SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL DI- AND TRISUBSTITUTED THIAZOLE DERIVATIVES

Irmantas Parašotas, a Eglė Urbonavičiūtė, a Kazimieras Anusevičius, a Ingrida Tumosienė, a Ilona Jonuškienė, a Kristina Kantminienė, b* Rita Vaickelionienė, a and Vytautas Mickevičius a

a Department of Organic Chemistry, Kaunas University of Technology, Radvilėnų pl. 19, LT-50254 Kaunas, Lithuania, b Department of Physical and Inorganic Chemistry, Kaunas University of Technology, Radvilėnų pl. 19, LT-50254 Kaunas, Lithuania (E-mail: kristina.kantminiene@ktu.lt)

Abstract – Novel di- and trisubstituted thiazole derivatives bearing heterocyclic, aromatic, chalcone, and carboxyalkyl-heterocyclic moieties were synthesized. Compounds possessing significant antibacterial activity, comparable to that of commercial antibacterial agent ampicillin, against Rhizobium radiobacter, Xanthomonas campestris, and Escherichia coli were identified. Some of the synthesized compounds exhibited a very high antioxidant activity.

INTRODUCTION

The growing environmental pollution and arising new pathogens, which can infect all types of life forms, prompt chemists of organic, medicinal, and pharmaceutical chemistry to combine forces for the search and design of new and effective compounds as pharmaceutical agents.

Thiazoles have been under investigation as therapeutic agents for a long time. Thiazole scaffold has been identified in a number of naturally occurring compounds, such as thiamine (vitamin B1), mycothiazole exhibiting cytotoxic activity,1 and cystothiazole A possessing antifungal activity.2 The examples of drugs bearing thiazole moiety are antibacterial sulfathiazole, antihelmintic tiabendazole, and antiviral ritonavir, and anti-inflammatory meloxicam.3 Thiazole derivatives have been shown to possess a broad spectrum of biological properties, such as anticonvulsant,4 antimicrobial5–7 antituberculous,8 cytotoxic, anti-inflammatory and psychotropic,9 potent in vivo neuroprotection10 activities, they also are effective against allergies.8 2-[(4-Chlorobenzyl)amino]-4-methyl-1,3-thiazole-5-carboxylic acid has been identified as potential antidiabetic, antioxidant and anti-inflammatory agent.11 Recently, 2-(2-((1H-indol-5-yl)-
methylene)hydrazinyl)-4-methylthiazole and its 4-phenyl analogue have been reported to possess free radical scavenging potential higher than that of a commercial standard trolox. Quinolones are a very important class of heterocyclic compounds due to their broad spectrum of biological activity. They are prescribed for the treatment of tuberculosis, HIV-1, microbial and viral infections, and are also used as anticancer pharmaceuticals. Chalcones and their derivatives are associated with a wide variety of different biological activities such as antimicrobial, antibacterial, anti-inflammatory, anticancer, anticonvulsant, antioxidant etc. Therefore, synthesis and biological evaluation of compounds containing thiazole, quinolone, and chalcone fragments is of great interest for organic and medicinal chemists.

As a continuation of search of biologically active compounds and investigation of the influence of different substituents and molecule fragments on antibacterial and antioxidant activity, herein we report on the synthesis and investigation of antibacterial and antioxidant activity of novel functionalized di- and trisubstituted thiazole derivatives bearing various aliphatic, aromatic, and heterocyclic substituents.

RESULTS AND DISCUSSION

Reaction of thioureido acid 1 with different 2-bromo-1-phenylethanones provided corresponding 3-[(4-methoxyphenyl)(4-arylsubstituted-1,3-thiazol-2-yl)amino]propanoic acids 2a-e (Scheme 1). In the course of these reactions, corresponding thiazolium bromide salts were formed, which underwent facile conversion into 1,3-thiazoles 2a–e. As an example, in the 1H NMR spectrum for 3-[(4-(4-chlorophenyl)thiazol-2-yl)(4-methoxyphenyl)amino]propanoic acid (2a), the singlet attributable to the SCH group proton is observed at 7.17 ppm, proving formation of the thiazole ring, and the increased number of aromatic proton peaks proves the presence of the second benzene ring in the molecule.

Among the compounds 2a–e screened for the antibacterial activity against Rhizobium radiobacter, Escherichia coli, and Xanthomonas campestris, 2a was identified as possessing the highest activity. Therefore, this compound was subjected to chemical transformations aiming to synthesize more active compounds. Ester 3a was obtained according to the usual procedure for esterification of carboxylic acids by heating at reflux acid 2a in methanol in the presence of concentrated sulfuric acid as a catalyst. Reaction of 3a with hydrazine monohydrate in dimethyl sulfoxide provided 3-[(4-(4-chlorophenyl)-1,3-thiazol-2-yl)(4-methoxyphenyl)amino]propanehydrazide (4a). Formation of hydrazide 4a has been proven by the presence of the 1H NMR resonances at 4.18 ppm and 9.11 ppm attributable to the protons of NH2 and NH groups, respectively. Condensation reaction of hydrazide 4a with hexane-2,5-dione in the presence of acetic acid resulted in formation of pyrrole derivative 5a. Proton resonances assigned to the
CH$_3$ groups in the pyrrole moiety are observed at 1.95 ppm in the $^1$H NMR spectrum for 5a, whereas a singlet integrated for two protons at 5.63 ppm confirms the existence of a pyrrole ring in this compound. Compound 6a bearing 1,3,4-oxadiazole moiety was synthesized in the reaction of 4a with carbon disulfide in ethanol in the presence of potassium hydroxide. Formation of the oxadiazole ring has been confirmed by the presence of carbon resonances at 164.20 ppm, attributed to the C=N group, and 169.71 ppm, attributed to C=S group, in the $^{13}$C NMR spectrum. 2-(3-((4-(4-Chlorophenyl)thiazol-2-yl)(4-methoxyphenyl)amino)propanoyl)-N-phenylhydrazine-1-carbothioamide (7a) and hydrazones 9–11a were synthesized by condensation reactions of 4a with phenyl isothiocyanate or heterocyclic aldehydes.

Scheme 1

Presence of the amide group in the structure of these compounds determines the splitting of resonances in $^1$H and $^{13}$C NMR spectra owing to the restricted rotation around the amide bond. In DMSO-$d_6$ solution these compounds exist as a mixture of E/Z isomers, where, in the majority of cases, the Z isomer predominates because of a hindered rotation around the CO–NH bond.$^{29,30}$ Thiosemicarbazide 7a underwent condensation to 5-(2-((4-(4-chlorophenyl)thiazol-2-yl)(4-methoxyphenyl)amino)ethyl)-4-phenyl-2,4-dihydro-3H-1,2,4-triazole-3-thione (8a) under treatment with 10% aqueous sodium
hydroxide solution. In the $^{13}$C NMR spectrum for 8a, the carbon resonance of the C=S group is observed at 169.62 ppm and is shifted downfield by approx. 10 ppm in comparison with the carbon signal attributed to the C=S group (180.86 ppm) in 7a.

The quinolone core has long been recognized as one of the important structures for the design of antimicrobial agents. Therefore, β-alanine fragment in acids 2a, b, d, e was employed in the synthesis of thiazole derivatives 12a, b, d, e bearing quinolone moiety by heating 2a, b, d, e at 110 °C in polyphosphoric acid. As an example, in the $^{13}$C NMR spectrum for 12a, the carbon resonance attributed to the C=O group at 192.78 ppm is shifted downfield in comparison with the corresponding carbon resonance in the β-alanine fragment in 2a (172.63 ppm). In the $^1$H NMR spectrum, the proton resonances in the aromatic region are integrated for one proton less proving formation of the quinolone ring. The analogous NMR resonances are observed in the spectra for other quinolone derivatives 12b, d, e. However, attempts to synthesize the corresponding quinolone from 2c under analogous reaction conditions failed due to the dealkylation reaction taking place. Instead, N-(4-methoxyphenyl)-4-(4-nitrophenyl)-1,3-thiazol-2-amine (13c) was isolated from the reaction mixture.

Compounds 12a, b, d, e were converted into hydroxyquinolones 14a, b, d, e by cleaving the ether bond with HBr.

Further on, polysubstituted thiazoles 15–21 were synthesized. 3-[(5-Acetyl-4-methylthiazol-2-yl)(4-methoxyphenyl)amino]propanoic acid (15) was synthesized from thioureido acid 1 and 3-chloropentane-2,4-dione in acetone at reflux temperature (Scheme 2). Sodium acetate was used to convert the formed aminothiazolium chloride into the base. The synthesis of the target chalcones 16a–f was accomplished by Claisen–Schmidt condensation of 5-acetyl-4-methylthiazole 15 with various aromatic aldehydes in methanol and 10% aqueous sodium hydroxide solution. The products were obtained in good and very good yields.

Structures of compounds 16a–f were unambiguously confirmed by the data of IR, $^1$H and $^{13}$C NMR spectroscopy, and elemental analysis. IR spectra showed absorptions at 1731–1713 cm$^{-1}$ (C=O) and sharp bands at 3436–3407 cm$^{-1}$ (OH). In the $^1$H NMR spectra, formation of chalcone moiety has been proven by the signals in the region of 2.55–2.64 ppm (CH$_3$), at ~ 7.08 ppm (CO–CH=), and 7.50 ppm (=CH–Ar). The CH=CH double bond in the enone moiety of chalcones can potentially adopt either a Z or an E configuration. The $^1$H NMR spectrum of each compound 16a–f displays the resonances attributable to the CH=CH protons in the region of 7.08–7.50 ppm, with J > 15 Hz. Thus, it can be assumed that chalcones 16a–f were synthesized in the E configuration.
Heterocyclization reactions of trisubstituted chalcone 16c with nitrogen nucleophiles, such as hydrazine, phenylhydrazine, and hydroxylamine, were investigated. 3-([5-{{5-(4-Chlorophenyl)-1H-pyrazol-3-yl}-4-methylthiazol-2-yl}[4-methoxyphenyl]amino}propanoic acid (17) was synthesized by treating chalcone 16c with hydrazine monohydrate in propan-2-ol in the presence of potassium hydroxide, whereas isoxazole derivative 18 was prepared by refluxing chalcone 16c with hydroxylamine hydrochloride in 1,4-dioxane in the absence of basic catalyst. Dihydropyrazole derivative 19 was synthesized from phenylhydrazine according to the synthesis procedure of 17. It should be noted that reactions of chalcone 16c with hydrazine monohydrate and hydroxylamine hydrochloride provided pyrazole 17 and isoxazole 18 derivatives in oxidized form as the main reaction products. In the $^{13}$C NMR spectra for 17–19, the carbon resonances of the newly formed pyrazole (17) and isoxazole (18) rings are shifted downfield in the aromatic region of the spectrum. In the $^{13}$C NMR spectrum for 19, carbon resonances of the new 4,5-dihydropyrazole moiety are observed in the region characteristic of aliphatic carbon atoms, i.e. at 44.57 ppm (CH$_2$CH) and 62.62 ppm (CH$_2$CH).

Reaction of thiazole 15 with hydrazine and phenylhydrazine provided hydrazine type compounds 20 and 21. The reactions were performed in methanol at reflux temperature in the presence of acetic acid as a catalyst. In the $^{13}$C NMR spectrum for 20, the resonance line of C=O is absent in comparison with the spectrum for the initial compound 15, whereas the signal at 150.37 ppm has proven the formation of
C=N-N=C bond. In the $^1$H NMR spectrum for 21, the singlet at 9.00 ppm ascribed to the NH group proton and the integral intensity of the signals of aromatic protons (9H) have proven formation of the target compound.

Some of the synthesized compounds (2a–19) (50–1000 µg/mL) were evaluated for their antibacterial activity against the strains of $R$. radiobacter, $X$. campestris, and $E$. coli by the diffusion technique (Tables 1–2). The activity of the tested compounds was compared with that of the known antibacterial agent ampicillin (50 µg/mL).

<table>
<thead>
<tr>
<th>Compound</th>
<th>$E$. coli 1000 µg/mL</th>
<th>$X$. campestris 1000 µg/mL</th>
<th>$R$. radiobacter 1000 µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>4.0</td>
<td>2.0</td>
<td>8.0</td>
</tr>
<tr>
<td>3a</td>
<td>3.0</td>
<td>–</td>
<td>7.4</td>
</tr>
<tr>
<td>4a</td>
<td>–</td>
<td>3.5</td>
<td>3.8</td>
</tr>
<tr>
<td>5a</td>
<td>1</td>
<td>3.2</td>
<td>2.4</td>
</tr>
<tr>
<td>6a</td>
<td>1.6</td>
<td>1.3</td>
<td>3</td>
</tr>
<tr>
<td>7a</td>
<td>4.0</td>
<td>–</td>
<td>6.0</td>
</tr>
<tr>
<td>8a</td>
<td>1.0</td>
<td>8.0</td>
<td>7.2</td>
</tr>
<tr>
<td>9a</td>
<td>1.3</td>
<td>2</td>
<td>3.5</td>
</tr>
<tr>
<td>11a</td>
<td>–</td>
<td>8.0</td>
<td>3.6</td>
</tr>
<tr>
<td>16c</td>
<td>4.0</td>
<td>5.8</td>
<td>6.0</td>
</tr>
<tr>
<td>17</td>
<td>5.0</td>
<td>5.0</td>
<td>–</td>
</tr>
<tr>
<td>18</td>
<td>5.0</td>
<td>6.3</td>
<td>4.0</td>
</tr>
<tr>
<td>19</td>
<td>4.0</td>
<td>6.8</td>
<td>5.0</td>
</tr>
<tr>
<td>Ampicillin 50 µg/mL</td>
<td>6.4</td>
<td>9.0</td>
<td>11.0</td>
</tr>
</tbody>
</table>

The evaluation of the antibacterial activity against $E$. coli has revealed that isoxazole derivative 18 is the most active (125 µg/mL). Chalcone derivative 16c and pyrazole derivative 17 showed significant activity as well. Replacement of hydrogen atom in amino group of pyrazole ring with benzene ring in 19 decreased the activity against $E$. coli. Triazole-3-thione derivative 8a and hydrazone 11a bearing a 4-nitrobenzene moiety have been indicated as the most active against $X$. campestris (50 µg/mL). It is interesting to note that 3-[[4-(4-chlorophenyl)-1,3-thiazol-2-yl]-4-methoxyanilino]propanoic acid (2a)
has shown significant activity, whereas its ester 3a is not active at all. On the other hand, acid 2a and its ester 3a suppressed growth of *R. radiobacter* at concentration of 50 μg/mL the most among the tested compounds. Their activity was followed closely by the triazole-3-thione derivative 8a. It should be noted that none of the tested compounds was more active than ampicillin.

**Table 2.** The inhibition zone diameters of selected compounds 2a–19 at 125 μg/mL and 50 μg/mL concentrations

<table>
<thead>
<tr>
<th>Compound</th>
<th>2a</th>
<th>3a</th>
<th>7a</th>
<th>8a</th>
<th>11a</th>
<th>16c</th>
<th>17</th>
<th>18</th>
<th>19</th>
<th>Ampicillin 50 μg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>4.0</td>
<td>4.0</td>
<td>3.0</td>
<td>4.0</td>
<td>4.0</td>
<td>2.0</td>
<td>6.4</td>
</tr>
<tr>
<td>3a</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3.7</td>
<td>3.6</td>
<td>3.0</td>
<td>0.6</td>
<td>0.8</td>
<td>2.0</td>
<td>9.0</td>
</tr>
<tr>
<td>7a</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3.0</td>
<td>3.6</td>
<td>2.0</td>
<td>0.7</td>
<td>0.8</td>
<td>2.5</td>
<td>11.0</td>
</tr>
<tr>
<td>8a</td>
<td>4.0</td>
<td>3.7</td>
<td>3.0</td>
<td>3.0</td>
<td>1.8</td>
<td>3.0</td>
<td>0.6</td>
<td>0.8</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>11a</td>
<td>4.0</td>
<td>3.7</td>
<td>3.0</td>
<td>3.0</td>
<td>1.8</td>
<td>3.0</td>
<td>0.6</td>
<td>0.8</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>16c</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
<td>1.8</td>
<td>3.0</td>
<td>0.6</td>
<td>0.8</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
<td>1.8</td>
<td>3.0</td>
<td>0.6</td>
<td>0.8</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
<td>1.8</td>
<td>4.0</td>
<td>0.6</td>
<td>0.8</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>1.8</td>
<td>2.0</td>
<td>0.6</td>
<td>0.8</td>
<td>2.5</td>
<td></td>
</tr>
</tbody>
</table>

The antioxidant properties of compounds 2a–19 were evaluated using different protocols including 2,2-diphenyl-1-(2,4,6-trinitrophenyl)hydrazyl (DPPH) radical scavenging method, the ferric reducing antioxidant power (FRAP), and the reducing power assay (Figures 1–3).

**Figure 1.** Antioxidant activity of compounds 2a–19 against DPPH
The DPPH assay is based on either a hydrogen atom transfer (HAT) or a single electron transfer (SET) mechanism. As seen from the results presented in Figure 1, propanamide 5a bearing 2,5-dimethylpyrrole moiety (81.8%), thiosemicarbazide 7a (78.6%), hydrazone 9a bearing 5-nitrofuran moiety (65.9%), and hydrazide 4a (61.6%) possess a very high DPPH radical scavenging ability. The higher free radical scavenging activities of these compounds could be attributed to the presence of an NH group, which can donate a hydrogen atom via a HAT mechanism leading to neutralization of the DPPH radical. 33

![Figure 2. Antioxidant activity of compounds 2a–19 evaluated by FRAP method](image)

The FRAP method is based on the reduction of a ferroin analog, the Fe$^{3+}$ complex of tripyridyltriazine Fe(TPTZ)$^{3+}$, to the intensely blue coloured Fe$^{2+}$ complex Fe(TPTZ)$^{2+}$ by antioxidants in an acidic medium. The results are obtained as the absorbance increases at 593 nm and can be expressed as a Fe$^{2+}$ µmol/L concentration. FRAP assay is based on a SET mechanism.

The results revealed (Figure 2) that hydrazide 4a (74.11 Fe$^{2+}$ µmol/L), hydrazone 9a bearing 5-nitrofuran moiety (29.17 Fe$^{2+}$ µmol/L), and pyrazole derivative 19 (29.06 Fe$^{2+}$ µmol/L) showed the highest antioxidant activity evaluated by FRAP method.

![Figure 3. Reducing power of the compounds 2a–19](image)
In the reducing power assay, the presence of reductants (antioxidants) in a sample would result in the reduction of Fe\(^{3+}\) to Fe\(^{2+}\) by donating an electron (SET mechanism). The amount of the Fe\(^{2+}\) complex can then be monitored by measuring the formation of Perl’s blue at 700 nm. The results of the reducing power assay (Figure 3) have demonstrated that compounds bearing fragments of hydrazide 4a, propanamide 5a, thiosemicarbazide 7a, and hydrazone 9a exhibit antioxidant effect. Interestingly, hydrazones 10a and 11a showed a very weak or moderate scavenging potential evaluated by any of the above assays.

CONCLUSIONS

In summary, various di- and trisubstituted thiazole derivatives with functionalized aromatic and heterocyclic substituents were synthesized. Screening of their antibacterial activity has revealed that Rhizobium radiobacter and Xanthomonas campestris were the most sensitive to chalcone derivative 16c, isoxazole derivative 18, and pyrazole derivative 19, all containing chlorine substituent in the benzene ring, at the concentration of 50 µg/mL, whereas the same compounds at the concentration of 125 µg/mL suppressed growth of Escherichia coli. Derivatives of 3-\{[4-(4-chlorophenyl)-1,3-thiazol-2-yl]-4-methoxyanilino\}propanoic acid bearing pyrrole 5a and thiosemicarbazide 7a moieties possess a very high DPPH free radical scavenging activity, 81.8% and 78.6% respectively. 3-\{[4-(4-Chlorophenyl)-1,3-thiazol-2-yl]-4-methoxyanilino\}propanohydrazide (4a) has been identified as possessing a significant antioxidant activity tested by FRAP method and reducing power assay.

EXPERIMENTAL

Synthesis

General Methods. The reagents and solvents were obtained from Sigma-Aldrich Chemie GmbH (Munich, Germany) and were used without further purification. The melting points were determined on a MEL-TEMP (Electrothermal, Bibby Scientific Company, Burlington, NJ, USA) melting point apparatus and are uncorrected. IR spectra (ν, cm\(^{-1}\)) were recorded on a Perkin–Elmer Spectrum BX FT–IR spectrometer (Perkin–Elmer Inc., Waltham, MA, USA) using KBr pellets. The \(^1\)H and \(^{13}\)C NMR spectra were recorded in DMSO-\(d_6\) on a Brucker Avance III (400 MHz, 101 MHz) spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) calibrated from TMS (0 ppm) as an internal standard for \(^1\)H NMR, and DMSO-\(d_6\) (39.43 ppm) for \(^{13}\)C NMR. Elemental analyses (C, H, N) were performed on an Elemental Analyzer CE-440 (Exeter Analytical, Inc., North Chelmsford, MA, USA). The reaction course and the purity of the synthesized compounds was monitored by TLC using Silica gel 60 F254 (Kieselgel 60 F254) (Merck, Darmstadt, Germany) plates.
General procedure for preparation of 1,3-thiazoles 2a–e. To a solution of thioureido acid 1 (0.76 g, 3 mmol) in acetone (15 mL), the corresponding α-haloketone (3.6 mmol) was added, and the reaction mixture was refluxed for 2–4 h. Afterwards, the reaction mixture was cooled down, the precipitate was filtered off, washed with acetone, and dried. Purification was performed by dissolving the crystals in 5% aqueous K2CO3 (15 mL), filtering and acidifying the filtrate with acetic acid to pH 6.

3-{4-(4-Chlorophenyl)-1,3-thiazol-2-yl}-4-methoxyanilino propanoic acid (2a). White solid, yield 0.94 g (81%), mp 148–149 °C; IR (KBr) νmax (cm⁻¹): 1726 (CO), 1508 (C=≡N); ¹H NMR (400 MHz, DMSO-d6) δ 2.65 (2H, t, J = 7.2 Hz, CH₂CO), 3.80 (3H, s, OCH₃), 4.14 (2H, t, J = 7.1 Hz, NCH₂), 7.05 (2H, d, J = 8.7 Hz, H₁Ar), 7.17 (1H, s, SCH), 7.37 (2H, d, J = 8.7 Hz, H₂Ar), 7.45 (2H, d, J = 8.4 Hz, H₃Ar), 7.88 (2H, d, J = 8.4 Hz, H₄Ar), 11.51 (1H, br. s, COOH); ¹³C NMR (101 MHz, DMSO-d6) δ 32.36 (CH₂CO), 48.55 (NCH₂), 55.36 (OCH₃), 103.42, 115.27, 127.34, 128.55, 129.00, 131.88, 133.51, 137.05, 149.09, 158.56 (C₁Ar, C₇Th), 169.97 (C=N), 172.63 (COOH). Anal. Calcld for C₁₉H₁₇ClN₂O₃S: %: C, 58.69; H, 4.41; N, 7.20. Found, %: C, 58.43; H, 4.35; N, 7.14.

3-{4-(4-Fluorophenyl)-1,3-thiazol-2-yl}-4-methoxyanilino propanoic acid (2b). Greenish solid, yield 0.89 g (80%), mp 128–129 °C; IR (KBr) νmax (cm⁻¹): 1727 (CO), 1511 (C≡N); ¹H NMR (400 MHz, DMSO-d6) δ 2.66 (2H, t, J = 7.2 Hz, CH₂CO), 3.80 (3H, s, OCH₃), 4.14 (2H, t, J = 7.2 Hz, NCH₂), 7.04 (2H, d, J = 8.8 Hz, H₁Ar), 7.08 (1H, s, SCH), 7.22 (2H, t, J = 8.8 Hz, H₂Ar), 7.37 (2H, d, J = 8.7 Hz, H₃Ar), 7.90 (2H, dd, J = 8.3 Hz, J = 5.7 Hz, H₄Ar), 12.24 (1H, br. s, COOH); ¹³C NMR (101 MHz, DMSO-d6) δ 32.37 (CH₂CO), 48.56 (NCH₂), 55.35 (OCH₃), 102.34, 115.25, 115.29, 115.41, 127.58, 127.63, 128.98, 131.30, 131.32, 137.13, 149.35, 158.51, 160.89, 162.28 (C₁Ar, C₇Th), 169.89 (C=N), 172.65 (COOH). Anal. Calcld for C₁₉H₁₇FNN₂O₃S: %: C, 61.28; H, 4.60; N, 7.52. Found, %: C, 61.21; H, 4.56; N, 7.48.

3-{4-Methoxy[4-(4-nitrophenyl)-1,3-thiazol-2-yl]anilino} propanoic acid (2c). Yellow solid, yield 0.95 g (79%), mp 149–150 °C; IR (KBr) νmax (cm⁻¹): 1710 (CO), 1509 (C≡N); ¹H NMR (400 MHz, DMSO-d6) δ 2.66 (2H, t, J = 7.3 Hz, CH₂CO), 3.81 (3H, s, OCH₃), 4.17 (2H, t, J = 7.2 Hz, NCH₂), 7.06 (2H, d, J = 8.9 Hz, H₁Ar), 7.38 (2H, d, J = 8.8 Hz, H₂Ar), 7.48 (1H, s, SCH), 8.11 (2H, d, J = 8.9 Hz, H₃Ar), 8.26 (2H, d, J = 8.9 Hz, H₄Ar), 12.30 (1H, br. s, COOH); ¹³C NMR (101 MHz, DMSO-d6) δ 32.34 (CH₂CO), 48.54 (NCH₂), 55.38 (OCH₃), 107.48, 115.34, 124.05, 126.42, 129.06, 136.87, 140.69, 146.20, 148.39, 158.67 (C₁Ar, C₇Th), 170.26 (C=N), 172.63 (COOH). Anal. Calcld for C₁₀H₁₇N₃O₅S: %: C, 57.13; H, 4.29; N, 10.52. Found, %: C, 57.00; H, 4.24; N, 10.46.

3-[4-Methoxyphenyl][4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl]amino] propanoic acid (2d). Yellow solid, yield 1.06 g (84%), mp 133–134 °C; IR (KBr) νmax (cm⁻¹): 3381 (OH), 1718 (CO), 1510 (C≡N); ¹H NMR (400 MHz, DMSO-d6) δ 2.66 (2H, t, J = 7.2 Hz, CH₂CO), 3.81 (3H, s, OCH₃), 4.20 (2H, t, J = 7.3 Hz, NCH₂), 7.06 (2H, d, J = 8.9 Hz, H₁Ar), 7.35–7.40 (3H, m, H₂Ar), 7.43 (1H, d, J = 8.3 Hz, H₃Ar), 7.56 (1H,
s, SCH), 7.61 (1H, t, J = 7.8 Hz, H_{Ar}), 7.88 (1H, d, J = 7.6 Hz, H_{Ar}), 8.64 (1H, s, H_{Ar}), 12.27 (1H, br. s, COOH); $^{13}$C NMR (101 MHz, DMSO-$_d_6$) δ 32.42 (CH$_2$CO), 48.28 (NCH$_2$), 55.38 (OCH$_3$), 109.70, 115.32, 115.85, 119.28, 120.44, 124.71, 128.81, 129.12, 131.57, 136.91, 138.41, 143.89, 152.28, 158.66, 158.76 (C_{Ar}, C_{Th}), 169.29 (C=N), 172.70 (COOH). Anal. Calcd for C$_{22}$H$_{18}$N$_2$O$_5$S, %: C, 62.55; H, 4.29; N, 6.63. Found, %: C, 62.44; H, 4.21; N, 6.58.

3-{{4-Methoxy-[4-(2-naphthyl)-1,3-thiazol-2-yl]anilino}propanoic acid (2e). White solid, yield 0.97 g (80%), mp 152–153 °C; IR (KBr) $\nu_{\text{max}}$ (cm$^{-1}$): 1709 (CO), 1509 (C=N); $^1$H NMR (400 MHz, DMSO-$_d_6$) δ 2.70 (2H, t, J = 7.2 Hz, CH$_2$CO), 3.81 (3H, s, OCH$_3$), 4.22 (2H, t, J = 7.2 Hz, NCH$_2$), 7.06 (2H, d, J = 8.8 Hz, H_{Ar}), 7.26 (1H, s, SCH), 7.40 (2H, d, J = 8.8 Hz, H_{Ar}), 7.47–7.54 (2H, m, H$_2$, m, H_{Ar}), 7.87–8.03 (4H, m, H_{Ar}), 8.40 (1H, s, H_{Ar}); $^{13}$C NMR (101 MHz, DMSO-$_d_6$) δ 32.46 (CH$_2$CO), 48.46 (NCH$_2$), 55.37 (OCH$_3$), 103.50, 115.28, 124.10, 124.11, 125.92, 126.39, 127.57, 128.01, 128.12, 129.08, 132.18, 132.46, 133.16, 137.09, 150.36, 158.56 (C_{Ar}, C_{Th}), 170.01 (C=N), 172.71 (COOH). Anal. Calcd for C$_{23}$H$_{20}$N$_2$O$_5$S, %: C, 68.30; H, 4.98; N, 6.93. Found, %: C, 68.26; H, 4.92; N, 6.89.

Methyl 3-{{[4-(4-chlorophenyl)-1,3-thiazol-2-yl]4-methoxyanilino}propanoate (3a). A mixture of acid 2a (5.83 g, 0.015 mol), MeOH (50 mL), and sulfuric acid (0.8 mL, 1.47 g, 0.015 mol) was refluxed for 20 h. The liquid fraction was evaporated under reduced pressure, the residue was washed with 10% aqueous Na$_2$CO$_3$ (15 mL), and recrystallized from MeOH to afford white solid, yield 5.53 g (92%), mp 140–141 °C; IR (KBr) $\nu_{\text{max}}$ (cm$^{-1}$): 1736 (CO), 1510 (C=N); $^1$H NMR (400 MHz, DMSO-$_d_6$) δ 2.75 (2H, t, J = 7.2 Hz, CH$_2$CO), 3.54 (3H, s, COOCH$_3$), 3.82 (3H, s, OCH$_3$), 4.19 (2H, t, J = 7.2 Hz, NCH$_2$), 7.06 (2H, d, J = 8.8 Hz, H_{Ar}), 7.19 (1H, s, SCH), 7.37 (2H, d, J = 8.8 Hz, H_{Ar}), 7.47 (2H, d, J = 8.4 Hz, H_{Ar}), 7.89 (2H, d, J = 8.4 Hz, H_{Ar}); $^{13}$C NMR (101 MHz, DMSO-$_d_6$) δ 32.95 (CH$_2$CO), 49.26 (NCH$_2$), 52.09 (COOCH$_3$), 56.05 (OCH$_3$), 104.17 (CH), 115.97, 128.01, 129.24, 129.69, 132.59, 134.21, 137.68, 149.86, 159.28 (C_{Ar}, C_{Th}), 170.59 (C=N), 172.27 (CO). Anal. Calcd for C$_{20}$H$_{19}$ClN$_2$O$_3$S, %: C, 59.62; H, 4.75; N, 6.95. Found, %: C, 59.55; H, 4.69; N, 6.89.

3-{{[4-(4-Chlorophenyl)-1,3-thiazol-2-yl]4-methoxyanilino}propanohydrazide (4a). A mixture of ester 3a (4.02 g, 0.01 mol), hydrazine monohydrate (0.64 g, 0.02 mol), and DMSO (10 mL) was stirred at 90–100 °C for 2 h. The precipitate was filtered off and recrystallized from propan-2-ol to afford white solid, yield 3.26 g (81%), mp 144–145 °C; IR (KBr) $\nu_{\text{max}}$ (cm$^{-1}$): 3298 (NH), 1631 (CO), 1537 (C=N); $^1$H NMR (400 MHz, DMSO-$_d_6$) δ 2.50 (2H, t, J = 7.2 Hz, CH$_2$CO), 3.82 (3H, s, OCH$_3$), 4.15 (2H, t, J = 7.2 Hz, NCH$_2$), 4.18 (1H, s, NH), 7.06 (2H, d, J = 9.2 Hz, H_{Ar}), 7.17 (1H, s, SCH), 7.37 (2H, d, J = 9.2 Hz, H_{Ar}), 7.47 (2H, d, J = 8.8 Hz, H_{Ar}), 7.92 (2H, d, J = 8.8 Hz, H_{Ar}), 9.11 (1H, s, NH); $^{13}$C NMR (101 MHz, DMSO-$_d_6$) δ 31.89 (CH$_2$CO), 49.22 (NCH$_2$), 55.26 (OCH$_3$), 103.21 (CH), 115.15, 127.30, 128.43, 128.87,
131.78, 133.51, 137.15, 149.13, 158.38 (C\textsubscript{Ar}, C\textsubscript{Th}), 169.34 (C=N), 169.80 (CO). Anal. Calcd for C\textsubscript{19}H\textsubscript{19}ClN\textsubscript{4}O\textsubscript{2}S, %: C, 56.64; H, 4.75; N, 13.91. Found, %: C, 56.54; H, 4.62; N, 13.87.

3-[(4-(4-Chlorophenyl)-1,3-thiazol-2-yl)-4-methoxyanilino]-N-(2,5-dimethyl-1H-pyrrol-1-yl)propanamide (5a). A mixture of 4a (0.60 g, 1.5 mmol), propan-2-ol (20 mL), hexane-2,5-dione (0.23 g, 0.16 mL, 2 mmol), and acetic acid (0.5 mL) was refluxed for 4 h. Then cold water (20 mL) was added. The precipitate was filtered off and recrystallized from propan-2-ol afforded pale taupe solid, yield 0.44 g (61%), mp. 131–132 °C; IR (KBr) \(\nu\)\textsubscript{max} (cm\textsuperscript{-1}): 3255 (NH), 1677 (CO), 1510 (C=N); \(^1\)H NMR (400 MHz, DMSO-\(\text{d}_6\)) \(\delta\) 1.95 (6H, s, 2 CH\textsubscript{3}), 2.78 (2H, t, \(J\) = 6.8 Hz, CH\textsubscript{2}CO), 3.83 (3H, s, OCH\textsubscript{3}), 4.28 (2H, t, \(J\) = 6.8 Hz, NCH\textsubscript{2}), 5.63 (2H, s, 2 CH), 7.08 (2H, d, \(J\) = 8.8 Hz, H\textsubscript{Ar}), 7.21 (1H, s, SCH), 7.38–7.53 (4H, m, H\textsubscript{Ar}), 7.93 (2H, d, \(J\) = 8.4 Hz, H\textsubscript{Ar}), 10.69 (1H, s, NH); \(^{13}\)C NMR (101 MHz, DMSO-\(\text{d}_6\)) \(\delta\) 10.80 (CH\textsubscript{3}), 31.63 (C\textsubscript{H}2CO), 48.67 (NCH\textsubscript{2}), 55.29 (OCH\textsubscript{3}), 102.81 (2 CH), 103.41 (CH), 115.19, 126.60, 127.29, 128.41, 128.84, 131.81, 133.47, 137.07, 149.07, 158.44 (C\textsubscript{Ar}, C\textsubscript{Th}), 169.60 (C=N), 169.87 (CO). Anal. Calcd for C\textsubscript{25}H\textsubscript{25}ClN\textsubscript{4}O\textsubscript{2}S, %: C, 62.43; H, 5.24; N, 11.65. Found, %: C, 62.32; H, 5.19; N, 11.62.

5-(2-[(4-(4-Chlorophenyl)-1,3-thiazol-2-yl)-4-methoxyanilino]ethyl)-1,3,4-oxadiazole-2(3H)-thione (6a). To a mixture of KOH (0.08 g, 1.5 mmol) and EtOH (15 mL), CS\textsubscript{2} (0.18 mL, 0.23 g, 1.5 mmol) was added drop-wise and the mixture was stirred at room temperature for 15 min. Afterwards, a mixture of hydrazide 4a (0.60 g, 1.5 mmol) and EtOH (10 mL) was added and the reaction mixture was refluxed for 72 h. The liquid fractions were removed under \textit{vacuo}, the residue was dissolved in H\textsubscript{2}O (15 mL) and acidified with HCl to pH 3–4. The precipitate was filtered off and recrystallized from propan-2-ol to afford white solid, yield 0.42 g (63%), mp 172–173 °C; IR (KBr) \(\nu\)\textsubscript{max} (cm\textsuperscript{-1}): 3477 (NH), 1511 (C=N); \(^1\)H NMR (400 MHz, DMSO-\(\text{d}_6\)) \(\delta\) 3.32 (2H, t, \(J\) = 6.4 Hz, CH\textsubscript{2}C), 3.82 (3H, s, OCH\textsubscript{3}), 4.33 (2H, t, \(J\) = 6.4 Hz, NCH\textsubscript{2}), 7.07 (2H, d, \(J\) = 8.8 Hz, H\textsubscript{Ar}), 7.18 (1H, s, SCH), 7.35 (2H, d, \(J\) = 8.8 Hz, H\textsubscript{Ar}), 7.47 (2H, d, \(J\) = 8.4 Hz, H\textsubscript{Ar}), 9.09 (1H, s, NH); \(^{13}\)C NMR (101 MHz, DMSO-\(\text{d}_6\)) \(\delta\) 23.03 (C\textsubscript{H}2C), 49.69 (NCH\textsubscript{2}), 55.30 (OCH\textsubscript{3}), 103.47 (CH), 115.19, 126.60, 127.29, 128.41, 128.84, 131.81, 133.47, 137.07, 149.07, 158.44 (C\textsubscript{Ar}, C\textsubscript{Th}), 169.60 (C=N), 169.87 (CO). Anal. Calcd for C\textsubscript{25}H\textsubscript{25}ClN\textsubscript{4}O\textsubscript{2}S, %: C, 62.43; H, 5.24; N, 11.65. Found, %: C, 62.32; H, 5.19; N, 11.62.

2-(3-[(4-(4-Chlorophenyl)-1,3-thiazol-2-yl)-4-methoxyanilino]propanoyl)-N-phenyl-1-hydrazinecarbothioamide (7a). A mixture of hydrazide 4a (0.40 g, 1 mmol), phenyl isothiocyanate (0.20 g, 0.18 mL, 0.23 g, 1.5 mmol) was added drop-wise and the mixture was stirred at room temperature for 15 min. Afterwards, a mixture of hydradize 4a (0.60 g, 1.5 mmol) and EtOH (10 mL) was added and the reaction mixture was refluxed for 72 h. The liquid fractions were removed under \textit{vacuo}, the residue was dissolved in H\textsubscript{2}O (15 mL) and acidified with HCl to pH 3–4. The precipitate was filtered off and recrystallized from propan-2-ol to afford white solid, yield 0.42 g (63%), mp 172–173 °C; IR (KBr) \(\nu\)\textsubscript{max} (cm\textsuperscript{-1}): 3477 (NH), 1511 (C=N); \(^1\)H NMR (400 MHz, DMSO-\(\text{d}_6\)) \(\delta\) 2.69 (2H, t, \(J\) = 7.6 Hz, CH\textsubscript{2}CO), 3.82 (3H, s, OCH\textsubscript{3}), 4.21 (2H, t, \(J\) = 7.6 Hz, NCH\textsubscript{2}), 7.07 (2H, d, \(J\) = 8.8 Hz, H\textsubscript{Ar}), 7.14–7.22 (2H, m, SCH + NH), 7.30–7.53 (7H, m, H\textsubscript{Ar}), 7.92 (2H, d, \(J\) = 8.4 Hz,
H$_{Ar}$), 9.56 (1H, s, NH), 10.00 (1H, s, NH); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 31.62 (CH$_2$), 48.43 (NCH$_2$), 53.30 (OCH$_3$), 103.31 (CH), 115.22, 125.05, 127.28, 127.96, 128.45, 128.61, 131.80, 132.10, 134.03, 149.12, 158.48 (C$_{Ar}$, C$_{Th}$), 169.34 (CN), 169.92 (CO), 180.86 (C=S). Anal. Calcd for C$_{26}$H$_{24}$ClN$_5$O$_2$S$_2$, %: C, 58.04; H, 4.50; N, 13.02. Found, %: C, 57.98; H, 4.45; N, 12.99.

5-(2-[[4-(4-Chlorophenyl)-1,3-thiazol-2-yl]-4-methoxyanilino]ethyl)-4-phenyl-2,4-dihydro-3$H$-1,2,4-triazole-3-thione (8a). A mixture of thiosemicarbazide 7a (0.27 g, 0.5 mmol) and 10% aqueous KOH solution (20 mL) was refluxed for 8 h and cooled down. Then concentrated HCl was added to pH 4. The precipitate was filtered off, washed with water, and recrystallized from DMF–H$_2$O mixture to afford white solid, yield 0.18 g (69%), mp 230–231 °C; IR (KBr) $\nu_{\text{max}}$ (cm$^{-1}$): 2920 (NH), 1509 (C=N), 1244 (C=S); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 2.93 (2H, t, $J = 7.2$ Hz, CH$_2$C), 3.82 (3H, s, OCH$_3$), 4.04 (2H, t, $J = 7.2$ Hz, NCH$_2$), 7.02 (2H, d, $J = 8.8$ Hz, H$_{Ar}$), 7.15 (1H, s, SCH), 7.21 (2H, d, $J = 8.8$ Hz, H$_{Ar}$), 7.31–7.37 (2H, m, H$_{Ar}$), 7.48 (2H, d, $J = 8.4$ Hz, H$_{Ar}$), 7.50–7.56 (3H, m, H$_{Ar}$), 7.79 (2H, d, $J = 8.4$ Hz, H$_{Ar}$), 11.76 (0.7H, s, NH); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 23.82 (C$_{H_2}$C), 49.52 (NCH$_2$), 55.32 (OCH$_3$), 103.42 (CH), 114.54, 115.15, 127.29, 128.36, 128.38, 128.84, 128.92, 131.72, 136.90, 137.46, 148.82, 151.55, 151.71, 160.16 (C$_{Ar}$, C$_{Th}$), 169.83 (C=N), 172.80 (CO). Anal. Calcd for C$_{26}$H$_{22}$ClN$_5$O$_2$S$_2$, %: C, 60.05; H, 4.26; N, 13.47. Found, %: C, 60.00; H, 4.21; N, 13.43.

**General procedure for preparation of compounds 9–11a.** A mixture of hydrazide 4a (0.10 g, 0.25 mmol), corresponding carbaldehyde (0.5 mmol), and MeOH (10 mL) was refluxed for 10 min (10a) or 1 h (9, 11a). The precipitate was filtered off, washed with MeOH, and recrystallized from DMF–H$_2$O mixture.

3-[[4-(4-Chlorophenyl)-1,3-thiazol-2-yl]-4-methoxyanilino]-N’-[(5-nitro-2-furyl)methylidene]propanohydrazide (9a). Yellow solid, yield 0.09 g (69%), mp 184–185 °C; IR (KBr) $\nu_{\text{max}}$ (cm$^{-1}$): 3204 (NH), 1676 (CO), 1510 (C=N); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 2.71 (0.6H, t, $J = 6.8$ Hz, CH$_2$CO), 3.06 (1.4H, t, $J = 6.8$ Hz, CH$_2$CO), 3.81 (3H, s, OCH$_3$), 4.21–4.31 (2H, m, NCH$_2$), 7.02–7.90 (11H, m, H$_{Ar}$), 7.95 (0.7H, s, N=CH), 8.11 (0.3H, s, N=CH), 11.76 (0.7H, s, NH), 11.84 (0.3H, s, NH); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 29.92 (CH$_2$CO), 47.79 (NCH$_2$), 55.18 (OCH$_3$), 103.35 (CH), 114.54, 115.15, 127.29, 128.36, 128.38, 128.84, 128.92, 131.72, 136.90, 137.46, 148.82, 151.55, 151.71, 160.16 (C$_{Ar}$, C$_{Th}$), 169.83 (C=N), 172.80 (CO). Anal. Calcd for C$_{24}$H$_{20}$ClN$_5$O$_5$S %: C, 54.81; H, 3.83; N, 13.32. Found, %: C, 54.78; H, 3.79; N, 13.29.

3-[[4-(4-Chlorophenyl)-1,3-thiazol-2-yl]-4-methoxyanilino]-N’-[(5-nitro-2-thienyl)methylidene]propanohydrazide (10a). Orange solid, yield 0.10 g (75%), mp 199–200 °C; IR (KBr) $\nu_{\text{max}}$ (cm$^{-1}$): 3110 (NH), 1675 (CO), 1509 (C=N); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ (Z/E isomeric mixture, 70/30): 2.71 (0.6H, t, $J = 6.8$ Hz, CH$_2$CO), 3.06 (1.4H, t, $J = 6.8$ Hz, CH$_2$CO), 3.81 (3H, s, OCH$_3$), 4.21–4.31 (2H, m, NCH$_2$), 7.02–7.90 (11H, m, H$_{Ar}$), 7.95 (0.7H, s, N=CH), 8.11 (0.3H, s, N=CH), 11.76 (0.7H, s, NH), 11.84 (0.3H, s, NH); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 29.92 (CH$_2$CO), 47.79 (NCH$_2$), 55.18 (OCH$_3$), 103.35 (CH), 114.54, 115.15, 127.29, 128.36, 128.38, 128.84, 128.92, 131.72, 136.90, 137.46, 148.82, 151.55, 151.71, 160.16 (C$_{Ar}$, C$_{Th}$), 169.83 (C=N), 172.80 (CO). Anal. Calcd for C$_{24}$H$_{20}$ClN$_5$O$_5$S %: C, 54.81; H, 3.83; N, 13.32. Found, %: C, 54.78; H, 3.79; N, 13.29.
Hz, NCH₂), 7.00–8.11 (11H, m, HAr), 8.14 (0.7H, s, N=CH), 8.41 (0.3H, s, N=CH), 11.78 (0.7H, s, NH), 11.82 (0.3H, s, NH); 13C NMR (101 MHz, DMSO-d₆) δ 30.71, 33.05 (CH₂CO), 48.67 (NCH₂), 55.19, 55.26 (OCH₃), 103.20, 103.29 (CH), 115.12, 115.16, 127.20, 127.27, 128.31, 128.37, 128.69, 128.80, 128.86, 130.31, 146.64, 146.77, 149.11, 150.20, 158.42 (CAr, CTh), 167.21, 169.76 (C=N), 172.63 (CO).


3-[[4-(4-Chlorophenyl)-1,3-thiazol-2-yl]-4-methoxyanilino]-N’-[4-nitrophenyl)methylidene]propahydrazide (11a). Dark orange solid, yield 0.12 g (92%), mp 210–211 °C; IR (KBr) νmax (cm⁻¹): 2958 (NH), 1677 (CO), 1509 (C=N); 1H NMR (400 MHz, DMSO-d₆) δ (Z/E isomeric mixture, 70/30): 2.71 (0.6H, t, J = 6.8 Hz, CH₂CO), 3.15 (1.4H, t, J = 6.8 Hz, CH₂CO), 3.80, 3.82 (3H, 2s, OCH₃), 4.26 (2H, t, J = 6.8 Hz, NCH₂), 7.05–8.30 (14H, m, HAr+N=CH), 11.68 (0.7H, s, NH), 11.76 (0.3H, s, NH); 13C NMR (101 MHz, DMSO-d₆) δ 30.77, 32.96 (CH₂CO), 49.02 (NCH₂), 55.24 (OCH₃), 103.28 (CH), 115.20, 123.69, 123.87, 127.20, 127.28, 127.36, 127.77, 128.38, 128.88, 128.94, 131.74, 133.46, 137.08, 137.17, 140.29, 140.38, 140.60, 143.47, 147.37, 147.63, 149.10, 158.43 (CAr, CTh), 167.05, 169.67 (C=N), 169.82, 172.79 (CO). Anal. Calcd for C₂₆H₂₂ClN₅O₄S %: C, 58.26; H, 4.14; N, 13.07. Found, %: C, 58.23; H, 4.11; N, 13.03.

General procedure for preparation of quinolones 12a, b, d, e and 1,3-thiazol-2-amine 13c. A mixture of corresponding thiazole 2a–e (2 mmol) and polyphosphoric acid (15 mL) was heated with stirring at 110–120 °C for 4–6 h. Then the reaction mixture was cooled down and crushed ice was added up to 50 mL. The precipitate was filtered off, washed with 5% aqueous Na₂CO₃ solution and water. The precipitate was recrystallized from glacial acetic acid.

1-[4-(4-Chlorophenyl)-1,3-thiazol-2-yl]-6-methoxy-2,3-dihydroquinolin-4(1H)-one (12a). Yellow solid, yield 0.50 g (67%), mp 149–150 °C; IR (KBr) νmax (cm⁻¹): 1684 (CO), 1526 (C=N); 1H NMR (400 MHz, DMSO-d₆) δ 2.85 (2H, t, J = 6.3 Hz, CH₂CO), 3.81 (3H, s, CH₃), 4.37 (2H, t, J = 6.3 Hz, NCH₂), 7.22–8.09 (8H, m, HAr and SCH); 13C NMR (101 MHz, DMSO-d₆) δ 37.57 (CH₂CO), 49.02 (NCH₂), 55.24 (OCH₃), 105.38, 109.31, 121.99, 122.23, 124.37, 127.45, 128.88, 128.94, 131.74, 133.46, 137.08, 137.17, 140.29, 140.38, 140.60, 143.47, 147.37, 147.63, 149.10, 158.43 (CAr, CTh), 167.05, 169.67 (C=N), 169.82, 172.79 (CO). Anal. Calcd for C₁₉H₁₅ClN₂O₂S %: C, 61.54; H, 4.08; N, 7.55. Found, %: C, 61.49; H, 4.01; N, 7.47.

1-[4-(4-Fluorophenyl)-1,3-thiazol-2-yl]-6-methoxy-2,3-dihydroquinolin-4(1H)-one (12b). Yellow solid, yield 0.49 g (69%), mp 132–133 °C; IR (KBr) νmax (cm⁻¹): 1683 (CO), 1501 (C=N); 1H NMR (400 MHz, DMSO-d₆) δ 2.85 (2H, t, J = 6.2 Hz, CH₂CO), 3.81 (3H, s, CH₃), 4.36 (2H, t, J = 6.2 Hz, NCH₂), 7.16–8.20 (8H, m, HAr and SCH); 13C NMR (101 MHz, DMSO-d₆) δ 37.56 (CH₂CO), 49.04 (NCH₂), 55.50 (OCH₃), 104.41, 109.28, 115.40, 115.61, 121.98, 122.25, 124.31, 127.82, 130.86, 139.58, 149.33, 155.19 (CAr, CTh), 166.41 (C=N), 192.78 (C=O). Anal. Calcd for C₁₉H₁₅FN₂O₂S, C, 61.54; H, 4.08; N, 7.55. Found, %: C, 61.49; H, 4.01; N, 7.47.
7.90. Found, %: C, 64.28; H, 4.20; N, 7.87.

6-Methoxy-1-[4-(2-oxo-2H-chromen-3-yl)-1,3-thiazol-2-yl]-2,3-dihydroquinolin-4(1H)-one (12d). Yellow solid, yield 0.52 g (64%), mp 196–197 °C; IR (KBr) $\nu_{\text{max}}$ (cm$^{-1}$): 1718, 1683 (2CO), 1523 (C=N); $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 2.87 (2H, t, $J = 6.3$ Hz, CH$_2$CO), 3.82 (3H, s, CH$_3$), 4.45 (2H, t, $J = 6.3$ Hz, NCH$_2$), 7.27–8.73 (8H, m, H$_{Ar}$ and H$_{chr}$), 7.86 (1H, s, SCH); $^{13}$C NMR (101 MHz, DMSO-d$_6$) $\delta$ 37.66 (CH$_2$CO), 48.86 (NCH$_2$), 55.54 (OCH$_3$), 109.39, 111.05, 115.90, 119.21, 120.07, 122.13, 122.34, 124.63, 124.76, 128.98, 131.84, 139.11, 139.46, 143.69, 152.41, 155.39, 158.76 (C$_{Ar}$, C$_{Th}$, C$_{chr}$), 165.75 (C=N), 192.84 (C=O). Anal. Calcd for C$_{22}$H$_{16}$N$_2$O$_4$S, C, 65.34; H, 3.99; N, 6.93. Found, %: C, 65.23; H, 4.01; N, 6.88.

6-Methoxy-1-[4-(naphthalen-2-yl)-1,3-thiazol-2-yl]-2,3-dihydroquinolin-4(1H)-one (12e). Yellow solid, yield 0.47 g (61%), mp 132–133 °C; IR (KBr) $\nu_{\text{max}}$ (cm$^{-1}$): 1687 (CO), 1523 (C=N); $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 2.88 (2H, t, $J = 6.3$ Hz, CH$_2$CO), 3.82 (3H, s, CH$_3$), 4.43 (2H, t, $J = 6.3$ Hz, NCH$_2$), 7.26–8.49 (10H, m, H$_{Ar}$), 7.63 (1H, s, SCH); $^{13}$C NMR (101 MHz, DMSO-d$_6$) $\delta$ 37.63 (CH$_2$CO), 49.04 (NCH$_2$), 55.51 (OCH$_3$), 105.42, 109.31, 121.95, 122.35, 123.99, 124.33, 124.42, 126.12, 126.48, 127.60, 128.20, 131.66, 132.58, 133.15, 136.73, 150.32, 155.16 (C$_{Ar}$, C$_{Th}$, C$_{chr}$), 166.32 (C=N), 192.83 (C=O). Anal. Calcd for C$_{23}$H$_{18}$N$_2$O$_2$S, C, 71.48; H, 4.69; N, 7.25. Found, %: C, 71.33; H, 4.62; N, 7.22.

N-(4-Methoxyphenyl)-4-(4-nitrophenyl)-1,3-thiazol-2-amine (13c). Brown solid, yield 0.38 g (58%), mp 146–147 °C; IR (KBr) $\nu_{\text{max}}$ (cm$^{-1}$): 3374 (NH), 1508 (C=N); $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 3.87 (3H, s, CH$_3$), 6.25 (1H, d, $J = 7.8$ Hz, SCH), 7.28–8.36 (8H, m, H$_{Ar}$), 8.68 (1H, s, NH); $^{13}$C NMR (101 MHz, DMSO-d$_6$) $\delta$ 55.56 (OCH$_3$), 105.58, 109.63, 119.06, 120.54, 122.31, 124.31, 126.84, 127.03, 134.32, 139.19, 142.04, 147.03, 149.40, 156.41 (C$_{Ar}$, C$_{Th}$), 160.76 (C=N). Anal. Calcd for C$_{16}$H$_{13}$N$_3$O$_3$S, C, 58.71; H, 4.00; N, 12.84; Found, %: C, 58.67; H, 3.96; N, 12.80.

**General procedure for preparation of quinolones 14a, b, d, e.** A mixture of corresponding quinolone 12a, b, d, e (1 mmol), hydrobromic acid (3 mL), and glacial acetic acid (5 mL) was refluxed for 20–30 h. Then the reaction mixture was cooled down and neutralized with dilute aqueous ammonia to pH 7. The precipitate was filtered off, washed with water, and recrystallized from glacial acetic acid.

1-[4-(4-Chlorophenyl)-1,3-thiazol-2-yl]-6-hydroxy-2,3-dihydroquinolin-4(1H)-one (14a). Yellow solid, yield 0.28 g (79%), mp 240–241 °C; IR (KBr) $\nu_{\text{max}}$ (cm$^{-1}$): 3431 (OH), 1693 (CO), 1561 (C=N); $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 2.79 (2H, t, $J = 6.2$ Hz, CH$_2$CO), 4.28–4.41 (2H, m, NCH$_2$), 7.05–7.96 (8H, m, H$_{Ar}$ and SCH); $^{13}$C NMR (101 MHz, DMSO-d$_6$) $\delta$ 55.56 (OCH$_3$), 105.58, 109.63, 119.06, 120.54, 122.31, 124.31, 126.84, 127.03, 134.32, 139.19, 142.04, 147.03, 149.40, 156.41 (C$_{Ar}$, C$_{Th}$), 160.76 (C=N). Anal. Calcd for C$_{18}$H$_{13}$ClN$_2$O$_2$S, C, 60.59; H, 3.67; N, 7.85. Found, %: C, 60.51; H, 3.62; N, 7.80.
1-[4-(4-Fluorophenyl)-1,3-thiazol-2-yl]-6-hydroxy-2,3-dihydroquinolin-4(1H)-one (14b). Greenish yellow solid, yield 0.28 g (82%), mp 144–145 °C; IR (KBr) ν\textsubscript{max} (cm\textsuperscript{-1}): 3344 (OH), 1669 (CO), 1506 (C=N); \textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}) δ 2.79 (2H, t, J = 6.0 Hz, CH\textsubscript{2}CO), 4.36 (2H, t, J = 6.0 Hz, NCH\textsubscript{2}), 7.06–7.99 (8H, m, H\textsubscript{Ar} and SCH); \textsuperscript{13}C NMR (101 MHz, DMSO-d\textsubscript{6}) δ 37.65 (CH\textsubscript{2}CO), 48.84 (NCH\textsubscript{2}), 103.98, 111.73, 115.40, 115.61, 122.23, 122.55, 124.91, 127.75, 127.83, 130.89, 138.24, 149.28, 153.64 (C\textsubscript{Ar}, C\textsubscript{Th}), 166.69 (C=N), 193.11 (C=O). Anal. Caled for C\textsubscript{18}H\textsubscript{13}FN\textsubscript{2}O\textsubscript{2}S, C; 63.52; H, 3.85; N, 8.23. Found: %: C, 63.44; H, 3.79; N, 8.19.

6-Hydroxy-1-[4-(2-oxo-2\textsubscript{H}-chromen-3-yl)-1,3-thiazol-2-yl]-2,3-dihydroquinolin-4(1\textsubscript{H})-one (14d). Yellow solid, yield 0.29 g (74 %), mp 269–270 °C; IR (KBr) ν\textsubscript{max} (cm\textsuperscript{-1}): 3417 (OH), 1722, 1681 (CO), 1528 (C=N); \textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}) δ 2.81 (2H, t, J = 6.2 Hz, CH\textsubscript{2}CO), 4.44 (2H, t, J = 6.2 Hz, NCH\textsubscript{2}), 7.05–8.72 (9H, m, H\textsubscript{Ar} and H\textsubscript{chr} and SCH); \textsuperscript{13}C NMR (101 MHz, DMSO-d\textsubscript{6}) δ 37.73 (CH\textsubscript{2}CO), 48.63 (NCH\textsubscript{2}), 110.62, 111.84, 115.87, 119.22, 120.07, 122.27, 122.58, 124.74, 125.14, 128.94, 131.77, 138.07, 139.02, 143.68, 152.38, 153.89, 158.75 (C\textsubscript{Ar}, C\textsubscript{Th}, C\textsubscript{chr}), 166.60 (C=N), 193.12 (C=O). Anal. Caled for C\textsubscript{21}H\textsubscript{14}N\textsubscript{2}O\textsubscript{4}S, C; 64.61; H, 3.61; N, 7.18. Found, %: C, 64.55; H, 3.57; N, 7.13.

6-Hydroxy-1-[4-(naphthalen-2-yl)-1,3-thiazol-2-yl]-2,3-dihydroquinolin-4(1\textsubscript{H})-one (14e). Greenish yellow solid, yield 0.27 g (72%), mp 183–184 °C; IR (KBr) ν\textsubscript{max} (cm\textsuperscript{-1}): 3396 (OH), 1686 (CO), 1529 (C=N); \textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}) δ 2.83 (2H, t, J = 6.3 Hz, CH\textsubscript{2}CO), 4.43 (2H, t, J = 6.2 Hz, NCH\textsubscript{2}), 7.09–8.46 (11H, m, H\textsubscript{Ar}); \textsuperscript{13}C NMR (101 MHz, DMSO-d\textsubscript{6}) δ 37.71 (CH\textsubscript{2}CO), 48.84 (NCH\textsubscript{2}), 104.97, 111.76, 122.19, 122.62, 124.01, 124.39, 124.91, 126.10, 126.47, 127.60, 128.17, 128.20, 131.73, 132.58, 133.16, 138.32, 150.29, 153.65 (C\textsubscript{Ar}, C\textsubscript{Th}, C\textsubscript{chr}), 166.65 (C=N), 193.14 (C=O). Anal. Caled for C\textsubscript{22}H\textsubscript{16}N\textsubscript{2}O\textsubscript{3}S, C; 70.95; H, 4.33; N, 7.52. Found: %: C, 70.81; H, 4.29; N, 7.47.

3-[(5-Acetyl-4-methylthiazol-2-yl)(4-methoxyphenyl)amino]propanoic acid (15). A mixture of acid 1 (0.76 g, 3 mmol), 3-chloro-2,4-pentanedione (0.44 g, 3.3 mmol), and acetone (15 mL) was refluxed for 3 h. The precipitate was filtered off, washed with acetone, dried, and purified by dissolving it in 5% aqueous K\textsubscript{2}CO\textsubscript{3} solution (15 mL), filtering and acidifying the filtrate with acetic acid to pH 6 to afford white solid, yield 0.72 g (72%), mp 156–157 °C; IR (KBr) ν\textsubscript{max} (cm\textsuperscript{-1}): 1713 (CO), 1510 (C=N); \textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}) δ 2.29 (3H, s, CH\textsubscript{3}), 2.48 (3H, s, OCCH\textsubscript{3}), 2.56 (2H, t, J = 7.3 Hz, CH\textsubscript{2}CO), 3.80 (3H, s, OCH\textsubscript{3}), 4.09 (2H, t, J = 7.3 Hz, NCH\textsubscript{2}), 7.06 (2H, d, J = 8.9 Hz, H\textsubscript{Ar}), 7.34 (2H, d, J = 8.9 Hz, H\textsubscript{Ar}); \textsuperscript{13}C NMR (101 MHz, DMSO-d\textsubscript{6}) δ 18.66 (CH\textsubscript{3}), 29.66 (OCCH\textsubscript{3}), 32.32 (CH\textsubscript{2}CO), 48.07 (NCH\textsubscript{2}), 55.53 (OCH\textsubscript{3}), 115.55, 122.53, 129.01, 135.96, 157.71, 159.15 (C\textsubscript{Ar}, C\textsubscript{Th}), 171.24 (C=N), 172.48 (COOH), 188.83 (C=O). Anal. Caled for C\textsubscript{16}H\textsubscript{18}N\textsubscript{2}O\textsubscript{4}S, %: C, 57.47; H, 5.43; N, 8.38. Found, %: C, 57.40; H, 5.38; N, 8.35.

**General procedure for synthesis of chalcones 16a-f.** To a solution of corresponding aldehyde (3.0
mmol) in 10% aqueous NaOH solution (2 mL) a solution of 15 (1.0 g, 3 mmol) in MeOH (12 mL) was added dropwise, and the reaction mixture was kept at 0–3 °C for 1.5 h. Then it was stirred at room temperature for 24 h. The reaction mixture was diluted with water (20 mL) and acidified with dilute acetic acid (1:1) to pH 6. The precipitate was filtered off, washed with water, dried, and purified by dissolving it in 5% aqueous NaOH solution (15 mL), filtering and acidifying the filtrate with dilute acetic acid (1:1) to pH 6. 16b, d, e, f were additionally recrystallized from the indicated solvents.

3-[(5-[(2E)-3-Phenylprop-2-enoyl]-4-methyl-1,3-thiazol-2-yl](4-methoxyphenyl)amino]propanoic acid (16a) was prepared according to the general procedure from 15 and benzaldehyde to afford yellow solid, yield 0.66 g (52%), mp 186–187 °C; IR (KBr) \( \nu_{\text{max}} \) (cm\(^{-1}\)): 3407 (OH), 1713 (CO), 1510 (C=N); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \( \delta \) 2.54–2.65 (5H, m, CH\(_3\)+CH\(_2\)CO), 3.82 (3H, s, OCH\(_3\)), 4.14 (2H, t, \( J = 7.2 \) Hz, NCH\(_2\)), 7.08 (2H, d, \( J = 8.8 \) Hz, H\(_{Ar}\)), 7.20 (1H, d, \( J = 15.5 \) Hz, CO-CH=CH), 7.37–7.42 (5H, m, H\(_{Ar}\)), 7.53 (1H, d, \( J = 15.4 \) Hz, CO-C\(=\)H=C\(\)), 7.67–7.73 (2H, m, H\(_{Ar}\)), 12.35 (1H, br. s, COOH); \(^{13}\)C NMR (101 MHz, DMSO-\(d_6\)) \( \delta \) 19.05 (CH\(_3\)), 32.21 (CH\(_2\)CO), 48.19 (NCH\(_2\)), 55.42 (OCH\(_3\)), 115.48, 122.27, 124.65, 125.77, 127.96, 128.49, 133.79, 134.83, 141.56, 158.89, 159.09 (C\(_{Ar}\), C\(_{Th}\)), 171.39 (C=N), 172.30 (COOH), 180.27 (C=O). Anal. Calcd for C\(_{23}\)H\(_{22}\)N\(_2\)O\(_4\)S, %: C, 65.38; H, 5.25; N, 6.63. Found, %: C, 65.33; H, 5.20; N, 6.59.

3-[(5-[(2E)-3-(4-Bromophenyl)prop-2-enoyl]-4-methyl-1,3-thiazol-2-yl](4-methoxyphenyl)amino]propanoic acid (16b) was prepared according to the general procedure from 15 and 4-bromobenzaldehyde to afford yellow solid, yield 0.93 g (62%), mp 200–201 °C (MeOH). IR (KBr) \( \nu_{\text{max}} \) (cm\(^{-1}\)): 1716 (CO), 1511 (C=N); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \( \delta \) 2.53–2.69 (5H, m, CH\(_3\)+CH\(_2\)CO), 3.82 (3H, s, OCH\(_3\)), 4.13 (2H, t, \( J = 7.3 \) Hz, NCH\(_2\)), 7.08 (2H, d, \( J = 8.9 \) Hz, H\(_{Ar}\)), 7.22 (1H, d, \( J = 15.5 \) Hz, CO-CH=CH), 7.39 (2H, d, \( J = 8.8 \) Hz, H\(_{Ar}\)), 7.45 (2H, d, \( J = 8.5 \) Hz, H\(_{Ar}\)), 7.49 (1H, d, \( J = 15.4 \) Hz, CO-CH=CH), 7.58 (2H, d, \( J = 8.5 \) Hz, H\(_{Ar}\)), 12.34 (1H, br. s, COOH); \(^{13}\)C NMR (101 MHz, DMSO-\(d_6\)) \( \delta \) 19.06 (CH\(_3\)), 32.26 (CH\(_2\)CO), 48.23 (NCH\(_3\)), 55.43 (OCH\(_3\)), 115.49, 122.15, 123.56, 125.45, 128.89, 130.43, 133.79, 135.81, 140.20, 159.10, 159.17 (C\(_{Ar}\)), 171.39 (C=N), 172.33 (COOH), 180.06 (C=O). Anal. Calcd for C\(_{23}\)H\(_{21}\)BrN\(_2\)O\(_4\)S, %: C, 55.10; H, 4.22; N, 5.59. Found, %: C, 55.03; H, 4.19; N, 5.52.

3-[(5-[(2E)-3-(4-Chlorophenyl)prop-2-enoyl]-4-methyl-1,3-thiazol-2-yl](4-methoxyphenyl)amino]propanoic acid (16c) was prepared according to the general procedure from 15 and 4-chlorobenzaldehyde to afford yellow solid, yield 1.08 g (79%), mp 191–192 °C; IR (KBr) \( \nu_{\text{max}} \) (cm\(^{-1}\)): 3407 (OH), 1716 (CO), 1510 (C=N); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \( \delta \) 2.55–2.63 (5H, m, CH\(_3\)+CH\(_2\)CO), 3.82 (3H, s, OCH\(_3\)), 4.13 (2H, t, \( J = 7.3 \) Hz, NCH\(_2\)), 7.08 (2H, d, \( J = 8.9 \) Hz, H\(_{Ar}\)), 7.20 (1H, d, \( J = 15.5 \) Hz, CO-CH=CH), 7.39 (2H, d, \( J = 8.8 \) Hz, H\(_{Ar}\)), 7.45 (2H, d, \( J = 8.5 \) Hz, H\(_{Ar}\)), 7.51 (1H, d, \( J = 15.5 \) Hz,
CO-CH=CH), 7.75 (1H, d, J = 8.5 Hz, HAr), 12.41 (1H, br. s, COOH); 13C NMR (101 MHz, DMSO-d6) δ 19.06 (CH3), 32.29 (CH2CO), 48.25 (NCH2), 55.42 (OCH3), 115.48, 122.15, 125.40, 128.89, 130.21, 133.47, 134.71, 135.81, 140.10, 159.09, 159.14 (CAr, CTh), 171.47 (C=N), 172.35 (COOH), 180.06 (C=O).


3-[(5-{(2E)-3-(4-Fluorophenyl)prop-2-enoyl}-4-methyl-1,3-thiazol-2-yl)(4-methoxyphenyl)amino]propanoic acid (16d) was prepared according to the general procedure from 15 and 4-fluorobenzaldehyde to afford yellow solid, yield 1.19 g (90%), mp 185–186 °C (EtOH); IR (KBr) νmax (cm⁻¹): 3435 (OH), 1724 (CO), 1509 (C=N); 1H NMR (400 MHz, DMSO-d6) δ 2.57–2.61 (5H, m, CH3+CH2CO), 3.82 (3H, s, OCH3), 4.13 (2H, t, J = 7.3 Hz, NCH2), 7.08 (2H, d, J = 8.9 Hz, HAr), 7.15 (1H, d, J=15.4 Hz, CO-CH=CH); 7.22 (2H, t, J = 8.6 Hz, HAr); 7.39 (2H, d, J = 8.9 Hz, HAr); 7.53 (1H, d, J = 15.4 Hz, CO-CH=CH); 7.80 (2H, dd, J = 7.3, 5.8 Hz, HAr); 12.33 (1H, br. s, COOH); 13C NMR (101 MHz, DMSO-d6) δ 18.59 (CH3), 19.09 (CH3), 32.23 (CH2CO), 48.20 (NCH2), 55.45, 55.06 (OCH3), 115.51, 115.84, 115.96, 122.22, 124.56, 128.94, 130.87, 130.92, 131.18, 131.19, 135.84, 140.41, 158.99, 159.12, 162.51, 163.92 (CAr, CTh), 171.43 (C=N), 172.36 (COOH), 180.19 (C=O). Anal. Caled for C23H23ClN2O4S, %: C, 62.71; H, 4.81; N, 6.63. Found, %: C, 62.61; H, 4.75; N, 6.56.

3-[(5-{(2E)-3-Furanprop-2-enoyl}-4-methyl-1,3-thiazol-2-yl)(4-methoxyphenyl)amino]propanoic acid (16e) was prepared according to the general procedure from 15 and furan-2-carbaldehyde to afford brown solid, yield 0.49 g (40%), mp 149–150 °C (MeOH); IR (KBr) νmax (cm⁻¹): 1731 (CO), 1510 (C=N); 1H NMR (400 MHz, DMSO-d6) δ 2.54–2.63 (5H, m, CH3+CH2CO), 3.82 (3H, s, OCH3), 4.13 (2H, t, J = 7.3 Hz, NCH2), 6.63 (1H, s, CHFur), 6.87 (1H, d, J = 15.2 Hz, CO-CH=CH), 6.98 (1H, s, CHFur), 7.08 (2H, d, J = 8.3 Hz, HAr), 7.33–7.43 (3H, m, HAr+CO-CH=CH), 7.81 (1H, s, OCHFur), 12.10 (1H, br. s, COOH); 13C NMR (101 MHz, DMSO-d6) δ 18.90 (CH3), 30.61, 32.32 (CH2CO), 48.28 (NCH2), 55.42 (OCH3), 112.94, 115.48, 116.45, 121.40, 121.95, 128.24, 128.88, 135.82, 145.81, 150.85, 158.79, 159.10 (CAr, CTh, CThioph), 171.20 (C=N), 172.39 (COOH), 179.39 (C=O). Anal. Caled for C21H20N2O5S, %: C, 61.15; H, 4.89; N, 6.79. Found, %: C, 61.02; H, 4.80; N, 6.76.

3-(4-Methoxy[4-methyl-5-{(E)-3-(2-thienyl)-2-propenoyl}-1,3-thiazol-2-yl]anilino)propanoic acid (16f) was prepared according to the general procedure from 15 and 2-thiophencarboxaldehyde to afford yellow solid, yield 0.54 g (46%), mp 167–168 °C (MeOH); IR (KBr) νmax (cm⁻¹): 3436 (OH), 1713 (CO), 1504 (C=N); 1H NMR (400 MHz, DMSO-d6) δ 2.54–2.62 (5H, m, CH3+CH2CO), 3.82 (3H, s, OCH3), 4.13 (2H, t, J = 7.3 Hz, NCH2), 6.87 (1H, d, J = 15.2 Hz, CO-CH=CH), 7.08 (2H, d, J = 8.9 Hz, HAr), 7.13 (1H, dd, J = 4.8 Hz, J = 3.8 Hz, CHThioph), 7.39 (2H, d, J = 8.8 Hz, HAr), 7.55 (1H, d, J = 3.3 Hz, CO-CH=CH), 7.70 (2H, dd, J = 10.5 Hz, J = 5.0 Hz, CHThioph), 12.38 (1H, br. s, COOH); 13C NMR (101 MHz, DMSO-d6) δ 18.96 (CH3), 32.28 (CH2CO), 48.23 (NCH2), 55.42 (OCH3), 115.48, 122.10, 122.93,
128.69, 128.87, 129.67, 132.32, 134.39, 135.81, 139.49, 158.68, 159.09 (C\textsubscript{Ar}, C\textsubscript{Th}, C\textsubscript{Thioph}), 171.23 (C=N), 172.37 (COOH), 179.54 (C=O). Anal. Calcd for C\textsubscript{21}H\textsubscript{20}N\textsubscript{2}O\textsubscript{4}S\textsubscript{2}, %: C, 58.86; H, 4.70; N, 6.54. Found, %: C, 58.79; H, 4.67; N, 6.50.

3-[(5-(4-Chlorophenyl)-1\textsubscript{H}-pyrazol-3-yl)-4-methylthiazol-2-yl][4-methoxyphenyl]amino)propanoic acid (17). A mixture of chalcone 16c (0.46 g, 1 mmol), hydrazine monohydrate (0.15 g, 3 mmol), KOH (0.17 g, 3 mmol), and propan-2-ol (15 mL) was stirred at 70–80 °C for 24 h. The liquid fraction was evaporated under reduced pressure; the residue was dissolved in water and acidified with acetic acid to pH 6. The precipitate was filtered off, washed with water, dried, and recrystallized from propan-2-ol to afford white solid, yield 0.25 g (53%), mp 201–202 °C; IR (KBr) \( \nu_{\text{max}} \) (cm\(^{-1}\)): 3329 (OH), 3156 (NH), 1717 (CO), 1524, 1511 (C=N) ; \(^1\)H NMR (400 MHz, DMSO-\textsubscript{d}6) \( \delta \) 2.38 (3H, s, CH\textsubscript{3}), 2.60 (2H, t, \( J = 7.3 \) Hz, CH\textsubscript{2}CO), 3.80 (3H, s, OCH\textsubscript{3}), 4.06 (2H, t, \( J = 7.3 \) Hz, CH\textsubscript{2}CO), 6.81 (1H, s, NHCC\textsubscript{H}), 7.05 (2H, d, \( J = 8.9 \) Hz, H\textsubscript{Ar}), 7.35 (2H, d, \( J = 8.9 \) Hz, H\textsubscript{Ar}), 7.62 (2H, d, \( J = 8.5 \) Hz, H\textsubscript{Ar}), 7.75 (2H, d, \( J = 8.5 \) Hz, H\textsubscript{Ar}), 12.71 (2H, br. s, N\textsubscript{H}CCH and OH); \(^{13}\)C NMR (101 MHz, DMSO-\textsubscript{d}6) \( \delta \) 16.87 (CH\textsubscript{3}), 32.40 (CH\textsubscript{2}CO), 47.92 (NCH\textsubscript{2}), 55.38 (OCH\textsubscript{3}), 100.74, 115.25, 120.94, 125.15, 127.09, 127.14, 128.84, 129.09, 129.76, 131.75, 136.96, 145.22, 158.74 (C\textsubscript{Ar}, C\textsubscript{Th}, C\textsubscript{Pyr}), 167.25 (C=N), 172.59 (COOH). Anal. Calcd for C\textsubscript{23}H\textsubscript{21}ClN\textsubscript{4}O\textsubscript{3}S, %: C, 57.82; H, 4.85; N, 11.24. Found, %: C, 57.78; H, 4.81; N, 11.19.

3-[(5-(4-Chlorophenyl)isoxazol-3-yl)-4-methylthiazol-2-yl][4-methoxyphenyl]amino)propanoic acid (18). A mixture of chalcone 16c (0.46 g, 1 mmol), hydroxylamine hydrochloride (0.21 g, 3 mmol), and 1,4-dioxane (15 mL) was refluxed for 40 h. The liquid fraction was evaporated under reduced pressure. Then the residue was dissolved in 10% aqueous K\textsubscript{2}CO\textsubscript{3} solution and acidified with acetic acid to pH 6. The precipitate was filtered off, washed with water, dried, and recrystallized from propan-2-ol to afford yellow solid, yield 0.28 g (60%), mp 198–199 °C; IR (KBr) \( \nu_{\text{max}} \) (cm\(^{-1}\)): 3413 (OH), 1715 (CO), 1525, 1511 (2C=N); \(^1\)H NMR (400 MHz, DMSO-\textsubscript{d}6) \( \delta \) 2.47 (3H, s, CH\textsubscript{3}), 2.60 (2H, t, \( J = 7.3 \) Hz, CH\textsubscript{2}CO), 3.81 (3H, s, OCH\textsubscript{3}), 4.10 (2H, t, \( J = 7.3 \) Hz, CH\textsubscript{2}CO), 7.05 (1H, s, OCCH\textsubscript{3}), 7.08 (2H, d, \( J = 8.9 \) Hz, H\textsubscript{Ar}), 7.39 (2H, d, \( J = 8.9 \) Hz, H\textsubscript{Ar}), 7.56 (2H, d, \( J = 8.6 \) Hz, H\textsubscript{Ar}), 7.91 (2H, d, \( J = 8.6 \) Hz, H\textsubscript{Ar}), 12.36 (1H, br. s, OH); \(^{13}\)C NMR (101 MHz, DMSO-\textsubscript{d}6) \( \delta \) 17.33 (CH\textsubscript{3}), 32.31 (CH\textsubscript{2}CO), 48.19 (NCH\textsubscript{2}), 55.43 (OCH\textsubscript{3}), 97.16 (CH-C=N-O), 105.73, 115.46, 127.35, 128.41, 129.09, 129.12, 134.89, 136.20, 150.81, 159.01 (C\textsubscript{Ar}, C\textsubscript{Th}, C\textsubscript{Pyr}), 167.25 (C=N), 172.59 (COOH). Anal. Calcd for C\textsubscript{23}H\textsubscript{21}ClN\textsubscript{4}O\textsubscript{3}S, %: C, 57.82; H, 4.85; N, 11.24. Found, %: C, 57.78; H, 4.81; N, 11.19.

3-([5-(4-Chlorophenyl)-1-phenyl-4,5-dihydro-1\textsubscript{H}-pyrazol-3-yl]-4-methylthiazol-2-yl][4-methoxyphenyl]amino)propanoic acid (19). A mixture of chalcone 16c (0.46 g, 1 mmol), phenylhydrazine (0.13 g, 1.2 mmol), KOH (0.17 g, 3 mmol), and propan-2-ol (15 mL) was stirred at 70–80 °C for 6 h. The liquid fraction was evaporated under reduced pressure; the residue was dissolved in water and acidified with
acetic acid to pH 6. The precipitate was filtered off, washed with water, dried, and recrystallized from propan-2-ol to afford brown solid, yield 0.40 g (73%), mp 121–122 °C; IR (KBr) νmax (cm⁻¹): 3416 (OH), 1714 (CO), 1511 (C=N); ¹H NMR (400 MHz, DMSO-d₆) δ 2.31 (3H, s, CH₃), 2.50–2.58 (2H, m, CH₂CO), 2.97–3.07 (1H, m, CHCH₂), 3.81 (3H, s, OCH₃), 3.84–3.96 (1H, m, CHCH₂), 3.97–4.11 (2H, m, NCH₂), 5.29–5.39 (1H, t, J = 7.3 Hz, H₆), 6.76 (2H, d, J = 7.8 Hz, H₆), 7.06 (4H, dd, J = 12.5 Hz, H₆), 7.19 (2H, d, J = 8.5 Hz, H₆), 7.35 (2H, d, J = 8.9 Hz, H₆), 7.51 (2H, d, J = 8.4 Hz, H₆); ¹³C NMR (101 MHz, DMSO-d₆) δ 17.16 (CH₃), 32.73 (CH₂), 44.57 (CH₂), 48.20 (NCH₂), 55.37 (OCH₃), 62.62 (CH₂C₂H), 112.63, 113.30, 115.29, 118.22, 120.42, 128.22, 128.83, 129.05, 131.84, 136.59, 141.73, 142.98, 144.10, 148.91, 149.72 (C₆Ar, C₆Th, N=N=C), 158.72 (C₆Ar, C₆Th), 168.00 (C=N), 172.71 (COOH). Anal. Calcd for C₂₉H₂₇ClN₄O₃S, %: C, 63.67; H, 4.97; N, 10.24. Found, %: C, 63.61; H, 4.91; N, 10.21.

3-[(2-{[(E)-2-(2-phenylhydrazono)ethyl]-3-Hydroxy-3-oxopropyl}-4-methoxyanilino]-4-methyl-1,3-thiazol-5-yl]-ethylidene)hydrazono[ethyl]-4-methyl-1,3-thiazol-5-yl]-4-methoxyanilino|propanoic acid (20). A mixture of thiazole 15 (0.67 g, 2 mmol), hydrazine monohydrate (0.20 g, 4 mmol), MeOH (20 mL), and acetic acid (1 mL) was refluxed for 30 h. Then the reaction mixture was cooled down and diluted with water (25 mL). The precipitate was filtered off, washed with water, dried, and purified by dissolving it in 5% aqueous Na₂CO₃ solution (15 mL), filtering and acidifying the filtrate with dilute acetic acid (1:1) to pH 6 to afford yellow solid, yield 0.55 g (41%), mp 180–181 °C; IR (KBr) νmax (cm⁻¹): 1714 (CO), 1510 (C=N); ¹H NMR (400 MHz, DMSO-d₆) δ 2.20 (6H, s, 2CH₃), 2.41 (6H, s, 2CH₃-C=N), 2.53 (4H, t, J = 7.1 Hz, 2CH₂CO), 3.79 (6H, s, 2OCH₃), 4.03 (4H, t, J = 7.1 Hz, 2NCH₂), 7.03 (4H, d, J = 8.5 Hz, H₆), 7.32 (4H, d, J = 8.5 Hz, H₆), 12.34 (2H, br. s, OH); ¹³C NMR (101 MHz, DMSO-d₆) δ 16.20 (CH₃), 18.74 (CH₃-C=N), 32.49 (CH₂CO), 47.98 (NCH₂), 55.34 (OCH₃), 115.23, 121.47, 128.94, 136.49, 150.37, 153.11, 156.56, 158.63 (C₆Ar, C₆Th), 168.47 (C=N), 172.62 (COOH). Anal. Calcd for C₃₂H₃₆N₃O₃S₂, %: C, 57.81; H, 5.46; N, 12.64. Found, %: C, 57.72; H, 5.33; N, 12.57.

3-[4-Methoxy|4-methyl-5-{1-[2-phenylhydrazono|ethyl]-1,3-thiazol-2-yl}anilino|propanoic acid (21). A mixture of thiazole 15 (0.67 g, 2 mmol), phenylhydrazine (0.43 g, 4 mmol), MeOH (20 mL), and acetic acid (1 mL) was refluxed for 22 h. Then the reaction mixture was cooled down and diluted with water (25 mL). The precipitate was filtered off, washed with water, dried, and dissolved in 5% aqueous Na₂CO₃ solution (15 mL), filtering and acidifying the filtrate with dilute acetic acid (1:1) to pH 6. The precipitate was recrystallized from MeOH to afford brown solid, yield 0.29 g (35%), mp 171–172°C; IR (KBr) νmax (cm⁻¹): 3331 (NH), 1709 (C=O), 1510 (C=N); ¹H NMR (400 MHz, DMSO-d₆) δ 2.29, 2.39 (6H, 2s, 2CH₃), 2.56 (2H, s, CH₂CO), 3.80 (3H, s, OCH₃), 3.97–4.14 (2H, m, 2NCH₂), 6.60–7.45 (9H, m, H₆), 9.00 (1H, s, NH), 12.33 (1H, br. s, OH); ¹³C NMR (101 MHz, DMSO-d₆) δ 18.53 (CH₃), 29.55
(CH$_3$-C=N), 32.42 (CH$_2$O), 48.06 (NCH$_2$), 55.41 (OCH$_3$), 112.40, 115.19, 115.43, 118.41, 121.67, 128.81, 128.87, 128.91, 135.90, 136.93, 137.90, 144.86, 145.93, 157.53, 158.44, 159.02, 166.44 (C$_{Ar}$, C$_{Th}$), 171.07 (C=N), 172.62 (COOH). Anal. Calcd for C$_{22}$H$_{24}$N$_4$O$_3$S, %: C, 62.24; H, 5.70; N, 13.20. Found, %: C, 62.18; H, 5.66; N, 13.14.

**Microbiology**

**Antibacterial activity of the compounds.** Antibacterial activity was tested using the disk diffusion technique. The microorganisms *Rhizobium radiobacter*, *Escherichia coli*, *Xanthomonas campestris* were purchased from the German Collection of Microorganisms and Cell Cultures (DSMZ). The zone of the inhibition of bacterial growth was investigated. The main solution (1 mg/mL) of the synthesized compounds was prepared in DMSO and then diluted to various concentrations (50–1000 µg/mL) in DMSO. Cultures of *R. radiobacter*, *X. campestris*, *E. coli* were cultivated in Petri dishes for 24 h at 37 ºC on the Luria–Bertani (LB) agar medium. A bacterial suspension was prepared from cultivated bacterial cultures, and 50 µL of the inoculum containing bacterial cells (10$^8$ CFU/mL) was spread over the LB agar medium. Filter paper disks were prepared by adding 25 µL of each compound solution, and then the disks were put on the LB agar medium. Ampicillin was used as the positive control, and DMSO was used as the negative control. The Petri dishes were incubated for 24 h at 37 ºC, and the zones of inhibition were then ascertained for each sample.$^{34,35}$ Each experiment was repeated three times.

**DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging assay.** The free radical scavenging activity of compounds was measured by DPPH using the widely used method.$^{36}$ Briefly, 1 mM solution of DPPH in EtOH was prepared, and this solution (1 mL) was added to the solutions of the tested compounds (1 mg/mL of DMSO). The mixture was shaken vigorously and allowed to stand at room temperature for 20 min. Afterwards, the absorbance was measured at 517 nm with a UV-200-RS spectrophotometer (MRC Ltd., Israel). The lower absorbance of the reaction mixture indicated a higher free radical scavenging activity. The capability to scavenge the DPPH radical was calculated according to the following equation:

$$\text{DPPH scavenging effect (\%)} = \left( \frac{A_0 - A_1}{A_0} \right) \times 100,$$

where $A_0$ is the absorbance of the control reaction and $A_1$ is the absorbance in the presence of the compounds. Each experiment was repeated three times.

**Reducing power assay.** The solutions of the tested compounds (1000 µg/mL) were mixed with the phosphate buffer (2.5 mL, 0.2 mol/L, pH 6.6) and potassium ferricyanide [K$_3$Fe(CN)$_6$] (2.5 mL, 1%). The mixture was incubated at 50 ºC for 20 min 10% TCA was added to the mixture, which was then centrifuged at 3000 rpm for 10 min. The upper layer of the solution was mixed with distilled water (2.5
mL), FeCl₃ (0.5 mL, 0.1%), and the absorbance was measured at 700 nm. The increased absorbance of the reaction mixture indicated an increased reducing power. Each experiment was repeated three times.

**Ferric reducing antioxidant power assay (FRAP).** The principle of this method is based on the reduction of a ferric-tripyridyl triazine complex to its ferrous coloured form in the presence of antioxidants. Briefly, the FRAP reagent contained 2.5 mL of a 10 mmol/L TPTZ (2,4,6-tripyridyl-s-triazine) solution in 40 mmol/L HCL as well as 2.5 mL of FeCl₃ (20 mmol/L) and 25 mL of acetate buffer (0.3 mol/L, pH = 3.6). The aliquots of 100 μL tested compounds (1000 µg/mL) were mixed with 3 mL of the FRAP reagent, and the absorbance of the reaction mixture at 593 nm was measured spectrophotometrically after incubation at 37 ºC for 10 min. For comprising of the calibration curve, five concentrations of FeSO₄·7 H₂O (5, 10, 15, 20, and 25 μmol/L) were used, and the absorbancies were measured as a sample solution. Each experiment was repeated three times.

**Statistical analysis.** Differences between means were assessed by the Student’s t-test at P = 0.05. Values were expressed as mean ± SD.

**REFERENCES**