

New Aryl-1,3-thiazole-4-carbohydrazides, Their 1,3,4-Oxadiazole-2-thione, 1,2,4-Triazole, Isatin-3-ylidene and Carboxamide Derivatives. Synthesis and Anti-HIV Activity

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A series of isatin-3-ylidene (**6a–i**) and arylthiazolyl-1,3,4-oxadiazole-2-thione derivatives **7a–i** derived from arylthiazolyl carbohydrazide analogs **4a–i** were synthesized. Analogously, coupling of **4f** with various amino acid methyl esters in the presence of HOBt/DCC reagents afforded the carboxamide derivatives **9a–d**. The newly synthesized compounds were assayed against HIV-1 and HIV-2 in MT-4 cells. All compounds are inactive, except compounds **9b** and **9c** which showed inhibition of HIV-1 with $EC_{50} = 2.34 \mu\text{g mL}^{-1}$, and $1.12 \mu\text{g mL}^{-1}$ with therapeutic indexes (SI) of 9 and <1, respectively.

Key words: anti-HIV Activity, Amino Acids, Imine Derivatives, Oxadiazoles, Thiazoles

Introduction

Acquired immune deficiency syndrome (AIDS) is one of the major causes of death in many countries of the world. This viral disease is caused by the retrovirus HIV-1 (human immunodeficiency virus type-1), a retrovirus of the lentivirus family. Integrase, reverse transcriptase and protease (the three viral enzymes) play a prominent role in the virus replication cycle. The formation of proviral DNA from viral RNA is catalyzed by viral reverse transcriptase (RT) and is responsible for viral replication [1], hence it is the main target in contemporary drug discovery against HIV-1 [2]. Numerous classes of non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as nevirapine [3], delaviridine [4] and efavirenz (EFV) [5], carrying a heterocyclic backbone, have been approved for the treatment of HIV infection [6], due to their unique antiviral potency, high specificity and low toxicity [7, 8]. New types of NNRTIs are continuously being developed, for example some 2,5-disubstituted 1,3,4-oxadiazoles [9–11] and certain adamantane derivatives [12] have been re-

ported to show anti-HIV activity. In addition, the 1,3,4-oxadiazole ring is of significant interest due to its chemotherapeutic history [13–15].

A series of thiazolylthioureas has exhibited activity against two NNRTI resistant HIV-1 isolates [2]. Thiazolidene benzenesulfonamides have inhibited HIV-1 replication and exhibited potent activity against the WT and Y181C RT and to a lesser extent against the K103N RT [16]. Moreover, thiazoles serve as important pharmacodynamic nuclei, and their incorporation in different heterocyclic scaffolds results in varied biological activities such as antitumor [17], anticonvulsant [18], antimicrobial [19–22], anti-inflammatory [23], antiprotozoal [24], and antityrosinase [25]. Furthermore, some amino acid derivatives such as the lysyl amide prodrug of 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole [26], amino acid derivatives of paclitaxol [27], pyroglutamic acid [28], cysteine-modifying agents [29], and isoquinoline carboxylic acid derivatives [30] were reported as potential HIV protease inhibitors [31]. Recently, Al-Masoudi *et al.* [32–36] have reported the synthesis of various naphthalene, coumarin and sebacoyl derivatives bear-

ing amino acid moieties as potential anti-HIV candidates.

In the present study, we selected 2-aryl-1,3-thiazole-4-carbohydrazide intermediates, of which some analogs have been reported previously [37], for the synthesis of 1,3,4-oxadiazole-2-thiones, their 1,2,4-triazole, isatin-3-ylidene and carboxamide derivatives and for the evaluation of their anti-HIV activity.

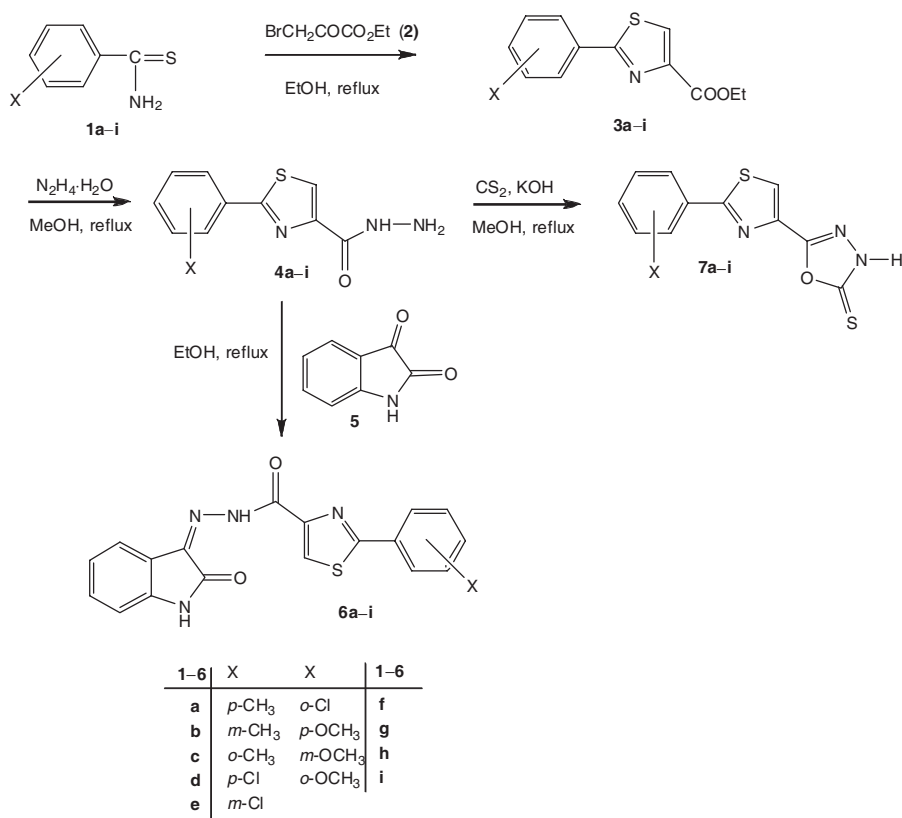
Results and Discussion

Synthesis

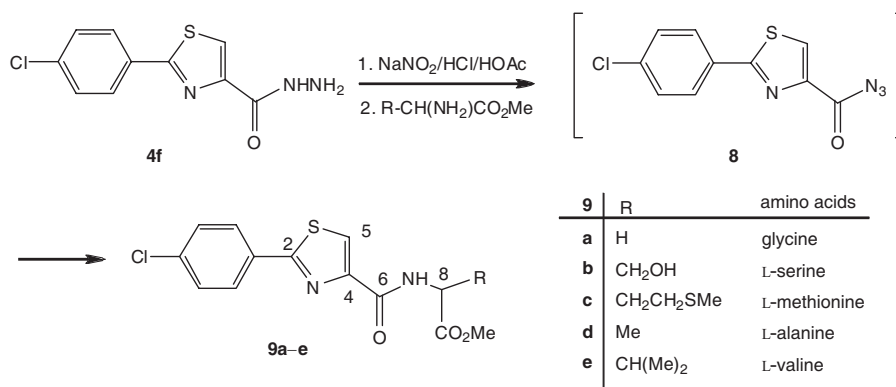
The synthesis of the target compounds was accomplished starting from arylthioamides **1a–i**, by treatment with ethyl bromopyruvate to give ethyl 2-aryl-1,3-thiazole-4-carboxylates **2a–i**, which were used directly without purification by treatment with hydrazine hydrate to furnish the corresponding carbohydrazide analogs **4a–i** in 68%–79% yield.

The carbohydrazides **4a–i** were used as common precursors for the synthesis of various potential analogs. Thus, treatment of **4a–i** with isatin (**5**) afforded the isatin-3-ylidene derivatives in 68%–74% yield. Analogously, reaction of **4a–i** with CS₂ in refluxing MeOH led to the cyclization of the carbohydrazide backbones, furnishing 5-(2-aryl-1,3-thiazol-4-yl)-1,3,4-oxadiazole-2-thione analogs **6a–i** (65%–75% yield). The reaction sequence is summarized in Scheme 1.

The structures of **4a–i**, **6a–i** and **7a–i** were assigned on the basis of IR, ¹H, ¹³C NMR and mass spectra. The IR spectra of **7a–i** showed strong absorptions in the range of 1241–1202 cm^{−1}, attributed to the C=S group. In the ¹H NMR spectra of **4a–i**, the singlets in the region δ = 8.09–8.42 ppm were attributed to 5-H of the thiazole backbone. Proton 5-H of the isatin-3-ylidene (**6a–i**) and oxadiazole (**7a–i**) derivatives appeared in the regions δ = 8.60–8.86 and 8.68–8.86 ppm with chemical shift differences of



Scheme 1. Synthesis of 2-aryl-1,3-thiazole-4-carbohydrazide, imino-isatin, 1,3-oxadiazole, and 4-amino-1,3,4-triazole-5-thione derivatives.



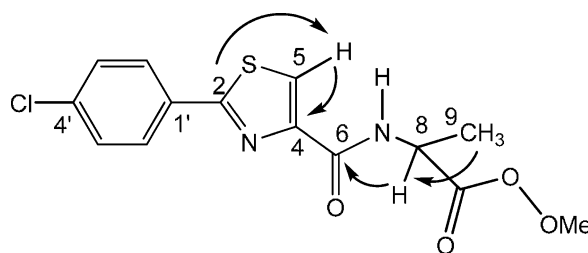
Scheme 2. Synthesis of alkyl 3-(4-chlorophenyl)thiazole-4-carboxamido-3-oxoalkanoate derivatives.

~ 0.45 and ~ 0.35 ppm, respectively, from those of carbohydrazides **4a–i**. The ¹³C NMR spectra of **4a–i**, **6a–i** and **7a–i** were assigned (*cf.* Experimental Section) based on the analysis made for **7f**. The spectrum showed a down-field signal at $\delta = 177.7$ ppm, attributed to the C=S group, which is indicative of **7f** existing predominantly in the thione form, as is also suggested by the IR and ¹H NMR spectra. The resonances at $\delta = 164.9$ and 156.9 ppm were assigned to C-4 and C-5 of the thiazole and oxadiazole residues, respectively. The signals at $\delta = 138.9$ and 137.6 ppm were assigned to C-4 and C-1 of the thiazole and the aromatic ring, respectively. The aromatic C(4)-Cl and C(2)-Cl carbon atoms gave signals at $\delta = 137.6$ and 131.4 ppm, respectively, and C-4, C-3, C-6, and C-2 appeared at $\delta = 131.1$, 130.6 , 128.9 , and 126.4 ppm, respectively.

Next, our target was the synthesis of new compounds having a thiazole backbone adjacent to an amino acid precursor *via* an amide linkage, aiming to evaluate their anti-HIV activity. The hydrazide **4f** was selected as starting material for the reaction with appropriate acylated amino acids, *via* the azide-coupling method. Thus, treatment of **4f** at -5°C in HOAc and 1 N HCl with NaNO₂, followed by the treatment of *in situ*-generated azide derivative **8** with the acylated amino acid derivatives (glycine, L-serine, L-methionine, L-alanine and L-valine acetates) in ethyl acetate containing Et₃N at 0°C gave, after neutralization, the desired carboxamides **9a–d** in 65%–77% yield (Scheme 2).

The structures of **9a–e** were assigned from their ¹H and ¹³C NMR, and mass spectra. The ¹H NMR spectra of **9a–e** showed a similar pattern of 1,3-

thiazole protons. The low-field broad singlets ($\delta = 9.95$ – 9.76 ppm) were assigned to NH signals, and the singlets in the range $\delta = 9.20$ – 9.09 ppm were assigned to 5-H of the thiazole backbone. The C-8 methylene protons of **9a** appeared as a doublet at $\delta = 4.19$ ppm ($J = 2.2$ Hz), whereas 8-H atoms of **9b–e** resonated as multiplets at $\delta = 4.36$, 4.39 , 4.29 , and 4.32 ppm, respectively. In the ¹³C NMR spectra of **9a–e**, the carbon atoms of the carboxylate groups resonated in the range $\delta = 173.2$ – 170.2 ppm, and C-2 and C-4 of the thiazole residues appeared in the ranges $\delta = 168.3$ – 167.1 and 150.1 – 148.7 ppm, respectively. The carbonyl groups adjacent to the thiazole precursor, C(6)=O, resonated at $\delta = 162.7$ – 160.9 ppm. The resonances at $\delta = 38.2$, 55.2 , 52.2 , 49.3 and 54.2 ppm were attributed to the C-8 atoms. The CH₂OH carbon signal of **9b** appeared at $\delta = 59.5$ ppm, while the CH₂S carbon atom of **9c** resonated at $\delta = 30.1$ ppm and the CH₂CH₂S carbon atom at $\delta = 32.2$ ppm. Compound **9d** was selected for further HMBC NMR studies [38]. A gradient-selected HMBC spectrum allowed the identification of C(4) and C(2) of the thiazole ring at $\delta = 167.7$ and 149.8 ppm, respectively, from the ²J_{C,H} and ³J_{C,H} correlations to 5-H of the thiazole

Fig. 1. $J_{\text{C,H}}$ correlations in the HMBC NMR spectrum of **9d**.

Entry	HIV-1 (III _B) EC ₅₀ (μg mL ⁻¹) ^c	HIV-2 (ROD) EC ₅₀ (μg mL ⁻¹) ^c	CC ₅₀ (μg mL ⁻¹) ^d	SI ^e (III _B)	SI ^e (ROD)
6a	> 84.85	> 84.85	84.85	< 1	< 1
6b	> 14.33	> 14.33	14.33	< 1	< 1
6c	> 14.82	> 14.82	14.82	< 1	< 1
6d	> 99.43	> 99.43	99.43	< 1	< 1
6e	> 119.33	> 119.33	119.33	< 1	< 1
6f	> 79.08	> 79.08	79.08	< 1	< 1
6g	> 111.0	> 111.0	111.0	< 1	< 1
6h	> 15.88	> 15.88	15.88	< 1	< 1
6i	> 92.10	> 92.10	92.10	< 1	< 1
7a	> 54.25	> 54.25	54.25	< 1	< 1
7b	> 52.20	> 52.20	52.20	< 1	< 1
7c	> 54.58	> 54.58	54.58	< 1	< 1
7d	> 51.28	> 51.28	51.28	< 1	< 1
7e	> 55.83	> 55.83	55.83	< 1	< 1
7f	> 57.03	> 57.03	57.03	< 1	< 1
7g	> 53.50	> 53.50	53.50	< 1	< 1
7h	> 52.80	> 52.80	52.80	< 1	< 1
7i	> 60.50	> 60.50	60.50	< 1	< 1
9a	> 23.10	> 23.10	23.10	< 1	< 1
9b	> 2.34	> 21.06	21.06	9	< 1
9c	> 1.12	> 1.12	1.12	< 1	< 1
9d	> 37.03	> 37.03	37.03	< 1	< 1
9e	> 29.82	> 29.82	29.82	< 1	< 1
Nevirapine	0.050	> 4.00	> 4.00	> 80	< 1
AZT	0.0022	0.00094	> 25	> 11 363	> 26 596

^a Anti-HIV-1 activity measured with strain III_B; ^b anti-HIV-2 activity measured with strain ROD; ^c compound concentration required to achieve 50% protection of MT-4 cells from the HIV-1 and 2-induced cytopathogenic effect; ^d compound concentration that reduces the viability of mock-infected MT-4 cells by 50%; ^e SI: selectivity index (CC₅₀/EC₅₀).

backbone at $\delta = 9.12$ ppm. Similarly, the CH₃ signal at $\delta = 19.6$ ppm and C-6 of the carbonyl group at $\delta = 162.7$ ppm were identified from their ²J_{C,H} and ³J_{C,H} correlations to 8-H at $\delta = 4.29$ ppm (Fig. 1). The mass fragmentation patterns were consistent with the suggested structures; however, the FAB-MS spectra showed the protonated molecular ions of these compounds.

In-vitro anti-HIV assay

Compounds **6a–i**, **7a–i** and **9a–e** were evaluated for their *in vitro* anti-HIV activity by using the III_B strain for HIV-1 and the ROD strain for HIV-2 in human T-lymphocyte (MT-4) cells. Cytotoxicity induced by these compounds was also measured in MT-4 cells parallel with the antiviral activity. The results are summarized in Table 1, in which the data for Nevirapine (BOE/BIRG587) [39] and azidothymidine (AZT) [40], are included for comparison. All the compounds are inactive except for **9a** and **9b** which showed EC₅₀ =

2.34 μg mL⁻¹ (SI = 9) and 1.12 μg mL⁻¹ (SI ≤ 1), respectively, for which the data can be discussed. However, none of our compounds approached the activity level of the reference compounds.

Compounds **9b** and **9c** are equipotent against HIV-1 and HIV-2 replication *in vitro* and, therefore, most probably they are no NNRTI's (Non-Nucleoside Reverse Transcriptase Inhibitors). The anti-HIV activity and the selectivity of these compounds are, however, too limited to perform extensive mode-of-action studies. The synthesis of new analogs of thiazolo-amino acid derivatives (carboxamide analogs **9b** and **9c**) may lead to the discovery of more potent and selective analogs that will allow the elucidation of their molecular mode-of-action.

Conclusion

In summary, *in vitro* anti-HIV screening led to the identification of the 1,3-thiazole backbone bearing amino acid derivatives **9b** and **9c** as new anti-HIV

Table 1. *In-vitro* anti-HIV-1^a and HIV-2^b activity and cytotoxicity of some new 1,3-thiazole derivatives.

candidates and promising agents for further structural modification and pharmacological evaluation.

Experimental Section

Melting points are uncorrected and were measured on a Gallenkamp melting point apparatus (MP-D). Microanalytical data were obtained with a Euro Vector EA 3000 Elemental apparatus. NMR spectra were recorded on a Bruker 300 MHz NMR spectrometer. The multiplicities are abbreviated as br s = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, at = apparent triplet, ddd = doublet of doublets, qn = quintet. IR spectra were recorded on a Shimadzu Fourier transform infrared spectrophotometer model 270, using the ATR facility. EI-MS spectra were recorded on an Agilent technologies 6890N (GC) mass spectrometer with an inert selective detector 5973. TLC plates 60 F₂₅₄ were purchased from Merck.

Synthesis of 2-phenyl-1,3-thiazole-4-carbohydrazides **4a–i**

A mixture of ethyl bromopyruvate (**2**) (1.5 mmol) and arylthioamide (1.5 mmol) in EtOH (25 mL) was refluxed for 8 h. After completion of the reaction (TLC), the mixture was concentrated, and water was added to the reaction mixture, followed by extraction with CH₂Cl₂ (3 × 50 mL). The combined organic extracts were dried (Na₂SO₄) and filtered, and the filtrate was evaporated to dryness. The crude esters **3a–i** were used for the synthesis of carbohydrazides **4a–i**, without further purification. To a solution of ethyl 2-aryl-1,3-thiazole-4-carboxylates **3a–i** (1.3 mmol) in MeOH (25 mL) was added slowly 80% hydrazine hydrate (2.6 mmol), and the reaction mixture was heated under reflux for 8–10 h. The progress of the reaction was monitored by TLC. After completion the mixture was concentrated *in vacuo*, followed by addition of cold water. The precipitated solid was filtered and recrystallized from aq. EtOH.

2-(4-Methylphenyl)-1,3-thiazole-4-carbohydrazide (**4a**)

Yield: 236 mg (78%), m. p. 181 °C. *R*_f = 0.69 (petroleum ether-acetone, 3 : 2). – IR (cm^{−1}): *v*_{max} = 3400, 3284 (2 × NH stretch.), 1655 (C=O stretch.), 1649 (C=N stretch.), 1557 (NH bend.). – ¹H NMR (CDCl₃): δ = 8.58 (1H, br s, NH), 8.09 (1H, s, 5-H_{thiazole}), 7.84 (2H, d, *J* = 7.8 Hz, 2-H_{arom} + 6-H_{arom}), 7.28 (2H, d, *J* = 8.1 Hz, 3-H_{arom} + 5-H_{arom}), 4.14 (2H, s, NH₂), 2.42 (3H, s, CH₃). – ¹³C NMR (CDCl₃): δ = 168.7 (C_{thiazole}-2), 161.9 (C=O), 148.8 (C_{thiazole}-4), 141.1 (C_{arom}-1), 130.0 (C_{arom}), 129.7 (C_{thiazole}-5), 126.5, 123.1 (C_{arom}), 21.5 (CH₃). – MS (EI): *m/z* = 233 [M]⁺. – C₁₁H₁₁N₃OS (233.29): calcd. C 56.63, H 4.75, N 18.01; found C 56.42, H 4.64, N 17.79.

2-(3-Methylphenyl)-1,3-thiazole-4-carbohydrazide (**4b**)

Yield: 265 mg (74%), m. p. 127 °C. *R*_f = 0.64 (petroleum ether-acetone, 3 : 2). – IR (cm^{−1}): *v*_{max} = 3299, 3207 (2 × NH stretch.), 1670 (C=O stretch.), 1624 (C=N stretch.), 1557 (NH bend.). – ¹H NMR (CDCl₃): δ = 9.77 (1H, br s, NH), 8.26 (1H, s, 5-H_{thiazole}), 7.91 (1H, s, 2-H_{arom}), 7.85 (1H, d, *J* = 7.5 Hz, 6-H_{arom}), 7.40 (1H, t, *J* = 7.7 Hz, 5-H_{arom}), 7.33 (1H, d, *J* = 7.5 Hz, 4-H_{arom}), 4.58 (2H, s, NH₂), 2.39 (3H, s, CH₃). – ¹³C NMR (CDCl₃): δ = 167.7 (C=O), 160.3 (C_{thiazole}-4), 150.0 (C_{thiazole}-2), 139.0 (C_{arom}-3), 131.8 (C_{thiazole}-5), 124.1, 123.6 (C_{arom}), 21.3 (CH₃). – MS (EI): *m/z* = 233 [M]⁺. – C₁₁H₁₁N₃OS (233.29): calcd. C 56.63, H 4.75, N 18.01; found C 56.39, H 4.62, N 18.21.

2-(2-Methylphenyl)-1,3-thiazole-4-carbohydrazide (**4c**)

Yield: 256 mg (72%), m. p. 151 °C. *R*_f = 0.67 (petroleum ether-acetone, 3 : 2). – IR (cm^{−1}): *v*_{max} = 3424, 3315 (2 × NH stretch.), 1681 (C=O stretch.), 1633 (C=N stretch.), 1524 (NH bend.). – ¹H NMR (CDCl₃): δ = 8.52 (1H, br s, -NH), 8.19 (1H, s, 5-H_{thiazole}), 7.70 (1H, d, *J* = 7.8 Hz, 6-H_{arom}), 7.70 (3H, m, 3-H_{arom} + 4-H_{arom} + 5-H_{arom}), 4.14 (2H, s, NH₂), 2.60 (3H, s, CH₃). – ¹³C NMR (CDCl₃): δ = 168.4 (C=O), 161.9 (C_{thiazole}-4), 148.4 (C_{thiazole}-2), 136.6 (C_{arom}-2 + C_{arom}-1), 131.7 (C_{thiazole}-5), 131.8, 130.1, 129.9, 126.3 (C_{arom}), 21.6 (CH₃). – MS (EI): *m/z* = 233 [M]⁺. – C₁₁H₁₁N₃OS (233.29): calcd. C 56.63, H 4.75, N 18.01; found C 56.77, H 4.69, N 17.80.

2-(4-Chlorophenyl)-1,3-thiazole-4-carbohydrazide (**4d**)

Yield: 277 mg (72%), m. p. 169 °C. *R*_f = 0.59 (petroleum ether-acetone, 3 : 2). – IR (cm^{−1}): *v*_{max} = 3444, 3243 (2 × NH stretch.), 1653 (C=O stretch.), 1614 (C=N stretch.), 1538 (N-H bend.), 1087 (C-Cl stretch.). – ¹H NMR (CDCl₃): δ = 9.82 (1H, br s, NH), 8.30 (1H, s, 5-H_{thiazole}), 8.09 (2H, d, *J* = 8.7 Hz, 2-H_{arom} + 6-H_{arom}), 7.60 (2H, d, *J* = 8.4 Hz, 3-H_{arom} + 5-H_{arom}), 4.58 (2H, s, NH₂). – ¹³C NMR (CDCl₃): δ = 166.2 (C_{thiazole}-4), 160.2 (C=O), 150.1 (C_{thiazole}-2), 135.7 (C_{arom}-Cl), 131.7, 129.7 (C_{arom}), 128.6 (C_{thiazole}-5). – MS (EI): *m/z* = 252/254 [M]⁺. – C₁₀H₈ClN₃OS (253.71): calcd. C 47.34, H 3.18, N 16.56; found C 47.02, H 3.04, N 16.37.

2-(3-Chlorophenyl)-1,3-thiazole-4-carbohydrazide (**4e**)

Yield: 296 mg (70%), m. p. 146 °C. *R*_f = 0.69 (petroleum ether-acetone, 3 : 2). – IR (cm^{−1}): *v*_{max} = 3414, 3314 (2 × NH stretch.), 1654 (C=O stretch.), 1614 (C=N stretch.), 1525 (NH bend.), 1084 (C-Cl stretch.). – ¹H NMR (CDCl₃): δ = 9.92 (1H, br s, N-H), 8.32 (1H, s, 5-H_{thiazole}), 8.25 (1H, s, 2-H_{arom}), 7.97 (1H, at, *J* = 5.1 Hz, 5-H_{arom}), 7.56 (2H, t, *J* = 7.8 Hz, 4-H_{arom} + 6-H_{arom}), 4.62 (2H, s, NH₂). – ¹³C NMR (CDCl₃): δ = 165.7 (C_{thiazole}-2), 160.1

(C=O), 150.1 (C_{thiazole}-4), 134.8 (C_{arom}-Cl), 131.6 (C_{arom}-1), 130.8 (C_{thiazole}-5), 126.3, 125.7 (C_{arom}). – MS (EI): $m/z = 252/254$ [M]⁺. – C₁₀H₈ClN₃OS (253.71): calcd. C 47.34, H 3.18, N 16.56; found C 47.08, H 3.07, N 16.29.

2-(2-Chlorophenyl)-1,3-thiazole-4-carbohydrazide (4f)

Yield: 220 mg (67%), m. p. 158 °C. $R_f = 0.68$ (petroleum ether-acetone, 3 : 2). – IR (cm⁻¹): $\nu_{\max} = 3423, 3318$ (2 × NH stretch.), 1678 (C=O stretch.), 1631 (C=N stretch.), 1524 (NH bend.), 1089 (C-Cl stretch.). – ¹H NMR (CDCl₃): $\delta = 9.88$ (1H, br s, NH), 8.54 (1H, m, 6-H_{arom}), 8.31 (1H, s, 5-H_{thiazole}), 7.67 (1H, m, 4-H_{arom}), 7.55 (2H, m, 3-H_{arom} + 5-H_{arom}), 4.59 (2H, s, NH₂). – ¹³C NMR (CDCl₃): $\delta = 162.7$ (C_{thiazole}-2), 160.2 (C=O), 148.9 (C_{thiazole}-4), 135.2 (C_{arom}-1), 132.1 (C_{arom}-Cl), 131.6, 131.0 (C_{arom}), 128.1 (C_{thiazole}-5), 125.3 (C_{arom}). – MS (EI): $m/z = 252/254$ [M]⁺. – C₁₀H₈ClN₃OS (253.71): calcd. C 47.34, H 3.18, N 16.56; found C 46.98, H 3.02, N 15.27.

2-(4-Methoxyphenyl)-1,3-thiazole-4-carbohydrazide (4g)

Yield: 237 mg (73%), m. p. 161 °C. $R_f = 0.67$ (petroleum ether-acetone, 3 : 2). – IR (cm⁻¹): $\nu_{\max} = 3448, 3307$ (2 × NH stretch.), 1663 (C=O stretch.), 1610 (C=N stretch.), 1522 (NH bend.). – ¹H NMR (CDCl₃): $\delta = 9.72$ (1H, br s, N-H), 8.17 (1H, s, 5-H_{thiazole}), 8.01 (2H, d, $J = 8.7$ Hz, 2-H_{arom} + 6-H_{arom}), 7.08 (2H, d, $J = 8.7$ Hz, 3-H_{arom} + 5-H_{arom}), 4.56 (2H, s, NH₂), 3.83 (3H, s, OCH₃). – ¹³C NMR (CDCl₃): $\delta = 167.5$ (C_{thiazole}-4), 161.6 (C=O), 160.3 (C_{arom}-OMe), 149.8 (C_{thiazole}-2), 128.5 (C_{arom}-2 + C_{arom}-6), 127.6 (C_{thiazole}-5), 115.1 (C_{arom}-3 + C_{arom}-5), 55.9 (OCH₃). – MS (EI): $m/z = 249$ [M]⁺. – C₁₁H₁₁N₃O₂S (249.29): calcd. C 53.00, H 4.45, N 16.86; found C 53.19, H 4.28, N 16.64.

2-(3-Methoxyphenyl)-1,3-thiazole-4-carbohydrazide (4h)

Yield: 250 mg (77%), m. p. 125 °C. $R_f = 0.63$ (petroleum ether-acetone, 3 : 2). – IR (cm⁻¹): $\nu_{\max} = 3422, 3316$ (2 × NH stretch.), 1654 (C=O stretch.), 1624 (C=N stretch.), 1527 (NH bend.). – ¹H NMR (CDCl₃): $\delta = 9.85$ (1H, br s, NH), 8.28 (1H, s, 5-H_{thiazole}), 7.71 (1H, at, $J = 2.4$ Hz, 2-H_{arom}), 7.58 (1H, d, $J = 7.5$ Hz, 6-H_{arom}), 7.44 (1H, t, $J = 7.8$ Hz, 5-H_{arom}), 7.09 (1H, dd, $J = 2.1, 7.8$ Hz, 4-H_{arom}), 4.59 (2H, s, NH₂), 3.85 (3H, s, OCH₃). – ¹³C NMR (CDCl₃): $\delta = 167.3$ (C_{thiazole}-2), 160.3 (C=O + C_{arom}-3), 150.0 (C_{thiazole}-4), 134.2 (C_{arom}-1), 130.8 (C_{arom}-5), 128.2 (C_{thiazole}-5), 124.2 (C_{arom}-6), 117.2 (C_{arom}-4), 111.4 (C_{arom}-2), 56.2 (OCH₃). – MS (EI): $m/z = 249$ [M]⁺. – C₁₁H₁₁N₃O₂S (249.29): calcd. C 53.00, H 4.45, N 16.86; found C 53.19, H 4.28, N 16.64.

2-(2-Methoxyphenyl)-1,3-thiazole-4-carbohydrazide (4i)

Yield: 230 mg (71%), m. p. 208 °C. $R_f = 0.55$ (petroleum ether-acetone, 3 : 2). – IR (KBr, cm⁻¹): $\nu_{\max} = 3406, 3310$ (2 × NH stretch.), 1681 (C=O stretch.), 1644 (C=N

stretch.), 1531 (NH bend.). – ¹H NMR (CDCl₃): $\delta = 9.81$ (1H, br s, N-H), 8.26 (1H, s, 5-H_{thiazole}), 8.54 (1H, dd, $J = 1.8, 8.1$ Hz, 6-H_{arom}), 7.49 (1H, m, 4-H_{arom}), 7.24 (1H, d, $J = 8.1$ Hz, Ar-H₃), 7.12 (1H, qn, $J = 7.8$ Hz, 5-H_{arom}), 4.57 (2H, s, NH₂), 4.03 (3H, s, OCH₃). – ¹³C NMR (CDCl₃): $\delta = 161.7$ (C_{thiazole}-2), 160.6 (C=O), 156.6 (C_{arom}-2), 148.3 (C_{thiazole}-4), 132.0 (C_{arom}-4), 128.8 (C_{arom}-6), 128.7 (C_{thiazole}-5), 124.1 (C_{arom}-1), 121.3 (C_{arom}-5), 112.6 (C_{arom}-3), 56.3 (OCH₃). – MS (EI): $m/z = 249$ [M]⁺. – C₁₁H₁₁N₃O₂S (249.29): calcd. C 53.00, H 4.45, N 16.86; found C 52.86, H 4.36, N 16.66.

Synthesis of N'-(2-oxoindolin-3-ylidene)-2-aryl-1,3-thiazole-4-carbohydrazides 6a–i

Compound **4** (1.0 mmol) and isatin (**5**) (1.0 mmol) were dissolved in warm EtOH (25 mL) containing glacial HOAc (0.5 mL). The reaction mixture was refluxed for 6–8 h. On completion of the reaction (TLC), excess solvent was removed under reduced pressure, and the precipitate obtained on cooling was collected by filtration and recrystallized from a DMF-water mixture.

N'-(2-Oxoindolin-3-ylidene)-2-(4-methylphenyl)-1,3-thiazole-4-carbohydrazide (6a)

From **4a** (233 mg). Yield: 268 mg (74%), m. p. 315 °C. $R_f = 0.67$ (CHCl₃-MeOH, 3 : 2). – IR (cm⁻¹): $\nu_{\max} = 3254$ (NH stretch.), 1685 (C=O stretch.), 1621 (C=N stretch.), 1585 (NH bend.). – ¹H NMR ([D₆]DMSO): $\delta = 14.52$ (1H, br s, NH), 11.24 (1H, br s, NH), 8.63 (1H, s, 5-H_{thiazole}), 7.98 (1H, d, $J = 7.8$ Hz, 2-H_{arom} + 6-H_{arom}), 7.63 (1H, d, $J = 7.5$ Hz, 16-H_{arom}), 7.42 (3H, t, $J = 7.8$ Hz, 3-H_{arom} + 5-H_{arom} + 15-H_{arom}), 7.13 (1H, t, $J = 7.5$ Hz, 14-H_{arom}), 6.98 (1H, d, $J = 7.8$ Hz, 13-H_{arom}), 2.38 (3H, s, CH₃). – ¹³C NMR ([D₆]DMSO): $\delta = 168.5$ (C_{thiazole}-2), 163.2 (C_{isatin}=O), 157.5 (C_{carbohydr}=O), 148.5 (C_{thiazole}-4), 143.2 (C_{isatin}-7a), 141.6 (C_{arom}-1), 139.0 (C_{isatin}-3), 132.4 (Me-C_{arom}-1 + C_{isatin}-6), 129.8 (C_{isatin}-4 + C_{arom}), 127.4 (C_{thiazole}-5 + C_{arom}), 123.0 (C_{arom}), 121.5 (C_{isatin}-7), 118.2 (C_{isatin}-3a), 21.5 (Me-C_{arom}-4). – MS (EI): $m/z = 362$ [M]⁺. – C₁₉H₁₄N₄O₂S (362.41): calcd. C 62.97, H 3.89, N 15.46; found C 62.72, H 3.79, N 15.21.

N'-(2-Oxoindolin-3-ylidene)-2-(3-methylphenyl)-1,3-thiazole-4-carbohydrazide (6b)

From **4b** (233 mg). Yield: 261 mg (72%), m. p. 328 °C. $R_f = 0.58$ (CHCl₃-MeOH, 3 : 2). – IR (cm⁻¹): $\nu_{\max} = 3348$ (N-H stretch.), 1694 (C=O stretch.), 1615 (C=N stretch.), 1520 (NH bend.). – ¹H NMR ([D₆]DMSO): $\delta = 14.52$ (1H, br s, NH), 10.90 (1H, br s, NH), 8.70 (1H, s, 5-H_{thiazole}), 6.97 (1H, t, $J = 7.8$ Hz, 4-H_{arom}), 7.14 (1H, m, 14-H_{arom}), 7.44 (3H, m, 2-H_{arom} + 4-H_{arom} + 13-H_{arom}),

7.99 (3H, m, 5-H_{arom} + 15-H_{arom} + 16-H_{arom}), 2.41 (3H, s, CH₃). – ¹³C NMR ([D₆]DMSO): δ = 167.1 (C_{thiazole}-2), 164.1 (C_{isatin}=O), 156.9 (C_{carbohydr}=O), 148.5 (C_{thiazole}-4), 143.1 (C_{isatin}-7a), 139.3 (Me-C_{arom}-3), 138.4 (C_{isatin}-3), 132.4 (C_{isatin}-5), 129.8 (C_{arom}-1 + C_{arom}), 127.6 (C_{thiazole}-5 + C_{arom}), 125.6 (C_{isatin}-5), 121.5 (C_{isatin}-7), 120.4 (C_{isatin}-3a), 21.4 (Me-C_{arom}-4). – MS (EI): *m/z* = 362 [M]⁺. – C₁₉H₁₄N₄O₂S (362.41): calcd. C 62.97, H 3.89, N 15.46; found C 62.75, H 3.72, N 15.59.

N'-(2-Oxoindolin-3-ylidene)-2-(2-methylphenyl)-1,3-thiazole-4-carbohydrazide (**6c**)

From **4c** (233 mg). Yield: 250 mg (69%), m. p. 283 °C. *R*_f = 0.64 (CHCl₃-MeOH, 3 : 2). – IR (cm⁻¹): ν_{max} = 3250 (N-H stretch.), 1694 (C=O stretch.), 1620 (C=N stretch.), 1557 (NH bend.). – ¹H NMR ([D₆]DMSO): δ = 14.41 (1H, br s, NH), 11.25 (1H, br s, NH), 8.74 (1H, s, 5-H_{thiazole}), 6.96 (1H, d, *J* = 7.8 Hz, 13-H_{arom}), 7.13 (1H, t, *J* = 7.5 Hz, 14-H_{arom}), 7.43 (4H, m, 4-H_{arom} + 5-H_{arom} + 6-H_{arom} + 15-H_{arom}), 7.63 (1H, d, *J* = 7.5 Hz, 3-H_{arom}), 7.87 (1H, d, *J* = 7.5 Hz, 16-H_{arom}), 2.71 (3H, s, CH₃). – ¹³C NMR ([D₆]DMSO): δ = 168.5 (C_{thiazole}-2), 163.1 (C_{isatin}=O), 157.7 (C_{carbohydr}=O), 148.3 (C_{thiazole}-4), 143.1 (C_{isatin}-7a), 138.9 (C_{arom}-1 + Me-C_{arom}-1), 137.0 (C_{isatin}=N), 132.3 (C_{isatin}-5), 131.6 (C_{isatin}-6), 130.8, 130.3, 128.1 (C_{arom} + C_{isatin}), 127.0 (C_{thiazole}-5), 120.9 (C_{isatin}-7), 120.4 (C_{isatin}-3a), 22.0 (Me-C_{arom}-4). – MS (EI): *m/z* = 362 [M]⁺. – C₁₉H₁₄N₄O₂S (362.41): calcd. C 62.97, H 3.89, N 15.46; found C 62.72, H 3.79, N 15.21.

N'-(2-Oxoindolin-3-ylidene)-2-(4-chlorophenyl)-1,3-thiazole-4-carbohydrazide (**6d**)

From **4d** (253 mg). Yield: 279 mg (73%), m. p. 341 °C. *R*_f = 0.59 (CHCl₃-MeOH, 3 : 2). – IR (cm⁻¹): ν_{max} = 3200 (NH stretch.), 1685 (C=O stretch.), 1619 (C=N stretch.), 1091 (C-Cl stretch.), 1521 (NH bend.). – ¹H NMR ([D₆]DMSO): δ = 14.48 (1H, br s, NH), 11.63 (1H, br s, NH), 8.70 (1H, s, 5-H_{thiazole}), 8.06 (2H, m, 2-H_{arom} + 6-H_{arom}), 7.67 (2H, dd, *J* = 10.5, 7.5 Hz, 3-H_{arom} + 5-H_{arom}), 7.47 (1H, m, 15-H_{arom}), 7.25 (1H, t, *J* = 7.2 Hz, 16-H_{arom}), 7.12 (1H, t, *J* = 7.2 Hz, 14-H_{arom}), 6.96 (1H, d, *J* = 6.0 Hz, 13-H_{arom}). – ¹³C NMR ([D₆]DMSO): δ = 167.1 (C_{thiazole}-2), 164.9 (C_{isatin}=O), 162.8 (C_{carbohydr}=O), 148.6 (C_{thiazole}-4), 144.4 (C_{arom}-1), 141.8 (C_{isatin}-7a), 136.2 (C_{isatin}=N), 133.6 (C_{arom}-4), 131.3 (C_{isatin}-6), 130.0 (C_{isatin}-4), 129.5 (C_{arom}-3 + C_{arom}-5), 128.1 (C_{arom}-2 + C_{arom}-6), 125.8 (C_{isatin}-5), 127.2 (C_{thiazole}-5), 122.7 (C_{isatin}-7), 116.0 (C_{isatin}-3a). – MS (EI): *m/z* = 381/383 [M]⁺. – C₁₈H₁₁ClN₄O₂S (382.82): calcd. C 56.47, H 2.90, N 14.64; found C 56.19, H 2.81, N 14.44.

N'-(2-Oxoindolin-3-ylidene)-2-(3-chlorophenyl)-1,3-thiazole-4-carbohydrazide (**6e**)

From **4e** (253 mg). Yield: 268 mg (70%), m. p. 326 °C. *R*_f = 0.55 (CHCl₃-MeOH, 3 : 2). – IR (cm⁻¹): ν_{max} = 3276 (NH stretch.), 1683 (C=O stretch.), 1622 (C=N stretch.), 1570 (NH bend.), 1099 (C-Cl stretch.). – ¹H NMR ([D₆]DMSO): δ = 14.55 (1H, br s, NH), 11.31 (1H, br s, NH), 8.76 (1H, s, 5-H_{thiazole}), 8.19 (1H, d, *J* = 1.6 Hz, 2-H_{arom}), 8.03 (1H, m, 6-H_{arom}), 7.64 (1H, d, *J* = 5.1 Hz, 16-H_{arom}), 7.60 (1H, d, *J* = 8.1 Hz, 13-H_{arom}), 7.51 (1H, t, *J* = 7.5 Hz, 15-H_{arom}), 7.43 (1H, t, *J* = 7.8 Hz, 14-H_{arom}), 7.14 (1H, m, 5-H_{arom}), 6.97 (1H, t, *J* = 7.5 Hz, 4-H_{arom}). – ¹³C NMR ([D₆]DMSO): δ = 166.5 (C_{thiazole}-2), 163.2 (C_{isatin}=O), 157.3 (C_{carbohydr}=O), 148.6 (C_{thiazole}-4), 142.0 (C_{isatin}-7a), 139.1 (C_{arom}-3), 136.0 (C_{isatin}=N), 134.6 (C_{arom}-1), 132.3 (C_{isatin}-4), 130.6 (C_{isatin}-6), 127.0 (C_{thiazole}-5), 126.1, 125.6, 123.1 (C_{arom} + C_{isatin}), 122.2 (C_{isatin}-7), 116.2 (C_{isatin}-3a). – MS (EI): *m/z* = 381/383 [M]⁺. – C₁₈H₁₁ClN₄O₂S (382.82): calcd. C 56.47, H 2.90, N 14.64; found C 56.19, H 2.81, N 14.44.

N'-(2-Oxoindolin-3-ylidene)-2-(2-chlorophenyl)-1,3-thiazole-4-carbohydrazide (**6f**)

From **4f** (253 mg). Yield: 264 mg (69%), m. p. 315 °C. *R*_f = 0.56 (CHCl₃-MeOH, 3 : 2). – IR (cm⁻¹): ν_{max} = 3352 (NH stretch.), 1650 (C=O stretch.), 1619 (C=N stretch.), 1588 (NH bend.), 1085 (C-Cl stretch.). – ¹H NMR ([D₆]DMSO): δ = 11.73 (1H, br s, NH), 10.91 (1H, br s, NH), 8.86 (1H, s, 5-H_{thiazole}), 8.36 (1H, d, *J* = 6.6 Hz, 16-H_{arom}), 7.96 (1H, d, *J* = 7.2 Hz, 15-H_{arom}), 7.72 (4H, t, *J* = 7.2 Hz, 3-H_{arom} + 4-H_{arom} + 5-H_{arom} + 6-H_{arom}), 7.14 (1H, t, *J* = 7.5 Hz, 14-H_{arom}), 6.98 (1H, d, *J* = 7.5 Hz, 13-H_{arom}). – ¹³C NMR ([D₆]DMSO): δ = 166.0 (C_{thiazole}-2), 163.2 (C_{isatin}=O), 156.1 (C_{carbohydr}=O), 147.5 (C_{thiazole}-4), 144.5 (C_{isatin}-7a), 143.1 (C_{arom}-1), 135.0 (C_{isatin}=N), 133.7 (C_{arom}-2), 132.6 (C_{isatin}-6), 131.6 (C_{arom}-4), 131.5 (C_{isatin}-6), 129.2 (C_{arom}), 127.4 (C_{thiazole}-5), 126.8, 125.0, 123.1, 122.4 (C_{arom} + C_{isatin}), 121.6 (C_{isatin}-7), 116.0 (C_{isatin}-3a). – MS (EI): *m/z* = 381/383 [M]⁺. – C₁₈H₁₁ClN₄O₂S (382.82): calcd. C 56.47, H 2.90, N 14.64; found C 56.19, H 2.77, N 14.43.

N'-(2-Oxoindolin-3-ylidene)-2-(4-methoxyphenyl)-1,3-thiazole-4-carbohydrazide (**6g**)

From **4g** (249 mg). Yield: 268 mg (71%), m. p. 320 °C. *R*_f = 0.68 (CHCl₃-MeOH, 3 : 2). – IR (cm⁻¹): ν_{max} = 3345 (NH stretch.), 1693 (C=O stretch.), 1608 (C=N stretch.), 1574 (NH bend.), 1159 (C-O stretch.). – ¹H NMR ([D₆]DMSO): δ = 14.50 (1H, br s, NH), 11.66 (1H, br s, NH), 8.60 (1H, s, 5-H_{thiazole}), 8.02 (2H, m, 2-H_{arom} + 6-H_{arom}), 7.62 (1H, d, *J* = 7.5 Hz, 16-H_{arom}), 7.47 (1H,

m, 15-H₁₅), 7.13 (3H, m, 4-H_{arom} + 5-H_{arom} + 6-H_{arom} + 15-H_{arom} Ar-H_{3,5,14}), 6.99 (1H, d, $J = 7.8$ Hz, Ar-H_{arom}), 3.84 (3H, s, OCH₃). – ¹³C NMR ([D₆]DMSO): $\delta = 168.0$ (C_{thiazole}-2), 163.2 (C_{isatin}=O), 160.2 (OMe-C_{arom}-4), 157.4 (C_{carbohydr}=O), 148.4 (C_{thiazole}-4), 143.1 (C_{isatin}-7a), 139.0 (C_{arom}-1), 133.6 (C_{isatin}=N), 132.3 (C_{isatin}-6), 131.1, 129.4, 128.3 (C_{arom}), 127.8 (C_{thiazole}-5), 123.1 (C_{arom} + C_{isatin}), 121.5 (C_{isatin}-7), 119.3 (C_{isatin}-3a), 111.6 (C_{arom}-3 + C_{arom}-5), 55.7 (OMe). – MS (EI): $m/z = 378$ [M]⁺. – C₁₉H₁₄N₄O₃S (378.40): calcd. C 60.31, H 3.73, N 14.81; found C 60.11, H 3.62, N 15.01.

N'-(2-Oxindolin-3-ylidene)-2-(3-methoxyphenyl)-1,3-thiazole-4-carbohydrazide (**6h**)

From **4h** (249 mg). Yield: 280 mg (74%), m. p. 266 °C. $R_f = 0.65$ (CHCl₃-MeOH, 3 : 2). – IR (cm⁻¹): $\nu_{\max} = 3200$ (NH stretch.), 1698 (C=O stretch.), 1601 (C=N stretch.), 1581 (NH bend.), 1175 (C-O stretch.). – ¹H NMR ([D₆]DMSO): $\delta = 14.56$ (1H, br s, NH), 11.28 (1H, br s, NH), 8.67 (1H, s, H⁵_{thiazole}), 7.69 (1H, d, $J = 1.5$ Hz, 2-H_{arom}), 7.62 (2H, d, $J = 7.2$ Hz, 13-H_{arom} + 16-H_{arom}), 7.50 (1H, t, $J = 8.1$ Hz, 14-H_{arom}), 7.42 (1H, dt, $J = 0.9, 7.5$ Hz, 15-H_{arom}), 7.15 (2H, m, 4-H_{arom} + 5-H_{arom}), 6.96 (1H, d, $J = 7.8$ Hz, 6-H_{arom}), 7. 3.88 (3H, s, OCH₃). – ¹³C NMR ([D₆]DMSO): $\delta = 168.3$ (C_{thiazole}-2), 163.1 (C_{isatin}=O), 162.0 (OMe-C-3), 157.6 (C_{carbohydr}=O), 148.3 (C_{thiazole}-4), 143.1 (C_{isatin}-7a), 138.9 (C_{arom}-1), 135.0 (C_{isatin}=N), 128.5 (C_{isatin}-6), 128.4 (C_{arom}-5), 126.8 (C_{isatin}-5), 123.1 (C_{arom}-6), 120.4 (C_{isatin}-7), 119.3 (C_{isatin}-3a), 115.2 (C_{arom}-4), 111.6 (C_{arom}-2), 55.9 (OMe). – MS (EI): $m/z = 378$ [M]⁺. – C₁₉H₁₄N₄O₃S (378.40): calcd. C 60.31, H 3.73, N 14.81; found C 60.11, H 3.62, N 15.01.

N'-(2-Oxindolin-3-ylidene)-2-(2-methoxyphenyl)-1,3-thiazole-4-carbohydrazide (**6i**)

From **4i** (249 mg). Yield: 261 mg (68%), m. p. 335 °C. $R_f = 0.69$ (CHCl₃-MeOH, 3 : 2). IR (cm⁻¹): $\nu_{\max} = 3424$ (NH stretch.), 1666 (C=O stretch.), 1619 (C=N stretch.), 1161 (C-O stretch.), 1524 (NH bend.). – ¹H NMR ([D₆]DMSO): $\delta = 14.63$ (1H, br s, NH), 11.25 (1H, br s, NH), 8.74 (1H, s, 5-H_{thiazole}), 7.60 (1H, d, $J = 7.5$ Hz, 6-H_{arom}), 8.50 (1H, d, $J = 7.8$ Hz, 16-H_{arom}), 7.54 (1H, t, $J = 7.8$ Hz, 4-H_{arom}), 7.39 (1H, t, $J = 7.8$ Hz, 5-H_{arom}), 7.31 (1H, d, $J = 8.4$ Hz, 3-H_{arom}), 7.19 (1H, t, $J = 7.5$ Hz, 15-H_{arom}), 7.13 (1H, t, $J = 7.8$ Hz, 14-H_{arom}), 6.98 (1H, d, $J = 7.5$ Hz, 13-H_{arom}), 4.05 (3H, s, OCH₃). – ¹³C NMR ([D₆]DMSO): $\delta = 168.0$ (C_{thiazole}-2), 163.2 (C_{isatin}=O), 157.7 (C_{carbohydr}=O), 156.9 (OMe-C_{arom}-2), 146.8 (C_{thiazole}-4), 143.0 (C_{isatin}-7a), 134.1 (C_{isatin}=N), 132.5 (C_{isatin}-6), 130.1 (C_{isatin}-4), 128.0 (C_{arom}-4 + C_{arom}-6), 125.4 (C_{isatin}-5), 123.0 (C_{arom}-6), 121.5 (C_{arom}-1), 120.8 (C_{arom}-5), 120.4 (C_{isatin}-7), 118.9. (C_{isatin}-3a), 56.4 (OMe). –

MS (EI): $m/z = 378$ [M]⁺. – C₁₉H₁₄N₄O₃S (378.40): calcd. C 60.31, H 3.73, N 14.81; found C 60.11, H 3.62, N 15.01.

Synthesis of 5-(2-(substituted-phenyl)-1,3-thiazol-4-yl)-1,3,4-oxadiazole-2-thiones 7a–i

To a mixture of hydrazide **4** (2.0 mmol) and KOH (2.4 mmol) in MeOH (30 mL) was added CS₂ (2.4 mmol) dropwise. The yellow solution obtained was refluxed till the evolution of hydrogen sulfide ceased (Pb(OAc)₄ test). After 3 h, the solution was cooled and filtered. The filtrate was poured into ice-cooled water and acidified with 6 N HCl to pH 3–4. The solid product obtained was filtered, dried (Na₂SO₄) and recrystallized from CHCl₃.

5-[2-(4-Methylphenyl)-1,3-thiazol-4-yl]-1,3,4-oxadiazole-2-thione (7a)

From **4a** (466 mg). Yield: 412 mg (75%), m. p. 258 °C. $R_f = 0.67$ (CHCl₃-MeOH, 3 : 2). – IR (cm⁻¹): $\nu_{\max} = 3313$ (NH stretch.), 1633 (C=N stretch.), 1530 (NH bend.), 1222 (C=S stretch.). – ¹H NMR ([D₆]DMSO): $\delta = 14.82$ (1H, br s, N-H), 8.54 (1H, s, 5-H_{thiazole}), 7.91 (2H, d, $J = 8.1$ Hz, 2-H_{arom} + 6-H_{arom}), 7.36 (2H, d, $J = 8.1$ Hz, 3-H_{arom} + 5-H_{arom}), 2.37 (3H, s, CH₃). – ¹³C NMR ([D₆]DMSO): $\delta = 177.6$ (C=S), 169.8 (C_{thiazole}-2), 157.0 (C_{oxadiazole}-5), 141.6 (C_{thiazole}-4), 139.1 (C_{arom}-1), 130.4 (Me-C_{arom}-4), 129.8 (C_{arom}-3 + C_{arom}-5), 126.9 (C_{arom}-2 + C_{arom}-6), 21.4 (CH₃). – MS (EI): $m/z = 275$ [M]⁺. – C₁₂H₉N₃OS₂ (275.35): calcd. C 52.34, H 3.29, N 15.26; found C 52.01, H 3.18, N 14.96.

5-[2-(3-Methylphenyl)-1,3-thiazol-4-yl]-1,3,4-oxadiazole-2-thione (7b)

From **4b** (466 mg). Yield: 402 mg (73%), m. p. 226 °C. $R_f = 0.62$ (CHCl₃-MeOH, 3 : 2). – IR (cm⁻¹): $\nu_{\max} = 3291$ (NH stretch.), 1632 (C=N stretch.), 1576 (NH bend.), 1230 (C=S stretch.). – ¹H NMR ([D₆]DMSO): $\delta = 14.83$ (1H, br s, N-H), 8.56 (1H, s, 5-H_{thiazole}), 7.82 (1H, d, $J = 6.3$ Hz, 6-H_{arom}), 7.77 (1H, s, 2-H_{arom}), 7.42 (1H, t, $J = 7.5$ Hz, 5-H_{arom}), 7.36 (1H, d, $J = 7.5$ Hz, 4-H_{arom}), 2.39 (3H, s, CH₃). – ¹³C NMR ([D₆]DMSO): $\delta = 177.6$ (C=S), 169.8 (C_{thiazole}-2), 156.9 (C_{oxadiazole}-2), 139.3 (C_{thiazole}-4), 139.1 (Me-C_{arom}-3), 132.3 (C_{arom}-2), 132.2 (C_{arom}-1), 129.7 (C_{arom}-4 + C_{arom}-5), 127.3 (C_{arom}-6), 21.2 (CH₃). – MS (EI): $m/z = 275$ [M]⁺. – C₁₂H₉N₃OS₂ (275.35): calcd. C 52.34, H 3.29, N 15.26; found C 51.94, H 3.19, N 15.95.

5-[2-(2-Methylphenyl)-1,3-thiazol-4-yl]-1,3,4-oxadiazole-2-thione (7c)

From **4c** (466 mg). Yield: 385 mg (70%), m. p. 203 °C. $R_f = 0.65$ (CHCl₃-MeOH, 3 : 2). – IR (cm⁻¹): $\nu_{\max} = 3213$ (NH stretch.), 1625 (C=N stretch.), 1555 (NH bend.), 1211 (C=S stretch.). – ¹H NMR ([D₆]DMSO): $\delta = 14.83$ (1H, br

s, NH), 8.56 (1H, s, 5-H_{thiazole}), 7.79 (1H, d, $J = 7.2$ Hz, 6-H_{arom}), 7.42 (3H, m, 3-H_{arom} + 4-H_{arom} + 5-H_{arom}), 2.51 (3H, s, CH₃). – ¹³C NMR ([D₆]DMSO): $\delta = 177.7$ (C=S), 169.3 (C_{thiazole}-2), 157.0 (C_{oxadiazole}-5), 138.7 (C_{thiazole}-4), 136.6 (C_{arom}-1), 132.2 (Me-C_{arom}-2), 130.2 (C_{arom}-3), 130.0 (C_{arom}-4), 127.0 (C_{arom}-6), 125.4 (C_{arom}-5), 21.6 (CH₃). – MS (EI): $m/z = 275$ [M]⁺. – C₁₂H₉N₃OS₂ (275.35): calcd. C 52.34, H 3.29, N 15.26; found C 52.31, H 3.20, N 15.02.

5-[2-(4-Chlorophenyl)-1,3-thiazol-4-yl]-1,3,4-oxadiazole-2(3H)-thione (7d)

From **4d** (506 mg). Yield: 395 mg (67%), m. p. 252 °C. $R_f = 0.67$ (CHCl₃-MeOH, 3 : 2). – IR (cm⁻¹): $\nu_{\max} = 3314$ (NH stretch.), 1634 (C=N stretch.), 1539 (NH bend.), 1217 (C=S stretch.), 1092 (C-Cl stretch.). – ¹H NMR ([D₆]DMSO): $\delta = 14.84$ (1H, br s, NH), 8.61 (1H, s, 5-H_{thiazole}), 8.62 (2H, d, $J = 8.7$ Hz, 2-H_{arom} + 6-H_{arom}), 7.60 (2H, d, $J = 8.7$ Hz, 3-H_{arom} + 5-H_{arom}). – ¹³C NMR ([D₆]DMSO): $\delta = 177.6$ (C=S), 168.3 (C_{thiazole}-2), 156.8 (C_{oxadiazole}-5), 139.4 (C_{thiazole}-4), 139.0 (C_{arom}-1), 131.2 (C_{arom}-4), 129.9 (C_{arom}-3 + C_{arom}-5), 128.7 (C_{arom}-2 + C_{arom}-6). – MS (EI): $m/z = 294/296$ [M]⁺. – C₁₁H₆ClN₃OS₂ (295.77): calcd. C 44.67, H 2.04, N 14.21; found C 44.42, H 1.95, N 13.97.

5-[2-(3-Chlorophenyl)-1,3-thiazol-4-yl]-1,3,4-oxadiazole-2-thione (7e)

From **4e** (506 mg). Yield: 395 mg (67%), m. p. 242 °C. $R_f = 0.57$ (CHCl₃-MeOH, 3 : 2). – IR (cm⁻¹): $\nu_{\max} = 3237$ (NH stretch.), 1629 (C=N stretch.), 1591 (NH bend.), 1222 (C=S stretch.), 1080 (C-Cl stretch.). – ¹H NMR ([D₆]DMSO): $\delta = 14.83$ (1H, br s), 8.63 (1H, s, 5-H_{thiazole}), 8.01 (1H, d, $J = 1.5$ Hz, 2-H_{arom}), 7.97 (1H, m, 5-H_{arom}), 7.60 (2H, m, 4-H_{arom} + 6-H_{arom}). – ¹³C NMR ([D₆]DMSO): $\delta = 177.6$ (C=S), 167.9 (C_{thiazole}-2), 156.8 (C_{oxadiazole}-5), 139.4 (C_{thiazole}-4), 134.2 (C_{arom}-3), 131.3 (C_{arom}-1), 129.1 (C_{arom}-5 + C_{arom}-6), 126.8 (C_{arom}-4), 125.8 (C_{arom}-2). – MS (EI): $m/z = 294/296$ [M]⁺. – C₁₁H₆ClN₃OS₂ (295.77): calcd. C 44.67, H 2.04, N 14.21; found C 44.39, H 1.96, N 13.99.

5-[2-(2-Chlorophenyl)-1,3-thiazol-4-yl]-1,3,4-oxadiazole-2-thione (7f)

From **4f** (506 mg). Yield: 384 mg (65%), m. p. 210 °C. $R_f = 0.65$ (CHCl₃-MeOH, 3 : 2). – IR (cm⁻¹): $\nu_{\max} = 3273$ (NH stretch.), 1632 (C=N stretch.), 1579 (NH bend.), 1202 (C=S stretch.), 1084 (C-Cl stretch.). – ¹H NMR ([D₆]DMSO): $\delta = 14.78$ (1H, br s), 8.74 (1H, s, 5-H_{thiazole}), 8.25 (1H, m, 6-H_{arom}), 7.71 (1H, m, 4-H_{arom}), 7.60 (2H, m, 3-H_{arom} + 5-H_{arom}). – ¹³C NMR ([D₆]DMSO): $\delta = 177.7$ (C=S), 164.9 (C_{thiazole}-2), 156.9 (C_{oxadiazole}-5), 138.3

(C_{thiazole}-4), 137.6 (C_{arom}-1), 131.4 (C_{arom}-2), 131.1 (C_{arom}-4), 130.6 (C_{arom}-3), 128.9 (C_{arom}-6), 126.4 (C_{arom}-5). – MS (EI): $m/z = 294/296$ [M]⁺. – C₁₁H₆ClN₃OS₂ (295.77): calcd. C 44.67, H 2.04, N 14.21; found C 44.48, H 1.95, N 14.40.

5-[2-(4-Methoxyphenyl)-1,3-thiazol-4-yl]-1,3,4-oxadiazole-2-thione (7g)

From **4g** (498 mg). Yield: 431 mg (74%), m. p. 270 °C. $R_f = 0.74$ (CHCl₃-MeOH, 3 : 2). – IR (cm⁻¹): $\nu_{\max} = 3292$ (NH stretch.), 1633 (C=N stretch.), 1572 (NH bend.), 1221 (C=S stretch.), 1162 (C-O stretch.). – ¹H NMR ([D₆]DMSO): $\delta = 14.80$ (1H, br s, NH), 8.49 (1H, s, 5-H_{thiazole}), 7.96 (2H, d, $J = 8.7$ Hz, 2-H_{arom} + 6-H_{arom}), 7.36 (2H, d, $J = 8.7$ Hz, 3-H_{arom} + 5-H_{arom}), 3.84 (3H, s, OCH₃). – ¹³C NMR ([D₆]DMSO): $\delta = 177.6$ (C=S), 169.5 (C_{thiazole}-2), 162.0 (OMe-C_{arom}-4), 157.0 (C_{oxadiazole}-5), 141.0 (C_{thiazole}-4), 136.2 (C_{arom}-1), 130.4 (C_{arom}-2 + C_{arom}-6), 116.9 (C_{arom}-3 + C_{arom}-5), 55.9 (OCH₃). – MS (EI): $m/z = 291$ [M]⁺. – C₁₂H₉N₃O₂S₂ (291.35): calcd. C 49.47, H 3.11, N 14.42; found C 49.31, H 3.20, N 14.22.

5-[2-(3-Methoxyphenyl)-1,3-thiazol-4-yl]-1,3,4-oxadiazole-2-thione (7h)

From **4h** (498 mg). Yield: 419 mg (72%), m. p. 259 °C. $R_f = 0.62$ (CHCl₃-MeOH, 3 : 2). – IR (cm⁻¹): $\nu_{\max} = 3274$ (NH stretch.), 1224 (C=S stretch.), 1632 (C=N stretch.), 1579 (NH bend.), 1224 (C=S stretch.), 1159 (C-O stretch.). – ¹H NMR ([D₆]DMSO): $\delta = 14.80$ (1H, br s, NH), 8.59 (1H, s, 5-H_{thiazole}), 7.58 (1H, dd, $J = 0.9, 7.5$ Hz, 6-H_{arom}), 7.50 (1H, m, 2-H_{arom}), 7.46 (1H, d, $J = 7.8$ Hz, 5-H_{arom}), 7.14 (1H, m, 4-H_{arom}), 3.85 (3H, s, OCH₃). – ¹³C NMR ([D₆]DMSO): $\delta = 177.0$ (C=S), 169.4 (C_{thiazole}-2), 160.2 (OMe-C_{arom}-3), 156.9 (C_{oxadiazole}-5), 141.8 (C_{thiazole}-4), 134.5 (C_{arom}-1), 131.1 (C_{arom}-5), 125.2 (C_{arom}-6), 117.5 (C_{arom}-4), 111.5 (C_{arom}-2), 55.8 (OCH₃). – MS (EI): $m/z = 291$ [M]⁺. – C₁₂H₉N₃O₂S₂ (291.35): calcd. C 49.47, H 3.11, N 14.42; found C 49.58, H 3.00, N 14.18.

5-[2-(2-Methoxyphenyl)-1,3-thiazol-4-yl]-1,3,4-oxadiazole-2-thione (7i)

From **4i** (498 mg). Yield: 419 mg (72%), m. p. 210 °C. $R_f = 0.57$ (CHCl₃-MeOH, 3 : 2). – IR (cm⁻¹): $\nu_{\max} = 3424$ (NH stretch.), 1635 (C=N stretch.), 1525 (NH bend.), 1241 (C=S stretch.), 1159 (C-O stretch.). – ¹H NMR ([D₆]DMSO): $\delta = 14.81$ (1H, br s, NH), 8.57 (1H, s, 5-H_{thiazole}), 8.32 (1H, d, $J = 7.8$ Hz, 6-H_{arom}), 7.56 (1H, d, $J = 7.5$ Hz, 4-H_{arom}), 7.30 (1H, d, $J = 8.4$ Hz, 3-H_{arom}), 7.15 (1H, t, $J = 7.5$ Hz, 5-H_{arom}), 4.05 (3H, s, OCH₃). – ¹³C NMR ([D₆]DMSO): $\delta = 177.6$ (C=S), 168.2 (C_{thiazole}-2), 163.6 (OMe-C_{arom}-2), 157.7 (C_{oxadiazole}-5), 157.3 (C_{thiazole}-4), 132.5 (C_{arom}-4), 128.0 (C_{arom}-6), 125.4 (C_{arom}-1), 121.5

(C_{arom}-5), 112.8 (C_{arom}-3), 56.5 (OCH₃). – MS (EI): m/z = 291 [M]⁺. – C₁₂H₉N₃O₂S₂ (291.35): calcd. C 49.47, H 3.11, N 14.42; found C 49.25, H 2.98, N 14.61.

General preparation of carboxamido-thiazoles **9a–d**

To a cold solution ($\sim -5^\circ\text{C}$) of **4f** (507 mg, 2.0 mmol) in HOAc (14 mL), 1 N HCl (7 mL), and water (30 mL) was added a solution of NaNO₂ (172 mg, 2.5 mmol) in cold water (4 mL). After stirring at -5°C for 15 min, a yellow syrup was formed. The azide was taken in cold ethyl acetate (30 mL), washed with a 3% solution of NaHCO₃, washed with water, and finally dried (Na₂SO₄). A solution of amino acid methyl ester (2.33 mmol) in ethyl acetate (20 mL) containing 3.5 mL of Et₃N was stirred at 0°C for 20 min and filtered, and the filtrate was added to the acid solution. The mixture was kept at -5°C for 12 h, then at 23°C for another 12 h, followed by washing with 0.5 N HCl, water and a 3% solution of NaHCO₃, and finally dried (Na₂SO₄). The solution was evaporated to dryness, and the residue was either an oil, purified on an SiO₂ column, or a solid, recrystallized from ethyl acetate-petroleum ether to give the desired products.

Methyl (2-(2-(4-chlorophenyl)thiazole)-4-carboxamido)-acetate (**9a**)

From glycine methyl ester (207 mg). Yield: 415 mg (67%), m. p. $163\text{--}166^\circ\text{C}$. – ¹H NMR ([D₆]DMSO): δ = 9.86 (1H, m, NH), 9.21 (1H, s, H⁵_{thiazole}), 7.97 (2H, d, J = 8.5 Hz, 2-H_{arom} + 6-H_{arom}), 7.42 (2H, d, J = 8.5 Hz, 3-H_{arom} + 5-H_{arom}), 4.19 (2H, d, J = 2.2 Hz, CH₂-8), 3.71 (3H, s, CO₂Me). – ¹³C NMR ([D₆]DMSO): δ = 170.2 (CO₂Me), 167.6 (C_{thiazole}-2), 162.7 (C=O), 149.8 (C_{thiazole}-4), 137.1 (C_{arom}-Cl), 133.3 (C_{arom}-4), 129.6 (C_{arom}-3 + C_{arom}-5), 128.7 (C_{arom}-2 + C_{arom}-6), 51.0 (CO₂Me), 38.2 (CH₂). – MS ((+)-FAB): m/z = 309/311 [M+H]⁺. – C₁₃H₁₁ClN₂O₃S (310.76): calcd. C 50.24, H 3.57, N 9.01; found C 49.98, H 3.46, N 9.20.

Methyl (3-(2-(4-chlorophenyl)thiazole)-4-carboxamido)-3-(hydroxymethyl)-3-oxopropanoate (**9b**)

From L-serine methyl ester (278 mg). Yield: 523 mg (77%), m. p. $172\text{--}175^\circ\text{C}$. – ¹H NMR ([D₆]DMSO): δ = 9.92 (1H, br s, NH), 9.15 (1H, s, 5-H_{thiazole}), 7.89 (2H, d, J = 8.7 Hz, 2-H_{arom} + 6-H_{arom}), 7.48 (2H, d, J = 8.7 Hz, 3-H_{arom} + 5-H_{arom}), 4.29 (2H, m, CH₂OH), 4.36 (1H, m, 8-H), 3.72 (3H, s, CO₂Me), 3.54 (1H, t, J = 5.0 Hz, CH₂OH). – ¹³C NMR ([D₆]DMSO): δ = 172.1 (CO₂Me), 167.8 (C_{thiazole}-2), 161.0 (C=O), 148.9 (C_{thiazole}-4), 138.2 (C_{arom}-1), 133.8 (C_{arom}-4), 129.6 (C_{arom}-3 + C_{arom}-5), 128.5 (C_{arom}-2 + C_{arom}-6), 59.5 (CH₂OH), 55.2 (C-8), 51.1 (CO₂Me). – MS ((+)-FAB): m/z = 339/341 [M+H]⁺. –

C₁₄H₁₃ClN₂O₄S (340.78): calcd. C 49.34, H 3.85, N 8.22; found C 49.03, H 3.77, N 7.98.

Methyl (2-(2-(4-chlorophenyl)thiazole)-4-carboxamido)-4-(methylthio)butanoate (**9c**)

From L-methionine methyl ester (380 mg). Yield: 498 mg (65%), m. p. $183\text{--}186^\circ\text{C}$. – ¹H NMR ([D₆]DMSO): δ = 9.77 (1H, br s, NH), 9.20 (1H, s, 5-H_{thiazole}), 8.00 (2H, d, J = 8.6 Hz, 2-H_{arom} + 6-H_{arom}), 7.52 (2H, d, J = 8.6 Hz, 3-H_{arom} + 5-H_{arom}), 4.39 (1H, m, 8-H), 3.75 (3H, s, CO₂Me), 2.58 (2H, t, J = 7.1 Hz, CH₂CH₂SMe), 2.41 (2H, t, J = 7.1 Hz, CH₂CH₂SMe), 2.09 (SMe). – ¹³C NMR ([D₆]DMSO): δ = 173.2 (CO₂Me), 167.7 (C_{thiazole}-2), 160.9 (C=O), 148.7 (C_{thiazole}-4), 139.2 (C_{arom}-1), 133.9 (C_{arom}-4), 129.5 (C_{arom}-3 + C_{arom}-5), 128.3 (C_{arom}-2 + C_{arom}-6), 52.2 (C-8), 51.3 (CO₂Me), 32.2 (CH₂CH₂SMe), 30.1 (CH₂CH₂SMe), 15.2 (SMe). – MS ((+)-FAB): m/z = 382/384 [M+H]⁺. – C₁₆H₁₇ClN₂O₃S₂ (384.90): calcd. C 49.93, H 4.45, N 7.28; found C 49.76, H 4.33, N 7.00.

Methyl (3-(2-(4-chlorophenyl)thiazole)-4-carboxamido)-2-methyl-3-oxopropanoate (**9d**)

From L-alanine methyl ester (240 mg). Yield: 422 mg (65%), m. p. $149\text{--}152^\circ\text{C}$. – ¹H NMR ([D₆]DMSO): δ = 9.82 (1H, br s, NH), 9.12 (1H, s, 5-H_{thiazole}), 7.95 (2H, d, J = 8.4 Hz, 2-H_{arom} + 6-H_{arom}), 7.51 (2H, d, J = 8.4 Hz, 3-H_{arom} + 5-H_{arom}), 3.74 (3H, s, CO₂Me), 4.29 (1H, m, 8-H), 1.42 (3H, d, J = 7.0 Hz, C₈-Me). – ¹³C NMR ([D₆]DMSO): δ = 172.8 (CO₂Me), 167.7 (C²_{thiazole}), 162.7 (C=O), 149.8 (C_{thiazole}-4), 137.1 (C_{arom}-1), 133.3 (C_{arom}-4), 129.6 (C_{arom}-3 + C_{arom}-5), 128.7 (C_{arom}-2 + C_{arom}-6), 49.3 (C-8), 51.0 (CO₂Me), 19.6 (Me-C-8). – MS ((+)-FAB): m/z = 323/325 [M+H]⁺. – C₁₄H₁₃ClN₂O₃S (324.78): calcd. C 51.77, H 4.03, N 8.63; found C 51.49, H 3.89, N 8.82.

Methyl (3-(2-(4-chlorophenyl)thiazole)-4-carboxamido)-2-methylbutanoate (**9e**)

From L-valine methyl ester (306 mg). Yield: 534 mg (65%), m. p. $139\text{--}142^\circ\text{C}$. – ¹H NMR ([D₆]DMSO): δ = 9.76 (1H, br s, NH), 9.09 (1H, s, 5-H_{thiazole}), 7.89 (2H, d, J = 8.6 Hz, 2-H_{arom} + 6-H_{arom}), 7.47 (2H, d, J = 8.5 Hz, 3-H_{arom} + 5-H_{arom}), 3.69 (3H, s, CO₂Me), 4.32 (1H, m, 8-H), 2.18 (1H, m, CH(Me)₂), 0.87, 0.85 (6H, 2d, J = 6.5 Hz, CH(Me)₂). – ¹³C NMR ([D₆]DMSO): δ = 170.9 (CO₂Me), 168.3 (C_{thiazole}-2), 161.9 (C=O), 150.1 (C_{thiazole}-4), 138.2 (C_{arom}-1), 133.9 (C_{arom}-4), 129.6 (C_{arom}-3 + C_{arom}-5), 128.3 (C_{arom}-2 + C_{arom}-6), 54.2 (C-8), 51.3 (CO₂Me), 29.7 (CH(Me)₂), 18.5 (CH(Me)₂). – MS ((+)-FAB): m/z = 351/353 [M+H]⁺. – C₁₆H₁₇ClN₂O₃S (352.84): calcd. C 54.46, H 4.86, N 7.94; found C 54.22, H 4.69, N 7.74.

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