Convenient synthesis & Antiviral Evaluation against cytomegalovirus (CMV) and Varicella-zoster virus (VZV) in human embryonic lung (HEL) cells of 7-[Substituted propoxy]-4-methyl-2H-chromen- 2-one and 4-methyl-2-oxo -2H-chromen-7-(Substituted)-yl acetate Via Pechmann Condensation

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Abstract

Synthesis of 7-Hydroxy-4-Methyl-Chromen-2-one **(1)** was achieved by the condensation reaction of commercially available resorcinol and ethyl acetoacetate via Pechmann Condensation reaction. Further Compound **(1)** was treated with 1-Bromo-3-chloropropane and Anhydrous Potassium carbonate in acetone to convert in 7-(3-chloropropoxy)-4-methyl-2*H*-chromen-2-one **(2)**. After treatment of **(2)** with Substituted Benzimidazole **(4)** gave 7-[3-(Substituted-benzimidazol-1-yl)propoxy]-4-methyl-2*H*-chromen-2-one **(5a-d).** In Another route Compound **(1)** undergoes condensation reaction with chloroacetyl chloride and Anhydrous K_2CO_3 in acetone to give 4-methyl-2-oxo-2*H*-chromen-7-yl chloroacetate **(3)** which on further treatment with Substituted Benzimidazole **(4)** gave 4-methyl-2-oxo-2*H*-chromen-7-yl Substituted-benzimidazol-1-ylacetate **(6a-d)**.

Keywords. Pechmann Condensation, 7-Hydroxy-4-Methyl-Chromen-2-one, Substituted Benzimidazole.

Introduction

Coumarin and its derivatives have been attracting great interest because they occupy a special place in the realm of natural products and synthetic organic chemistry [1]. Coumarin and its derivatives were successfully made great interesting targets for organic chemist due to their chemical properties. The various coumarin derivatives contribute to the expansion of pharmacological, biochemical and therapeutics material.Coumarin derivatives also find applications in pharmaceutical and agrochemical industries [2-4]. Chromenes are naturally occurring benzopyrene derivatives known to exhibit wide spectrum of biological activities [5-9] like diuretic, analgesic myorelaxant [10-11],Ulcerogenic[12] and antifungal [13]. Naturallyoccurring angelicin (furanocoumarin) and its various synthetic derivatives were already reported to have good antifungal activity (14). It is suggested that chromene exhibit antifungal activity may be due to either killing the microbes or blocking their active sites [15-16].Coumarins have important effects in plant biochemistry and physiology, acting as antioxidants, enzyme inhibitors and precursors of toxic substances. [17-21].

Material & Methods

All chemicals and solvents were obtained from commercial sources. Melting points were determined in an open capillary melting point apparatus and are uncorrected. The structures of the compounds were confirmed by the IR and proton NMR spectra. Purity of the compounds was checked on silica gel TLC plates of 2 mm thickness using n-hexane and ethyl acetate as solvent system. The visualization of spot was carried out in an Ultraviolet chamber. The IR spectra were recorded on Perkin-Elmer spectrometer. The 1H NMR spectra were scanned on a Bruker DRX-300 MHz. spectrometer (300 MHz) in ($CDCl_3$) using TMS as internal standard and chemical shifts are expressed in δ ppm.

Synthesis of 7-Hydroxy-4-methyl-chromen-2-one (1):

The method of Pechmann was followed for the preparation of 7-hydroxy-4- methyl chromen-2-one. Hundred mL of conc. H_2SO_4 was kept in an ice-bath. When temperature fell below 10^OC, a solution of resorcinol (10 g, 0.091mol) and ethyl acetoacetate (13 mL, 0.103 mol) was added with continuous stirring during 2 h. The temperature was maintained below 10^OC throughout the addition. The reaction mixture was kept at room temperature for 18 hrsafter which it was poured with vigorous stirring into the mixture of 200 g of crushed ice and 300 mL of distilled water. The precipitatewas collected by vacuum filtration and washed with cold water (45 mL). The solid was dissolved in 150 mL of 5% NaOH, filtered, and 2 M H_2SO_4 (55 mL) was added to it with vigorous stirring until the solution was acidic. The crude coumarin was collected by filtration at the pump, washed with cold water and dried. The product wasrecrystallized from ethanol**.**

Yield: 89%., m.p. 183 °C.IR (KBr, cm-1): 3499 (Ar-OH), 3104 (aromatic C-H), 2818 (aliphatic C-H), 1670 (C=O), 1605 (aromatic C=C), 1275 (C-O). ^{1}H NMR ($CDCl_3$, δ, ppm,): 5.92 (s, 1H, Ar-**OH** $_{broad}$), 7.43 (d, 1H, Ar-H), 6.82 (d, 1H, Ar-H), 6.75(s, 1H, Ar-H), 6.03 (s, 1H, HC-C=O), 2.38 (s, 3H, CH_3). Analysis: for $C_{10}H_8O_3$calcd.: C, 68.18; H, 4.58%; found: C, 68.02; H, 4.45%.

Synthesis of 7-(3-chloropropoxy)-4-methyl-2H-chromen-2-one (2):

A mixture of compound **(1)** (0.01 mol), 1-Bromo-3-chloropropane (0.01 mol) and Anhydrous potassium carbonate (0.01 mol) in dry acetone (50 ml) was refluxed for 12 hrs. After the completion of reaction monitored via TLC the reaction mixture was cooled and solution was evaporated until dryness. The resultant residue was washed with water, dried & recrystallized from ethanol.

Yield:80%., m.p.145 °C**.** IR (KBr, cm^{-1}): 3093 (aromatic C-H), 2959, 2887 (aliphatic C-H), 1692 ($C=O_{ring}$), 1611 (aromatic C=C), 706 (C-Cl). ^{1}H NMR ($CDCl_3$, δ, ppm): 7.53-6.09 (m, 4H, Ar- H), 4.17 (t, 2H, CH_2-O), 3.9 (t, 2H, CH_2-Cl), 2.82 (quintet, 2H, CH_2-C**H$_2$**-CH_2), 2.42 (s, 3H, CH_3)**.** Analysis: for $C_{13}H_{13}ClO_3$ calcd.: C, 61.79; H, 5.19; Cl, 14.03%; found: C, 61.72; H, 5.01; Cl, 13.86%.

Synthesis of 4-methyl-2-oxo-2H-chromen-7-yl chloroacetate (3):

Compound **(1)**(0.01 mol), chloroacetyl chloride (0.012 mol) andanhyd. K_2CO_3 (0.01 mol) in 40 ml acetone was refluxed for 8 hrs.,reaction is monitoring by TLC. The reaction mixture was cooled and solvent was distilled off. The resultant product was washed with water, filtered, dried at 60^OC and recrystallized from alcohol.

Yield: 76%., m. p. 187 ^OC. IR (KBr, cm^{-1}): 3088 (Ar-H), 2881 (C-H), 1745 (C=O), 1673 ($C=O_{ring}$), 1609 (C=C), 709 (C-Cl). ^{1}H NMR ($CDCl_3$, δ): 7.62-6.96 (m, 4H, Ar-H), 3.52 (s, 2H, CH_2Cl), 2.49 (s, 3H, CH_3). Analysis for $C_{12}H_9ClO_4$calcd.: C, 57.05; H, 3.59; Cl, 14.03%; found: C, 57.01; H, 3.40; Cl, 13.89%.

Synthesis of 7-[3-(substituted-benzimidazol-1-yl)propoxy]-4-methyl-2H-chromen-2-one (5a-e).

A Mixture of compound (**2**) (0.01 mol), benzimidazole (**4**)(0.01 mol) in ethanol 30 ml and pyridine (0.01 mol) use as base, the reaction mixture was refluxed for 12 hr. After completion of reaction excess of solvent and pyridine was removed by distillation in vacuum pump. The resultant residue was poured in ice-water, filters the solid, washed with water, dried and recrystallized from alcohol. Yield: 81%., m. p. 210 °C

Compounds (**5b-d**) were synthesized after the change in reflux time.

7-[3-(1H-benzimidazol-1-yl)propoxy]-4-methyl-2H-chromen-2-one (5a):

IR (KBr, cm^{-1}): 3112 (Ar-H. str.), 2995 (C-H str.), 1698 ($C=O_{ring}$),1610 (C=N str.) 1569 (C=C str.);^{1}H NMR ($CDCl_3$, δ): 7.96-6.70 (m, 8H, Ar-H), 5.73 (s,1H, N=CH), 4.42 (t, 2H, CH_2-O), 3.73 (t, 2H, CH_2-N), 2.82 (quintet, 2H, CH_2-C**H$_2$**-CH_2), 2.68 (s, 3H, CH_3); MS: m/z 334 [M+]., 217, 204, 146, 117. Analysis for $C_{20}H_{18}N_2O_3$ calcd.:C, 71.84; H, 5.43; N; 8.38%; found: C, 71.63; H, 5.36; N 8.51%.

Synthesis of 7-[3-(methyl-benzimidazol-1-yl)propoxy]-4-methyl-2H-chromen-2-one (5b):

Yield: 78%., m. p. 180 °C.; IR (KBr, cm^{-1}): 3080 (Ar-H. str.), 2982 (C-H str.), 1702 ($C=O_{ring}$), 1605 (C=N str.), 1560 (C=C str.), 1210 (C-O-C str.); ^{1}H NMR ($CDCl_3$, δ): 7.90-6.82 (m, 8H, Ar-H str.), 4.12 (t, 2H, CH_2-O), 3.60 (t, 2H, CH_2-N), 3.08 (s, 3H CH_3), 2.91 (quintet, 2H, CH_2-C**H$_2$**-CH_2), 2.85 (s, 3H, CH_3); MS: 348 [M+]., 333, 217, 189, 176, 131, 118. Analysis for $C_{21}H_{20}N_2O_3$ Calcd.: C, 72.40; H, 5.79; N, 8.04%; found: C, 72.18; H, 5.54; N, 8.24%.

Synthesis of 7-[3-(phenyl-benzimidazol-1-yl)propoxy]-4-methyl-2H-chromen-2-one (5c):

Yield: 79%., m. p. 169°C.;IR (KBr, cm^{-1}): 3105 (Ar-H. str.), 2990 (C-H str.), 1710 ($C=O_{ring}$), 1610 (C=N str.), 1565 (C=C str.), 1222 (C-O-C str.); ^{1}H NMR ($CDCl_3$, δ): 7.99-7.10 (m, 13H, Ar-H str.), 4.19 (t, 2H, CH_2-O),

3.65 (t, 2H, CH_2-N), 3.05 (quintet, 2H, CH_2-C**H$_2$**-CH_2), 2.94 (s, 3H, CH_3); MS: 410 [M+]., 217, 193, 159, 131, 105, 77. Analysis for $C_{26}H_{22}N_2O_3$ Calcd.: C, 76.08; H, 5.40; N, 6.82% found: C, 76.01; H, 5.22; N, 6.93%.

Synthesis of 7-[3-(4-aminophenyl-benzimidazol-1-yl)propoxy]-4-methyl-2H-chromen-2-one (5d):

Yield: 73%., m. p. 255 °C.; IR (KBr, cm^{-1}): 3455,3410 (s, 2H, NH_2), 3119 (Ar-H. str.), 2917 (C-H str.), 1745 (C=O $_{ring}$), 1625 (C=N str.), 1590 (C=C str.), 1219 (C-O-C str.); ^{1}H NMR ($CDCl_3$, δ): 7.99-7.10 (m, 12H, Ar-H str.), 5.06 (s, 2H, NH_2), 4.12(t, 2H, CH_2-O), 3.60 (t, 2H, CH_2-N), 2.95 (quintet, 2H, CH_2-C**H$_2$**-CH_2), 2.82 (s, 3H, CH_3); MS: 425 [M+]., 333, 217, 147, 119, 116, 92. Analysis for $C_{26}H_{23}N_3O_3$ calcd.: C, 73.39; H, 5.45; N, 9.88% found: C, 73.22; H, 5.39; N, 9.93%.

Synthesis of substituted benzoimidazol-1-yl-acetic acid 4-methyl-2-oxo-2H-chromen-7-yl ester (6a-d):

An equimolar mixture of compound (**3**), substituted benzimidazole (**4**) and pyridine in 30 ml ethanol, reflux for 8 hrs. After completion of reaction the reaction mixture poured over crushed ice. The resultant solid was washed with water, dried and recrystallized from absolute alcohol.Yield: 69%, m. p. 175°C

(benzoimidazol-1-yl)-aceticacid 4-methyl-2-oxo-2H-chromen-7-yl ester (6a):

IR (KBr, cm^{-1}): 3105 (Ar-H. str.), 2892 (C-H str.), 1745 (C=O, str.), 1685 (C=O, str. ring), 1640 (C=N, str.), 1570 (C=C, str.), 1202 (C-O-C str.);^{1}H NMR ($CDCl_3$, δ): 7.80-6.90 (m, 8H, Ar-H str.), 6.29 (s, 1H,N=C-H), 3.85 (s,2H, CH_2), 2.90 (s, 3H, CH_3); MS: 334 [M+]., 217, 203, 190, 163, 119,116. Analysis for $C_{19}H_{14}N_2O_4$ Calcd.: C, 68.26; H, 4.22; N, 8.38% found: C, 68.12; H, 4.16; N, 8.27%.

(2-Methyl-benzoimidazol-1-yl)-acetic acid 4-methyl-2-oxo-2H-chromen-7-yl ester (6b):

Yield: 71%., m. p. 195°C.; IR (KBr, cm^{-1}): 3080 (Ar-H. str.), 2898 (C-H str.), 1742 (C=O, str.), 1690 (C=O, str. ring), 1652 (C=N, str.), 1538 (C=C, str.), 1208 (C-O-C str.); ^{1}H NMR ($CDCl_3$, δ):7.85-6.85 (m, 8H, Ar-H str.), 4.12 (s, 3H, CH_3), 3.52 (s,2H, CH_2), 3.16 (s, 3H, CH_3); MS: 248 [M+]., 203, 190, 134, 131, 121. Analysis for$C_{20}H_{16}N_2O_4$ calcd.: C, 68.96; 4.63; N, 8.04% found: 68.75; H, 4.55; N, 8.14%.

(2-Phenyl-benzoimidazol-1-yl)-acetic acid 4-methyl-2-oxo-2H-chromen-7-yl ester (6c):

Yield: 65%., m. p. 215°C.;IR (KBr, cm^{-1}): 3125 (Ar-H. str.), 3012 (C-H str.), 1740 (C=O, str.), 1702 (C=O, str. ring), 1668 (C=N, str.), 1547 (C=C, str.), 1222 (C-O-C str.); ^{1}H NMR ($CDCl_3$, δ):8.27-7.05 (m, 13H, Ar-H str.), 4.02 (s,2H, CH_2), 3.28 (s, 3H, CH_3); MS: 410 [M+]., 203, 193, 175, 119, 79, 77. Analysis for $C_{25}H_{18}N_2O_4$ calcd.: C, 73.16; H, 4.42; N, 6.83% found: C, 73.04; H, 4.45; N, 6.81%.

[2-(4-Amino-phenyl)-benzoimidazol-1-yl]-aceticacid 4-methyl-2-oxo-2H-chromen-7-yl ester (6d);

Yield: 70%., m. p. 156°C.;IR (KBr, cm^{-1}): 3412, 3390 (s, 2H, NH_2 str.), 3022 (Ar-H. str.), 2952 (C-H str.), 1765 (C=O, str.), 1718 (C=O, str. ring), 1625 (C=N, str.), 1581 (C=C, str.), 1238 (C-O-C str.); ^{1}H NMR ($CDCl_3$, δ):8.26-7.12 (m, 12H, Ar-H str.), 5.68 (s, 2H, NH_2)4.72 (s,2H, CH_2), 3.20 (s, 3H, CH_3); MS: 425 [M+]., 333, 203, 174, 162, 159, 92. Analysis for $C_{25}H_{19}N_3O_4$ Calcd.: C, 70.58; H, 4.50; N, 9.88% found: C, 70.44; H, 4.36; N, 9.73%.

Result and Discussion

Synthesis of 7-Hydroxy-4-Methyl-Chromen-2-one **(1)** was achieved by the condensation reaction of commercially available resorcinol and ethyl acetoacetate*via* Pechmann Condensation reaction. Which is confirmed by disappear of one OH peak and quartet, triplet signal in ^{1}HNMR spectra.In the next step compound **(1a)** was refluxed with 1-bromo-3-chloropropane in the presence of anhydrous potassium carbonate for 8 hrs. to afford 7-(3-chloropropoxy)-4-methyl-2*H*-chromen-2-one **(2).** This compound is confirmed by two triplet in ^{1}HNMR spectra at 4.17 (t, 2H, CH_2-O), 3.9 (t, 2H, CH_2-Cl).Compound **(2)** condensed withbenzimidazole to give 7-[3-(Benzimidazol-1-yl)propoxy]-4-methyl-2H-chromen-2-one(**5a**). In this compound N-H peak is disappear in IR as well as ^{1}HNMR spectra. In Another path compound (**1)** 7-Hydroxy-4-methyl-chromen-2-one treated with chloroacetyl chloride in presence of potassium carbonate & reflux for 8 hrs.to afford 4-methyl-2-oxo-2*H*-chromen-7-yl chloroacetate **(3)**. It shows two (C=O) carbonyl frequency at 1745 (C=O), 1673 (C=O $_{ring}$). Further compound **(3)**treated with benzimidazole **(4)** give 4-methyl-2 ro-oxo-2*H*-chromen-7-yl 1*H*-benzimidazol-1-ylacetate **(6a),** It is also confirmed by disappear of NH peak in IR as well as ^{1}HNMR spectra.

Antiviral activity

The antiviral activities of compounds **5 (a–d)** and **6 (a–d)** were evaluated against a variety of viruses **(Table 1 & 2)**. The following viruses and host cells were used for the evaluation: (a) HeLa cell cultures: vesicular stomatitis virus, Coxsackie B4 virus, and respiratory syncytial virus (RSV). (b) HEL cell cultures: herpes simplex virus-1 (KOS), herpes simplex virus-2 (G), herpes simplex virus-1 (TK–KOS ACVR), vaccinia virus (VV), and vesicular stomatitis virus (VSV) in (Table 1). For each compound, the minimum inhibitory

concentration (MIC) and the minimal cytotoxic concentration (MCC) or the cytotoxic concentration required to reduce cell growth by 50 % (CC_{50}), were obtained.

(S)-9-(2,3-dihydroxypropyl)adenine [(S)-DHPA], ribavirin, acyclovir, cidofovir and ganciclovir were used as the reference compounds. In the tests with viruses described in (a), (b), and (c) antiviral activity and, in parallel, cytotoxicity were monitored with the compound concentrations up to 200 μM. The cut-off point for specific antiviral activity was 5-fold lower than the cytotoxic concentration (MCC or CC50).

All synthesized compounds were also screened against cytomegalovirus (CMV) [strains AD-169 and Davis], varicella-zoster virus (VZV) [TK+ VZV strain OKA, and TK– VZV strain 07/1] in human embryonic lung (HEL) cells (Table 2). Compound **5d** was found active against AD-169 is **9.46** μg/ml, and Davis strains of cytomegalovirus are **8.67.** Whereas cytotoxicity (MCC) of this compound in HEL cells was observed at **150** μg/ml. Compounds **5d** and **6a** show activity against Antiviral activity EC_{50} (μg/ml) (TK– **VZV** 07/1 strain) value of **6.79** μg/ml and **5.84** μg/ml respectively.

Acknowledgements

Authors are thankful to the Head, Department of Chemistry and Head, Department of pharmacy MEWAR UNIVERSITY, CHITTORGARH for providing laboratory facilities and microbiological activity facilities. Authors are thankful to the IIT Delhi, India for providing spectral and analytical data.

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Reaction Scheme

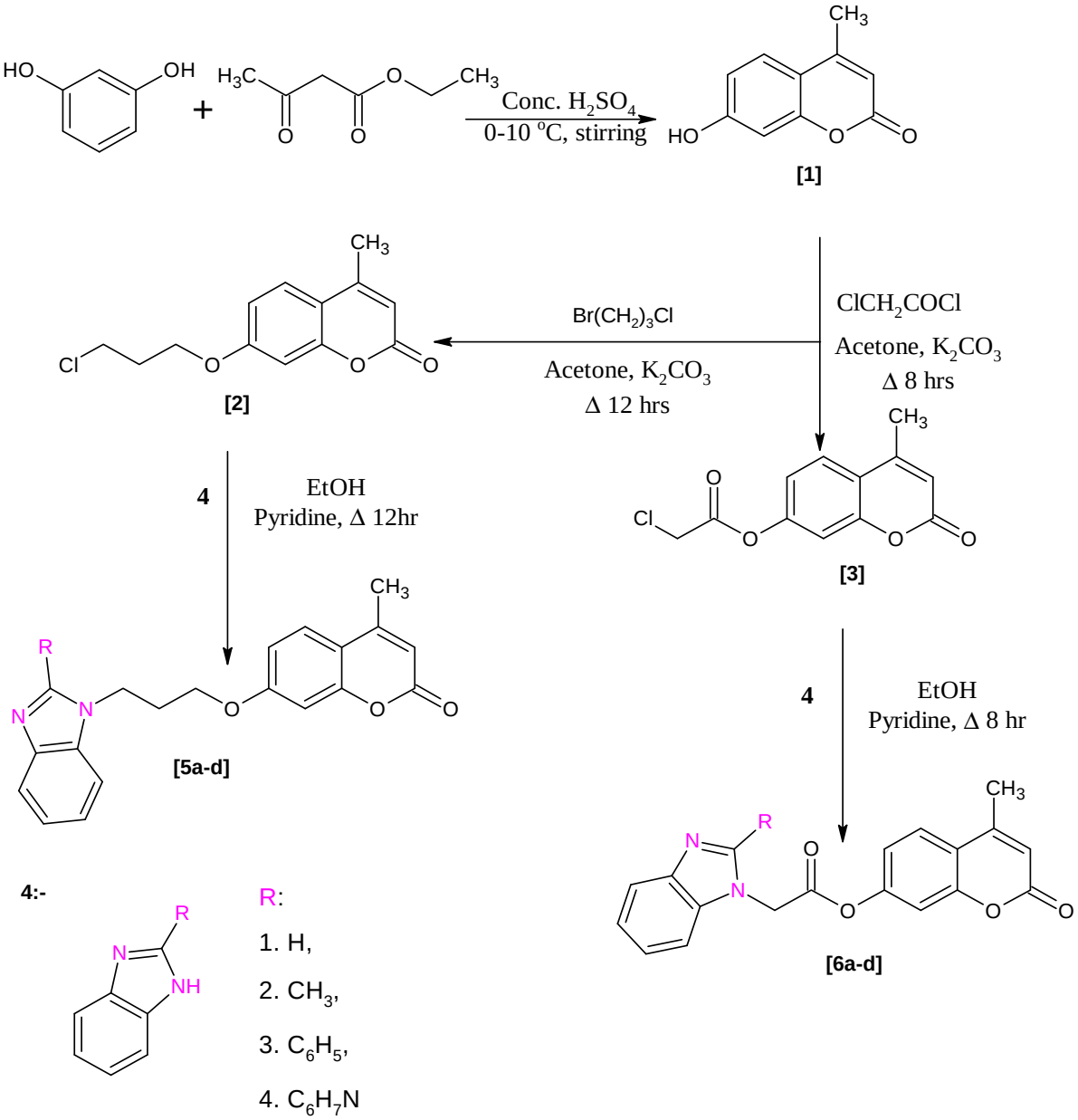

Table 1: Cytotoxicity and antiviral activity of compounds 5 (a–e) and 6 (a–e) in HEL and HeLa cell cultures

Comp.	**HEL cell cultures**						**HeLa cell cultures**			
	Min inhibitory conc. b (μg/ml)						Min inhibitory conc. b (μg/ml)			
	Min cytotoxic conc. [a] (μg/ml)	HSV-1 (KOS)	HSV-2 (G)	Vaccinavirus	Vesicular stomatitis virus	**HSV-1 TK KOS**ACV[r]	Min inhibitory conc. [b] (μg/ml)	Vesicular stomatitis virus	Coxsackie virus B4	Respiratorysyncytial virus
5a	>100	>50	>100	>100	>100	50	>200	>150	>50	>100
5b	>100	>50	>100	>100	>50	>30	>100	>50	>40	>50
5c	>150	>100	>50	>50	>40	40	>150	>100	>20	>80
5d	>100	40	>40	>55	>30	>50	100	>100	>15	>50
6a	>200	>100	>50	>100	>45	30	50	>40	>50	10
6b	100	>50	>90	>50	>20	>30	40	20	>15	8
6c	>50	>40	>20	>25	>40	15	>95	>50	>100	>40
6d	>100	>40	50	>40	35	>100	>150	>50	>40	>150
Brivudin (μM)	>250	0.08	20	10	>200	>250	>250	>250	>250	>250
Ribavirin (μM)	>250	>250	>150	>150	>100	40	50	30	150	50
Acyclovir (μM)	>250	0.4	0.4	>150	>250	50	-	-	-	-
Ganciclovir (μM)	>100	.032	.0064	100	>100	2.4	-	-	-	-
(S)-DHPA (μM)	_	_	_	_	_	_	>250	150	150	>250

a Required to cause a microscopically detectable alteration of normal cell morphology.

b Required to reduce virus-induced cytopathogenicity by 50 %.

Table 2: Cytotoxicity and antiviral activity of compounds 5 (a–e) and 6 (a–e) against cytomegalovirus (CMV) and Varicella-zoster virus (VZV) in human embryonic lung (HEL) cells.

Comp.	Antiviral activity EC50 (μg/ml)a		Cytotoxicity (μg/ml)		Antiviral activity EC50 (μg/ml)a		Cytotoxicity (μg/ml)	
	CMV AD-169 strain	**CMV** Davis strain	Cell morphology (MCC)b	Cell growth (CC50)c	TK+ **VZV** OKA strain	TK– **VZV** 07/1 strain	Cell morphology (MCC)b	Cell growth (CC50)c
5a	>10	>20	>50	>65	>100	>100	>100	>100
5b	>100	>55	>100	>90	>50	>100	>100	>100
5c	>100	>100	>95	>100	>100	>100	>100	>100
5d	**9.46**	**8.69**	>20	>25	>20	>10	>55	16
6a	>15	>10	>15	>24	>10	**6.79**	>20	>17
6b	>20	>10	>35	>60	20.5	**5.84**	20	20
6c	>30	>20	>20	>50	>20	>25	>40	>50
6d	>40	>100	>100	>60	>10	>50	100	15
Ganciclovir	1.4	1.7	400	80	-	-	-	-
Cidofovir	0.24	0.37	400	57	-	-	-	-
Acyclovir	-	-	-	-	1	15	>50	190
Brivudin	-	-	-	-	.0096	12.6	>50	244

a :Effective concentration required to reduce virus plaque formation by 50%. Virus input was 20 plaque forming units (PFU).

b :Minimum cytotoxic concentration that causes a microscopically detectable alteration of cell morphology.

c : Cytotoxic concentration required to reduce cell growth by 50%.