

# Synthesis and antiviral activity evaluation of new 4-thiazolidinones bearing an imidazo[2,1-*b*]thiazole moiety

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**ABSTRACT:** A series of new 4-thiazolidinone derivatives were synthesized and evaluated against diverse DNA- and RNA-viruses in mammalian cell cultures. Some of the compounds were found to exhibit moderate antiviral activity. 3-Propyl-2-[[[(6-(4-chlorophenyl)imidazo[2,1-*b*]thiazol-3-yl)acetyl)hydrazono]-5-methyl-4-thiazolidinone **13**, displayed modest yet consistent activity against three strains of influenza A virus, including the 2009 pandemic virus A/H1N1 Virginia/ATCC3/2009 (cytotoxicity >100 µM). Compounds **6** and **11** displayed activity against vesicular stomatitis virus in HeLa cells (antiviral EC<sub>50</sub> values of 9 (cytotoxicity 100 µM) and 2 µM (cytotoxicity 20 µM), respectively). Neither of the compounds was active against HIV.

**KEYWORDS:** Imidazo[2,1-*b*]thiazoles, 4-thiazolidinones, antiviral activity, synthesis.

## 1. INTRODUCTION

Despite significant advances in antiviral drug development during the past two decades, viral infections continue to cause serious morbidity and mortality world-wide. Diverse antiviral drugs are now available for the treatment of infections by HIV, herpes-, influenza, hepatitis B or hepatitis C viruses. Except for the broad antiviral agent ribavirin, there is no approved therapy for diverse emerging RNA viruses. In addition, new antiviral molecules are required to tackle the problems of drug toxicity and rapid development of drug resistance, which is particularly problematic for mutation-prone RNA viruses. Since virus replication occurs within host cells, and host cell metabolism and viral replication are tightly integrated, the development of compounds which selectively interfere with virus-specific process is one of the main challenges in antiviral drug design.

Imidazo[2,1-*b*]thiazole derivatives can have diverse pharmacological properties, such as antioxidant [1], cytotoxic [2], anti-infectious [3], antimicrobial [4], cystic fibrosis transmembrane conductance regulator (CFTR)-selective potentiators [5], 5-HT<sub>6</sub> ligands [6], orexin receptor antagonists [7], selective cardiodepressant activity [8], inhibitors of insulin-like growth factor receptor and members of the epidermal growth factor family of receptor tyrosine kinases [9], anticancer [10, 11] and hence occupy a prominent place in medicinal chemistry. There have been a few reports on imidazo[2,1-*b*]thiazole derivatives displaying antiviral activities [12-14]. Since our laboratory has built synthetic expertise in this chemical scaffold and related heterocyclic systems [15-20], we here synthesized new imidazo[2,1-*b*]thiazole derivatives and evaluated their potential antiviral properties in cell-based assays. We chose to combine the imidazo[2,1-*b*]thiazole skeleton with a 4-thiazolidinone ring. Several researchers have incorporated this moiety into various biologically active compounds [21-32] (including antiviral molecules) (either as a substituent group or as a replacement for another cyclic system). For instance, several 2,3-diaryl-1,3-thiazolidin-4-ones have proved to be potent non-nucleoside HIV reverse transcriptase inhibitors (NNRTIs) [33, 34]. The HIV RT is a prime target for designing HIV inhibitors [35, 36].

We here report the synthesis, structural determination and antiviral evaluation of . 3-alkyl/aryl-2-[[[(6-(phenyl/4-chlorophenyl)imidazo[2,1-*b*]thiazol-3-yl)acetyl)hydrazono]-5-nonsubstituted/methyl-4-thiazolidinones.

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## 2. RESULTS AND DISCUSSION

The target compounds were prepared from 2-[6-(phenyl/4-chlorophenyl)imidazo[2,1-*b*]thiazol-3-yl]acetohydrazides (C/D) [37], by a five step synthesis as shown in Figure 1. By heating ethyl (6-(phenyl/4-chlorophenyl)imidazo[2,1-*b*]thiazol-3-yl)acetate hydrobromides (A/B) and hydrazine-hydrate in ethanol, 2-[6-(phenyl/4-chlorophenyl)imidazo[2,1-*b*]thiazol-3-yl]acetohydrazides were obtained. Hydrazides and alkyl/aryl isothiocyanates were heated in ethanol to yield 4-alkyl/aryl-1-[(6-(phenyl/4-chlorophenyl)imidazo[2,1-*b*]thiazol-3-yl)acetyl]-3-thiosemicarbazides E1-14 [38, 39]. The thiosemicarbazides were then reacted with ethyl  $\alpha$ -bromoacetate/ethyl 2-bromopropionate in the presence of anhydrous sodium acetate in absolute ethanol to yield 3-alkyl/aryl-2-[[6-(phenyl/4-chlorophenyl)imidazo[2,1-*b*]thiazol-3-yl)acetyl]hydrazono]-5-nonsubstituted/methyl-4-thiazolidinones 1-14.

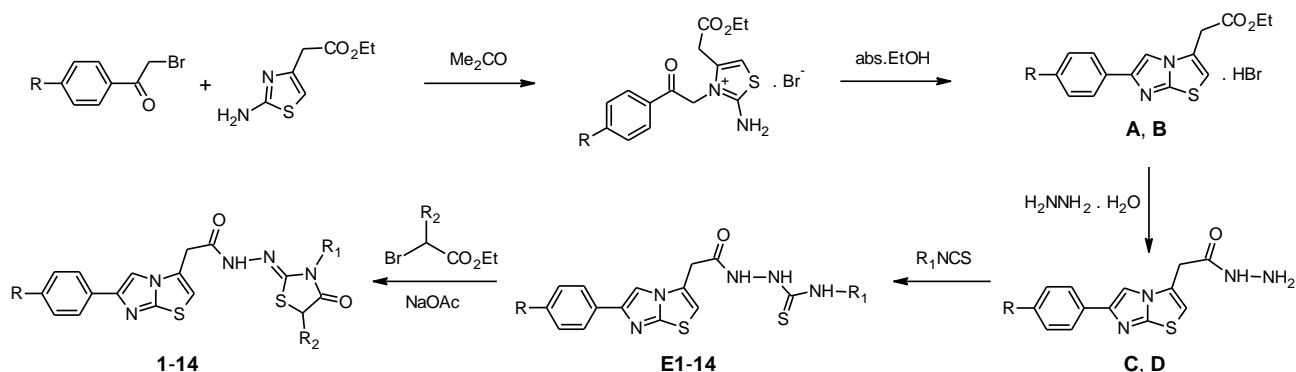


Figure 1. The synthetic route for preparation of 1-14.

The yields and melting points of the compounds are given in Table 1. The structures of the obtained compounds were elucidated by spectral data.

Table 1. Yields and melting points (M.p.) of 4-thiazolidinone derivatives 1-14.

Compound	R	R <sub>1</sub>	R <sub>2</sub>	Yield (%)	M.p. (°C)
1	H	C <sub>6</sub> H <sub>5</sub>	H	87	272-273
2	H	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H	96	266-267
3	H	4-ClC <sub>6</sub> H <sub>4</sub>	H	36	295-296
4	H	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	69	198-199
5	H	C <sub>3</sub> H <sub>7</sub>	CH <sub>3</sub>	78	187-188
6	H	CH <sub>2</sub> =CH-CH <sub>2</sub>	CH <sub>3</sub>	83	182-183
7	H	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	84	221-222
8	H	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	56	244-245
9	H	4-ClC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	40	204-205
10	Cl	C <sub>3</sub> H <sub>7</sub>	H	82	222-223
11	Cl	CH <sub>3</sub>	CH <sub>3</sub>	65	238-239
12	Cl	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	41	234-235
13	Cl	C <sub>3</sub> H <sub>7</sub>	CH <sub>3</sub>	66	241-242
14	Cl	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	69	253-254

4-Thiazolidinones 1-14 obtained from thiosemicarbazide gave absorption bands at 198-202 and 257-263 nm in UV spectra. In the IR spectra, some significant stretching bands due to N-H and C=O were observed at 3107-3257 cm<sup>-1</sup> and 1635-1695 cm<sup>-1</sup>, respectively. A new strong band at 1695-1751 cm<sup>-1</sup> (in some compounds two bands [40] due to isomers) in the spectra of 1-14 provided firm support for ring closure [41]. <sup>1</sup>H-NMR and <sup>13</sup>C-NMR data were also in agreement with the formation of 4-thiazolidinone ring. NH signals of 1-14 appeared at  $\delta$  10.06-11.37 ppm. The exocyclic methylene protons of 4-6 and 10-13 displayed two singlets at  $\delta$  3.86-3.88 and  $\delta$  4.06-4.10 ppm or multiplets at  $\delta$  3.97-4.14 ppm for 1-3, 7-9 and 14 indicating the presence of two isomers in unequal proportions in DMSO-d<sub>6</sub>. This may be explained on the basis of the difference in the relative stability of the *E* and *Z* isomers formed due to the rotational restriction about the exocyclic N=C bond

at position 2 of the 4-thiazolidinone ring [38, 39]. In the  $^1\text{H-NMR}$  spectra of compounds **4-9**, **11-14**,  $\text{CH-CH}_3$  protons appeared as a quartet (1H) at  $\delta$  4.37-4.53 ppm and  $\text{CH-CH}_3$  protons appeared as a doublet (3H) at  $\delta$  1.51-1.57 ppm which proved the closure of 4-thiazolidinone ring [42]. On the other hand, peak resonated at  $\delta$  43.24; 43.64,  $\delta$  157.16 and  $\delta$  174.25; 174.75 ppm in the  $^{13}\text{C-NMR}$  (APT),  $^{13}\text{C-NMR}$  (DEPT) and  $^1\text{H-}^{13}\text{C}$  HSQC NMR spectrum of compound 3-ethyl-2-[(6-phenylimidazo[2,1-*b*]thiazol-3-yl)acetyl]hydrazono]-5-methyl-4-thiazolidinone (**4**), assigned for S-CH, C=N and C=O moieties, confirms the carbon skeleton of 4-thiazolidinone ring. These peaks were observed at  $\delta$  40.42; 40.48,  $\delta$  151.82; 152.10 and  $\delta$  172.47; 172.62 ppm in the  $^{13}\text{C-NMR}$  (APT) spectrum of compounds **14**. ESI (+) MS of the selected compounds **4** displayed protone molecular ion  $[\text{M}+1]^+$  at  $m/z$  414 which confirmed molecular weight.

The synthesized compounds were evaluated against a broad and diverse panel of RNA- and DNA-viruses using cytopathic effect (CPE) reduction assays in appropriate cell culture models (see Experimental Section for the full list of viruses). As shown in Table 2, compound **6** had moderate activity against vesicular stomatitis virus (VSV) with an antiviral  $\text{EC}_{50}$  value of 9  $\mu\text{M}$  and selectivity index (SI: ratio of cytotoxic to antiviral concentration) of 11. Compound **11** displayed an antiviral  $\text{EC}_{50}$  value of 2  $\mu\text{M}$  against VSV as well as respiratory syncytial virus (RSV), with a SI of 10. For **14**, anti-RSV activity was 5-fold lower but the SI was again 10. These three molecules (i.e., **6**, **11** and **14**) all have a methyl substituent at position  $\text{R}_2$ . Evaluation of the compounds against influenza virus (Table 3) revealed that some compounds displayed weak activity as visible by CPE or MTS assay. Compound **13** (which again carries a methyl at  $\text{R}_2$ ) was the only one in the series with equal activity in the CPE and MTS assays, and its activity was consistent for three different strains of influenza A virus belonging to two subtypes (H1N1 and H3N2). However, its  $\text{EC}_{50}$  values were rather high (in the range of 60  $\mu\text{M}$ ). Finally, compound **7** displayed weak activity against adenovirus ( $\text{EC}_{50}$ : 42  $\mu\text{M}$ ; data not shown), but not against any other DNA-virus tested. Neither of the synthesized compounds was found active against HIV-1 or -2. In combination, these antiviral data suggested that the 5-methylsubstituted thiazolidinone derivatives were more active than their nonsubstituted counterparts.

Table 2. Antiviral activity and cytotoxicity of compounds **1-14** in HeLa cells.

Compound	Cytotoxicity MCC <sup>a</sup> ( $\mu\text{M}$ )	Antiviral $\text{EC}_{50}$ <sup>b</sup> ( $\mu\text{M}$ )		
		Vesicular stomatitis virus	Coxsackie B4 virus	Respiratory syncytial virus
<b>1</b>	>100	>100	>100	>100
<b>2</b>	>100	>100	>100	>100
<b>3</b>	$\geq 20$	>100	>100	>100
<b>4</b>	100	>100	>100	>100
<b>5</b>	$\geq 20$	>100	>100	>100
<b>6</b>	100	9	>100	>100
<b>7</b>	$\geq 100$	>100	>100	>100
<b>8</b>	ND	ND	ND	ND
<b>9</b>	$\geq 20$	>100	>100	>100
<b>10</b>	>100	>100	>100	>100
<b>11</b>	20	2	>100	$\geq 2$
<b>12</b>	100	>100	>100	>100
<b>13</b>	$\geq 20$	>100	>100	>100
<b>14</b>	100	>100	>100	10
DS-5000 <sup>c</sup>	>100	3.5	79	4
Ribavirin	>250	16	112	16

<sup>a</sup>Minimum cytotoxic concentration, i.e. compound concentration that causes minimal alterations in cell morphology as assessed by microscopy. <sup>b</sup> $\text{EC}_{50}$ : 50% effective concentration or concentration producing 50% inhibition of virus-induced cytopathic effect, as determined by visual scoring of the cytopathic effect (CPE). <sup>c</sup>DS-5000: dextran sulfate MW 5000; these data are expressed in  $\mu\text{g}/\text{ml}$ . ND, not done.

The diverse virus testing panel allowed to estimate the cytotoxicity of the compounds in various mammalian cell lines (Table 4). Most were not cytotoxic at 100  $\mu\text{M}$ , the highest concentration tested. Compound **9** was the only compound showing cytotoxicity in all cell lines examined; depending on the cell line, its cytotoxic concentrations varied between 4 and 100  $\mu\text{M}$ .

**Table 3.** Anti-influenza virus activity and cytotoxicity of compounds **1-14** in MDCK<sup>a</sup> cells.

Compound	Cytotoxicity (μM)		Antiviral EC <sub>50</sub> <sup>b</sup> (μM)							
	(μM)		Influenza A/H1N1 (A/PR/8/34)		Influenza A/H1N1 (A/Virginia/ATCC3/2009)		Influenza A/H3N2 (A/HK/7/87)		Influenza B (B/HK/5/72)	
	CC <sub>50</sub> <sup>c</sup>	MCC <sup>d</sup>	CPE	MTS	CPE	MTS	CPE	MTS	CPE	MTS
<b>1</b>	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
<b>2</b>	>100	≥100	>100	>100	>100	>100	>100	24	>100	>100
<b>3</b>	>100	>100	>100	>100	>100	32	>100	>100	>100	>100
<b>4</b>	>100	≥100	20	<0.80	>100	>100	>100	>100	>100	>100
<b>5</b>	>100	≥100	>100	>100	>100	>100	>100	>100	>100	>100
<b>6</b>	>100	≥100	>100	>100	>100	>100	>100	>100	>100	>100
<b>7</b>	≥83	100	>100	>100	>100	>100	>100	6.5	>100	>100
<b>8</b>	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
<b>9</b>	4.8	4.0	>100	>100	>100	>100	>100	>100	>100	>100
<b>10</b>	>100	≥100	>100	>100	>100	>100	>100	50	>100	>100
<b>11</b>	74	73	>100	>100	>100	>100	>100	>100	>100	>100
<b>12</b>	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
<b>13</b>	>100	>100	>100	65	79	56	>100	69	>100	>100
<b>14</b>	11	≥4.0	>100	>100	>100	>100	>100	>100	>100	>100
<b>Zanamivir</b>	>100	>100	0.36	0.77	20	5.6	5.8	4.8	45	26
<b>Ribavirin</b>	>100	≥20	7.6	9.4	8.9	12	8.9	8.7	12	8.7
<b>Amantadine</b>	>500	≥500	197	101	>500	>500	0.56	0.64	>500	>500
<b>Rimantadine</b>	336	500	20	7.3	>500	>500	0.062	0.057	>500	>500

<sup>a</sup>MDCK: Madin-Darby canine kidney cells. <sup>b</sup>EC<sub>50</sub>: 50% effective concentration or concentration producing 50% inhibition of virus-induced cytopathic effect, as determined by visual scoring of the cytopathic effect (CPE) or by measuring cell viability with the colorimetric formazan-based MTS assay. <sup>c</sup>50% Cytotoxic concentration, as determined by measuring cell viability with the colorimetric formazan based MTS assay. <sup>d</sup>Minimum cytotoxic concentration, i.e. compound concentration that causes minimal alterations in cell morphology as assessed by microscopy. ND, not done.

### 3. CONCLUSION

In conclusion, we synthesized a series of imidazo[2,1-*b*]thiazoles bearing 4-thiazolidinone moieties. The new compounds were characterized by UV, IR, NMR spectra, mass spectra as well as elemental analyses. Antiviral activity testing revealed that some of the compounds exhibited antiviral activity against diverse RNA viruses (cytotoxic concentrations range of >100-20 μM). In order to improve the antiviral potency, chemical synthesis of additional thiazolidinone fused imidazo[2,1-*b*]thiazoles is warranted.

### 4. MATERIALS AND METHODS

#### 4.1. Chemistry

Melting points were determined by using a Büchi B-540 melting point apparatus in open capillary tubes and are uncorrected. Elemental analyses were performed on a Thermo Finnigan Flash EA 1112 elemental analyzer. IR spectra were recorded on KBr discs, using a Shimadzu IR Affinity-1 FT-IR spectrophotometer. <sup>1</sup>H-NMR, <sup>13</sup>C-NMR (APT), <sup>13</sup>C-NMR (DEPT) and HSQC (<sup>1</sup>H-<sup>13</sup>C) spectra were measured on a Varian UNITY INOVA (500 MHz) spectrometer using DMSO-*d*<sub>6</sub>. Mass spectra were recorded on a Thermo Finnigan LCQ Advantage Max instrument. The starting materials were either commercially available or synthesized according to the references cited.

**Table 4.** Cytotoxicity of compounds **1-14** in diverse mammalian cell lines<sup>a</sup>.

Compound	MCC <sup>b</sup> (μM)				CC <sub>50</sub> <sup>c</sup> (μM)	
	HEL	HeLa	Vero	MDCK	CRFK	MT4
<b>1</b>	>100	>100	>100	>100	>100	>125
<b>2</b>	100	>100	>100	≥100	>100	73
<b>3</b>	>100	≥20	≥20	>100	>100	>125
<b>4</b>	>100	100	100	≥100	>100	50
<b>5</b>	>100	≥20	100	≥100	>100	30
<b>6</b>	>100	100	>100	≥100	>100	39
<b>7</b>	>100	≥100	100	100	>100	62
<b>8</b>	ND	ND	ND	ND	ND	ND
<b>9</b>	100	≥20	100	4.0	15	34
<b>10</b>	>100	>100	≥20	≥100	>100	52
<b>11</b>	>100	20	≥100	73	>100	24
<b>12</b>	>100	100	>100	>100	>100	>125
<b>13</b>	100	≥20	≥20	>100	>100	>125
<b>14</b>	>100	100	>100	≥4.0	>100	58
<b>DS-5000<sup>d</sup></b>	ND	>100	>100	ND	ND	ND
<b>Ribavirin</b>	>250	>250	>250	100	ND	ND
<b>Ganciclovir</b>	>100	ND	ND	ND	>100	ND
<b>Azidothymidine</b>	ND	ND	ND	ND	ND	>25

<sup>a</sup>HEL: human embryonic lung fibroblast cells; HeLa: human cervix carcinoma cells; Vero: African green monkey kidney cells; MDCK: Madin-Darby canine kidney cells; CRFK: Crandell-Rees feline kidney cells; MT4: human T-lymphoblast cells.

<sup>b</sup>MCC: minimum inhibitory concentration, or compound concentration causing minimal changes in cell morphology, as assessed by microscopy. <sup>c</sup>CC<sub>50</sub>: 50% cytotoxic concentration, assessed by the spectroscopic MTS cell viability assay.

<sup>d</sup>DS-5000: dextran sulfate with MW 5000; these data are expressed in μg/ml. ND, not done.

#### 4.1.1. Preparation of ethyl (6-(phenyl/4-chlorophenyl)imidazo[2,1-b]thiazol-3-yl)acetate hydrobromides (A, B)

These compounds were obtained according to the procedure described by Robert *et al* [43].

#### 4.1.2. Preparation of 2-[6-(phenyl/4-chlorophenyl)imidazo[2,1-b]thiazol-3-yl]acetohydrazides (C, D)

These compounds were prepared according to the procedure described by Kuhmstedt *et al* [44].

#### 4.1.3. Preparation of 4-alkyl/aryl-1-[(6-(phenyl/4-chlorophenyl)imidazo[2,1-b]thiazol-3-yl)acetyl]-3-thiosemicarbazides (E1-14)

To a solution of 2-[6-(phenyl/4-chlorophenyl)imidazo[2,1-b]thiazole-3-yl]acetohydrazides (**A**) (0.005 mol) in ethanol (30 mL) were added the appropriate isothiocyanate (0.005 mol). The resulting mixture was heated under reflux for 3 h. After cooling, the precipitate was separated and purified by washing with hot ethanol.

#### 4.1.4. General procedure for preparation of 3-alkyl/aryl-2-[(6-(phenyl/4-chlorophenyl)imidazo[2,1-b]thiazol-3-yl)acetyl]hydrazono]-5-nonsubstituted/methyl-4-thiazolidinones derivatives (1-14)

To a suspension of 4-alkyl/aryl-1-[(6-(phenyl/4-chlorophenyl)imidazo[2,1-b]thiazol-3-yl)acetyl]-3-thiosemicarbazides (**E1-14**) (0.005 mol) in absolute ethanol (30 mL) were added anhydrous sodium acetate (0.02 mol) and ethyl bromoacetate/ethyl 2-bromopropionate (0.005 mol). The reaction mixture was refluxed for 5 h (for **1-4**, **6-10** and **14**) or 20 h (for **5**, **11-13**), then cooled, diluted with water and allowed to stand overnight. The crystals were filtered, dried and purified by crystallization from ethanol or ethanol/water.

#### 3-Phenyl-2-[(6-phenylimidazo[2,1-b]thiazol-3-yl)acetyl]hydrazono]-4-thiazolidinone (**1**)

UV λ<sub>max</sub> (nm): 200 (ε 134124), 259 (ε 38398). IR ν<sub>max</sub> (cm<sup>-1</sup>): 3244, 3116 (N-H stretching), 3024 (aromatic C-H stretching), 2964, 2908 (C-H stretching), 1739 (thiazolidinone C=O stretching), 1678, 1643 (amide I C=O stretching), 1593, 1523 (C=N, C=C stretching and amide II, N-H bending vibrations combined with C-N stretching), 1471, 1384 (C-H bending), 1276 (amide III, N-H bending vibrations combined with C-N stretching), 707 (aromatic substitution bending). <sup>1</sup>H-NMR δ (ppm): 4.03-4.13 (m, 2H, CH<sub>2</sub>CO), 4.20 (s, 2H, thiazolidinone 5-CH<sub>2</sub>), 6.91 (d, 2H, J = 7.32 Hz, thiazolidinone 3-Ph C<sub>2,6</sub>-H), 7.14 (s, 1H, imidazothiazole C<sub>2</sub>-H), 7.16-7.27 (m, 4H, thiazolidinone 3-Ph C<sub>3,4,5</sub>-H ve Ph C<sub>4</sub>-H), 7.35 and 7.37 (2d, 2H, J=8.30; 7.32 Hz, Ph C<sub>3,5</sub>-H), 7.65 (d, 2H, J =

8.30 Hz, Ph C<sub>2,6</sub>-H), 8.09 (s, 1H, imidazothiazole C<sub>5</sub>-H), 11.33 (s, 1H, CONH). Anal. Calcd. for C<sub>22</sub>H<sub>17</sub>N<sub>5</sub>O<sub>2</sub>S<sub>2</sub>: C, 59.04; H, 3.83; N, 15.65; Found: C, 58.99; H, 3.48; N, 15.42.

3-(4-Methylphenyl)-2-[(6-phenylimidazo[2,1-b]thiazol-3-yl)acetyl]hydrazono]-4-thiazolidinone (2)

UV  $\lambda_{\max}$  (nm): 199 ( $\epsilon$  138954), 260 ( $\epsilon$  34865). IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3257, 3116 (N-H stretching), 3026 (aromatic C-H stretching), 2953, 2904 (C-H stretching), 1735 (thiazolidinone C=O stretching), 1681, 1643 (amide I C=O stretching), 1602, 1521 (C=N, C=C stretching and amide II, N-H bending vibrations combined with C-N stretching), 1471, 1379 (C-H bending), 1267 (amide III, N-H bending vibrations combined with C-N stretching), 823, 705 (aromatic substitution bending). <sup>1</sup>H-NMR  $\delta$  (ppm): 2.29 (s, 3H, thiazolidinone 3-Ph 4-CH<sub>3</sub>), 4.01-4.11 (m, 2H, CH<sub>2</sub>CO), 4.17 (s, 2H, thiazolidinone 5-CH<sub>2</sub>), 6.79 (d, 2H, J = 8.30 Hz, thiazolidinone 3-Ph C<sub>3,5</sub>-H), 7.13 (s, 1H, imidazothiazole C<sub>2</sub>-H), 7.15 (s, 1H, Ph C<sub>4</sub>-H), 7.19-7.26 (m, 4H, Ph C<sub>3,5</sub>-H ve tiy. 3-Ph C<sub>2,6</sub>-H), 7.65 (d, 2H, J=8.30 Hz, Ph C<sub>2,6</sub>-H), 8.10 (s, 1H, imidazothiazole C<sub>5</sub>-H), NH proton not observed. Anal. Calcd. for C<sub>23</sub>H<sub>19</sub>N<sub>5</sub>O<sub>2</sub>S<sub>2</sub>: C, 59.85; H, 4.15; N, 15.17; Found: C, 59.30; H, 3.74; N, 14.82.

3-(4-Chlorophenyl)-2-[(6-phenylimidazo[2,1-b]thiazol-3-yl)acetyl]hydrazono]-4-thiazolidinone (3)

UV  $\lambda_{\max}$  (nm): 201 ( $\epsilon$  145345), 263 ( $\epsilon$  30605). IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3207, 3124 (N-H stretching), 3010 (aromatic C-H stretching), 2954, 2900 (C-H stretching), 1732 (thiazolidinone C=O stretching), 1674, 1651 (amide I C=O stretching), 1589, 1525 (C=N, C=C stretching and amide II, N-H bending vibrations combined with C-N stretching), 1471, 1381 (C-H bending), 1274 (amide III, N-H bending vibrations combined with C-N stretching), 1089 (aromatic C-Cl stretching), 829, 704 (aromatic substitution bending). <sup>1</sup>H-NMR  $\delta$  (ppm): 4.06-4.10 (m, 2H, CH<sub>2</sub>CO), 4.22 (s, 2H, thiazolidinone 5-CH<sub>2</sub>), 6.91 (d, 2H, J= 8.30 Hz, thiazolidinone 3-Ph C<sub>3,5</sub>-H), 7.13 (s, 1H, imidazothiazole C<sub>2</sub>-H), 7.19-7.27 (m, 3H, thiazolidinone 3-Ph C<sub>2,6</sub>-H and Ph C<sub>4</sub>-H), 7.37-7.39 (2d, 2H, J=8.30; 8.78 Hz, Ph C<sub>3,5</sub>-H), 7.63 (d, 2H, J=7.32 Hz, Ph C<sub>2,6</sub>-H), 8.07 (s, 1H, imidazothiazole C<sub>5</sub>-H), 11.34 (s, 1H, CONH). Anal. Calcd. for C<sub>22</sub>H<sub>16</sub>ClN<sub>5</sub>O<sub>2</sub>S<sub>2</sub>: C, 54.82; H, 3.35; N, 14.53; Found: C, 54.27; H, 3.06; N, 14.26.

3-Ethyl-2-[(6-phenylimidazo[2,1-b]thiazol-3-yl)acetyl]hydrazono]-5-methyl-4-thiazolidinone (4)

UV  $\lambda_{\max}$  (nm): 199 ( $\epsilon$  128642), 258 ( $\epsilon$  59380). IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3182, 3151 (N-H stretching), 3103 (aromatic C-H stretching), 2976, 2933 (C-H stretching), 1716 (thiazolidinone C=O stretching), 1695, 1672 (amide I C=O stretching), 1618, 1556 (C=N, C=C stretching and amide II, N-H bending vibrations combined with C-N stretching), 1438, 1390 (C-H bending), 1219 (amide III, N-H bending vibrations combined with C-N stretching), 705 (aromatic substitution bending). <sup>1</sup>H-NMR  $\delta$  (ppm): 1.12 and 1.22 (2t, 3H, J=7.32; 7.32 Hz, thiazolidinone N-CH<sub>2</sub>-CH<sub>3</sub>), 1.52 (d, 3H, J=7.32 Hz, thiazolidinone 5-CHCH<sub>3</sub>), 3.68 and 4.06 (2q, 2H, J=7.32; 7.32 Hz, thiazolidinone N-CH<sub>2</sub>), 3.88 and 4.10 (2s, 2H, CH<sub>2</sub>CO), 4.38 (q, 1H, J=7.32 Hz, thiazolidinone 5-CHCH<sub>3</sub>), 7.05 and 7.18 (2s, 1H, imidazothiazole C<sub>2</sub>-H), 7.23-7.27 (m, 1H, Ph C<sub>4</sub>-H), 7.38 and 7.41 (2d, 2H, J=7.32; 7.32 Hz, Ph C<sub>3,5</sub>-H), 7.81 and 7.82 (2d, 2H, J=7.32; 7.32 Hz, Ph C<sub>2,6</sub>-H), 8.18 and 8.20 (2s, 1H, imidazothiazole C<sub>5</sub>-H), 10.65 (s, 1H, CONH). <sup>1</sup>H-NMR (D<sub>2</sub>O)  $\delta$  (ppm): 1.07 and 1.17 (2t, 3H, J=7.32; 6.84 Hz, thiazolidinone N-CH<sub>2</sub>-CH<sub>3</sub>), 1.47 (d, 3H, J=7.32 Hz, thiazolidinone 5-CH-CH<sub>3</sub>), 3.66 and 4.03 (2q, 2H, J=7.32; 7.32 Hz, thiazolidinone N-CH<sub>2</sub>), 3.94 (HDO), 3.85 and 4.05 (2s, 2H, CH<sub>2</sub>CO), 4.29 (q 1H, J= 7.32 Hz, thiazolidinone 5-CHCH<sub>3</sub>), 7.00 and 7.11 (2s, 1H, imidazothiazole C<sub>2</sub>-H), 7.24-7.26 (m, 1H, Ph C<sub>4</sub>-H), 7.35 ve 7.38 (2d, 2H, J=6.84; 7.32 Hz, Ph C<sub>3,5</sub>-H), 7.74 and 7.76 (2d, 2H, J=9.27; 7.81 Hz, Ph C<sub>2,6</sub>-H), 8.06 and 8.12 (2s, 1H, imidazothiazole C<sub>5</sub>-H). <sup>13</sup>C-NMR (APT) (125 MHz  $\delta$  (ppm): 12.81; 13.91 (thiazolidinone N-CH<sub>2</sub>CH<sub>3</sub>) 19.51; 19.62 (thiazolidinone 5-CH<sub>3</sub>), 32.82; 33.84 (CH<sub>2</sub>), 38.36; 39.17 (thiazolidinone N-CH<sub>2</sub>), 43.24; 43.64 (thiazolidinone 5-CH), 109.08; 109.27 (imidazothiazole C<sub>5</sub>), 110.63; 111.56 (imidazothiazole C<sub>2</sub>), 125.32; 125.35 (Ph C<sub>2,6</sub>), 126.07; 127.30 (imidazothiazole C<sub>3</sub>), 127.73; 127.75 (Ph C<sub>4</sub>), 129.35; 129.37 (Ph C<sub>3,5</sub>), 134.87; 134.94 (Ph C<sub>1</sub>), 146.66; 146.74 (imidazothiazole C<sub>6</sub>), 149.28; 149.34 (imidazothiazole C<sub>7a</sub>), 157.16 (thiazolidinone C<sub>2</sub>=N), 167.32; 169.75 (CONH), 174.25; 174.75 (thiazolidinone C=O). <sup>13</sup>C-NMR (DEPT) (125 MHz)  $\delta$  (ppm): 12.81; 13.91 (thiazolidinone N-CH<sub>2</sub>CH<sub>3</sub>), 19.51; 19.62 (thiazolidinone 5-CH<sub>3</sub>), 32.82; 33.83 (CH<sub>2</sub>), 38.36; 39.17 (thiazolidinone N-CH<sub>2</sub>) 43.24; 43.64 (thiazolidinone 5-CH), 109.08; 109.28 (imidazothiazole C<sub>5</sub>), 110.64; 111.57 (imidazothiazole C<sub>2</sub>), 125.32; 125.35 (Ph C<sub>2,6</sub>), 127.73; 127.75 (Ph C<sub>4</sub>) 129.35; 129.37 (Ph C<sub>3,5</sub>). <sup>13</sup>C-NMR (HSQC) (125 MHz)  $\delta$  (ppm): 12.81; 13.91 (thiazolidinone N-CH<sub>2</sub>CH<sub>3</sub>), 19.51; 19.62 (thiazolidinone 5-CH<sub>3</sub>), 32.82; 33.84 (CH<sub>2</sub>), 38.36; 39.17 (thiazolidinone N-CH<sub>2</sub>), 43.24; 43.64 (thiazolidinone 5-CH), 109.08; 109.27 (imidazothiazole C<sub>5</sub>), 110.64; 111.57 (imidazothiazole C<sub>2</sub>), 125.32; 125.35 (Ph C<sub>2,6</sub>), 126.07; 127.30 (imidazothiazole C<sub>3</sub>), 127.73; 127.75 (Ph C<sub>4</sub>), 129.35; 129.37 (Ph C<sub>3,5</sub>), 134.87; 134.94 (Ph C<sub>1</sub>), 146.66; 146.74 (imidazothiazole C<sub>6</sub>), 149.28; 149.34 (imidazothiazole C<sub>7a</sub>), 157.16 (thiazolidinone C<sub>2</sub>=N), 167.32; 169.75 (CONH), 174.25; 174.74 (thiazolidinone

C=O). Anal. Calcd. for  $C_{19}H_{19}N_5O_2S_2$ : C, 55.19; H, 4.63; N, 16.94; Found: C, 55.48; H, 4.65; N, 17.27. ESI (+) MS:  $m/z$   $[M+1]^+$  414 (100), 256 (6), 214 (3), 175 (4).

*3-Propyl-2-(((6-phenylimidazo[2,1-b]thiazol-3-yl)acetyl)hydrazono]-5-methyl-4-thiazolidinone (5)*

UV  $\lambda_{max}$  (nm): 199 ( $\epsilon$  126637), 258 ( $\epsilon$  31808). IR  $\nu_{max}$  ( $cm^{-1}$ ): 3186, 3155 (N-H stretching), 3024 (aromatic C-H stretching), 2964, 2933 (C-H stretching), 1716, 1695 (thiazolidinone C=O stretching), 1670 (amide I C=O stretching), 1618, 1550 (C=N, C=C stretching and amide II, N-H bending vibrations combined with C-N stretching), 1469, 1390 (C-H bending), 1228 (amide III, N-H bending vibrations combined with C-N stretching), 705 (aromatic substitution bending).  $^1H$ -NMR  $\delta$  (ppm): 0.82 (t, 3H,  $J = 7.32$  Hz, thiazolidinone N-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 1.52 (d, 3H,  $J = 6.83$  Hz, thiazolidinone 5-CHCH<sub>3</sub>), 1.56-1.64 (m, 2H, N-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 3.61 (t, 2H,  $J = 7.32$  Hz, thiazolidinone N-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 3.87 and 4.08 (2s, 2H, CH<sub>2</sub>CO), 4.40 (q, 1H,  $J = 7.32$  Hz, thiazolidinone 5-CHCH<sub>3</sub>), 7.01 ve 7.05 (2s, 1H, imidazothiazole C<sub>2</sub>-H), 7.24-7.27 (m, 1H, Ph C<sub>4</sub>-H), 7.38 and 7.40 (2d, 2H,  $J = 7.81; 7.32$  Hz, Ph C<sub>3,5</sub>-H), 7.82 (d, 2H,  $J = 7.32$  Hz, Ph C<sub>2,6</sub>-H), 8.14 and 8.20 (2s, 1H, imidazothiazole C<sub>5</sub>-H), 10.52 and 10.66 (2s, 1H, CONH). Anal. Calcd. for  $C_{20}H_{21}N_5O_2S_2$ : C, 56.18; H, 4.95; N, 16.38; Found: C, 55.95; H, 4.55; N, 16.22.

*3-Allyl-2-(((6-phenylimidazo[2,1-b]thiazol-3-yl)acetyl)hydrazono]-5-methyl-4-thiazolidinone (6)*

UV  $\lambda_{max}$  (nm): 199 ( $\epsilon$  128932), 257 ( $\epsilon$  45530). IR  $\nu_{max}$  ( $cm^{-1}$ ): 3186, 3155 (N-H stretching), 3103 (aromatic C-H stretching), 2987, 2931 (C-H stretching), 1724 (thiazolidinone C=O stretching), 1681, 1662 (amide I C=O stretching), 1610, 1558 (C=N, C=C stretching and amide II, N-H bending vibrations combined with C-N stretching), 1469, 1381 (C-H bending), 1224 (amide III, N-H bending vibrations combined with C-N stretching), 705 (aromatic substitution bending).  $^1H$ -NMR  $\delta$  (ppm): 1.53 (d, 3H,  $J = 7.14$  Hz, thiazolidinone 5-CHCH<sub>3</sub>), 3.87 and 4.06 (2s, 2H, CH<sub>2</sub>CO), 4.25 and 4.29 (2d, 2H,  $J = 4.11; 5.21$  Hz, N-CH<sub>2</sub>-CH=CH<sub>2</sub>), 4.45 (q, 1H,  $J = 7.13$  Hz, thiazolidinone 5-CHCH<sub>3</sub>), 5.10 (dd, 1H,  $J = 10.71$  Hz; 1.10 Hz, N-CH<sub>2</sub>-CH=CH<sub>2</sub> cis), 5.14 (dd, 1H,  $J = 17.29$  Hz; 1.10 Hz, N-CH<sub>2</sub>-CH=CH<sub>2</sub> trans), 5.78-5.87 (m, 1H, N-CH<sub>2</sub>-CH=CH<sub>2</sub>), 7.01 and 7.04 (2s, 1H, imidazothiazole C<sub>2</sub>-H), 7.24-7.27 (m, 1H, Ph C<sub>4</sub>-H), 7.38 and 7.40 (2d, 2H,  $J = 7.41; 7.68$  Hz, Ph C<sub>3,5</sub>-H), 7.83 (d, 2H,  $J = 8.24$  Hz, Ph C<sub>2,6</sub>-H), 8.12 and 8.20 (2s, 1H, imidazothiazole C<sub>5</sub>-H), 10.66 (s, 1H, CONH). Anal. Calcd. for  $C_{20}H_{19}N_5O_2S_2$ : C, 56.45; H, 4.50; N, 16.46; Found: C, 56.80; H, 4.56; N, 16.22.

*3-Phenyl-2-(((6-phenylimidazo[2,1-b]thiazol-3-yl)acetyl)hydrazono]-5-methyl-4-thiazolidinone (7)*

UV  $\lambda_{max}$  (nm): 199 ( $\epsilon$  131615), 260 ( $\epsilon$  40342). IR  $\nu_{max}$  ( $cm^{-1}$ ): 3441 (O-H), 3253, 3124 (N-H stretching), 3026 (aromatic C-H stretching), 2980, 2868 (C-H stretching), 1749, 1699 (thiazolidinone C=O stretching), 1643 (amide I C=O stretching), 1589, 1539 (C=N, C=C stretching and amide II, N-H bending vibrations combined with C-N stretching), 1467, 1386 (C-H bending), 1269 (amide III, N-H bending vibrations combined with C-N stretching), 819, 736 (aromatic substitution bending).  $^1H$ -NMR  $\delta$  (ppm): 1.05 (t, 3H,  $J = 7.32$  Hz, EtOH, CH<sub>3</sub>), 1.52 and 1.57 (2d, 3H,  $J = 7.32; 7.32$  Hz, thiazolidinone 5-CH-CH<sub>3</sub>), 3.45 (q, 3H,  $J = 7.32$  Hz, EtOH, CH<sub>2</sub>), 4.02-4.14 (m, 2H, CH<sub>2</sub>CO), 4.34 (t, 3H,  $J = 5.37$  Hz, EtOH, OH), 4.49 and 4.53 (2q, 1H,  $J = 7.32; 7.32$  Hz, thiazolidinone 5-CHCH<sub>3</sub>), 6.89 (d, 2H,  $J = 7.32$  Hz, thiazolidinone 3-Ph C<sub>2,6</sub>-H), 7.14 (s, 1H, imidazothiazole C<sub>2</sub>-H), 7.15-7.27 (m, 4H, thiazolidinone 3-Ph C<sub>3,4,5</sub>-H ve Ph C<sub>4</sub>-H), 7.33 and 7.35 (2d, 2H,  $J = 7.81; 7.32$  Hz, Ph C<sub>3,5</sub>-H), 7.64 and 7.66 (2d, 2H,  $J = 7.32; 6.83$  Hz, Ph C<sub>2,6</sub>-H), 8.08 and 8.09 (2s, 1H, imidazothiazole C<sub>5</sub>-H), 11.37 (s, 1H, CONH). Anal. Calcd. for  $C_{23}H_{19}N_5O_2S_2 \cdot C_2H_5OH$ : C, 59.15; H, 4.96; N, 13.80; Found: C, 58.91; H, 4.28; N, 13.74.

*3-(4-Methylphenyl)-2-(((6-phenylimidazo[2,1-b]thiazol-3-yl)acetyl)hydrazono]-5-methyl-4-thiazolidinone (8)*

UV  $\lambda_{max}$  (nm): 198 ( $\epsilon$  124654), 262 ( $\epsilon$  52693). IR  $\nu_{max}$  ( $cm^{-1}$ ): 3211, 3111 (N-H stretching), 3022 (aromatic C-H stretching), 2937, 2866 (C-H stretching), 1749, 1705 (thiazolidinone C=O stretching), 1643 (amide I C=O stretching), 1604, 1539 (C=N, C=C stretching and amide II, N-H bending vibrations combined with C-N stretching), 1469, 1388 (C-H bending), 1273 (amide III, N-H bending vibrations combined with C-N stretching), 823, 725 (aromatic substitution bending).  $^1H$ -NMR  $\delta$  (ppm): 1.52 and 1.56 (2d, 3H,  $J = 7.32; 6.84$  Hz, thiazolidinone 5-CH-CH<sub>3</sub>), 2.29 (s, 3H, thiazolidinone 3-Ph 4-CH<sub>3</sub>), 4.02-4.13 (m, 2H, CH<sub>2</sub>CO), 4.48 and 4.50 (2q, 1H,  $J = 7.32; 7.32$  Hz, thiazolidinone 5-CHCH<sub>3</sub>), 6.79 (d, 2H,  $J = 7.80$  Hz, thiazolidinone 3-Ph C<sub>3,5</sub>-H), 7.13 (s, 1H, imidazothiazole C<sub>2</sub>-H), 7.14 (d, 1H,  $J = 7.81$  Hz, Ph C<sub>4</sub>-H), 7.19-7.27 (m, 4H, Ph C<sub>3,5</sub>-H and thiazolidinone 3-Ph C<sub>2,6</sub>-H), 7.64 and 7.66 (2d, 2H,  $J = 6.35; 6.83$  Hz, Ph C<sub>2,6</sub>-H), 8.08 (s, 1H, imidazothiazole C<sub>5</sub>-H), 11.33 (s, 1H, CONH). Anal. Calcd. for  $C_{24}H_{21}N_5O_2S_2$ : C, 60.61; H, 4.45; N, 14.73; Found: C, 60.48; H, 4.27; N, 14.42.

**3-(4-Chlorophenyl)-2-(((6-phenylimidazo[2,1-b]thiazol-3-yl)acetyl)hydrazono]-5-methyl-4-thiazolidinone (9)**

UV  $\lambda_{\max}$  (nm): 202 ( $\epsilon$  147459), 262 ( $\epsilon$  39855). IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3230, 3107 (O-H and N-H stretching), 3018 (aromatic C-H stretching), 2980, 2908 (C-H stretching), 1745, 1685 (thiazolidinone C=O stretching), 1654 (amide I C=O stretching), 1600, 1523 (C=N, C=C stretching and amide II, N-H bending vibrations combined with C-N stretching), 1475, 1400 (C-H bending), 1247 (amide III, N-H bending vibrations combined with C-N stretching), 831, 711 (aromatic substitution bending). <sup>1</sup>H-NMR  $\delta$  (ppm): 1.52 and 1.57 (2d, 3H,  $J$  = 6.84; 6.83 Hz, thiazolidinone 5-CH-CH<sub>3</sub>), 3.97-4.10 (m, 2H, CH<sub>2</sub>CO), 4.48 and 4.53 (2q, 1H,  $J$  = 7.32; 7.32 Hz, thiazolidinone 5-CHCH<sub>3</sub>), 6.90 (d, 2H,  $J$  = 8.79 Hz, thiazolidinone 3-Ph C<sub>3,5</sub>-H), 7.12 (s, 1H, imidazothiazole C<sub>2</sub>-H), 7.19-7.64 (m, 7H, Ph C<sub>2,6</sub>-H and thiazolidinone 3-Ph C<sub>2,6</sub>-H), 8.10 and 8.17 (2s, 1H, imidazothiazole C<sub>5</sub>-H), 10.06 (s, 1H, CONH). Anal. Calcd. for C<sub>23</sub>H<sub>18</sub>ClN<sub>5</sub>O<sub>2</sub>S<sub>2</sub>: C, 53.74; H, 3.92; N, 13.62; Found: C, 53.24; H, 3.58; N, 14.10.

**3-Propyl-2-(((6-(4-chlorophenyl)imidazo[2,1-b]thiazol-3-yl)acetyl)hydrazono]-4-thiazolidinone (10)**

UV  $\lambda_{\max}$  (nm): 200 ( $\epsilon$  138598), 258 ( $\epsilon$  93444). IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3186, 3149 (N-H stretching), 3028 (aromatic C-H stretching), 2964, 2931 (C-H stretching), 1716 (thiazolidinone C=O stretching), 1689, 1666 (amide I C=O stretching), 1616, 1548 (C=N, C=C stretching and amide II, N-H bending vibrations combined with C-N stretching), 1462, 1386 (C-H bending), 1234 (amide III, N-H bending vibrations combined with C-N stretching), 1083 (aromatic C-Cl stretching), 846 (aromatic substitution bending). <sup>1</sup>H-NMR  $\delta$  (ppm): 0.82 (t, 3H,  $J$  = 7.32 Hz, thiazolidinone N-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 1.49-1.62 (m, 2H, N-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 3.59 (t, 2H,  $J$  = 7.32 Hz, thiazolidinone N-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 3.82 and 4.09 (2s, 2H, thiazolidinone 5-CH<sub>2</sub>), 3.86 and 4.07 (2s, 2H, CH<sub>2</sub>CO), 7.03 and 7.06 (2s, 1H, imidazothiazole C<sub>2</sub>-H), 7.45 (d, 2H,  $J$  = 8.30 Hz, Cl-Ph C<sub>3,5</sub>-H), 7.81-7.85 (m, 2H, Cl-Ph C<sub>2,6</sub>-H), 8.20 ve 8.25 (2s, 1H, imidazothiazole C<sub>5</sub>-H), 10.52 and 10.64 (2s, 1H, CONH). Anal. Calcd. for C<sub>19</sub>H<sub>18</sub>ClN<sub>5</sub>O<sub>2</sub>S<sub>2</sub>: C, 50.94; H, 4.05; N, 15.63; Found: C, 50.92; H, 3.82; N, 15.48.

**3-Methyl-2-(((6-(4-chlorophenyl)imidazo[2,1-b]thiazol-3-yl)acetyl)hydrazono)-5-methyl-4-thiazolidinone (11)**

UV  $\lambda_{\max}$  (nm): 200 ( $\epsilon$  137685), 259 ( $\epsilon$  91342). IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3134, 3111 (N-H stretching), 3053 (aromatic C-H stretching), 2980, 2935 (C-H stretching), 1722, 1712 (thiazolidinone C=O stretching), 1668 (amide I C=O stretching), 1614, 1556 (C=N, C=C stretching and amide II, N-H bending vibrations combined with C-N stretching), 1465, 1365 (C-H bending), 1265 (amide III, N-H bending vibrations combined with C-N stretching), 1066 (aromatic C-Cl stretching), 839 (aromatic substitution bending). <sup>1</sup>H-NMR  $\delta$  (ppm): 1.52 (d, 3H,  $J$  = 7.13 Hz, thiazolidinone 5-CHCH<sub>3</sub>), 3.09 and 3.13 (2s, 3H, thiazolidinone N-CH<sub>3</sub>), 3.87 and 4.10 (2s, 2H, CH<sub>2</sub>CO), 4.38 (q, 1H,  $J$  = 7.14 Hz, thiazolidinone 5-CHCH<sub>3</sub>), 7.06 (s, 1H, imidazothiazole C<sub>2</sub>-H), 7.45 (d, 2H,  $J$  = 8.51 Hz, Cl-Ph C<sub>3,5</sub>-H), 7.83 (d, 2H,  $J$  = 8.51 Hz, Cl-Ph C<sub>2,6</sub>-H), 8.20 and 8.24 (2s, 1H, imidazothiazole C<sub>5</sub>-H), 10.63 (s, 1H, CONH). Anal. Calcd. for C<sub>18</sub>H<sub>16</sub>ClN<sub>5</sub>O<sub>2</sub>S<sub>2</sub>: C, 49.82; H, 3.72; N, 16.14; Found: C, 50.09; H, 3.85; N, 15.80.

**3-Ethyl-2-(((6-(4-chlorophenyl)imidazo[2,1-b]thiazol-3-yl)acetyl)hydrazono)-5-methyl-4-thiazolidinone (12)**

UV  $\lambda_{\max}$  (nm): 199 ( $\epsilon$  132775), 260 ( $\epsilon$  51201). IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3180, 3151 (N-H stretching), 3113 (aromatic C-H stretching), 2978, 2933 (C-H stretching), 1716 (thiazolidinone C=O stretching), 1691, 1662 (amide I C=O stretching), 1614, 1556 (C=N, C=C stretching and amide II, N-H bending vibrations combined with C-N stretching), 1462, 1390 (C-H bending), 1226 (amide III, N-H bending vibrations combined with C-N stretching), 1085 (aromatic C-Cl stretching), 846 (aromatic substitution bending). <sup>1</sup>H-NMR  $\delta$  (ppm): 1.12 (t, 3H,  $J$  = 7.14 Hz, thiazolidinone N-CH<sub>2</sub>-CH<sub>3</sub>), 1.51 (d, 3H,  $J$  = 7.14 Hz, thiazolidinone 5-CHCH<sub>3</sub>), 3.68 (q, 2H,  $J$  = 7.13 Hz, thiazolidinone N-CH<sub>2</sub>), 3.87 and 4.09 (2s, 2H, CH<sub>2</sub>CO), 4.37 (q, 1H,  $J$  = 7.14 Hz, thiazolidinone 5-CHCH<sub>3</sub>), 7.04 and 7.06 (2s, 1H, imidazothiazole C<sub>2</sub>-H), 7.45 (d, 2H,  $J$  = 8.51 Hz, Cl-Ph C<sub>3,5</sub>-H), 7.84 (d, 2H,  $J$  = 8.78 Hz, Cl-Ph C<sub>2,6</sub>-H), 8.21 and 8.25 (2s, 1H, imidazothiazole C<sub>5</sub>-H), 10.52 and 10.64 (2s, 1H, CONH). Anal. Calcd. for C<sub>19</sub>H<sub>18</sub>ClN<sub>5</sub>O<sub>2</sub>S<sub>2</sub>: C, 50.94; H, 4.05; N, 15.63; Found: C, 51.29; H, 4.19; N, 15.37.

**3-Propyl-2-(((6-(4-chlorophenyl)imidazo[2,1-b]thiazol-3-yl)acetyl)hydrazono)-5-methyl-4-thiazolidinone (13)**

UV  $\lambda_{\max}$  (nm): 199 ( $\epsilon$  130740), 260 ( $\epsilon$  33216). IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3180, 3151 (N-H stretching), 3080 (aromatic C-H stretching), 2968, 2933 (C-H stretching), 1720 (thiazolidinone C=O stretching), 1689, 1666 (amide I C=O stretching), 1614, 1556 (C=N, C=C stretching and amide II, N-H bending vibrations combined with C-N stretching), 1465, 1388 (C-H bending), 1230 (amide III, N-H bending vibrations combined with C-N stretching), 1085 (aromatic C-Cl stretching), 844 (aromatic substitution bending). <sup>1</sup>H-NMR  $\delta$  (ppm): 0.82 (t, 3H,  $J$  = 7.32 Hz, thiazolidinone N-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 1.52 (d, 3H,  $J$  = 7.32 Hz, thiazolidinone 5-CHCH<sub>3</sub>), 1.54-1.63 (m, 2H, thiazolidinone N-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 3.61 (t, 2H,  $J$  = 7.32 Hz, thiazolidinone N-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 3.86 and 4.07 (2s,



2H, CH<sub>2</sub>CO), 4.39 (q, 1H, *J* = 7.32 Hz, thiazolidinone 5-CHCH<sub>3</sub>), 7.03 and 7.06 (2s, 1H, imidazothiazole C<sub>2</sub>-H), 7.45 (d, 2H, *J* = 8.78 Hz, Cl-Ph C<sub>3,5</sub>-H), 7.84 (d, 2H, *J* = 8.29 Hz, Cl-Ph C<sub>2,6</sub>-H), 8.20 and 8.25 (2s, 1H, imidazothiazole C<sub>5</sub>-H), 10.64 (s, 1H, CONH). Anal. Calcd. for C<sub>20</sub>H<sub>20</sub>ClN<sub>5</sub>O<sub>2</sub>S<sub>2</sub>: C, 52.00; H, 4.36; N, 15.16; Found: C, 51.72; H, 4.19; N, 14.80.

#### 3-Phenyl-2-[[[(6-(4-chlorophenyl)imidazo[2,1-b]thiazol-3-yl)acetyl]hydrazono]-5-methyl-4-thiazolidinone (14)

UV λ<sub>max</sub> (nm): 201 (ε 148651), 261 (ε 44491). IR ν<sub>max</sub> (cm<sup>-1</sup>): 3240, 3115 (N-H stretching), 3078 (aromatic C-H stretching), 2978, 2860 (C-H stretching), 1751, 1705 (thiazolidinone C=O stretching), 1635 (amide I C=O stretching), 1589, 1537 (C=N, C=C stretching and amide II, N-H bending vibrations combined with C-N stretching), 1458, 1392 (C-H bending), 1274 (amide III, N-H bending vibrations combined with C-N stretching), 1089 (aromatic C-Cl stretching), 829 (aromatic substitution bending). <sup>1</sup>H-NMR δ (ppm): 1.52 and 1.57 (2d, 3H, *J* = 7.32; 7.32 Hz, thiazolidinone 5-CH-CH<sub>3</sub>), 4.02-4.14 (m, 2H, CH<sub>2</sub>CO), 4.48 and 4.52 (2q, 1H, *J* = 7.32; 7.32 Hz, thiazolidinone 5-CHCH<sub>3</sub>), 6.89 (d, 2H, *J* = 7.32 Hz, thiazolidinone 3-Ph C<sub>2,6</sub>-H), 7.14-7.17 (m, 2H, imidazothiazole C<sub>2</sub>-H and thiazolidinone 3-Ph C<sub>4</sub>-H), 7.28 and 7.30 (2d, 2H, *J* = 8.78; 8.30 Hz, thiazolidinone 3-Ph C<sub>3,5</sub>-H), 7.33 and 7.35 (2d, 2H, *J* = 7.33; 8.29 Hz, Cl-Ph C<sub>3,5</sub>-H), 7.63 and 7.65 (2d, 2H, *J* = 8.29; 8.79 Hz, Cl-Ph C<sub>2,6</sub>-H), 8.13 (s, 1H, imidazothiazole C<sub>5</sub>-H), 11.36 (s, 1H, CONH). <sup>13</sup>C-NMR (APT) (125 MHz) δ (ppm): 19.69; 19.86 (thiazolidinone 5-CH<sub>3</sub>), 33.00; 33.05 (CH<sub>2</sub>), 40.42; 40.48 (thiazolidinone 5-CH), 109.21 (imidazothiazole C<sub>5</sub>), 111.80; 111.85 (imidazothiazole C<sub>2</sub>), 121.44 (Cl-Ph C<sub>4</sub>), 125.29; 125.34 (thiazolidinone 3-Ph C<sub>2,6</sub>), 126.22; 126.25 (thiazolidinone 3-Ph C<sub>4</sub>), 126.85 (imidazothiazole C<sub>3</sub>), 129.24 (Cl-Ph C<sub>2,6</sub>), 130.13 (thiazolidinone 3-Ph C<sub>3,5</sub>), 131.94 (Cl-Ph C<sub>3,5</sub>), 133.64; 133.66 (Cl-Ph C<sub>1</sub>), 145.57 (imidazothiazole C<sub>6</sub>), 148.15; 148.20 (thiazolidinone 3-Ph C<sub>1</sub>), 149.63 (imidazothiazole C<sub>7a</sub>), 151.82; 152.10 (thiazolidinone C<sub>2</sub>=N), 166.35; 166.42 (CONH), 172.47; 172.62 (thiazolidinone C=O). Anal. Calcd. for C<sub>23</sub>H<sub>18</sub>ClN<sub>5</sub>O<sub>2</sub>S<sub>2</sub>: C, 55.70; H, 3.66; N, 14.12; Found: C, 56.06; H, 3.75; N, 13.82.

## 4.2. Biological activity

### 4.2.1. Antiviral activity

The compounds (1-14) were evaluated for activity against diverse RNA- and DNA-viruses, using the following cell-based assays [45]: (a) Crandell-Rees Feline Kidney (CRFK) cells infected with feline corona virus or feline herpes virus; (b) human embryonic lung (HEL) fibroblast cells infected with herpes simplex virus-1 or -2, vaccinia virus, vesicular stomatitis virus, an acyclovir-resistant herpes simplex virus-1 strain, or adenovirus-2; (c) human cervixcarcinoma HeLa cells infected with vesicular stomatitis virus, coxsackie B4 virus or respiratory syncytial virus; (d) African green monkey kidney Vero cells infected with para-influenza-3 virus, reovirus-1, Sindbis virus, Coxsackie B4 virus or Punta toro virus; (e) Madin-Darby canine kidney (MDCK) cells infected with influenza A/H1N1 subtype (A/PR/8/34 or A/Virginia/ATCC/3/2009), influenza A/H3N2 subtype (A/HK/7/87) or influenza B (B/HK/5/72); and (f) (human T-lymphoblast MT4-) cells infected with HIV-1 or HIV-2.

To perform the antiviral assays, the virus was added to subconfluent cell cultures in 96-well plates, and at the same time, the test compounds were added at serial dilutions. Appropriate reference compounds were included, i.e. the virus entry inhibitor dextran sulfate 5000, the broad antiviral agent ribavirin, the antiherpetic drug ganciclovir, and the HIV inhibitor azidothymidine. After 3-6 days incubation at 37 °C (or 35 °C in the case of influenza virus), the cultures were examined by microscopy to score the compounds' inhibitory effect on virus-induced cytopathic effect (CPE) or their cytotoxicity. For some viruses, antiviral and cytotoxic activities were confirmed by the colorimetric MTS cell viability assay [46].

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