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New acetamide derivatives containing (ω-*p*-bromophenoxyalkyl)uracil moiety and their anticytomegalovirus activity

Maria P. Paramonova,[a] Robert Snoeck,[b] Graciela Andrei,[b] Anastasia L. Khandazhinskaya*[c] and Mikhail S. Novikov[a]

[a] *Department of Pharmaceutical & Toxicological Chemistry, Volgograd State Medical University, 400131 Volgograd, Russian Federation*
[b] *Rega Institute for Medical Research, KU Leuven, B-3000 Leuven, Belgium*
[c] *V. A. Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 1405; e-mail: khandazhinskaya@bk.ru*

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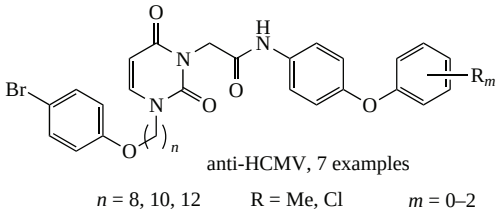
New *N*-aryl-2-{3-[ω-(4-bromophenoxy)alkyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl}acetamides have been obtained from 1-[ω-(4-bromophenoxy)alkyl]uracil and 2-chloro-*N*-(4-phenoxyphenyl)acetamide derivatives. Investigation of their antiviral properties against human cytomegalovirus revealed that the representative with dodecane-1,12-diyl linker exhibited powerful virus inhibitory activity *in vitro*.

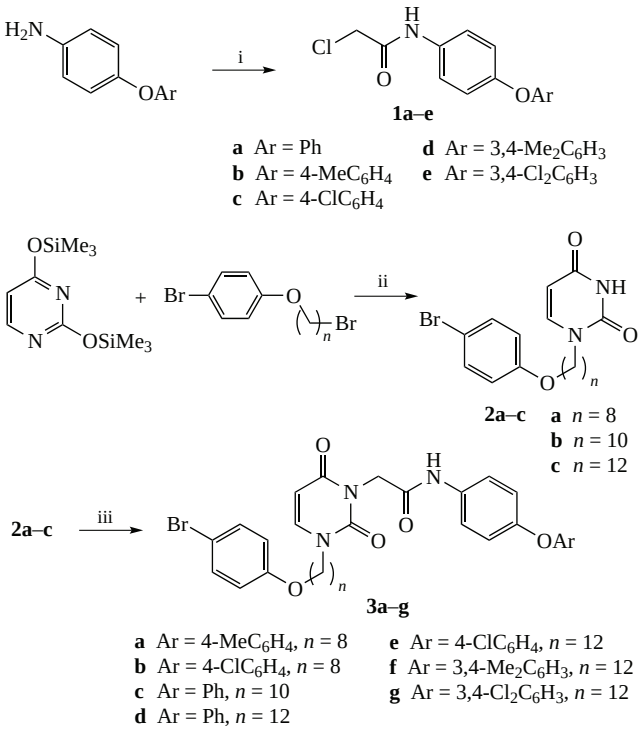


Keywords: human cytomegalovirus, uracil derivative, acetamide, diaryl oxide, bromoarene, antiviral activity.

Human cytomegalovirus (HCMV) is a member of the family *Herpesviridae* and belongs to the subfamily *Betaherpesvirinae*. One of the key characteristics of herpes viruses, including HCMV, is their ability to establish a latent infection, which can be reactivated when the immune status is lowered.[1–10] The anti-HCMV drugs currently used in the clinic to treat HCMV infection include ganciclovir,[11] cidofovir[12] and foscarnet.[13] These drugs inhibit the synthesis catalyzed by HCMV polymerase and reduce the viral reproduction in patients with established clinical symptoms of HCMV infection. However, their use is accompanied by undesirable effects.[14–17] Therefore, the search for new effective anti-HCMV agents represent an urgent task.

Earlier, we synthesized uracil derivatives containing acetanilide fragment at N^3 atom of the uracil residue.[18,19] Compounds of this series demonstrated a broad spectrum of antiviral activity against cytomegaloviruses, varicella-zoster virus[19] and hepatitis C virus.[20] We also recently obtained uracil derivatives containing coumarin residue at the 3-position, which were active against HCMV and varicella-zoster virus.[21] This allows one to suggest that the size of the substituent at N^3 atom of the uracil residue plays a key role in the antiviral properties. In continuation of these studies, we have synthesized a family of compounds based on acetanilide uracil derivatives containing a longer polymethylene bridge, as well as various substituents in the acetanilide fragment.

The synthesis of this series of compounds (Scheme 1) consisted of the preparation of starting chloroacetanilides **1a**–**e**, which included treatment of 4-phenoxyaniline and its substituted derivatives with chloroacetyl chloride in 1,2-dichloroethane in the presence of K_2CO_3 at 0 °C under the conditions described.[18] The preparation of 1-[8-(4-bromophenoxy)octyl]uracil **2a** was known.[19] The synthesis of its decane-1,10-diyl and dodecane-1,12-diyl homologues **2b**,**c** was carried out under the conditions of silyl version of the Hilbert–Johnson reaction by condensation



Scheme 1 *Reagents and conditions*: i, $ClCH_2C(O)Cl$, K_2CO_3, 1,2-dichloroethane, 0 °C, 2 h, 75–78%; ii, $4\text{-}BrC_6H_4O(CH_2)_nBr$, 160–170 °C, 1 h, 80–82%; iii, **1a**–**e**, K_2CO_3, DMF, room temperature, 24 h, 72–81%.

of equimolar amounts of 2,4-bis(trimethylsilyloxy)pyrimidine and the corresponding 1-bromo-ω-(*p*-bromophenoxy)alkanes at 160–170 °C for 1 h (see Scheme 1) as described.[21,22] The yields of products **2b** and **2c** were 82 and 80%, respectively. Subsequent treatment of compounds **2a**–**c** with chloroacetanilides **1a**–**e** in DMF in the presence of K_2CO_3 at room temperature afforded the

desired amides **3a**–**g** in 72–81% yields (for details, see Online Supplementary Materials).

Antiviral properties of new compounds **3a**–**g** against HCMV strains AD-169 and Davis were studied in a culture of HEL cells (Table 1). Earlier, we detected a noticeable anti-HCMV activity of 1-[8-(4-bromophenoxy)octyl]uracil containing unsubstituted acetanilide fragment at N^3 atom of the pyrimidine ring,[19] however, accompanied by high cytotoxicity. The introduction of methyl group (compound **3a**) or chlorine atom (compound **3b**) into the acetanilide moiety did not improve their expected properties. Homologous derivative **3c** with $(CH_2)_{10}$ linker was also toxic. Fortunately, lengthening the bridge to $(CH_2)_{12}$ in compound **3d** caused a significant decrease in cytotoxicity. Product **3d** did not affect the morphology and cell growth at concentrations up to 100 μM. Moreover, its inhibitory effect value EC_{50} against HCMV replication was 0.8 and 1.52 μM for strains AD-169 and Davis, respectively, which was comparable to that of cidofovir and was an order of magnitude better than the effect of ganciclovir. Further modifications of structure **3d**, namely the introduction of chlorine atoms (compounds **3e** and **3g**) or methyl groups (compound **3f**) into the acetanilide fragment, led to complete loss of anti-HCMV activity.

In summary, we have discovered an effective inhibitor of HCMV replication in cell culture, which contains a chain of 12 methylene groups linking the uracil residue and the 4-bromophenoxyl fragment. Compound **3d** is superior to ganciclovir and, despite its low solubility in water, can serve as a basis for a targeted search for new anti-HCMV drugs.

Table 1 Activity of compounds **3a**–**g** in HEL cell culture.

Compound	Anti-HCMV activity, EC_{50}/μM[a]		Cytotoxicity	
	AD-169 strain	Davis strain	Morphology, MEC/μM[b]	Cell growth, GI_{50}/μM[c]
3a	<0.032	<0.032	⩾0.032	–[d]
3b	<0.032	<0.032	0.16	–[d]
3c	0.032	0.032	0.8	86.77
3d	0.8	1.52	>100	>100
3e	>20	>20	20	–[d]
3f	>20	>20	100	–[d]
3g	>20	>20	100	–[d]
Ganciclovir	7.05	4.73	350	>350
Cidofovir	1.01	1.27	300	>300

[a] Concentration required to reduce virus plaque formation by 50% at virus input of 100 plaque forming units (PFU). [b] Minimum concentration that causes a microscopically detectable alteration of cell morphology. [c] Concentration required to reduce cell growth by 50%. [d] Not determined.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.09.016.

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