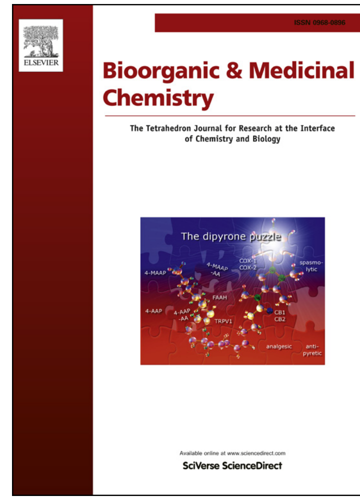

Toward the discovery of dual HCMV-VZV inhibitors: synthesis, structure activity relationship analysis, and cytotoxicity studies of long chained 2-uracil-3-yl-N-(4-phenoxyphenyl)acetamides

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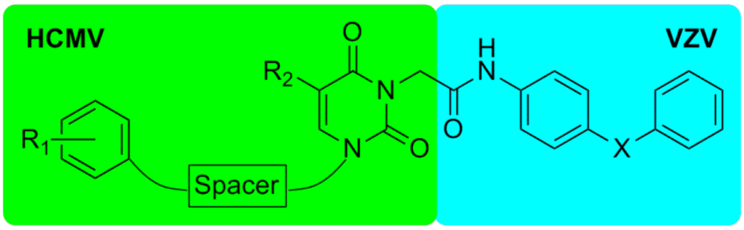
Dual inhibitors



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ABSTRACT

The need for novel therapeutic options to fight herpesvirus infections still persists. Herein we report the design, synthesis and antiviral evaluation of a new family of non-nucleoside antivirals, derived from 1-[ω-(4-bromophenoxy)alkyl]uracil derivatives – previously reported inhibitors of human cytomegalovirus (HCMV). Introduction of the N-(4-phenoxyphenyl)acetamide side chain at N3 increased their potency and widened activity spectrum. The most active compounds in the series exhibit submicromolar activity against different viral strains of HCMV and varicella zoster virus (VZV) replication in HEL cell cultures. Inactivity against other DNA and RNA viruses, including herpes simplex virus 1/2, points to a novel mechanism of antiviral action.

1. Introduction

Human cytomegalovirus (HCMV, or human herpesvirus-5) and varicella zoster virus (VZV, also known as human herpesvirus-3) belong to the viral family known as Herpesviridae. Despite modern prevention and treatment strategies, they remain a common opportunistic pathogen associated with serious morbidity and mortality, particularly in immunocompromised individuals such as transplant recipients[1] and AIDS patients.[2,3] All drugs currently licensed for the treatment of HCMV and VZV infections (Figure 1) target the viral DNA polymerase. Unfortunately they are associated with severe toxicity issues, including marrow toxicity for ganciclovir, valganciclovir, and cidofovir, and renal toxicity for foscarnet and cidofovir.[4,5] The emergence of drug resistance is also a significant problem.[6] Moreover, our understanding of the full spectrum of risks of HCMV infection and its interactions with the host immune system remains far from complete.[7] While the past two decades have seen progress toward novel treatments for herpesviruses, the need for better drugs that exhibit an improved toxicity profile persists.[8]

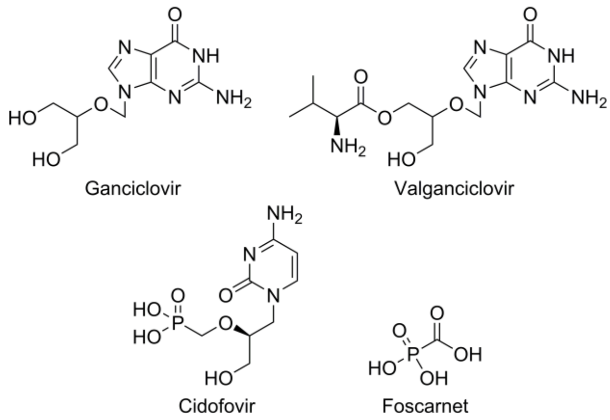


Figure 1. Clinically approved anti-HCMV and anti-VZV drugs.

Previously, we have described a series of 1-[ω-(phenoxy)alkyl]uracil derivatives that were found to exhibit high specificity and promising inhibitory activity against HCMV replication in HEL cell cultures with EC_{50} values within 5.5–12 μM range.[9] These results provided strong impetus to further explore structure-activity relationships and the antiviral activity spectrum of similar scaffolds. The present paper describes lead development of N-(4-phenoxyphenyl)acetamide derivatives (Figure 2).

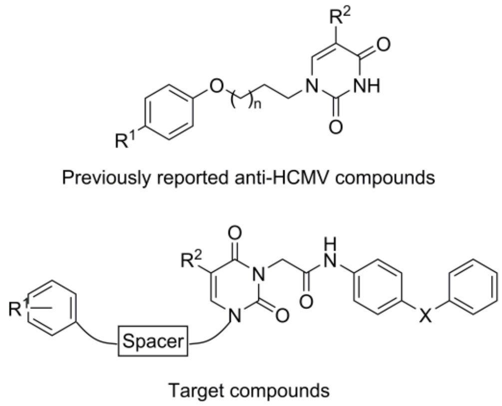


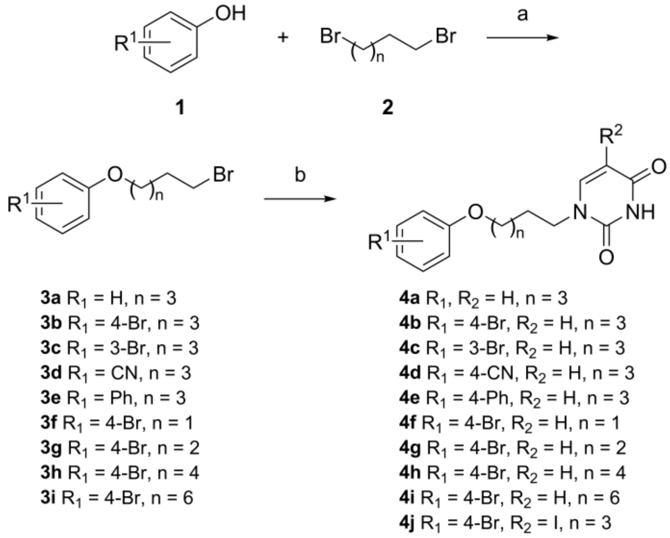
Figure 2. Target compounds.

2. Results and Discussion

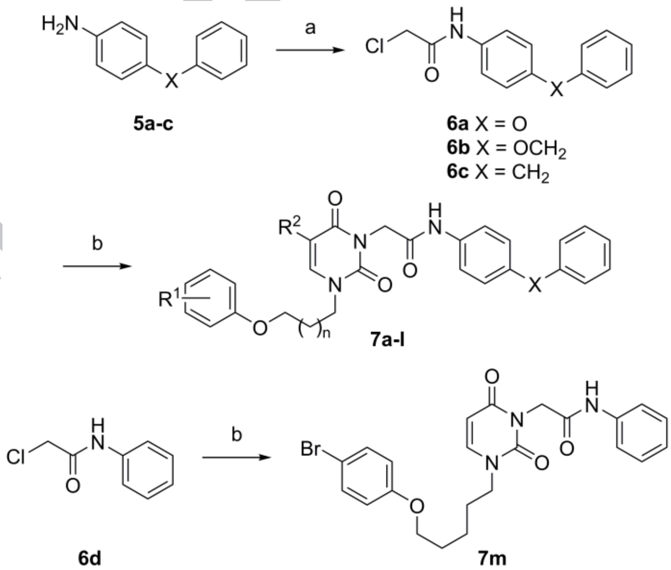
2.1. Chemistry

The synthesis of the compound library relied on three key steps: synthesis of 1-[ω-(phenoxy)alkyl]uracil derivatives and related compounds, synthesis of 2-chloro-*N*-(4-phenoxyphenyl)acetamides, and their subsequent conjugation to realize the target compounds. Based on the successful synthesis of several previously reported compounds,[9] a series of analogues were synthesized following the classical synthetic approach reported in Scheme 1. This first set of derivatives is characterized by focused modifications on the aromatic ring. The synthesis of compounds **4a-j** started from commercially available phenols **1** (R_1 = H, 3-Br, 4-Br, 4-Ph or 4-CN), which were treated with 4-fold excess of α,ω-dibromoalkanes **2** (n = 1–4, 6 or 8) to produce bromides **3a-i** according to known procedures.[10-12] A modified silyl Hilbert-Johnson reaction, i.e. condensation of equimolar amounts of 2,4-bis(trimethylsilyloxy)pyrimidines[13] with bromides **3a-e**, was performed at 160–170 °C in the absence of solvent[9] to afford target compounds **4a-e** in 76-88% yield. Compounds **4f-j** comprising 3, 4, 6, and 8 methylene units, respectively, were obtained in an analogous manner as was used for compounds **4a-e** (Scheme 1).

Intermediate 2-chloroacetamides **6a-c** were readily obtained via acylation of the commercially available 4-(phenoxy)- (**5a**), 4-(benzyloxy)- (**5b**) and 4-benzyl- (**5c**) anilines with chloroacetyl chloride promoted by anhydrous K_2CO_3 in aprotic media.[14] 2-Chloroacetamide **6d** was obtained as we described previously.[15] Treatment of potassium salts of uracil derivatives **4a-j** with 2-chloroacetamides **6a-d** in anhydrous DMF afforded target compounds **7a-i** and **7k-m** in good yields (Scheme 2). To avoid possible complications due to iodine elimination, compound **7j** was obtained from **4j** and 2-chloroacetamide **6a** employing NaH as the base.[16] Target compound **7j** was subsequently isolated in 86% yield.[15]

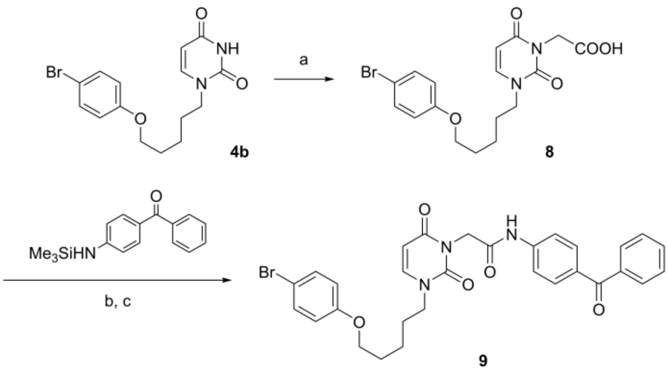


Scheme 1. Reagents and conditions: (a) K_2CO_3, acetone, reflux, 12 h; (b) 2,4-bis(trimethylsilyloxy)-5-R_2-pyrimidine, neat, 160–170 °C, 1 h.



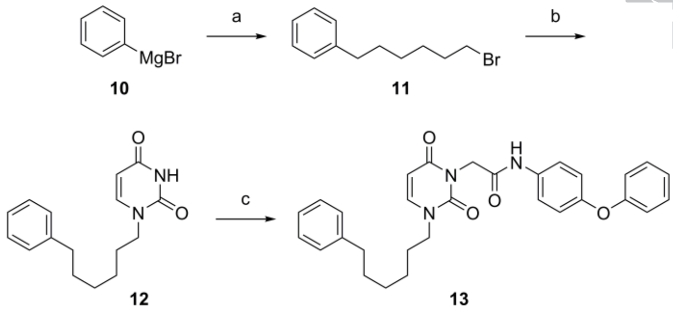
Scheme 2. Reagents and conditions: (a) chloroacetyl chloride, K_2CO_3, DCE, 0 °C, 2 h; (b) **4a-i**, K_2CO_3, DMF, 80 °C → RT, 24 h (for **7a-i** and **7k-m**) or **4j**, NaH, DMF, RT, 24 h (for **7j**).

In order to obtain benzophenone derivative **9**, the appropriate building blocks were obtained in a somewhat different order. First, acid **8** was synthesized quantitatively via treatment of **4b** with ethyl bromoacetate in the presence of K_2CO_3, followed by hydrolysis using LiOH according to published procedures.[17] Subsequent conversion of acid **8** into the corresponding acyl chloride, followed by condensation with the *N*-trimethylsilyl derivative of 4-(benzoyl)aniline led to **9** in 57% yield (Scheme 3).[15] It should be noted that utilization of base-free conditions for the synthesis of **9** avoids the by-products that typically arise from Knoevenagel condensation between the benzophenone carbonyl and the active methylene of the acetic acid residue.[18]



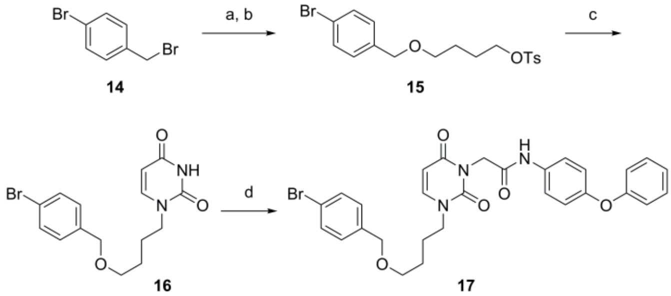
Scheme 3. Reagents and conditions: (a) (i) ethyl bromoacetate, K_2CO_3, DMF, 80 °C → RT, 24 h; (ii) LiOH, EtOH/H_2O, RT, 2 h; (b) (i) $SOCl_2$, DCE, reflux, 1 h; (ii) DCE, −15 °C, overnight.

To further explore the SAR of these compounds we then designed a second set of analogues featuring a modified spacer linking the N^1 of the uracil with the aromatic moiety. Synthesis of the various target structures demanded different, but related approaches. Copper–catalyzed coupling of phenylmagnesium bromide (**10**) with excess of 1,6-dibromohexane[19] in THF media produced bromide **11**, which was condensated with 2,4-bis(trimethylsilyloxy)pyrimidine to afford 1-(6-phenylhexyl)uracil (**12**), however in an unexpectedly mediocre 30% yield (Scheme 4). This was somewhat surprising since our previous observations for this reaction involving similar ω-(phenoxy)alkyl bromides **3a-i** as alkylating agents were, in contrast, quite efficient.[9]



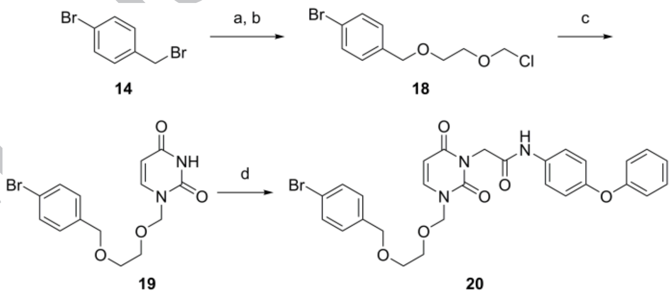
Scheme 4. Reagents and conditions: (a) 1,6-dibromohexane, 5 mol% $Li_2[CuICl_2]$, THF, RT, 2 h; (b) 2,4-bis(trimethylsilyloxy)pyrimidine, neat, 160–170 °C, 1 h; (c) **6a**, K_2CO_3, DMF, 80 °C → RT, 24 h.

Silyl Hilbert-Johnson reactions between 2,4-bis(trimethylsilyloxy)pyrimidine and alkyl bromides are known to be associated with the release of trimethylsilyl bromide. This subsequently, and efficiently, cleaves dialkyl ethers at elevated temperatures.[20] As a result, in order to obtain 1-[4-(4-bromobenzyloxy)butyl]uracil (**16**), it was necessary to alkylate uracil with tosylate **15**, which was obtained via a Williamson ether synthesis between 1,4-butanediol and 4'-bromobenzyl bromide[18] followed by condensation with 4-toluenesulfonyl chloride in the presence of pyridine (Scheme 5).



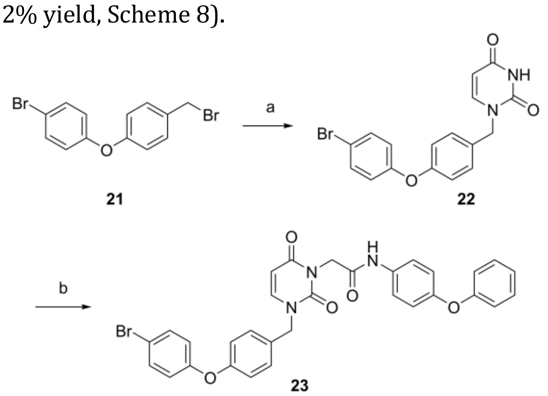
Scheme 5. Reagents and conditions: (a) $HO(CH_2)_4OH$, KOH, 24 h; (b) TsCl, Py, DCE, 0–5 °C; (c) uracil, K_2CO_3, DMF, 80 °C, 24 h; (d) **6a**, K_2CO_3, DMF, 80 °C → RT, 24 h.

In addition, an analogue featuring two oxygen atoms in the spacer chain was pursued as shown in Scheme 6. Chloromethyl ether **18** was obtained via the classical Henry method.[21] Condensation with equimolar amount of 2,4-bis(trimethylsilyloxy)pyrimidine led to 1-([2-(4-bromobenzyl)ethoxy]methyl)uracil (**19**) in 67% yield. Being more reactive than bromides **3a-i** and **11**, the reaction proceeds under rather mild conditions in 1,2-dichloroethane at ambient temperature.[22]

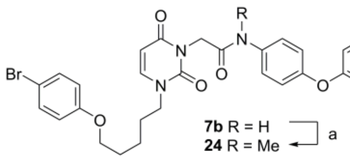


Scheme 6. Reagents and conditions: (a) $HO(CH_2)_2OH$, KOH, 12 h; (b) $(CH_2O)_n$, HCl, DCE, 0 °C, 2 h; (c) 2,4-bis(trimethylsilyloxy)pyrimidine, DCE, RT, 16 h; (d) **6a**, K_2CO_3, DMF, 80 °C → RT, 24 h.

Next, the flexible spacer was replaced with a rigid 4-(4-bromophenoxy)benzyl moiety, which was introduced at the N^1 of uracil employing previously reported procedures.[23] As outlined in Scheme 7, 2,4-bis(trimethylsilyloxy)pyrimidine and 4-(4-bromophenoxy)benzyl bromide (**21**) were reacted in DCE at reflux for 20 h to give **23**. Finally, to investigate the potential role of an amide nitrogen, methylation of **7b** with methyl iodide/NaH in DMF successfully produced compound **24** (92% yield, Scheme 8).



Scheme 7. Reagents and conditions: (a) 2,4-bis(trimethylsilyl-oxy)pyrimidine, DCE, reflux, 24 h; (b) **6a**, K_2CO_3, DMF, 80 °C → RT, 24 h.



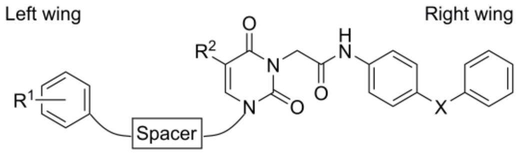
Scheme 8. Reagents and conditions: (a) MeI, NaH, DMF, 0 °C, 4 h.

2.2. Biological activities

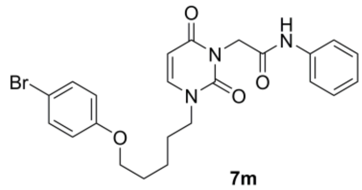
2.2.1. Anti-HCMV activity

The antiviral activity of the target compounds was evaluated *in vitro* against different human herpesviruses [i.e. HCMV (AD-169 and Davis strains), VZV (OKA and 07-1 strains), and herpes simplex virus 1 and 2 (HSV-1 and HSV-2)] in HEL cell cultures. The results for HCMV and VZV are summarized, respectively, in Tables 1 and 2. The results reveal that the majority of the target compounds share marked inhibitory properties. In examining the results for HCMV, the SAR studies revealed that the nature of the R_1 substituent significantly influences the antiviral activity: **7a** (R_1 = H) ≈ **7c** (R_1 = 3-Br) < **7b** (R_1 = 4-Br) < **7e** (R_1 = 4-Ph) ≈ **7d** (R_1 = 4-CN). Since compound **7b** showed a selectivity (ratio CC_{50}/EC_{50}) of about 9 for both HCMV strains and lower toxicity (alteration of cell morphology) than compound **7d**, it was considered as the basis for further modifications.

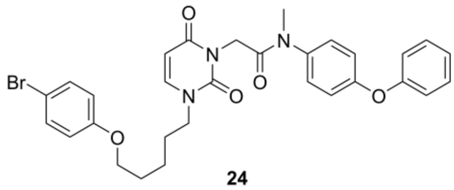
Table 1. Anti-HCMV activity in human embryonic lung (HEL) cells



7a-n, 9, 13, 17, 20, 23



7m



24

Comp	R_1	Spacer	R_2	X	Antiviral activity, EC_{50} (μM)[a]		Cytotoxicity (μM)	
					AD-169 strain	Davis strain	Cell morphology (MCC)[b]	Cell growth (CC_{50})[c]
7a	H	$O(CH_2)_5$	H	O	3.6 ± 0.6	4.0 ± 2.8	≥20	5.4 ± 2.0
7b	4-Br	$O(CH_2)_5$	H	O	0.93 ± 0.75	0.97 ± 0.95	20	8.7 ± 5.4
7c	3-Br	$O(CH_2)_5$	H	O	2.0 ± 0.3	3.1 ± 1.3	≥100	6.3 ± 1.3
7d	4-CN	$O(CH_2)_5$	H	O	0.53 ± 0.12	0.44 ± 0.11	≥4	4.9 ± 1.3
7e	4-Ph	$O(CH_2)_5$	H	O	0.51 ± 0	1.04 ± 0.33	20	2.8 ± 0.5
7f	4-Br	$O(CH_2)_3$	H	O	3.8 ± 2.0	3.9 ± 3.4	≥100	15.2 ± 6.8
7g	4-Br	$O(CH_2)_4$	H	O	1.79 ± 0	1.64 ± 0	≥20	7.7 ± 7.2
7h	4-Br	$O(CH_2)_6$	H	O	0.29 ± 0.06	0.20 ± 0.18	4	11.7 ± 11.7
7i	4-Br	$O(CH_2)_8$	H	O	<0.032	<0.032	≥0.16	-
7j	4-Br	$O(CH_2)_5$	I	O	>20	>20	100	-
7k	4-Br	$O(CH_2)_5$	H	CH_2	0.44 ± 0.11	0.57 ± 0.33	4	8.7 ± 1.7
7l	4-Br	$O(CH_2)_5$	H	OCH_2	>20	4	≥20	-
7m	-	-	-	-	>4	>4	20	-
9	4-Br	$O(CH_2)_5$	H	CO	1.79 ± 0	1.64 ± 0	≥20	5.8 ± 0.6
13	H	$(CH_2)_6$	H	O	>20	>20	100	-
17	4-Br	$CH_2O(CH_2)_4$	H	O	1. 8 ± 0.3	≥1.2 ± 0.6	≥4	4.8 ± 1.1
20	4-Br	$CH_2O(CH_2)_2OCH_2$	H	O	>20	>20	100	-
23	4-Br	*p*-$OC_6H_4CH_2$	H	O	>0.8	>0.8	4	-
24	-	-	-	-	0.98 ± 0.93	1.29 ± 1.27	≥4	6.1 ± 2.3
GCV					13.9 ± 10.6	7.8 ± 3.4	>350	≥319 ± 102
CDV					0.83 ± 0.40	0.84 ± 0.29	>300	≥208 ± 116

[a] Effective concentration required to reduce virus plaque formation by 50%. Virus input was 100 plaque forming units (PFU).

[b] Minimum cytotoxic concentration that causes a microscopically detectable alteration of cell morphology.

[c] Cytotoxic concentration required to reduce cell growth by 50%.

Notably, the nature of the spacer between the uracil and the left aromatic "wing" significantly influences the anti-HCMV activity of the compounds. For example, elongation of the spacer from 3 to 8 methylene groups progressively lowers EC_{50} values, as demonstrated by **7f** (n = 3) < **7g** (n = 4) < **7b** (n = 5) < **7h** (n = 6) < **7i** (n = 8). Specifically, introduction of five methylene groups to **7f** to give **7i** increases the activity 43-73 fold, however a concomitant increase in cytotoxicity was also observed.

Replacement of the oxygen atom for a methylene (compound **13**) resulted in a loss of activity, which points to the potential role of an ether functionality in the spacer region. A shift in position of the oxygen on the aromatic moiety did not markedly affect activity (1.2 to 2-fold change of **17** as compared to **7b**), while introduction of an additional oxygen (compound **20**) renders the compound completely inactive. Use of a rigid spacer (compound **23**) also proved unfavorable. Overall, incorporation of an alkoxyphenyl side chain proved to be optimal.

Interestingly, the one modification made to the uracil moiety proved deleterious. Substitution of the H5 of the uracil with iodine rendered **7j** completely inactive.

Next, the SAR studies involving modifications to the right "wing" revealed that the presence of a second benzene core in the acetamide side chain is mandatory for inhibitory properties (compound **7k**). Investigation of the role of the linker between the aromatic residues shows that oxygen provides the optimal activity profile. The corresponding methylene analogue retains a similar level of activity, but is more cytotoxic (**7k**), while use of a carbonyl (**9**) or OCH_2 (**7l**) group renders the compound significantly less active. *N*-Methylation of the parent **7b** has no significant influence on the potency as compound **24** shows.

2.2.2. Anti-VZV activity

Similar activity trends were observed for the anti-VZV properties of the target compounds. The 4-bromo-substituted compound **7b** blocks VZV replication at 1.14 μM (OKA strain), which is comparable with acyclovir. At the same time, thymidine kinase deficient strain 07-1 was also susceptible to **7b**. Since thymidine kinase is required for the activation of nucleoside analogues (e.g. acyclovir and brivudin), it is likely these compounds are acting as nonnucleoside inhibitors.[24] Other substituents at R_1 were found inactive (**7a**, **7c-e**). As was noted for the HCMV inhibition, elongation of the spacer has a pronounced positive impact on the anti-VZV properties. Compound **7i** featuring 8 methylene units proved the most active, with EC_{50}'s of ≥0.12 μM and ≥0.16 μM for the OKA and 07-1 strains, respectively. Again however, an increase in activity was accompanied by higher cytotoxicity for both **7h** and **7i**. Other spacer modifications, including oxygen (**13**), a position shift (**17**), and introduction of additional oxygen (**20**), or a benzene moiety (**23**) all resulted in a loss of activity. Thus, the nature of the spacer once again plays a crucial role in the antiviral properties.

In terms of substituents, introduction of a substituent at C5 of uracil renders compound **7j** completely inactive. Substitution of the oxygen linker between aromatic residues on the acetamide side chain (right wing) led to more the cytotoxic methylene derivative **7k** and the less potent **7l** (X = OCH_2) and **9** (X = CO). In addition, *N*-methyl derivative **24** and compound **7m**, both lacking the phenoxy core, indicated that the *N*-(4-phenoxyphenyl)acetamide side chain is likely a key element required for antiviral properties of the scaffold.

Table 2. Anti-VZV activity in human embryonic lung (HEL) cells

Comp	Antiviral activity, EC_{50} (μM)[a]		Cytotoxicity (μM)	
	TK⁺ VZV (OKA strain)	TK⁻ VZV (07-1 strain)	Cell morphology (MCC)[b]	Cell growth (CC_{50})[c]
7a	>100	>100	>100	-
7b	1.6 ± 0.7	2.34 ± 0.18	>100	8.7 ± 5.4
7c	>100	>100	>100	-
7d	>100	>100	>100	-
7e	>20	>20	100	-
7f	5.4 ± 0.5	4.6 ± 0.9	≥100	15.2 ± 6.8
7g	3.1 ± 0.1	2.8 ± 0.6	>100	7.7 ± 7.2
7h	0.8 ± 0	0.51 ± 0.01	4	11.7 ± 11.7
7i	≥0.12 ± 0.05	≥0.16 ± 0	0.8	11.7 ± 11.7
7j	>100	>100	>100	-
7k	0.8	4	≥4	-
7l	>4	11.7	≥20	-
7m	>4	15	≥20	-
9	>100	>100	>100	-
13	>100	>100	>100	-
17	>100	>100	>100	-
20	>100	>100	>100	-
23	>4	>4	20	-
24	8.0 ± 0.3	7.7 ± 1.5	≥100	6.0 ± 2.4
Acyclovir	1.82 ± 0.67	54.5 ± 50.6	>440	>440
Brivudin	0.029 ± 0.017	38.6 ± 45.5	>300	≥79.3

[a] Effective concentration required to reduce virus plaque formation by 50%. Virus input was 100 plaque forming units (PFU).

[b] Minimum cytotoxic concentration that causes a microscopically detectable alteration of cell morphology.

[c] Cytotoxic concentration required to reduce cell growth by 50%.

Interestingly, the compounds were inactive against HSV-1 and HSV-2. This is somewhat surprising since most anti-herpes drugs targeting viral DNA polymerase share a broad spectrum activity against the various herpesviruses.[25-29] The mechanism of action for compounds **7a-m**, **9**, **13**, **17**, **20**, **23**, and **24** however, remains unclear, thus further investigation is warranted.

In addition, the target compounds were screened against a large panel of additional DNA and RNA viruses. No activity was observed for Vaccinia virus, Vesicular stomatitis virus, Coxsackie virus B4, Influenza A virus H1N1 subtype, Influenza A virus H3N2 subtype, Influenza B virus, Parainfluenza-3 virus, Reovirus-1, Sindbis virus, Punta Toro virus, Feline Corona Virus, HIV-1 and HIV-2.

3. Conclusions

Herein we have described the synthesis, preliminary biological evaluation and SAR studies for a series of novel uracil derivatives as potential dual HCMV-VZV agents. The majority of the synthesized compounds exhibited potent antiviral activity in cell cultures. Experimental data undoubtedly shows that ω-(4-bromophenoxy)alkyl substituent at N^1 and *N*-(4-phenoxyphenyl)acetamide side chain at N^3 of uracil are the key elements responsible for both anti-HCMV and anti-VZV activity. The mode of action for the reported series is not yet fully elucidated and will be published elsewhere once it has been studied further. In the meantime, the most active compounds in the series **7b**, **7h** and **7i** represent an excellent starting point for further optimization.

4. Experimental

4.1. General

All reagents were obtained at the highest grade available from Sigma and Acros Organics, and were used without further purification unless otherwise noted. Anhydrous DMF and isopropyl alcohol were purchased from Sigma-Aldrich Co. Anhydrous acetone, DCE, and EtOAc were obtained by distillation over P_2O_5. TLC was performed on Merck TLC Silica gel 60 F_{254} plates eluting with the specified solvents and samples were made visual with a UV lamp, VL-6.LC (France). Acros Organics (Belgium) silica gel (Kieselgur 60–200 μm, 60A) 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., USA). NMR spectra were obtained using Bruker Avance 400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) and Bruker Avance 600 (600 MHz for ^{1}H and 150 MHz for ^{13}C) spectrometers in DMSO-d_6 or $CDCl_3$ with tetramethylsilane as an internal standard. High-resolution mass spectra were measured on Bruker micrOTOF II instruments using electrospray ionization (HRESIMS). The measurements were run in positive ion mode (interface capillary voltage –4500 V) in a mass range from m/z 50 to m/z 3000 Da; external or internal calibration was performed with ESI Tuning MixTM (Agilent Technologies). A syringe injection was used for solutions in MeCN (flow rate = 3 μL/min). N_2 was applied as a dry gas; the interface temperature was set at 180 °C.

4.2. Synthesis

*4.2.1. Compounds **4a**, **4b**, **4d-k***

The synthesis and characterization data for were reported previously.[9]

*4.2.1.1. 1-[5-(3-Bromophenoxy)pentyl]uracil (**4c**)*

An equimolar mixture of the 1-bromo-5-(3-bromophenoxy)pentane (**3c**) (4.35 g, 13.51 mmol) and 2,4-bis(trimethylsilyloxy)pyrimidine (3.43 g, 13.38 mmol) was heated at 160-170 °C for 1 h. The resulting melt was dissolved in EtOAc (50 mL) and treated with *i*-PrOH (10 mL). The precipitated product was collected and purified by short-column flash chromatography using EtOAc/DCE (1:5). Subsequent recrystallization from a mixture of EtOAc/hexane (2:1) provided the desired product as white crystals (3.87 g, 82%); mp 124.5-126 °C; R_f 0.42 (ethyl acetate); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.38 (2H, quin, *J* = 7.6 Hz, CH_2), 1.62 (2H, quin, *J* = 7.5 Hz, CH_2), 1.71 (2H, quin, *J* = 7.5 Hz, CH_2), 3.66 (2H, t, *J* = 7.2 Hz, NCH_2), 3.97 (2H, t, *J* = 6.5 Hz, OCH_2), 5.53 (1H, dd, *J* = 7.8 and 2.2 Hz, Ura-H-5), 6.93 (1H, dd, *J* = 8.3 and 2.2 Hz, H-6'), 7.06-7.14 (2H, m, H-2', H-4'), 7.22 (1H, t, *J* = 8.2 Hz, H-5'), 7.65 (1H, d, *J* = 7.8 Hz, Ura-H-6), 11.22 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.6, 28.4, 47.6, 67.9, 101.1, 114.3, 117.5, 122.4, 123.6, 131.5, 146.0, 151.3, 160.0, 164.1.

*4.2.1.2. 1-(6-Phenylhexyl)uracil (**12**)*

An equimolar mixture of the 1-bromo-6-phenylhexane (**11**) (2.15 g, 8.91 mmol) and 2,4-bis(trimethylsilyloxy)pyrimidine (2.26 g, 8.81 mmol) was heated at 160-170 °C for 1 h. The resulting melt was dissolved in EtOAc (50 mL) and treated with *i*-PrOH (10 mL). Precipitate was filtered off, and the filtrate evaporated, taken up into acetone (30 mL) and EtOAc (5 mL) and purified by short-column flash chromatography using EtOAc to give **12** as white crystals (0.72 g, 30%); mp 78-79 °C, R_f 0.61 (ethyl acetate); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.26-1.34 (4H, m, CH_2), 1.55-1.59 (4H, m, CH_2), 2.55 (2H, t, *J* = 7.4 Hz, $PhCH_2$), 3.64 (2H, t, *J* = 7.2 Hz, NCH_2), 5.53 (1H, dd, *J* = 7.8 and 1.6 Hz, Ura-H-5), 7.13-7.17 (3H, m, H-2', H-4', H-6'), 7.26 (2H, t, *J* = 7.4 Hz, H-3', H-5'), 7.59 (2H, d, *J* = 7.8 Hz, Ura-H-6), 11.11 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.6, 28.2, 28.4, 30.7, 35.1, 47.5, 100.8, 125.6, 128.2, 142.2, 145.6, 151.0, 163.8.

*4.2.1.3. 1-[4-[(4-Bromobenzyl)oxy]butyl]uracil (**16**)*

A mixture of uracil (3.1 g, 27.66 mmol) and K_2CO_3 (1.40 g, 10.13 mmol) in anhydrous DMF (10 mL) was stirred at 80°C for 40 min. After cooling to room temperature, 4-(4-bromobenzyloxy)butyl *p*-toluenesulfonate (**15**) (3.80 g, 9.19 mmol) was added and stirring continued for 24 h. The reaction mixture was filtered, concentrated under reduced pressure and purified by short-column flash chromatography using a mixture of $CHCl_3$/EtOH (10:1). Analytical sample was recrystallized from EtOAc to give compound **16** as white crystals (1.20 g, 37%), mp 95.5-97.5 °C, R_f 0.44 (ethyl acetate); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.51 (2H, quin, *J* = 7.4 Hz, CH_2), 1.63 (2H, quin, *J* = 7.4 Hz, CH_2), 3.42 (2H, t, *J* = 6.1 Hz, NCH_2), 3.66 (2H, t, *J* = 7.1 Hz, OCH_2), 4.41 (2H, s, CH_2O), 5.53 (1H, d, *J* = 7.8 Hz, Ura-H-5), 7.27 (2H, d, *J* = 8.1 Hz, H-2, H-6), 7.53 (2H, d, *J* = 8.1 Hz, H-3, H-5), 7.63 (1H, d, *J* = 7.8 Hz, Ura-H-6), 11.21 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.8, 26.4, 47.6, 69.6, 71.3, 101.1, 120.7, 129.8, 131.5, 138.4, 146.0, 151.3, 164.1.

*4.2.1.4. 1-[[2-(4-Bromobenzyloxy)ethoxy]methyl]-uracil (**19**)*

To a solution of 2,4-bis(trimethylsilyloxy)pyrimidine (4.58 g, 17.84 mmol) in anhydrous methylene chloride (30 mL) was added a solution of [[2-(4-bromobenzyloxy)ethoxy]methoxy]methyl chloride (**18**) (5.0 g, 17.88 mmol) in methylene chloride (20 mL) and stirred for 16 h at room temperature. Ethanol (95%, 10 ml) was added and the resulting mixture was stirred for 30 min, filtered, evaporated to dryness under reduced pressure and purified by short-column flash chromatography using a mixture of $CHCl_3$/EtOH (10:1). Analytical sample was recrystallized from ethyl acetate to give compound **19** as white crystals (4.25 g, 67%), mp 103.5-104.5 °C, R_f 0.39 (ethyl acetate); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.54 (2H, dd, *J* = 5.9 and 3.2 Hz, CH_2), 3.66 (2H, dd, *J* = 5.5 and 3.5 Hz, CH_2), 4.44 (2H, s, NCH_2), 5.10 (2H, s, OCH_2), 5.60 (1H, d, *J* = 7.8 Hz, Ura-H-5), 7.26 (2H, d, *J* = 8.3 Hz, H-2', H-6'), 7.52 (2H, d, *J* = 8.3 Hz, H-3', H-5'), 7.70 (1H, d, *J* = 8.1 Hz, Ura-H-6), 11.33 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 68.4, 69.2, 71.5, 76.9, 101.9, 120.7, 129.8, 131.5, 138.2, 145.3, 151.4, 163.9.

*4.2.1.5. 1-[4-(4-Bromophenoxy)benzyl]uracil (**22**)*

A solution of 2,4-bis(trimethylsilyloxy)-pyrimidine (3.44 g, 13.40 mmol) and 4-(bromophenoxy)benzylbromide (**21**) (4.6 g, 13.45 mmol) in anhydrous DCE (50 mL) was heated at reflux for 24 h, cooled to room temperature and treated with *i*-PrOH (15 mL). The resulting precipitate was collected and purified by short-column flash chromatography using a mixture of $CHCl_3$/EtOH (10:1). An analytical sample was recrystallized from a mixture of DMF/*i*-PrOH/H_2O (2:2:1) to give compound **22** as white crystals (2.60 g, 52%), mp 164-165.5 °C, R_f 0.46 (ethyl acetate); ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.85 (2H, s, CH_2), 5.60 (Hz, dd, J = 7.8 and 2.2 1H, Ura-H-5), 6.95 (2H, d, J = 9.0 Hz, H-2", H-6"), 7.03 (d, J = 8.6 Hz, 2H, H-3", H-6"), 7.35 (d, J = 8.8 Hz, 2H, H-2', H-6'), 7.54 (d, J = 8.8 Hz, 2H, H-3', H-5'), 7.78 (d, J = 8.1 Hz, 1H, Ura-H-6), 11.34 (d, J = 2.0 Hz, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 50.0, 101.7, 115.4, 119.4, 120.9, 129.9, 132.7, 133.1, 145.9, 151.3, 156.0, 156.4, 164.0.

*4.2.2. General procedure for the synthesis of 2-chloro-N-(4-substituted phenyl)acetamide **6a-c***

Chloroacetyl chloride (0.47 mL, 5.90 mmol) was added dropwise to a stirred mixture of the appropriate aniline **5a-c** (5.56 mmol) and K_2CO_3 (0.90 g, 6.51 mmol) in anhydrous DCE (20 mL) at 0 °C. The reaction mixture was stirred for 2 hours and allowed to warm to room temperature overnight. The inorganic materials were filtered through a pad of silica gel and washed with DCE (25 mL). The filtrate was evaporated under reduced pressure and the residue was purified by recrystallization from a mixture of hexane/ethyl acetate (3 : 2).

*4.2.2.1. 2-Chloro-N-(4-phenoxyphenyl)acetamide (**6a**)*

Yield 80%, mp 105-106 °C, R_f 0.62 (hexane/ethyl acetate, 1:1); ^{1}H NMR (600 MHz, DMSO-d_6): δ 4.24 (2H, s, $COCH_2$), 6.97 (2H, d, J = 8.7 Hz, H-3', H-5'), 7.00 (2H, d, J = 9.0 Hz, H-2", H-6"), 7.10 (1H, t, J = 7.4 Hz, H-4"), 7.36 (2H, t, J = 8.5 Hz, H-3", H-5"), 7.61 (2H, d, J = 9.0 Hz, H-2', H-6'), 10.30 (1H, s, NH); ^{13}C NMR (150 MHz, DMSO-d_6): δ 47.7, 122.2, 123.6, 125.4, 134.2, 138.5, 156.6, 161.4, 168.7.

*4.2.2.2. N-(4-Benzylphenyl)-2-chloroacetamide (**6b**)*

Yield 78%, mp 142.5-144 °C, R_f 0.52 (hexane/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.89 (2H, s, $PhCH_2$), 4.23 (2H, s, $COCH_2$), 7.15-7.21 (m, 5H, C_6H_5), 7.25-7.29 (2H, m, aromatic H), 7.51 (2H, d, J = 8.6 Hz, H-2', H-6'), 10.24 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 40.9, 43.9, 119.9, 126.3, 128.7, 128.9, 129.4, 136.8, 137.1, 141.7, 164.8.

*4.2.2.3. N-[4-(Benzyloxy)phenyl]-2-chloroacetamide (**6c**)*

Yield 88%, mp 142-144 °C, R_f 0.63 (hexane/ethyl acetate, 1:1); ^{1}H NMR (600 MHz, DMSO-d_6) δ 4.19 (2H, s, $COCH_2$), 5.05 (2H, 2H, s, $PhCH_2$), 6.97 (2H, d, J = 9.1 Hz, H-3', H-5'), 7.31 (1H, t, J = 7.4 Hz, H-4"), 7.37 (2H, t, J = 7.6 Hz, H-3", H-5"), 7.42 (2H, d, J = 7.0 Hz, H-2", H-6"), 7.49 (2H, d, J = 9.0 Hz, H-2', H-6'), 10.16 (1H, s, NH); ^{13}C NMR (150 MHz, DMSO-d_6): δ 47.7, 73.6, 119.2, 125.3, 131.9, 132.0, 132.6, 135.9, 141.3, 159.0, 168.5.

*4.2.3. General procedure for the synthesis of **7a-l**, **9**, **13**, **17**, **20**, and **23***

A mixture of the appropriate 1-substituted uracil **4a-i**, **12**, **16**, **19** or **22** (1.42 mmol) and K_2CO_3 (0.29 g, 2.10 mmol) in anhydrous DMF (10 mL) was stirred at 80°C for 40 min. After cooling to room temperature, the corresponding 2-chloroacetamide **6a-c** (1.56 mmol) was added and stirring continued for 24 h. The reaction mixture was filtered, concentrated under reduced pressure and purified by short-column flash chromatography using DCE. Analytical samples were recrystallized from a mixture of hexane/ethyl acetate (1:1).

*4.2.3.1. 2-[2,6-Dioxo-3-(5-phenoxypentyl)-3,6-dihydropyrimidin-1(2H)-yl]-N-(4-phenoxyphenyl) acetamide (**7a**)*

Yield 92%, mp 114-115.5 °C, R_f 0.39 (DCE/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.41 (2H, quin, J = 7.1 Hz, CH_2), 1.67 (2H, quin, J = 7.1 Hz, CH_2), 1.74 (2H, quin, J = 7.8 Hz, CH_2), 3.76 (2H, t, J = 7.0 Hz, NCH_2), 3.94 (2H, t, J = 6.3 Hz, OCH_2), 4.60 (2H, s, $COCH_2$), 5.75 (1H, d, J = 7.9 Hz, H-5), 6.87-6.91 (3H, m, H-4', H-2", H-6"), 6.95-6.99 (4H, m, H-2‴, H-6‴, H-2', H-6'), 7.10 (1H, dt, J = 7.3 and 1.0 Hz, H-4‴), 7.36 (2H, dt, J = 7.3 and 1.8 Hz, H-3‴, H-5‴), 7.36 (2H, dt, J = 8.6 and 1.3 Hz, H-3', H-5'), 7.57 (2H, d, J = 9.0 Hz, H-3", H-5"), 7.78 (1H, d, J = 7.8 Hz, H-6), 10.26 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.7, 28.5, 28.6, 43.4, 48.8, 67.4, 100.3, 114.7, 118.2, 119.8, 120.7, 121.0, 123.3, 130.0, 130.3, 135.0, 144.9, 151.4, 152.1, 157.6, 158.9, 162.6, 165.4; HRMS: found *m/z* 500.2181; calcd for $C_{29}H_{29}N_3O_5$ $[M+H]^+$ 500.2180.

*4.2.3.2. 2-[3-[5-(4-Bromophenoxy)pentyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl]-N-(4-phenoxyphenyl)acetamide (**7b**)*

Yield 87%, mp 128-130 °C, R_f 0.47 (DCE/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.40 (2H, quin, J = 7.8 Hz, CH_2), 1.66 (2H,quin, J = 7.2 Hz, CH_2), 1.72 (2H, quin, J = 7.3 Hz, CH_2), 3.76 (2H, t, J = 7.0 Hz, NCH_2), 3.93 (2H, t, J = 6.4 Hz, OCH_2), 4.61 (2H, s, $COCH_2$), 5.75 (1H, d, J = 7.8 Hz, H-5), 6.88 (2H, d, J = 8.9 Hz, H-2", H-6"), 6.96 (2H, d, J = 8.2 Hz, H-2‴, H-6‴), 6.98 (2H, d, J = 8.4 Hz, H-2', H-6'), 7.09 (1H, dt, J = 7.3 and 0.9 Hz, H-4‴), 7.36 (2H, t, J = 7.6 Hz, H-3‴, H-5‴), 7.40 (2H, d, J = 8.8 Hz, H-3', H-5'), 7.57 (2H, d, J = 8.9 Hz, H-3", H-5"), 7.77 (1H, d, J = 8.0 Hz, H-6), 10.27 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.3, 25.5, 28.1, 43.2, 48.5, 67.6, 100.0, 111.8, 116.7, 118.0, 119.5, 120.7, 123.0, 130.0, 132.1, 134.7, 144.6, 151.1, 151.8, 157.3, 157.9, 162.3, 165.1; HRMS: found *m/z* 578.1287; calcd for $C_{29}H_{28}BrN_3O_5$ $[M+H]^+$ 578.1285.

*4.2.3.3. 2-[3-[5-(3-Bromophenoxy)pentyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl]-N-(4-phenoxyphenyl)acetamide (**7c**)*

Yield 91%, mp 125-126.5 °C, R_f 0.53 (DCE/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 1.40 (quin, J = 6.4 Hz, 2H, CH_2), 1.66 (quin, J = 7.3 Hz, 2H, CH_2), 1.73 (quin, J = 7.8 Hz, 2H, CH_2), 3.76 (t, J = 7.3 Hz, 2H, CH_2N), 3.96 (t, J = 6.4 Hz, 2H, CH_2O), 4.61 (s, 2H, CH_2CO), 5.76 (d, J = 7.8 Hz, 1H, H-5), 6.93 (dd, J = 8.3, 2.3 Hz, 1H, H-4'), 6.95-7.00 (m, 4H, H-2", H-6", H-2‴, H-6‴), 7.07-7.12 (m, 3H, H-2', H-6', H-4‴), 7.20 (t, J = 8.0 Hz, 1H, H-5'), 7.36 (dt, J = 7.6, 2.4 Hz, 2H, H-3‴, H-5‴), 7.57 (d, J = 9.0 Hz, 2H, H-3", H-5"), 7.77 (d, J = 8.0 Hz, 1H, H-6), 10.27 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm 22.6, 28.4, 40.7, 43.4, 48.8, 67.9, 100.3, 114.3, 117.5, 118.2, 119.8, 121.0, 122.4, 123.3, 123.6, 130.3, 131.5, 135.0, 144.8, 151.4, 152.1, 157.6, 160.0, 162.6, 165.4; HRMS: found *m/z* 578.1280; calcd for $C_{29}H_{28}BrN_3O_5$ $[M+H]^+$ 578.1285.

*4.2.3.4. 2-[3-[5-(4-Cyanophenoxy)pentyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl]-N-(4-phenoxyphenyl)acetamide (**7d**)*

Yield 83%, mp 127-128.5 °C, R_f 0.33 (DCE/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.41 (2H, quin, *J* = 8.5 Hz, CH_2), 1.67 (2H, quin, *J* = 7.4 Hz, CH_2), 1.76 (2H, quin, *J* = 7.6 Hz, CH_2), 3.76 (2H, t, *J* = 7.1 Hz, NCH_2), 4.05 (2H, t, *J* = 6.4 Hz, OCH_2), 4.60 (2H, s, $COCH_2$), 5.75 (1H, d, *J* = 8.0 Hz, H-5), 6.96 (2H, d, *J* = 8.8 Hz, H-2'', H-6''), 6.98 (2H, d, *J* = 8.8 Hz, H-2''', H-6'''), 7.08 (2H, d, *J* = 9.1 Hz, H-2', H-6'), 7.09 (1H, t, *J* = 7.6 Hz, H-4'''), 7.36 (2H, dt, *J* = 7.4 and 1.2 Hz, H-3''', H-5'''), 7.57 (2H, d, *J* = 8.8 Hz, H-3', H-5'), 7.72 (2H, d, *J* = 8.8 Hz, H-3'', H-5''), 7.77 (1H, d, *J* = 7.8 Hz, H-6), 10.27 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.5, 28.3, 28.4, 43.4, 48.7, 68.2, 100.3, 103.0, 115.8, 118.2, 119.5, 119.8, 121.0, 123.3, 130.3, 134.5, 135.0, 144.8, 151.4, 152.1, 157.6, 162.4, 162.5, 165.4; HRMS: found *m/z* 525.2126; calcd for $C_{30}H_{28}N_4O_5$ $[M+H]^+$ 525.2132.

*4.2.3.5. 2-[3-[5-(4-Phenylphenoxy)pentyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl]-N-(4-phenoxyphenyl)acetamide (**7e**)*

Yield 78%, mp 138.5-139.5 °C, R_f 0.42 (DCE/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.43 (2H, quin, *J* = 8.1 Hz, CH_2), 1.68 (2H, quin, *J* = 7.1 Hz, CH_2), 1.76 (2H, quin, *J* = 7.6 Hz, CH_2), 3.78 (2H, t, *J* = 7.0 Hz, NCH_2), 3.99 (2H, t, *J* = 6.3 Hz, OCH_2), 4.61 (2H, s, $COCH_2$), 5.76 (1H, d, *J* = 8.0 Hz, H-5), 6.94-7.01 (6H, m, H-2', H-6', H-2'', H-6'', H-2''', H-6'''), 7.09 (1H, dt, *J* = 7.3 and 1.0 Hz, H-4'''), 7.29 (1H, dt, *J* = 7.3 and 1.0 Hz, Ph-H^4), 7.35 (dt, *J* = 7.6, 1.0 Hz, 2H, H-3''', H-5'''), 7.41 (t, *J* = 7.3 Hz, 2H, Ph-H^3, Ph-H^5), 7.54-7.59 (6H, m, H-3', H-5', H-3'', H-5'', Ph-H^2, Ph-H^6), 7.79 (1H, d, *J* = 7.8 Hz, H-6), 10.27 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.7, 28.5, 28.6, 43.4, 45.4, 48.8, 67.6, 100.3, 115.2, 118.2, 119.8, 121.0, 123.3, 126.5, 127.0, 128.0, 129.2, 130.3, 132.7, 135.1, 140.2, 144.9, 151.4, 152.1, 157.7, 158.6, 162.6, 165.4; HRMS: found *m/z* 576.2487; calcd for $C_{35}H_{33}BrN_3O_5$ $[M+H]^+$ 576.2493.

*4.2.3.6. 2-[3-[3-(4-Bromophenoxy)propyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl]-N-(4-phenoxyphenyl)acetamide (**7f**)*

Yield 71%, mp 127.5-129 °C, R_f 0.38 (DCE/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) d 1.96-2.13 (2H, m, CH_2), 3.92 (2H, t, *J* = 6.7 Hz, NCH_2), 3.96-4.06 (2H, m, OCH_2), 4.60 (2H, s, CH_2CO), 5.74 (1H, d, *J*=7.9 Hz, H-5), 6.84-6.91 (2H, m, H-2'', H-6''), 6.93-7.03 (4 H, m, H-2''', H-6''', H-2', H-6'), 7.07-7.14 (1H, m, H-4'''), 7.30-7.47 (4H, m, H-3', H-5', H-3''', H-5'''), 7.53 - 7.64 (2H, m, H-3'', H-5''), 7.74 (1 H, d, *J*=7.9 Hz, H-6), 10.25 (1 H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.8, 43.1, 46.3, 65.2, 100.0, 100.8, 112.0, 116.7, 117.9, 119.4, 120.7, 123.0, 129.9, 132.0, 134.6, 144.6, 145.7, 151.1, 157.6, 162.2, 165.0; HRMS: found *m/z* 550.0968; calcd for $C_{27}H_{24}BrN_3O_5$ $[M+H]^+$ 550.0972.

*4.2.3.7. 2-[3-[4-(4-Bromophenoxy)butyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl]-N-(4-phenoxyphenyl)acetamide (**7g**)*

Yield 69%, mp 151-152 °C, R_f 0.39 (DCE/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.72 (4H, m, CH_2CH_2), 3.80 (2H, t, *J* = 6.6 Hz, CH_2), 3.97 (2H, t, *J* = 5.9 Hz, CH_2), 4.60 (2H, s, CH_2CO), 5.76 (1H, d, *J* = 7.8 Hz, H-5), 6.90 (2H, d, *J* = 9.1 Hz, H-2'', H-6''), 6.94-7.00 (4H, m, H-2''', H-6''', H-2', H-6'), 7.10 (1H, dt, *J* = 7.2 and 1.0 Hz, H-4'''), 7.36 (2H, t, 7.6 Hz, H-3''', H-5'''), 7.42 (2H, d, *J* = 9.0 Hz, H-3', H-5'), 7.57 (2H, d, *J* = 9.1 Hz, H-3'', H-5''), 7.79 (1H, d, *J* = 8.1 Hz, H-6), 10.27 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.5, 25.8, 43.5, 48.7, 67.7, 100.4, 112.2, 117.1, 118.2, 119.8, 121.0, 123.3, 130.3, 132.4, 135.0, 144.8, 151.4, 152.1, 157.6, 158.2, 162.5, 165.4; HRMS: found *m/z* 564.1127; calcd for $C_{28}H_{26}BrN_3O_5$ $[M+H]^+$ 564.1129.

*4.2.3.8. 2-[3-[6-(4-Bromophenoxy)hexyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl]-N-(4-phenoxyphenyl)acetamide (**7h**)*

Yield 77%, mp 143-144 °C, R_f 0.48 (DCE/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (2H, quin, *J* = 7.6 Hz, CH_2), 1.52 (2H, quin, *J* = 7.1 Hz, CH_2), 1.73-1.79 (4H, m, CH_2CH_2), 3.76 (2H, t, *J* = 7.8 Hz, NCH_2), 3.93 (2H, t, *J* = 6.3 Hz, OCH_2), 4.77 (2H, s, $COCH_2$), 5.77 (1H, d, *J* = 7.8 Hz, H-5), 6.76 (2H, d, *J* = 8.8 Hz, H-2'', H-6''), 6.93 (2H, d, *J* = 8.8 Hz, H-2''', H-6'''), 6.97 (2H, d, *J* = 8.3 Hz, H-2', H-6'), 7.07 (1H, dt, *J* = 7.1 and 0.9 Hz, H-4'''), 7.14 (1H, d, *J* = 7.9 Hz, H-6), 7.28-7.37 (4H, m, H-3''', H-5''', H-3', H-5'), 7.44 (2H, d, *J* = 8.8 Hz, H-3'', H-5''), 7.95 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.4, 25.9, 28.7, 28.8, 49.6, 67.9, 101.2, 116.3, 118.4, 119.3, 122.9, 129.5, 132.1, 142.5, 151.3, 162.6; HRMS: found *m/z* 592.1437; calcd for $C_{30}H_{30}BrN_3O_5$ $[M+H]^+$ 592.1442.

*4.2.3.9. 2-[3-[8-(4-Bromophenoxy)octyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl]-N-(4-phenoxyphenyl)acetamide (**7i**)*

Yield 71%, mp 128-129 °C, R_f 0.54 (DCE/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (6H, m, $CH_2 \times 6$), 1.42 (2H, quin, *J* = 7.6 Hz, CH_2), 1.71 (2H, quin, *J* = 7.1 Hz, CH_2), 1.75 (2H, quin, *J* = 8.1 Hz, CH_2), 3.73 (2H, t, *J* = 7.4 Hz, NCH_2), 3.90 (2H, t, *J* = 6.6 Hz, OCH_2), 4.81 (2H, s, $COCH_2$), 5.80 (1H, d, *J* = 7.8 Hz, H-5), 6.77 (2H, d, *J* = 9.0 Hz, H-2'', H-6''), 6.88 (2H, d, *J* = 8.8 Hz, H-2''', H-6'''), 6.94 (d, *J* = 7.8 Hz, 2H, H-2', H-6'), 7.06 (t, *J* = 7.3 Hz, 1H, H-4'''), 7.17 (d, *J* = 7.8 Hz, 1H, H-6), 7.30-7.37 (4H, m, H-3''', H-5''', H-3', H-5'), 7.43 (2H, d, *J* = 8.8 Hz, H-3'', H-5''), 8.52 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.7, 26.2, 28.8, 28.91, 28.94, 29.0, 44.2, 49.9, 68.0, 76.6, 76.9, 77.3, 101.2, 112.4, 116.2, 118.2, 119.3, 121.2, 122.8, 129.6, 132.1, 133.3, 143.0, 151.3, 153.1, 156.9, 158.1, 162.9, 164.8; HRMS: found *m/z* 620.1749; calcd for $C_{32}H_{34}BrN_3O_5$ $[M+H]^+$ 620.1755.

*4.2.3.10. 2-[3-[5-(4-Bromophenoxy)pentyl]-5-iodo-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl]-N-(4-phenoxyphenyl)acetamide (**7j**)*

A mixture of 1-[5-(4-bromophenoxy)pentyl]-5-iodouracil (**4j**) (0.48 g, 1.00 mmol) and NaH (60% dispersion in mineral oil, 0.05 g, 1.25 mmol) in anhydrous DMF (15 mL) was stirred at room temperature for 1 h followed by addition of 2-chloro-*N*-(4-phenoxyphenyl)acetamide (**6a**, 0.26 g, 0.99 mmol). After 4 h, the reaction mixture was filtered, concentrated under reduced pressure and purified by short-column flash chromatography using DCE. Analytical sample was recrystallized from a mixture of hexane/EtOAc (1:1) to give compound **7j** as a white powder (0.60 g, 86%), mp 151-153 °C, R_f 0.74 (DCE/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.39 (quin, *J* = 8.1 Hz, 2H, CH_2), 1.66 (quin, *J* = 7.1 Hz, 2H, CH_2), 1.72 (quin, *J* = 7.9 Hz, 2H, CH_2), 3.78 (t, *J* = 7.0 Hz, 2H, NCH_2), 3.93 (t, *J* = 6.6 Hz, 2H, OCH_2), 4.65 (s, 2H, $COCH_2$), 6.88 (d, *J* = 9.0 Hz, 2H, H-2'', H-6''), 6.96 (d, *J* = 8.1 Hz, 2H, H-2''', H-6'''), 6.98 (d, *J* = 8.8 Hz, 2H, H-2', H-6'), 7.10 (dt, *J* = 7.3, 0.9 Hz, 1H, H-4'''), 7.36 (dt, *J* = 7.5, 1.0 Hz, 2H, H-3''', H-5'''), 7.40 (d, *J* = 9.0 Hz, 2H, H-3', H-5'), 7.56 (d, *J* = 9.0 Hz, 2H, H-3'', H-5''), 8.37 (s, 1H, H-6), 10.28 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.5, 28.4, 28.5, 45.0, 49.1, 67.2, 67.9, 112.1, 117.1, 118.3, 119.8, 121.0, 123.4, 130.3, 132.4, 134.9, 149.1, 151.0, 152.2, 157.6, 158.2, 160.2, 165.2; HRMS: found *m/z* 704.0248; calcd for $C_{29}H_{27}BrIN_3O_5$ [M+H]$^+$ 704.0252.

*4.2.3.11. N-(4-Benzylphenyl)-2-[3-[5-(4-bromophenoxy)pentyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl]acetamide (**7k**)*

Yield 80%, mp 117-118 °C, R_f 0.42 (DCE/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 1.39 (2H, quin, J = 6.9 Hz, CH_2), 1.65 (2H, quin, J = 7.1 Hz, CH_2), 1.72 (2H, quin, J = 7.1 Hz, CH_2), 3.75 (2H, t, J = 6.9 Hz, NCH_2), 3.87 (2H, s, $PhCH_2$), 3.92 (2H, t, J = 6.4 Hz, OCH_2), 4.59 (2H, s, $COCH_2$), 5.75 (1H, d, J = 7.8 Hz, H-5), 6.88 (2H, d, J = 9.1 Hz, H-2", H-6"), 7.13-7.20 (5H, m, aromatic H), 7.25-7.28 (2H, m, aromatic H), 7.40 (2H, d, J = 9.0 Hz, H-3", H-5"), 7.46 (2H, d, J = 8.5 Hz, H-3', H-5'), 7.77 (1H, d, J = 7.8 Hz, H-6), 10.20 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm 22.6, 28.4, 43.4, 48.7, 67.8, 100.28, 112.1, 117.0, 119.4, 126.2, 128.7, 128.9, 129.3, 132.4, 136.5, 137.1, 141.7, 144.8, 151.4, 158.2, 162.6, 165.4; HRMS: found *m/z* 576.1487; calcd for $C_{30}H_{30}BrN_3O_4$ [M+H]$^+$ 576.1492.

*4.2.3.12. N-[4-(Benzyloxy)phenyl]-2-[3-[5-(4-bromophenoxy)pentyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl]acetamide (**7l**)*

Yield 80%, mp 172.5-174.5 °C, R_f 0.46 (DCE/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.38 (2H, quin, J = 7.8 Hz, CH_2), 1.64 (2H, quin, J = 7.4 Hz, CH_2), 1.71 (2H, quin, J = 7.5 Hz, CH_2), 3.74 (2H, t, J = 7.1 Hz, NCH_2), 3.91 (2H, t, J = 6.4 Hz, OCH_2), 4.58 (2H, s, $COCH_2$), 5.05 (2H, s, OCH_2Ph), 5.74 (1H, d, J = 8.1 Hz, H-5), 6.87 (2H, d, J = 9.1 Hz, H-3', H-5'), 6.94 (2H, d, J = 8.2 Hz, H-2"', H-6"'), 7.31 (1H, t, J = 7.1 Hz, H-4"), 7.35-7.46 (8H, m, aromatic H), 7.73 (1H, d, J = 8.0 Hz, H-6), 10.13 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.6, 28.4, 43.4, 48.8, 67.9, 69.7, 100.3, 112.0, 115.2, 117.0, 120.8, 128.0, 128.1, 128.7, 132.4, 137.4, 144.8, 151.4, 154.6, 158.2, 162.6, 165.1; HRMS: found *m/z* 592.1437; calcd for $C_{30}H_{30}BrN_3O_5$ [M+H]$^+$ 592.1442.

*4.2.3.13. 2-[3-[5-(4-Bromophenoxy)pentyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl]-N-phenyl-acetamide (**7m**)*

Yield 78%, mp 157-158.5 °C, R_f 0.37 (DCE/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.39 (2H, quin, J = 7.6 Hz, CH_2), 1.72 (2H, quin, J = 7.2 Hz, CH_2), 1.66 (2H, quin, J = 7.6 Hz, CH_2), 3.75 (2H, t, J = 7.2 Hz, NCH_2), 3.93 (2H, t, J = 6.4 Hz, OCH_2), 4.61 (2H, s, CH_2CO), 5.76 (1H, d, J = 7.8 Hz, Ura-H-5), 6.88 (2H, d, J = 8.8 Hz, H-2, H-6), 7.04 (1H, t, J = 7.3 Hz, H-4'), 7.30 (2H, t, J = 8.1 Hz, H-3', H-5'), 7.40 (2H, d, J = 9.0 Hz, H-3, H-5), 7.55 (2H, dd, J = 8.4 and 1.1 Hz, H-2, H-6), 7.77 (1H, d, J = 8.1 Hz, Ura-H-6), 10.25 (1H, s, 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, 144.8, 151.4, 158.2, 162.6, 165.6; HRMS: found *m/z* 486.1020; calcd for $C_{23}H_{24}BrN_3O_4$ [M+H]$^+$ 486.1023.

*4.2.3.14. 2-[2,6-Dioxo-3-(6-phenylhexyl)-3,6-dihydropyrimidin-1(2H)-yl]-N-(4-phenoxyphenyl)-acetamide (**13**)*

Yield 90%, mp 135-136 °C, R_f 0.48 (DCE/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.22-1.37 (4H, m, CH_2), 1.49-1.65 (4H, m, CH_2), 2.55 (2H, t, J = 7.4 Hz, CH_2), 3.72 (2H, t, J = 7.1 Hz, CH_2), 4.61 (2H, s, CH_2), 5.74 (1H, d, J = 7.8 Hz, Ura-H-5), 6.93-7.00 (4H, m, H-3', H-5', H-2", H-6"), 7.07-7.12 (1H, m, H-4"), 7.13-7.19 (3H, m, H-4, H-2, H-6), 7.21-7.27 (2H, m, H-3, H-5), 7.33-7.39 (2H, m, H-2', H-6'), 7.54-7.60 (2H, m, H-3", H-5"), 7.75 (1H, d, J = 7.8 Hz, Ura-H-6), 10.27 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.9, 28.5, 28.6, 31.1, 35.3, 43.4, 48.9, 100.2, 118.2, 119.8, 121.0, 123.3, 125.9, 128.5, 128.5, 130.3, 135.0, 142.5, 144.8, 151.4, 152.1, 157.6, 162.6, 165.4; HRMS: found *m/z* 498.2386; calcd for $C_{30}H_{31}N_3O_4$ [M+H]$^+$ 498.2387.

*4.2.3.15. 2-[3-[4-(4-Bromobenzyloxy)butyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl]-N-(4-phenoxyphenyl)acetamide (**17**)*

Yield 63%, mp 114-116 °C, R_f 0.28 (DCE/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.54 (2H, quin, J = 6.3 Hz, CH_2), 1.67 (2H, quin, J = 7.4 Hz, CH_2), 3.44 (2H, t, J = 6.1 Hz, CH_2), 3.75 (2H, t, J = 7.1 Hz, CH_2), 4.42 (2H, s, $ArCH_2$), 4.60 (2H, s, CH_2CO), 5.75 (1H, d, J = 7.9 Hz, H-5), 6.96 (2H, d, J = 8.1 Hz, H-2"', H-6"'), 6.98 (2H, d, J = 9.1 Hz, H-2", H-6"), 7.09 (t, J = 7.3 Hz, 1H, H-4"'), 7.27 (d, J = 8.3 Hz, 2H, H-2', H-6'), 7.36 (2H, dt, J = 7.6 and 2.0 Hz, H-3"', H-5"'), 7.52 (2H, d, J = 8.3 Hz, H-3', H-5'), 7.57 (2H, d, J = 7.1 Hz, H-3", H-5"), 7.76 (1H, d, J = 7.8 Hz, H-6), 10.27 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.7, 26.4, 43.4, 45.4, 48.8, 69.6, 71.3, 100.3, 118.2, 119.8, 120.7, 121.0, 123.3, 129.9, 130.3, 131.5, 135.0, 138.4, 144.8, 151.4, 152.1, 157.6, 162.6, 165.4; HRMS: found *m/z* 578.1287; calcd for $C_{29}H_{28}BrN_3O_5$ [M+H]$^+$ 578.1285.

*4.2.3.16. 2-[3-[[2-(4-Bromobenzyloxy)ethoxy]methyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl]-N-(4-phenoxyphenyl)acetamide (**20**)*

Yield 75%, mp 147.5-149.5 °C, R_f 0.53 (DCE/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.55 (2H, t, J = 5.9 Hz, CH_2), 3.68 (2H, t, J = 4.9 Hz, CH_2), 4.45 (2H, s, $ArCH_2$), 4.61 (2H, s, CH_2CO), 5.19 (2H, s, NCH_2O), 5.82 (1H, d, J = 7.8 Hz, H-5), 6.96 (2H, d, J = 9.0 Hz, H-2"', H-6"'), 6.98 (d, J = 9.0 Hz, 2H, H-2", H-6"), 7.09 (t, J = 7.3 Hz, 1H, H-4"'), 7.27 (d, J = 8.3 Hz, 2H, H-2', H-6'), 7.36 (2H, dt, J = 8.6 and 1.0 Hz, H-3"', H-5"'), 7.52 (2H, d, J = 8.3 Hz, H-3', H-5'), 7.56 (2H, d, J = 7.1 Hz, H-3", H-5"), 7.83 (1H, d, J = 7.9 Hz, H-6), 10.30 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 43.4, 68.6, 69.2, 71.5, 78.0, 101.1, 118.3, 119.8, 120.7, 121.0, 123.3, 129.9, 130.3, 131.5, 135.0, 138.2, 144.2, 151.6, 152.1, 157.6, 162.4, 165.3; HRMS: found *m/z* 580.1073; calcd for $C_{28}H_{26}BrN_3O_6$ [M+H]$^+$ 580.1078.

*4.2.3.17. 2-[3-[4-(4-Bromophenoxy)benzyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl]-N-(4-phenoxyphenyl)acetamide (**23**)*

Yield 64%, mp 201.5-202.5 °C, R_f 0.43 (DCE/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.62 (2H, s, $COCH_2$), 4.95 (2H, s, $ArCH_2$), 5.82 (2H, 1H, d, J = 7.8 Hz, H-5), 6.94-6.98 (6H, m, H-2", H-6", H-2"', H-6"', H-3"", H-5""), 7.04 (d, J = 8.5 Hz, H-2', H-6'), 7.09 (1H, dt, J = 7.3 and 1.0 Hz, H-4"'), 7.36 (2H, dt, J = 8.6, 1.2 Hz, H-3"', H-5"'), 7.38 (2H, d, J = 8.5 Hz, H-3', H-5'), 7.54 (2H, d, J = 8.8 Hz, H-2"", H-6""), 7.57 (2H, d, J = 9.1 Hz, H-3", H-5"), 7.91 (1H, d, J = 7.8 Hz, H-6), 10.30 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 43.6, 51.2, 100.9, 115.5, 118.2, 119.4, 119.8, 121.0, 123.3, 130.0, 130.3, 132.4, 133.1, 135.0, 144.7, 151.5, 152.1, 156.1, 156.3, 157.6, 162.5, 165.4; HRMS: found *m/z* 598.0969; calcd for $C_{31}H_{24}BrN_3O_5$ [M+H]$^+$ 598.0972.

*4.2.4. 2-(3-(5-(4-Bromophenoxy)pentyl)-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)acetic acid (**8**)*

A mixture of 1-[5-(4-bromophenoxy)pentyl]uracil (**4b**) (1.42 mmol) and K_2CO_3 (0.29 g, 2.10 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 short-column flash chromatography using DCE. Crude product was dissolved in EtOH (20 mL). Then LiOH (0.20 g, 8.35 mmol) and water (10 mL) was added, and the resulting mixture was stirred at room temperature for 2 h. After adjusting pH to 2 with addition of 1 M HCl resulting precipitate was filtered and recrystallized from a mixture of hexane/*i*-PrOH (1:2) to give the desired product as white powder (2.68 g, 100%), R_f 0.54 (*i*-PrOH/EtOAc/NH_4OH, 9:6:5), mp 142.5-145°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.37 (2H, quin, J = 7.4 Hz, CH_2), 1.55 (2H, quin, J = 7.4 Hz, CH_2), 1.71 (2H, quin, J = 7.4 Hz, CH_2), 3.79 (2H, t, J = 7.3 Hz, NCH_2), 3.92 (2H, t, J = 6.5 Hz, OCH_2), 4.45 (2H, s, CH_2), 5.72 (1H, d, J = 7.8 Hz, Ura-H-5), 6.89 (2H, d, J = 8.8 Hz, H-2, H-6), 7.41 (2H, d, J = 8.8 Hz, H-3, H-5), 7.65 (1H, d, J = 7.8 Hz, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.1, 27.1, 28.5, 50.0, 67.8, 100.4, 112.0, 117.0, 132.4, 144.9, 151.4, 158.2, 162.7, 169.8.

4.2.5. *N-(4-Benzoylphenyl)-2-[3-[5-(4-bromo-phenoxy)pentyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl]acetamide (**9**)*

A mixture of acid **8** (0.70 g, 1.70 mmol) and thionyl chloride (0.15 mL, 2.06 mmol) in anhydrous DCE (10 mL) was refluxed with the exclusion of moisture for 2 h. The volatile materials were evaporated under reduced pressure and the residue was dissolved in DCE (10 mL) and cooled to –15 °C. The resulting solution was added dropwise to a stirred solution of *N*-(trimethylsilyl)-4-benzoylaniline, which was prepared *in situ* by heating 4-benzoylaniline (0.34 g, 1.72 mmol) with excess of HMDS. The reaction mixture was stirred overnight at room temperature and diluted with *i*-PrOH (8 mL). Solvents were evaporated under reduced pressure and crude product was purified with short-column flash chromatography using hexane/EtOAc (1:2) to give compound **9** as a white powder (0.57 g, 57%), mp 162.5-164 °C, R_f 0.39 (DCE/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.40 (2H, quin, J = 8.1 Hz, CH_2), 1.66 (2H, quin, J = 7.1 Hz, CH_2), 1.72 (2H, quin, J = 7.8 Hz, CH_2), 3.76 (2H, t, J = 7.1 Hz, NCH_2), 3.92 (2H, t, J = 6.3 Hz, OCH_2), 4.67 (2H, s, $COCH_2$), 5.77 (1H, d, J = 7.8 Hz, H-5), 6.87 (2H, d, J = 9.1 Hz, H-2', H-6'), 7.39 (2H, d, J = 9.0 Hz, H-3', H-5'), 7.54 (2H, t, J = 7.3 Hz, H-3''', H-5'''), 7.65 (1H, dt, J = 7.6 and 1.5 Hz, H-4'''), 7.69-7.75 (6H, m, H-2", H-6", H-3", H-5", H-2''', H-6'''), 7.79 (1H, d, J = 8.0 Hz, H-6), 10.67 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.6, 28.4, 43.7, 48.8, 67.8, 100.3, 112.1, 117.0, 118.6, 128.8, 129.7, 131.6, 131.8, 132.4, 132.6, 137.9, 143.2, 144.9, 151.4, 158.2, 162.5, 166.3, 194.9; HRMS: found m/z 590.1283; calcd for $C_{30}H_{28}BrN_3O_5$ $[M+H]^+$ 590.1285.

4.2.6. *2-[3-[5-(4-Bromophenoxy)pentyl]-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl]-N-methyl-N-(4-phenoxyphenyl)acetamide (**24**)*

NaH as a 60% dispersion in mineral oil (0.03 g, 0.75 mmol) was added to a solution of compound **7b** in DMF (10 mL) at 0°C followed with MeI (0.08 mL, 1.29 mmol) after 20 min. Stirring was continued for 4 h. DMF was evaporated under reduced pressure, residue was dissloved in DCE (20 mL), washed with a 5% solution of Na_2SO_3 (80 mL), water (50 mL), and evaporated. Recrystallisation from a mixture of hexane/EtOAc (1:1) gave compound **23** as a white powder (0.33 g, 92%), mp 135.5-137 °C, R_f 0.75 (DCE/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.37 (2H, quin, J = 7.8 Hz, CH_2), 1.63 (2H, quin, J = 7.1 Hz, CH_2), 1.71 (2H, quin, J = 7.1 Hz, CH_2), 3.14 (3H, s, CH_3), 3.72 (2H, t, J = 7.0 Hz, NCH_2), 3.93 (2H, t, J = 6.3 Hz, OCH_2), 4.26 (2H, s, $COCH_2$), 5.70 (1H, d, J = 7.8 Hz, H-5), 6.88 (2H, d, J = 8.5 Hz, H-2", H-6"), 7.06-7.11 (4H, m, H-2', H-6', H-2''', H-6'''), 7.18 (1H, t, J = 7.5 Hz, H-4'''), 7.39-7.43 (6H, m, H-3', H-5', H-3", H-5", H-3''', H-5'''), 7.73 (1H, d, J = 7.8 Hz, H-6); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.6, 28.4, 37.4, 42.3, 48.7, 60.1, 67.8, 100.2, 112.1, 117.0, 119.4, 119.8, 124.3, 129.5, 130.5, 132.4, 133.0, 137.8, 144.7, 151.2, 156.7, 158.2, 162.4, 166.2; HRMS: found m/z 592.1439; calcd for $C_{30}H_{30}BrN_3O_5$ $[M+H]^+$ 592.1442.

4.3. *Biological assays*

4.3.1. *Antiviral Activity Assays other than HIV*

The compounds were evaluated against the following viruses: herpes simplex virus type 1 (HSV-1) strain KOS, thymidine kinase-deficient (TK^-) HSV-1 KOS strain resistant to ACV (ACV^r), herpes simplex virus type 2 (HSV-2) strains Lyons and G, human cytomegalovirus (HCMV) (strains AD-169 and Davis), varicella-zoster virus (strains OKA and YS), vaccinia virus Lederle strain, respiratory syncytial virus (RSV) strain Long, vesicular stomatitis virus (VSV), Coxsackie B4, Parainfluenza 3, Influenza virus A (subtypes H1N1, H3N2), influenza virus B, Reovirus-1, Sindbis and Punta Toro. The antiviral assays were based on inhibition of virus-induced cytopathicity or plaque formation in human embryonic lung (HEL) fibroblasts, African green monkey cells (Vero), human epithelial cells (HeLa) or Madin-Darby canine kidney cells (MDCK). Confluent cell cultures in microtiter 96-well plates were inoculated with 100 $CCID_{50}$ of virus (1 $CCID_{50}$ being the virus dose to infect 50% of the cell cultures) or 10 or 100 plaque forming units (PFU) (for VZV and HCMV) in the presence of varying concentrations of the test compounds. Viral cytopathicity or plaque formation was recorded as soon as it reached completion in the control virus-infected cell cultures that were not treated with the test compounds. Antiviral activity was expressed as the EC_{50} or compound concentration required to reduce virus-induced cytopathogenicity or viral plaque formation by 50%.

4.3.2. *Anti-HIV Activity Assays*

Inhibition of HIV-1(III_B)- and HIV-2(ROD)-induced cytopathicity in CEM cell cultures was measured in microtiter 96-well plates containing ~3 × 10^5 CEM cells/mL infected with 100 $CCID_{50}$ of HIV per milliliter and containing appropriate dilutions of the test compounds. After 4–5 days of incubation at 37 °C in a CO_2-controlled humidified atmosphere, CEM giant (syncytium) cell formation was examined microscopically. The EC_{50} (50% effective concentration) was defined as the compound concentration required to inhibit HIV-induced giant cell formation by 50%.

4.3.3. *Cytostatic Activity Assays*

Cytotoxicity measurements were based on the inhibition of cell growth. HEL cells were seeded at a rate of 5 x 10^3 cells/well into 96-well microtiter plates and allowed to adhere and proliferate for 24 h. Then, medium containing different concentrations of the test compounds was added. After 3 days of further incubation at 37 °C, the cell number was determined with a Coulter counter. The cytostatic concentration was calculated as the CC_{50}, or the compound concentration required reducing cell proliferation by 50% relative to the number of cells in the untreated controls. CC_{50} values were estimated from graphic plots of the number of cells (percentage of control) as a function of the concentration of the test compounds. Alternatively, cytotoxicity of the test compounds was expressed as the minimum cytotoxic concentration (MCC) or the compound concentration that caused a microscopically detectable alteration of cell morphology. Selectivity indexes were calculated as the ratio CC_{50} to EC_{50}.

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