SYNTHESIS AND EVALUATION OF ANTICANCER AND ANTIVIRAL ACTIVITY OF SOME 2-ARYL-3-(4-(2H-1-BENZOPYRAN-2-ONE-3-YL)-2-THIAZOLYL)-5-METHYL-4-THIAZOLIDINONES

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Abstract: 2-Aryl-3-(4-(2H-1-benzopyran-2-one-3-yl)-2-thiazolyl)-5-methyl-4-thiazolidinones (**3**), have been prepared by the reaction of Schiff's bases (**2**) with 2-mercaptopropionic acid. The Schiff's bases in turn are obtained by the reaction of various aldehydes with 3-(2-amino-4-thiazolyl)coumarins. The compounds **3** have been evaluated for their anticancer and antiviral activity.

Introduction

The coumarin nucleus is found in a variety of natural products which exert varied pharmacological effects. Numerous reports have appeared in the literature describing HIV protease inhibiting, α-chymotrypsin inhibiting, analgesic, antimicrobial activity and anticancer activity[1-5] of 3-heterocyclyl coumarins. Further 4-thiazolidinone play a vital role owing to their wide range of biological activities[6-9] and industrial importance as stabilizers for polymeric materials. The chemistry of the 4-thiazolidinone ring system was reviewed in depth[10]. In order to explore the activities associated with both coumarin and thiazolidinone rings, we report herein the synthesis and anticancer and antiviral activities of the new derivatives of thiazolidinones.

In our ongoing search for potential anticancer agents we present our results on the design of 2-aryl-3-(4-(2H-1-benzopyran-2-one-3-yl)-2-thiazolyl)-5-methyl-4-thiazolidinones. The compounds presented here were assayed *in vitro* for their anticancer and antiviral activity.

Reaction of 3-(2-bromoacetyl)coumarins with thiourea resulted in the formation of 3-(2-amino-4-thiazolyl)coumarins (**1**). Condensation of these compounds with various aromatic aldehydes in presence of piperidine resulted in the Schiff bases **2**. The Schiff's bases on reaction with mercaptopropionic acid in dry benzene under reflux gave **3** (Scheme-1). IR spectrum of **3** showed an intense peak at 1680 cm^{-1} indicating the presence of an amide of thiazolidinone ring. The **3** has been identified as a diastereomeric mixture. Compound **3h**(i) and **3h(ii)** are formed in the ratio of 54:46. The ^1H NMR data given confirm the diastereomeric excess to the extent of 8% in case of trimethoxy sunbstituted thiazolidinone **3h**(i) and **3h**(ii). The absolute configuration of the diastereomers are assigned tentatively[11,12] on the basis of ^1H NMR spectra as trans 2R, 5R(i) and cis 2R, 5S (ii). ^1H NMR spectra of **3h(i)** and **3h(ii)** showed two distinct doublets at δ 1.79 and 1.69 for

C_5-CH_3 of thiazolidinone ring and two distinct quartets at δ 4.20 and 4.35 for C_5-H protons. Similarly C_2-H showed two independent singlets at 6.60 and 6.70. The product formation was further supported by mass spectrum which showed molecular ion at m/z 510.

The diastereomeric mixture could not be resolved into individual diastereomers by silica gel chromatography by using various solvent systems[6,7]. This is due to their very close proximity in their Rf values.

Experimental

All melting points were determined in open capillary tubes using sulphuric acid bath and are uncorrected. IR Spectra (ν_{max} in cm^{-1}) were recorded in Perkin-Elmer – 282 instrument (USA), ^{1}H-NMR spectra on varian 200 MHz spectrometer (Darmstudt, Germany) using TMS as internal standard (Chemical Schifts in δ ppm) and mass spectra on Jeol-JMS-D mass spectrometer at 70 eV.

The various derivatives of 3-(2-bromoacetyl)coumarins and 3-(2-amino-4-thiazolyl)coumarins were prepared according to our earlier procedure[13-14]. Representative methods of preparation of compounds 2 and 3 along with spectral data are described as:

Preparation of 3-(2-(Arylmethylene)amino-4-thiazolyl)-2H-1-benzo- pyran-2-one **(2).** A mixture of 0.244 g (0.001 mol) of 3-(2-amino-4-thiazolyl)coumarin and aromatic aldehyde (0.001 mol) was refluxed in ethanol containing catalytic amount of piperidine for 4 hours. The reaction mixture was cooled and the separated solid was filtered and crystallized from a suitable solvents to yield 2 in the pure form.

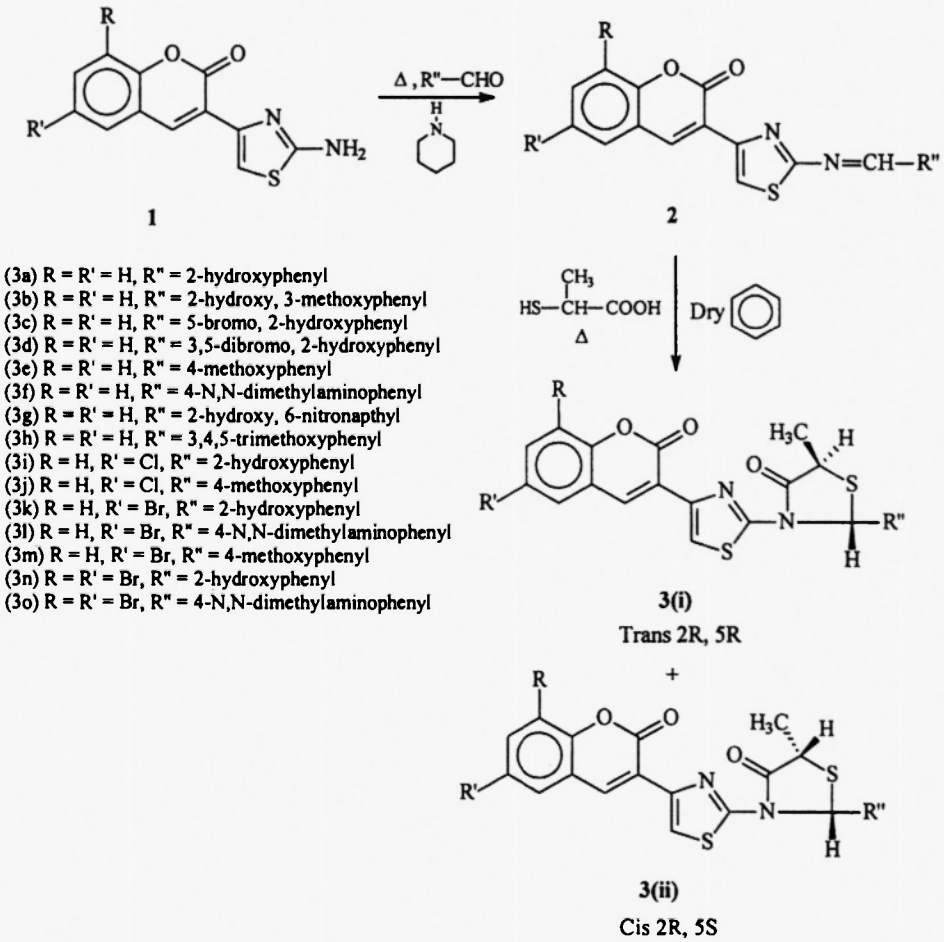
3-(2-(Arylmethylene)amino-4-thiazolyl)-2H-1-benzopyran-2-one (2a). IR (cm^{-1}) : 1600 (-C=N-), 1720 (-C=O), 3300-3600 (-OH). ^{1}H NMR ($CDCl_3$, δ ppm) : 6.9 (s, 1H, methylene), 7.0-7.6 (m, 8H, aromatic), 8.3 (s, 1H, C_5 of thiazole), 8.6 (s, 1H, coumarin C_4), 9.1 (s, 1H, phenolic OH). MS : m/z 348, 315, 286, 256, 244, 216, 174, 43 (100).

3-(2-(2-*o*-Hydroxy aryl methyleneamino)-4-thiazolyl)-6-chloro-2H-1-benzopyran-2-one (2i). IR (cm^{-1}) : 1610 (-C=N-), 1720 (-C=O), 3300-3600 (-OH), ^{1}H NMR ($CDCl_3$, δ ppm) : 6.8 (s, 1H, -CH=), 7.0-8.0 (m, 7H, Ar-H), 8.4 (s, 1H, C_5 of thiazole), 9.0 (s, 1H, C_4 of coumarin), 9.8 (s, 1H, OH).

3-(2-*o*-Hydroxy methyleneamino)-4-thiazolyl)-6-bromo-2H-1-benzopyran-2-one (2k). IR (cm^{-1}) : 1600 (-C=N-), 1720 (-C=O), 3600 (-OH). ^{1}H NMR ($CDCl_3$ + DMSO-d_6) : 6.9

(s, 1H, -CH=), 7.0-7.8 (m, 7H, Ar-H), 8.4 (s, 1H, C_5 of thiazole), 9.2 (s, 1H, C_4 of coumarin), 11.9 (s, 1H, -OH).

Preparation of 2-aryl-3-(4-2H-1-benzopyran-2-one-3-yl)-2-thiazolyl)-5-methyl-4-thiazolidinone, 3(i) and 3(ii). To a well stirred solution of Schiff's base 2 (0.001 mol) in dry benzene (50 ml), 2-mercaptopropionic acid 0.1061 g (0.001 mol) was added. The contents were refluxed for 6 hours. The reaction mixture was cooled. The separated solid was washed with sodium bicarbonate and recrystallised from benzene to yield **3** as diastereomeric mixture. The diastereomeric mixture could not be resolved into individual diastereomers by silica gel chromatography.



Scheme - 1

2-*o*-Hydroxy aryl-3-(4-2H-1-benzopyran-2-one-3-yl)-2-thiazolyl)-5-methyl-4-thiazolidinone (3a). IR (cm^{-1}) : 1610 (-C=N-), 1685 (-CONH-) and 1720 (-C=O). **3a(i) :**

^{1}H NMR ($CDCl_3$, δ ppm) : 1.70 (d, J = 6.8 Hz, CH_3 of thiazolidinone), 4.1 (q, J = 6.8 Hz, 1H, C_5 of thiazolidinone), 6.78 (s, 1H, thiazolidinone C_2-H), 7.18-7.26 (m, 8H, ArH), 8.00 (s, 1H, C_5' of thiazole), 8.20 (s, 1H, C_4 of coumarin) and 9.6 (s, 1H, phenolic OH). **3a(ii) :** δ : 1.90 (d, J = 6.8 Hz, CH_3 thiazolidinone), 4.50 (q, J = 6.8 Hz, C_5-H of thiazolidinone), 7.30 – 7.40 (m, 8 ArH), 8.10 (s, 1H, C_5' of thiazole), 8.30 (s, 1H, C_4 of coumarin) and 9.6 (s, 1H, phenolic OH).

2-*p*-N,N-Dimethylamino-3-(4-2H-1-benzopyran-2-one-3-yl)-2-thiazolyl)-5-methyl-4-thiazolidinone (3f). IR (cm^{-1}) : 1590 (-C=N-), 1680 (-CON-), 1710 (-CO-). **3f(i)** ^{1}H NMR ($CDCl_3$, δ ppm) : 1.70 (d, J = 6.8 Hz, CH_3 of thiazolidinone), 2.9 (s, 6H, $N(CH_3)_2$), 4.1 (q, J = 8 Hz, 1H, C_5 of thiazolidinone), 6.5 (s, 1H, thiazolidinone C_2-H), 6.60-6.70 and 7.20-7.58 (m, 8H, Ar-H), 8.10 (s, 1H, C_5' of thiazole) and 8.30 (s, 1H, C_4 of coumarin). **3f(ii)** δ : 1.80 (d, J = 6.8 Hz, 3H, CH_3 of thiazolidinone), 3.10 (s, 6H, $N(CH_3)_2$), 4.30 (q, J = 6.8 Hz, 1H of thiazolidinone), 6.60 (s, 1H, thiazolidinone C_2-H) and 7.45 – 7.58 (m, 8H, Ar-H), 8.18 (s, 1H, C_5' of thiazole) and 8.50 (s, 1H, C_4 of coumarin).

2-(3,4,5-Trimethoxyphenyl-3-(4-2H-1-benzopyran-2-one-3-yl)-2-thiazolyl)-5-methyl-4-thiazolidinone (3h).

3h : IR (KBr, ν_{max} cm^{-1}) 1600 (-C=N-), 1680 (-CO-N-) and 1720 (-O-CO-). **3h (i) :** ^{1}H NMR (200 MHz) $CDCl_3$ δ; 1.69 (d, 3H, J = 6.8 Hz, thiazolidinone CH_3), 3.85 (s, 9H, 3 x OCH_3), 4.20 (q, 1H, J = 6.8 Hz, thiazolidinone 5-H), 6.60 (s, 1H, C_2-H of thiazolidinone), 7.20-7.38 (m, 6H, Ar-H), 8.0 (s, 1H, C_5' of thiazole) and 8.19 (s, 1H, C_4 of coumarin). **3h(ii) :** 1.79 (d, 3H, J = 6.8 Hz, thiazolidinone CH_3), 3.85 (s, 9H, 3 x OCH_3), 4.35 (q, 1H, J = 6.8 Hz, thiazolidinone 5-H), 6.65 (s, 1H, C_2-H of thiazolidinone), 6.50-6.70 (m, 2H, Ar-H), 7.40-7.58 (m, 6H, Ar-H), 8.1 (s, 1H C_5' of thiazole) and 8.20 (s, 1H, C_4 of coumarin). MS : m/z 510, 454, 421, 391, 289, 271, 244 and 211 (100%).

2-*o*-Hydroxy aryl-3-(6,8-dibromo-2H-1-benzopyran-2-one-3-yl)-2-thiazolyl)-5-methyl-4-thiazolidinone (3n).

IR (cm^{-1}) : 1610 (-C=N-), 1690 (-CON-) and 1720 (-CO-). **3n(i) :** ^{1}H NMR ($CDCl_3$, δ ppm) : 1.70 (d, J = 6.8 Hz, CH_3 of thiazolidinone), 4.20 (q, J = 6.8 Hz, 1H of thiazolidinone), 6.70 (s, 1H, C_2-H of thiazolidinone), 7.20 – 7.38 (m, 6H, ArH), 8.0 (s, 1H, C_5' of thiazole), 8.20 (s, 1H, C_4 of coumarin) and 9.60 (s, 1H, phenolic OH). **3n(ii)** δ : 1.90 (d, J = 6.8 Hz, CH_3 of thiazolidinone), 4.50 (q, J = 6.8 Hz, 1H of thiazolidinone), 6.90 (s,

1H, C_2-H of thiazolidinone), 7.20 – 7.38 (m, 6H, ArH), 8.10 (s, 1H, C_5' of thiazole), 8.20 (s, 1H, C_4 of coumarin) and 9.60 (s, 1H, phenolic OH).

Biological Evaluation

The synthesized compounds were screened for their anticancer and antiviral activities. Biological studies on 2-aryl-3-(4-(2H-1-benzopyran-2-one-3-yl)-2-thiazolyl)-5-methyl-4-thiazolidinones 3a-3o were carried against murine leukemia cells and human T-Lymphocyte cells and results are shown in Table – 1. The antiviral activity of 3a-3o were carried out against varicella-zoster virus in human embryonic lung (HEL) cells. The antiviral activities of these compounds are given in Table-2. The anticancer and antiviral activity has been carried out at Rega Medical Research Institute, Luven, Belgium.

Anticancer Activity

It is evident from the results that there is in general good agreement between the different murine and human cell lines. 3a, 3b, 3d and 3i were the most cytotoxic. However, we believe that the cytotoxic activities are not sufficient pronounced for the compounds to be considered for further persuit as antitumor leads. Most of the compounds of thiazolidinones, except for 3h,3l and 3m also inhibited the proliferation of tumor cells i.e. murine leukemia cells and human T-lymphocytic cells,with in the concentration range of 10-100 μg/ml. Their cytostatic activity did not vary significantly from one cell line to another. When evaluated under the same conditions, melphalan exhibited cytostatic activity with in the 0.5 –1.0 μg/ml concentration range.

The method[15] used to measure cytostatic activity was as follows.

All assays were performed in 96 well microtiter plates (Falcon 3072; Becton Dickinson , Paramus, NJ) . To each cell were added ca. 6×10^4 murine leukemia L1210 , or human lymphocyte molt $4/C_8$ and CEM cells (100 μl) and a given amount of the test compound (100μl) . The cells were allowed to proliferate for 48 to 72 h at 37^0c in humidified CO_2 controlled atmospuere . At the end of the incubation period , the cells were counted in a coulter counter (model ZB; coulter Electronics Ltd; Harpender, Hertfordshire, England). 50% Cytostatic concentration (CC50) was defined as the concentration of compound that inhibited cell proliferation by 50%.(Table-2)

Table-1 : Analytical data of compounds 2 and 3

Compd	R	R'	R''	m.p. °C	Yield	Mol. formula (mol.wt)	Found (Calcd.) (%)	
							N	S
2a	H	H	2-Hydroxy phenyl	194-196	78	$C_{19}H_{12}N_2O_3S$ (348)	8.00 (8.05)	9.08 (9.10)
2b	H	H	2-Hydroxy -3-methoxy phenyl	197-199	75	$C_{20}H_{14}N_2O_4S$ (378)	7.36 (7.40)	8.42 (8.46)
2c	H	H	2-Hydrxy-5-bromophenyl	275-277	80	$C_{19}H_{11}BrN_2O_3S$ (427)	6.50 (6.55)	7.46 (7.50)
2d	H	H	3,5-Dibromo-2-hydroxy phenyl	256-258	76	$C_{19}H_{10}Br_2N_2O_3S$ (506)	5.52 (5.53)	6.30 (6.32)
2e	H	H	4-Methoxy phenyl	191-193	78	$C_{20}H_{14}N_2O_3S$ (362)	7.70 (7.73)	8.80 (8.83)
2f	H	H	4-N,N-dimethyl aminophenyl	168-170	80	$C_{21}H_{17}N_3O_2S$ (375)	11.16 (11.20)	8.50 (8.53)
2g	H	H	2-Hydroxy-6-nitronaphthyl	257-259	72	$C_{19}H_{11}O_5N_2S$ (379)	7.35 (7.38)	8.40 (8.44)
2h	H	H	3,4,5-Trimethoxy phenyl	195-197	74	$C_{22}H_{18}O_5N_2S$ (422)	6.61 (6.63)	7.55 (7.58)
2i	H	Cl	2-Hydroxy phenyl	220-222	80	$C_{19}H_{11}O_3N_2SCl$ (382.5)	7.30 (7.32)	8.34 (8.36)
2j	H	Cl	4-Methoxy phenyl	150-152	68	$C_{20}H_{13}O_3N_2SCl$ (396.5)	7.00 (7.06)	8.00 (8.07)

Contd...

Continued Table-1: Analytical data of compounds 2 and 3

Compd	R R'	R"	m.p. °C	Yield	Moi formula (moi.wt)	Found (Calcd.) (%) N	 S
2k	H Br	2-Hydroxy phenyl	265-267	72	$C_{19}H_{11}O_3N_2SBr$ (427)	6.52 (6.55)	7.45 (7.49)
2l	H Br	4-N,N-dimethyl aminophenyl	162-164	76	$C_{21}H_{16}O_2N_3SBr$ (454)	9.18 (9.25)	6.98 (7.04)
2m	H Br	4-Methoxy phenyl	150-152	74	$C_{20}H_{13}O_3N_2SBr$ (441)	6.29 (6.35)	7.14 (7.25)
2n	H Br	2-Hydroxy phenyl	142-144	78	$C_{19}H_{11}O_3N_2SBr$ (427)	6.49 (6.55)	7.43 (7.49)
2o	Br Br	4-N,N-dimethyl aminophenyl	130-132	75	$C_{21}H_{15}O_2N_3SBr_2$ (533)	7.82 (7.88)	5.93 (6.00)
3a	H H	2-Hydroxy phenyl	245-247	74	$C_{22}H_{16}N_2O_4S_2$ (436)	6.38 (6.42)	14.62 (14.67)
3b	H H	2-Hydroxy-3-methoxyphenyl	270-272	76	$C_{23}H_{18}O_5N_2S_2$ (466)	5.93 (6.00)	13.68 (13.73)
3c	H H	5-Bromo-2-hydroxyphenyl	210-212	80	$C_{21}H_{15}BrN_2O_4S_2$ (515)	5.41 (5.43)	12.38 (12.42)
3d	H H	3,5-Dibromo-2-hydroxyphenyl	212-214	75	$C_{22}H_{14}Br_2N_2O_4S_2Br_2$ (594)	4.63 (4.69)	10.68 (10.73)
3e	H H	4-Methoxy phenyl	200-202	70	$C_{23}H_{18}N_2O_4S_2$ (450)	6.18 (6.22)	14.20 (14.22)

Con'd..

Continued Table-1: Analytical data of compounds 2 and 3

Compd	R R'	R"	m.p. °C	Yield	Mol formula (mol.wt)	Found (Calcd.) (%) N	 S
3f	H H	4-N,N-Dimethyl aminophenyl	120-122	72	$C_{24}H_{21}N_3O_3S_2$ (463)	9.01 (9.07)	13.78 (13.82)
3g	H H	2-Hydroxy-6-nitronaphthyl	270-272	74	$C_{26}H_{17}N_3O_6S_2$ (531)	7.85 (7.90)	11.99 (12.05)
3h	H H	3,4,5-Trimethoxy phenyl	240-242	78	$C_{25}H_{22}N_2O_5S_2$ (510)	5.43 (5.49)	12.49 (12.54)
3i	H Cl	2-Hydroxyphenyl	200-202	76	$C_{22}H_{15}ClN_2O_4S_2$ (470.5)	5.89 (5.95)	13.58 (13.60)
3j	H Cl	4-Methoxy phenyl	100-102	74	$C_{23}H_{17}ClN_2C_4S_2Cl$ (484.5)	5.73 (5.78)	13.18 (13.21)
3k	H Br	2-Hydroxyphenyl	180-182	76	$C_{22}H_{15}BrN_2O_4S_2$ (515)	5.35 (5.43)	12.39 (12.42)
3l	H Br	4-N,N-dimethyl aminophenyl	120-122	75	$C_{21}H_{20}N_3O_3S_2Br$ (542)	7.69 (7.75)	11.75 (11.80)
3m	H Br	4-Methoxyphenyl	220-222	78	$C_{23}H_{17}N_2O_4S_2Br$ (465)	5.98 (6.02)	13.70 (13.76)
3n	Br Br	2-Hydroxyphenyl	230-232	75	$C_{22}H_{14}N_2S_2O_4Br_2$ (594)	4.66 (4.71)	10.72 (10.77)
3o	Br Br	4-N,N-dimethyl aminophenyl	140-142	76	$C_{24}H_{19}N_3S_2O_3Br_2$ (621)	6.73 (6.76)	10.27 (10.30)

Compounds 2a to 2o were crystallized from benzene, remaining compounds were crystallized from ethanol.

Antiviral Activity

Compounds 3e and compound 3k demonstrated a slight but selective activity against CMV, with a selectivity index (SI) (or ratio of CC_{50} to IC_{50}) of > 5. Compounds 3k and 3n demonstrated some activity against both TK^+ and TK^- strains of VZU with a SI ranging from >4 to >12.5.From the series of thiazolidinones,the following showed an appreciable activity against both thymidine kinase-encoding(TK^+)and thymidine kinase-deficient (TK^-)VZV strains:3c,3d,3e,3f,3g,3j,3k and 3n ,albeit at concentrations that were in the best cases not lower than a tenth of the minimum cytotoxic concentration. This means that even the most specific compounds, i.e.3f,3k and 3n did not show a selectivity index greater than ten. This contrasts with the activity shown by BVDU(brivudin) against TK^+ VZV, which was inhibited by BVDU with a selectivity of greater than 50,000.

Table-2 : Inhibitory effects of compounds on the proliferation of murine leukemia cells (L1 210/0) and human T-lymphocyte cells (MOLT4/C8, CEM/0)

Compound	IC_{50} (μg/ml)		
	L1210/0	MOLT4/C8	CEM/0
3a	8.4 ± 0.2	14 ± 2	12 ± 3
3b	61 ± 7	99 ± 26	74 ± 20
3c	12 ± 0	12 ± 8	8.5 ± 3.2
3d	14 ± 0	18 ± 2	16 ± 3
3e	88 ± 0	28 ± 13	47 ± 2
3f	88 ± 1	25 ± 0	35 ± 7
3g	83 ± 2	38 ± 9	38 ± 5
3h	152 ± 15	180 ± 28	152 ± 5
3i	88 ± 3	75 ± 8	75 ± 5
3j	13 ± 1	15 ± 1	10 ± 1
3k	31 ± 4	22 ± 3	17 ± 0
3l	198 ± 4	≥ 200	≥ 200
3m	186 ± 19	146 ± 4	151 ± 17
3n	16 ± 1	21 ± 4	16 ± 2
3o	91 ± 7	70 ± 8	59 ± 3

50% inhibitory concentration

The method used to measure anti-VZV activity was as follows :

The activity of the test compounds against the laboratory wild-type VZV (varicella-zoster virus) strains (Oka and Ys) and the thymidine kinase-deficient VZV strains (0.7-

1and YS-R) was measured as previously described[16]. Briefly, confluent human embryonic lung (HEL) fibro blasts grown in 96-well microtiter plates were inoculated with VZV at an input of 20 plaque forming units (PFU) per well. After a 2h incubation period, residual virus was removed and the infected cells were further incubated with medium containing variying concentrations of the test compounds. After 5days of incubation, virus plaque formation was determined and antiviral activity was expressed as 50%, inhibitory concentration (IC50) or compound concentration required to reduce viral plaque formation by 50% compared to the untreated control cytotoxicity was expressed as the 50% cytostatic concentration (CC50),defined as the compound concentration required to inhibit cell growth by 50%, and the MCC (minimae cytotoxic concentration), defined as the compound concentration required to cause a microscopically detectable alteration of normal cell morphology. (Table 3and 4)

Table-3 : Activity of compounds against varicella-zoster virus in human embryonic lung (HEL) cells

Compound	Antiviral activity (μg/ml)[a]		Cytotoxicity (μg/ml)	
	TK^+ VZV OKA strain	TK^+ VZV 07/1 strain	Cell morphology (MCC)[b]	Cell growth (CC_{50})[c]
3a	>2	>2	5	20
3b	>5	>2	≥5	32
3c	1.8	>2	≥5	10.2
3d	2.9	4.5	20	9.3
3e	11	14	≥50	>50
3f	3	10	≥50	34
3g	>5	11	≥20	36
3h	46	50	>50	48
3i	>5	>5	20	16.6
3j	1.5	>2	≥5	17
3k	4	11	50	>50
3l	39	27	>50	>50
3m	>20	>5	≥20	>50
3n	4	5	≥20	>50
3o	23	30	>50	>50
ACV	0.44	50	>50	>200
BVDU	0.001	>50	>50	>200

[a]Inhibitory concentration required to reduce virus plaque formation by 50%. Virus input was 100 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%

Table -4 : Activity of compounds against cytomegalovirus in human embryonic lung (HEL) cells

Compound	Antiviral activity IC_{50} (μg/ml)[a]		Cytotoxicity (μg/ml)	
	AD-169 strain	Davis strain	Cell morphology (MCC)[b]	Cell growth (CC_{50})[c]
3a	>5	>2	≥ 5	20
3b	>2	>2	5	32
3c	>2	>2	5	10.2
3d	3	>0.5	20	9.3
3e	12	10	>50	>50
3f	10	10	>50	34
3g	10	10	50	36
3h	>50	38	>50	48
3i	>5	>5	20	16.6
3j	>5	>5	20	17
3k	10	10	50	>50
3l	>50	>50	>50	>50
3m	>50	>20	≥50	>50
3n	>5	>5	20	>50
3o	35	33	>50	>50
DHPG	1.0	2.7	>50	>200
(S)-HPMC	0.3	0.9	>50	192

[a]Inhibitory concentration required to reduce virus plaque formation by 50%. Virus input was 100 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%

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