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Novel 1-[5-(4-bromophenoxy)pentyl]-3-(2-arylamino-2-oxoethyl)uracils and their antiviral properties

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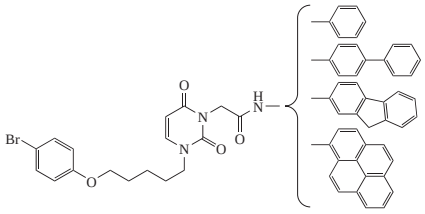
The title compounds were prepared from 1-[5-(4-bromophenoxy)pentyl]uracil by the introduction of *N*-arylacetamide moiety at the 3-position, the better approach involving the use of *N*-aryl-2-chloroacetamides as the reactants. Antiviral activity of the obtained compounds was estimated.

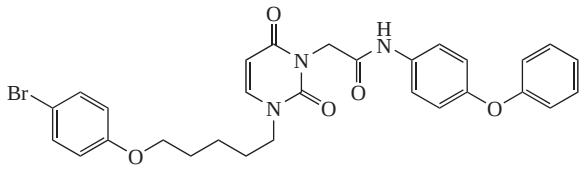


Human cytomegalovirus (HCMV) is a member of the subfamily *Betaherpesvirinae;* it is prevalent in nearly 90% of the adult population worldwide.[1] HCMV infection is associated with viral persistence in a latent form similar to other herpesviruses and reactivation of HCMV is a serious issue for patients with impaired immune systems. For example, there is a high probability of serious coinfections such as pneumonia and gastrointestinal diseases, among others, in recipients of donor organs and bone marrow transplants or HIV-infected patients.[2] Because of the high prevalence of the virus throughout the human population, HCMV is the most common cause of congenital viral infections in newborns.[3] HCMV is able to penetrate the placenta and subsequently infect the fetus, leading to stillbirths[4] and innate deformities.[5]

The current treatment for HCMV infections is focused on five FDA-approved drugs: ganciclovir,[6] its oral prodrug form valganciclovir,[7] foscarnet,[8] cidofovir and its prodrug brincidofovir.[9]

Unfortunately, these drugs also cause some serious side effects, which significantly limit their clinical utility.[10] Aside from low bioavailability these drugs also exhibit significant toxicity. In particular, foscarnet and cidofovir lead to nephrotoxicity,[11] while ganciclovir inhibits the functions of bone marrow, thereby leading to thrombocytopenia and granulocytopenia.[12] Further, it has been found that long-term treatment of HCMV infections leads to the generation of resistant HCMV variants.[13] As a result, there is an urgent need to find safer compounds that exhibit potent anti-HCMV activity, which is not accompanied by such serious side effects.

Previously we have synthesized a series of 1-[ω-(aryloxy)alkyl] uracil derivatives containing an *N*-(4-phenoxyphenyl)acetamide fragment at the N^3 atom of the pyrimidine ring. These compounds exhibited potent inhibitory activity against HCMV in HEL cell cultures.[14] The most active was uracil derivative **1** bearing five methylene groups.[14] We have now designed and synthesized a new series of analogues for the purpose of gaining a better understanding of their structure–activity relationships. The targets proposed herein are based on a series of 2-{3-[5-(4-bromophenoxy)pentyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl}-*N*-arylacetamides (1-[5-(4-bromophenoxy)pentyl]-3-(2-arylamino-2-oxoethyl)uracils) **2**–**5** (Scheme 1).



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Initially target *N*-arylamides **2**–**5** were prepared by conversion of 1-[5-(4-bromophenoxy)pentyl]uracil **6** to uracil-3-acetic acid derivative **7** (Scheme 1, Method A), whose synthesis was described previously.[14] Subsequent treatment of acid **7** with thionyl chloride and condensation of the resulting acyl chloride with the appropriate arylamines (aniline, 4-phenylaniline, 2-amino-9*H*-fluorene or 1-aminopyrene) in the presence of pyridine in 1,2-dichloroethane led to the desired *N*-arylamides **2**–**5** in 56–74% yields.

The second route (Scheme 1, Method B) was proposed to potentially increase the yields of the target compounds.[†] This approach employed substituted *N*-aryl-2-chloroacetamides as alkylating agents. We have previously described the synthesis of several related compounds by this method.[15] Conversion of the corresponding anilines into their *N*-trimethylsilyl derivatives was

[†] All reagents of the highest grade were available from Sigma and Acros Organics and used as purchased unless otherwise noted. Anhydrous solvents were purified according to the standard procedures. TLC was performed on Merck TLC silica gel 60 F254 plates eluting with the specified solvents and the plates visualized with a UV lamp, VL-6.LC. Acros Organics silica gel (Kieselgur 60–200 μm, 60 Å) was used for column chromatography. Yields refer to spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials. Melting points were determined in glass capillaries on a Mel-Temp 3.0 (Laboratory Devices Inc.).

*2-Chloro-*N*-phenylacetamide* **8** was obtained according to published procedures.[14]

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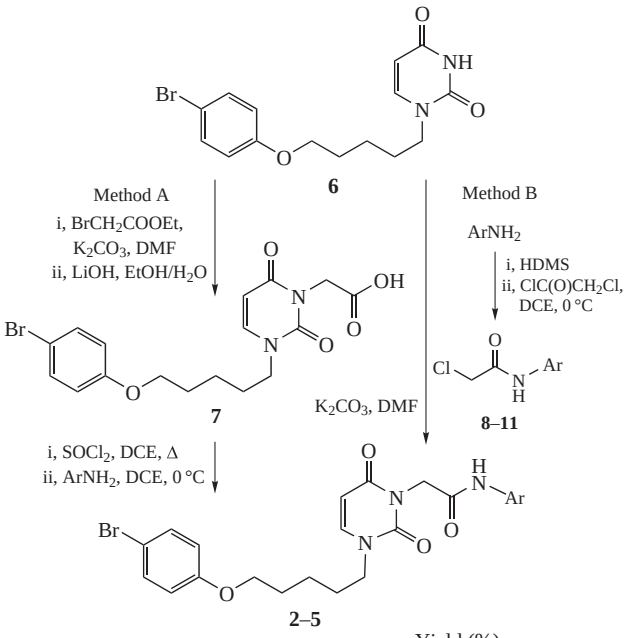

Product	Ar	Yield (%)	
		Method A	Method B
2	Ph	74	90
3	4-PhC_6H_4	72	87
4	9*H*-fluoren-2-yl	66	88
5	pyren-1-yl	56	78

Scheme 1

accomplished by boiling the reaction components in excess HMDS, followed by treatment (without further purification) with chloroacetyl chloride in anhydrous 1,2-dichloroethane to give the new N^3-substituted chloroacetamides. Thus, chloroacetamides **8**–**11** were obtained in 78–89% yields.

Similarly, alkylation of 1-[5-(4-bromophenoxy)pentyl]uracil **6**[16] with the corresponding chloroacetamides **8**–**11** in DMF in the presence of a 1.5-fold excess of potassium carbonate led to the target compounds **2**–**5** in 78–90% yields.

Compounds **2**–**5** were then evaluated as potential inhibitors against a broad set of DNA and RNA viruses, including HIV-1,

N-*Arylacetamides* **9**–**11** *(general procedure)*. A mixture of 8.14 mmol of arylamine, HMDS (15 ml) and NH_4Cl (0.1 g) was refluxed for 12 h until a homogeneous solution was obtained. Excess HMDS was removed under reduced pressure, and the residual clear oil was dissolved in anhydrous 1,2-dichloroethane (40 ml). A solution of chloroacetyl chloride (0.7 ml, 8.80 mmol) in anhydrous 1,2-dichloroethane (10 ml) was added dropwise with stirring at 0 °C. The mixture was stirred overnight at room temperature and then evaporated under reduced pressure to 1/3 volume. Hexane (20 ml) was added and the mixture was kept overnight in a refrigerator. The resulting precipitate was filtered and recrystallized from a mixture of EtOAc–hexane (1 : 1 or 1 : 2).

2-Chloro-N-*(4-phenylphenyl)acetamide* **9**. Yield 89%, mp 180–182 °C, R_f 0.59 (hexane–EtOAc, 1 : 1). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.28 (s, 2H, $COCH_2$), 7.33 (tt, 1H, H-4′, *J* 9.1, 1.8 Hz), 7.44 (t, 2H, H-3′, H-5′, *J* 8.1 Hz), 7.64 (d, 2H, H-3, H-5 *J* 7.1 Hz), 7.65 (d, 2H, H-2′, H-6′, *J* 9.1 Hz), 7.67 (d, 2H, H-2, H-6, *J* 9.3 Hz), 10.41 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 43.9, 120.1, 126.6, 127.4, 127.5, 129.6, 135.8, 138.3, 139.9, 165.0.

2-Chloro-N-*(9*H*-fluoren-2-yl)acetamide* **10**. Yield 80%, mp 194.5–196 °C, R_f 0.63 (hexane–EtOAc, 1 : 1). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.91 (s, 2H, CH_2), 4.28 (s, 2H, $COCH_2$), 7.27 (dt, 1H, H-7, *J* 7.6, 1.0 Hz), 7.35 (t, 1H, H-6, *J* 7.3 Hz), 7.55 (d, 2H, H-5, H-8, *J* 7.8 Hz), 7.82 (d, 1H, H-3, *J* 7.1 Hz), 7.83 (d, 1H, H-4, *J* 8.1 Hz), 7.92 (s, 1H, H-1), 10.39 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 36.9, 44.0, 116.5, 118.5, 119.9, 120.6, 125.4, 126.6, 127.1, 137.3, 137.8, 141.2, 143.2, 144.2, 164.9.

2-Chloro-N-*(pyren-1-yl)acetamide* **11**. Yield 78%, mp 240–241 °C, R_f 0.60 (hexane–EtOAc, 1 : 1). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.55 (s, 2H, $COCH_2$), 8.07 (t, 1H, H-7, *J* 7.5 Hz), 8.15 (m, 2H, H_{Ar}), 8.22–8.25 (m, 2H, H_{Ar}), 8.28–8.31 (m, 4H, H_{Ar}), 10.68 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 43.8, 122.4, 123.7, 124.1, 124.5, 124.7, 125.3, 125.5, 125.8, 126.8, 127.2, 127.5, 127.7, 129.0, 130.7, 131.1, 131.2, 166.2.

*2-{3-[5-(4-Bromophenoxy)pentyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl}*-N-*arylacetamides* **2**–**5** *(general procedure)*. *Method A.* A mixture of carboxylic acid derivative **7** (0.7 g, 1.70 mmol) and thionyl chloride (0.15 ml, 2.06 mmol) in anhydrous 1,2-dichloroethane (10 ml) was refluxed with the exclusion of moisture for 6 h. The volatiles were evaporated under reduced pressure and the residue was dissolved in anhydrous 1,2-dichloroethane (10 ml). The resulting solution was added dropwise to a stirred and cooled (0 °C) solution of arylamine (1.72 mmol) and pyridine (2 ml) in anhydrous 1,2-dichloroethane (40 ml), and this was stirred for an additional 3 h at 0 °C and then kept overnight at room temperature. The mixture was then washed with 4% aqueous HCl (2 × 30 ml) and water (2 × 30 ml), the solvents were evaporated under reduced pressure, and the crude product purified by flash chromatography eluting with 1,2-dichloroethane–EtOAc (1 : 2). The product was recrystallized from a mixture of hexane–EtOAc (1 : 1).

Method B. A mixture of 1-[5-(4-bromophenoxy)pentyl]uracil **6** (0.5 g, 1.42 mmol) and K_2CO_3 (0.3 g, 2.17 mmol) in DMF (10 ml) was stirred at 80 °C for 1 h. After cooling to room temperature, the corresponding 2-chloroacetamide **8**–**11** (1.46 mmol) was added and stirring was continued for 24 h. The reaction mixture was filtered, concentrated under reduced pressure, purified by flash chromatography eluting with 1,2-dichloroethane–EtOAc (1 : 2) and then recrystallized from a mixture of hexane–EtOAc (1 : 1).

*2-{3-[5-(4-Bromophenoxy)pentyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl}*-N-*phenylacetamide* **2**: mp 157–158.5 °C, R_f 0.58 (1,2-dichloroethane–EtOAc, 1 : 1). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.39 (quin., 2H, CH_2, *J* 7.1 Hz), 1.66 (quin., 2H, CH_2, *J* 7.1 Hz), 1.72 (quin., 2H, CH_2, *J* 7.1 Hz), 3.75 (t, 2H, NCH_2, *J* 7.4 Hz), 3.93 (t, 2H, OCH_2, *J* 6.3 Hz), 4.61 (s, 2H, $COCH_2$), 5.76 (d, 1H, Ura-H-5, *J* 7.8 Hz), 6.88 (d, 2H, H-2′, H-6′, *J* 8.8 Hz), 7.04 (t, 1H, H-4″, *J* 7.2 Hz), 7.30 (t, 2H, H-3″, H-5″, *J* 8.3 Hz), 7.40 (d, 2H, H-3′, H-5′, *J* 9.0 Hz), 7.55 (dd, 2H, H-2″, H-6″, *J* 8.3, 1.0 Hz), 7.77 (d, 1H, Ura-H-6, *J* 7.9 Hz), 10.25 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 22.6, 28.4, 43.5, 48.8, 67.8, 100.3, 112.1, 117.0, 119.3, 123.6, 129.1, 132.4, 139.1, 144.9, 151.4, 158.2, 162.6, 165.6.

*2-{3-[5-(4-Bromophenoxy)pentyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl}*-N-*(4-phenylphenyl)acetamide* **3**: mp 178–179 °C, R_f 0.45. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.40 (quin., 2H, CH_2, *J* 7.1 Hz), 1.66 (quin., 2H, CH_2, *J* 7.1 Hz), 1.73 (quin., 2H, CH_2, *J* 7.6 Hz), 3.76 (t, 2H, NCH_2, *J* 7.3 Hz), 3.93 (t, 2H, OCH_2, *J* 6.4 Hz), 4.64 (s, 2H, $COCH_2$), 5.77 (d, 1H, Ura-H-5, *J* 7.9 Hz), 6.88 (d, 2H, H-2″, H-6″, *J* 9.1 Hz), 7.32 (t, 1H, H-4‴, *J* 7.3 Hz), 7.40 (d, 2H, H-3′, H-5′, *J* 9.0 Hz), 7.43 (t, 2H, H-3‴, H-5‴, *J* 7.6 Hz), 7.60–7.66 (m, 6H, H-2′, H-6′, H-3″, H-5″, H-2‴, H-6‴), 7.78 (d, 1H, Ura-H-6, *J* 7.8 Hz), 10.36 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 22.6, 28.4, 43.5, 48.7, 67.9, 100.3, 112.1, 117.0, 119.7, 126.6, 127.3, 127.4, 129.2, 132.4, 135.3, 138.6, 139.9, 144.9, 151.4, 158.2, 162.6, 165.6.

*2-{3-[5-(4-Bromophenoxy)pentyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl}*-N-*(9*H*-fluoren-2-yl)acetamide* **4**: mp 119–121 °C, R_f 0.68. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.40 (quin., 2H, CH_2, *J* 7.9 Hz), 1.66 (quin., 2H, CH_2, *J* 7.9 Hz), 1.72 (quin., 2H, CH_2, *J* 7.3 Hz), 3.76 (t, 2H, NCH_2, *J* 7.1 Hz), 3.87 (s, 2H, CH_2), 3.93 (t, 2H, OCH_2, *J* 6.3 Hz), 4.64 (s, 2H, $COCH_2$), 5.77 (d, 1H, Ura-H-5, *J* 7.9 Hz), 6.88 (d, 2H, H-2″, H-6″, *J* 9.0 Hz), 7.27 (t, 1H, H-7″, *J* 7.6 Hz), 7.35 (t, 1H, H-6′, *J* 7.6 Hz), 7.40 (d, 2H, H-3′, H-5′, *J* 8.8 Hz), 7.51–7.54 (m, 2H, H-5′, H-8′), 7.77–7.81 (m, 3H, Ura-H-6, H-3′, H-4′), 7.87 (s, 1H, H-1′), 10.34 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 22.6, 28.4, 36.8, 43.6, 48.7, 67.9, 100.3, 112.1, 116.2, 117.0, 118.1, 119.8, 120.5, 125.3, 126.5, 127.1, 132.4, 136.8, 138.1, 141.3, 143.1, 144.1, 144.8, 151.4, 158.2, 162.6, 165.5.

*2-{3-[5-(4-Bromophenoxy)pentyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl}*-N-*(pyren-1-yl)acetamide* **5**: mp 176.5–178 °C, R_f 0.60. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.40 (quin., 2H, CH_2, *J* 7.6 Hz), 1.65–1.75 (m, 4H, 2 × CH_2), 3.80 (t, 2H, NCH_2, *J* 7.1 Hz), 3.90 (t, 2H, OCH_2, *J* 6.4 Hz), 4.88 (s, 2H, $COCH_2$), 5.81 (d, 1H, Ura-H-5, *J* 7.8 Hz), 6.83 (d, 2H, H-2″, H-6″, *J* 9.1 Hz), 7.35 (d, 2H, H-2″, H-6″, *J* 9.0 Hz), 7.80 (d, 1H, Ura-H-6, *J* 7.8 Hz), 8.07 (t, 1H, H-7, *J* 7.6 Hz), 8.15 (m, 2H, H_{Ar}), 8.18–8.25 (m, 2H, H_{Ar}), 8.28–8.36 (m, 4H, H_{Ar}), 10.62 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 22.6, 28.4, 43.6, 48.8, 67.8, 100.4, 112.0, 117.0, 122.7, 123.5, 124.2, 124.7, 125.3, 125.6, 126.8, 127.0, 127.6, 128.7, 130.8, 131.2, 131.7, 132.4, 144.9, 151.5, 158.2, 162.7, 166.8, 170.0.

HIV-2, HSV-1, HSV-2, HCMV, VZV, Vaccinia virus, Parainfluenza-3 virus, Reovirus-1, Sindbis virus, Vesicular stomatitis virus, Respiratory syncytial virus, Coxsackie virus B4 or Feline Corona Virus, *etc.*, using standard methods.[16] Disappointingly, none of the compounds in this series showed any meaningful antiviral activity. However, in further analyzing the screening results it appears that the oxygen atom of the acetanilide fragment of **1** likely makes a critical contribution to the anti-HCMV activity. Thus, the new uracil acetamide derivatives seem to be a promising class of viral replication inhibitors and warrant further structure–activity investigations.

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*2-{3-[5-(4-Bromophenoxy)pentyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl}acetic acid* **7**. A mixture of 1-[5-(4-bromophenoxy)pentyl]-uracil **6** (0.5 g, 1.42 mmol) and K_2CO_3 (0.3 g, 2.17 mmol) in anhydrous DMF (10 ml) was stirred at 80 °C for 40 min. After cooling to room temperature, ethyl bromoacetate (0.17 ml, 1.56 mmol) was added and stirring was continued for 24 h. The reaction mixture was filtered, concentrated under reduced pressure and purified by flash chromatography eluting with 1,2-dichloroethane. The crude product was then dissolved in EtOH (20 ml), LiOH (0.2 g, 8.35 mmol) and water (10 ml) were added, and the resulting mixture was stirred at room temperature for 12 h. After adjusting the pH to 2 with the addition of 1 M HCl, the resulting precipitate was filtered and recrystallized from a mixture of hexane–Pr^{i}OH (1 : 2) to give the desired product as a white powder (2.68 g, 100%), R_f 0.54 (Pr^{i}OH–EtOAc–NH_4OH, 9 : 6 : 5), mp 142.5–145 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.39 (quin., 2H, CH_2, *J* 7.4 Hz), 1.65 (quin., 2H, CH_2, *J* 7.4 Hz), 1.72 (quin., 2H, CH_2 *J* 7.3 Hz), 3.75 (t, 2H, NCH_2, *J* 7.1 Hz), 3.93 (t, 2H, OCH_2, *J* 6.4 Hz), 4.44 (s, 2H, $COCH_2$), 5.74 (d, 1H, Ura-H-5, *J* 7.8 Hz), 6.89 (d, 2H, H-2′, H-6′, *J* 8.8 Hz), 7.42 (d, 2H, H-3′, H-5′, *J* 8.8 Hz), 7.77 (d, 1H, Ura-H-6, *J* 7.8 Hz), 12.90 (br.s, 1H, COOH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 22.6, 28.37, 28.41, 41.9, 48.8, 67.8, 100.2, 112.1, 117.1, 132.4, 145.0, 151.2, 158.2, 162.3, 169.5.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2017.01.027.

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