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Original article

# Conversion of some 2(3*H*)-furanones bearing a pyrazolyl group into other heterocyclic systems with a study of their antiviral activity

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**Abstract**

3-(1,3-Diphenylpyrazol-4-yl-methylene)-5-aryl-2(3*H*)-furanones **2** were prepared and converted into a variety of heterocyclic systems of synthetic and biological importance. Benzylamine reacted with the furanones **2**; the product was found to depend on the reaction conditions. Thus, at room temperature the open-chain *N*-benzylamides **3** were obtained, whereas under refluxing conditions the 2(3*H*)-pyrrolones were obtained. Hydrazine hydrate affected ring opening of the furanones to give the corresponding acid hydrazides **5**. The latter products were used as key starting materials for the synthesis of pyridazinones **7** and **8**, 1,3,4-oxadiazoles **11** and **13** and 1,2,4-triazoles **12** and **14** all bearing pyrazolyl moiety as a side-chain. Evaluation of antiviral activity of selected examples of the compounds obtained was performed using two viruses: HAV and HSV-1. Some of the tested compounds showed promising activities.


*Keywords:* Antiviral activity; 2(3*H*)-Furanones; 2(3*H*)-Pyrrolones; 1,2,4-Triazoles; Viruses: HAV and HSV-1

## 1. Introduction

In a recent work, we prepared 3-(1,3-diphenylpyrazol-4-yl-methylene)-5-aryl-2(3*H*)-furanones [1] **2** by cyclodehydrating 3-aroylpropionic acids **1** using a mixture of thionyl chloride and *N*,*N*-dimethylformamide [2], followed by condensation with 1,3-diphenylpyrazole-4-carboxaldehyde (cf. Scheme 1).

The conversion of 2(3*H*)-furanones into other heterocyclic systems of biological importance was described by our research group in a number of publications [3–9]. Pyrazole derivatives show a wide spectrum of biological activities. Some substituted pyrazoles have antipyretic [10], hyperglycemic [10], anti-inflammatory [11] and antidepressant [12] activities. Important applications of pyrazole derivatives as antibiotics have also been reported [13,14].

These diverse pharmacological activities, coupled with our interest in the chemistry of furanones, prompted us to try the conversion of the furanones **2** into other heterocycles bearing a pyrazolyl moiety. The study, aims also to evaluate the antiviral activity of some selected examples of the compounds obtained.

## 2. Results and discussion

### 2.1. Synthesis

When the furanones **2** were allowed to react with benzylamine, the product obtained was found to depend mainly on the reaction conditions. Thus, when the reaction was carried out in benzene at 70 °C for 1 h or in ethanol at room temperature, ring opening afforded the open-chain benzylamides **3**. But, refluxing in ethanol or benzene for 3 h, the 2(3*H*)-pyrrolones **4** were the only isolable products. The latter products are formed via the intermediates of the open-chain amides **3**, since when the latter were refluxed in HCl/AcOH mixture, ring closure led to the formation of the pyrrolones **4** (cf. Scheme 2).

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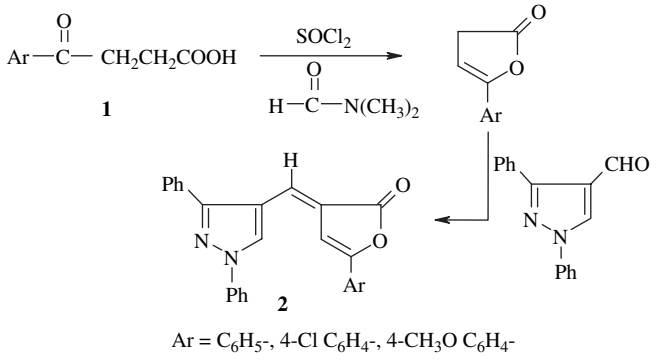



Scheme 1.

The structures of the *N*-benzylamides **3** and the 2(3*H*)-pyrrolones **4** were illustrated from analytical, as well as, spectral data (cf. Table 1).

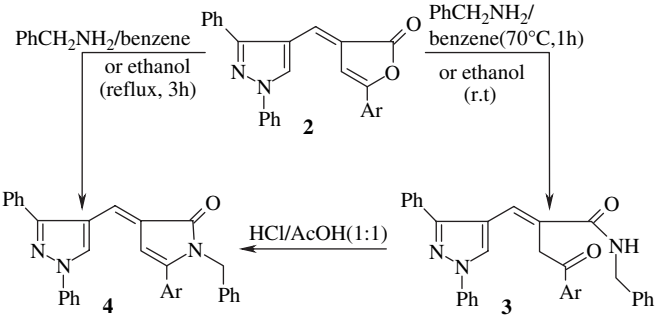
Pyridazinones, 1,3,4-oxadiazoles and 1,2,4-triazoles are heterocyclic systems of diverse biological activities. It was of interest to the authors to convert the pyrazolyl furanones **2** into the above ring systems bearing a pyrazolyl moiety.

Acid hydrazides represent important and versatile synthons of a wide variety of heterocyclic compounds. Thus, the conversion of the furanones **2** into the previously mentioned heterocyclic systems should involve, in the first step, ring opening of the furanones into the corresponding acid hydrazides. Treating the furanones **2** with hydrazine hydrate in ethanol, led to the formation of 3-aroyl-2-(1,3-diphenylpyrazol-4-yl-methylene)-propionic acid hydrazides **5**. The latter hydrazides **5** were utilized as the key starting materials for the synthesis of the pyridazinones, 1,3,4-oxadiazoles and 1,2,4-triazole derivatives all bearing a pyrazolyl moiety as illustrated by Scheme 3.

The structures of all the products obtained were inferred from their analytical, as well as, spectral data (cf. Table 2).

### 2.2. Evaluation of the antiviral activity

The different heterocyclic ring systems obtained in this investigation are known 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.




Scheme 2.

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 [15].

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 evaluation of the tested compounds are listed in (Table 3) and illustrated by Figs. 1 and 2.

The results presented by Table 3 and Figs. 1 and 2 reveal the following.

1. Furanone **2b**, *N*-benzylamide **3b** and diaroylhydrazine **6b** show highest activities towards the *HAV virus* compared with the other tested compounds. Their activities, especially at concentration 20 μg/ml, are comparable with amantadine.
2. Semicarbazide **9b** showed the highest activity towards *HSV-1* compared with the other tested compounds.
3. Other compounds tested show moderate activities especially at concentration 20 μg/ml.

## 3. Experimental

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. IR spectra were measured on a Unicam SP-1200 spectrophotometer using KBr wafer technique. $^1$H NMR spectra were measured in DMSO-$d_6$ on a Varian Plus instrument (300 MHz).

### 3.1. 5-Aryl-3-(1,3-diphenylpyrazol-4-yl)-methylene-2 (3H )-furanones (2)

These compounds were prepared according to the procedure described by previous investigators [2].

### 3.2. Reactions of the 5-aryl-3-(1,3-diphenylprazol-4-yl-methylene)-2(3H )-furanones (2) with benzylamine

To a solution of the furanone (**2**) (1 mmol) in benzene or ethanol (20 ml), benzylamine (1 mmol) was added. The reaction mixture was refluxed in benzene at 60 °C for 1 h or left at room temperature for 5 min in ethanol. The product was filtered off, washed with benzene and finally recrystallized from a suitable solvent to give the amides (**3**) (cf. Table 4).

The reaction mixture was heated at 100 °C for 3 h, and the product obtained was filtered off, washed with benzene and recrystallized from the suitable solvent (cf. Table 4), 5-aryl-1-benzyl-3-(1,3-diphenylpyrazol-4-yl-methylene)-2(3*H*)-pyrrolones (**4**) were the isolable products.

### 3.3. Reaction of the 5-aryl-3-(1,3-diphenylpyrazol-4-yl-methylene)-2(3H )-furanones (2) with hydrazine hydrate

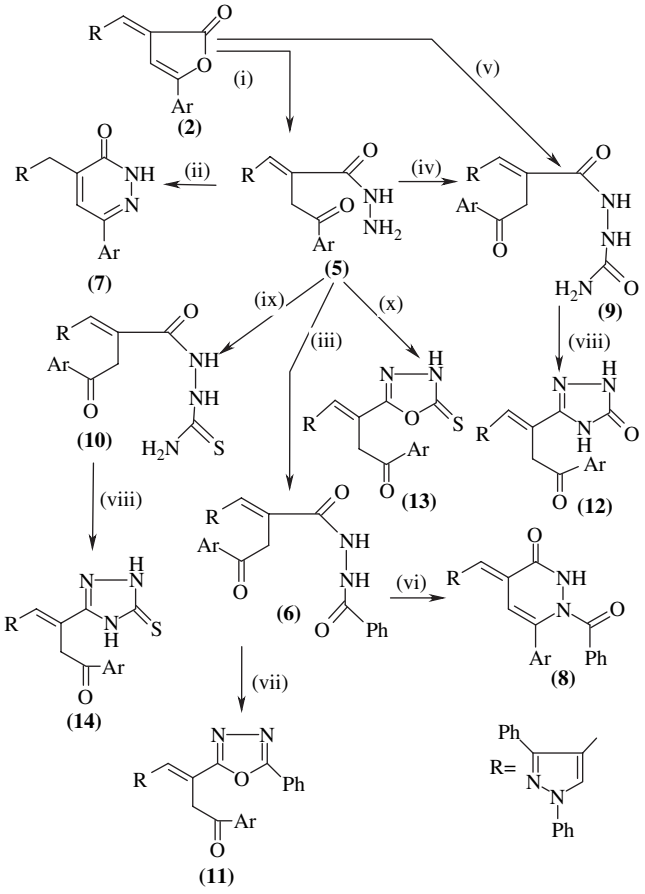
To a solution of the furanones (**2**) (1 mmol) in ethanol (20 ml), hydrazine hydrate (1.1 mmol) was added. The reaction mixture was left at room temperature with occasional

Table 1
Spectral data of the *N*-benzylamides (**3**) and the 2(3*H*)-pyrrolones (**4**)

| Compound | IR ($\nu_{max}$) KBr ($cm^{-1}$) | | $^1$H NMR (DMSO-$d_6$) |
|---|---|---|---|
| | $\nu_{NH}$ | $\nu_{C=O}$ | |
| **3a** | 3200 | 1678 | $\delta = 3.29$ (s, 2H, $CH_2$–CO), 3.90 (s, 2H, NH–$CH_2$), 6.80–7.95 (m, 21H, Ar-H), 8.35 |
| | | 1654 | (s, 1H, =CH), 13.01 (br s, 21H, NH, exchangeable). |
| **3b** | 3200 | 1680 | |
| | | 1648 | |
| **3c** | 3266 | 1678 | $\delta = 3.25$ (s, 2H, $CH_2$–CO), 3.77 (s, 3H, $OCH_3$), 3.95 (s, 2H, NH–$CH_2$), 6.97–7.90 |
| | | 1650 | (m, 20H, Ar-H), 8.42 (s, 1H, =CH), 13.04 (br s, 1H, NH, exchangeable). |
| **4a** | – | 1653 | $\delta = 3.95$ (s, 2H, NH–$CH_2$), 7.01–7.90 (m, 21H, Ar-H), 8.60 (s, 1H, =CH). |
| **4b** | – | 1675 | |
| **4c** | – | 1660 | $\delta = 3.78$ (s, 3H, $OCH_3$), 3.95 (s, 2H, NH–$CH_2$), 6.97–7.89 (m, 20H, Ar-H), 8.419 (s, 1H, =CH). |

shaking. The product obtained was filtered off, washed with ethanol and was found to be 3-aroyl-2-(1,3-diphenylpyrazol-4-yl-methylene)-propionic acid hydrazide (**5**) (cf. Table 4).

When the reaction mixture was refluxed in ethanol the product was found to be 5-aryl-4-(1,3-diphyenylpyrazol-4-yl-methylene)-pyridazin-3-one (**7**) which was recrystallized from the suitable solvent (cf. Table 4).




a,Ar =$C_6H_5$-;b,Ar = 4-$ClC_6H_4$-;c,Ar = 4-$CH_3OC_6H_4$-

Scheme 3. Reagents and conditions: (i) $NH_2NH_2$/EtOH, r.t; (ii) HCl/AcOH, reflux; (iii) PhCOCl/benzene; (iv) KNCO; (v) semicarbazide hydrochloride/AcONa/EtOH, reflux; (vi) HCl/AcOH, reflux; (vii) $POCl_3$; (viii) 2 N NaOH; (ix) KNCS; (x) $CS_2$/alc. NaOH.

### *3.4. Reaction of the hydrazides (**5**) with benzoyl chloride*

To a solution of the hydrazides (**5**) (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 yellow solid obtained was washed thoroughly with water, drained, and recrystallized from the suitable solvent (cf. Table 4) to give 1-benzoyl-2-[3-aroyl-2-(1,3-diphenylpyrazol-4-yl-methylene)-propanoyl hydrazine (**6**).

### *3.5. Ring closure of the hydrazides (**5**) and diaroylhydrazines (**6**) using HCl/AcOH mixture*

A solution of (**5**) or (**6**) (1 g) in a mixture of HCl/AcOH, 1:1 (30 ml), was heated under reflux for 1 h and then left to cool. The solid obtained was filtered off, washed with water and recrystallized from the suitable solvent (cf. Table 4) to give 5-aryl-4-(1,3-diphenylpyrazol-4-yl-methylene)-pyridazin-3-ones (**7**) or 6-aryl-1-benzoyl-4-(1,3-diphenyl-pyrazol-4-yl-methylene)-pyridazin-3-ones (**8**), respectively.

### *3.6. Ring closure of the diaroylhydrazines (**6**) using phosphorus oxychloride*

Phosphorus oxychloride (10 ml) was added dropwise to 1.0 g of the diaroylhydrazine (**6**). The reaction mixture was refluxed for 20 min, left to cool, and poured onto crushed ice. The solid obtained was filtered off, washed with water and recrystallized from the suitable solvent (cf. Table 4) to give 2-phenyl-5-[3-aroyl-1-(1,3-diphenylpyrazol-4-yl)]-2-propenyl-1,3,4-oxadiazoles (**11**).

### *3.7. Reaction of the hydrazides (**5**) with potassium isocyanate and potassium isothiocyanate*

A solution of potassium isocyanate or potassium isothiocyanate (0.022 mol) in water (10 ml) was added dropwise with stirring at 0 °C to a solution of the hydrazide derivative (**5**) (0.02 mmol) in acetic acid/water (1:1 by volume) mixture. The reaction mixture was stirred at room temperature for 3 h. The product obtained was filtered off, washed thoroughly with water, and finally recrystallized form the suitable solvent

Table 2
Spectral data of compounds **5**−**14**

| Compound | IR ($\nu_{max}$) KBr ($cm^{-1}$) | | | $^1$H NMR (DMSO-$d_6$) |
|---|---|---|---|---|
| | $\nu_{NH}$ | $\nu_{C=O}$ | $\nu_{C=S}$ | |
| **5a** | 3320 | 1685 | | $\delta = 3.10$ (s, 2H, $CH_2$−CO), 4.20 (s, 2H, $NH_2$, exchangeable), 6.46 (s, 1H, NH−CO, exchangeable), 6.90−8.00 (m, 16H, Ar-H), 8.50 (s, 1H, =CH). |
| | 3266 | 1660 | | |
| **5b** | 3325 | 1682 | | |
| | 3260 | 1659 | | |
| **5c** | 3323 | 1685 | | $\delta = 3.13$ (s, 2H, $CH_2$−CO), 3.76 (s, 3H, $OCH_3$), 4.29 (s, 2H, $NH_2$, exchangeable), 6.48 (s, 1H, NH−CO, exchangeable), 6.92−7.99 (m, 15H, Ar-H), 8.67 (s, 1H, =CH). |
| | 3265 | 1657 | | |
| **6a** | 3350 | 1688 | | $\delta = 3.22$ (s, 2H, CH), 7.50−7.90 (m, 21H, Ar-H), 8.60 (s, 1H, =CH), 10.40 (s, 2H, NH−NH, exchangeable). |
| | 3205 | 1655 | | |
| **6b** | 3332 | 1687 | | $\delta = 3.17$ (s, 2H, $CH_2$), 7.20−7.99 (m, 20H, Ar-H), 8.68 (s, 1H, =CH), 10.49 (s, 2H, NH−NH, exchangeable). |
| | 3200 | 1649 | | |
| **6c** | 3300 | 1685 | | |
| | 3200 | 1650 | | |
| **7a** | 3300 | 1659 | | $\delta = 3.11$ (s, 2H, $-CH_2$), 6.90−7.80 (m, 17H, Ar-H), 11.00 (br s, 1H, NH, exchangeable), |
| **7b** | 3315 | 1659 | | |
| **7c** | 3321 | 1660 | | $\delta = 3.16$ (s, 2H, $-CH_2$), 3.95 (s, 3H, $OCH_3$), 6.92−7.99 (m, 16H, Ar-H), 11.15 (br s, 1H, NH, exchangeable). |
| **8a** | 3190 | 1680 | | $\delta = 7.5$−8.20 (m, 22H, Ar-H), 8.65 (s, 1H, =CH), 12.06 (s, 1H, NH, exchangeable). |
| | | 1650 | | |
| **8b** | 3191 | 1678 | | |
| | | 1650 | | |
| **8c** | 3191 | 1688 | | $\delta = 3.94$ (s, 3H, $OCH_3$), 7.18−8.08 (m, 20H, Ar-H), 8.68 (s, 1H, =CH), 12.04 (s, 1H, NH, exchangeable). |
| | | 1647 | | |
| **9a** | 3300 | 1700 | | $\delta = 3.75$ (s, 2H, $CH_2$), 7.02−7.98 (m, 16H, Ar-H), 8.50 (s, 1H, =CH,), 8.90 (s, 2H, $NH_2$, exchangeable), 10.40 (s, 2H, NH−NH, exchangeable). |
| | | 1649 | | |
| **9b** | 3350 | 1700 | | |
| | | 1650 | | |
| **9c** | 3390 | 1702 | | $\delta = 3.90$ (s, 3H, $OCH_3$), 3.95 (s, 2H, $CH_2$), 6.97−7.90 (m, 15H, Ar-H), 8.44 (s, 1H, =CH), 9.23 (s, 2H, $NH_2$, exchangeable), 10.49 (s, 2H, NH−NH, exchangeable). |
| **10a** | 3300 | 1680 | 1250 | $\delta = 3.90$ (s, 2H, $CH_2$), 7.30−7.90 (m, 16H, Ar-H), 8.54 (s, 1H, =CH), 10.40 (s, 1H, NH−CO, exchangeable), 12.10 (br s, 2H, $NH_2$ C=S, exchangeable), 13.09 |
| | 3250 | | | (s, 1H, NH−C=O, exchangeable). |
| **10b** | 3323 | 1685 | 1248 | $\delta = 3.94$ (s, 2H, $CH_2$), 7.36−7.94 (m, 15H, Ar-H), 8.40 (s, 1H, =CH), 10.49 (s, 1H, NH−CO, exchangeable), 12.16 (br s, 2H, $NH_2$−C=S, exchangeable), 13.04 |
| | 3266 | | | (s, 1H, NH−C=O, exchangeable). |
| **10c** | 3320 | 1683 | 1250 | |
| | 3250 | | | |
| **11a** | − | 1680 | | $\delta = 3.25$ (s, 2H, $CH_2$), 7.50−8.01 (m, 21H, Ar-H), 8.50 (s, 1H, =CH). |
| **11b** | − | 1684 | | $\delta = 3.17$ (s, 2H, $CH_2$), 7.20−7.86 (m, 20H, Ar-H), 8.51 (s, 1H, =CH). |
| **11c** | − | 1682 | | |
| | | 1650 | | |
| **12a** | 3253 | 1655 | | $\delta = 3.70$ (s, 2H, $CH_2$), 7.40−8.01 (m, 16H, Ar-H), 8.50 (s, 1H, =CH), 9.10 (s, 2H, NH, exchangeable). |
| **12b** | 3253 | 1650 | | $\delta = 3.94$ (s, 2H, $CH_2$), 7.44−7.89 (m, 15H, Ar-H), 8.40 (s, 1H, =CH), 9.18 (s, 2H, NH, exchangeable). |
| **12c** | 3250 | 1660 | | |
| **13a** | 3210 | 1665 | 1250 | $\delta = 3.95$ (s, 2H, $CH_2$), 7.05−7.80 (m, 16H, Ar-H), 8.40 (s, 1H, =CH), 13.05 (s, 1H, NH, exchangeable). |
| **13b** | 3211 | 1660 | 1254 | $\delta = 3.95$ (s, 2H, $CH_2$), 6.97−7.89 (m, 15H, Ar-H), 8.41 (s, 1H, =CH), 13.01 (s, 1H, NH, exchangeable). |
| **13c** | 3200 | 1663 | 1251 | |
| **14a** | 3200 | 1662 | 1250 | $\delta = 3.90$ (s, 2H, $CH_2$), 6.95−8.50 (m, 16H, Ar-H), 8.50 (s, 1H, =CH), 13.09 (s, 2H, NH, exchangeable). |
| **14b** | 3214 | 1659 | 1252 | $\delta = 3.78$ (s, 2H, $CH_2$), 6.92−7.99 (m, 15H, Ar-H), 8.66 (s, 1H, =CH), 13.09 (s, 2H, NH, exchangeable). |
| **14c** | 3220 | 1665 | 1249 | |

Table 3
Antiviral activity of the tested compounds

| Compound | Percentage of reduction (%) | | | |
|---|---|---|---|---|
| | HSV-1 | | HAV | |
| | 10 μg/ml | 20 μg/ml | 10 μg/ml | 20 μg/ml |
| **2b** | 0 | 0 | 40 | 60 |
| **3b** | 4 | 23.8 | 40 | 60 |
| **4c** | 23 | 45 | 0 | 0 |
| **5b** | 26 | 42.8 | 20 | 30 |
| **7c** | 21 | 47 | 20 | 50 |
| **6b** | 10 | 38 | 30 | 60 |
| **9b** | 42.8 | 52 | 0 | 20 |
| **12b** | 0 | 14 | 0 | 10 |
| **13b** | 14 | 45 | 0 | 0 |
| **14b** | 0 | 38 | 40 | 50 |

(cf. Table 4) to give 3-[3-aroyl-1-(1,3-diphenylpyrazol-4-yl)-propen-2-yl]semicarbazides (**9**) and thiosemicarbazides (**10**).

The same semicarbazide derivatives (**9**) were also obtained from heating a solution of 2(3*H*)-furanones (**2**) (1 mol) in ethanol (30 ml) with a mixture of semicarbazide hydrochloride (1 mmol), anhydrous sodium acetate (1 mmol) under reflux for 1 h. The solid obtained was filtered off and recrystallized form the suitable solvent (cf. Table 4). The product obtained in each case was identical in all respects (m.p., mixed m.p. and TLC) with that obtained from the reaction between hydrazides (**5**) and potassium isocyanate.

### *3.8. Ring closure of the semicarbazide derivatives (**9**) and thiosemicarbazide derivatives (**10**)*

A solution of 2 N NaOH (40 ml) was added to the semicarbazide or thiosemicarbazide derivatives (**9**) or (**10**) (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 (cf. Table 4) to give 3-[3-aroyl-1-(1,3-diphenylpyrazol-4-yl)-propen-2-yl]-1,2,4-triazol-5-one (**12**) and 3-[3-aroyl-1-(1,3-diphenylpyrazol-4-yl)-propen-2-yl]-1,2,4-triazol-5-thiones (**14**), respectively.

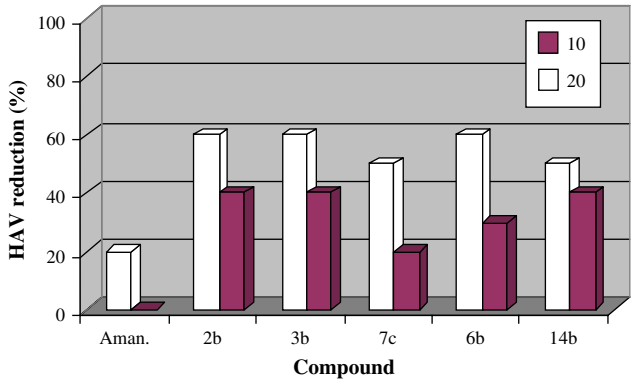



Fig. 1. Effect of some compounds on HAV in comparison with amantadine (Aman.) as a control at two different concentrations 10 and 20 μg/ml.

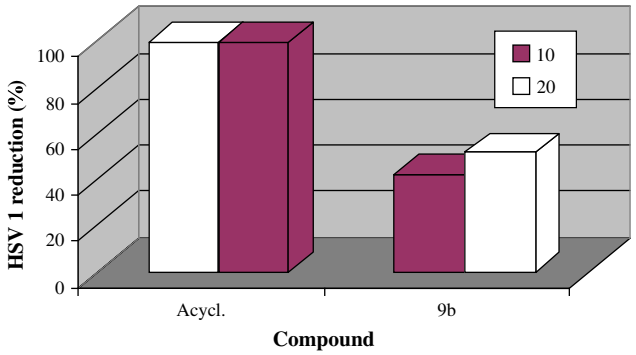



Fig. 2. Effect of some compounds on HSV-1 in comparison with acyclovir (Acycl.) as a control at two different concentrations 10 and 20 μg/ml.

### *3.9. Reaction of the hydrazides (**5**) with carbon disulphide*

To a solution of hydrazide (**5**) (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 refluxed for 2 h, cooled at room temperature and then poured into ice cold water. Acidification with conc. HCl, gave a yellow precipitate which was filtered off and finally recrystallized from the suitable solvent (cf. Table 4) to give 2-[3-aroyl-1-(1,3-diphenylpyrazol-4-yl)]propen-2-yl-1,3,4-oxadiazol-5-thiones (**13**).

## 4. Antiviral bioassay

### *4.1. Cells*

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

### *4.2. Viruses*

1. *Herpes Simplex Virus type 1*, obtained from Environmental Virology lab., Department of Water Pollution Res., National Research Center.
2. *Hepatitis A Verena Gauss-Muller*, Luebeck University of Medicine, Institute of Molecular Virology, Germany.

### *4.3. Antiviral activity*

Plaque infectivity reduction assay for rapid screening.

### *4.4. Method*

#### *4.4.1. Preparation of synthetic compounds for bioassay*

The tested compounds were dissolved as 100 mg each in 1 ml of 10% DMSO in water. The final concentration was 100 μg/μl (stock solution). The dissolved stock solutions

Table 4
Physical and analytical data of compounds (**3**–**14**)

| Compound | M.p. °C (color) | Yield % | Solvent for cryst. | Mol. formula (M. wt) | Analysis (calcd/found) % | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | C | H | N | S |
| **3a** | 275–276 (colorless) | 75 | Benzene | $C_{33}H_{27}N_3O_2$ (497) | 79.68/79.80 | 5.43/5.40 | 8.45/8.43 | |
| **3b** | 260–262 (colorless) | 70 | Benzene | $C_{33}H_{26}ClN_3O_2$ (531.5) | 74.51/74.39 | 4.89/4.87 | 7.90/7.95 | |
| **3c** | 257–259 (colorless) | 75 | Benzene | $C_{34}H_{29}N_3O_3$ (527) | 77.42/77.43 | 5.50/5.56 | 7.97/7.97 | |
| **4a** | 229–230 (colorless) | 65 | EtOH | $C_{33}H_{25}N_3O$ (479) | 82.67/82.98 | 5.22/5.20 | 8.77/8.59 | |
| **4b** | 225–226 (colorless) | 60 | EtOH | $C_{33}H_{24}ClN_3O$ (513.5) | 77.12/77.11 | 4.67/4.69 | 8.18/8.15 | |
| **4c** | 217–219 (colorless) | 73 | EtOH | $C_{34}H_{27}N_3O_2$ (509) | 80.16/80.12 | 5.30/5.30 | 8.25/8.20 | |
| **5a** | 230–232 (colorless) | 80 | Benzene | $C_{26}H_{22}N_4O_2$ (422) | 73.93/73.85 | 5. 21/5.16 | 13.27/13.23 | |
| **5b** | 223–224 (colorless) | 75 | Benzene | $C_{26}H_{21}ClN_4O_2$ (456.5) | 68.35/68.30 | 4.60/4.63 | 12.27/12.24 | |
| **5c** | 240–241 (colorless) | 70 | Benzene | $C_{27}H_{24}N_4O_2$ (452) | 71.68/71.64 | 5. 31/5.30 | 12.39/12.32 | |
| **6a** | 225–227 (colorless) | 50 | EtOH | $C_{33}H_{26}N_4O_3$ (526) | 75.29/75.12 | 4.94/4.64 | 10.65/10.50 | |
| **6b** | 220–222 (colorless) | 35 | EtOH | $C_{33}H_{25}ClN_4O_3$ (560.5) | 70.65/70.56 | 4.46/4.30 | 9.99/9.68 | |
| **6c** | 230–231 (colorless) | 40 | EtOH | $C_{34}H_{28}N_4O_4$ (556) | 73.38/73.27 | 5.04/4.92 | 10.07/9.91 | |
| **7a** | 178–180 (colorless) | 75 | EtOH | $C_{26}H_{20}N_4O$ (404) | 77.23/77.19 | 4.95/4.90 | 13.86/13.82 | |
| **7b** | 160–162 (colorless) | 60 | EtOH | $C_{26}H_{19}ClN_4O$ (438.5) | 71.15/71.12 | 4.33/4.28 | 12.77/12.59 | |
| **7c** | 190–192 (colorless) | 70 | EtOH | $C_{27}H_{22}N_4O_2$ (434) | 74.65/74.64 | 5.07/5.04 | 12.90/12.78 | |
| **8a** | 182–183 (colorless) | 50 | EtOH | $C_{33}H_{24}N_4O_2$ (508) | 77.95/77.90 | 4.72/4.71 | 11.02/11.05 | |
| **8b** | 175–177 (colorless) | 65 | EtOH | $C_{33}H_{23}ClN_4O_2$ (542.5) | 72.99/72.91 | 4.24/4.21 | 10.32/10.27 | |
| **8c** | 168–170 (colorless) | 60 | EtOH | $C_{33}H_{26}N_4O_3$ (538) | 75.84/75.80 | 4.83/4.87 | 10.41/10.36 | |
| **9a** | 235–237 (colorless) | 50 | EtOH | $C_{27}H_{23}N_5O_3$ (465) | 69.68/69.62 | 4.95/4.93 | 15.05/15.02 | |
| **9b** | 230–232 (colorless) | 30 | EtOH | $C_{27}H_{22}ClN_5O_3$ (499.5) | 64.86/64.80 | 4.40/4.60 | 14.01/14.00 | |
| **9c** | 239–240 (colorless) | 35 | EtOH | $C_{28}H_{25}N_5O_4$ (495) | 67.88/67.82 | 5.05/5.10 | 14.14/14.10 | |
| **10a** | 165–166 (colorless) | 30 | EtOH | $C_{27}H_{23}N_5O_2S$ (481) | 67.36/67.27 | 4.78/4.75 | 14.55/14.53 | 6.65/6.87 |
| **10b** | 170–172 (colorless) | 35 | EtOH | $C_{27}H_{22}ClN_5O_2S$ (515.5) | 62.85/62.80 | 4.27/4.24 | 13.58/13.50 | 6.20/6.03 |
| **10c** | 180–182 (colorless) | 35 | EtOH | $C_{28}H_{25}N_5O_3S$ (511) | 65.75/65.69 | 4.89/4.82 | 13.70/13.63 | 6.26/6.35 |
| **11a** | 175–176 (colorless) | 35 | EtOH | $C_{33}H_{24}N_4O_2$ (508) | 77.95/77.87 | 4.72/4.70 | 11.02/11.01 | |
| **11b** | 182–183 (colorless) | 40 | EtOH | $C_{33}H_{23}ClN_4O_2$ (542.5) | 72.99/73.06 | 4.24/4.22 | 10.32/10.30 | |
| **11c** | 187–188 (colorless) | 40 | EtOH | $C_{34}H_{26}N_4O_3$ (538) | 75.84/75.80 | 4.83/4.80 | 10.41/10.45 | |
| **12a** | 245–247 (colorless) | 35 | EtOH | $C_{27}H_{20}N_5O_2$ (446) | 72.65/72.60 | 4.48/4.43 | 15.69/15.65 | |
| **12b** | 230–232 (colorless) | 45 | EtOH | $C_{27}H_{19}ClN_5O_2$ (480.5) | 67.43/67.41 | 3.95/3.92 | 14.57/14.50 | |
| **12c** | 239–240 (colorless) | 30 | EtOH | $C_{28}H_{22}N_5O_3$ (476) | 70.59/70.53 | 4.62/4.68 | 14.71/14.70 | |
| **13a** | 149–150 (yellow) | 80 | EtOH | $C_{27}H_{20}N_5O_2S$ (464) | 69.83/69.78 | 4.31/4.30 | 12.07/12.04 | 6.90/6.68 |
| **13b** | 140–142 (yellow) | 65 | EtOH | $C_{28}H_{22}N_5O_3S$ | 64.99/64.95 | 3.81/3.80 | 11.23/11.15 | 6.42/6.25 |
| **13c** | 145–146 (yellow) | 75 | EtOH | $C_{28}H_{22}N_5O_3S$ (494) | 68.02/68.10 | 4.45/4.40 | 11.34/11.31 | 6.48/6.64 |
| **14a** | 250–251 (colorless) | 30 | EtOH | $C_{27}H_{20}N_5OS$ (462) | 70.13/70.08 | 4.33/4.25 | 15.15/15.10 | 6.93/6.75 |
| **14b** | 239–241 (colorless) | 25 | EtOH | $C_{27}H_{19}ClN_5OS$ (496.5) | 65.26/65.20 | 3.83/3.81 | 14.09/14.12 | 6.45/6.21 |
| **14c** | 244–246 (colorless) | 35 | EtOH | $C_{28}H_{22}N_5O_2S$ (492) | 68.29/68.20 | 4.47/4.40 | 14.23/14.15 | 6.50/6.80 |

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.

*4.4.2. Plaque reduction assay*

A 6-well plate was cultivated with Vero cell culture ($10^5$ cell/ml) and incubated for 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 virus compound mixture was inoculated (100 μl/well). After 1 h contact time, the inoculum was aspirated and 3 ml of MEM with 1% agarose 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 in 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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