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Synthesis and anti-myxovirus activity of some novel *N,N'*-disubstituted thioureas

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Summary — A series of new *N,N'*-disubstituted thioureas were prepared and evaluated *in vitro* for their activity against myxoviruses. Compound *N*-[4-(3-propoxy-1*H*-1,2,4-triazol-1-yl)phenyl]-*N'*-(2-pyrazinyl)thiourea **5d** exhibited specific activity against respiratory syncytial virus in HeLa cells. Compounds *N*-(1-adamantanyl)-*N'*-[4-(3-ethoxy-1*H*-1,2,4-triazol-1-yl)phenyl]thiourea **5g** and *N*-(1-adamantanyl)-*N'*-[4-(3-propoxy-1*H*-1,2,4-triazol-1-yl)phenyl]thiourea **5h** proved active against influenza A in Madin–Darby canine kidney (MDCK) cells and respiratory syncytial virus in HeLa cells.

antiviral agents / respiratory syncytial virus / influenza A virus / *N,N'*-disubstituted thioureas

Introduction

N,N'-Disubstituted thioureas were reported to show antiviral activity both *in vitro* and *in vivo* [1–4]. Structure–activity analysis of several thioureas revealed that the presence of an intact NH-(C=S)-NH group is essential for the antiviral effect [5]. Furthermore, several 1*H*-1,2,4-triazole derivatives have also been reported to possess antiviral activity [6–10].

Following these observations we have designed and synthesised a series of *N,N'*-disubstituted thioureas where *N* is substituted by the 3-alkoxy-1-phenyl-1*H*-1,2,4-triazole moiety while *N'* bears a number of different substituents, *ie* aryl-, heteroaryl-, adamantanyl- or β-1-D-glucopyranosyl moieties.

These derivatives were evaluated *in vitro* for their activity against various myxoviruses (influenza A and B and respiratory syncytial virus).

Chemistry

The synthetic pathway followed for the preparation of the thioureas (**5a–l**, tables I, II) is represented in scheme 1. 3-Hydroxy-1-(4-nitrophenyl)-1*H*-1,2,4-triazole **1**, which was obtained by the cyclisation of 4-nitrophenylsemicarbazide [11] with 85% HCOOH and concentrated H_2SO_4 at 100°C [12], reacted with the appropriate alkylbromide in the presence of NaH in DMF at 65°C to afford the intermediate 3-alkoxy-1-(4-nitrophenyl)-1*H*-1,2,4-triazoles **2a**, **b**. Catalytic hydrogenation [13] of the latter with Pd/C in anhydrous ethanol resulted in the corresponding amines **3a,b**. The amines were converted *via* the modified Kaluza synthesis [14] to their isothiocyanates **4a**, **b**, by treatment with carbon disulfide and ethyl chloroformate successively. The isothiocyanates were refluxed with the appropriate amines in acetone for 4–5 h to afford the requisite thioureas **5a–h** [15]. Derivatives **5i, j** were obtained by reaction of the 2,3,4,6-tetra-*O*-acetyl-β-1-D-glucopyranosyl isothiocyanate with the amines **3a**, **b**, as previously described for derivatives **5a–h** [15]. Treatment of the intermediate esters **5i, j** with methanolic ammonia at room temperature afforded the desired thioureas **5k, l**.

In the ^{1}H-NMR spectra of the compounds **5a–h** the NH protons appear as singlets which disappear upon addition of D_2O. As for the compounds **5i–l**, the proton of the NH attached to the sugar moiety appears as a doublet and couples with the H-1' sugar proton which appears as multiplet. Upon addition of D_2O the NH signal dissapears while the H-1' becomes a doublet (J = 9 Hz).

Results and discussion

The results of the antiviral activity assays are presented in table III. Cytotoxicity for uninfected host cells

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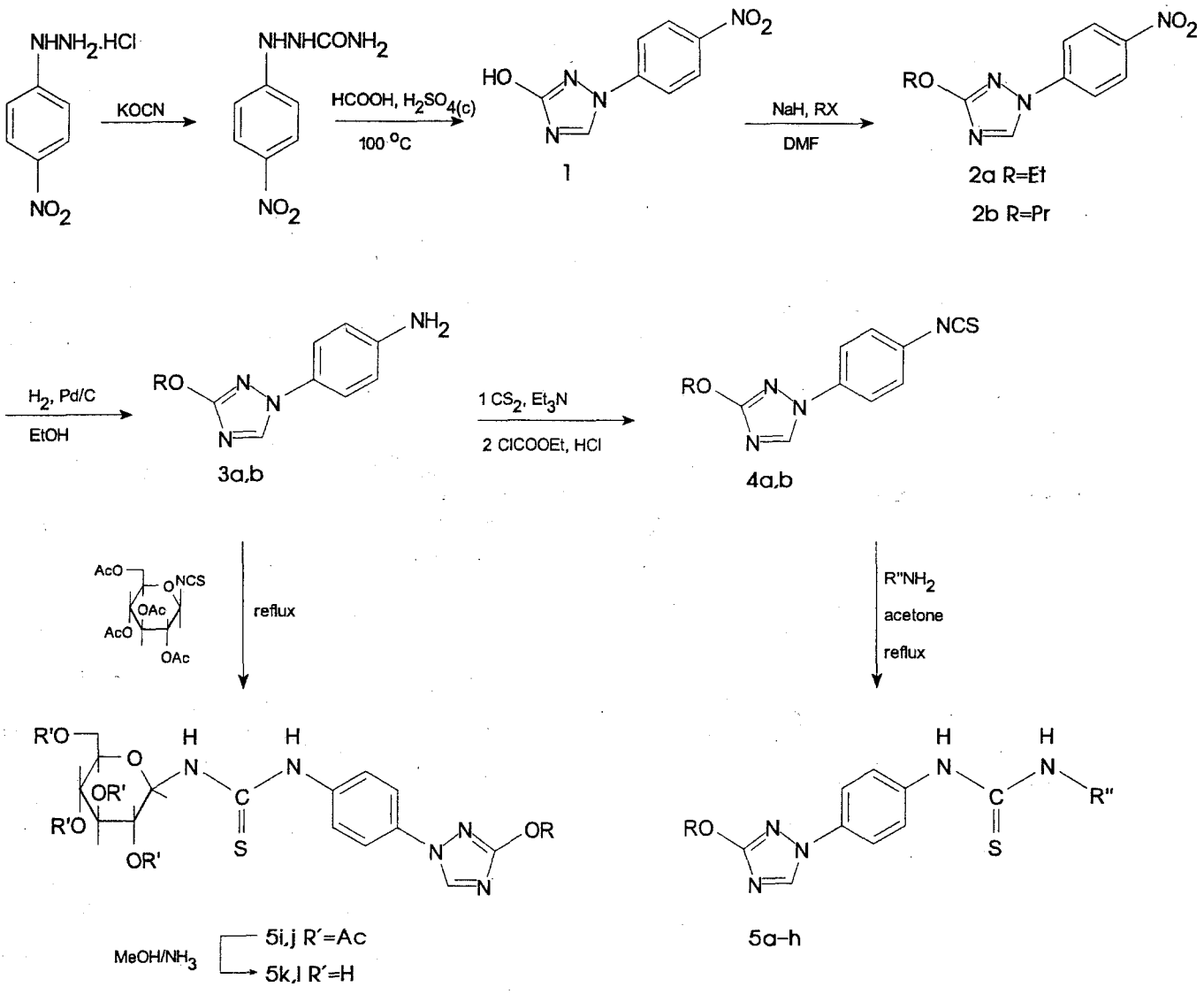
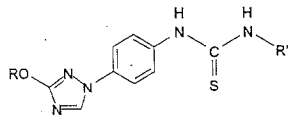


Scheme 1.

was determined under the same conditions as antiviral activity, *ie* microscopic evaluation of cell morphology of confluent cell monolayers which had or had not been inoculated with virus. The criterion of specific antiviral activity was taken as the inhibition of virus-induced cytopathicity at a concentration that was at least 5-fold lower than the concentration required to alter the morphology of uninfected host cells. According to this criterion, the activity noted for the adamantane derivatives **5g, 5h** against the influenza A virus (in MDCK cells) and for respiratory syncytial virus (in HeLa cells) and for the pyrazine derivative **5d** against the respiratory syncytial virus (in HeLa cells) could be considered as indicative of antiviral specificity. These compounds may be considered as lead compounds for the development of anti-myxovirus agents that are active against the influenza A virus and the respiratory syncytial virus.

Table I. Thioureas **5a–l**.



No.	R	R''	mp (°C)	Yield (%)	Formula
5a	C_2H_5		177-178[a]	70	$C_{17}H_{17}N_5O_2S$
5b	C_3H_7		178-180[a]	73	$C_{18}H_{19}N_5O_2S$
5c	C_2H_5		195-197[a]	65	$C_{15}H_{15}N_7OS$
5d	C_3H_7		182-184[a]	65	$C_{16}H_{17}N_7OS$
5e	C_2H_5		117-119[a]	65	$C_{15}H_{15}N_7OS$
5f	C_3H_7		199-200[a]	60	$C_{16}H_{17}N_7OS$
5g	C_2H_5		191-192[b]	75	$C_{21}H_{27}N_5OS$
5h	C_3H_7		142-144[b]	70	$C_{22}H_{29}N_5OS$
5i	C_2H_5		178-179[c]	90	$C_{25}H_{31}N_5O_{10}S$
5j	C_3H_7		173-175[c]	90	$C_{26}H_{33}N_5O_{10}S$
5k	C_2H_5		189-191[d]	90	$C_{17}H_{23}N_5O_6S$
5l	C_3H_7		194-196[d]	90	$C_{18}H_{25}N_5O_6S$

[a]Methanol; [b]acetone; [c]ether ethyl acetate; [d]ethanol.

Experimental protocols

Chemical synthesis

Melting points were determined using a Buchi capillary apparatus and are uncorrected. Microanalyses were performed by Service Central de Microanalyse (CNRS) France and the results obtained were within ±0.4% of the theoretical values. Fourier transform proton magnetic resonance (^{1}H-NMR) spectra were recorded on a Bruker AC 200 MHz spectrometer in deuterated dimethylsulfoxide (DMSO–d_6) and chloroform ($CDCl_3$) and are reported in δ units relative to tetramethylsilane (TMS) as internal standard.

4-Nitrophenylsemicarbazide
Aqueous solutions of 4-nitrophenylhydrazine hydrochloride (19 g, 0.1 mol) and potassium cyanate (8.1 g, 0.1 mol) were mixed together under cooling and continuous stirring. The precipitated 4-nitrophenylsemicarbazide was filtered, washed with water and used for the next step without further purification. Yield 18.6 g (95%); mp: 210–212°C (ref [11] mp 211–212°C).

3-Hydroxy-1-(4-nitrophenyl)-1H-1,2,4-triazole ***1***
A mixture of 4-nitrophenylsemicarbazide (19.6 g, 0.1 mol), 85% HCOOH (13.5 g) and concentrated H_2SO_4 (2.5 g) was heated at 95–100°C for 6 h. After cooling the mixture was diluted with water and the precipitated solid was filtered and washed with water. Yield 19.6 g (95%); mp: >250°C (acetonitrile) [12].

3-Alkoxy-1-(4-nitrophenyl)-1H-1,2,4-triazole ***2a,b***
Sodium hydride (0.33g, 0.011 mol) in 80% suspension in oil was added to a suspension of **1** (2.1 g, 0.01 mol) in anhydrous DMF (40 ml) and the mixture was stirred at room temperature for 20 min. The appropriate alkylbromide (0.02 mol) was added and stirring was continued at 65°C for 8 h. After cooling the mixture was diluted with water and the precipitated solid was filtered and recrystallised from aqueous ethanol.

3-Ethoxy-1-(4-nitrophenyl)-1H-1,2,4-triazole ***2a.*** Yield 1.5 g (65%); mp: 170–172°C (acetonitrile). Anal $C_{10}H_{10}N_4O_3$ (C, H, N). ^{1}H-NMR (200 MHz) $CDCl_3$ δ: 1.35 (t, 3H, OCH_2CH_3, J = 7 Hz), 4.30 (q, 2H, OCH_2CH_3, J = 7 Hz), 7.70–7.87 (m, 2H, ArH), 8.35–8.50 (m, 3H, ArH + triazole H).

1-(4-Nitrophenyl)-3-propoxy-1H-1,2,4-triazole ***2b.*** Yield 1.6 g (65%); mp: 110–112°C (ethanol). Anal $C_{11}H_{12}N_4O_3$ (C, H, N). ^{1}H-NMR (200 MHz) $CDCl_3$ δ: 1.00 (t, 3H, $OCH_2CH_2CH_3$, J = 7.3 Hz), 1.75–1.95 (m, 2H, $OCH_2CH_2CH_3$), 4.32 (t, 2H, $OCH_2CH_2CH_3$, J = 6.6 Hz), 7.75–7.85 (m, 2H, ArH), 8.30–8.45 (m, 3H, ArH + triazole H).

3-Alkoxy-1-(4-aminophenyl)-1H-1,2,4-triazoles ***3a,b***
Compounds **3a,b** were prepared by catalytic hydrogenation of **2a,b** respectively with Pd/C in anhydrous EtOH at 25°C/1 atm for 6 h in quantitative yield. The amines were converted to their hydrochlorides.

1-(4-Aminophenyl)-3-ethoxy-1H-1,2,4-triazole hydrochloride ***3a.*** mp: 248–250°C (ethanol-ether). Anal $C_{10}H_{13}ClN_4O$ (C, H, N). IR (cm^{-1}, KBr) νNH 3460–3315, νC-N 1328. ^{1}H-NMR (200 MHz) DMSO–d_6 δ: 1.35 (t, 3H, OCH_2CH_3, J = 7 Hz), 3.80–4.15 (m, 3H, NH_3^+), 4.30 (q, 2H, OCH_2CH_3, J = 7 Hz), 7.37-7.60 (m, 2H, ArH), 7.77–7.93 (m, 2H, ArH), 8.97 (s, 1H, triazole H).

1-(4-Aminophenyl)-3-propoxy-1H-1,2,4-triazole hydrochloride ***3b.*** mp: 185–187°C (ethanol-ether). Anal $C_{11}H_{15}ClN_4O$ (C, H, N). IR (cm^{-1}, KBr) νNH 3470–3300, νC-N 1330. ^{1}H-NMR (200 MHz) DMSO–d_6 δ: 1.00 (t, 3H, $OCH_2CH_2CH_3$, J = 7.3 Hz), 1.65–1.85 (m, 2H, $OCH_2CH_2CH_3$), 3.80–4.15 (m, 3H, NH_3^+), 4.20 (t, 2H, $OCH_2CH_2CH_3$, J = 6.6 Hz), 7.35–7.62 (m, 2H, ArH), 7.75–7.95 (m, 2H, ArH), 8.95 (s, 1H, triazoles H).

4-(3-Alkoxy-1H-1,2,4-triazol-1-yl)phenyl isothiocyanates ***4a,b***
The appropriate amine (0.1 mol) was dissolved in benzene (20 ml) and reacted with carbon disulfide (6.6 ml, 0.1 mol) and triethylamine (14 ml, 0.1 mol) at 0°C. The precipitated triethylammonium dithiocarbamate salt was filtered, washed with anhydrous ether and dissolved in chloroform (100 ml) which contained triethylamine (14 ml, 0.1 mol). Ethyl chloroformate (10.2 ml, 0.1 mol) was added dropwise at 0°C over a period of 15–20 min and stirring was continued for 1 h at room temperature. The chloroform solution was washed once with 3 M HCl and twice with water, dried over Na_2SO_4 and evaporated *in vacuo* to afford the desired isothiocyanate.

Table II. ^{1}H-NMR spectral data of thioureas **5a–l**.

No	*^{1}H-NMR*[a,b]
5a	1.35 (t, 3H, OCH_2CH_3, J = 7), 4.35 (q, 2H, OCH_2CH_3, J = 7), 6.50–7.18 (m, 4H, ArH), 7.55–7.78 (m, 4H, ArH), 8.95 (s, 1H, triazole H), 9.50 (s, 1H, OH), 9.85 (s, 2H, NH)
5b	1.25 (t, 3H, $OCH_2CH_2CH_3$, J = 7.3), 1.65–1.85 (m, 2H, $OCH_2CH_2CH_3$), 4.20 (t, 2H, $OCH_2CH_2CH_3$, J = 6.6), 6.45–7.15 (m, 4H, ArH), 7.55–7.78 (m, 4H, ArH), 8.95 (s, 1H, triazole H), 9.48 (s, 1H, OH), 9.83 (s, 2H, NH)
5c	1.35 (t, 3H, OCH_2CH_3, J = 7), 4.30 (q, 2H, OCH_2CH_3, J = 7), 7.70–7.90 (m, 4H, ArH), 8.25–8.40 (m, 2H, pyrazine H), 8.60–8.68 (m, 1H, pyrazine H), 9.00 (s, 1H, triazole H), 11.30 (s, 1H, NH), 12.90 (s, 1H, NH)
5d	1.00 (t, 3H, $OCH_2CH_2CH_3$, J = 7.3), 1.70–1.90 (m, 2H, $OCH_2CH_2CH_3$), 4.25 (t, 2H, $OCH_2CH_2CH_3$, J = 6.6), 7.70–7.90 (m, 4H, ArH), 8.30–8.40 (m, 2H, pyrazine H), 8.68–8.72 (m, 1H, pyrazine H), 9.00 (s, 1H, triazole H), 11.30 (s, 1H, NH), 12.95 (s, 1H, NH)
5e	1.35 (t, 3H, OCH_2CH_3, J = 7), 4.30 (q, 2H, OCH_2CH_3, J = 7), 7.25 (m, 1H, pyrimidine H), 7.75–7.90 (m, 4H, ArH), 8.73 (m, 2H, pyrimidine H), 9.01 (s, 1H, triazole H), 9.85 (s, 1H, NH), 11.20 (s, 1H, NH)
5f	1.00 (t, 3H, $OCH_2CH_2CH_3$, J = 7.3), 1.68–1.88 (m, 2H, $OCH_2CH_2CH_3$), 4.25 (t, 2H, $OCH_2CH_2CH_3$, J = 6.6), 7.25 (m, 1H, pyrimidine H), 7.75–7.90 (m, 4H, ArH), 8.73 (m, 2H, pyrimidine H), 9.01 (s, 1H, triazole H), 9.80 (s, 1H, NH), 11.25 (s, 1H, NH)
5g	1.35 (t, 3H, OCH_2CH_3, J = 7), 1.55–2.28 (m, 15H, adamantane H), 4.30 (q, 2H, OCH_2CH_3, J = 7), 7.40 (s, 1H, NH), 7.58–7.72 (m, 4H, ArH), 8.95 (s, 1H, triazole H), 9.45 (s, 1H, NH)
5h	1.00 (t, 3H, $OCH_2CH_2CH_3$, J = 7.3), 1.55–2.30 (m, 17H, adamantane H + $OCH_2CH_2CH_3$), 4.20 (t, 2H, $OCH_2CH_2CH_3$, J = 6.6), 7.40 (s, 1H, NH), 7.55-7.72 (m, 4H, ArH), 9.02 (s, 1H, triazole H), 9.48 (s, 1H, NH)
5i	1.33 (t, 3H, OCH_2CH_3, J = 7), 1.92, 1.94, 2.00, 2.05 (4s, 12H, 4 x $COCH_3$), 3.90–4.40 (m, 5H, H-5' + H-6'$_{ab}$ + OCH_2CH_3), 4.86–5.10 (m, 2H, H-4' + H-2'), 5.36 (t, 1H, H-3', J = 9), 5.78-6.00 (m, 1H, H-1'), 7.60 (d, 2H, ArH, J = 8.5), 7.70 (d, 2H, ArH, J = 8.5), 8.35 (d, 1H, NH, J = 9), 8.95 (s, 1H, triazole H), 10.02 (s, 1H, NH)
5j[c]	1.00 (t, 3H, $OCH_2CH_2CH_3$, J = 7.3), 1.70–1.90 (m, 2H, $OCH_2CH_2CH_3$), 1.95, 1.98, 2.03, 2.08 (4s, 12H, 4 x $COCH_3$), 3.80–4.40 (m, 5H, H-5' + H-6'$_{a,b}$ + $OCH_2CH_2CH_3$), 4.85–5.15 (m, 2H, H-4', H-2'), 5.35 (t, 1H, H-3', J = 9), 5.75–5.90 (m, 1H, H-1'), 6.91 (d, 1H, NH, J = 9), 7.40 (d, 2H, ArH, J = 8.5), 7.66 (d, 2H, ArH, J = 8.5), 8.30 (s, 1H, triazole H), 8.52 (s, 1H, NH)
5k	1.25 (t, 3H, OCH_2CH_3, J = 7), 3.00–3.80 (m, 6H, H-2', H-3', H-4', H-5', H-6'$_{ab}$), 4.23 (q, 2H, OCH_2CH_3, J = 7), 4.36–4.55 (m, 1H, OH), 4.60–4.80 (m, 1H, H-1'), 4.80–5.11 (m, 1H, OH); 5.30 (d, 1H, OH, J = 7.2), 5.55 (d, 1H, OH, J = 7.2), 7.40–7.70 (m, 4H, ArH), 8.15–8.30 (m, 1H, NH), 8.80 (s, 1H, triazole H), 9.80 (s, 1H, NH)
5l	1.00 (t, 3H, $OCH_2CH_2CH_3$, J = 7.3), 1.65–1.85 (m, 2H, $OCH_2CH_2CH_3$), 3.05–3.85 (m, 6H, H-2', H-3', H-4', H-5', H-6'$_{ab}$), 4.20 (q, 2H, $OCH_2CH_2CH_3$, J = 6.6), 4.45–4.65 (m, 1H, OH), 4.67–4.90 (m, 1H, H-1'), 5.05–5.18 (m, 1H, OH), 5.35 (d, 1H, OH, J = 7.2), 5.62 (d, 1H, OH, J = 7.2), 7.51–7.80 (m, 4H, ArH), 8.20–8.35 (m, 1H, NH), 8.80 (s, 1H, triazole), 9.85 (s, 1H, NH)

[a]In DMSO–d_6; [b]J values quoted in Hz, chemical shifts in δ units relative to TMS internal standard; [c]in $CDCl_3$.

4-(3-Ethoxy-1H-1,2,4-triazol-1-yl)phenyl isothiocyanate ***4a***.
Yield 18.7 g (76%); mp: 117–118°C (benzene/petroleum ether). Anal $C_{11}H_{10}N_4OS$ (C, H, N). IR (cm^{-1}, KBr) νN=C=S 2054–2000. ^{1}H-NMR (200 MHz) DMSO–d_6 δ: 1.30 (t, 3H, OCH_2CH_3, J = 7 Hz), 4.30 (q, 2H, OCH_2CH_3, J = 7 Hz), 7.60 (d, 2H, ArH, J = 7.9 Hz), 7.85 (d, 2H, ArH, J = 7.9 Hz), 9.05 (s, 1H, triazole H).

4-(3-Propoxy-1H-1,2,4-triazol-1-yl)phenyl isothiocyanate ***4b***.
Yield 20.8 g (80%); mp: 128–130°C (benzene/petroleum ether). Anal $C_{12}H_{12}N_4OS$ (C, H, N). IR (cm^{-1}, KBr) νN=C=S 2040–2000. ^{1}H-NMR (200 MHz) DMSO–d_6 δ: (t, 3H, $OCH_2CH_2CH_3$, J = 7.3 Hz), 1.65–1.85 (m, 2H, $OCH_2CH_2CH_3$), 4.20 (t, 2H, $OCH_2CH_2CH_3$, J = 6.6 Hz), 7.60 (d, 2H, ArH, J = 7.9 Hz), 7.85 (d, 2H, ArH, J = 7.9 Hz), 9.05 (s, 1H, triazole H).

N,N'-Disubstituted thioureas ***5a–h***
A solution of the appropriate isothiocyanate (0.085 mol) in anhydrous acetone (100 ml) was added dropwise to a solution of the appropriate amine (0.085 mol) in anhydrous acetone (100 ml). The resulting mixture was refluxed for 4–5 h and the solvent was evaporated *in vacuo* to give the crude thioureas **5a–j**, which were purified by recrystallisation from the solvents indicated in table I.

N-(2,3,4,6-Tetra-O-acetyl-β-1-D-glucopyranosyl)-N'-[4-(3-alkoxy-1H-1,2,4-triazol-1-yl)phenyl]thioureas ***5i,j***
(2,3,4,6-Tetra-O-acetyl-β-1-D-glucopyranosyl) isothiocyanate was reacted with the appropriate amine (**3a** or **3b**) as described above (see tables I and II).

N-(β-1-D-Glucopyranosyl)-N-[4-(3-alkoxy-1H-1,2,4-triazol-1-yl)phenyl] thioureas ***5k,l***
A solution of **5i,j** (0.01 mol) in methanol (135 ml) saturated at

Table III. Antiviral activity and cytotoxicity of compounds **5a–h**, **5k** and **5l**.

Compounds	*IC_{50} (μg/ml)*[a]						*MTC (μg/ml)*[b]			
	Influenza virus A (Ishikawa strain) MDCK		*Influenza virus B (Singapore strain) MDCK*		*Respiratory syncytial virus (Long strain) HeLa*		*MDCK (Madin–Darby canine kidney) 5 d*		*HeLa 5 d*	
	Exp 1	*Exp 2*	*Exp 1*	*Exp 2*	*Exp 1*	*Exp 2*	*Exp 1*	*Exp 2*	*Exp 1*	*Exp 2*
5a	100	100	> 200	> 200	8.0	20	> 200	> 200	40	40
5b	> 100	> 100	> 100	> 100	40	20	100	100	100	100
5c	> 20	> 20	> 20	> 20	8.0	8.0	20	20	20	20
5d	≥ 100	≥100	> 100	> 100	4.0	8.0	100	100	100	100
5e	> 8.0	> 4.0	> 8.0	> 8.0	> 4.0	> 4.0	8.0	4.0	40	20
5f	40	40	> 100	> 100	20	20	100	100	40	20
5g	20	8.0	> 200	> 200	8.0	20	> 200	> 200	200	200
5h	20	20	> 100	> 100	1.6	4.0	100	100	20	100
5k	> 200	> 200	> 200	> 200	40	100	> 200	> 200	100	100
5l	> 200	> 200	> 200	> 200	100	100	> 200	> 200	> 200	≥ 200

[a]50% inhibitory concentration, or concentration required to reduce virus-induced cytopathicity by 50%; virus-induced cytopathicity was recorded when it reached its maximum in the control uninfected cell cultures; [b]MTC: minimum toxic concentration, or concentration required to cause a microscopically detectable alteration of normal cell morphology.

0°C with ammonia was set aside at room temperature for 24 h. The solvent was removed *in vacuo* and the residue was recrystallised from ethanol (see tables I and II).

Biological evaluation

Antiviral activity assays

The procedures for measuring anti-myxovirus activity have been described previously [16]. Briefly, confluent cell cultures (Madin–Darby canine kidney MDCK) or HeLa cells were seeded in microtiter trays. MDCK cells were inoculated with influenza A virus (Ishikawa/7/82(H_3H_2) strain) or influenza B (Singapore/222/79 strain) and HeLa cells were inoculated with respiratory syncytial virus (Long strain) at a multiplicity of 20 $CCID_{50}$ (50% cell culture infective doses) per well in the presence of various concentrations of the test compounds. After 5 d incubation, virus-induced cytopathicity was recorded. The concentration of compound required to inhibit the appearance of virus-induced cytopathicity by 50% was determined as the 50% inhibitory concentration (IC_{50}). Cytotoxicity of the test compounds was based on a microscopically detectable alteration of normal cell morphology, as described previously [17].

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