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Novel 4-thiazolidinone derivatives bearing imidazo[2,1-*b*]thiazole moiety: design, synthesis, and antiviral activity evaluation

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ABSTRACT: This paper aimed to synthesize novel compounds carrying imidazo[2,1-b]thiazole nucleus, characterize them with various spectroscopic methods, moreover evaluate their antiviral activity. All novel derivatives were evaluated for their antiviral activity against Coxsackie B4 virus, Respiratory syncytial virus, Influenza A/H1N1 virus, Influenza A/H3N2, and Influenza B virus. Some of the compounds, particularly the derivatives carrying 4-methylphenyl and 4-bromophenyl moiety, exhibited higher and comparable activities against both Coxsackie B4 and Respiratory syncytial viruses, moreover the compounds with *N*-propyl and *N*-butyl at thiazolidinone ring showed high antiviral activities against Influenza Influenza A/H3N2 viruses. Consequently, the results obtained from in vitro assay data shed light on improving novel antiviral.

KEYWORDS: Imidazo[2,1-*b*]thiazole; 4-thiazolidinone; antiviral activity; coxscakie b4 virus, influenza

1. INTRODUCTION

For a long time, fused heterocyclic systems have attracted researchers due to their various biological activities. Among these heterocyclic compounds bearing Imidazo[2,1-*b*]thiazole nuclei occupy a strong place in pharmaceutical chemistry because of their wide spectrum of pharmacological activities including: antifungal [1, 2], antibacterial [1, 3], anticancer [4, 5], antiviral [3, 6], cardiotonic [7]. Levamisole, which was a drug used commonly for the treatment of parasitic, viral, and bacterial infections [8] was approved by Food & Drug Administration (FDA) in 1990 as an adjuvant treatment for colon cancer [9]. Additionally, the clinical efficacy of cobicistat which is used for HIV treatment showed the medicinal significance of thiazole scaffold for antiviral activity (figure 1) [10].

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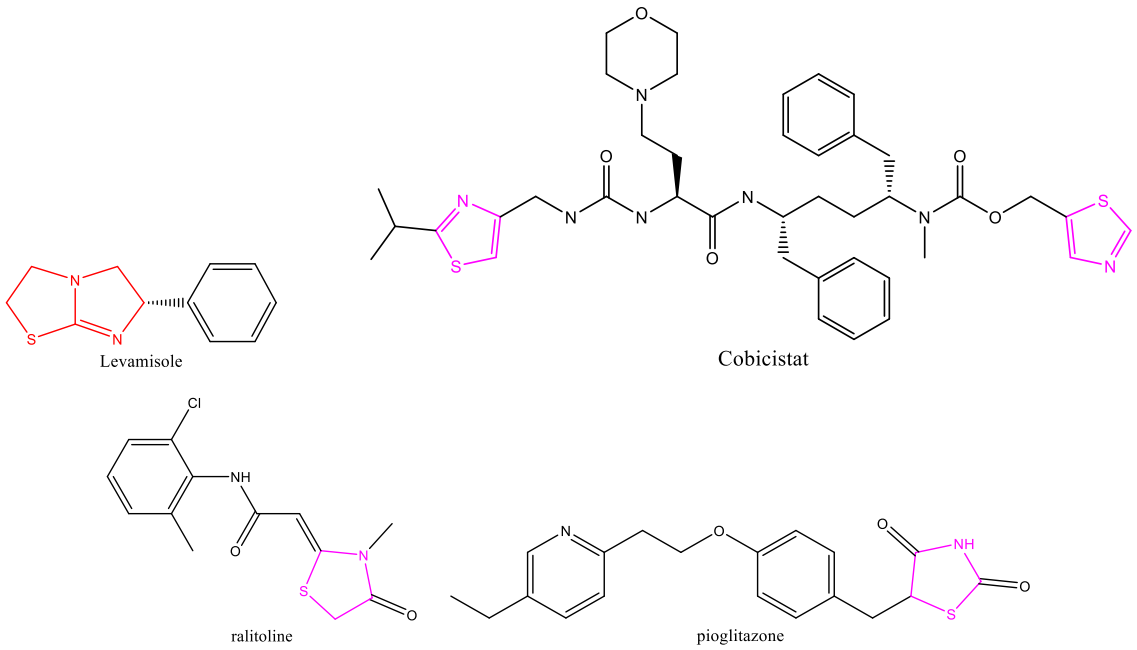


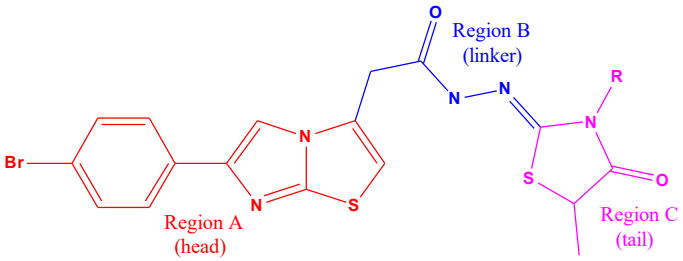
Figure 1. Drugs containing thiazole or imidazo[2,1-b]thiazole nucleus approved by FDA

The thiazolidine derivatives form with sulfur, nitrogen, and a carbonyl at positions one, three, and four respectively are called 4-thiazolidinones. The nucleus is a marvellous pharmacophore in terms of biological effectiveness [11-14]. Moreover, the 4-thiazolidinone scaffold is present in many FDA-approved drug such as ralitoline (anticonvulsant), pioglitazone (hypoglycemic) [9].

By considering the literature, our research group designed a series of thiosemicarbazides and 4-thiazolidinones in 2016. However, 4-thiazolidinone derivatives had not shown antiviral activity whereas thiosemicarbazide derivatives bearing an indole ring [15]. Furthermore, a different series of 4-thiazolidinone bearing imidazo[2,1-b]thiazole scaffolds were designed, synthesized, and evaluate for their antiviral activities. Consequently, especially some derivatives carrying allyl and methyl groups on the thiazolidinone ring exhibited great antiviral activity [16].

All in all, in this present study, the novel compounds were allocated as the head group (Region A), the linker chain (Region B), and the tail group (Region C) to shed a light on future studies (Scheme 1). The head group was taken as an Imidazo[2,1-*b*]thiazole derivative. The tail group was taken from 4-thiazolidinedinone with methyl substituent at third position and the linker between the head and tail groups was designated as hydrazone. The tail group that was expected to be key important for the antiviral activity consists of 3-ethylthiazolidinone, 3-propylthiazolidinone, 3-allylthiazolidinone, 3-butylthiazolidinone, 3-phenylthiazolidinone, 3-(4-methylphenyl)thiazolidinone, 3-(4-chlorophenyl)thiazolidinone, 3-(4-butylphenyl)thiazolidinone, 3-(4-nitrophenyl)thiazolidinone.

The designed novel compounds were evaluated their antiviral activities against Coxsackie B4 virus, Respiratory syncytial virus, Influenza A/H1N1 virus, Influenza A/H3N2, and Influenza B virus.



Scheme 1. Fragmentation of the compounds template for SAR study.

2. RESULTS AND DISCUSSION

3.1. Chemistry

Both ethyl 2-aminothiazole-4-acetic acid ester and 4-bromophenacyl bromide were dissolved in adequate acetone (approx. 30-35 mL) and reacted by occasionally stirring under room temperature for 3 days. As known, thiazole ring is susceptible to both electrophilic and nucleophilic attacks because of the movement of electrons through nitrogen[17]. Therefore, a partially positive carbon atom attacks nitrogen, found in the thiazole ring as embedded. thus, compound **1** was produced with a pretty high yield.

Compound **2** was obtained in about 20 minutes using a simple method that has been used many times by our group before. The hydrobromide form of compound **1** was obtained by heating compound **1** in a sufficient amount of absolute alcohol under refluxing cooler for 20 minutes[18].

Hydrazides are usually synthesized by reaction ester derivative with hydrazine. Moreover, these reaction conditions are utterly simple. Herein, compound **2**, an ester derivative, was reacted with hydrazine hydrate by heating under reflux for 5 hours. This reaction was carried out using exceed hydrazide hydrate. Order to make thiazolidinone derivatives, different isothiocyanate and ethyl 2-bromopropionate was added respectively directly into an acetone solution that contains compound **3** and boiled for 3-5 hours under reflux and constantly stirring. At the end of the reactions, the designed compounds (**5a-i**) were produced with between 22.40%.-95.00% yields.

When the chemical structures of the synthesized compounds were examined, it was observed that there was just one carbonyl group belonging to the hydrazinecarbothioamide moiety of **4a-i** whereas there were totally two carbonyl groups belonging to hydrazide-hydrazone moiety and thiazolidinone moiety of **5a-i**. Also according to the IR spectroscopy results, the stretching bands belonging to the carbonyl ring of hydrazide-hydrazone moiety of **5a-i** were between 1666-1635 cm^{-1}. Besides, the stretching bands belonging the carbonyl group of the thiazolidinone ring of **5a-i** were between 1753-1689 cm^{-1}. The presence of the stretching bands belonging to the two different carbonyl groups mentioned of **5a-i** indicated the formation of **5a-i** from **4a-i**. The IR values belonging to the carbonyl groups of **5a-i** were in agreement with literature [4, 14].

In addition, there were three diverse N-H protons belonging to the hydrazinecarbothioamide moiety of **4a-i** whereas there was just one N-H proton belonging to hydrazide-hydrazone moiety of **5a-i**. In the ^{1}H NMR analysis, decreasing the number of N-H peaks from three to one indicated the formation of **5a-i** from **4a-i**. The mentioned N-H peaks of **5a-i** were in the range of 11.44-10.62 ppm as singlet and this approved the formation of **5a-i** from **4a-i**.

Besides, the peaks belonging to CH and CH_3 protons of 5-$CHCH_3$ moiety of triazoles were distinctive indicators displaying the formation of **5a-i**. The mentioned CH peaks of **5a-i** were between 4.61-4.38 as quartet. In addition, the peaks belonging to the CH_3 protons of 5-$CHCH_3$ moiety of **5a-i** were between 1.60-1.50 ppm as doublets.

The IR, ^{1}H-NMR, ^{13}C-NMR and MS spectra of the novel compounds were in agreement with the assigned structures [19-21]. No unacceptable side reactions were observed.

3.2. Antiviral Activity

Since HeLa cells were started to use as the first human cell line, it is adopted entire the world to use for antiviral research. Many different viruses can be grown in HeLa cell line alongside poliovirus [22]. Therefore, in this study, HeLa cell line was used to identify EC_{50} values of the synthesized compounds against Coxsackie B4 virus and Respiratory syncytial virus.

According to the results of *in vitro* studies, compounds **5f**, and **5h** exhibited considerable activities against Coxsackie B4 virus and Respiratory syncytial virus with 9 uM and 12 µM (see Table 1). In comparison with Ribavirin their activities, it is obvious that their activities on Coxsackie B4 virus and Respiratory syncytial virus are higher fold approximately 8 times, and 1.5 times, respectively. However, the other derivatives have no considerable activities. On the other hand, we assume that an unsaturated group can able to get rid of the antiviral activity. Because derived thiazolidinone ring with allyl has shown no activity.

Aliphatic and phenyl substitutions didn't increase activity whereas the activity pretty raised with 4-bromophenyl (compound **5h**) and 4-methylphenyl (compound **5f**) substitutions. All in all, we believe that addition of atoms or atom groups with low electronegativity to the 4th position of the aromatic ring can increase antiviral activity.

Furthermore, on our previously researched we reported that any 4-thiazolidinone derivatives bearing either phenyl or 4-chlorophenyl (Region A) weren't shown any activity against Coxsackie B4 virus. However, the activity sharply increased by addition bromide at *para* position of phenyl (Region A). Therefore, we believe that p-bromo substitution might be affect the activity against Coxsackie B4 virus.

In addition, all compounds have no show cytotoxic effect except compound **5b** with ≥20 uM.

Table 1. Antiviral in HeLa cell cultures infected with Coxsackie B4 virus andRespiratory syncytial virus and cytotoxic activities in HeLa cell cultures.

Compounds	Antiviral EC_{50}[a] value (uM)		
	Coxsackie B4 virus	Respiratory syncytial virus	CC_{50}[c]
5a	>20	>20	100
5b	>20	>20	≥20
5c	>100	>100	≥100
5d	>20	>20	100
5e	>20	>20	100
5f	9	12	100
5g	>20	>20	100
5h	9	12	100
5i	>20	>20	100
DS-5000[b]	73	4	>100
(S)-DHPA	>250	>250	>250
Ribavirin	69	16	>250

[a] EC_{50}: 50% effective concentration, producing 50% inhibition of virus-induced cytopathic effect, as determined by microscopy.
[b] DS-5000: dextran sulfate of MW 5000.
[c] CC_{50}: 50% cytotoxic concentration, assessed by the spectroscopic MTS cell viability assay
All Data are expressed in µM.

Furthermore, particularly compounds **5b**, and **5d** displayed great antiviral effects against A/H3N2 (bird flu) by comparison with Amantadine and Ribavirin. However, their antiviral activity on Influenza A/H3N2 has displayed less effect than Zanamivir and Rimantadine as well. Nevertheless, derived compounds with aromatic rings have shown activity against none of the influenza viruses. Although the antiviral activities of

the compounds were increased by the addition of aliphatic moieties to the nitrogen of the thiazolidinone ring, the addition of an unsaturated aliphatic group completely abolished the effect. A similar situation was observed in efficacy against coxsackie B4 virus and Respiratory syncytial virus as well. Therefore, we believe that an unsaturated structure may adversely affect the antiviral effect. In addition, the antiviral effect may increase with the elongation of the aliphatic chain. Because when the effects of ethyl, propyl, and butyl derivatives were compared, the butyl derivative showed the best effect (see Table 2). On another hand, some derivatives (compounds **5a, 5e-i**) exhibited cytotoxic effects whereas none show antiviral activities against all kinds of influenza.

Table 1. Antiviral activity in MDCK cell cultures infected with Influeanza A/H1N1, Influenza A/H3N2 and Influenza B and cytotoxic activities of the title compounds in MDCK cell line

Compounds	Antiviral EC_{50}[a] value (uM)				
	Influeanza A/H1N1	**Influenza A/H3N2**	**Influenza B**	**CC_{50}[b]**	**MCC[c]**
5a	>100	>100	>100	36	20
5b	**25**	**11**	>100	>100	≥20
5c	>100	>100	>100	>100	≥100
5d	**35**	**2.9**	>100	>100	≥100
5e	>100	>100	>100	13	20
5f	>100	>100	>100	7.9	9.3
5g	>100	>100	>100	4.2	9.3
5h	>100	>100	>100	5.4	9.3
5i	>100	>100	>100	8.7	9.3
Zanamivir	1.2	3.7	25	>100	>100
Ribavirin	7.6	6.9	4.2	>100	≥20
Amantadine	119	0.50	>500	>500	≥500
Rimantadine	5.3	0.046	>500	-	-

[a] EC_{50}: 50% effective concentration, producing 50% inhibition of virus-induced cytopathic effect, as determined by microscopy.
[b] CC_{50}: 50% cytotoxic concentration, assessed by the spectroscopic MTS cell viability assay.
[c] MCC: minimum inhibitory concentration, or compound concentration causing minimal changes in cell morphology, as assessed by microscopy.
All data are expressed in µM

3. CONCLUSION

The fact is that various viruses are still dangerous in the present day. Therefore, novel probable antiviral molecule design and evaluation are vital. In the present study, novel 4-thiazolidinone derivatives bearing imidazo[2,1-*b*]thiazole nucleus were synthesized using simple and practical methods, and furthermore, their structure was characterized using various spectroscopic methods such as FT-IR, ^{1}H-NMR, ^{13}C-NMR, elemental analysis, and mass spectroscopy. All synthesized compounds were investigated for their antiviral activities against diverse viruses such as Coxsackie B4 virus, Respiratory syncytial virus, Influenza A/H1N1 virus, Influenza A/H3N2 virus, and Influenza B virus. Especially the compounds carrying 4-methylphenyl and 4-bromophenyl substitution at the N position of 4-thiazolidinone ring showed high antiviral activities against both Coxsackie B4 virus and Respiratory syncytial virus. Additionally, the compounds carrying propyl and butyl at the same position of 4-thiazolidinone ring displayed significant antiviral activities against Influenza A/H3N2 virus. The biological assay data and also SAR evaluation obtained from this study may assist in the future discovery of new and better antiviral compounds.

4. MATERIALS AND METHODS

4.1. Materials

All purchased solvents and reagents From Merck, Fluka, and Sigma-Aldrich were used with no further purification. Melting points of all synthesized compounds were detected on Büchi B-540 melting point apparatus in open capillary tubes and are uncorrected. Elemental analyses were achieved using hermo Finnigan Flash EA 1,112 elemental analyser. FT-IR spectrums were performed on KBR discs using Shimadzu IR Affinity-1 FT-IR spectrophotometer a Varian UNITY INOVA (500 MHz) spectrometer was worked to record ^{1}H-NMR, ^{13}C-NMR (APT), ^{13}C-NMR (DEPT), and HSQC (^{1}H-^{13}C) spectra, and DMSO-D6 was used as the solvent. Mass spectra were recorded on a Thermo Finnigan LCQ Advantage Max instrument.

4.2. Chemical Synthesis

4.2.1. The Procedure for the synthesis of compounds

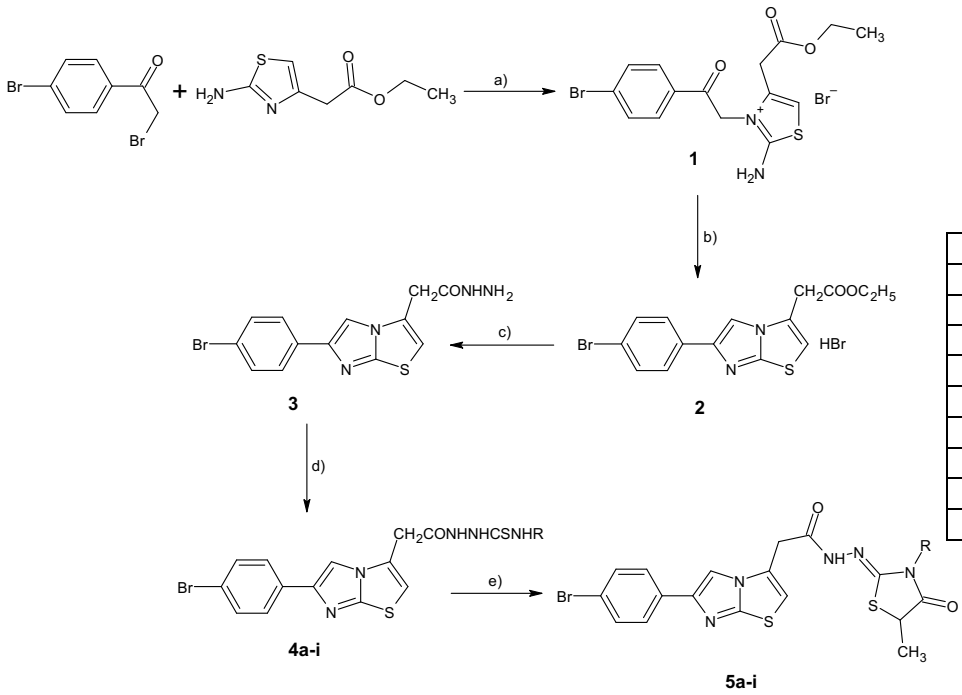
Compounds **1, 2,** and **3** were synthesized using previously reported method [18].

4-Alkyl/aryl-1-[[6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl]acetyl]thiosemicarbazides (4a-i)

In 30 ml of ethanol 99%, 0.005 mol compound 3 was heated under reflux in a water bath until a clear solution is formed. After 3 hours, 0.005 moles of alkyl/aryl isothiocyanate was added and heated. The precipitated product was filtered and refined by crystallization from ethanol or washed with ethanol after the reaction mixture was cooled to room temperature.

2-(6-(4-Bromophenyl)imidazo[2,1-b]thiazol-3-yl)-N′-(3-(alkyl/alkenyl/aryl)-5-methyl-4-oxothiazolidin-2-ylidene)acetohydrazide (5a-i)

0.005 mol of compound 4a-I and ethyl 2-bromopropiponate were prepared as a mixture in 25 mL of anhydrous ethanol presence with 0.02 mol of fused sodium acetate and the mixture was heated under reflux for 5 hours in a water bath. The reaction mixture was cooled, diluted with water, and allowed to stand overnight. The precipitate was filtered, dried, and recrystallized from ethanol 96%.



Comp.	R
5a	Et
5b	Pr
5c	Allyl
5d	Bu
5e	Ph
5f	4-MePh
5g	4-ClPh
5h	4-BrPh
5i	4-NO_2Ph

Scheme 2. The synthetic method for the preparation of the thiazolidinone derivatives. Reaction conditions: a) aceton, rt, 72h; b) absolute ethanole, 20 min; c) $NH_2NH_2.H_2O$, reflux, 5h; d) R-NCS, reflux, 3h; e) $CH_3CHBrCOOC_2H_5$, CH_3COONa, reflux (130°C), 5h

2-(6-(4-Bromophenyl)imidazo[2,1-*b*]thiazol-3-yl)-N′-(3-ethyl-5-methyl-4-oxothiazolidin-2-ylidene)acetohydrazide (5a)

White solid, mp 248-249 °C, yield: 40.6%. Anal. Calcd. For $C_{19}H_{18}BrN_5O_2S_2$: C, 46.34; H, 3.68; N, 14.22%. Found: C, 46.30; H, 3.80; N, 14.05%. IR υmax (KBr, cm^{-1}): 3178, 3149 (N-H stretching), 3078 (ar. C-H stretching), 2976, 2891 (aliph. C-H asymmetric and symmetric stretching), 1716, 1691 (thiazolidinone C=O stretching), 1662 (amide I C=O stretching), 1610, 1558 (imid.thia. C=N, C=C, ar. C=C stretching and amide II N-H bending and C-N stretching combination bands), 1462, 1388 (aliph. C-H asymmetric and symmetric bending), 1226 (amide III N-H bending and C-N stretching combination bands), 1064 (ar. C-Br stretching band), 844 (ar. 1,4-disubstitution). ^{1}H NMR (500 MHz) (DMSO-d_6/TMS) δ (ppm): 1.12 (t, 3H, *J* =7.32 Hz, thia. N-CH_2-$C\underline{H_3}$), 1.52 (d, 3H, *J* = 7.32 Hz, thia. 5-CHC$\underline{H_3}$), 3.67 (q, 2H, *J* = 7.32 Hz, thia. N-CH_2), 3.86 and 4.09 (2s, 2H, CH_2CO), 4.38 (q, 1H, *J* = 6.38 Hz, tiy. 5-C$\underline{H}$CH3), 7.04 and 7.06 (2s, 1H, imid.thia. C_2-H), 7.58 (t, 2H, *J* = 8.79 Hz, Br-Ph $C_{3,5}$-H), 7.76-7.79 (m, 2H, Br-Ph $C_{2,6}$-H), 8.22 and 8.26 (2s, 1H, imid.thia. C_5-H), 10.64 (s, 1H, CONH).

2-(6-(4-Bromophenyl)imidazo[2,1-*b*]thiazol-3-yl)-*N*′-(3-propyl-5-methyl-4-oxothiazolidin-2-ylidene)acetohydrazide (5b)

White solid, mp 240-241 °C, yield: 45%. Anal. Calcd. For $C_{20}H_{20}BrN_5O_2S_2$: C, 47.43; H, 3.98; N, 18.83%. Found: C, 47.14; H, 3.98; N, 13.66%. IR υmax (KBr, cm^{-1}): 3178, 3149 (N-H stretching), 3078 (ar. C-H stretching), 2966, 2889 (aliph. C-H asymmetric and symmetric stretching), 1718, 1689 (thiazolidinone C=O stretching), 1666 (amide I C=O stretching), 1614, 1558 (imid.thia. C=N, C=C, ar. C=C stretching and amide II N-H bending and C-N stretching combination bands), 1463, 1388 (aliph. C-H asymmetric and symmetric bending), 1228 (amide III N-H bending and C-N stretching combination bands), 1064 (ar. C-Br stretching band), 840 (ar. 1,4-disubstitution). ^{1}H NMR (500 MHz) (DMSO-d_6/TMS) δ (ppm): 0.82 (t, 3H, *J* = 7.32 Hz, thia. N-CH_2-CH_2-$C\underline{H_3}$), 1.52 (d, 3H, *J* = 7.32 Hz, thia. 5-CHC$\underline{H_3}$), 1.60 (sext., 2H, *J* = 7.32 Hz, thia. N-CH_2-$C\underline{H_2}$-CH_3), 3.61 (t, 2H, *J* = 7.32 Hz., N-$C\underline{H_2}$-CH_2-CH_3), 3.86 and 4.07 (2s, 2H, CH_2CO), 4.39 (q, 1H, *J* = 7.32 Hz, thia. 5-C$\underline{H}$$CH_3$), 7.03 and 7.06 (2s, 1H, imid.thia. C_2-H), 7.58 (t, 2H, *J* =8.78, Br-Ph, $C_{3,5}$-H), 7.76-7.79 (m, 2H, Br-Ph $C_{2,6}$-H), 8.22 and 8.26 (2s, 1H, imid.thia. C_5-H), 10.64 (s, 1H, CONH).

2-(6-(4-Bromophenyl)imidazo[2,1-*b*]thiazol-3-yl)-*N'*-(3-allyl-5-methyl-4-oxothiazolidin-2-ylidene)acetohydrazide (5c)

White solid, mp 235-236 °C, yield: 95%. Anal. Calcd. For $C_{20}H_{18}BrN_5O_2S_2$: C, 47.62; H, 3.60; N, 13.88%. Found: C, 47.47; H, 3.73; N, 13.69%. IR υmax (KBr, cm^{-1}): 3176, 3149 (N-H stretching), 3080 (ar. C-H stretching), 2983, 2891 (aliph. C-H asymmetric and symmetric stretching), 1718, 1689 (thiazolidinone C=O stretching), 1666 (amide I C=O stretching), 1610, 1558 (imid.thia. C=N, C=C, ar. C=C stretching and amide II N-H bending and C-N stretching combination bands), 1463, 1381 (aliph. C-H asymmetric and symmetric bending), 1226 (amide III N-H bending and C-N stretching combination bands), 1062 (ar. C-Br stretching band), 842 (ar. 1,4-disubstitution). ^{1}H NMR (500 MHz) (DMSO-d_6/TMS) δ (ppm): 1.54 (d, 3H, *J* = 7.32 Hz, thia. 5-CHC<u>H</u>$_3$), 3.86 and 4.05 (2s, 2H, CH_2CO), 4.28 (d, 2H, *J* = 5.37 Hz, thia. N-C<u>H</u>$_2$-CH_2=CH_2), 4.44 (q, 1H, *J* = 7.32 Hz, thia. 5-C<u>H</u>CH_3), 5.11 (dd, 1H, *J* = 11.22 ; 1.47 Hz, N-CH_2-CH=C<u>H</u>$_2$ cis), 5.16 (dd, 1H, *J* = 17.08 ; 1.46 Hz, N-CH_2-CH=C<u>H</u>$_2$ trans), 5.79-5.85 (m, 1H, N-CH_2-C<u>H</u>=CH_2), 7.03 and 7.06 (2s, 1H, imid.thia. C_2-H), 7.58 (t, 2H, *J* = 8.29 Hz, Br-Ph $C_{3,5}$-H), 7.76-7.79 (m, 2H, Br-Ph $C_{2,6}$-H), 8.19 and 8.25 (2s, 1H, imid.thia. C_5-H), 10.65 (s, 1H, CONH).

2-(6-(4-Bromophenyl)imidazo[2,1-*b*]thiazol-3-yl)-*N'*-(3-butyl-5-methyl-4-oxothiazolidin-2-ylidene)acetohydrazide (5d)

White solid, mp 221-223 °C, yield: 22.4%. Anal. Calcd. For $C_{21}H_{22}BrN_5O_2S_2$: C, 48.46; H, 4.26; N, 13.46. Found: C, 48.18; H, 4.16; N, 13.49%. IR υmax (KBr, cm^{-1}): 3182, 3153 (N-H stretching), 3016 (ar. C-H stretching), 2955, 2868 (aliph. C-H asymmetric and symmetric stretching), 1716, 1689 (thiazolidinone C=O stretching), 1664 (amide I C=O stretching), 1618, 1556 (imid.thia. C=N, C=C, ar. C=C stretching and amide II N-H bending and C-N stretching combination bands), 1464, 1386 (aliph. C-H asymmetric and symmetric bending), 1226 (amide III N-H bending and C-N stretching combination bands), 1072 (ar. C-Br stretching band), 827 (ar. 1,4-disubstitution). ^{1}H NMR (500 MHz) (DMSO-d_6/TMS) δ (ppm): 0.87 (t, 3H, *J* = 7.32 Hz, thia. N-CH_2-CH_2-CH_2-C<u>H</u>$_3$), 1.24 (sext. 2H, *J* = 7.32 Hz, thia. N-CH_2-CH_2-C<u>H</u>$_2$-CH_3), 1.50-1.58 (m, 5H, thia. 5-CHC<u>H</u>$_3$ and thia N-CH_2-C<u>H</u>$_2$-CH_2-CH_3), 3.66 (t, 2H, *J* = 7.32 Hz, thia. N-C<u>H</u>$_2$-CH_2-CH_2-CH_3), 3.86 and 4.07 (2s, 2H, CH_2CO), 4.39 (q, 1H, *J* = 7.32 Hz, thia. 5-C<u>H</u>CH_3), 7.03 and 7.06 (2s, 1H, imid.thia. C_2-H), 7.58 (t, 2H, *J* = 8.29 Hz, Br-Ph $C_{3,5}$-H), 7.76-7.79 (m, 2H, Br-Ph $C_{2,6}$-H), 8.22 and 8.26 (2s, 1H, imid.thia. C_5-H), 10.62 (s, 1H, CONH).

2-(6-(4-Bromophenyl)imidazo[2,1-*b*]thiazol-3-yl)-*N'*-(3-phenyl-5-methyl-4-oxothiazolidin-2-ylidene)acetohydrazide (5e)

White solid, mp 248-250 °C, yield: 36%. Anal. Calcd. For $C_{23}H_{18}BrN_5O_2S_2$: C, 51.12; H, 3.36; N, 12.96%. Found: C, 51.23; H, 3.46; N, 12.86%. IR υmax (KBr, cm^{-1}): 3115 (N-H stretching), 3020 (ar. C-H stretching), 2928, 2860 (aliph. C-H asymmetric and symmetric stretching), 1751, 1705 (thiazolidinone C=O stretching), 1635 (amide I C=O stretching), 1589, 1531 (imid.thia. C=N, C=C, ar. C=C stretching and amide II N-H bending and C-N stretching combination bands), 1458, 1392 (aliph. C-H asymmetric and symmetric bending), 1238 (amide III N-H bending and C-N stretching combination bands), 1064 (ar. C-Br stretching band), 825 (ar. 1,4-disubstitution). ^{1}H NMR (500 MHz) (DMSO-d_6/TMS) δ (ppm): 1.53 and 1.58 (2d, 3H, *J* = 6.84; 6.83 Hz, thia. 5-CH-C<u>H</u>$_3$), 4.03-4.15 (m, 2H, CH_2CO), 4.48 and 4.53 (2q, 1H, *J* = 7.32; 7.33 Hz, thia. 5-C<u>H</u>CH3), 6.89 and 6.91 (dd, 2H, $J_{2,3 \text{ and } 6,5}$ = 7.32 Hz, $J_{2,4 \text{ and } 6,4}$= 1.47 Hz, thia. 3-Ph $C_{2,6}$-H), 7.16-7.18 (m, 2H, imid.thia. C_2-H and thia. 3-Ph C_4-H), 7.34-7.36 (tt, 2H, $J_{3,2/3,4 \text{ and } 5,6/5,4}$ = 7.32 Hz, $J_{3,5/5,3}$ = 1.95 Hz, thia. 3-Ph $C_{3,5}$-H), 7.40-7.43 (m, 2H, Br-Ph $C_{3,5}$-H), 7.57-7.61 (m, 2H, Br-Ph $C_{2,6}$-H), 8.16 (s, 1H, imid.thia. C_5-H), 11.39 (s, 1H, CONH).

^{1}H-NMR (D_2O) (500 MHz) (DMSO-d_6 /TMS) δ (ppm): 1.49 and 1.52 (2d, 3H, *J* = 6.84; 7.33 Hz, thia. 5-CH-C<u>H</u>$_3$), 3,98-4,09 (m, 2H, CH_2CO), 4,37 and 4,40 (2q, 1H, *J* = 7.32; 7.32 Hz, thia. 5-C<u>H</u>CH3), 6.85 and 6.86 (dd, 2H, $J_{2,3 \text{ and } 6,5}$= 7,32 Hz, $J_{2,4 \text{ and } 6,4}$ = 1.47 Hz, thia. 3-Ph $C_{2,6}$-H), 7.09-7.13 (m, 2H, imid.thia. C_2-H and thia. 3-Ph C_4-H), 7.28-7.30 (tt, 2H, $J_{3,2/3,4 \text{ and } 5,6/5,4}$= 7.81 Hz, $J_{3,5/5,3}$ = 1,95 Hz, thia. 3-Ph $C_{3,5}$-H), 7.34-7.37 (m, 2H, Br-Ph $C_{3,5}$-H), 7.50-7.52 (m, 2H, Br-Ph $C_{2,6}$-H), 8.09 (s, 1H, imid.thia. C_5-H).

^{13}C-NMR (APT) (125 MHz) (DMSO-d_6 /TMS) δ (ppm): 19.70, 19.88 (thia. 5-CH_3), 33.03, 33.08 (CH_2), 40.38, 40.44 (thia. 5-CH), 109.26 (imid.thia. C_5), 111.83, 111.87 (imid.thia. C_2), 120.47 (Br-Ph C_4), 121.46 (thia. 3-Ph $C_{2,6}$), 125.29; 125.34 (thia. 3-Ph C_4), 126.23, 126.26 (imid. thia. C_3), 127.18 (Br-Ph $C_{2,6}$), 130.13 (thia. 3-Ph $C_{3,5}$),

132.15 (Br-Ph $C_{3,5}$), 134.01, 134.02 (Br-Ph C_1), 145,63 (imid.thia. C_6), 148.16, 148.20 (thia. 3-Ph C_1), 149.65 (imid.thia. C_{7a}), 151.82, 152.11 (thia. C_2=N), 166.37, 166.44 (CONH), 172.48, 172.62 (thia. C=O).

^{13}C-NMR (DEPT) (125 MHz) (DMSO-d_6 /TMS) δ (ppm**):** 19.70, 19.88 (thia. 5-CH_3), 33.02, 33.08 (CH_2), 40.38, 40.44 (thia. 5-CH), 109.23, 109.25 (imid.thia. C_5), 111.83, 111.87 (imid.thia. C_2), 121.46 (thia. 3-Ph $C_{2,6}$), 125.29, 125.34 (thia. 3-Ph C_4), 127.18 (Br-Ph $C_{2,6}$), 130,13 (thia. 3-Ph $C_{3,5}$), 132.15 (Br-Ph $C_{3,5}$).

^{13}C-NMR (HSQC) (125 MHz) (DMSO-d_6 /TMS) δ (ppm): 19.70, 19.88 (thia. 5-CH_3), 33.03, 33.09 (CH_2), 40.32, 40.44 (thia. 5-CH), 109.23, 109.26 (imid.thia. C_5), 111.83, 111.87 (imid.thia. C_2), 120.47 (Br-Ph C_4), 121.46 (thia. 3-Ph $C_{2,6}$), 125.29, 125.34 (thia. 3-Ph C_4), 126.23, 126.26 (imid.thia. C_3), 127.18 (Br-Ph $C_{2,6}$), 130.13, 130.22 (thia. 3-Ph $C_{3,5}$), 132.15 (Br-Ph $C_{3,5}$), 134.00, 134.02 (Br-Ph C_1), 145,63 (imid.thia. C_6), 148.16, 148.20 (thia. 3-Ph C_1), 149.65 (imid.thia. C_{7a}), 151.82, 152.11 (thia. C_2=N), 166.37, 166.44 (CONH), 172.48, 172.62 (thia. C=O).

ESI (+) MS m/z (%): 542 ([M+H+2]$^+$, 100), 540 ([M+H]$^+$, 85), 337 (3), 336 (20), 335 (2), 334 (19), 321 (39), 319 (39), 294 (2), 292 (2), 222 (1).

ESI (+) MS2 m/z (%):542 ([M+H+2]$^+$, 17), 540 ([M+H]$^+$, 36), 337 (0.3), 336 (1), 335 (0.5), 321 (100), 319 (40), 222 (11).

2-(6-(4-Bromophenyl)imidazo[2,1-*b*]thiazol-3-yl)-*N*′-(3-(4-metylphenyl)-5-methyl-4-oxothiazolidin-2-ylidene)acetohydrazide (5f)

White solid, mp 272-273 °C, yield: 30%. Anal. Calcd. For $C_{24}H_{20}BrN_5O_2S_2$: C, 51.99; H, 3.64; N, 12.63%. Found: C, 51.59; H, 3.56; N, 12.51%. IR υmax (KBr, cm^{-1}): 3115 (N-H stretching), 3024 (ar. C-H stretching), 2912, 2866 (aliph. C-H asymmetric and symmetric stretching), 1749, 1714 (thiazolidinone C=O stretching), 1643 (amide I C=O stretching), 1604, 1539 (imid.thia. C=N, C=C, ar. C=C stretching and amide II N-H bending and C-N stretching combination bands), 1460, 1388 (aliph. C-H asymmetric and symmetric bending), 1271(amide III N-H bending and C-N stretching combination bands), 1074 (ar. C-Br stretching), 829 (ar. 1,4-disubstitution).

^{1}H-NMR (500 MHz) (DMSO-d_6 /TMS) δ (ppm): 1.52 and 1.56 (2d, 3H, *J* = 7.32 ; 7.32 Hz, thia. 5-CH-C$\underline{H}_3$), 2.30 (s, 3H, thia. 3-Ph 4-CH_3), 3.99-4.13 (m, 2H, CH_2CO), 4.46 and 4.50 (2q, 1H, *J* = 7.32; 7.32 Hz, thia. 5-C$\underline{H}$CH3), 6.77 (d, 2H, *J* = 8.30 Hz, thia. 3-Ph $C_{3,5}$-H), 7.12-7.15 (m, 3H, imid.thia. C_2-H and thia. 3-Ph $C_{2,6}$-H), 7.38 (t, 2H, *J* = 8.30 Hz, Br-Ph $C_{3,5}$-H), 7.52-7.54 (m, 2H, Br-Ph $C_{2,6}$-H), 8.13 and 8.14 (2s, 1H, imid.tiy. C_5-H).

2-(6-(4-Bromophenyl)imidazo[2,1-*b*]thiazol-3-yl)-*N*′-(3-(4-chlorophenyl)-5-methyl-4-oxothiazolidin-2-ylidene)acetohydrazide (5g)

White solid, mp 270-271 °C, yield: 51%. Anal. Calcd. For $C_{23}H_{17}BrClN_5O_2S_2$: C, 48.05; H, 2.98; N, 12.18%. Found: C, 47.62; H, 3.12; N, 11.44%. IR υmax (KBr, cm^{-1}): 3118 (N-H stretching), 3001 (ar. C-H stretching), 2933, 2868 (aliph. C-H asymmetric and symmetric stretching), 1753, 1716 (thiazolidinone C=O stretching), 1647 (amide I C=O stretching), 1587, 1539 (imid.thia. C=N, C=C, ar. C=C stretching and amide II N-H bending and C-N stretching combination bands), 1462, 1396 (aliph. C-H asymmetric and symmetric bending), 1273 (amide III N-H bending and C-N stretching combination bands), 1076 (ar. C-Br stretching), 835 (ar. 1,4-disubstitution).

^{1}H-NMR (500 MHz) (DMSO-d_6 /TMS) δ (ppm): 1.52 and 1.57 (2d, 3H, *J* = 7.32; 7.32 Hz, thia. 5-CH-C$\underline{H}_3$), 4.00-4.14 (m, 2H, CH_2CO), 4.50 and 4.55 (2q, 1H, *J* = 7.32 ; 6.83 Hz, thia. 5-C$\underline{H}$CH$_3$), 6.88 (d, 2H, *J* = 8.78 Hz, thia. 3-Ph $C_{3,5}$-H), 7.15 (s, 1H, imid.thia. C_2-H), 7.37 (d, 2H, *J* = 8.78 Hz, thia. 3-Ph $C_{2,6}$-H), 7.40-7.43 (m, 2H, Br-Ph $C_{3,5}$-H), 7.52-7.55 (m, 2H, Br-Ph $C_{2,6}$-H), 8.10 (s, 1H, imid.thia. C_5-H), 11.33 and 11.38 (2s, 1H, CONH).

2-(6-(4-Bromophenyl)imidazo[2,1-*b*]thiazol-3-yl)-*N*′-(3-(4-bromophenyl)-5-methyl-4-oxothiazolidin-2-ylidene)acetohydrazide (5h)

White solid, mp 281-282 °C, yield: 74%. Anal. Calcd. For $C_{23}H_{17}Br_2N_5O_2S_2$: C, 44.60; H, 2.77; N, 11.31%. Found: C, 44.98; H, 2.83; N, 11.40 %. IR υmax (KBr, cm^{-1}): 3119 (N-H stretching), 3032 (ar. C-H stretching), 2931, 2868 (aliph. C-H asymmetric and symmetric stretching), 1753, 1716 (thiazolidinone C=O stretching), 1649 (amide I C=O stretching), 1581, 1539 (imid.thia. C=N, C=C, ar. C=C stretching and amide II N-H bending and C-N stretching combination bands), 1460, 1388 (aliph. C-H asymmetric and symmetric bending), 1271 (amide III N-H bending and C-N stretching combination bands), 1068 (ar. C-Br stretching), 833 (ar. 1,4-disubstitution).

^{1}H-NMR (500 MHz) (DMSO-d_6 /TMS) δ (ppm): 1.52 and 1.57 (2d, 3H, *J* = 7.32 ; 7.32 Hz, thia. 5-CH-C$\underline{H}_3$), 4.00-4.14 (m, 2H, CH_2CO), 4.51 and 4.55 (2q, 1H, *J* = 6.83 ; 7.33 Hz, thia. 5-C$\underline{H}CH_3$), 6.83 (d, 2H, *J* = 8.30 Hz, thia. 3-Ph $C_{3,5}$-H), 7.15 (s, 1H, imid.thia. C_2-H), 7.40-7.43 (m, 2H, Br-Ph $C_{3,5}$-H), 7.47-7.54 (m, 4H, thia. 3-Ph $C_{2,6}$-H and Br-Ph $C_{2,6}$-H), 8.09 (s, 1H, imid.thia. C_5-H), 11.33 and 11.37 (2s, 1H, CONH).

2-(6-(4-Bromophenyl)imidazo[2,1-*b*]thiazol-3-yl)-*N*′-(3-(4-nitrophenyl)-5-methyl-4-oxothiazolidin-2-ylidene)acetohydrazide (5i)

White solid, mp 267-268 °C, yield: 91%. Anal. Calcd. For $C_{23}H_{17}BrN_6O_4S_2$: C, 47.19; H, 2.93; N, 14.35%. Found: C, 47.02; H, 2.97; N, 14.26%. IR υmax (KBr, cm^{-1}): 3130 (N-H stretching), 3095 (ar. C-H stretching), 2981, 2931 (aliph. C-H asymmetric and symmetric stretching), 1749, 1693 (thiazolidinone C=O stretching), 1645 (amide I C=O stretching), 1581, 1539 (imid.thia. C=N, C=C, ar. C=C stretching and amide II N-H bending and C-N stretching combination bands), 1462, 1386 (aliph. C-H asymmetric and symmetric bending), 1286 (amide III N-H bending and C-N stretching combination bands), 1076 (ar. C-Br stretching), 858 (ar. 1,4-disubstitution).

^{1}H-NMR (500 MHz) (DMSO-d_6 /TMS) δ (ppm): 1.54 and 1.60 (2d, 3H, *J* = 7.32; 6.83 Hz, thia. 5-CH-C$\underline{H}_3$), 4.02-4.14 (m, 2H, CH_2CO), 4.55 and 4.61 (2q, 1H, *J* = 7.32 ; 6.83 Hz, thia. 5-C$\underline{H}CH_3$), 7.05 (d, 2H, *J* = 8.78 Hz, thia. 3-Ph $C_{2,6}$-H), 7.16 (s, 1H, imid.thia. C_2-H), 7.40-7.42 (m, 2H, Br-Ph $C_{3,5}$-H), 7.53-7.55 (m, 2H, Br-Ph $C_{2,6}$-H), 8.12 (s, 1H, imid.thia. C_5-H), 8.16 (d, 2H, *J* = 6.83 Hz, thia. 3-Ph $C_{3,5}$-H), 11.44 (s, 1H, CONH).

4.3. Biological Study

The designed and synthesized compounds **5a-i** were evaluated against various viruses, using the following cell-based assays: a) Human cervix carcinoma HeLa cells infected with Coxsackie B4 virus or respiratory syncytial virus b) Mardin-Darby canine kidney (MDCK) cells infected with influenza A/H1N1, A/H3N2 or influenza B virus.

To achieved 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 and moreover DS-5000, (S)-DHPA, Ribavirin, Zanamivir, Amantadine, and Rimantadine were used as appropriate reference compounds. The cultures were analyzed by microscopy to determine the compounds' inhibitory effect on virus-induced cytopathic effect (CPE) or their cytotoxicity after 3-6 days incubation at 37°C (or 35°C in the case of influenza virus). The colorimetric MTS cell viability assay was used to confirm antiviral and cytotoxic activities for some viruses [23].

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