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MICROWAVE ASSISTED ONE POT MULTICOMPONENT SYNTHESIS OF 2-(-4-OXO-2-(1-(2-OXO-2H-CHROMEN-3-YL) ETHYLIDENE)HYDRAZONO)THIAZOLIDIN-5-YL) ACETIC ACID DERIVATIVES AND THEIR ANTIVIRAL ACTIVITY

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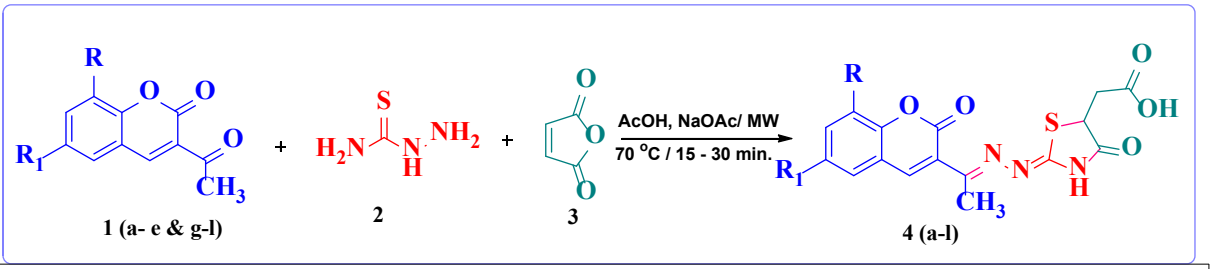
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Abstract

A novel series of hydrazonothiazolidinyl acetic acid derivatives were synthesized via a straightforward microwave irradiated one pot multicomponent reaction approach using substituted 3-acetylcoumarins (1a-l), thiosemicarbazide (2) and maleic anhydride (3). The synthesis was carried out by using sodium acetate and acetic acid as a solvent at 70°C, afforded target molecules in a shorter reaction time, simple reaction workup with high yields. All the synthesized compounds were well characterized by analytical data (^{1}H, ^{13}C NMR and Mass spectra). In vitro antiviral activity of thiazolidinyl acetic acid derivatives were evaluated against a broad panel of human viruses in different cell lines among which compound **4d** exhibited excellent activity against *Herpes simplex virus*-1 .

Graphical abstract



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Key words

3-Acetylcoumarin, thiazolidinyl acetic acid derivatives, microwave irradiation, multicomponent reaction and antiviral activity.

1. Introduction

Development of new synthetic methodologies for the construction of highly structural complex and diverse molecules with enhancing therapeutic properties is a great challenge in drug discovery programmes. Multicomponent reactions (MCRs) have evolved as powerful synthetic tool in organic synthesis [1,2] and medicinal chemistry [3,4] for the generation of highly diversified functionalities in a single molecular frame work through simple operational procedures. MCRs have vast advantages in comparison to multistep synthesis in terms of reaction time, atom economy, excellent yields and high purity.

Antibiotic drugs are considered to be very promising therapeutic agents for minimizing the infectious diseases. According to the world health organization, antibiotic resistance is among relevant human health issues and have the most significant proportions of mortality across the globe. In addition, the treatment of viral infections remains an important challenge due to the mutations, resulting in escape of viral mutants and drug resistant virus strains. Consequently there is a need for continuous development of novel therapeutic agents that have minimum side effects, high therapeutic indices and are effective against various circulating resistant virus strains.

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Among the Nitrogen and Sulphur heterocyclic compounds, thiazolidinone is a versatile and most privileged five membered heterocyclic molecule with excellent biological applications. Based on literature survey, the study of thiazolidinones has become an area of interest. The biodynamic thiazolidinone ring containing therapeutic agents play an important role in bioorganic, medicinal chemistry with vast biological activities such as antibacterial, [5,6] antifungal, [7,8] antitubercular, [9,10] anticancer, [11-14] antioxidant, [15,16] antiviral, [17,18] anti inflammatory, [19-21] HIV inhibitors [22] and antihyperglycemic activities. [23,24] Substituted coumarin derivatives have exceptional biological applications such as antibacterial, [25-27] antitubercular, [28,29] anticancer, [30,31] antioxidant, [32-34] anti inflammatory, [35,36] anticoagulant [37,38] and anti HIVagents. [39,40] The structures of clinically used thiazolidinone and coumarins are given in **Fig. 1**.

Considering the multifarious biological applications of thiazolidinones and coumarins, in continuation of our interest in design and synthesis of biologically active heterocyclic compounds, we felt that it is significant to explore the synthesis and biological evaluation of coumarin substituted thiazolidinone hybrid heterocycles.These hetocycles were obtained via simple and efficient one pot three component reaction approach of substituted 3-acetyl coumarins, thiosemicarbazide and maleic anhydride.The present study also focused on evaluation of antiviral properties against a broad panel of human viruses in different cell lines.

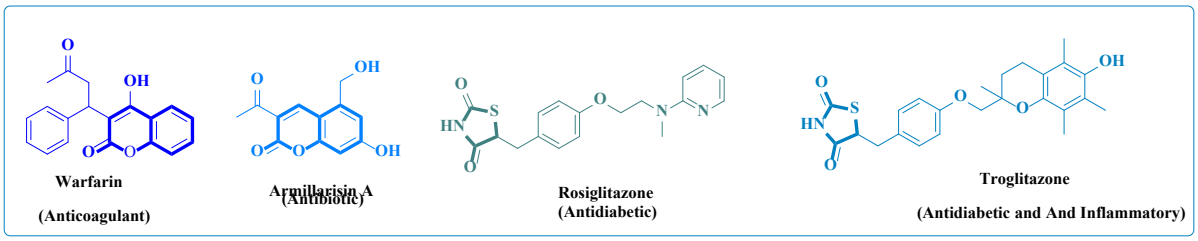


Fig. 1. The structures of clinically used coumarins and thiazolidinones derivatives.

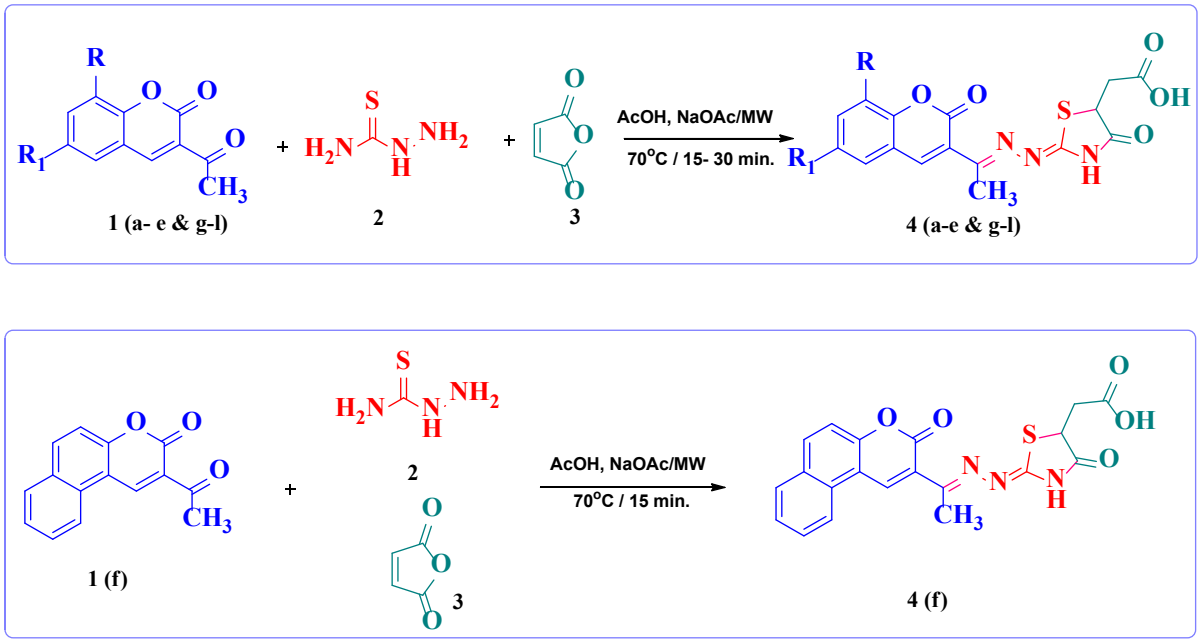
2. Results and Discussion

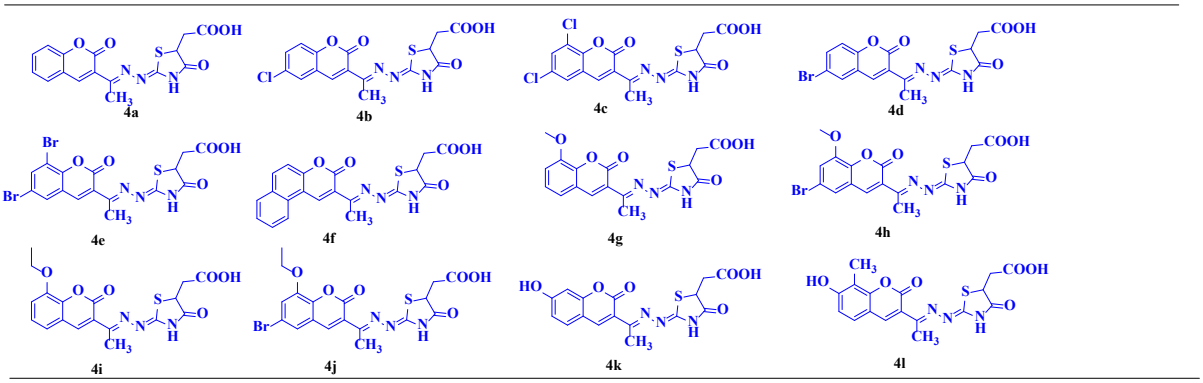
2.1 Chemistry

The synthetic strategy for novel hydrazonothiazolidinyl acetic acid derivatives (**4a-l**) via a facile microwave irradiated one pot multicomponent reaction approach of various substituted 3-acetylbenzo[f]coumarin/coumarins (**1a-l**), thiosemicarbazide (**2**) and maleic anhydride (**3**) as shown in **scheme 1**. The title compounds were obtained by using sodium acetate in presence of acetic acid under microwave condition with high yields. The method

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applied to synthesize the hydrazono thiazolidinyl acetic acid derivatives is found to be simple and easier reaction work up in shorter reaction time with good yields.





Scheme 1 Synthesis of 2-(-4-oxo-2-(1-(2-oxo-2h-chromen-3-yl) ethylidene) hydrazono) thiazolidin-5-yl) acetic acid derivatives (**4a-l)**

Initially we attempted the synthesis of the target hydrazono thiazolidinyl acetic acid derivatives by conventional method from 3-acetylcoumarin (**1a**), thiosemicarbazide and maleic anhydride in ethanol under reflux conditions. We could get the product by this method, however, reaction time was high and yields were poor. To improve the reaction efficiency, we have performed the reaction in various solvents like methanol, acetic acid, dimethyl formamide, toluene etc. at different temperature conditions. To minimize the reaction time, we explored microwave irradiation using same set of solvents used for

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conventional method. Again acetic acid was found to be the best, both in terms of reaction time as well as yield (**Table 1 and 1a)**.

Table 1. Reaction optimization conditions for the synthesis of hydrazono thiazolidinyl acetic acid derivatives under conventional and microwave irradiation

Entry	Solvent	Conventional			Microwave		
		Temperature (°C)	Time (h)	Yield (%)	Temperature (°C/W)	Time (h)	Yield (%)
1	Methanol	70	16	20	70/210	1	30
2	Ethanol	75	18	45	70/210	1	40
3	DMF	120	16	40	70/210	1	35
4	DMSO	120	16	35	70/210	1	25
5	Toluene	110	16	20	70/210	1	30
6	Acetic acid	100	**6**	**60**	70/210	**0.5**	**85**
7	Acetonitrile	80	16	25	70/210	1	30
8	Dioxane	80	16	20	70/210	1	25

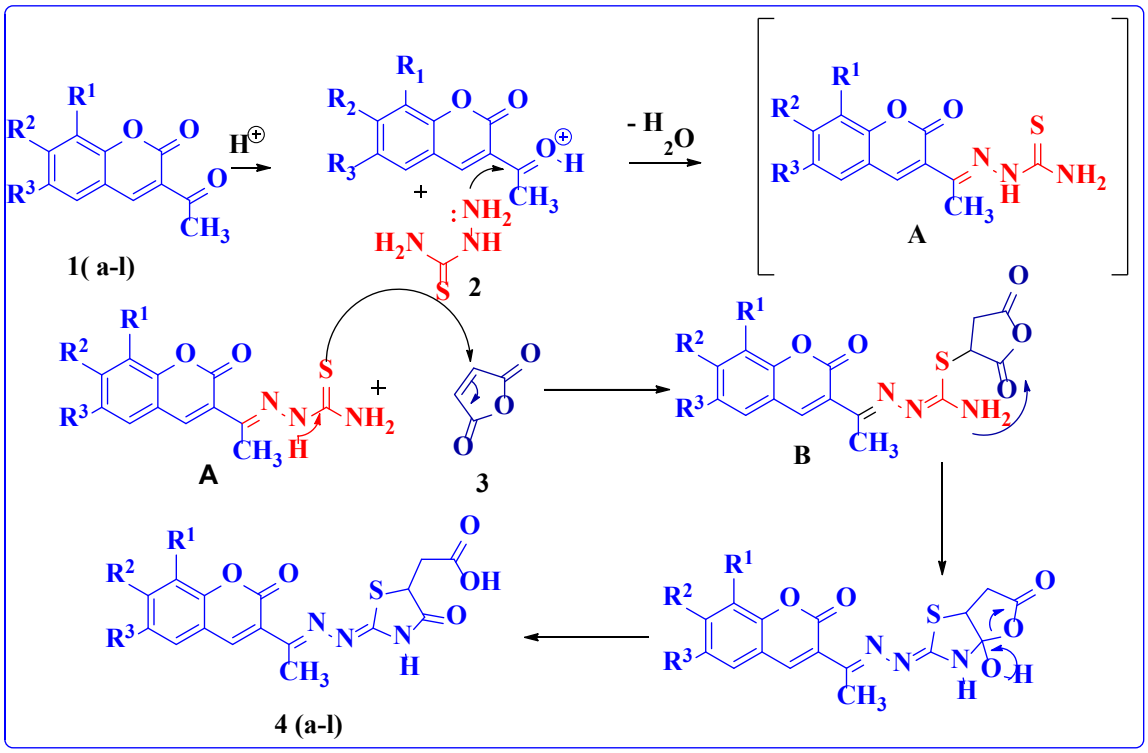
Table 1a. Reaction time and yields of hydrazono thiazolidinyl acetic acid derivatives (**4a-l**)

S. No.	Compound [a]	R^1	R^2	R^3	Reaction Time (min)	Yield (%) [b]
1	**4a**	H	H	H	15	82
2	**4b**	H	H	Cl	25	85
3	**4c**	H	Cl	Cl	30	88
4	**4d**	H	H	Br	25	88
5	**4e**	H	Br	Br	25	90
6	**4f**		Benzo[f]		15	92
7	**4g**	OCH_3	H	H	15	81
8	**4h**	OCH_3	H	Br	20	85
9	**4i**	OC_2H_5	H	H	20	82
10	**4j**	OC_2H_5	H	Br	30	84
11	**4k**	H	OH	H	20	79
12	**4l**	CH_3	OH	H	25	82

[a] **Reaction condition**: substituted 3-acetyl coumarin (1 mmol), thiosemicarbazide (1 mmol), maleic anhydride (1 mmol) and sodium acetate (10 mol percentage) in AcOH at 70°C.
[b] Isolated yields.

Based on the experimental protocol for the synthesis of 4-thiazolidinones, the plausible reaction mechanism was proposed. Reaction of substituted 3-acetylcoumarins (**1a-l)** with thiosemicarbazide (**2)** generates the intermediate 2-(1-(2-oxo-2*H*-chromen-3-yl)ethylidene) hydrazinecarbothioamide (**A**). Intermediate A further reacts with maleic anhydride (**3)** in presence of acetic acid and forms the intermediate 2,5-dioxotetrahydrofuran-3-yl N'-(1-(2-oxo-2*H*-chromen-3-yl)ethylidene)carbamohydrazonothioate (**B**). The

intermediate (**B**) undergoes cyclization via 1, 5-nucleophilic attack of NH_2 on C=o to generate the title compounds **4a-l** (**Scheme 2**).



Scheme 2 Plausible reaction mechanism for 2-(-4-oxo-2-(1-(2-oxo-2h-chromen-3-yl) ethylidene)hydrazono)thiazolidin-5-yl) acetic acid derivatives (4a-l)

The newly synthesized target molecules were well characterized by physical and analytical spectral data (IR, ^{1}H NMR, ^{13}C NMR and Mass spectral data). IR spectrum of compound **4a** exhibited strectching freqncies of carboxylic acid at 3393 cm^{-1}, hydrazone NH at 3148 cm^{-1}, lactone carbonyl at 1730 cm^{-1}, amide carbonyl at 1621 cm^{-1} and C=N at1604 cm^{-1} respectively. The ^{1}H NMR spectrum of compound **4a** exhibited characteristic peaks, the proton present at fifth position of thiazolidinone ring exhibited characteristic ABX splitting pattern and displayed double doublets (dd) at δ 4.33 – 4.36 (dd, J_1 = 3.6 Hz, J_2 = 8.8 Hz, 1H, -CH) and methylene protons exhibited double doublets at δ 2.85 - 2.91 (dd, J_1 = 8.8 Hz, J_2 = 17.6 Hz, 1H, -CH_2), 2.98 – 3.03 (dd, J_1 = 3.6 Hz, J_2 = 17.2 Hz, 1H, -CH_2). The Mass spectrum of compound **4a** exhibited molecular ion peak at m/z =359.9$[M+H]^+$ as a base peak. The spectral analysis data of the final compounds clearly indicates the formation of target compounds.

2.2 Biology

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The target compounds (**4a-l)** were evaluated for the antiviral activity against a broad panel of human viruses in different cells. The HEL cell culture was used to evaluate the compounds against *Herpes simplex* virus type-I (KOS) [HSV-1 KOS], *Herpes simplex* virus type-2 (G) [HSV-2 G], *Vaccinia* virus [VV], *Vesicular stomatitis* virus (VSV), thymidine kinase-deficient *Herpes simplex* virus type-1 (HSV-1 TK^- KOS ACV^r) and *Adeno* virus type-2 (AV-2), Vero cells were utilized to evaluate the compounds against *Parainfluenza* type-3 virus (PI-3V), *Reo* virus type-1 (RV-1), *Sindbis* virus (SV), *Coxsackie* virus B4 (CV B4) and *Punta toro* virus (PTV), The MDCK cell line was used infected with *Influenza* A virus type H1N1 (strain A/Ned/378/05) and type H3N2 (strain A/HK/7/87), and *Influenza* B virus (strain B/Ned/537/05). Based on the microscopical analysis of the virus-induced cytopathic effect (CPE), the antiviral potency of the compounds was determined and compared to different reference antiviral drugs (brivudin, cidofovir, acyclovir, ganciclovir, zalcitabine and alovudine).

The antiviral activity of compounds (**4a-l)** were shown in **Table 2-6**. The compound **4d** exhibited good antiviral activity against *Herpes simplex* virus type 1 (KOS) [HSV-1 KOS], *Herpes simplex* virus type 2 (G) [HSV-2 G], *Vaccinia* virus [VV] and *Vesicular stomatitis* virus (VSV) with EC_{50} of 4, 7, 5 and 7 μM concentrations respectively (**Table 2**). Compounds **4h** and **4j** also showed promising antiviral activity against tested viral starins with EC_{50} of 8, and 16 μM concentrations respectively. The remaining compounds exhibited moderate antiviral activity against the screened viruses with respect to standard antiviral drugs (brivudin, cidofovir, acyclovir and ganciclovir).

Similarly of the compounds tested for *Vesicular stomatitis, Coxsackie* virus B4, *Respiratory syncytial* virus, *Para influenza-3, Sindbis* virus, *Coxsackie* virus B4, *Punta toro* virus *Yellow fever* virus, *Feline corona* virus (FIPV), *Feline herpes* Virus, *Influenza* A/H1N1A/Ned/378/05, *Influenza* A/H3N2A/HK/7/87, *Influenza* BB/Ned/537/05 in different cell lines. Compound **4d** exhibited better activity with EC_{50} of 15, 10, 15 μM concentrations respectively (**Table 3**). The compounds **4b**, **4h** and **4i** showed good activity against *Respiratory syncytial* virus with EC_{50} of 15 μM. Compounds **4a** and **4h** have moderate activity against *Vesicular stomatitis* virus with EC_{50} of 20 μM concentration The remaining compounds showed less antiviral activity with respect to standard antiviral drugs (DS-10.000 and Ribavirin).

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Table 2. Cytotoxicity and antiviral activity of compounds (**4a-l**) in HEL cell cultures

Compound	Minimum cytotoxic concn (μM)[a]	EC_{50} [b] (μM)					
		Herpes simplex virus-1 (KOS)	*Herpes simplex* virus-2 (G)	*Vaccinia* virus	*Vesicular stomatitis* virus	*Herpes simplex* virus-1TK-KOS ACV^r	*Adeno* virus-2
4a	>100	20	25	20	**10**	20	>100
4b	>100	**10**	20	20	20	20	>100
4c	>100	**10**	22	30	20	30	>100
4d	>100	**4**	**7**	**5**	**7**	25	>100
4e	>100	**16**	**10**	20	30	25	>100
4f	>100	30	30	40	40	25	>100
4g	>100	25	35	30	20	20	>100
4h	≥20	**8**	**10**	**10**	20	**10**	>100
4i	>100	28	25	30	30	25	>100
4j	>100	**10**	**10**	**10**	20	**10**	>100
4k	>100	20	25	30	20	30	>100
4l	>100	25	**15**	20	>100	25	>100
Brivudin	>250	**0.04**	**250**	**50**	**10**	-	**>250**
Cidofovir	>250	**2.0**	**2.0**	**2.0**	**10**	**10**	**>250**
Acyclovir	>250	**0.3**	**0.4**	**>183**	**>250**	-	**>250**
Ganciclovir	>100	**0.03**	**0.09**	**2.0**	**>100**	-	**>100**
Zalcitabine	>250	-	-	-	-	**10**	-
Alovudine	>250	-	-	-	-	**5.8**	-

Table 3. Cytotoxicity and antiviral activity of compounds (**4a-l**) in HeLa cell cultures

Compound	Minimum cytotoxic concn (μM)[a]	EC_{50} [b] (μM)		
		Vesicular stomatitis virus	*Coxsackie* virus B4	*Respiratory syncytial* virus
4a	>100	20	25	20
4b	>100	30	20	15
4c	>100	25	25	20
4d	>100	**15**	**10**	**15**
4e	100	30	30	25
4f	100	35	25	30
4g	>100	25	25	25
4h	100	20	20	15
4i	>100	30	25	15
4j	100	50	20	20
4k	>100	25	25	25

4l	>100	25	25	25
DS-10.000	>100	1.8	10	0.8
Ribavirin	>250	22	12	5.8

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

Table 4. Cytotoxicity and antiviral activity of compounds (**4a-l**) in Vero cell cultures

Compound	**Minimum cytotoxic concn (μM)[a]**	**EC_{50} [b] (μM)**					
		Para influenza-3	***Reo* virus**	***Sindbis* virus**	***Coxsackie* virus B4**	***Punta toro* virus**	***Yellow fever* virus**
4a	>100	>100	>100	>100	>100	>100	>100
4b	100	50	50	40	>100	>100	>100
4c	>100	40	50	50	>100	50	50
4d	≥100	**20**	**20**	40	>100	50	40
4e	≥100	>100	>100	>100	>100	>100	>100
4f	100	>100	>100	>100	>100	>100	>100
4g	>100	>100	>100	>100	>100	>100	>100
4h	≥20	50	40	50	>100	50	50
4i	>100	>100	>100	>100	>100	>100	>100
4j	>100	50	20	50	>100	50	50
4k	>100	>100	>100	>100	>100	>100	>100
4l	≥100	>100	>100	>100	>100	>100	>100
DS-10.000	>100	**>100**	**>100**	**20**	**58**	**100**	**>1000**
Ribavirin	>250	**250**	**250**	**250**	**>250**	**50**	**>250**
Mycophenolic acid	>100	**0.8**	**4.0**	**20**	**>250**	**10**	**6.8**

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

Table 5. Cytotoxicity and antiviral activity of compounds (**4a-l**) in CRFK cell cultures

Compound	**Minimum cytotoxic concn (μM)[a]**	**EC_{50} [b] (μM)**	
		***Feline corona* virus (FIPV)**	***Feline herpes* virus**
4a	>100	>100	>100
4b	>100	>100	>100
4c	>100	>100	>100
4d	>100	>100	>100
4e	48.7	>100	>100
4f	>100	>100	>100
4g	>100	>100	>100
4h	>100	>100	>100
4i	>100	>100	>100
4j	61.2	>100	>100
4k	>100	>100	>100

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4l	>100	>100	>100
HHA	**>100**	**39.3**	**9.7**
UDA	**>100**	**6.9**	**8.1**
Ganciclovir	**>100**	**>100**	**0.8**

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

Table 6. Cytotoxicity and antiviral activity of compounds (**4a-l**) in MDCK cell cultures

Compound	Cytotoxicity		Antiviral EC_{50}[c]					
	CC_{50}[a]	Minimum Cytotoxic concn[b]	*Influenza A/H1N1 A/Ned/378/05*		*Influenza A/H3N2 A/HK/7/87*		*Influenza B B/Ned/537/05*	
			visual CPE score	MTS	visual CPE score	MTS	visual CPE score	MTS
4a	>100	>100	>100	>100	>100	>100	>100	>100
4b	55.1	≥20	>100	>100	>100	>100	>100	>100
4c	55.1	≥20	>100	>100	>100	>100	>100	>100
4d	56.8	≥20	>100	>100	>100	>100	>100	>100
4e	46.5	20	>100	>100	>100	>100	>100	>100
4f	65.9	≥20	>100	>100	>100	>100	>100	>100
4g	57.0	100	>100	>100	>100	>100	>100	>100
4h	53.0	100	>100	>100	>100	>100	>100	>100
4i	60.1	100	>100	>100	>100	>100	>100	>100
4j	53.5	100	>100	>100	>100	>100	>100	>100
4k	>100	100	>100	>100	>100	>100	>100	>100
4l	85.8	≥0.8	>100	>100	>100	>100	>100	>100
Zanamivir	>100	>100	0.2	0.3	0.8	2.7	0.4	0.3
Ribavirin	>100	≥100	8.9	8.7	8.9	2.8	4.0	1.6
Amantadine	>100	>100	8.0	2.1	0.8	0.8	>200	>200
Rimantadine	>200	>200	1.6	2.2	0.2	0.3	>200	>200

[a]50% Cytotoxic concentration, as determined by measuring the cell viability with the colorimetric formazan-based MTS assay.
[b]Minimum compound concentration that causes a microscopically detectable alteration of normal cell morphology.
[c]50% Effective concentration or concentration producing 50% inhibition of virus-induced cytopathic effect, as determined by visual scoring of the CPE, or by measuring the cell viability with the colorimetric formazan-based MTS assay.
MDCK cells: Madin Darby canine kidney cells.

The compounds tested for *Para influenza-3, Reo* virus, *Sindbis, Coxsackie* virus B4, *Punta toro* virus and *Yellow fever* virus in Vero cell cultures exhibited moderate antiviral

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activity as shown in **Table 4**. Similarly, hydrazonothiazolidinyl acetic acid derivatives were screened against *Feline Corona Virus (FIPV), Feline Herpes Virus* (**Table 5**), *Influenza A/H1N1 A/Ned/378/05*, *Influenza A/H3N2 A/HK/7/87 and Influenza B B/Ned/537/05* (**Table 6**) and exhibited very less activity.

The structure activity relationship (SAR) of the newly synthesized coumarin substituted hydrazonothiazolidinyl acetic acid compounds having different substituents on coumarin ring were tested against *Herpes simplex* virus type-I (KOS) [HSV-1 KOS], *Herpes simplex* virus type-2 (G) [HSV-2 G], *Vaccinia* virus [VV] and *Vesicular stomatitis* virus (VSV) in HEL cells (**Table 2**) Initially all the twelve coumarin derivatives were evaluated at a single dose (100 μM). From this screening, compounds having electron withdrawing functional groups like chlorine and bromine groups (4b, 4c, 4d, 4h and 4j) had shown good activity against the tested viral strains. Subsequently all the synthesized compounds were screened at different concentrations (2.5, 5, 10, 20 and 100 μM) to evaluate their antiviral and cytotoxicity activities. The compound **4d** having bromine substitution at 6^{th} position on coumarin showed excellent antiviral activity against *Herpes simplex* virus type I (KOS) [HSV-1 KOS], *Herpes simplex* virus type 2 (G) [HSV-2 G], *Vaccinia* virus [VV] and *Vesicular stomatitis* virus (VSV) with EC_{50} of 4, 7, 5 and7 μM concentrations respectively. Similarly compound **4h** having bromine at 6^{th} position and methoxy at 8^{th} position and compound **4j** having bromine at 6^{th} position and ethoxy at 8^{th} position on coumarin exhibited good antiviral activity with EC_{50} of 8 and 10 μM concentrations. Compounds, **4b** (chlorine at 6^{th} position), **4c** (chlorine at 6^{th} and 8^{th} position) and **4e** (bromine at 6^{th} and 8^{th} position) also exhibited good antiviral activity in the HeL cell line with EC_{50} values ranging from 10 to 16 μM (**Table 2**). In contrast, electron releasing group like OMe, OEt and CH_3 (4g, 4i and 4l) showed moderate antiviral activity. From these antiviral biological studies, we were able to identify potent molecules which exhibited good antiviral activity.

3. Experimental

The organic solvents and the reagents like thiosemicarbazide, maleic anhydride, sodium acetate were procured from commercial sources and used as such without any further purification. In the present study, 3-acetylcoumarins (**1a-l**) were used as starting materials for the synthesis of the given target molecules. Various substituted 3-acetylcoumarins were

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prepared in two steps from salicylaldehyde. The reaction progress was monitored through thin layer chromatography using pre coated silica gel plates and the spots were visualized under UV light. Stuart melting point apparatus (SMP-30) was used to record melting points in open capillary melting tube and are uncorrected. Infra red spectra were recorded on Perkin-Elmer (Spectrum -100S) spectrophotometer. The ^{1}H and ^{13}C were analyzed by using Bruker spectrometer at 400 and 100 MHz using tetramethylsilane (TMS) as internal standard. The mass spectra were recorded on Water micromass API instrument.

3.1 General procedure for synthesis of 2-(-4-oxo-2-(-(1-(2-oxo-2*H*-chromen-3-yl)ethylidene)hydrazono)thiazolidin-5-yl) acetic acid derivatives (4a-l)

The reaction mixture of 3-acetyl-2*H*-chromen-2-ones (**1a-l)** (1.0 mmol), thiosemicarbazide **2** (0.091 g, 1.0 mmol), maleic anhydride **3** (0.098 g, 1.0 mmol) and Sodium acetate (0.008 g, 0.1 mmol) were taken in microwave vial containing acetic acid (5 mL) solvent and irradiated at 70°C for about 15 - 30 minutes. The progress of the reaction was monitored through thin layer chromatography by using hexane: ethyl acetate (2:1) solvent medium. After completion of the reaction, the reaction mixture was cooled to room temperature and the isolated product was filtered, washed with water and dried. The product was recrystallized from ethanol.

1) ***2-(4-oxo-2-(1-(2-oxo-2H-chromen-3-yl)ethylidene)hydrazono)thiazolidin-5-yl) acetic acid (4a)***

White solid; yield: (82%); m.p.: 225 – 227 ^{o}C; FTIR (KBr, υ_{max} cm^{-1}): 3393 (-COOH), 3148 (-NH), 1730 (lactone -C=O), 1621 (amide-C=O) 1604 (-C=N); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.30 (s, 3H, -CH_3), 2.85 -2.91 (dd, J = 8.8 Hz, 17.6 Hz, 1H, -CH_2), 2.98 – 3.03 (dd, J = 3.6 Hz, 17.2 Hz, 1H, -CH_2), 4.33 – 4.36 (dd, J = 3.6 Hz, 8.8 Hz 1H, -CH), 7.38 (d, J = 7.2 Hz, 1H, -Ar-H), 7.43 (t, J = 8.4 Hz, 1H, -Ar-H), 7.64 – 7.68 (m, 1H, -Ar-H), 7.88 – 7.90 (m, 1H, -Ar-H), 8.19 (s, 1H, -C_4-H of coumarin), 12.03 (bs, 1H, -NH), 12.66 (bs, 1H, -COOH); ^{13}C NMR (100 MHz, DMSO-d_6): δ; 16.95, 36.61, 43.37, 115.97, 118.70, 124.75, 126.48, 129.36, 132.56, 141.48, 153.48, 159.00, 159.45, 164.20, 171.65, 175.21 ppm; MS (ESI m/z): 359.9 $[M+H]^{+}$.

2) ***2-(2-(1-(6-chloro-2-oxo-2H-chromen-3-yl)ethylidene)hydrazono)-4-oxothiazolidin-5-yl) acetic acid (4b)***

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Yellow solid; yield: (85%); m.p.: 203 – 204 °C; FTIR (KBr, υ_{max} cm^{-1}): 3411 (-COOH), 3134 (-NH), 1724 (lactone-C=O), 1620 (amide –C=O), 1588 (-C=N). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.25 (s, 3H, -CH_3), 2.82 -2.88 (dd, *J* = 8.8 Hz, 17.2 Hz 1H, -CH_2), 2.97 – 3.02 (dd, *J* = 4 Hz, 18 Hz, 1H, -CH_2), 4.32 – 4.35 (dd, *J* = 4 Hz, 8.8 Hz, 1H, -CH), 7.48 (d, *J* = 8.8 Hz, 1H, -Ar-H), 7.66 – 7.69 (m, 1H, -Ar-H), 7.84 (d, *J* = 2.4 Hz, 1H, -Ar-H), 7.91 (bs, 1H, -NH), 8.42 (s, 1H, -C_4-H of coumarin), 10.51 (bs, 1H, -COOH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 15.84, 36.62, 43.36, 117.96, 120.30, 126.81, 127.61, 127.90,128.32, 131.77, 140.60, 145.34, 151.94, 158.62, 175.34, 179.30 ppm; MS (ESI m/z): 393.9 $[M+H]^+$.

3) *2-(2-(1-(6,8-dichloro-2-oxo-2H-chromen-3-yl)ethylidene)hydrazono)-4-oxothiazolidin-5-yl) acetic acid (4c)*

Yellow solid; yield: (88%); m.p.: 200 – 202 °C; FTIR (KBr, υ_{max} cm^{-1}): 3411 (-COOH), 3134 (-NH), 1725 (lactone-C=O), 1620 (amide –C=O), 1588 (-C=N); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 2.25 (s, 3H, -CH_3), 2.85 - 2.91 (dd, *J* = 8.8 Hz, 17.6 Hz ,1H, -CH_2), 2.98 – 3.03 (dd, *J* = 3.6 Hz, 17.6 Hz, 1H, -CH_2), 4.34 – 4.37 (dd, *J* = 4 Hz, 8.8 Hz ,1H, -CH), 7.66 – 7.69 (m, 1H, -Ar-H), 7.84 (d, *J* = 2.4 Hz, 1H, -Ar-H), 7.91 (s, 1H, -NH), 8.42 (s, 1H, -C_4-H of coumarin), 10.50 (s, 1H, -COOH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 15.82, 36.61, 43.38, 117.92, 120.28, 126.78, 127.51, 127.88, 128.31, 131.74, 140.17, 145.31, 151.92, 158.59, 175.81, 179.31 ppm; MS (ESI m/z): 428.3$[M+H]^+$ and 429.3$[M+2H]^+$.

4) *2-(2-(1-(6-bromo-2-oxo-2H-chromen-3-yl)ethylidene)hydrazono)-4-oxothiazolidin-5-yl) acetic acid (4d)*

Yellow solid; yield: (88%); m.p.: 210 – 212 °C; FTIR (KBr, υ_{max} cm^{-1}): 3382 (-COOH), 3127 (-NH), 1714 (lactone-C=O), 1632 (amide C=O), 1599 (-C=N); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.25 (s, 3H, -CH_3), 2.82 – 2.88 (dd, *J* = 8.4 Hz, 16 Hz, 1H, -CH_2), 2.97 – 3.02 (dd, *J* = 4 Hz, 15.2 Hz, 1H, -CH_2), 4.32 – 4.35 (dd, *J* = 4 Hz, 8.4 Hz, 1H, -CH), 7.87 – 7.90 (m, 1H, -Ar-H), 7.97 (d, *J* = 2 Hz, 1H, -Ar-H), 8.22 (d, *J* = 2 Hz, 1H, -Ar-H), 8.46 (s, 1H, --NH), 8.60 (s, 1H, -C_4-H of coumarin), 10.51 (bs, 1H, -COOH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 15.87, 38.07, 43.16, 116.16, 118.38, 120.83, 126.77, 130.96, 134.57, 136.57, 140.57, 145.61, 152.38, 158.61, 175.31, 179.32 ppm; MS (ESI m/z): 438.9 $[M+H]^+$ and 439.8$[M+2H]^+$.

2-(2-(1-(6,8-dibromo-2-oxo-2H-chromen-3-yl)ethylidene)hydrazono)-4-oxothiazolidin-5-yl) acetic acid (4e)

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Yellow solid; yield: (90%); m.p.: 190 – 192 °C; FTIR (KBr, υ_{max} cm^{-1}): 3315 (-COOH), 3186 (-NH), 1704 (lactone-C=O), 1629 (amide C=O), 1603 (-C=N); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.25 (s, 3H, -CH_3), 2.85 – 2.91 (dd, *J*= 8.8 Hz, 17.6 Hz, 1H, -CH_2), 2.98 – 3.04 (dd, *J* = 4 Hz, 17.6 Hz, 1H, -CH_2), 4.29 – 4.32 (dd, *J* = 4 Hz, 8.8 Hz, 1H, -CH), 7.90 (bs, 1H, -NH), 8.22 – 8.28 (m, 1H, -Ar-H), 8.42 – 8.45 (m, 1H, -Ar-H), 8.58 (s, 1H, -C_4-H of coumarin);10.50 (bs, 1H, -COOH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 15.89, 36.59, 43.45, 116.21, 118.25, 121.80, 128.10, 134.55, 136.47, 139.85, 149.23, 157.96, 158.61, 175.22, 179.28 ppm; MS (ESI m/z): 517.8 $[M]^+$; 519.8 $[M+2H]^+$.

6) 2-(4-oxo-2-(1-(3-oxo-3H-benzo[f]chromen-2-yl)ethylidene)hydrazono)thiazolidin-5-yl) acetic acid (4f)

Yellow solid; yield: (92%); m.p.: 228 – 230 °C; FTIR (KBr, υ_{max} cm^{-1}): 3359 (-COOH), 3168 (-NH), 1712 (lactone –C=O), 1631 (amide-C=O), 1602 (-C=N); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.32 (s, 3H, -CH_3), 2.84 – 2.89 (dd, *J* = 8.8 Hz, 14 Hz, 1H, -CH_2), 2.96 – 3.01 (dd, *J* = 4 Hz, 17.2 Hz, 1H, -CH_2), 4.31 – 4.34 (dd, *J*= 4 Hz, 9.2 Hz, 1H, -CH), 7.59 – 7.67 (m, 1H, -Ar-H), 7.77 (t, *J* = 7.6 Hz, 1H, -Ar-H), 8.07 (d, *J* = 8 Hz, 1H, -Ar-H), 8.16 (s, 1H, -Ar-H), 8.22 (d, *J* = 9.2 Hz, 1H, -Ar-H), 8.43 (bs, 1H, -NH), 8.73 (d, *J* = 8.4 Hz, 1H, -Ar-H), 9.10 (s, 1H, -C_4-H of coumarin), 10.43 (bs, 1H, -COOH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 16.24, 38.14, 43.18, 113.07, 116.36, 122.93, 124.97, 126.21, 128.28, 128.81, 129.03, 129.92, 133.72, 137.66, 146.38, 153.26, 159.15, 174.92, 179.23 ppm; MS (ESI m/z): 410.31$[M+H]^+$.

7) 2-(2-(1-(8-methoxy-2-oxo-2H-chromen-3-yl)ethylidene)hydrazono)-4-oxothiazolidin-5-yl) acetic acid (4g)

Yellow solid; yield: (81%); m.p.: 206 – 208 °C; FTIR (KBr, υ_{max} cm^{-1}): 3457 (-COOH), 3248 (-NH), 1709 (lactone-C=O), 1627 (amide-C=O), 1603 (-C=N), 1268 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.25 (s, 3H, -CH_3), 2.85 - 2.91 (dd, *J* = 8.8 Hz, 17.6 Hz, 1H, -CH_2), 2.98 – 3.03 (dd, *J* = 3.6 Hz, 17.6 Hz, 1H, -CH_2), 3.92 (s, 3H, -OCH_3), 4.33 – 4.36 (dd, *J* = 4 Hz, 8.8 Hz, 1H, -CH), 7.32 (t, *J* = 5.6 Hz, 1H, -Ar-H), 7.41 – 7.43 (m, 1H, -Ar-H), 7.96 (bs, 1H, -NH), 8.16 (d, *J* = 2 Hz, 1H, -Ar-H), 8.40 (s, 1H, -C_4-H of coumarin), 10.44 (s, 1H, --COOH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 15.96, 36.57, 43.35, 56.11, 114.77, 120.43, 124.66, 125.87, 142.67, 142.81, 145.89, 146.25, 158.71, 159.41, 164.19, 175.18, 179.23 ppm; MS (ESI m/z): 390.24 $[M+H]^+$.

8) 2-(2-(1-(6-bromo-8-methoxy-2-oxo-2H-chromen-3-yl)ethylidene)hydrazono)-4-oxo thiazolidin-5-yl) acetic acid (4h)

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Yellow solid; yield: (85%); m.p.: 213 – 215 ^{o}C; FTIR (KBr, υ_{max} cm^{-1}): 3458 (-COOH), 3171 (-NH), 1738 (lactone –C=O), 1607 (-amide – C=O), 1579 (-C=N), 1244 (-C-O-C). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.72 (s, 3H, -CH_3), 2.88 - 2.94 (dd, J = 9.2 Hz, 17.6 Hz, 1H, -CH_2), 2.98 – 3.03 (dd, J = 3.6 Hz, 18 Hz, 1H, -CH_2), 3.92 (s, 3H, -OCH_3), 4.33 – 4.36 (dd, J_1 = 3.6 Hz, J_2 = 8.4 Hz, 1H, -CH), 7.32 (bs, 1H, -NH), 7.50 (s, 1H, - Ar-H), 7.97 (s, 1H, -Ar-H), 8.40 (s, 1H, -C_4-H of coumarin), 10.45 (s, 1H, -COOH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 15.85, 36.73, 43.16, 56.67, 116.04, 117.07, 120.73, 121.80, 122.03, 126.86, 140.81, 142.00, 145.33, 147.17, 158.30, 175.16, 179.30 ppm; MS (ESI m/z): 468.37 $[M+H]^+$ and 469.34$[M+2H]^+$.

9) 2-(2-(1-(8-ethoxy-2-oxo-2H-chromen-3-yl)ethylidene)hydrazono)-4-oxothiazolidin-5-yl).acetic acid (4i)

Yellow solid; yield: (82%); m.p.: 198 – 200 ^{o}C; FTIR (KBr, υ_{max} cm^{-1}): 3443 (-COOH), 3261 (-NH), 1707 (lactone-C=O), 1628 (amide –C=O), 1609 (-C=N), 1278 (-C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 1.42 (t, J = 4.8 Hz, 3H, -CH_3), 2.25 (s, 3H, -CH_3), 2.84 -2.91 (dd, J = 8.8 Hz, 17.6 Hz, 1H, -CH_2), 2.97 – 3.03 (dd, J = 3.6 Hz, 17.2 Hz, 1H, -CH_2), 4.17 – 4.20 (m, 2H, -OCH_2), 4.33 – 4.36 (dd, J = 4 Hz, 8.8 Hz, 1H, -CH_2), 7.29- 7.34 (m, 1H, -Ar-H), 7.40 – 7.42 (m, 1H, -Ar-H), 7.96 (bs, 1H, -NH), 8.15 (s, 1H, -Ar-H), 8.40 (s, 1H, -C_4-H of coumarin), 10.43 (bs, 1H, -COOH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.54, 15.96, 36.59, 43.34, 64.39, 119.55, 120.15, 124.63,125.81, 126.53, 141.67, 142.15, 142.77, 145.46, 158.77, 164.16, 175.17, 179.22 ppm; MS (ESI m/z): 404.25 $[M+H]^+$.

10) 2-(2-(1-(6-bromo-8-ethoxy-2-oxo-2H-chromen-3-yl)ethylidene)hydrazono)-4-oxo thiazolidin-5-yl) acetic acid (4j)

Yellow solid; yield: (84%); m.p.: 181 – 183 ^{o}C; FTIR (KBr, υ_{max} cm^{-1}): 3365 (-COOH), 3276 (-NH), 1713 (lactone –C=O), 1601 (-C=N), 1237 (-C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 1.27 (t, J = 4.4 Hz, 3H, -CH_3), 2.24 (s, 3H, -CH_3), 2.86 -2.92 (dd, J = 8 Hz, 16.8 Hz, 1H, -CH_2), 2.98 – 3.05 (dd, J = 4 Hz, 17.6 Hz, 1H, -CH_2), 4.00 – 4.05 (m, 2H, -OCH_2), 4.18 – 4.23 (dd, J= 3.6 Hz, 9.6 Hz, 1H, -CH), 7.14- 7.19 (m, 1H, -Ar-H), 7.46– 7.51 (m, 1H, -Ar-H), 7.91 (bs, 1H, -NH), 8.45 (s, 1H, -C_4-H of coumarin), 10.49 (bs, 1H, -COOH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.43, 15.89, 38.00, 44.54, 65.02, 116.02, 117.26, 120.81, 121.94, 126.85, 140.84, 145.36, 146.42, 158.39, 165.02, 175.36, 179.27 ppm; MS (ESI m/z): 482.8$[M+H]^+$ and 483.9 $[M+2H]^+$.

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11) 2-(2-(1-(7-hydroxy-2-oxo-2H-chromen-3-yl)ethylidene)hydrazono)-4-oxothiazolidin-5-yl) acetic acid (4k)

White solid; yield: (79%); m.p.: 214 – 216 ^{o}C; FTIR (KBr, υ_{max} cm^{-1}): 3374 (-COOH), 3239 (-OH), 3192 (-NH), 1725 (lactone –C=O), 1614 (-C=N); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.23 (s, 3H, -CH_3), 2.85 -2.92 (dd, J = 8.8 Hz, 18 Hz, 1H, -CH_2), 2.98 – 3.04 (dd, J = 3.6 Hz, 17.2 Hz, 1H, -CH_2), 4.34 - 4.37 (dd, J = 4 Hz, 8.8 Hz, 1H, -CH), 6.73 (d, J = 2 Hz, 1H, -Ar-H), 6.81 – 6.84 (m, 1H, -Ar-H), 7.58 (d, J = 8.4 Hz, 1H, -Ar-H), 7.90 (bs, 1H, -NH), 8.38 (s, 1H, -C_4-H of coumarin), 10.34 (bs, 1H, -Ph-OH), 10.73 (bs, 1H, -COOH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 16.02**,** 38.01, 44.51, 101.73, 111.39, 113.66, 120.98, 130.56, 132.49, 142.61, 146.57, 155.49, 159.50, 161.90, 175.49, 179.02 ppm; MS (ESI m/z): 376.0 $[M+H]^+$.

12) 2-(2-(1-(7-hydroxy-8-methyl-2-oxo-2H-chromen-3-yl)ethylidene)hydrazono)-4-oxothiazolidin-5-yl) acetic acid (4l)

White solid; yield: (82%); m.p.: 196 – 198 ^{o}C; FTIR (KBr, υ_{max} cm^{-1}): 3380 (-COOH), 3266 (-OH), 3184 (-NH), 1725 (lactone –C=O), 1691 (amide –C=O), 1605 (-C=N); ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.16 (s, 3H, -Ar-CH_3), 2.30 (s, 3H, -CH_3), 2.82 -2.87 (dd, J = 8.8 Hz, 18 Hz, 1H, -CH_2), 2.96 – 3.01 (dd, J = 3.2 Hz, 17.2 Hz, 1H, -CH_2), 4.30 - 4.33 (dd, J = 3.6 Hz, 9.2 Hz, 1H, -CH_2), 7.53 (d, J = 8.4 Hz, 1H, -Ar-H), 7.91 (bs, 1H, -NH), 8.07 (s, 1H, -Ar-H), 8.33 (s, 1H, -C_4-H of coumarin), 10.33 (bs, 1H, -Ph-OH), 10.72 (s, 1H, -COOH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 7.78, 15.99, 37.04, 43.55, 112.54, 113.22, 120.40, 121.02, 127.31, 127.56, 129.52, 142.96, 146.67, 153.42, 159.65, 175.28, 179.03 ppm; MS (ESI m/z): 390.27 $[M+H]^+$.

3.2 Antiviral activity evaluation

The antiviral activity of the new compounds was determined in different cell types. HEL cells were seeded in 96-well plates and incubated for 6 days at 37°C until confluency was reached. Medium was aspirated and replaced by serial dilutions of the test compounds (100 µl per well). One hundred microliters of the virus (*Herpes simplex* virus type-1*, Herpes simplex* virus type-2*, Herpes simplex* virus type-1 TK- ACV^{r}*, Vaccinia virus, Adeno* virus-2 or *Vesicular stomatitis* virus), diluted in medium to obtain a virus input of 100 $CCID_{50}$ (1 $CCID_{50}$ being the virus dose that is able to infect 50% of the cell cultures), was added to each well. Mock-treated cell cultures receiving solely the test compounds were included, to

determine the cytotoxicity. After 4 days of incubation at 37°C, microscopical analysis was performed to score the virus-induced cytopathicity. Similar method was adopted for Vero cells, HeLa cells, MDCK cells and CRFK cells and virus-induced cytopathicity was determined by measuring the cell viability with the colorimetric formazan-based MTS assay.[41,42]

4. Conclusion

In conclusion, we have synthesized 2-(-4-oxo-2-(-(1-(2-oxo-2*H*-chromen-3-yl)ethylidene)hydrazono)thiazolidin-5-yl) acetic acid derivatives **4a-l** via microwave assisted one pot multicomponent reaction approach. The method applied for the synthesis of the target compounds was simple with easy reaction workup and yielded good yields with a shorter reaction time. All the synthesized compounds were evaluated for antiviral activity and the compound **4d** is found to have good activity against *Herpes simplex* virus type-1 (KOS) [HSV-1 KOS], *Herpes simplex* virus type-2 (G) [HSV-2 G], *Vaccinia* virus [VV] and *Vesicular stomatitis* virus (VSV).

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Conflict of Interest

The authors declare no conflict of interest.

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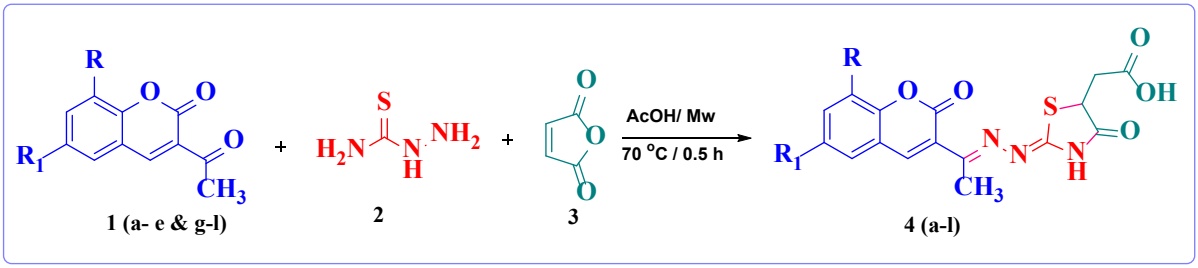
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GRAPHICAL ABSTRACT:



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