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New Acylated 1,2,4-Triazoles as Antiviral Agents

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The syntheses and antiviral properties of the new acylated 1,2,4-triazole derivatives **4** are described. In cell culture experiments 6 out of 99 compounds specifically inhibit rubella virus replication to a high degree. Structure-activity relationships are discussed.

Neue acylierte 1,2,4-Triazole als antivirale Wirkstoffe

Die Synthese und die antivirale Aktivität einiger neuer acylierten 1,2,4-Triazole **4** wird beschrieben. In Zell-Kulturen erwiesen sich 6 von 99 Verbindungen als hoch wirksam und spezifisch gegen das Rubella Virus. Struktur-Aktivitäts-Beziehungen werden diskutiert.

Antiviral chemotherapy must be directed to the development of compounds with activity against virus replication without affecting any cellular metabolic processes.

The most valuable compounds specifically inhibit virus multiplication; 9-(2-hydroxyethoxymethyl)guanine and (*E*)-5-(2-bromovinyl)-deoxyuridine have been reported as exhibiting highly selective antiviral activity against the growth of herpes simplex virus[1–4].

Till the present time there have been only few papers about the triazole derivatives posessing antiviral activity. Thus 3-mercapto-5-(4-pyridyl)-4*H*-1,2,4-triazole is active orally against neurovaccinia in mice[5]. Other 1,2,4-triazole derivatives weakly inhibit the multiplication of ranikhet disease virus in a stationary culture of chorioallantoic membranes of chick embryo[6]. Triazolotriazino[5,6-*b*]indole derivatives show some activity against herpes simplex virus[7]. 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide is a nucleoside which inhibits some of the DNA- and RNA-virus replications[8,9].

The present study reports the synthesis of new acylated 1,2,4-triazoles with a selective antiviral activity against the rubella virus infected cell[10]. The synthetic procedure followed the route below.

The known reaction of N-cyano-carbonimidodithioic acid dialkyl esters **1** with hydrazine offered a good possibility to get large variable starting materials[11–14], 3-alkylthio-5-amino-1*H*-1,2,4-triazoles **2** in a simple way.

2 can be acylated in an organic aprotic solvent, e. g. dioxane in the presence of an organic base, e. g. pyridine at room temperature, to the 1-benzoylated triazoles **3**.

3 can be submitted to a thermal rearrangement either in an organic inert solvent, e. g. sulfolane, dimethylformamide, dimethylsulfoxide or without solvent at a temperature of

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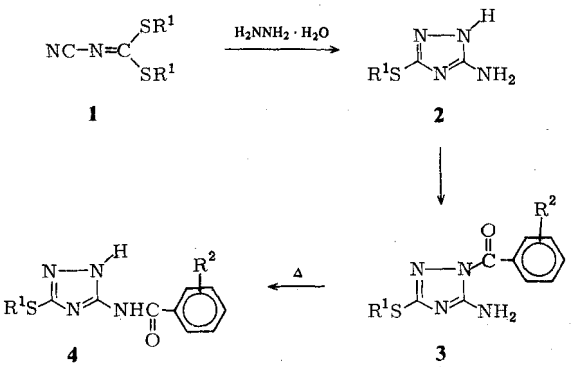
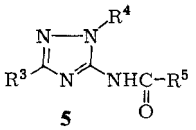


200–250 °C[15–17]. The spectroscopic features of the compounds **3** and **4** will be published later in detail[18].

To extend the SAR studies it became of interest to synthesize a few compounds of analogous structure **5** but with different substituents on the triazole ring:



R^3 = H, alkylthio, subst. amino, R^1SO_n (n = 1,2)
R^4 = H, alkyl, phenyl
R^5 = alkyl, subst. benzyl, phenoxymethyl, ethoxycarbonyl, tetrahydrophenyl, cyclohexyl, cyclohexenyl

Assay of antiviral activity

RK 13, HeLa and Hep-2 cell lines were used to measure the virus-specific cytopathic effects of rubella virus (Judith strain), herpes simplex virus (type 1) and adenovirus (type 5) strains, respectively. The rolling drum type of the minced chorioallantoic membrane suspension method was used for influenza virus titration[19].

Cultures containing multiplying cells were used to measure the cytotoxicity (CT) of compounds. The 50 (CT_{50}) and 0 (CT_0) per cent cytotoxicities of compounds were determined graphically[20]. The technique for measuring specific antiviral activity of compounds is described in detail elsewhere[21].

Measurement of the antiviral activity of compounds

The above mentioned cell lines and virus strains were used to measure the antiviral effects of the compounds synthesized. In cell culture experiments the CT_0 concentrations of the compounds were

Tab. 1: *Chemical and virological data of the compounds* **3** *and* **4**

Compound 3 and 4	R^1	R^2	Mp. °C 3	Mp. °C 4	Molecular formula (Mol. w.)	CT_0 log μM to RK 13 for 4	D for 4
a	Me	H	150–152	229–231	$C_{10}H_{10}N_4OS$(234,3)		0
b	Me	2-F	157–159	207–209	$C_{10}H_9FN_4OS$(252,3)		0
c	Me	2-Cl	164–166	214–215	$C_{10}H_9ClN_4OS$(268,7)	1.77	⩾5.3
d	Me	3-Cl	157–158	229–230			0
e	Me	4-Cl	175–177	264–266			0
f	Bu	2-Cl	111–112	148–150	$C_{13}H_{15}ClN_4OS$(310,8)		0
g	Bz	2-Cl	147–149	196–197	$C_{16}H_{13}ClN_4OS$(344,8)		0
h	4-NO_2-Bz	2-Cl	168–170	266–269	$C_{16}H_{12}ClN_5O_3S$(389,8)		0
i	Me	2-Br	164–166	204–206	$C_{10}H_9BrN_4OS$(313,2)	1.91	⩾6.9
j	Me	4-Br	180–182	268–270			0
k	Me	2-I	160–161	201–204	$C_{10}H_9IN_4OS$(360,2)		0
l	Me	4-I	187–189	290–293			0
m	Me	2-Me	154–156	208–209	$C_{11}H_{12}N_4OS$(248,3)	1.71	⩾6.8
n	Me	3-Me	155–157	193–195			0
o	Me	4-Me	186–188	263–265			0
p	Me	3-CF_3	157–158	230–231	$C_{11}H_9F_3N_4OS$(302,3)		0
q	Me	2-MeO	145–148	206–208	$C_{11}H_{12}N_4O_2S$(262,3)		0
r	Me	2-NO_2	226–229	259–262	$C_{10}H_9N_5O_3S$(279,2)	1.75	3.0
s	Me	4-NO_2	220–221	283–285			0
t	Me	2-MeS	175–178	248–250	$C_{11}H_{12}N_4OS_2$(280,3)	1.75	⩾5.8
u	Et	2-Me	87– 90	156–158	$C_{12}H_{14}N_4OS$(262,3)	1.48	⩾6.0
v	Me	2,4-Cl_2	181–182	227–229	$C_{10}H_8Cl_2N_4OS$(303,2)		0
x	Me	2,5-Cl_2	175–177	252–254			0
y	Me	2,6-Cl_2	201–203	269–271			0

CT_0: 0 % reduction in cell growth
D: decrease in the virus infectivity titer at CT_0 compared to the control level in log units

Tab. 2: *Chemical data of the compounds* **5***

Compound 5	R^3	R^5	MP °C	Molecular formula (Mol.w.)
a	H	2-Cl–C_6H_4	273–275	$C_9H_7ClN_4O$(222,6)
b	MeS	Et	236–239	$C_6H_{10}N_4OS$(186,2)
c	MeS	Pr^i	200–202	$C_7H_{12}N_4OS$(200,2)
d	MeS	CO_2Et	181–183	$C_7H_{10}N_4O_3S$(230,2)
e	MeS	$CH_2OC_6H_5$	171–174	$C_{11}H_{12}N_4O_2S$(264,3)
f	MeS	C_6H_{11}	216–218	$C_{10}H_{16}N_4OS$(240,3)
g	NH_2	2-Cl–C_6H_4	294–297	$C_9H_8ClN_5O$(237,7)
h		2-Cl–C_6H_4	203–205	$C_{14}H_{16}ClN_5O$(305,7)
i		2-Cl–C_6H_4	214–216	$C_{13}H_{14}ClN_5O_2$(307,7)
j	MeSO	2-Me–C_6H_4	148–150	$C_{11}H_{12}N_4OS$(248,3)
k	$MeSO_2$	2-Me–C_6H_4	198–200	$C_{11}H_{12}N_4O_2S$(264,3)
l	MeSO	2-Cl–C_6H_4	194–195	$C_{10}H_9ClN_4O_2S$(300,7)

* In all cases R^4 = H

routinely used to determine the "D" value, which is the decrease in virus infectivity titer in the presence of the compounds compared with the control level in log units[21].

None of the newly synthesized compounds show antiviral activity against herpes simplex, adeno- and influenza virus replications. Table 1 demonstrates that some of the compounds **(4c, i, m, r, t** and **u)** inhibit the multiplication of rubella virus with 3–6,8 log units.

Results

On the basis of the antiviral data the most important structure-activity relationships are:

1. Influence of R^1: C_1-C_3-alkyl substitution of **4** is necessary for the antiviral activity; molecules with longer than C_4-alkyl or benzyl side chain were inactive.

2. Influence of R^2: one substituent in the ortho-position is necessary; the most active compounds have methyl, chloro, bromo or methylthio substituents, but *only* in the 2-position. Other substitution (methoxy, alkoxycarbonyl) or more than one substituent on the phenyl ring lead to the loss of the antiviral activity.

3. Ring N^1-substitution, either by an acyl group **(3)** or an alkyl or one phenyl **(5)** resulted in inactive compounds.

4. Compounds with a subst. amino, sulfone or sulfoxide group in the position-3 are inactive compounds.

The antiviral effects of the active compounds will be published in detail elsewhere[22].

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Experimental Part

MP: Boetius apparatus, uncorr. *Analyses*: (C, H, N, S and halogen) were within ± 0.4 % of the theoretical values.

General procedure for the preparation of **3** *and* **5**

A solution of 0.1 mole subst. benzoylchloride in 25 ml dioxane is added dropwise during 30 min to a mixture of 0.09 mole of 3-alkylthio-5-amino-1*H*-1,2,4-triazole[23], 0.15 mole of pyridine and 75 ml dioxane at constant stirring and temp. of 0 to 5 °C. The reaction mixture is stirred for 30 min at this temp., then for 4 h at room temp. and is finally poured into 300 ml water. The precipitate formed is washed with water and dried. Yield: 85–95 %.

General procedure for the preparation of **4**

A mixture of 2 g of 1-substituted benzoyl-3-alkylthio-5-amino-1,2,4-triazole in 15 ml sulfolane – or without solvent – is heated for 60–90 min to 220–250 °C, then poured into 50 ml water, filtered, washed and refluxed with ethanol. Yield: 90–95 %.

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Polycarbonylmethyl-Derivate: Reaktionen von 2-(3-Methyl-5-isoxazolyl)-1-phenylethanon

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