ORIGINAL RESEARCH

Synthesis, characterization and antiviral evaluation of 1,3-Thiazolidine-4-one derivatives bearing L-Valine side chain

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ABSTRACT: 1,3-Thiazolidine-4-ones have been known to possess anti-HIV and anti-HCV activity as they are, respectively, HIV-1 non-nucleoside reverse transcriptase inhibitors and HCV NS5B RNA-dependent RNA-polymerase inhibitors. Some novel 1-[2-(benzoylamino)-3-methylbutyryl]-4-alkyl/arylalkylthiosemicarbazides, 2-[2-(benzoylamino)-3-methylbutyryl-hydrazono]-3-alkyl-/arylalkyl- 5-non substituted/methyl-1,3-thiazolidinones, were synthesized and evaluated for their antiviral activity. Antiviral activity of the synthesized compounds were screened against various types of viruses *(Feline Corona Virus (FIPV), Feline Herpes Virus, HSV-1(KOS), HSV-1(TK-KOS ACVr), HSV-2(G), Vaccinia virus, Vesicular stomatitis virus, Varicella-ZosterVirus TK+VZV, Varicella-ZosterVirus TK-VZV, Cytomegalovirus, Respiratory syncytial virus, Coxsackie B4 virus, Parainfluenza-3 virus, Reovirus-1, Sindbis virus and Punta Toro virus)* in CRFK, HEL, HeLa and Vero cell cultures. Anti-HIV and cytotoxicity data were also obtained with the compounds using the strains HIV-1 (III_B) and HIV-2 (ROD) in an MT-4/MTT based assay. None of the tested compounds showed antiviral activity at subtoxic concentrations. For all the synthesized compounds anti-HCV NS5B RdRp activity was not observed at the concentration of 100 μM which was the highest concentration tested.

KEYWORDS: 4-Thiazolidinones, L-valine, anti-HIV activity, anti-HCV activity.

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INTRODUCTION

The 4-thiazolidinone ring system comprises a large number of biologically active compounds which have been evaluated as antibacterial (1-3), antitubercular (4-7), antifungal (8), antimalarial (9), or antiviral (10-23). Since infectious diseases are one of the leading causes of death worldwide (24) the infectious agents continue to evolve and adapt to existing therapies, via giving rise to resistance. Researchers have persisted in performing synthesis and biological evaluation of novel therapeutics.

AIDS (Acquired Immune Deficiency Syndrome) is one of the most spread and most deadly diseases in the modern era. According to the statistical data on the AIDS epidemic provided in 2010 by WHO, there were 33.3 million people living with HIV, 2.6 million new HIV infections and 1.8 million AIDS-related deaths in 2009 (25). AIDS is the end-stage disease of HIV (human immunodeficiency virus) infection which was identified as a disease in 1981. HIV is a retrovirus which only replicates in certain human cells. With the aim of suppressing the infectivity, replication and virulence of HIV lots of new compounds were synthesized and among these compounds 25 of them have been licensed until 2008 (26). To infect its host cells, the retrovirus uses three essential enzymes: reverse transcriptase (RT), integrase (IN), protease (PR) (27). RT has been a major target for antiretroviral drug development and more than half of the currently approved drugs for the treatment of HIV-1 infection are RT inhibitors (28). There are five NNRTIs approved for clinical use: nevirapine, delavirdine, efavirenz, etravirine and rilpivirine (Figure 1). According to crystallographic studies of HIV-1 RT, the common binding mode of first-generation NNRTIs such as nevirapine and delavirdine could be defined as "butterfly-like" despite the chemical diversity of NNRTIs (29). The next-generation NNRTIs, diarylpyrimidine (DAPY) analogues such as etravirine and rilpivirine adopt different conforma-

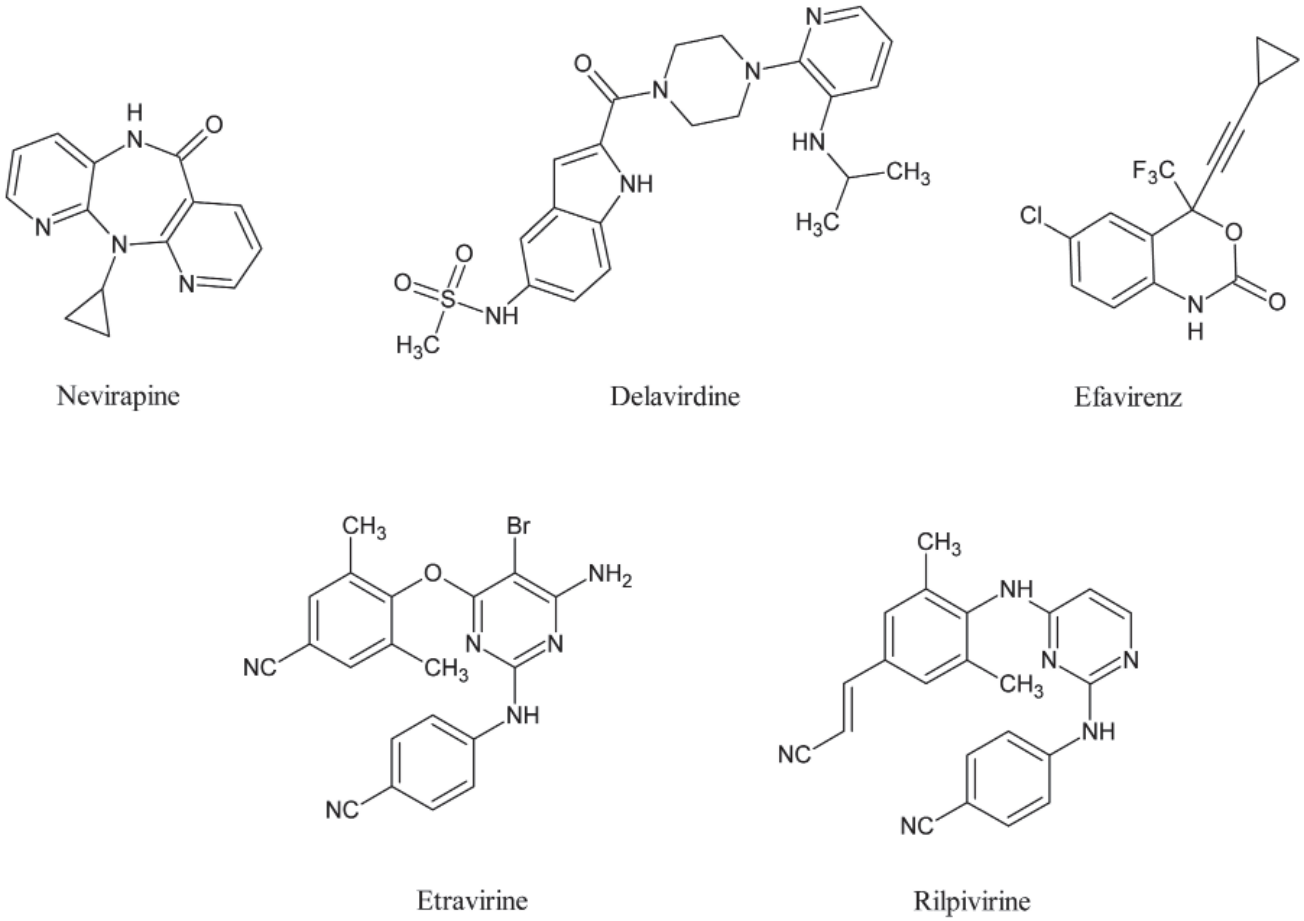


FIGURE 1. Structures of approved non-nucleoside reverse transcriptase inhibitors.

tional modes through their torsional flexibility and ability to reposition within the NNRTI binding pocket (26, 30-31). The resistance to NNRTIs following accumulation of two or more amino acid mutations as compared with the wild-type strain has led to the synthesis of new HIV-1 RT inhibitors bearing 1,3-thiazolidine-4-one core (Figure 2) (11-18). Therefore, we synthesized novel 1,3-thiazolidine-4-ones and studied their antiviral activity in accordance with our antiviral drug development attempt (6, 32-35).

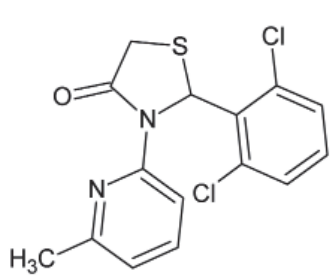
Furthermore, 4–thiazolidinone derivatives have also been shown to exhibit anti-hepatitis C virus (HCV)activity as HCV NS5B polymerase inhibitors (20-21) and HCV NS5A inhibitors (Figure 2) (22-23). The therapeutic potential of the thiazolidinone scaffold against HCV NS5B employing 2′,4′-difluoro-4-hydroxybiphenyl-3-carboxylic acid [2-(5-nitro-2-furyl / substituted phenyl)-4-thiazolidinone-3-yl] amides were explored by Kaushik-Basu et.al (20). Of these evaluated derivatives the lead compound; 2′,4′-difluoro-4-hydroxybiphenyl-3-carboxylic acid[2-(2-fluorophenyl)-4-thiazolidinone-3-yl]amide, which was previously synthesized by Küçükgüzel *et al.* (3), exhibited an IC_{50} value of 48 microM. Taken together, 1,3-thiazolidine-4-ones synthesized in the present study were also assessed for their hepatitis C virus NS5B polymerase inhibitory activity.

Due to the fact of recurrent or persistent co-infections with the GB virus C (GBV-C), HBV, HCV, HSV-2 increases morbidity and mortality among *HIV-infected* individuals by the reason of increasing the HIV viral load (36-38), there is an urgent need for the treatment of these co-infections. The 4-thiazolidinone scaffold has not been shown to exhibit activity against *Feline Corona Virus (FIPV), Feline Herpes Virus, HSV-1(KOS), HSV-1(TK-KOS ACV^r), HSV-2(G), Vaccinia virus, Vesicular stomatitis virus, Varicella-ZosterVirus TK$^+$VZV, Varicella-ZosterVirus TK$^-$VZV, Cytomegalovirus, Vesicular stomatitis virus, Respiratory syncytial virus, Coxsackie B4 virus, Parainfluenza-3 virus, Reovirus-1, Sindbis virus, Coxsackie B4 virus, and Punta Toro virus* yet. Since 4-thiazolidinone derivatives may be optimized for generating new analogues against the viruses mentioned above the antiviral activity of the synthesized 1,3-thiazolidine-4-ones were also studied against most of these viruses.

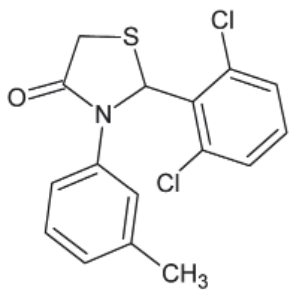
EXPERIMENTAL

Chemistry

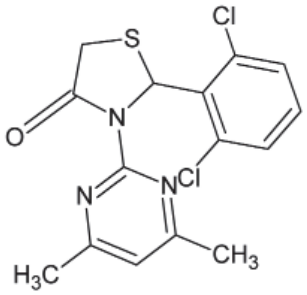
All solvents and reagents were obtained from commercial sources and used without purification. All melting points (^{o}C, uncorrected) were determined using Kleinfeld SMP-II basic model melting point apparatus. Elemental analysis was obtained using Leco CHNS-932 and is consistent with the assigned structures. Infrared spectra were recorded on Schimadzu FTIR 8400S and expressed in wavenumber (cm^{-1}). NMR



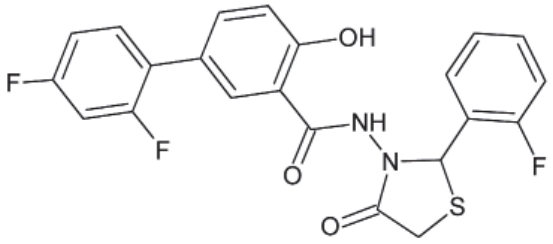
EC_{50} (HIV-1_{IIIB}) =0.044 μM
(Ref. 7)



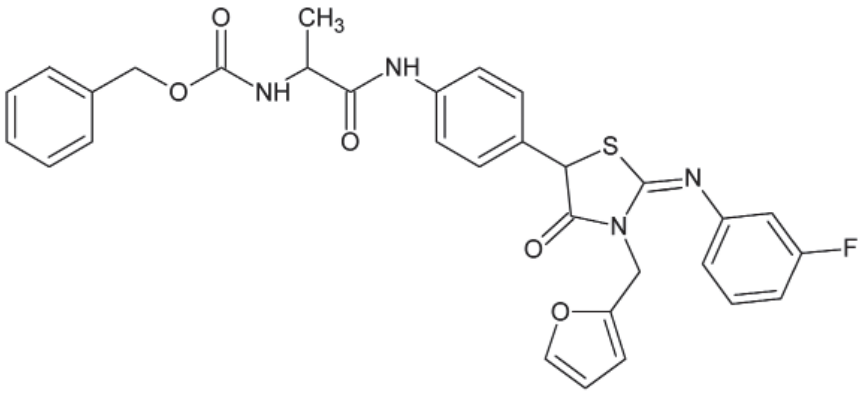
EC_{50} (HIV-1_{IIIB}) =0.080 μM
(Ref. 8)



EC_{50} (HIV-1_{IIIB}) =0.017 μM
(Ref. 9)



IC_{50} (HCV NS5B RdRp inhibitor) =48 μM
(Ref. 20)



BMS-858
EC_{50} (HCV NS5A) =0.57-1 μM
(Ref. 22)

FIGURE 2. New HIV-1 RT, HCV NS5B RdRp and HCV NS5A inhibitors bearing 1,3-thiazolidine-4-one core.

spectra were recorded on Bruker AVANCE-DPX 400 at 400 MHz for ^{1}H-NMR and 100 MHz for ^{13}C-NMR (DEPT and Decoupled), the chemical shifts were expressed in δ (ppm) downfield from tetramethylsilane (TMS) using DMSO-d_6 as solvent. The liquid chromatographic system consists of an Agilent technologies 1100 series instrument equipped with a quaternary solvent delivery system and a model Agilent series G1315 A photodiode array detector. A Rheodyne syringe loading sample injector with a 50 µl sample loop was used for the injection of the analytes. Chromatographic data were collected and processed using Agilent Chemstataion Plus software. The separation of compounds **3** and **4-18** were performed at ambient temperature by using a reversed phase Waters; µ-Bondapak CN (RP) (3.9 **x** 150 mm, 10 µm particle size) column. All experiments were employed in isocratic mode. The mobile phase was prepared by mixing acetonitrile and TEA-phosphate buffer pH=4.56 (1:99, v/v) and filtered through a 0.45 µm membrane and degassed by ultrasonication, prior to use. Solvent

delivery was employed at a flow rate of 1 ml.min^{-1}. Detection of the analytes were carried out at 254 nm.

2- (Benzoylamino)-3-methylbutyric acid (1)

(2*S*)-2-Amino-3-methylbutyric acid (L-valine, 1.17 g, 0.01 mol) was dissolved in sodium hydroxide solution (100 ml, 0.02 mol) and benzoyl chloride (1.40 g, 0.01 mol) was added to the reaction medium with stirring in an ice bath. The crude product was precipitated by conc.HCl, filtered and dried and washed with boiling petroleum ether. Yield 38%. M.p**.** 136-137ºC (39). HPLC t_R (min.): 1.5. IR, υ (cm^{-1}): 3298 (N-H), 3228 (H-bonded O-H), 3066 (=C-H), 2960, 2874 (C-H), 1722, 1695 (C=O), 1639 (C=O).

2- (Benzoylamino)-3-methylbutyric acid methyl ester (2)

(2*S*)-2-(Benzoylamino)-3-methylbutyric acid (0.01 mol) was dissolved in 20 ml methanol and 1 ml conc. H_2SO_4 was added. The reaction mixture was heated under reflux for 3 h. The crude product was precipitated by using $NaHCO_3$ solution (5%), filtered, dried and crystallized from petroleum ether. Yield 82%. M.p. 111-114ºC (40). HPLC t_R (min.): 3.54. IR, υ (cm^{-1}): 3074 (=C-H), 2966, 2874 (C-H), 1735 (C=O), 1639 (C=O), 1240 (C-O).

2- (Benzoylamino)-3-methylbutyric acid hydrazide (3)

(2*S*)-2-(Benzoylamino)-3-methylbutyric acid methyl ester (0.01 mol) and hydrazine hydrate were heated under reflux for 1 h and 25 ml methanol was added to the reaction medium. The mixture was heated under reflux for 1h. The crude product was filtered and washed with boiling petroleum ether. Yield 77%. M.p. 210-211ºC (41). HPLC t_R (min.): 1.88. IR, υ (cm^{-1}): 3269, 3184 (N-H), 1660 (C=O), 1624 (C=O).

General procedure for the synthesis of 1-[2-(benzoylamino)-3-methylbutyryl]-4-alkyl/arylalkyl-thiosemicarbazides (4-8).

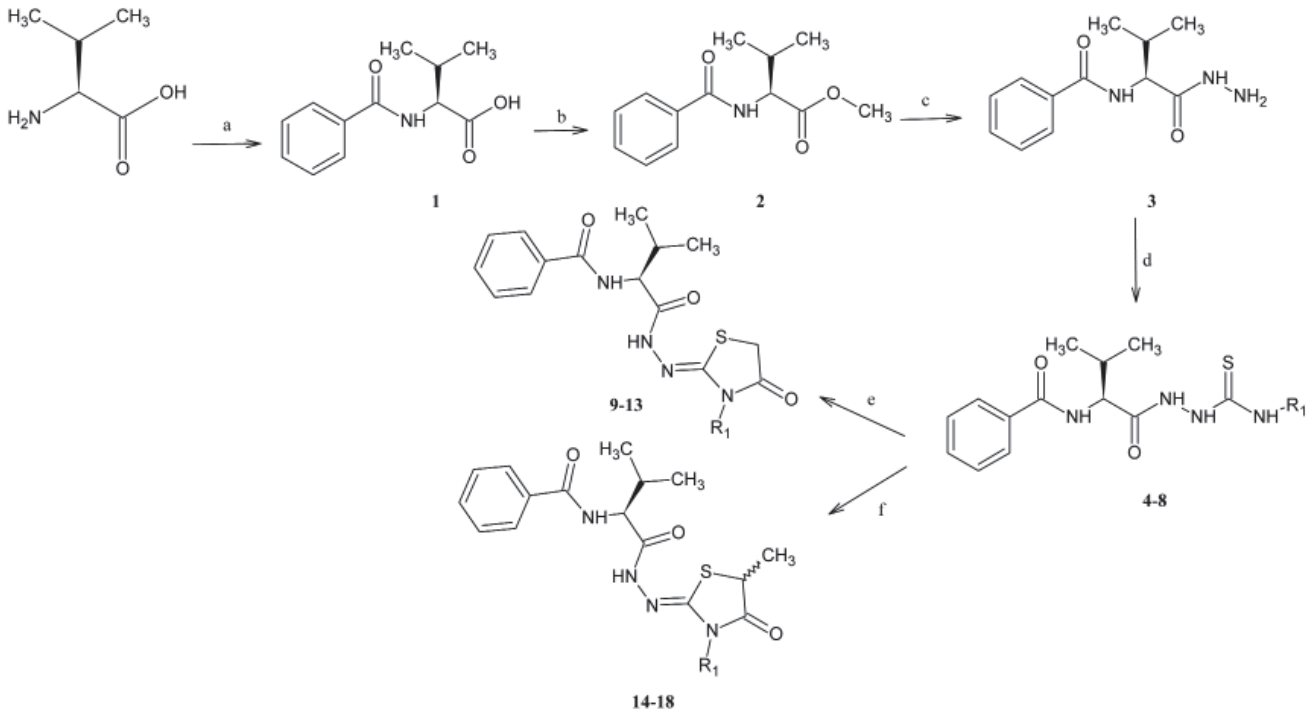
(2*S*)-2-(Benzoylamino)-3-methylbutyric acid hydrazide (0.01 mol) **(3)** was heated with methyl, ethyl, propyl, allyl, benzyl isothiocyanates (0.01 mol) under reflux for 4 h in ethanol. The crude products **4-8** were filtered and recrystallized from appropriate solvents.

General procedure for the synthesis of 2-[2-(benzoylamino)-3-methylbutyrylhydrazono]-3-alkyl/arylalkyl-1,3-thiazolidinones (9-13).

A mixture of appropriate thiosemicarbazide **4-8** (0.01 mol), anhydrous sodium acetate (99%, 0.04 mol) and ethyl bromoacetate (0.011 mol) in 20 ml absolute ethanol were heated under reflux for 4h. The mixture was cooled and the crude products (**9-13**) were filtered, dried and crystallized from appropriate solvents.

General procedure for the synthesis of 2-[2-(benzoylamino)-3-methylbutyrylhydrazono]-3-alkyl/arylalkyl-5-methyl-1,3-thiazolidinones (14-18).

A mixture of appropriate thiosemicarbazide **4-8**, anhydrous sodium acetate (99%, 0.04 mol) and ethyl 2-bromopropionate (0.011 mol) in 20 ml absolute ethanol were heated under reflux for 20h. The mixture was evaporated under vacuo and extracted with chloroform to eliminate sodium acetate crystals. The organic phase was evaporated in vacuo and the oily product



SCHEME 1. Synthetic route to compounds **1-18**.

Reagents and conditions: (a) C_6H_5COCl / NaOH; (b) MeOH / H_2SO_4, reflux; (c) $NH_2NH_2.H_2O$, reflux; (d) R_1-N=C=S, reflux; (e) $BrCH_2COOC_2H_5$, anhydrous CH_3COONa, absolute EtOH, reflux (f) $CH_3CHBrCOOC_2H_5$, anhydrous CH_3COONa, absolute EtOH, reflux.

TABLE 1. Physical and spectral data for compounds **4-18.**

Compound	R_1	Molecular formula	M.p (^{0}C)	Yield (%) & Crystallization solvent	HPLC Rt (min.)	HREI/FAB-MS (m/z) calculated/ found
4	CH_3	$C_{14}H_{20}N_4O_2S$	191-193	67 Ethanol	5.835	-
5	C_2H_5	$C_{15}H_{22}N_4O_2S$	180-181	59 Ethanol	7.542	-
6	C_3H_7	$C_{16}H_{24}N_4O_2S$	182-185	81 Ethanol	10.850	-
7	$CH_2CH{=}CH_2$	$C_{16}H_{22}N_4O_2S$	195-199	75 Ethanol	8.431	-
8	$CH_2C_6H_5$	$C_{20}H_{24}N_4O_2S$	205	81 Ethanol	26.606	-
9	CH_3	$C_{16}H_{20}N_4O_3S$	218-220	53 Ethanol	6.886	348.1256 / 348.1218
10	C_2H_5	$C_{17}H_{22}N_4O_3S$	227	67 Ethanol	8.647	362.1412 / 362.1438
11	C_3H_7	$C_{18}H_{24}N_4O_3S$	222-224	90 Ethanol	12.575	376.1569 / 376.1559
12	$CH_2CH{=}CH_2$	$C_{18}H_{22}N_4O_3S$	205-207	69 Ethanol	10.483	374.1412 /374.1418
13	$CH_2C_6H_5$	$C_{22}H_{24}N_4O_3S$	235-238	86 EtOH:DMF (99:1)	39.037	424.1569 / 424.1567
14	CH_3	$C_{17}H_{22}N_4O_3S$	183-185	10 Diethylether	9.821	362.1412 / 362.1422
15	C_2H_5	$C_{18}H_{24}N_4O_3S$	235	62 EtOH:H_2O (50:50)	12.809	376.1569 / 376.1571
16	C_3H_7	$C_{19}H_{26}N_4O_3S^c$	147/164	20 Diethylether	16.758	391.1798 / 391.1809
17	$CH_2CH{=}CH_2$	$C_{19}H_{24}N_4O_3S$	172-173	30 Ethanol	14.804	388.1569 / 388.1558
18	$CH_2C_6H_5$	$C_{23}H_{26}N_4O_3S$	192-194	54 Methanol	56.690	438.1725 / 438.1706

Elemental analysis data for compounds 4-8 (calculated / found): Compound 4: C%: 52.61 / 52.97; H%: 5.65 / 5.65; N%:17.49 / 17.65; S%: 9.97 / 10.10. **Compound 5:** C%: 55.88 / 55.89; H%: 6.88 / 6.29; N%:17.38 / 17.36; S%: 9.94 / 9.80. **Compound 6:** C%: 56.50 / 56.93; H%: 7.24 / 6.65; N%:16.43 / 16.61; S%: 9.40 / 9.43. **Compound 7:** C%: 57.46 / 57.40; H%: 6.63 / 7.05; N%:16.75 / 16.72; S%: 9.59 / 9.48. **Compound 8:** C%: 62.48 / 62.29; H%: 6.29 / 7.33; N%:14.57 / 14.68; S%: 8.34 / 8.04. **IR spectral data, υ (cm-1): Compounds 4-8:** 3383-3173 (N-H str.), 1699-1681 (C=O str.), 1635-1633 (C=O str.), 1205-1028 (C=S str.). **Compounds 9-13:** 3252-3155 (N-H str.), 1724-1718 (C=O str.), 1672-1662 (C=O str.), 1631-1629 (C=O str.), 1600-1579 (C=N str.). **Compounds 14-18:** 3250-3173 (N-H str.), 1726-1724 (C=O str.), 1666-1660 (C=O str.), 1629-1627 (C=O str.), 1602-1577 (C=N str.).

was triturated with ice-cold ether in order to be solidified. The crude products (**14-18**) were filtered, dried and recrystallized from appropriate solvents.

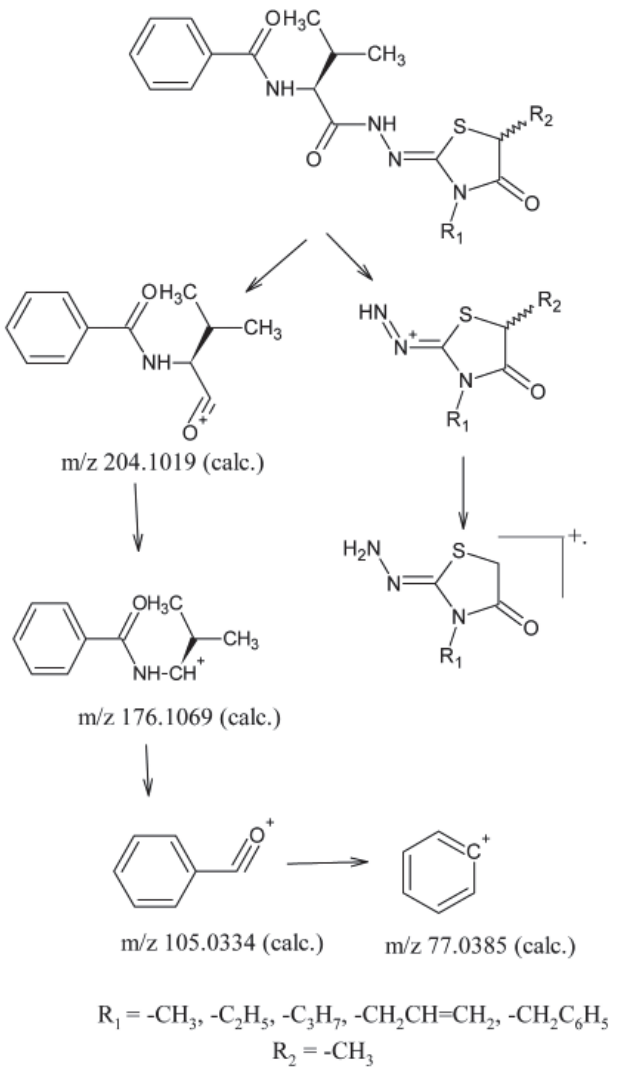
In Vitro Antiviral Assays

Inhibition of HIV-induced cytopathicity in MT-4 cells

Evaluation of the antiviral activity of the compounds against *HIV-1 strain* III_B and *HIV-2 strain (ROD)* in MT-4 cells was performed using the MTT assay as previously described (42). Stock solutions (10 x final concentration) of test compounds were added in 25 µl volumes to two series of triplicate wells so as to allow simultaneous evaluation of their effects on mock- and HIV-infected cells at the beginning of each experiment. Serial 5-fold dilutions of test compounds were made directly in flat-bottomed 96-well microtiter trays using a Biomek 2000 robot (Beckman instruments, Fullerton, CA). Untreated control HIV-and mock-infected cell samples were included for each samples.

HIV-1(III_B*)* (43) or *HIV-2 (ROD)* (44) stock (50 µl) at 100-300 $CCID_{50}$ (cell culture infection dose) or culture medium was added to either the infected or mock-infected wells of the microtiter tray. Mock-infected cells were used to evaluate the effect of test compound on uninfected cells in order to assess the cytotoxicity of the test compound. Exponentially growing MT-4 cells (45) were centrifuged for 5 minutes at 1000 rpm and the supernatant was discarded. The MT-4 cells were resuspended at 6 x 10^5 cells/ml, and 50 µl volumes were transferred to the microtiter tray wells. Five days after infection, the viability of mock-and HIV-infected cells was examined spectrophotometrically by the MTT assay.

The MTT assay is based on the reduction of yellow coloured 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (Acros Organics, Geel, Belgium) by mitochondrial dehydrogenase of metabolically active cells to a blue-purple formazan that can be measured spectrophotometrically. The absorbances were read in an eight-channel computer-controlled photometer (Multiscan Ascent Reader, Labsystems, Helsinki, Finland), at two wavelenghths (540 and 690 nm). All data were calculated using the median OD (optical density) value of tree wells. The 50% cytotoxic concentration (CC_{50}) was defined as the concentration of the test compound that reduced the absorbance (OD_{540}) of the mock-infected control sample by 50%. The concentration achieving 50% protection



SCHEME 2. Common fragmentation pathway for the compounds **9-13, 14-15, 17-18**.

from the cytopathic effect of the virus in infected cells was defined as the 50% effective concentration (EC_{50}).

Antiviral assays

The antiviral assays, other than HIV-1, were based on inhibition of virus-induced cytopathicity in HEL cells (*HSV-1(KOS), HSV-1(TK-KOS ACV^r), HSV-2(G), Vaccinia virus, Vesicular stomatitis virus*), hela cells (*Vesicular stomatitis virus, Respiratory syncytial virus, Coxsackie B4 virus*) and Vero cells (*Parainfluenza-3 virus, Reovirus-1, Sindbis virus, Coxsackie B4 virus, Punta Toro virus*), following previously established procedures (46-48). Briefly, confluent cell cultures in microtiter 96-well plates were inoculated with 100 $CCID_{50}$ of virus, 1 $CCID_{50}$ being the virus dose required to infect 50% of the cell cultures. After a 1h virus adsorption period, residual virus was removed, and the cell cultures were incubated in the presence of varying concentrations 400, 200, 100, … µg/ml) of the test compounds. Viral cytopathicity was recorded as soon as it reached completion in the control virus-infected cell cultures that had not been treated with the test compounds.

NS5B inhibition assay

The biological activity of the compounds against NS5B polymerase were evaluated in a reaction buffer containing 20 mM Tris-HCl (pH 7.0), 100 mM NaCl, 100 mM sodium glutamate, 0.1 mM DTT, 0.01% BSA, 0.01% Tween-20, 5% glycerol, 20 U/mL of RNase Out, 0.25 µM of poly rA/U_{12}, 25 µM UTP, 2 µCi [∞-^{32}P]UTP, 300 ng of NS5BCΔ21 and 1.0 mM $MnCl_2$ with or without inhibitors (100 µM) in a total volume of 25 µl for 1h at 30^{o}C as previously described (20, 49) Reactions were terminated by the addition of ice-cold 5% (v/v) trichloroacetic acid (TCA) containing 0.5 mM pyrophosphate. Reaction products were precipitated on GF-B filters and quantified on a liquid scintillation counter. NS5B activity in the presence of DMSO control was set at 100% and that in the presence of the compounds was determined relative to this control.

RESULTS AND DISCUSSION

Chemistry

2-(Benzoylamino)-3-methylbutyric acid **(1)** was prepared by benzoylation of L-valine. 2-(Benzoylamino)-3-methylbutyric acid methyl ester **(2)** was obtained by esterification of compound **1.** 2-(Benzoylamino)-3-methylbutyric acid hydrazide **(3)** was obtained by heating compound **2** with hydrazine hydrate. 1-[2-(Benzoylamino)-3-methylbutyryl]-4-alkyl/arylalkylthiosemicarbazides **(4-8**) were carried out by refluxing compound **3** with methyl, ethyl, propyl, allyl, benzyl isothiocyanates in ethanolic medium. 2-[2-(Benzoylamino)-3-methylbutyrylhydrazono]-3-alkyl/arylalkyl-1,3-thiazolidine-4-ones **(9-13)** were synthesized by refluxing compounds **4-8** with ethyl 2-bromoacetate in the presence of anhydrous sodium acetate in absolute ethanol. 2-[2-(Benzoylamino)-3-methylbutyrylhydrazono]-3-alkyl/arylalkyl-5-methyl-1,3-thiazolidine-4-ones **(14-18)** were synthesized by refluxing compounds **4-8** with ethyl 2-bromopropionate in the presence of anhydrous sodium acetate in absolute ethanol.

Purities of compounds **4-18** were assessed through HPLC data and confirmed by elemental analysis. The synthesized compounds were characterized by their IR, ^{1}H-NMR, ^{13}C-NMR, HR-EI and HR-FAB Mass Spectral data. Physical and spectral data for compounds **4-18** are given in Table 1.

The IR spectra of compound **1** was characterized by the presence of a new C=O absorption band at 1639 cm^{-1}. The bands at 1735 cm^{-1} and 1660 cm^{-1} were attributed to the C=O streching band of ester (compound **2**) and hydrazide (compound **3**), respectively. Absorption bands at 1205-1028 cm^{-1}, which were attributed to the C=S streching vibrations, were observed in the IR spectra of compounds **4-8**. New C=O bands (1718-1726 cm^{-1}) in the IR spectra of 1,3-thiazolidine-4-ones **9-18** provided confirmatory evidence for ring closure (3, 7). IR spectral data for compounds **4-18** are given in Table 1.

The exhibited chemical shifts obtained from ^{1}H-NMR spectra of compounds **4-8** (see Table 2) all supported the proposed structures of the compounds. Resonances assigned to the N^1-H, N^2-H, N^4-H protons of thiosemicarbazides **4-8** were detected at 10.17-10.31, 9.36-9.56, 7.61-8.25 ppm respectively which are supported by the literature (50).

Signals at about 4.02-4.12 ppm that were attributed to the CH_2 protons at the 5th position of the 1,3-thiazolidine-4-one ring, supported the exact structures of **9-13** (see Table 2)**.** The CH

TABLE 2. ^{1}H-NMR and ^{13}C-NMR spectral data for compounds **4-18**

Comp.	^{1}H-NMR δ (ppm)
4	0.79-1.16 (m, 6H, >CHCH(CH_3)$_2$), 2.07-2.26 (q, 1H, >CHCH(CH_3)$_2$), 2.93 (d, 3H, J: 4.23 Hz, NH-CH_3), 4.02 (brs, 1H, >CHCH(CH_3)$_2$), 7.47-7.59 (m, 3H, Ar- H), 7.78 (s, 1H, N^{4}H), 7.89 (d, 2H, J:7.07 Hz, Ar- H), 8.65 (s, 1H, Ar-CONH-), 9.40 (s, 1H, N^2-H), 10.17 (s, 1H, N^1-H).
5	0.95 &1.02 (d, 3H, J:6.75 Hz & d, 3H, J:6.59 Hz, >CHCH(CH_3)$_2$), 1.12 (t, 3H, J:7.21 Hz, J:7.21 Hz, NH-CH_2-CH_3), 2.11-2.16 (q, 1H, >CHCH(CH_3)$_2$), 3.42-3.53 (m, 2H, NH-CH_2-CH_3), 3.93 (brs, 1H, >CHCH(CH_3)$_2$), 7.49 (t, 2H, J: 7.68 Hz, J: 7.09 Hz, Ar- H), 7.55-7.59 (m, 1H, Ar- H), 7.64 (s, 1H, N^{4}H-CH_2CH_3), 7.88 (d, J:7.68 Hz, 2H, Ar- H), 8.71 (s, 1H, Ar-CONH-), 9.36 (s, 1H, N^2-H), 10.21 (s, 1H, N^1-H).
6	0.82 (t, 3H, J:7.,37 Hz, J:7.44 Hz, NH-CH_2-CH_2-CH_3), 0.96 & 1.02 (d, 3H, J:6.73 Hz & d, 3H, J:6.58 Hz, >CHCH(CH_3)$_2$), 1.51-1.57 (m, 2H, NH-CH_2-CH_2-CH_3), 2.11-2.17 (q, 1H, >CHCH(CH_3)$_2$), 3.38-3.44 (m, 2H, NH-CH_2-CH_2-CH_3), 3.93 (brs, 1H, >CHCH(CH_3)$_2$), 7.49 (t, 2H, J:7.71 Hz, J:7.11 Hz, Ar-H), 7.55 (t, J:5.24 Hz, J: 4.31 Hz, 1H, Ar-H), 7.61 (s, N^{4}H), 7.89 (d, 2H, J: 7.11 Hz, Ar-H), 8.71 (s, 1H, Ar-CONH-), 9.38 (s, 1H, N^2-H), 10.22 (s, 1H, N^1-H).
7	0.96 & 1.03 (d, 3H, J:6.67 Hz & t, 3H, J:10.62 Hz, J:6.55 Hz, >CHCH(CH_3)$_2$), 2.14-2.17 (q, 1H, >CHCH(CH_3)$_2$), 3.97 (brs, 1H, >CHCH(CH_3)$_2$), 4.15 (brs, 2H, NH-CH_2-CH=CH_2), 5.03 (d, 1H, J:11.78 Hz, NH-CH_2-CH=CH_2, cis), 5.13 (d, 1H, J: 18.91 Hz, NH-CH_2-CH=CH_2, trans), 5.81-5.88 (m, 1H, NH-CH_2-CH=CH_2), 7.48 (t, 2H, J: 7.82 Hz, J:7.24 Hz, Ar-H), 7.54-7.58 (t, J: 7.1 Hz, J: 6.29 Hz, 1H, Ar-H), 7.82 (s, 1H, N^{4}H), 7.86 (d, 2H, J:7.88 Hz, Ar-H), 8.70 (s, 1H, Ar-CONH-), 9.49 (s, 1H, N^2-H), 10.25 (s, 1H, N^1-H).
8	0.88-1.02 (m, 6H, >CHCH(CH_3)$_2$), 2.12-2.17 (q, 1H, >CHCH(CH_3)$_2$), 3.96 (brs, 1H, >CHCH(CH_3)$_2$), 4.73, 4.77, 4.83, 4.87 (4d, 2H, J : 5.28 Hz, J: 5.37 Hz, J: 5.94 Hz, J: 6.10 Hz, NH-CH_2-C_6H_5), 7.17-7.31 (m, 5H, NH-CH_2-C_6H_5), 7.38 (t, 2H, J: 7.73 Hz, J: 7.58 Hz, Ar-H), 7.49-7.53 (q, 1H, Ar-H), 7.62 (d, 2H, J: 7.46 Hz, Ar-H), 8.25 (s, N^{4}H), 8.69 (d, 1H, J: 4.05 Hz Ar-CONH-), 9.56 (s, 1H, N^2-H), 10.31 (s, 1H, N^1-H).
9	0.96 (d, 6H, J: 6.57 Hz, >CHCH(CH_3)$_2$), 2.12-2.16 (m, 1H, >CHCH(CH_3)$_2$), 3.09 (d, 2H, J: 7.26 Hz, N-CH_3), 4.03 (s, 2H,-SCH_2-), 4.40 (t, 1H, J: 8.62 Hz, J: 8.,61 Hz , >CHCH(CH_3)$_2$), 7.45-7.56 (m, 3H, Ar-H), 7.88 (d, 2H, J: 8.52 Hz, Ar-H), 8.39 (d, 1H, J: 8.53 Hz, Ar-CONH-), 10.43 (s, 1H, -CO-NH-N=).
10	0.94-0.99 (q, 6H, >CHCH(CH_3)$_2$), 1.11-1.18 (q, 3H, N-CH_2CH_3), 2.15-2.18 (m, 1H, >CHCH(CH_3)$_2$), 3.65-3.71 (q, 2H, N-CH_2CH_3), 4.02 & 4.05 (s & s, 2H, -S-CH_2-), 4.38 (t, 1H, J: 8.53 Hz, J: 8.55 Hz, >CHCH(CH_3)$_2$), 7.47 (t, 2H, J: 7.58 Hz, J: 7.10 Hz, Ar-H), 7.54 (t, 1H, J: 7.24 Hz, J: 7.17 Hz, Ar-H), 7.91 (d, 2H, J: 7.14 Hz, Ar-H), 8.39 (d, 1H, J: 8.43 Hz, Ar-CONH-), 10.43 (s, 1H, -CO-NH-N=).
11	0.85 (t, J: 7.46 Hz, J: 7.42 Hz, 3H, N-$CH_2CH_2CH_3$), 0.94-0.99 (m, 6H, >CHCH(CH_3)$_2$), 1.57-1.63 (q, 2H, N-$CH_2CH_2CH_3$), 2.14-2.16 (m, 1H, >CHCH(CH_3)$_2$), 3.61 (t, 2H, J: 6.89 Hz, J: 7.67 Hz, N-$CH_2CH_2CH_3$), 4.04 & 4.07 (s & s, 2H, -S-CH_2-), 4.38 (t, 1H, J: 8.56 Hz, J: 8.55 Hz, >CHCH(CH_3)$_2$), 7.47 (t, 2H, J: 7.69 Hz, J: 7.17 Hz, Ar-H), 7.54 (t, 1H, J :7.22 Hz, J: 7.34 Hz, Ar-H), 7.91 (d, 2H, J: 7.24 Hz, Ar-H), 8.38 (d, 1H, J: 8.49 Hz, Ar-CONH-), 10.42 (s, 1H, -CO-NH-N=)
12	0.91-0.98 (m, 6H, >CHCH(CH_3)$_2$), 2.12-2.17 (m, 1H, >CHCH(CH_3)$_2$), 4.07 (s, 2H, -S-CH_2-), 4.25 (d, 2H, NH-CH_2-CH=CH_2, J: 5.28 Hz), 4.38 (t, 1H, J: 8.55 Hz, J: 8.55 Hz, >CHCH(CH_3)$_2$), 5.13-5.18 (m, 2H, NH-CH_2-CH=CH_2), 5.79-5.86 (m, 1H, NH-CH_2-CH=CH_2), 7.45-7.56 (m, 3H, Ar-H), 7.88 (d, J: 8.54 Hz, 2H, Ar-H), 8.37 (d, 1H, J: 8.48 Hz, Ar-CONH-), 10.44 (s, 1H, -CO-NH-N=).
13	0.56, 0.75, 0.96-0.98 (d, J: 6.79 Hz d, J: 6.75 Hz, q, 6H, >CHCH(CH_3)$_2$), 1.91-2.26 (q, 1H, >CHCH(CH_3)$_2$), 4.12 (s, 2H, -S-CH_2-), 4.39 (t, 1H, J: 8.53 Hz, J: 8.55 Hz, >CHCH(CH_3)$_2$), 4.84 (s, 2H, N-$CH_2C_6H_5$), 7.27-7.29 (m, 5H, N-$CH_2C_6H_5$), 7.44-7.54 (m, 3H, Ar-H), 7.89 (d, 2H, J: 8.50 Hz, Ar-H), 8.38 (d, 1H, J: 8.55 Hz, Ar-CONH-), 10.48 (s, 1H, -CO-NH-N=).
14	0.96, 1.09, 1.24 (d, J: 6.68 Hz, t, J: 7.01 Hz, J: 7.03 Hz, s, 6H, >CHCH(CH_3)$_2$), 1.51 (d, 3H, J: 7.18 Hz, -S-CH-CH_3), 2.12-2.17 (q, 1H, >CHCH(CH_3)$_2$), 3.10 (s, 3H, J: 7.23 Hz, N-CH_3), 4.32-4.42 (m, 2H, -S-CH-CH_3 & >CHCH(CH_3)$_2$), 7.45-7.56 (m, 3H, Ar-H), 7.88 (d, 2H, J: 7.24 Hz, Ar-H), 8.38 (d, 1H, J: 8.46 Hz, Ar-CONH-), 10.42 (s, 1H, -CO-NH-N=).
15	0.82-1.24 (m, 9H >CHCH(CH_3)$_2$, N-CH_2CH_3), 1.50 &1.60 (d, J: 7.18 Hz & d, J: 7.26 Hz 3H, -S-CH-CH_3), 2.06-2.17 (m, 1H, >CHCH(CH_3)$_2$), 3.62 (t, 2H, J: 6.55 Hz, J: 7.93 Hz N-CH_2CH_3), 4.01-4.39 (m, 2H, >CHCH(CH_3)$_2$ & -S-CH-CH_3), 7.44-7.55 (m, 3H, Ar-H), 7.78-7.91 (m, 2H, Ar-H), 8.29-8.41 (m, 1H, Ar-CONH-), 9.45 & 10.43 (s & s, 1H, -CO-NH-N=).
16	0.85-1.22 (m, 9H >CHCH(CH_3)$_2$, N-$CH_2CH_2CH_3$), 1.49 (d, 3H, J: 7.18 Hz, -S-CH-CH_3), 1.63 (s, 2H, N-$CH_2CH_2CH_3$), 2.12-2.20 (m, 1H, >CHCH(CH_3)$_2$), 3.65-3.71 (q, 2H, N-$CH_2CH_2CH_3$), 3.88-4.47 (m, 2H, >CHCH(CH_3)$_2$ & -S-CH-CH_3), 7.43-7.55 (m, 3H, Ar-H), 7.85-7.92 (m, 2H, Ar-H), 8.52 & 8.66 (d, J: 8.79 Hz & s, 1H, Ar-CONH-), 9.45 (s, 1H, -CO-NH-N=).
17	0.93, 0.96 & 1.24 (d, J: 6.23 Hz, d, J: 6.71 Hz & s, 6H, >CHCH(CH_3)$_2$), 1.53 (d, 3H, J: 7.25 Hz,-S-CH-CH_3), 2.13 (m, 1H, >CHCH(CH_3)$_2$), 4.25 (d, 2H, NH-CH_2-CH=CH_2, J: 5.28 Hz), 4.36-4.41 (m, 2H,-S-CH-CH_3 & >CHCH(CH_3)$_2$), 5.11-5.16 (m, 2H, NH-CH_2-CH=CH_2), 5.80-5.87 (q, 1H, NH-CH_2-CH=CH_2), 7.45-7.54 (m, 3H, Ar-H), 7.88 (t, 2H, J: 7.05Hz, J: 6.65 Hz, Ar-H), 8.36 & 8.38 (dd, J: 2.56Hz, J: 2.55 Hz, 1H, Ar-CONH-), 10.43 (s, 1H, -CO-NH-N=).
18	0.65-0.67, 0.83, 0.97 (q, d, J: 6.73 Hz, d, J: 6.71 Hz, 6H, >CHCH(CH_3)$_2$), 1.52-1.59 (m, 3H,-S-CH-CH_3), 2.11-2.17 (q, 1H, >CHCH(CH_3)$_2$), 4.37-4.47 (m, 2H, -S-CH-CH_3 & >CHCH(CH_3)$_2$), 4.80-4.86 (m, 2H, N-$CH_2C_6H_5$), 7.25-7.56 (m, 8H, N-$CH_2C_6H_5$, Ar-H), 7.87-7.90 (q, 2H, Ar-H), 8.35-8.38 (dd, J: 3.18 Hz, J: 3.12 Hz, 1H, Ar-CONH-), 10.47 (s, 1H, -CO-NH-N=).

^{13}C-NMR (DEPT) spectral data: Compound 13: 19.56 & 19.83 (>CHCH(CH3)2), 30.51 (>CHCH(CH3)2), 33.17 (thiazolidinone-C5), 45.95 (>N-CH2-C6H5), 58.47 (>CHCH(CH3)2), 127.97 (Ar-C3, Ar-C5, Ar-C2′, Ar-C6′), 128.05 & 128.33 (Ar-C2, Ar-C6), 128.64 & 128.83 (Ar-C4′), 128.95 (Ar-C3′, Ar-C5′), 131.74 (Ar-C4), 134.64 (Ar-C1), 136.35 (Ar-C1′), 159.45 (thiazolidinone-C2), 166.98 (CONHN=), 168.02 (Ar-CONH), 172.03 (thiazolidinone-C4). **Compound 15:** 12.65 (>N-CH2CH3), 19.32 & 19.65 (>CHCH(CH3)2), 25.45 (thiazolidinone-C5-CH3), 30.48 & 30.58 (>CHCH(CH3)2), 38.02 (>N-CH2CH3), 42.54 (thiazolidinone-C5), 58.73, 59.32 & 59.41 (>CHCH(CH3)2), 127.88 & 128.01 (Ar-C3, Ar-C5), 128.57 & 128.61 (Ar-C2, Ar-C6), 131.59 (Ar-C4), 134.75 &134.87 (Ar-C1), 166.75 (thiazolidinone-C2), 168.22 (CONHN=), 170.91 (Ar-CONH), 173.63, 174.65 & 174,72 (thiazolidinone-C4).

proton at the 5th position of the 1,3-thiazolidine-4-on ring and the hydrogen attached to the chiral carbon were detected as a multiplet signal between 3.88-4.47 ppm in the ^{1}H-NMR spectra of the compounds **14-18** (See Table 2). The methyl protons at the 5th position of the 1,3-thiazolidine-4-on ring were detected between 1.49-1.59 ppm in accordance with literature (51). The endocyclic -*CH_2*- protons are expected to be detected as a singlet peak with an integration of two protons but in our work they were detected as two singlet peaks with an integration of two protons in the ^{1}H-NMR spectra of compounds **10-11** and this revealed the presence of two isomers. The methyl proton attached to the endocyclic -*CH*- proton is used to be detected as a doublet but in our work we observed these protons as two doublets with an integration of one proton in the ^{1}H-NMR spectra of compound **15.** Compounds **13** and **15** were selected as prototypes and ^{13}C-NMR spectra of these compounds were observed for further support of geometric isomerism (see Table 2). Detecting C=O of the thiazolidinone ring (only for compound **15**) and some of the aliphatic and aromatic C atoms

TABLE 3. Anti-Feline Corona Virus (FIPV) and anti-Feline Herpes Virus activity and cytotoxicity of compounds **4-18** in CRFK cell cultures.

Compound	CC_{50}[a] (μM)	EC_{50}[b] (μM)	
		Feline Corona Virus(FIPV)	Feline Herpes Virus
4	>100	>100	>100
5	>100	>100	>100
6	>100	>100	>100
7	>100	>100	>100
8	85.3	>20	>20
9	>100	>100	>100
10	>100	>100	>100
11	>100	>100	>100
12	>100	>100	>100
13	>100	>100	>100
14	>100	>100	>100
15	>100	>100	>100
16	>100	>100	>100
17	>100	>100	>100
18	>100	>100	>100
HHA (μg/ml)	>100	0.8	2.7
UDA (μg/ml)	>100	1.6	2.6
Ganciclovir	>100	>100	2.9

[a] 50% Cytotoxic concentration, as determined by measuring the cell viability with the colorimetric formazan-based MTS assay.
[b] 50% Effective concentration, or concentration producing 50% inhibition of virus-induced cytopathic effect, as determined by measuring the cell viability with the colorimetric formazan-based MTS assay.
CRFK cells: Crandell-Rees Feline Kidney cells.

TABLE 4. Cytotoxicity and antiviral activity of compounds **4-18** in HEL cell cultures.

Compound	Minimum cytotoxic concentration[a] (μM)	EC_{50}[b] (μM)				
		Herpes simplex virus-1 (KOS)	Herpes simplex virus-2 (G)	Vaccinia virus	Vesicular stomatitis virus	Herpes simplex virus-1 TK$^-$ KOS ACV^r
4	>100	>100	>100	>100	>100	>100
5	>100	>100	>100	>100	>100	>100
6	>100	>100	>100	>100	>100	>100
7	>100	>100	>100	>100	>100	>100
8	>100	>100	>100	>100	>100	>100
9	>100	>100	>100	>100	>100	>100
10	>100	>100	>100	>100	>100	>100
11	>100	>100	>100	>100	>100	>100
12	>100	>100	>100	>100	>100	>100
13	>100	>100	>100	>100	>100	>100
14	>100	>100	>100	>100	>100	>100
15	>100	>100	>100	>100	>100	>100
16	>100	>100	>100	>100	>100	>100
17	>100	>100	>100	>100	>100	>100
18	>100	>100	>100	>100	>100	>100
Brivudin	>250	0.04	10	2	>250	50
Ribavirin	>250	50	50	5	>250	150
Acyclovir	>250	0.4	0.4	146	>250	50
Ganciclovir	>100	0.03	0.03	>250	>100	0.8

[a]Required to cause a microscopically detectable alteration of normal cell morphology. [b]Required to reduce virus-induced cytopathogenicity by 50 %.

(compound **13** and **15**) as two peaks instead of one, provided confirmatory evidence for geometric isomerism (52-54).

In the HR mass spectra, compounds **9-13** fragmented via a prominent pathway to afford fragment at m/z 204.1019 by -CONH bond cleavage and 2-hydrazinylidene-3-methyl-1,3-thiazolidin-4-one moiety. By expulsion of CO from m/z 204.1019 fragment, 2-methyl-1-[(phenylcarbonyl)amino]prop-1-ylium cation (m/z 176.1069) was detected. Benzoyl cation

TABLE 5. Cytotoxicity and antiviral activity of compounds **4-18** in HeLa cell cultures.

Compound	Minimum cytotoxic concentration[a] (μM)	EC_{50}[b] (μM)		
		Vesicular stomatitis virus	Coxsackie virus B4	Respiratory syncytial virus
4	>100	>100	>100	>100
5	>100	>100	>100	>100
6	>100	>100	>100	>100
7	>100	>100	>100	>100
8	>100	>100	>100	>100
9	>100	>100	>100	>100
10	>100	>100	>100	>100
11	>100	>100	>100	>100
12	>100	>100	>100	>100
13	>100	>100	>100	>100
14	>100	>100	>100	>100
15	>100	>100	>100	>100
16	>100	>100	>100	>100
17	>100	>100	>100	>100
18	>100	>100	>100	>100
Brivudin	>250	>250	>250	>250
(S)-DHPA	>250	146	>250	>250
Ribavirin	>250	2	146	10

TABLE 6. Cytotoxicity and antiviral activity of compounds **4-18** in Vero cell cultures.

Compound	Minimum cytotoxic concentration[a] (μM)	EC_{50}[b] (μM)				
		Para-influenza-3 virus	Reovirus-1	Sindbis virus	Coxsackie virus B4	Punta Toro virus
4	>100	>100	>100	>100	>100	>100
5	>100	>100	>100	>100	>100	>100
6	>100	>100	>100	>100	>100	>100
7	>100	>100	>100	>100	>100	>100
8	>100	>100	>100	>100	>100	>100
9	>100	>100	>100	>100	>100	>100
10	>100	>100	>100	>100	>100	>100
11	>100	>100	>100	>100	>100	>100
12	>100	>100	>100	>100	>100	>100
13	>100	>100	>100	>100	>100	>100
14	>100	>100	>100	>100	>100	>100
15	>100	>100	>100	>100	>100	>100
16	>100	>100	>100	>100	>100	>100
17	>100	>100	>100	>100	>100	>100
18	>100	>100	>100	>100	>100	>100
Brivudin	>250	>250	>250	>250	>250	>250
(S)-DHPA	>250	50	>250	>250	>250	>250
Ribavirin	>250	50	>250	>250	>250	150

TABLE 7. Anti-HIV activity and cytotoxicity of compounds **4-18.**

Compound	Strain	IC_{50} (μg/ml)	CC_{50} (μg/ml)	SI	Maximum P rotection (%)
4	III_B	>125	>125	X 1	6
		>125	>125	X 1	0
	ROD	>125	>125	X 1	6
		>125	>125	X 1	2
5	III_B	>125	>125	X 1	4
		>125	>125	X 1	1
	ROD	>125	>125	X 1	6
		>125	>125	X 1	4
6	III_B	>125	>125	X 1	4
		>119	=119	< 1	1
	ROD	>125	>125	X 1	4
		>125	>125	X 1	0
7	III_B	>125	>125	X 1	3
		>125	>125	X 1	1
	ROD	>125	>125	X 1	5
		>125	>125	X 1	4
8	III_B	>66.1	=66.1	< 1	4
		>72.7	=72.7	< 1	1
	ROD	>73.5	=73.5	< 1	2
		>68.1	=68.1	< 1	0
9	III_B	>125	>125	X 1	3
		>125	>125	X 1	2
	ROD	>125	>125	X 1	2
		>125	>125	X 1	1
10	III_B	>125	>125	X 1	10
		>94.2	=94.2	< 1	0
	ROD	>125	>125	X 1	4
		>125	>125	X 1	1
11	III_B	>125	>125	X 1	7
		>118	=118	< 1	1
	ROD	>125	>125	X 1	4
		>125	>125	X 1	0
12	III_B	>125	>125	X 1	2
		>125	>125	X 1	0
	ROD	>125	>125	X 1	2
		>125	>125	X 1	0
13	III_B	>125	>125	X 1	4
		>121	=121	< 1	1
	ROD	>125	>125	X 1	7
		>125	>125	X 1	7
14	III_B	>125	>125	X 1	3
		>125	>125	X 1	0
	ROD	>125	>125	X 1	3
		>125	>125	X 1	0
15	III_B	>125	>125	X 1	2
		>125	>125	X 1	2
	ROD	>125	>125	X 1	3
		>125	>125	X 1	2
16	III_B	>111	=111	< 1	4
		>93.9	=93.9	< 1	0
	ROD	>125	>125	X 1	2
		>125	>125	X 1	1
17	III_B	>125	>125	X 1	7
		>121	=121	< 1	0
	ROD	>125	>125	X 1	4
		>125	>125	X 1	3
18	III_B	>59.2	=59.2	< 1	2
		>84.8	=84.8	< 1	0
	ROD	>72.9	=72.9	< 1	4
		>80.8	=80.8	< 1	0

TABLE 8: Anti-HCV NS5B RdRp activity of compounds **4-18.**

Compound	% Inhibition	Compound	% Inhibition
4	N.I.	12	N.I.
5	N.I.	13	6.4
6	N.I.	14	N.I.
7	12.4	15	N.I.
8	N.I.	16	N.D.
9	N.I.	17	N.I.
10	N.I.	18	N.I.
11	N.I.		

aPercent inhibition was determined at 100 μM concentration of the indicated compound and represents an average of at least two independent measurements in duplicate. N.D.: not determined. N.I.: no inhibition.

(m/z 105.0334) was determined through cleavage of amide bond of the fragment at m/z 176.1076. Except for compound **16** fragmented via quasi-molecular ion by HR-FAB, compounds **14-15**, **17-18** fragmented to afford m/z 204.1019 by –CONH- bond cleavage and 2-hydrazinylidene-3,5-dimethyl-1,3-thiazolidin-4-one moiety. The prosecuting fragmentation was observed in the same manner as compounds **9-18**.

Antiviral evaluation

In view of the antiviral activity ascertained for similar 1,3-thiazolidine-4-ones, the synthesized compounds were subjected to a preliminary screening for their antiviral effects against various types of viruses in HEL, HeLa, Vero and CRFK (Crandell-Rees Feline Kidney) cell cultures. Compounds **4-18** were not found to be active against *Feline Corona Virus (FIPV), Feline Herpes Virus, HSV-1(KOS), HSV-1(TK-KOS ACV^r), HSV-2(G), Vaccinia virus, Varicella-ZosterVirus TK$^+$VZV, Varicella-Zoster-Virus TK$^-$VZV, Cytomegalovirus, Vesicular stomatitis virus, Respiratory syncytial virus, Coxsackie B4 virus, Parainfluenza-3 virus, Reovirus-1, Sindbis virus and Punta Toro virus* (see Tables 3-6). Compounds **4-18** were also evaluated for their anti-HIV activity. None of the synthesized compounds showed any significant activity against HIV-1 (III_B) or HIV-2 (strain ROD) in MT-4 cells (See Table 7) at subtoxic concentrations.

The anti-HCV activity of the compounds was also investigated employing the *in vitro* HCV NS5B RdRp inhibition assay as described in the experimental section. Highest inhibition against HCV NS5B RdRp activity at 100 µM were observed with compounds **7** and **13** by 12.4% and 6.4%, respectively. Remaining compounds exhibited no inhibition at this concentration, thus suggesting that none of the compounds specifically target HCV NS5B polymerase (see Table 8).

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L-Valin yan zinciri taşıyan 1,3-tiyazolidin-4-on türevlerinin sentezi, yapılarının aydınlatılması ve antiviral etkilerinin tespiti

ÖZET: 1,3-Tiyazolidin-4-on türevi bileşiklerin, HIV-1 non-nükleozit ters transkriptaz ve HCV NS5B RNA-bağımlı RNA polimeraz enzimlerini inhibe etmek suretiyle anti-HIV ve anti-HCV etki gösterdikleri literatürlerde bildirilmiştir. Bu bilgiden hareketle, literatürde kayıtlı olmayan 1-[2-(benzoilamino)-3-metilbutiril]-4-alkil/arilalkiltiyosemikarbazit ve 2-[2-(benzoilamino)-3- metilbutirilhidrazono]-3-alkil-/arilalkil-5-non sübstitüe / metil-1,3-tiyazolidinon türevi bileşikler sentezlenmiş ve antiviral etki potansiyeli açısından değerlendirilmişlerdir. Sentezlenen bileşiklerin antiviral etkileri; CRFK, HEL, HeLa ve Vero hücre kültürü ortamlarında çeşitli virüslere (Kedi Korona virüsü (FIPV), Kedi Herpes virüsü, HSV-1(KOS), HSV-1(TK-KOS ACV^r), HSV-2(G), Vaksinya virüsü, Veziküler stomatitis virüsü, Varicella-ZosterVirüsü TK+VZV, Varicella-ZosterVirüsü TK-VZV, Sitomegalovirüs, Respiratuvar sinsitiyal virüs, Koksaki B4 virüsü, Parainfluenza-3 virüsü, Reovirüs-1, Sindbis virüsü, Punta Toro virüsü) karşı araştırılmıştır. Bileşiklerin sitotoksisitesi ve anti-HIV etkileri HIV-1 (IIIB) and HIV-2 (ROD) suşlarına karşı MT-4/MTT yöntemi kullanılarak taranmış ve non-toksik dozlarda antiviral etki göstermedikleri saptanmıştır. Sentezlenen bileşikler, anti-HCV NS5B RdRp etki potansiyalleri açısından da değerlendirilmiş; ancak en yüksek derişim olan 100 μM'da HCV NS5B RdRp'a karşı inhibitör etki göstermedikleri tespit edilmiştir.

ANAHTAR SÖZCÜKLER: 4-Tiyazolidinon, L-valin, anti-HIV etki, anti-HCV etki.

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