₆): δ_H 2.63 (2H, t, J 7.0 Hz, CH₂COO), 2.94, 3.04 (6H, 2s, 2CH₃), 4.23 (2H, t, J 7.0 Hz, NCH₂), 6.73, 6.78 (2_H arom, 2d, J 8.6 Hz, J 8.7 Hz, 2CH), 7.27 (2_H arom, d, J 8.5 Hz, 2CH), 7.43 (2_H arom, t, J 8.5 Hz, 2CH), 7.53 (1H, s, S-C=CH), 7.64-7.70 (2_H arom, m, 2CH), 12.48 (1H, s, OH). ¹³C NMR (100 MHz, DMSO-d₆): δ_C 32.0 (CH₂COO), 39.6, 39.7 (2CH₃), 49.7 (NCH₂), 111.1, 112.1, 117.0 (d, Ĵ_{CF 22.8 Hz}), 120.4, 122.2, 124.5, 131.0 (d, Ĵ_{CF 9.1 Hz}), 131.5-131.6, 131.7, 136.6 (d, Ĵ_{CF 2.5 Hz}), 151.1, 162.2 (d, Ĵ_{CF 250.6 Hz}) (14C, benzene, S-C=CH), 172.1 (COOH), 176.1 (C=O), 180.1 (C=N); Anal. Calcd for C₂₁H₂₀FN₃O₃S (413.47): C, 61.00, H, 4.88, N, 10.16%. Found: C, 61.24, H, 5.01, N, 9.93%.

3-[[5-(4-Fluorophenyl)(4-hydroxybenzylidene)-4-oxo-4,5-dihydro-1,3-thiazol-2-yl]amino]-propanoic acid (8). Dark yellow solid, yield 77%, 1.49 g, mp 140-141 °C; IR (ν_max, cm⁻¹): 3114 (OH), 1727 and 1677 (C=O), 1532 (C=N). ¹H NMR (400 MHz, DMSO-d₆): δ_H 2.58 (2H, t, J 6.9 Hz, CH₂COO), 4.22 (2H, t, J 7.2 Hz, NCH₂), 6.83 (2_H arom, d, J 8.6 Hz, 2CH), 7.29 (2_H arom, d, J 8.6 Hz, 2CH), 7.41 (2_H arom, t, J 8.6 Hz, 2CH), 7.55 (1H, s, S-C=CH), 7.62-7.68 (2aromH, m, 2CH), 10.37 (2H, s, 2OH). ¹³C NMR (100 MHz, DMSO-d₆): δ_C 32.4 (CH₂COO), 50.3 (NCH₂), 116.3, 117.0 (d, Ĵ_{CF 23.1 Hz}), 124.4, 124.8, 130.9 (d, Ĵ_{CF 9.1 Hz}), 131.7, 131.2, 131.4, 136.4 (d, Ĵ_{CF 2.8 Hz}), 159.7, 162.3 (d, Ĵ_{CF 247.7 Hz}) (14C, benzene, S-C=CH), 172.1 (COOH), 176.3 (C=O), 180.0 (C=N); Anal. Calcd for C₁₉H₁₅FN₂O₃S (386.40): C, 59.06, H, 3.91, N, 7.25%. Found: C, 59.32, H 3.91, N 7.12%. 

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3-\{5-(4-Fluorobenzylidene)(4-fluorophenyl)-4-oxo-1,3-thiazol-2-yl|amino\}-propanoic acid (9). Light yellow solid, yield 77%, 1.49 g, mp. 230-231 °C; IR (ν_{max}, cm⁻¹): 3415 (OH), 1725 and 1655 (C=O), 1538 (C=N). ¹H NMR (400 MHz, DMSO-d₆): δH 2.63 (2H, t, J 7.3 Hz, CH₂COO), 4.26 (2H, t, J 7.3 Hz, NCH₂), 7.28 (2H_aroms t, J 8.8 Hz, 2CH), 7.43 (2H_aroms, t, J 8.6 Hz, 2CH), 7.48-7.54 (2H_aroms, m, 2CH), 7.64-7.70 (2H_aroms, m, 2CH), 7.66 (1H, s, S-C=CH), 12.50 (1H, s, OH). ¹³C NMR (100 MHz, DMSO-d₆): δC 31.9 (CH₂COO), 50.1 (NCH₂), 116.4 (d, ^2JCF 22.1 Hz), 117.1 (d, ^2JCF 22.9 Hz), 128.8 (d, J 2.4 Hz), 129.5, 130.3 (d, ^4JCF 3.0 Hz), 130.9 (d, ^3JCF 9.3 Hz), 131.9 (d, ^3JCF 8.7 Hz), 136.2 (d, ^4JCF 2.8 Hz), 162.4 (d, ^1JCF 247.6 Hz), 162.6 (d, ^1JCF 249.5 Hz) (14C, benzene, S-C=CH), 172.0 (COOH), 176.4 (C=O), 179.5 (C=N); Anal. Calcd for C₁₉H₁₄F₂N₂O₃S (388.40): C, 58.76; H, 3.63; N, 7.21%. Found: C, 58.68, H, 3.72, N, 7.07%.

3-\{5-(4-Bromobenzylidene)(4-fluorophenyl)-4-oxo-1,3-thiazol-2-yl|amino\}-propanoic acid (10). Light yellow solid, yield 76%, 1.71 g, mp. 257-258 °C; IR (ν_{max}, cm⁻¹): 3379 (OH), 1726 and 1697 (C=O), 1536 (C=N). ¹H NMR (400 MHz, DMSO-d₆): δH 2.61 (2H, t, J 6.9 Hz, CH₂COO), 4.25 (2H, t, J 6.9 Hz, NCH₂), 7.36-7.48 (4H_aroms, m, 4CH), 7.60-7.70 (4H_aroms m, 4CH), 7.62 (1H, s, S-C=CH), 12.72 (1H, s, OH). ¹³C NMR (100 MHz, DMSO-d₆): δC 32.1 (CH₂COO), 50.3 (NCH₂), 117.2 (d, ^2JCF 23.2 Hz), 123.4, 129.5, 129.9, 131.0 (d, ^3JCF 9.2 Hz), 131.54, 132.4, 133.0, 136.3 (d, ^4JCF 2.2 Hz), 162.5 (d, ^1JCF 247.5 Hz) (14C, benzene, S-C=CH), 172.3 (COOH), 176.4 (C=O), 179.6 (C=N); Anal. Calcd for C₁₉H₁₄BrFN₂O₃S (449.30): C, 50.79, H, 3.14; N, 6.23%. Found: C, 50.68, H, 3.24; N, 6.06%.

3-\{5-(4-Fluorobenzylidene)(3,4-dimethoxybenzylidene)-4-oxo-1,3-thiazol-2-yl|amino\}propanoic acid (11). Dark yellow solid, yield 58%, 1.25 g, mp. 210-211 °C; IR (ν_{max}, cm⁻¹): 3436 (OH), 1734 and 1696 (C=O), 1536 (C=N). ¹H NMR (400 MHz, DMSO-d₆): δH 2.64 (2H, t, J 7.4 Hz, CH₂COO), 3.72 and 3.75 (6H, 2s, 2OCH₃), 4.25 (2H, t, J 7.4 Hz, NCH₂), 6.97 (1H_aroms dd, J 8.4 Hz, J 1.9 Hz, CH), 7.05 (1H_aroms, d, J 8.5 Hz, CH), 7.15 (1H_aroms, d, J 1.9 Hz, CH), 7.43 (2H_aroms, t, J 8.7 Hz, 2CH), 7.62 (1H, s, S-C=CH), 7.64-7.69 (2H_aroms m, 2CH), 12.45 (1H, s, OH). ¹³C NMR (100 MHz, DMSO-d₆): δC 31.9 (CH₂COO), 49.8 (NCH₂), 55.5 and 55.6 (2OCH₃), 112.2, 114.2, 117.0 (d, ^2JCF 23.0 Hz), 121.8, 126.4 (d, J 12.8 Hz), 130.9 (d, ^3JCF 9.1 Hz), 131.0, 136.3, 148.8, 150.3, 162.3 (d, ^1JCF 247.7 Hz) (13C, benzene, S-C=CH), 172.0 (COOH), 176.4 (C=O), 179.7 (C=N); Anal. Calcd for C₂₁H₁₉FN₂O₅S (430.46): C, 58.60, H, 4.45, N, 6.51%. Found: C, 58.74, H, 4.41, N, 6.35%.

3-\{5-(4-Fluorophenyl)(4-nitrobenzylidene)-4-oxo-1,3-thiazol-2-yl|amino\}-propanoic acid (12). Light yellow solid, yield 87%, 1.81 g, mp. 230-231 °C; IR (ν_{max}, cm⁻¹): 3391 (OH), 1729 and 1691(C=O), 1543 (C=N). ¹H NMR (400 MHz, DMSO-d₆): δH 2.61 (2H, t, J 7.3 Hz, CH₂COO), 4.27 (2H, t, J 7.4 Hz, NCH₂), 7.45 (2H_aroms t, J 8.7 Hz, 2CH), 7.66-7.72 (4H_aroms m, 4CH), 7.74 (1H, s, S-C=CH), 8.25 (2H_aroms, d, J 8.8 Hz, 2CH), 12.57 (1H, s, OH). ¹³C NMR (100 MHz, DMSO-d₆): δC 32.2 (CH₂COO), 50.6 (NCH₂), 117.1 (d, ^2JCF 23.3 Hz), 124.3, 128.0, 130.5, 130.9 (d, ^3JCF 9.0 Hz), 133.3, 136.0 (d, ^4JCF 3.1 Hz), 140.1, 147.2, 162.4 (d, ^1JCF 248.0 Hz) (14C, benzene, S-C=CH), 172.3 (COOH), 176.2 (C=O), 179.1 (C=N); Anal. Calcd for C₁₉H₁₄FN₃O₅S (415.40): C, 54.94, H, 3.40, N, 10.12%. Found: C, 54.75; H, 3.36; N, 9.97%. 


3-{(4-Fluorophenyl)[4-oxo-5-(3-phenylprop-2-en-1-ylidene)-4,5-dihydro-1,3-thiazol-2-yl]-amino}propanoic acid (13). Yellow solid, yield 94%, 1.87 g, mp. 225-226 °C; IR (ν_max, cm⁻¹): 3417 (OH), 1720 and 1650 (C=O), 1531 (C=N). ¹H NMR (400 MHz, DMSO-d₆): δ_H 2.59 (2H, t, J 6.7 Hz, CH₂COO), 4.21 (2H, t, J 6.4 Hz, NCH₂), 6.85-6.94 (1H, m, =CH-CH=CH), 7.14 (1H, d, J 15.2 Hz, =CH-CH=CH), 7.26-7.46 (6H arom, 1H, m, 6CH), 7.31 (1H, d, J 15.4 Hz, =CH-CH=CH), 7.58-7.69 (3H arom, m, 3CH), 12.42 (1H, b s, OH). ¹³C NMR (100 MHz, DMSO-d₆): δ_C 32.2 (CH₂COO), 49.8 (NCH₂), 117.0 (d, J_CF 23.1 Hz), 125.1, 127.6, 128.8, 128.9 (d, J₆ 6.5 Hz), 129.3, 130.5, 131.0 (d, J_CF 9.5 Hz), 135.9, 136.5 (d, J_CF 2.4 Hz), 142.0, 162.63 (d, J_CF 248.4 Hz) (16C, benzene, thiazole, =CH-CH=CH), 172.4 (COOH), 175.9 (C=O), 179.2 (C=N); Anal. Calcd for C₂₁H₁₇FN₂O₃S (396.44): C, 63.62, H, 4.32, N, 7.07. Found: C, 63.48, H, 4.46, N, 6.96.

3-{(4-Fluorophenyl)[5-(furan-2-ylmethylidene)-4-oxo-4,5-dihydro-1,3-thiazol-2-yl]amino}propanoic acid (14). Light brown solid, yield 68%, 1.22 g, mp. 192-193 °C; IR (ν_max, cm⁻¹): 3491 (OH), 1733 and 1724 (C=O), 1526 (C=N). ¹H NMR (400 MHz, DMSO-d₆): δ_H 2.63 (2H, t, J 7.3 Hz, CH₂COO), 4.24 (2H, t, J 7.3 Hz, NCH₂), 6.65, 6.96, 7.89 (3H fur, 3s, 3CH), 7.40-7.48 (2H arom, 1H, m, 2CH, S-C=CH), 7.61-7.70 (2H arom, m, 2CH), 12.44 (1H, b s, OH); ¹³C NMR (100 MHz, DMSO-d₆): δ_C 31.9 (CH₂COO), 49.8 (NCH₂), 113.3, 117.0 (d, J_CF 23.0 Hz), 117.1, 117.3, 126.3, 130.9 (d, J₆ 9.2 Hz), 136.3 (d, J_CF 2.6 Hz), 146.7, 149.4, 162.3 (d, J_CF 247.6 Hz) (12C, benzene, S-C=CH, furan), 172.0 (COOH), 177.1 (C=O), 179.4 (C=N); Anal. Calcd for C₁₇H₁₃FN₂O₄S (360.37): C, 56.66, H, 3.64, N, 7.77. Found: C, 56.71, H, 3.61, N, 7.52.

3-{(4-Fluorophenyl)[4-oxo-5-(thiophen-2-ylmethylidene)-4,5-dihydro-1,3-thiazol-2-yl]amino}propanoic acid (15). Light brown solid, yield 71%, 1.34 g, mp. 209-210 °C; IR (ν_max, cm⁻¹): 3360 (OH), 1735 and 1687 (C=O), 1541 (C=N). ¹H NMR (400 MHz, DMSO-d₆): δ_H 2.63 (2H, t, J 7.3 Hz, CH₂COO), 4.24 (2H, t, J 7.3 Hz, NCH₂), 7.19 (1H fur, t, J 4.3 Hz, CH), 7.44 (2H arom, t, J 8.6 Hz, 2CH), 7.53 (1H fur, d, J 3.2 Hz, CH), 7.63-7.71 (2H arom, m, 2CH), 7.79 (1H fur, d, J 4.9 Hz, CH), 7.87 (1H, s, S-C=CH); ¹³C NMR (100 MHz, DMSO-d₆): δ_C 31.9 (CH₂COO), 49.8 (NCH₂), 117.0 (d, J_CF 22.9 Hz), 123.5, 127.2, 128.9, 130.9 (d, J_CF 9.3 Hz), 131.5, 133.4, 136.3 (d, J_CF 2.6 Hz), 138.4, 162.3 (d, J_CF 247.9 Hz) (12C, benzene, S-C=CH, furan), 172.0 (COOH), 175.6 (C=O), 179.2 (C=N); Anal. Calcd for C₁₇H₁₃FN₂O₄S₂ (376.43): C, 54.24, H, 3.48, N, 7.44. Found: C, 54.53, H, 3.57, N, 7.69.

3-{(5-[4-[[2-[(3-Hydroxy-3-oxopropyl)(4-fluorophenyl)]-4-oxo-1,3-thiazol-5-yliden]phenyl)methyliden]-4-oxo-4,5-dihydro-1,3-thiazol-2-yl](4-fluorophenyl))propanoic acid (16). A mixture of the compound 2 (1.41 g, 5 mmol), terephthaldehyde (0.34 g, 2.5 mmol), sodium carbonate (1.59 g, 15 mmol), glycine (0.38 g, 5 mmol), and water (25 ml) was heated at 80 °C under stirring for 6 h. Upon completion of the reaction (TLC), the reaction mixture was cooled to r.t. and acidified with acetic acid to pH 6. The precipitate was filtered off and washed with water. Purification was performed by dissolving crystals in 5% aqueous sodium hydroxide, filtering, and acidifying the filtrate with acetic acid to pH 6 to give 16 as a dark yellow solid, yield 46%, 1.52 g, mp 183-184 °C; IR (ν_max, cm⁻¹): 3392 (OH), 1692 (C=O), 1540 (C=N). ¹H NMR (400 MHz, DMSO-d₆): δ_H 2.59 (4H, t, J 7.3 Hz, CH₂COO), 4.24 (4H, t, J 7.4 Hz, NCH₂),
7.39-7.51 (8H$_{\text{arom}}$, m, 8CH), 7.58-7.68 (4H$_{\text{arom}}$, m, 4CH), 7.59 (2H, s, =CH), 12.32 (2H, b s, OH).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta_{C}$ 32.2 (CH$_2$COO), 50.4 (NCH$_2$), 117.1 (d, $^2$JCF 22.9 Hz), 129.4, 130.0 (d, J 5.6 Hz), 130.2 (d, $^3$JCF 8.2 Hz), 130.8 (d, $^3$JCF 9.2 Hz), 134.6, 136.2 (d, $^4$JCF 2.8 Hz), 162.3 (d, $^1$JCF 248.0 Hz), 162.4 (d, $^1$JCF 248.3 Hz) (22C, benzene, S-C=CH), 172.1 (COOH), 176.3 (C=O), 179.5 (C=N); MS (ESI): m/z 663.75 [M + H]$^+$; Anal. Calcd for C$_{32}$H$_{24}$F$_2$N$_4$O$_6$S$_2$ (662.70) $\bullet$ C, 58.00, H, 3.65, N, 8.45. Found: C, 57.81, H, 3.66, N, 8.29.

3-[(4-Fluorophenyl)(1,3-thiazol-2-yl)amino]propanoic acid (17). A mixture of compound 1 (1.21 g, 5 mmol), chloroacetaldehyde 50% aqueous solution (3.5 mL, 10 mmol) and water (15 mL) was refluxed for 4 h. Then sodium acetate (0.82 g, 10 mmol) was added, and the mixture was stirred for 5 min at r.t. The precipitate was filtered off, washed with water and dried. Purification was performed by dissolving crystals in 10% aqueous sodium carbonate, filtering and acidifying the filtrate with acetic acid to pH 6 to give product 17 as a white solid, yield 72%, 0.96 g, mp 137-138 $^\circ$C; IR ($\nu$$_{max}$, cm$^{-1}$): 3423 (OH), 1713 (C=O), 1508 (C=N). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$H 2.61 (2H, t, $^7$J 7.2 Hz, CH$_2$COO), 4.07 (2H, t, $^7$J 7.2 Hz, NCH$_2$), 6.72 (1H, d, $^3$J 3.6 Hz, SCH), 7.18 (1H, d, $^3$J 3.6 Hz, NCH), 7.31 (2H$_{\text{arom}}$, t, J 8.7 Hz, 2CH), 7.43-7.53 (2H$_{\text{arom}}$, m, 2CH), 12.29 (1H, b s, OH). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$C 32.2 (CH$_2$COO), 48.6 (NCH$_2$), 108.2 (SCH), 116.8 (d, $^2$JCF 22.7 Hz), 129.4 (d, $^3$JCF 8.9 Hz), 139.2, 141.0 (d, $^4$JCF 2.8 Hz), 160.6 (d, $^1$JCF 244.7 Hz) (8C, benzene, thiazole), 169.8 (C=N), 172.5 (COOH); Anal. Calcd for C$_{12}$H$_{11}$FN$_2$O$_2$S (266.30) $\bullet$ C, 54.13, H, 4.16, N, 10.52. Found: C, 54.34, H, 4.03, N, 10.52.

General synthetic procedure for 3-[(4-fluorophenyl)(4-substituted or 4,5-disubstituted 1,3-thiazol-2-yl)amino]propanoic acids 18-21 and 23. To a solution of thioureido acid 1 (1.21 g, 5 mmol) in acetone (15 mL), the haloketone or halodiketone [chloroacetone (0.29 g, 6 mmol), 2-bromoacetophenone (1.19 g, 6 mmol), 2-bromo-2'-acetonaphthone (1.49 g, 6 mmol), 3-(bromoacetyl)coumarin (1.60 g, 6 mmol) or 3-chloro-2,4-pentanedione (0.81 g, 6 mmol) as indicated] was added, and the mixture was refluxed for 4 h. Then the reaction mixture was cooled down, diluted with water (20 mL), and sodium acetate (0.49 g, 6 mmol) was added, and the mixture was stirred for 10 min at r.t. The precipitate was filtered off, washed with water and dried. Purification was performed by dissolving crystals in 10% aqueous potassium carbonate, filtering and acidifying the filtrate with acetic acid to pH 6 to give products 18-21.

3-[(4-Fluorophenyl)(4-methyl-1,3-thiazol-2-yl)amino]propanoic acid (18). White solid, yield 76%, 1.06 g, mp 109-110 $^\circ$C; IR ($\nu$$_{max}$, cm$^{-1}$): 3434 (OH), 1713 (C=O), 1507 (C=N). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$H 2.15 (3H, s, CH$_3$), 2.59 (2H, t, $^7$J 7.3 Hz, CH$_2$COO), 4.07 (2H, t, J 7.2 Hz, NCH$_2$), 6.72 (1H, d, J 3.6 Hz, SCH), 7.18 (1H, d, J 3.6 Hz, NCH), 7.31 (2H$_{\text{arom}}$, t, J 8.7 Hz, 2CH), 7.43-7.53 (2H$_{\text{arom}}$, m, 2CH), 12.29 (1H, b s, OH). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$C 17.3 (CH$_3$), 32.2 (CH$_2$COO), 48.4 (NCH$_2$), 102.2, 116.8 (d, $^2$JCF 22.7 Hz), 129.4 (d, $^3$JCF 8.9 Hz), 139.2, 141.0 (d, $^4$JCF 2.8 Hz), 160.6 (d, $^1$JCF 244.7 Hz) (8C, benzene, thiazole), 169.8 (C=N), 172.5 (COOH); Anal. Calcd for C$_{13}$H$_{13}$FN$_2$O$_2$S (280.32) $\bullet$ C, 56.67, H, 4.67, N, 9.99. Found: C, 56.57, H, 4.70, N, 9.74.

3-[(4-Fluorophenyl)(4-phenyl-1,3-thiazol-2-yl)amino]propanoic acid (19). White solid, yield 56%, 0.96 g, mp 158-159 $^\circ$C; IR ($\nu$$_{max}$, cm$^{-1}$): 3400 (OH), 1706 (C=O), 1541 (C=N). $^1$H NMR
3-[(4-Fluorophenyl)[4-(naphthalen-2-yl)-1,3-thiazol-2-yl]amino]propanoic acid (20). White solid, yield 94%, 1.84 g, mp 143-144 °C; IR (νmax, cm⁻¹): 3436 (OH), 1714 (C=O), 1506 (C=NC). ¹H NMR (400 MHz, DMSO-d₆): δH 2.37 (2H, t, J 8.1 Hz, CH₂COO), 4.16 (2H, t, J 8.1 Hz, NCH₂), 7.27 (1H, s, SCH), 7.31 (2H arom, t, J 8.8 Hz, 2CH), 7.45-7.57 (4H arom, m, 4CH), 7.86-8.01 (4H arom, m, 4CH), 8.38 (1H arom, s, CH); ¹³C NMR (100 MHz, DMSO-d₆): δC 35.8 (CH₂COO), 50.8 (NCH₂), 103.2, 116.6 (d, 2JCF 22.5 Hz), 124.0 (d, J 9.8 Hz), 125.8, 126.3, 127.5, 128.0 (d, 3JCF 8.7 Hz), 132.2, 132.4, 133.1, 129.3 (d, 3JCF 8.7 Hz), 141.0 (d, 4JCF 2.7 Hz), 150.4, 160.5 (d, 1JCF 244.3 Hz) (18C, benzene, thiazole, naphthalene), 169.2 (C=NC), 174.8 (COOH); Anal. Calcd for C₂₂H₁₇FN₂O₂S (392.46): C, 67.33, H, 4.37, N, 7.14 %. Found: C, 67.12, H, 4.59, N, 7.21 %.

3-[(4-Fluorophenyl)[4-(2-oxo-2H-chromen-3-yl)-1,3-thiazol-2-yl]amino]propanoic acid (21). White solid, yield 92%, 1.89 g, mp 171-172 °C; IR (νmax, cm⁻¹): 3408 (OH), 1737 and 1716 (C=O), 1508 (C=NC). ¹H NMR (400 MHz, DMSO-d₆): δH 2.53 (2H, t, J 7.4 Hz, CH₂COO), 4.15 (2H, t, J 7.4 Hz, NCH₂), 7.27-7.61 (8H arom, m, 8CH), 7.85 (1H arom, d, J 7.5 Hz, CH), 8.59 (1H, s, SCH), 12.07 (1H, s, OH). ¹³C NMR (100 MHz, DMSO-d₆): δC 33.9 (CH₂COO), 49.4 (NCH₂), 109.5, 115.7, 116.8 (d, 2JCF 22.6 Hz), 124.0 (d, J 9.8 Hz), 125.8, 126.3, 127.5, 128.0 (d, J 11.4 Hz), 132.2, 132.4, 133.1, 129.3 (d, 3JCF 8.7 Hz), 141.0 (d, 4JCF 2.7 Hz), 150.4, 160.5 (d, 1JCF 244.3 Hz) (18C, benzene, thiazole, naphthalene), 169.2 (C=NC), 174.8 (COOH); Anal. Calcd for C₂₂H₁₇FN₂O₄S (410.43): C, 61.46, H, 3.68, N, 6.83 %. Found: C, 61.63, H, 3.48, N, 6.59 %.

3-[(5-Acetyl-4-methylthiazol-2-yl)(4-fluorophenyl)amino]propanoic acid (23). White solid, yield 70%, 1.13 g, mp 135-136 °C; IR (νmax, cm⁻¹): 3416 (OH), 1720 and 1657 (C=O), 1504 (C=NC). ¹H NMR (400 MHz, DMSO-d₆): δH 2.31 (3H, s, CH₃), 2.49 (3H, s, CH₃CO), 2.59 (2H, t, J 7.2 Hz, CH₂COO), 4.12 (2H, t, J 7.2 Hz, NCH₂), 7.27-7.61 (8H arom, m, 8CH), 8.38 (1H, s, OH). ¹³C NMR (100 MHz, DMSO-d₆): δC 18.6 (CH₃), 29.6 (CH₃CO), 32.2 (CH₂COO), 48.2 (NCH₂), 117.2 (d, 2JCF 22.8 Hz), 122.8, 130.0 (d, 3JCF 9.0 Hz), 139.6 (d, 4JCF 2.9 Hz), 157.4, 161.4 (d, 1JCF 246.0 Hz) (8C, benzene, thiazole), 170.5 (COOH), 172.4 (C=NC), 188.8 (COCH₃); Anal. Calcd for C₁₅H₁₅FN₂O₃S (322.36): C, 54.78, H, 4.56, N, 8.35 %. Found: C, 54.89, H, 4.69, N, 8.49 %.

N-(4-Fluorophenyl)-N-(4-phenylthiazol-2-yl)acetamide (22). A mixture of the 3-[(4-fluorophenyl)[4-phenyl-1,3-thiazol-2-yl]amino]propanoic acid (19) (1.71 g, 5 mmol) and acetic anhydride (25 mL) was refluxed for 2 h, cooled to r.t. and diluted with ammonia (20 mL). The precipitate was filtered off, washed with water, dried to give 22 as a white solid, yield 88%, 1.37 g, mp 155-156 °C (from methanol); IR (νmax, cm⁻¹): 1678 (C=O), 1512 (C=NC). ¹H NMR (400 MHz, DMSO-d₆): δH 2.01 (3H, s, CH₃), 7.24 (1H, t, J 7.3 Hz, H arom), 7.32 (2H, t, J 7.6 Hz,
Harom), 7.42 (2H, t, J 8.7 Hz, H_{arom}), 7.57-7.65 (4H, m, H_{arom}), 7.71 (1H, s, S-CH). 13C NMR (400 MHz, DMSO-d$_6$): δC 23.8 (CH$_3$), 109.4, 116.5 (d, $^2$JC 22.8 Hz), 125.5, 127.8, 128.6, 131.4 (d, $^3$JC 8.9 Hz), 134.0, 136.4 (d, $^4$JC 3.1 Hz), 148.0, 159.8, 161.9 (d, $^1$JC 245.6 Hz) (15C, benzene, thiazole), 169.8 (C=O); Anal. Calcd for C$_{17}$H$_{13}$FN$_2$OS (312.37): C, 65.37, H, 4.19, N, 8.97% Found: C, 65.52, H, 4.38, N, 9.11%.

General synthetic procedure for 3-[(4-fluorophenyl){4-methyl-5-[3-(substituted phenyl)prop-2-enoyl]-1,3-thiazol-2-yl}amino]propanoic acids 24-28. A round-bottomed flask equipped with a magnetic stirring bar was charged with a cooled solution of the corresponding aromatic aldehyde (5 mmol) in aqueous 10% NaOH (5 mL), and the compound 23 (1.61 g, 5 mmol) solution in methanol (20 mL) was added dropwise. The mixture was kept at 0 °C for 1.5 h and then stirred at r.t. for 22 h. Then the reaction mixture was diluted with water (25 mL) and acidified with acetic acid to pH 6. The precipitate was filtered off, washed with water, dried and purified by dissolving crystals in 10% aqueous sodium hydroxide, filtering and acidifying the filtrate with acetic acid to pH 6 to give products 24-28.

3-[(4-Fluorophenyl){4-methyl-5-[3-(4-fluorophenyl)prop-2-enoyl]-4,5-dihydro-1,3-thiazol-2-yl}amino]propanoic acid (24). Yellow solid, yield 79%, 1.62 g, mp 227-228 °C; IR (ν$_{max}$, cm$^{-1}$): 3438 (OH), 1728 and 1631 (C=O), 1508 (C= N). 1H NMR (400 MHz, DMSO-d$_6$): δH 2.61 (3H, s, CH$_3$), 2,61 (2H, t, J 7.2 Hz, CH$_2$COO), 4.15 (2H, t, J 7.3 Hz, NCH$_2$), 7.23 (1H, d, J 15.5 Hz, CO-CH=CH), 7.35-7.45 (5H arom, m, 5CH), 7.49-7.58 (2H arom, m, 2CH), 7.54 (1H, d, J 15.7 Hz, CO-CH=CH), 7.68-7.78 (2H arom, m, 2CH), 12.41 (1H, b s, OH). 13C NMR (100 MHz, DMSO-d$_6$): δC 19.1 (CH$_3$), 32.2 (CH$_2$COO), 48.4 (NCH$_2$), 117.3 (d, $^2$JC 22.8 Hz), 122.5, 124.6, 128.6, 129.0, 130.0 (d, $^3$JC 8.9 Hz), 130.4, 134.5, 139.5 (d, $^4$JC 2.8 Hz), 141.8, 158.8, 161.5 (d, $^1$JC 246.1 Hz) (16C, benzene, thiazole, CO-CH=CH), 170.8 (COOH), 172.4 (C=O), 180.4 (C=N); Anal. Calcd for C$_{22}$H$_{19}$FN$_2$O$_3$S (410.47): C, 64.38, H, 4.67, N, 6.82% Found: C, 64.56, H, 4.85, N, 6.83%.

3-[(4-Fluorophenyl){4-methyl-5-[3-(4-fluorophenyl)prop-2-enoyl]-4,5-dihydro-1,3-thiazol-2-yl}amino]propanoic acid (25). Yellow solid, yield 74%, 1.58 g, mp 185-186 °C; IR (ν$_{max}$, cm$^{-1}$): 3435 (OH), 1718 and 1651 (C=O), 1509 (C= N). 1H NMR (400 MHz, DMSO-d$_6$): δH 2.60 (5H, b s, CH$_3$, CH$_2$COO), 4.15 (2H, t, J 6.6 Hz, NCH$_2$), 7.23 (1H, d, J 15.6 Hz, CO-CH=CH), 7.24 (2H$_{arom}$, t, J 8.5 Hz, 2CH), 7.39 (2H$_{arom}$, t, J 8.3 Hz, 2CH), 7.51-7.59 (2H$_{arom}$, m, 2CH), 7.52 (1H, d, J 15.1 Hz, CO-CH=CH), 7.78-7.85 (2H$_{arom}$, m, 2CH), 12.41 (1H, b s, OH). 13C NMR (100 MHz, DMSO-d$_6$): δC 19.1 (CH$_3$), 32.2 (CH$_2$COO), 48.4 (NCH$_2$), 115.9 (d, $^2$JC 21.9 Hz), 117.3 (d, $^3$JC 9.2 Hz), 131.0 (d, $^4$JC 8.8 Hz), 131.2 (d, $^1$JC 249.8 Hz) (16C, benzene, thiazole, CO-CH=CH), 170.9 (COOH), 172.4 (C=O), 180.3 (C=N); Anal. Calcd for C$_{22}$H$_{18}$F$_2$N$_2$O$_3$S (428.46): C, 61.67, H, 4.23, N, 6.54%; Found: C, 61.44, H, 4.06, N, 6.50%.

3-[(4-Fluorophenyl){4-methyl-5-[3-(4-chlorophenyl)prop-2-enoyl]-4,5-dihydro-1,3-thiazol-2-yl}amino]propanoic acid (26). Yellow solid, yield 78%, 1.74 g, mp 222-223 °C; IR (ν$_{max}$, cm$^{-1}$): 3422 (OH), 1719 and 1630 (C=O), 1508(C=N). 1H NMR (400 MHz, DMSO-d$_6$): δH 2.60 (3H,
s, CH₃), 2.61 (2H, t, J 7.2 Hz, CH₂COO), 4.15 (2H, t, J 7.2 Hz, NCH₂), 7.22 (1H, d, J 15.5 Hz, CO-CH=CH), 7.39 (2H arom, t, J 8.7 Hz, 2CH), 7.45 (2H arom, d, J 8.5 Hz, 2CH), 7.52 (1H, d, J 15.4 Hz, CO-CH=CH), 7.53-7.58 (2H arom, m, 2CH), 7.76 (2H arom, d, J 8.6 Hz, 2CH), 12.42 (1H, b s, OH). ¹³C NMR (100 MHz, DMSO-d₆): δC 19.1 (CH₃), 32.3 (CH₂COO), 48.4 (NCH₂), 117.3 (d, 2JC 22.8 Hz), 122.4, 125.3, 128.9, 130.0 (d, 3JC 9.1 Hz), 130.3, 133.5, 134.8, 139.5 (d, 4JC 2.9 Hz), 140.3, 159.0, 161.5 (d, ¹JC 246.2 Hz) (16C, benzene, thiazole, CO-CH=CH), 170.8 (C=O), 172.3 (C=O), 180.1 (C=N); Anal. Calcd for C₂₂H₁₈ClFN₂O₃S (444.92): C, 59.39, H, 4.08, N, 6.30%; Found: C, 59.00, H, 3.99, N, 6.43%.

3-[(4-Fluorophenyl){4-methyl-5-[3-(4-bromophenyl)prop-2-enoyl]-4,5-dihydro-1,3-thiazol-2-yl}amino]propanoic acid (27). Yellow solid, yield 85%, 2.08 g, mp 241-242 °C; IR (νmax, cm⁻¹): 3421 (OH), 1717 and 1630 (C=O), 1508 (C= N). ¹H NMR (400 MHz, DMSO-d₆): δH 2.55 (2H, t, J 6.6 Hz, CH₂COO), 2.60 (3H, s, CH₃), 4.13 (2H, t, J 6.4 Hz, NCH₂), 7.24 (1H, d, J 15.5 Hz, CO-CH=CH), 7.38 (2H arom, t, J 8.6 Hz, 2CH), 7.50 (1H, d, J 15.5 Hz, CO-CH=CH), 7.52-7.57 (2H arom, m, 2CH), 7.59 (2H arom, d, J 8.5 Hz, 2CH), 7.69 (2H arom, d, J 8.5 Hz, 2CH). ¹³C NMR (100 MHz, DMSO-d₆): δC 19.1 (CH₃), 32.8 (CH₂COO), 48.9 (NCH₂), 117.3 (d, 2JC 22.7 Hz), 122.3, 123.7, 125.4, 130.0 (d, 3JC 8.7 Hz), 130.5, 131.9, 133.8, 139.5 (d, ⁴JC 3.0 Hz), 140.4, 159.1, 161.5 (d, ¹JC 246.3 Hz) (16C, benzene, thiazole, CO-CH=CH), 170.9 (COOH), 172.8 (C=O), 180.1 (C=N); Anal. Calcd for C₂₂H₁₈BrFN₂O₃S (489.37): C, 54.00, H, 3.71, N, 5.72%; Found: C, 53.88, H, 3.83, N, 5.91%.

3-[(4-Fluorophenyl){4-methyl-5-[3-(4-nitrophenyl)prop-2-enoyl]-4,5-dihydro-1,3-thiazol-2-yl}amino]propanoic acid (28). Yellow solid, yield 66%, 1.50 g, mp 208-209 °C; IR (νmax, cm⁻¹): 3421 (OH), 1712 and 1639 (C=O), 1510 (C= N). ¹H NMR (400 MHz, DMSO-d₆): δH 2.62 (5H, s, CH₃, CH₂COO), 4.16 (2H, t, J 7.1 Hz, NCH₂), 7.37-7.47 (2H arom, m, 2CH), 7.39 (1H, d, J 15.3 Hz, CO-CH=CH), 7.51-7.59 (2H arom, m, 2CH), 7.61 (1H, d, J 15.5 Hz, CO-CH=CH), 8.01 (2H arom, d, J 8.6 Hz, 2CH), 8.21 (2H arom, d, J 8.6 Hz, 2CH), 12.43 (1H, b s, OH). ¹³C NMR (100 MHz, DMSO-d₆): δC 19.2 (CH₃), 32.3 (CH₂COO), 48.9 (NCH₂), 117.3 (d, 2JC 22.7 Hz), 122.3, 123.7, 125.4, 130.0 (d, 3JC 8.7 Hz), 130.5, 131.9, 133.8, 139.5 (d, ⁴JC 3.0 Hz), 140.4, 159.1, 161.5 (d, ¹JC 246.3 Hz) (16C, benzene, thiazole, CO-CH=CH), 170.9 (COOH), 172.8 (C=O), 180.1 (C=N); Anal. Calcd for C₂₂H₁₈BrFN₂O₃S (455.47): C, 58.02, H, 3.98, N, 9.23%; Found: C, 58.08, H, 3.73, N, 9.12%.

3-[(5-{1-[{(1-{2-[{(2-Carboxyethyl)(4-fluorophenyl)amino]-4-methylthiazol-5-yl}ethylidene}hydrazono}ethyl}-4-methylthiazol-2-yl)-(4-fluorophenyl)amino]propionic acid (29). To a solution of 3-[(5-acetyl-4-methylthiazol-2-yl)(4-fluorophenyl)amino]propanoic acid (23) (1.61 g, 5 mmol) in methanol (15 mL), the hydrazine monohydrate (0.25 g, 5 mmol) and acetic acid (1 mL) was added, and the mixture was refluxed for 5.5 h. Then the reaction mixture was cooled down, and the formed precipitate was filtered off, washed with methanol, dried to give 29 as a yellow solid, yield 30%, 0.96 g, mp 199-200 °C (from methanol); IR (νmax, cm⁻¹): 3436 (OH), 1712 (C=O), 1509 (C=N). ¹H NMR (400 MHz, DMSO-d₆): δH 2.21 (6H, s, 2CH₃), 2.42 (6H, s, 2CH₃-C=N), 2.58 (4H, t, J 7.2 Hz, 2CH₂COO), 4.07 (4H, t, J 7.2 Hz, 2NCH₂), 7.30-7.35 (4H arom, m, 4CH), 7.45-7.51 (4H arom, m, 4CH), 12.21 (2H, b s, 2OH). ¹³C NMR (100 MHz, DMSO-d₆):
\[ \delta_{C} 16.2, 18.7 (4\text{CH}_3), 32.3 (2\text{CH}_2\text{COO}), 48.0 (2\text{NCH}_2), 116.9 (d, ^2J CF 22.7 \text{ Hz}), 121.8, 129.8, (d, ^3J CF 8.8 \text{ Hz}), 140.1 (d, ^4J CF 2.4 \text{ Hz}), 150.4, 156.7, 161.0 (d, ^1J CF 245.5 \text{ Hz}) (18\text{C, benzene, thiazole, } C=\text{N-N}=C), 167.9, 172.4 (2 \text{C=\text{N, COOH}}); \text{MS (ESI): } m/z 641.80 [\text{M + H}]^+; \text{Anal. Calcd for } C_{30}H_{30}F_2N_6O_4S_2 (640.74): \text{C, 56.24, H, 4.72, N, 13.12\%}. \text{Found: C, 56.24, H, 4.56, N, 13.35\%.}

**Antifungal and antibacterial evaluation.** The antibacterial activity of compounds was evaluated by diffusion in peptone on a nutrient medium (meat-extract agar for bacteria and wort agar for fungi). The microbial loading was \(10^9\) cells (spores)/1 mL. The required incubation periods were 24 h at 35 °C for bacteria and 48–72 h at 28–30 °C for fungi. The results were recorded by measuring the zones surrounding the disk. The control disk contained vancomycin (for bacteria) or nystatin (for fungi) as a standard.

Testing was performed in a flat-bottomed 96-well tissue culture plate. The tested compounds were dissolved in DMSO applying the necessary concentration. The exact volume of the solution of compounds is brought into a nutrient medium. The bacteria and fungi were inoculated in a nutrient medium (meat-extract agar for bacteria and wort agar for fungi). The duration of incubation was 24–72 h at 37 °C for bacteria and 30 °C for fungi. The results were estimated according to the presence or absence of microorganism growth.

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