Full Paper

Conversion of 3-Arylazo-5-phenyl-2(3*H*)-furanones into Other Heterocycles of Anticipated Biological Activity

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3-Arylazo-5-phenyl-2(3*H*)-furanones **3** were prepared and converted into a variety of heterocyclic systems of synthetic and biological importance. Hydrazine hydrate reacted with furanones as nucleophiles and gave the corresponding acid hydrazides **4**. The latter products were used as starting materials for the synthesis of 1,3,4-oxadiazoles **6**, **9**, and the 1,2,4-triazoles **8**. Evaluation of the antiviral activity of selected compounds obtained was performed using two viruses: HAV and HSV-1. Some of the tested compounds showed promising activities.

Keywords: Furanones / HAV / HSV-1 / Oxadiazoles / Triazoles

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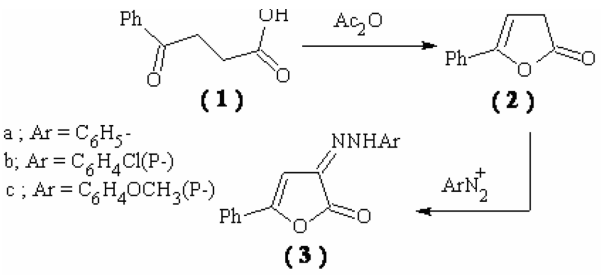
Introduction

Different examples of the conversion of 2(3*H*)-furanones into other heterocyclic systems of biological importance were already described by our research group [1 – 7]. Pyrazole derivatives show a wide spectrum of biological activities. Some substituted pyrazoles have antipyretic [8], hyperglycemic [9], anti-inflammatory [10], and antidepressant [11] activities. Important applications of pyrazole derivatives as antibiotics have also been reported otherwise [12, 13].

These diverse pharmacological activities, coupled with our interest in the chemistry of furanones, prompted us to try the conversion of the furanones **3** into other heterocycles bearing a pyrazolyl moiety. The study aims also to evaluate the antiviral activity of some selected examples of the compounds obtained.

The starting materials, 3-arylazo-5-phenyl-2(3*H*)-furanones **3** were prepared using a previously described procedure [14] which involves coupling of diazotized anilines with 5-phenyl-2(3*H*)-furanone **2**, via ring closure of 4-oxo-4-phenylbutanoic acid **1** using acetic anhydride (Scheme 1).



Scheme 1. Synthesis route of compounds **1 – 3**.

Results and discussion

Chemistry

Pyridazinones, 1,3,4-oxadiazoles and 1,2,4-triazoles are heterocyclic systems of diverse biological activities. Therefore, it was of interest to convert the 3-arylazo-5-phenyl-2(3*H*)-furanones **3** into the above ring systems bearing a pyrazolyl moiety. Acid hydrazides represent key compounds for this study and for the further synthesis of other used heterocyclic compounds Thus, the conversion of the furanones **3** into the previously mentioned heterocyclic systems should involve in the first step, ring opening of the furanones into the corresponding acid hydrazides. This should lead to the formation of 4-(oxo-4-phenyl-2-aryl-hydrazono)butyric acid hydrazides **4** by treating the furanones **3** with hydrazine hydrate in etha-

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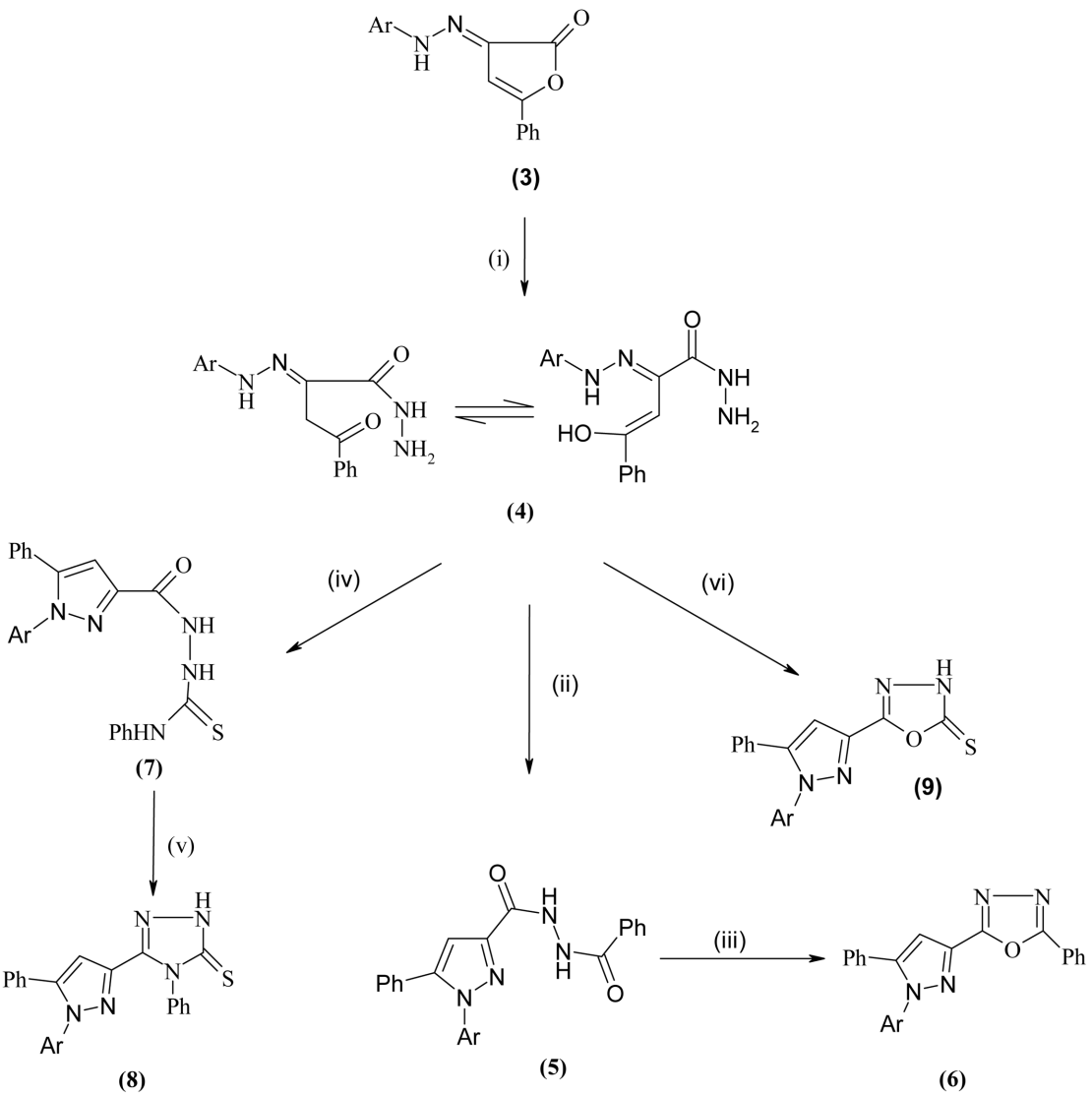

Reagents and conditions: (i) NH_2NH_2/EtOH, r.t; (ii) PhCOCl/benzene; (iii) $POCl_3$; (iv) PhNCS/benzene 700C; (v) 2N NaOH; (vi) CS_2/alc. NaOH.

Scheme 2. Synthesis route of compounds **4–6**.

nol. The latter hydrazides **4** were utilized as the key starting materials for the synthesis of the 1,3,4-oxadiazole and 1,2,4-triazole derivatives all bearing a pyrazolyl moiety as illustrated in Scheme 2.

The structures of all the products obtained were inferred from their analytical, as well as, spectral data (Table 1).

Antiviral activity

The different heterocyclic ring systems obtained in this investigation are expected to exhibit diverse biological activities. This initiated our interest to evaluate the antiviral activity of some of these compounds. Ten products were selected, representing the different classes for evaluating their activities.

Two viruses were utilized: hepatitis A virus (HAV) and herpes simplex virus type 1 (HSV-1). The plague infectivity reduction assay rapid screening method was applied [13]. The two known drugs commonly utilized for therapeutic treatments of HAV and HSV-1 are amantadine and acyclovir, respectively. So, these two drugs were considered as control. The results obtained from the antiviral

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Table 1. Spectral data of compounds **4 – 9**.

No.	IR (νmax) KBr(cm^{-1})			^1H – NMR (DMSO – d_6)
	ν_{NH}	$\nu_{C=O}$	$\nu_{C=S}$	
4a	3353 – 3280	1685 1648		2.8 – 3.2 (s, 2H, $-CH_2$), 3.9 (s, 2H, NH_2 exchangeable), 6.7 – 7.4 (m, 11H, 2 Ar-H + NHCO – exchangeable), 9.6 (s, 1H, NH-Ar exchangeable)
4b	3340 – 3275	1689 1655		2.75 – 3.2 (s, 2H, $-CH_2$), 3.85(s, 2H, NH_2 exchangeable), 6.75 (s, 1H, NHCO – exchangeable), 7.1 – 7.45 (m, 9H, Ar-H), 9.75 (s, 1H, NH-Ar exchangeable)
4c	3255 – 3280	1676 1651		2.9 – 3.2 (s, 2H, $-CH_2$), 3.8 (s, 3H, $-OCH3$), 4.4 (br, 2H, NH_2 exchangeable), 6.85 (d, 2H, Ar-H), 7.11 (d, 2H, Ar-H), 7.23 (s, 1H, NHCO – exchangeable), 7.31 – 7.41(m, 5H, Ar-H), 9.43 (s, 1H, NH-Ar exchangeable)
5a	3209 – 3213	1685		7.15 (s,1H, Pyrazole H),7.2 – 7.6 (m, 13H, 3 Ar – H), 7.9 (m, 2H, Ar-H), 10.3 (s,1H, NH exchangeable), 10.45 (s, 1H, NH exchangeable)
5b	3206 – 3220	1676		7.15 (s, 1H, Pyrazole H), 7.25 – 7.6 (m, 12H, Ar-H), 7.9 (m, 2H, Ar-H), 10.4 (s, 1H, NH exchangeable), 10.6 (s, 1H, NH exchangeable)
5c	3338 – 3340	1693		3.75 (s,3H, $-OCH3$), 6.9 (d, 2H, Ar-H) 7.05 (s, 1H, pyrazole H), 7.25 (m, 7H, Ar-H), 7.5 (m, 3H, Ar-H), 7.7 (m, 2H, Ar-H), 10.2 (s, 1H, NH exchangeable), 10.45 (s, 1H, NH exchangeable)
6a				7.3 – 7.5 (m, 8H, pyrazole H + 7Ar-H), 7.6 (m, 3H, Ar-H), 8.2 (m, 2H, Ar-H).
6b				7.1 (d, 2H, Ar-H), 7.3 – 7.5 (m, 8H, pyrazole H + Ar-H), 7.7 (m, 3H, Ar-H), 8.2 (m, 2H, Ar-H)
6c				3.75 (s, 3H, $-OCH3$), 7.0 (d, 2H, Ar-H) 7.2 – 7.4 (m, 8H, pyrazole H + Ar-H), 7.6 (m, 3H, Ar-H), 8.1 (m, 2H, Ar-H)
7a	3292 – 3199	1655	1250	7.11 (s, 1H, Pyrazole H), 7.2 – 7.5(m, 15H, Ar-H), 9.75 (br, 2H, NH exchangeable), 10.37 (s, 1H, NH exchangeable)
7b	3292 – 3199	1649	1255	7.2 (s, 1H, Pyrazole H), 7.3 – 7.9 (m, 14H, Ar-H), 9.8 (br, 2H, NH exchangeable), 10.4 (s ,1H, NH exchangeable)
7c	3322 – 3223	1648	1252	3.77 (s, 3H, $-OCH_3$), 7.1 (s, 1H, Pyrazole H),7.35 – 7.8 (m, 14H, Ar-H), 9.9 (br, 2H, NH exchangeable), 10.4 (s, 1H, NH exchangeable)
8a	3076 – 3100		1250	6.60 (s, 1H, Pyrazole H) ,6.9 – 7.56 (m, 15H, Ar-H), 14.16 (br, 1H, NH exchangeable)
8b	3084 – 3105		1250	6.75 (s, H, Pyrazole H), 7.0 – 7.7 (m, 14H, Ar-H), 13.75 (br, 1H, NH exchangeable)
8c	3085 – 3104		1254	3.8 (s, 3H, $-OCH_3$), 6.8 (s, 1H, Pyrazole H) ,7.15 – 7.75 (m, 15H, Ar-H), 14.16 (br, 1H, NH exchangeable)
9a	3077 – 3110		1250	7.19 (s, 1H, Pyrazole H), 7.2 – 7.4 (m, 10H, Ar-H), 14.7 (br, 1H, NH exchangeable)
9b	3095 – 3115		1251	7.15 (s, 1H, Pyrazole H), 7.15 – 7.50 (m, 9H, Ar-H), 14.4 (br, 1H, NH exchangeable)
9c	3076 – 3114		1250	3.8 (s, 3H, $-OCH_3$), 7.13 (s, 1H, Pyrazole H), 7.2 – 7.6 (m, 9H, Ar-H), 14.5 (br, 1H, NH exchangeable)

evaluation of the tested compounds are listed in (Table 2) and are illustrated by (Figs. 1 and 2). The physical data of compounds **3 – 14** are listed in Table 3.

The results presented in Table 2 and Figs. 1 and 2 reveal that oxadiazole **6b**, thiosemicarbazide **7b**, and oxadiazolethione **9a** show the highest activities towards the HAV virus compared with the other tested compounds. Their activities are comparable to that of amantadine, especially at a concentration of 20 μg/mL, while oxadiazolethione **9b** showed the highest activity towards HSV-1 compared to that of the other compounds tested, which show moderate activities especially at the aforementioned concentration.

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Table 2. Antiviral activity of the compounds (**5–9**).

Compound Nº	HSV-1		HAV	
	Percentage of reduction (%)		Percentage of reduction (%)	
	10 μg/mL	20 μg/mL	10 μg/mL	20 μg/mL
5c	0	13	37	44
6b	33	10	33	53
7b	20	T	67	94
7c	26	42.8	20	30
7c	22	36	0	4.9
8a	13	20	0	44
8b	0	16	4.9	8.1
9a	11	38	24	34
9b	25	68	24	34
9c	60	93	24	34

Table 3. Physical data of compounds **3–14**.

No.	M.p. (°C) (Color)	Yield (%)	Solvent of cryst.	Mol. Formula (MW)
4a	175-7 (colorless)	71	Benzene	$C_{16}H_{16}N_4O_2$ (296.3)
4b	161-2 (colorless)	63	Benzene	$C_{16}H_{15}N_4O_2Cl$ (330.7)
4c	125-6 (colorless)	52	Benzene	$C_{17}H_{18}N_4O_3$ (326.3)
5a	100-3 (colorless)	66	Benzene	$C_{23}H_{18}N_4O_4$ (382.4)
5b	225-6 (colorless)	63	Benzene	$C_{23}H_{17}ClN_4O_2$ (416.8)
5c	217-9 (colorless)	55	Benzene	$C_{24}H_{20}N_4O_3$ (412.4)
6a	178-9 (colorless)	71	Benzene	$C_{23}H_{16}N_4O$ (364.3)
6b	149-151 (colorless)	75	Benzene	$C_{23}H_{18}ClN_4O$ (456.5)
6c	175-7 (colorless)	67	Benzene	$C_{24}H_{18}N_4O_2$ (394.4)
7a	203-4 (colorless)	81	EtOH-Benzene	$C_{23}H_{19}N_5OS$ (413.4)
7b	211-13 (colorless)	75	EtOH- Benzene	$C_{23}H_{18}ClN_5OS$ (447.9)
7c	209-210 (colorless)	79	EtOH- Benzene	$C_{24}H_{21}N_5O_2S$ (443.5)
8a	228-9 (colorless)	68	EtOH- Water	$C_{23}H_{17}N_5S$ (395.4)
8b	283-4 (colorless)	73	EtOH- Water	$C_{23}H_{16}ClN_5S$ (429.9)
8c	260-1 (colorless)	59	EtOH- Water	$C_{24}H_{19}N_5OS$ (425.5)
9a	70-2 (yellow)	61	Benzene-Petro	$C_{17}H_{12}N_4OS$ (320.3)
9b	74-5 (yellow)	79	Benzene-Petro	$C_{17}H_{11}ClN_4OS$ (354.8)
9c	82-3 (yellow)	69	Benzene-Petro	$C_{18}H_{14}N_4O_2S$ (350.3)

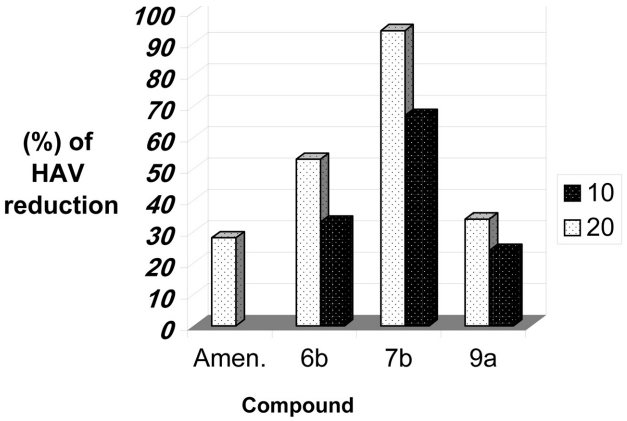

Figure 1. Effect of some compounds on HAV in comparison to amantadine (amen.) as control at two different concentrations (10 and 20 μg/mL).

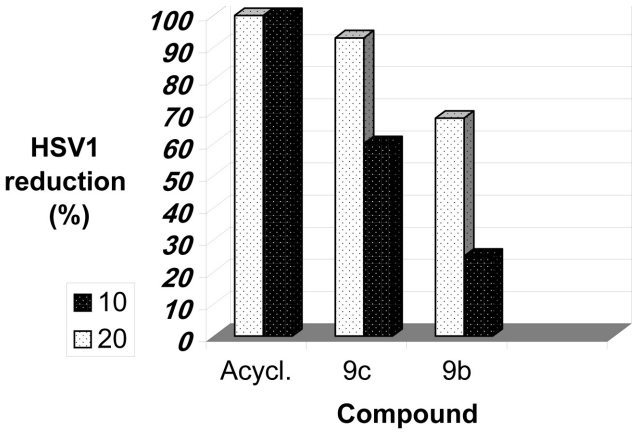

Figure 2. Effect of some compounds on HSV-1 in comparison to acyclovir (acycl.) as control at two different concentrations (10 and 20 μg/mL).

Experimental

Chemistry

Melting points were measured on an electrothermal melting point apparatus and are uncorrected. Elemental analyses were carried out at the Micro-Analytical Unit, Cairo University, Giza, Egypt. IR Spectra were measured on a Unicam SP-1200 spectrophotometer (Pye Unicam Ltd. Cambridge, UK) using KBr-wafer technique. 1H-NMR spectra were measured in DMSO–d_6 on a Varian Plus instrument (300 MHz; Varian Inc. Palo Alto, CA, USA).

*3-Arylazo-5-phenyl-2(3H)-furanones **3***

These compounds were prepared according to the procedure described previously [14].

Reaction of the 3-arylazo-5-phenyl-2(3*H*)-furanones **3** with hydrazine hydrate: To a solution of the furanones **3** (1 mmol) in ethanol (20 mL), hydrazine hydrate (1.1 mmol) was added. The reaction mixture was left at room temperature with occasional shaking. The product obtained was filtered off, washed with ethanol, and was shown to be 4-(oxo-4-phenyl-2-aryl-hydrazono)-butyric acid hydrazides **4** (Table 3).

*N′-[1-Aryl-5-phenyl-1H-pyrazole-3-carbonyl]-hydrazides **5***

Reaction of the hydrazides **4** with benzoyl chloride: To a solution of the hydrazides **4** (0.01 mol) in dry benzene (20 mL), benzoyl chloride (0.01 mol) was added. The reaction mixture was heated under reflux for 2 h. The solvent was distilled off under reduced pressure, and the solid residue was washed thoroughly with water, drained, and recrystallized from the suitable solvent (Table 3) to give benzoic acid *N′*-[1-aryl-5-phenyl-1*H*-pyrazole-3-carbonyl]-hydrazides **5**.

*2-(1-Aryl-5-phenyl-1H-pyrazol-3-yl)-5-phenyl-[1,3,4]-oxadiazoles **6***

Ring closure of the diaroyl hydrazine **5** using phosphorus oxychloride: Phosphorus oxychloride (10 mL) was added dropwise

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to 1.0 g of the diaroylhydrazine **5**. The reaction mixture was refluxed for 20 min, left to cool, and was then poured onto crushed ice. The solid obtained was filtered off, washed with water, and recrystallized from the suitable solvent (Table 3) to give 2-(1-aryl-5-phenyl-1*H*-pyrazol-3-yl)-5-phenyl-[1,3,4]-oxadiazoles **6**.

*1-Phenyl-3-(1-aryl-5-phenylpyrazol-3-yl) thiosemicarbazides **7***

Reaction of the hydrazides **4** with phenyl isothiocyanate: A solution of 2(3*H*)-furanones **3** (3 mmol) in ethanol (30 mL) with a phenyl isothiocyanate (3.1 mmol) was refluxed for 2 h. The solid obtained was filtered off and recrystallized from a suitable solvent to give 1-phenyl-3-(1-aryl-5-phenylpyrazol-3-yl) thiosemicarbazides **7** (Table 3).

*5-[1-(Aryl)-5-phenyl-1H-pyrazol-3-yl]-4-phenyl-2,4-dihydro-[1,2,4]triazole-3-thione **8***

Ring closure of the thiosemicarbazide derivatives **7**. A solution of 2N NaOH (40 mL) was added to thiosemicarbazide derivatives **7** (0.01 mol). The reaction mixture was refluxed for 2 h, filtered while hot, acidified with hydrochloric acid, and diluted with 60 mL water. The solid separated out was filtered off, washed with water, and recrystallized from the suitable solvent (Table 3) to give 5-[1-(aryl)-5-phenyl-1*H*-pyrazol-3-yl]-4-phenyl-2,4-dihydro-[1,2,4]triazole-3-thione **8**.

*5-(1-Aryl-5-phenyl-1H-pyrazol-3-yl)-3H-[1,3,4]-oxadiazole-2-thiones **9***

Reaction of the hydrazides **4** with carbon disulphide: To a solution of hydrazide **4** (0.01 mmol) in 10% alcoholic sodium hydroxide (3 g NaOH in 30 mL ethanol), carbon disulphide (10 mL) was added, whereby the reaction mixture became brown in color. The reaction mixture was stirred at room temperature for 6 h. Acidification with conc. HCl gave a yellow precipitate which was filtered off and finally recrystallized from the suitable solvent (Table 3) to give 5-(1-aryl-5-phenyl-1*H*-pyrazol-3-yl)-3*H*-[1,3,4]-oxadiazole-2-thiones **9**.

Antiviral assay

African green monkey kidney-derived cells (Vero cells) were used. The cells were propagated in Dulbecco's Minimum Essential Medium (DMEM) supplemented with 10% fetal bovine serum, 1% antibiotic-antimycotic mixture. The pH was adjusted at 7.2 – 7.4 by 7.5% sodium bicarbonate solution.

The used viruses are: 1) Herpes simplex virus type 1, obtained from Environmental Virology Lab. Department of Water Pollution Res., National Research Center; 2) Hepatitis A, Verena Gauss-Müller, Luebeck University of Medicine, Institute of Molecular Virology, Germany.

Antiviral activity was measured by plaque infectivity reduction assay for rapid screening. The tested compounds were dissolved as 100 mg each in 1 mL of 10% DMSO in water. Final concentration was 100 μg/μL (stock solution). The dissolved stock solutions were sterilized by addition of 50 μg/mL antibiotic-antimycotic mixture (10 000 U) penicillin G sodium, 10 000 μg streptomycin sulfate, and 250 μg amphotericin B. A 6-well plate was cultivated with Vero cell culture (10^5 cells/mL) and incubated for two days at 37°C. HSV-1 and HAV were diluted to give 10^4 PFU/mL final concentration for each virus and mixed with the tested compound at the previous concentration and incubated overnight at 4°C. Growth medium was removed from the multi-well plate and the virus-compound mixture was inoculated (100 μL/well). After 1 h contact time, the inoculum was aspirated and 3 mL of MEM with 1% agars was overlaid the cell sheets.

The plates were left to solidify and incubated at 37°C until the development of virus plaques. Cell sheets were fixed with 10% formalin solution for 2 h and stained with crystal violet stain. Control virus and cells were treated identically without chemical compound. Virus plaques were counted and the percentage of reduction was calculated.

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