Accepted Manuscript

Dihydropyrimidinone/1,2,3-triazole hybrid molecules: Synthesis and anti-varicella-zoster virus (VZV) evaluation

Hanane Kaoukabi, Youssef Kabri, Christophe Curti, Moha Taourirte, Juan C. Rodriguez-Ubis, Robert Snoeck, Graciela Andrei, Patrice Vanelle, Hassan B. Lazrek

PII: S0223-5234(18)30519-1

DOI: 10.1016/j.ejmech.2018.06.028

Reference: EJMECH 10498

To appear in: *European Journal of Medicinal Chemistry*

Received Date: 2 May 2018

Revised Date: 28 May 2018

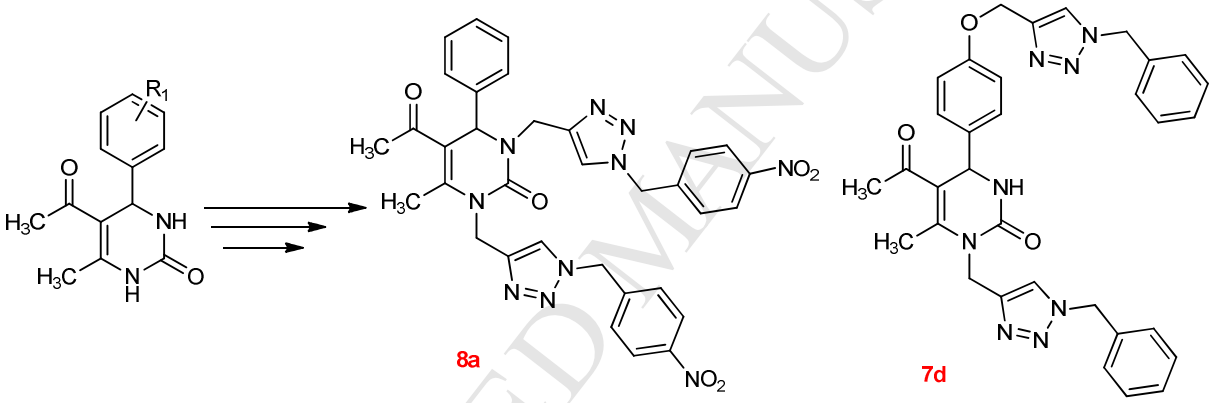
Accepted Date: 11 June 2018

Please cite this article as: H. Kaoukabi, Y. Kabri, C. Curti, M. Taourirte, J.C. Rodriguez-Ubis, R. Snoeck, G. Andrei, P. Vanelle, H.B. Lazrek, Dihydropyrimidinone/1,2,3-triazole hybrid molecules: Synthesis and anti-varicella-zoster virus (VZV) evaluation, *European Journal of Medicinal Chemistry* (2018), doi: 10.1016/j.ejmech.2018.06.028.

Dihydropyrimidinone/1,2,3-triazole hybrid molecules synthesis and anti-varicella-zoster virus (VZV) evaluation

Hanane Kaoukabi[1,2], Youssef Kabri[3], Christophe Curti[3], Moha Taourirte[1], Juan C. Rodriguez-Ubis[4], Robert Snoeck[5], Graciela Andrei[5], Patrice Vanelle*[3], Hassan B. Lazrek*[2]

E-Mail : patrice.vanelle@univ-amu.fr

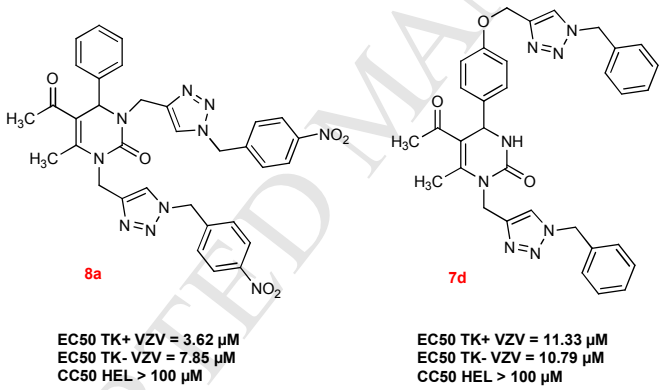


Dihydropyrimidinone/1,2,3-triazole hybrid molecules: synthesis and anti-varicella-zoster virus (VZV) evaluation

Hanane Kaoukabi[1,2], Youssef Kabri[3], Christophe Curti[3], Moha Taourirte[1], Juan C. Rodriguez-Ubis[4], Robert Snoeck[5], Graciela Andrei[5], Patrice Vanelle*[3], Hassan B. Lazrek*[2]

[1] Laboratory of Bioorganic and Macromolecular Chemistry, Department of Chemistry, Faculty of Sciences and Technology Gueliz (FSTG), Marrakesh, Morocco.
[2] Laboratory of Biomolecular and Medicinal Chemistry, Department of Chemistry, Faculty of Sciences Semlalia (FSSM), Marrakesh, Morocco.
[3]Aix Marseille University, Institut de Chimie Radicalaire ICR, UMR CNRS 7273, Laboratoire de Pharmaco-Chimie Radicalaire, Faculté de Pharmacie, 27 Boulevard Jean Moulin-CS 30064,13385 Marseille CEDEX 05, France.
[4] Laboratory Organic-Inorganic Solids and Luminiscent Probes (M01-L207), Department of Organic Chemistry, Faculty of Sciences, University Autonoma, Madrid, Spain.
[5] Rega Institute for Medical Research, KU Leuven, Leuven, Belgium.

E-Mail : patrice.vanelle@univ-amu.fr, hblazrek@uca.ac.ma



Abstract: By combining the structural features of dihydropyrimidinone and 1,2,3-triazole heterocycles, novel hybrid compounds were synthesized using a simple and convenient method. A series of novel mono and bis 1,2,3-triazole was synthesized via copper-catalyzed Huisgen azide-alkyne cycloadditions (CuAAC) under microwave irradiation. The newly synthesized compounds were evaluated for their antiviral activity against varicella-zoster virus (VZV). Compounds **6aa**, **7ab**, **6ba** and **6da** showed valuable antiviral activities, with EC_{50} values ranging from 3.6 to 11.3 µM against TK+ and TK- VZV and without measurable cell-growth inhibition.

Keywords: Biginelli reaction; 1,3-dipolar cycloaddition; 1,2,3 triazole; microwave; hybrid molecules; anti-VZV.

Introduction

The prevalence of Herpesviruses in the developed world is a major source of disease. Infection with varicella-zoster virus (VZV) results in varicella (chickenpox), which usually takes a mild course in children but may be more severe in adults. However, reactivation of the virus is a serious threat in immunocompromised individuals, e.g. recipients of solid-organ and hematopoietic stem cell

transplants, patients under aggressive chemotherapy or individuals with acquired immunodeficiency syndrome (AIDS). Under these circumstances, efficacious antiviral drugs are crucial [1-3].

Recent trends in medicinal chemistry illustrate the popularity of molecular hybridization for drug design and development. This is based on combining pharmacophoric moieties of different bioactive substances to make a new hybrid molecule with enhanced affinity and efficacy, compared to the parent drug [4-6].

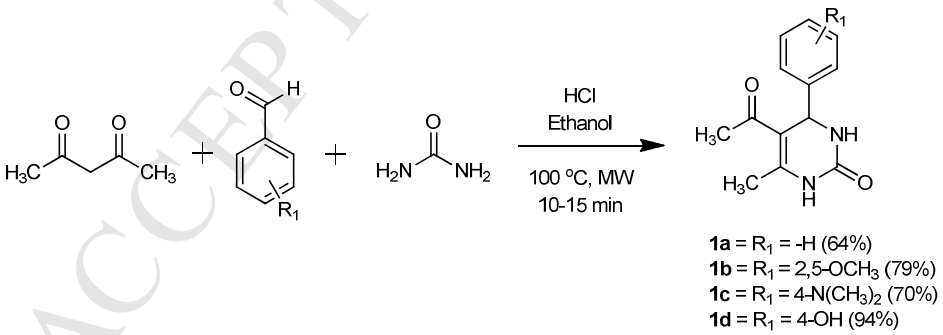
One strategy for producing high potency drug molecules is to combine two bioactive molecules belonging to a particular therapeutic category. For instance, the 1,2,3-triazole based heterocycles have been well exploited for the generation of many medicinal scaffolds exhibiting antiviral activities (anti-HIV, anti VZV, …) [7]. On the other hand, the multi-functionalized pyrimidinone scaffold represents a class of heterocyclic compounds with significant pharmacological efficiency, including anti-viral activity [8]. These findings suggest that it would be useful to synthesize novel hybrid molecules with increased activity and/or decreased toxicity

In an attempt to correlate structure with antiviral activity, herein we report the synthesis and antiviral evaluation against varicella-zoster virus (VZV) in human embryonic lung (HEL) cells and against cytomegalovirus in human embryonic lung (HEL) cells.

Results and Discussion

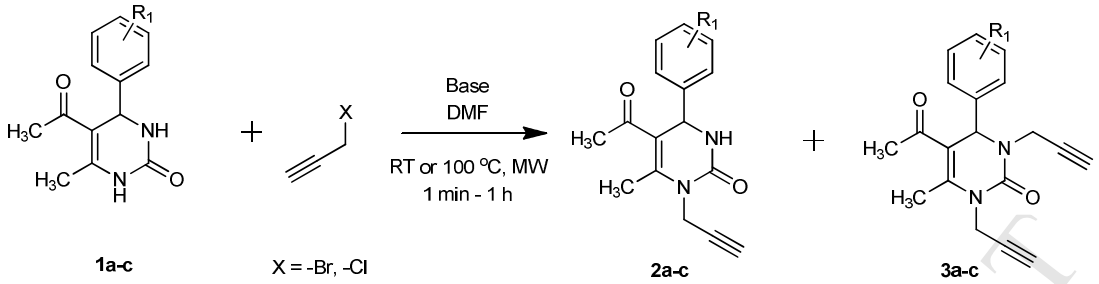
Chemistry

The general route to the synthesis of the target pyrimidine–triazole hybrids is depicted in Scheme 1. The starting materials 5-Acetyl-6-methyl-4-aryl-3,4-dihydropyrimidin-2(*1H*)-ones **1a-d** were synthesized by multi-component reaction from aryl aldehyde, acetylacetone and urea, using Biginelli reaction conditions [9]. The literature contains several reports on catalytic methods to improve the yields and scope of this reaction often using Brønsted or Lewis acid catalysis [10, 11, 12].
First, reactions were launched at room temperature. Under these conditions, compounds **1a-d** were obtained in moderate yields (49-55%) in 3-5 h. Yields were dramatically increased under microwave irradiation (Scheme 1) and reaction times were moreover highly reduced.



Scheme 1: 5-Acetyl-6-methyl-4-aryl-3,4-dihydropyrimidin-2(*1H*)-ones (**1a-d**).

In the next step, compounds **1a-c** reacted with propargyl halide to give *N*-alkylated dihydropyrimidinones (Scheme 2). To determine the optimum reaction conditions, the type and the number of equivalents of base (*t*-BuOK, NaH) were investigated (Table 1). As expected, yields obtained with propargyl bromide (Entries 3-12) were higher than those obtained with propargyl chloride (Entries 1-2). Moreover, the N_1-monoalkylated product was obtained as the major product using *t*-BuOK as base and the N_1, N_3-bisalkyled product was obtained as the major product using NaH as base.



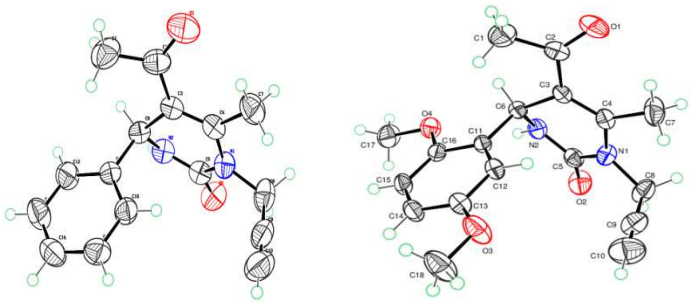
Scheme 2: *N*-alkylation of dihydropyrimidin-2(1*H*)-one derivatives **1a-c**

Table 1: Optimization of reaction conditions

Entry	Product	Propargyl halide (equiv)	Base (equiv)	Reaction time (min)	Temperature	Products (Yields %)[a]	
						2a-c	**3a-c**
1	**1b**	-Cl (1.0)	*t*-BuOK (1.0)	60	25 °C	**2b** (40)	**3b** (5)
2	**1b**	-Cl (2.2)	*t*-BuOK (2.2)	60	25 °C	**2b** (53)	**3b** (5)
3	**1b**	-Br (2.2)	*t*-BuOK (2.2)	60	25 °C	**2b** (80)	**3b** (10)
4	**1b**	-Br (2.2)	*t*-BuOK (2.2)	60	50 °C	**2b** (83)	**3b** (10)
5	**1b**	-Br (2.2)	*t*-BuOK (2.2)	5	100 °C[b]	**2b** (85)	**3b** (10)
6	**1b**	-Br (2.2)	NaH (2.2)	60	25 °C	**2b** (5)	**3b** (95)
7[c]	**1b**	-Br (2.2)	NaH (2.2)	60	25 °C	**2b** (15)	**3b** (80)
8	**1b**	-Br (2.2)	NaH (2.2)	1	100 °C[b]	**2b** (2)	**3b** (98)
9	**1a**	-Br (2.2)	*t*-BuOK (2.2)	5	100 °C[b]	**2a** (80)	**3a** (15)
10	**1a**	-Br (2.2)	NaH (2.2)	1	100 °C[b]	**2a** (1)	**3a** (99)
11	**1c**	-Br (2.2)	*t*-BuOK (2.2)	5	100 °C[b]	**2c** (85)	**3c** (10)
12	**1c**	-Br (2.2)	NaH (2.2)	1	100 °C[b]	**2c** (2)	**3c** (98)

a. Yield of isolated product based on the corresponding pyrimidinone.
b. Reaction launched under microwave irradiation.
c. THF was used as solvent.

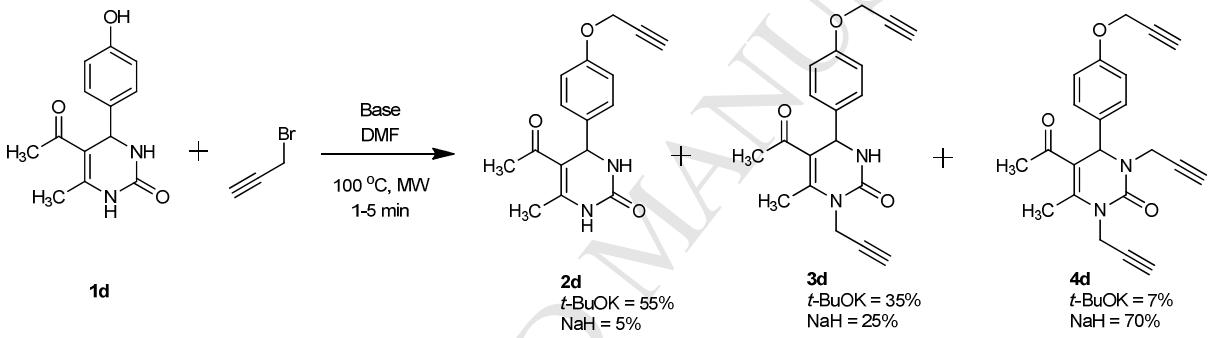
The position of *N*-alkylation was determined using ^{1}H, ^{13}C NMR and confirmed as *N*1- alkylated dihydropyrimidinone by single-crystal X-ray diffraction (XRD) for compounds **2a** and **2b**. It should be noted that during the process of single-crystal formation from the racemic mixture of compound **2a** and **2b**, only the R-isomer was crystallized out (Scheme 3). This is known as “chiral amnesia” [13, 14].



2a **2b**

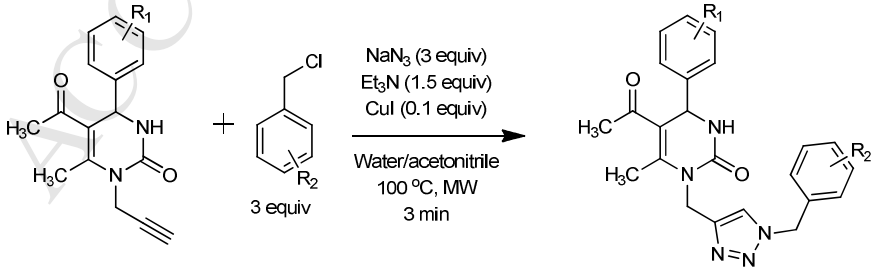
Scheme 3: Single-crystal X-ray diffraction structure of compound **2a** and **2b** (R-isomer).

With this convenient base-dependent protocol, three alkylated isomers (**2d, 3d, 4d**) were also synthesized with good yields (Scheme 4). In line with NMR spectras, propargylation began on the phenol moiety, then *N*1 and finally *N*3 were propargylated. As reported, increasing the strength of the base increased the rate of propargylation and consequently increased yields of tripropargylated derivative **4d**.



Scheme 4: Synthesis of mono- di- and tripropargylated derivatives (**2d, 3d, 4d**)

Then, 1,3-dipolar cycloadditions [15, 16] were performed by *one-pot* three-component reactions under microwave irradiation. These reactions were performed in water/acetonitrile mixture with 3 equivalents of sodium azide, 3 equivalents of alkyl halide, 1.5 equivalent of trimethylamine and 0.1 equiv of CuI as catalyst. Under these conditions, dihydropyrimidinone hybrid molecules **5a-c, 6a-c** substituted on N_1 with one 1,2,3-triazole were obtained in almost quantitative yields (Scheme 5).



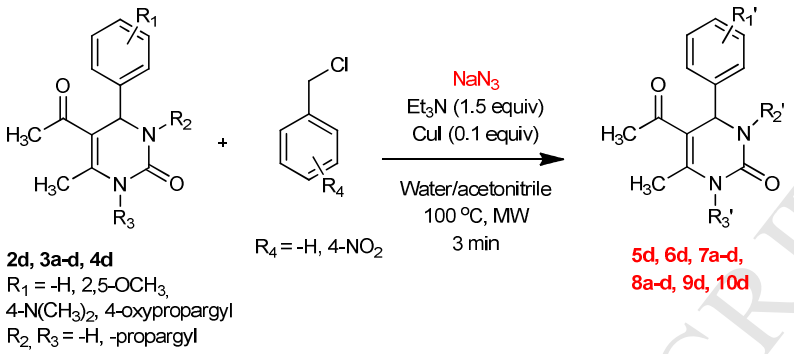
2a = R_1 = -H
2b = R_1 = 2,5-OCH_3
2c = R_1 = 4-$N(CH_3)_2$

R_2 = -H, 4-NO_2

5a (98%) = R_1 = -H R_2 = -H
5b (98%) = R_1 = 2,5-OCH_3 R_2 = -H
5c (96%) = R_1 = 4-$N(CH_3)_2$ R_2 = -H
6a (97%) = R_1 = -H R_2 = 4-NO_2
6b (98%) = R_1 = 2,5-OCH_3 R_2 = 4-NO_2
6c (95%) = R_1 = 4-$N(CH_3)_2$ R_2 = 4-NO_2

Scheme 5: Synthesis of dihydropyrimidinone hybrid molecules **5a-c, 6a-c**

Finally, these reaction conditions were applied to oxypropargylated **2d**, bis-propargylated **3a-d** and tripropargylated **4d** dihydropyrimidinones (Scheme 6) to obtain a wide variety of hybrid molecules *N* and/or *O*-substituted with one, two or three 1,2,3-triazoles. Yields are reported in Table 2.



Scheme 6: Synthesis of dihydropyrimidinone hybrid molecules mono- bi- and trisubstituted with 1,2,3-triazoles

Table 2: Extension of the synthesis of dihydropyrimidinone-1,2,3-triazole hybrid molecules

Entry	Starting material	R_1	R_2	R_3	R_4	Product obtained	Yields (%)[a]
1[b]	**2d**	4–O	-H	-H	-H	**5d**	99
2[b]	**2d**	4–O	-H	-H	4-NO_2	**6d**	97
3[c]	**3a**	-H			-H	**7a**	96
4[c]	**3a**	-H			4-NO_2	**8a**	95
5[c]	**3b**	2,5-OCH_3			-H	**7b**	98
6[c]	**3b**	2,5-OCH_3			4-NO_2	**8b**	96
7[c]	**3c**	4-$N(CH_3)_2$			-H	**7c**	97
8[c]	**3c**	4-$N(CH_3)_2$			4-NO_2	**8c**	94
9[c]	**3d**	4–O	-H		-H	**7d**	99
10[c]	**3d**	4–O	-H		4-NO_2	**8d**	99
11[c]	**4d**	4–O			-H	**9d**	95
12[c]	**4d**	4–O			4-NO_2	**10d**	96

a. Yield of isolated product based on the corresponding pyrimidinone.
b. NaN_3: 3 equiv, alkyl halide: 3 equiv.
c. NaN_3: 5 equiv, alkyl halide: 5 equiv.

Antiviral activity

All the eighteen synthesized compounds, **5a-d, 6a-d, 7a-d, 8a-d, 9d and 10d**, were tested for their antiviral activities against the human varicella-zoster virus (VZV), both wild type and thymidine kinase deficient (TK^-). Nine derivatives of the tested compounds showed moderate to good antiviral activities (Table 3) and compounds **7a**, **8a**, **7b** and **7d** emerged as the most active derivatives (Scheme 7). The nine other compounds did not show measurable activity against VZV. We assume that cell-growth inhibition was only studied for the four compounds that exhibited an antiviral activity lower than 20 µM.

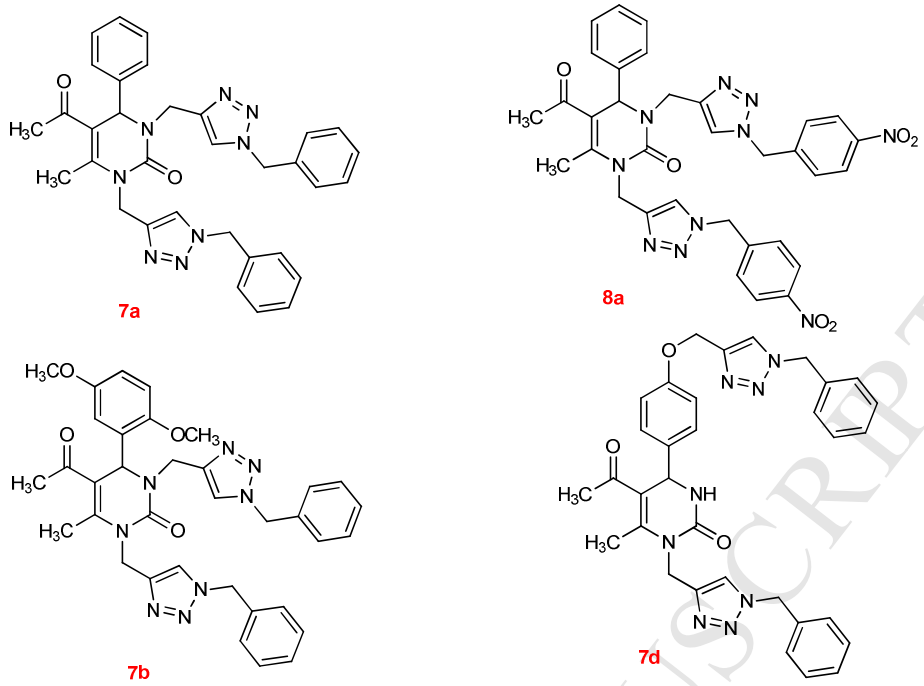
Table 3: Antiviral activity against varicella-zoster virus (VZV) in HEL cell cultures and cell growth inhibition for compounds **5b**, **6a-b**, **7a-d, 8a, 10d**.

	Antiviral activity EC_{50} (µM)		
	TK+ VZV strain (OKA)	TK- VZV strain (07-1)	Cell Growth Inhibition CC_{50} (µM)
5b	48.90	50.17	ND[a]
6a	48.90	42.65	ND[a]
6b	44.72	48.12	ND[a]
7a	8.38[b]	6.08[b]	7.02
8a	3.62[b]	7.85[b]	>100
7b	9.85[b]	8.87[b]	>100
7c	23.15	17.03	ND[a]
7d	11.33[b]	10.79[b]	>100
10d	69.93	>20	ND[a]
Acyclovir	2.35[b]	133.30[b]	>440
Brivudin	0.025[b]	104.28[b]	>300

a. Not determined
b. Mean value of two experiments

The antiviral activities of synthesized dihydropyrimidinone-1,2,3-triazole hybrid molecules were lower than the antiviral activities of reference compounds acyclovir and brivudin against the TK+ VZV strain, but were better than that those of the reference compounds against the TK- VZV strain. Moreover, when antiviral activities against TK+ and TK- strains were compared, only a slight decrease in antiviral activities was observed for each active hybrid molecule, suggesting a class effect. As the TK- VZV strain is known for its resistance to conventional antiviral drugs, dihydropyrimidinone-1,2,3-triazole hybrid molecules appear to be a useful alternative as a second-line treatment.

Except for molecule **7a**, none of the dihydropyrimidinone-1,2,3-triazole hybrid molecules showed quantifiable cell-growth inhibition.



Scheme 7: Dihydropyrimidinone-1,2,3-triazole hybrid molecules with antiviral activity

Compounds bearing two substituted triazolylmethyl moieties showed higher activities than those bearing one or three substituent moieties. Molecule **8a** had the highest antiviral activity, with an EC_{50} of 3.6 µM against TK+ VZV strain, decreasing to an EC_{50} of 7.8 µM against TK- strain. Interestingly, molecule **7d**, substituted on nitrogen and oxygen by triazole rings, displayed similar antiviral activities against TK+ and TK- VZV strains (with respective EC_{50} of 11.3 and 10.8 µM). This could suggest that *N*,*O*-triazole substitution on dihydropyrimidinone leads to molecules whose antiviral activities are unaffected by the degree of thymidine kinase resistance. Moreover, for the active compounds, the replacement of the benzyl group (**7a**) by 4-nitrobenzyl (**8a**) improved the antiviral activities against TK+ VZV strains and decreased considerably the cell-growth inhibition. Unfortunately, molecule **8d** bearing 4-NO_2 (like **8a**) and *N*,*O*-triazole substituted (like **7d**) displayed no antiviral activity.

All compounds were also tested against cytomegalovirus in human embryonic lung (HEL) cells (HCMV) [AD-169 and Davis strain]. None of the tested compounds exhibited measurable antiviral activity against HCMV. These negative results, correlated to the activity found against VZV could suggest a selectivity of dihydropyrimidinone/1,2,3-triazole hybrid molecules into the herpesviridae family against VZV. This phenomenon was already described for other antiviral molecules, such as the bicyclic furanopyrimidine nucleosides FV-100 [17]. To confirm these promising results, investigations on dihydropyrimidinone/1,2,3-triazole hybrid molecules are actually in progress.

Conclusion

New dihydropyrimidinone derivatives have been synthesized and evaluated for their activity against varicella-zoster virus. Four out of the tested compounds showed interesting antiviral activities against VZV TK+ strains at EC_{50} as low as 3.6 µM without measurable cell-growth inhibition. However, only slight decreases in antiviral activities against VZV TK- strains were observed. The easy and economical synthetic protocol described herein offers a new approach to developing this new class of hybrid molecules as novel anti varicella-zoster virus agents.

Experimental

Chemistry

General

Melting points were determined on Büchi B-540 and are uncorrected. 300 MHz ^{1}H NMR spectra (reference $CDCl_3$ δ = 7.26, DMSO-d_6 δ = 2.50) and 75 MHz ^{13}C NMR spectra (reference $CDCl_3$ δ = 77.0, DMSO-d_6 δ = 39.7) were recorded on a Bruker ARX at the Faculty of Sciences, University Autonoma, Madrid, Spain. The following adsorbent was used for column chromatography: silica gel 60 (Merck, particle size 0.063-0.200 mm, 70-230 mesh ASTM). TLC was performed on 5 cm x 10 cm aluminium plates coated with silica gel 60F-254 (Merck) in an appropriate eluent. HRMS was carried out at the Spectropole, Faculté des Sciences et Techniques de Saint-Jérôme, Marseille. HRMS spectra were recorded on a QStar Elite (Applied Biosystems SCIEX) spectrometer. PEG was a matrix for HRMS. Microwave reactions were performed with a Biotage® Initiator Microwave oven using 10-20 mL sealed vials; temperatures were measured with an IR-sensor and reaction times are given as hold times.

General procedure for the synthesis of the 5-acetyl-3,4-dihydro-6-methyl-4-arylpyrimidin-2(1*H*)-ones 1a-d

To a mixture of 1.50 g (15 mmol) of acetylacetone, 0.90 g (15 mmol) of urea and of substituted benzaldehyde (15 mmol) in ethanol (20 mL), four drops of HCl (37%) were added as catalyst. The mixture was irradiated in the microwave oven for 10 to 15 min at 100 °C. The crude product precipitated after cooling was filtered, washed with ethanol (50%), and then recrystallized in ethanol.

5-Acetyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one 1a:

Yield 64%, white solid, mp 235 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 9.14 (s, 1H, NH), 7.77 (s, 1H, NH), 7.11 (m, 5H, 5 H_{Ar}), 5.19 (d, 1H, *J* = 4.0 Hz, CH), 2.24 (s, 3H, CH_3), 2.06 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 194.3, 152.1, 148.1, 144.2, 128.5, 128.5, 127.3, 126.5, 126.5, 109.5, 53.7, 30.2, 18.8 ppm. HRMS: calcd. for $C_{13}H_{14}N_2O_2$ [M + H^+] 230.1102; found 230.1105.

5-Acetyl-4-(2,5-dimethoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one 1b:

Yield 79%, white solid, mp 251 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 9.14 (s, 1H, NH), 7.34 (s, 1H, NH), 6.92-6.97 (m, 1H, H_{Ar}), 6.79-6.84 (m,1H, H_{Ar}), 6.57 (d, 1H, *J* = 3.0 Hz, H_{Ar}), 5.52 (d, 1H, *J* = 3.2 Hz, CH), 3.77 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3), 2.03 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 194.6, 153.3, 152.3, 150.5, 148.2, 132.5, 113.9, 112.4, 112.3, 108.0, 56.1, 55.4, 49.0, 29.8, 18.7 ppm. HRMS: calcd. for $C_{15}H_{18}N_2O_4$ [M + H^+] 290.1261; Found 290.1271.

5-Acetyl-4-(4-dimethylaminophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one 1c:

Yield 70%, white solid, mp 213 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 9.10 (s, 1H, NH), 7.69 (s, 1H, NH), 7.06 (d, 2H, *J* = 8.2 Hz, 2 H_{Ar}), 6.78 (br, 2H, 2 H_{Ar}), 5.14 (d, 1H, *J* = 3.0 Hz, CH), 2.88 (s, 6H, $N(CH_3)_2$), 2.26 (s, 3H, CH_3), 2.05 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 194.5, 156.7, 154.3, 152.1, 149.8, 147.4, 131.9, 127.2, 112.3, 109.5, 102.1, 53.6, 30.7, 30.7, 18.7 ppm. Anal. Calcd. for $C_{15}H_{19}N_3O_2$: C 65.91; H 7.01; N 15.37. Found: C 65.85; H 7.11; N 15.48.

5-Acetyl-4-(4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one 1d:

Yield 94%, white solid, mp 232 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 9.35 (s, 1H, OH), 9.09 (s, 1H, NH), 7.69 (s, 1H, NH), 7.67 (d, 2H, *J* = 8.4 Hz, 2 H_{Ar}), 7.01 (d, 2H, *J* = 8.4 Hz, 2 H_{Ar}), 5.12 (d, 1H, *J* = 4.0 Hz, CH), 2.25 (s, 3H, CH_3), 2.04 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 194.5, 156.6, 152.1, 147.5, 134.7, 127.6, 127.6, 115.1, 115.1, 109.6, 53.5, 30.0, 18.8 ppm. Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C 63.41; H 5.69; N 11.38. Found: C 63.50; H 5.68; N 11.35. HRMS: Calcd. for $C_{13}H_{14}N_2O_3$ [M + H^+] 246.1004; Found 246.1018.

General procedure for the synthesis of the mono- and dialkylated 5-acetyl-3,4-dihydro-6-methyl-4-aryl pyrimidin-2(1*H*)-ones 2a-d and dialkylated 3d respectively.

5-Acetyl-3,4-dihydro-6-methyl-4-arylpyrimidin-2(1*H*)-ones **1a-d** (1 mmol) and *t*BuOK (2.2 equiv, 2.2 mmol, 247 mg) were dissolved in dry DMF (2.5 mL). The mixture was stirred for 15 min at room temperature and propargyl bromide (2.2 equiv, 2.2 mmol, 0.17 mL) was added dropwise. The mixture was irradiated in the microwave oven at 100 °C for 10 min. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic phase was dried over Na_2SO_4, evaporated under vacuum and the crude product was purified by column chromatography using hexane/acetate (90:10, v/v) as eluent.

5-Acetyl-6-methyl-4-phenyl-1-(prop-2-yn-1-yl)-3,4-dihydropyrimidin-2(1*H*)-one 2a:

Yield 80%, yellow solid, mp 151 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 8.13 (s, 1H, NH), 7.27-7.32 (m, 5H, 5 H_{Ar}), 5.22 (s, 1H, CH), 4.39-4.62 (m, 2H, CH_2), 3.26 (s, 1H, CH), 2.53 (s, 3H, CH_3), 2.09 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 196.1, 151.9, 147.3, 143.0, 128.6, 128.6, 127.7, 126.5, 126.5, 113.2, 80.3, 74.3, 53.0, 31.7, 30.3, 16.1. HRMS: Calcd. for $C_{16}H_{16}N_2O_2$ [M + H$^+$] 269.1285 found 269.1285.

5-Acetyl-4-(2,5-dimethoxyphenyl)-6-methyl-1-(prop-2-yn-1-yl)-3,4-dihydropyrimidin-2(1*H*)-one 2b:

Yield 85%, white solid, mp 98-100 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 7.80 (s, 1H, NH), 6.65-6.97 (m, 2H, 2 H_{Ar}), 6.62-6.64 (s, 1H, H_{Ar}), 5.49 (s, 1H, CH), 4.34-4.67 (m, 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.28 (s, 1H, CH), 2.50 (s, 3H, CH_3), 2.08 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 196.3, 153.2, 152.3, 150.1, 146.4, 131.2, 113.3, 112.4, 112.1, 111.9, 80.7, 74.1, 55.8, 55.3, 47.7, 31.4, 29.6, 15.7. HRMS: Calcd. for $C_{18}H_{20}N_2O_4$ [M + H$^+$ + Na$^+$] 351.1315 found 351.1315.

5-Acetyl-4-(4-dimethylaminophenyl)-6-methyl-1-(prop-2-yn-1-yl)-3,4-dihydropyrimidin-2(1*H*)-one 2c:

Yield 85%, yellow solid, mp 91 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 7.99 (d, 1H, *J* = 3.2 Hz, NH), 7.06 (d, 2H, *J* = 8.5 Hz, 2 H_{Ar}), 6.63 (d, 2H, *J* = 8.5 Hz, 2 H_{Ar}), 5.08 (d, 1H, *J* = 3.0 Hz, CH), 4.43-4.57 (m, 2H, CH_2), 3.29 (s, 1H, CH), 2.85 (s, 6H , $N(CH_3)_2$), 2.52 (s, 3H, CH_3), 2.05 (s, 3H ,CH_3) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 196.3, 151.9, 149.9, 146.6, 130.4, 127.4, 127.4, 113.3, 112.3, 112.3, 80.4, 74.3, 52.8, 41.3, 41.3, 31.5, 30.1, 15.9 ppm. HRMS: Calcd. for $C_{18}H_{21}N_3O_2$ [M + H$^+$] 312.1707 found 312.1707.

5-Acetyl-6-methyl-4-[4-(prop-2-yn-1-yloxy)phenyl]-3,4-dihydropyrimidin-2(1*H*)-one 2d:

Yield 55%, white solid, mp 143 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 9.14 (s, 1H, NH), 7.75 (s, 1H, NH), 7.16 (d, 2H, *J* = 7.0 Hz, 2 H_{Ar}), 6.92 (d, 2H, *J* = 7.1 Hz, 2 H_{Ar}), 5.19 (s, 1H, CH), 4.74 (s, 2H, CH_2), 3.53 (s, 1H, CH), 2.26 (s, 3H, CH_3), 2.07 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 194.3, 156.4, 152.0, 147.8, 137.1, 127.6, 127.6, 114.8, 114.8, 109.6, 79.3, 78.1, 55.4, 53.3, 30.2, 18.8. HRMS: Calcd. for $C_{16}H_{16}N_2O_3$ [M + H$^+$] 285.1234 found 285.1235.

5-Acetyl-6-methyl-1-(prop-2-yn-1-yl)-4-[4-(prop-2-yn-1-yloxy)phenyl]-3,4-dihydropyrimidin-2(1*H*)-one 3d.

Yield 35%, yellow solid, mp 125 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 8.11 (s, 1H, NH), 7.18 (d, 2H, *J* = 7.9 Hz, 2 H_{Ar}), 6.91 (d, 2H, *J* = 8.1 Hz, 2 H_{Ar}), 5.17 (s, 1H, CH), 4.76 (s, 2H, CH_2), 4.40-4.60 (m, 2H, CH_2), 3.53 (s, 1H, CH), 3.28 (s, 1H, CH), 2.53 (s, 3H, CH_3), 2.08 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 196.1, 156.7, 151.9, 147.2, 135.9, 127.8, 127.8, 114.9, 114.9, 113.3, 80.4, 79.2, 78.2, 74.3, 55.4, 52.5, 30.7, 30.3, 16.0 ppm. HRMS: Calcd. for $C_{19}H_{18}N_2O_3$ [M + H$^+$] 323.1390 found 323.1388.

General procedure for the synthesis of the di- and trialkylated 5-acetyl-3,4-dihydro-6-methyl-4-aryl

pyrimidin-2(1*H*)-ones 3a-c and trialkylated 4d respectively.

5-Acetyl-3,4-dihydro-6-methyl-4-aryl-2(1*H*)-pyrimidinones **1a-d** (1 mmol) were dissolved in dry DMF (2.5 mL) at 0 °C and NaH (2.2 equiv, 2.2 mmol, 53 mg) was added and stirred for 15 min at room temperature. Afterwards, propargyl bromide (2.2 equiv, 2.2 mmol, 0.17 mL) was added dropwise and the mixture was irradiated in the microwave oven at 100 °C for 5 min. The reaction mixture was diluted with water (20 mL), extracted with ethyl acetate (3 × 20 mL) and the organic layer was dried over Na_2SO_4 and evaporated under vacuum. The crude product was purified by column chromatography using hexane/acetate (90:10, v/v) as eluent.

5-Acetyl-6-methyl-4-phenyl-1,3-di(prop-2-yn-1-yl)-3,4-dihydropyrimidin-2(1*H*)-one 3a:

Yield 99%, yellow solid, mp 81 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.30 (s, 5H, 5 H_{Ar}), 5.61 (s, 1H, CH), 4.72-4.87 (m, 2H, CH_2), 4.41-4.49 (m, 1H, CH), 3.47-3.55 (m, 1H, CH), 2.59 (s, 3H, CH_3), 2.34-2.37 (m, 2H, CH_2),

2.20 (s, 3H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 196.3, 151.8, 146.1, 138.3, 129.0, 129.0, 128.6, 127.3, 127.3, 114.6, 79.0, 77.7, 73.6, 72.5, 57.4, 34.8, 33.2, 30.6, 16.6 ppm. HRMS: Calcd. for $C_{19}H_{18}N_2O_2$ [M + H^+] 307.1441 found 307.1441.

5-Acetyl-4-(2,5-dimethoxyphenyl)-6-methyl-1,3-di(prop-2-yn-1-yl)-3,4-dihydropyrimidin-2(1*H*)-one 3b:

Yield 98%, brown solid, mp 159 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ = 6.75-6.81 (m, 3H, H_{Ar}), 5.96 (s, 1H, CH), 4.66-4.82 (m, 2H, CH_2), 4.35-4.45 (m, 1H, CH), 3.82 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.61 (d, 1H, *J* = 2.4 Hz, CH), 2.54 (s, 3H, CH_3), 2.22-2.32 (m, 2H, CH_2), 2.18 (s, 3H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 197.1, 154.1, 153.8, 150.7, 145.6, 128.0, 114.5, 114.1, 114.0, 111.7, 79.4, 78.8, 72.5, 71.8, 55.8, 55.8, 51.9, 35.5, 33.1, 29.7, 16.2 ppm. HRMS: Calcd. for $C_{21}H_{22}N_2O_4$ [M + H^+] 367.1652 found 367.1653.

5-Acetyl-4-[4-(dimethylamino)phenyl]-6-methyl-1,3-di(prop-2-yn-1-yl)-3,4-dihydropyrimidin-2(1*H*)-one 3c:

Yield 98%, yellow solid, mp 161 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.25-7.28 (m, 2H, 2 H_{Ar}), 6.72-6.78 (m, 2H, 2 H_{Ar}), 5.58 (s, 1H, CH), 4.84-4.96 (m, 2H, CH_2), 4.57 (d, 1H, *J* = 2.2 Hz, CH), 3.59-3.65 (m, 1H, CH), 3.04 (s, 6H, $N(CH_3)_2$), 2.70 (s, 3H, CH_3), 2.46 (d, 2H, *J* = 1.3 Hz, CH_2), 2.27 (s, 3H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 196.8, 151.9, 150.7, 145.5, 128.5, 128.5, 125.5, 114.6, 112.5, 112.5, 79.3, 78.2, 73.3, 72.4, 57.2, 40.4, 40.4, 34.47, 33.1, 30.4, 16.5 ppm. HRMS: Calcd. for $C_{21}H_{23}N_3O_2$ [M + H^+] 350.1863 found 350.1861.

5-Acetyl-6-methyl-1,3-di(prop-2-yn-1-yl)-4-[4-(prop-2-ynyloxy)phenyl]-3,4-dihydropyrimidin-2(1*H*)-one 4d:

Yield 70%, yellow solid, mp 61 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.22-7.27 (m, 2H, 2 H_{Ar}), 6.89-6.98 (m, 2H, 2 H_{Ar}), 5.56 (s, 1H, CH), 4.71-4.85 (m, 2H, CH_2), 4.66 (d, 2H, *J* = 2.3 Hz, CH_2), 4.38-4.48 (m, 1H, CH), 3.45-3.55 (m, 1H, CH), 2.59 (s, 3H, CH_3), 2.52 (s, 1H, CH), 2.36 (br, 2H, CH_2), 2.19 (s, 3H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 196.3, 162.5, 157.7, 151.8, 145.9, 131.4, 128.7, 128.7, 115.3, 115.3, 114.7, 79.1, 78.3, 75.9, 73.7, 72.6, 56.9, 55.8, 36.5, 31.4, 30.5, 16.6 ppm. HRMS: Calcd. for $C_{22}H_{20}N_2O_3$ [M + H^+] 361.1547 found 361.1547.

General procedure for the synthesis of the mono-1, 2, 3-triazole analogues of DHPMs 5a-d, 6a-d:

A solution of propargylated compounds **2a-d** (1 mmol), sodium azide (3 equiv, 3 mmol, 200 mg), alkyl halide (3 equiv, 3 mmol), Et_3N (1.5 equiv, 1.5 mmol, 0.2 mL), CuI (0.1 equiv, 0.1 mmol, 19 mg) in water/acetonitrile mixture (10 mL, v/v), was irradiated in the microwave oven at 100 °C for 3 min. The reaction mixture was diluted with 25 mL of water at 0 °C and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried with Na_2SO_4, concentrated and the crude product was purified by column chromatography using CH_2Cl_2/MeOH mixture (99:1, *v/v*) as eluent.

5-Acetyl-[1-(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one

5a:

Yield 98%, yellow solid, mp 191 °C. ^1H NMR (DMSO-d_6, 300 MHz) δ = 8.06 (s,1H, H_{Ar}), 7.86 (s, 1H, NH), 7.19-7.34 (m, 10H, 10 H_{Ar}), 5.55 (s, 2H, CH_2), 5.19 (s, 1H, CH), 4.84-5.00 (m, 2H, CH_2), 2.49 (s, 3H, CH_3), 2.07 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 197.6, 153.0, 148.7, 143.2, 136.0, 129.3, 129.3, 129.1, 129.1, 128.9, 128.9, 128.4, 128.4, 128.3, 126.8, 126.8, 123.8, 113.7, 53.4, 51.8, 37.1, 30.7, 17.1 ppm. HRMS: Calcd. for $C_{23}H_{23}N_5O_2$ [M + H^+] 402.1925; found 402.1924.

5-Acetyl-6-methyl-1-{[1-(4-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl]methyl}-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one 6a:

Yield 97%, yellow solid, mp 153 °C. ^1H NMR (DMSO-d_6, 300 MHz) δ = 8.21 (d, 2H, *J* = 8.4 Hz, 2 H_{Ar}), 8.08 (d, 1H, *J* = 2.7 Hz, H_{Ar}), 7.97 (s, 1H, NH), 7.52 (d, 2H, *J* = 8.3 Hz, H_{Ar}), 7.20 (m, 5H, 5 H_{Ar}), 5.74 (s, 2H, CH_2), 5.20 (s, 1H, CH), 4.81-5.01 (m, 2H, CH_2), 2.53 (s, 3H, CH_3), 2.07 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 196.6, 152.8, 148.5, 147.7, 145.1, 143.8, 143.8, 129.6, 129.6, 129.6, 129.0, 129.0, 128.0, 127.0, 127.0, 124.4, 124.4, 113.3, 53.6, 52.3, 38.0, 30.9, 17.1 ppm. HRMS: Calcd. for $C_{23}H_{22}N_6O_4$ [M + H^+] 447.1773; found 447.1773.

5-Acetyl-1-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-4-(2,5-dimethoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one 5b:

Yield 98%, yellow solid, mp 119 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 7.91 (s, 1H, H_{Ar}), 7.67 (s, 1H, NH), 7.27-7.36 (m, 5H, 5 H_{Ar}), 6.90 (d, 1H, *J* = 2.9 Hz, H_{Ar}), 6.78 (d, 1H, *J* = 2.9 Hz, H_{Ar}), 6.55 (d, 1H, *J* = 2.9 Hz, H_{Ar}), 5.54 (s, 2H, CH_2), 5.48 (s, 1H, CH), 4.79-5.01 (m, 2H, CH_2), 3.70 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 2.47 (s, 3H, CH_3), 2.04 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 197.5, 161.8, 152.9, 151.2, 147.0, 135.4, 131.1, 129.1, 129.1, 129.1, 128.7, 128.7, 128.7, 128.2, 128.2, 113.0, 112.2, 112.0, 55.7, 55.4, 52.9, 47.8, 37.2, 29.5, 16.2 ppm. HRMS: Calcd. for $C_{25}H_{27}N_5O_4$ [M + H^+] 462.2136; found 462.2136.

5-Acetyl-1-[(1-(4-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl]-4-(2,5-dimethoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one 6b:

Yield 98%, yellow solid, mp 95 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 8.20 (d, 2H, *J* = 8.5 Hz, 2 H_{Ar}), 8.02 (s, 1H, H_{Ar}), 7.70 (d, 1H, *J* = 3.0 Hz, NH), 7.48 (d, 2H, *J* = 8.4 Hz, 2 H_{Ar}), 6.90 (d, 1H, *J* = 8.9 Hz, H_{Ar}), 6.77 (d, 1H, *J* = 2.9 Hz, H_{Ar}), 6.54 (d, 1H, *J* = 2.9 Hz, H_{Ar}), 5.73-5.75 (d, 2H, *J* = 3.5 Hz, CH_2), 5.48 (s, 1H, CH), 4.81-4.98 (m, 2H, CH_2), 3.71 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 2.49 (s, 3H, CH_3), 2.07 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 197.4, 152.9, 152.9, 150.1, 147.2, 142.9, 130.9, 128.9, 128.9, 128.9, 128.9, 123.8, 123.8, 123.8, 123.8, 113.0, 112.2, 112.0, 55.7, 55.2, 52.0, 47.9, 37.2, 29.5, 16.3. HRMS: Calcd. for $C_{25}H_{26}N_6O_6$ [M + H^+] 507.1987 found 507.1988.

5-Acetyl-1-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-4-[4-(dimethylamino)phenyl]-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one 5c:

Yield 96%, yellow solid, mp 101 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 7.92 (s, 1H, H_{Ar}), 7.83 (s, 1H, NH), 7.28-7.33 (m, 5H, 5 H_{Ar}), 6.99 (d, 2H, *J* = 8.4 Hz, 2 H_{Ar}), 6.57 (d, 2H, *J* = 8.6 Hz, 2 H_{Ar}), 5.56 (s, 2H, CH_2), 5.07 (s, 1H, CH), 4.78-4.98 (m, 2H, CH_2), 2.84 (s, 6H, $N(CH_3)_2$), 2.49 (s, 3H, CH_3), 2.03 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 196.9, 152.9, 150.4, 147.8, 145.1, 136.5, 131.2, 129.2, 129.2, 128.6, 128.3, 128.3, 127.9, 126.7, 123.9, 113.4, 112.7, 112.7, 53.3, 53.2, 40.6, 40.6, 37.2, 31.2, 16.9 ppm. HRMS: Calcd. for $C_{25}H_{28}N_6O_2$ [M + H^+] 445.2347; found 445.2347.

5-Acetyl-1-[(1-(4-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl]methyl]-4-[4-(dimethylamino)phenyl]-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one 6a:

Yield 95%, yellow solid, mp 105 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 8.25 (d, 1H, *J* = 8.6 Hz, H_{Ar}), 8.20 (d, 2H, *J* = 7.7 Hz, 2 H_{Ar}), 8.05-8.08 (m, 1H, NH), 7.91 (d, 2H, *J* = 7.7 Hz, 2 H_{Ar}), 7.47 (d, 2H, *J* = 7.7 Hz, 2 H_{Ar}), 6.97 (d, 1H, *J* = 7.7 Hz, H_{Ar}), 6.56 (d, 1H, *J* = 7.7 Hz, H_{Ar}), 5.72 (s, 2H, CH_2), 5.05 (s, 1H, CH), 4.79-4.97 (m, 2H, CH_2), 2.80 (s, 6H, $N(CH_3)_2$), 2.47 (s, 3H, CH_3), 2.00 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 197.4, 152.9, 150.4, 147.9, 145.0, 136.3, 131.0, 129.3, 129.3, 129.3, 128.7, 128.3, 128.3, 128.3, 127.8, 123.8, 113.6, 112.7, 53.3, 53.2, 40.5, 40.5, 31.1, 30.5, 16.9 ppm. HRMS: Calcd. for $C_{25}H_{27}N_7O_4$ [M + H^+] 512.2017 found 512.2034.

5-Acetyl-4-{4-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]phenyl}-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one 5d:

Yield 99%, white solid, mp 215 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 9.15 (s, 1H, NH), 8.28 (s, 1H, H_{Ar}), 7.77 (s, 1H, NH), 7.29-7.39 (m, 5H, 5 H_{Ar}), 7.15 (d, 2H, *J* = 8.6 Hz, 2 H_{Ar}), 6.97 (d, 2H, *J* = 8.6 Hz, 2 H_{Ar}), 5.61 (s, 2H, CH_2), 5.21 (d, 1H, *J* = 3.2 Hz, CH), 5.11 (s, 2H, CH_2), 2.28 (s, 3H, CH_3), 2.08 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 195.5, 157.7, 152.7, 148.5, 143.5, 137.0, 136.2, 129.3, 129.3, 129.3, 128.8, 128.4, 128.4, 128.4, 128.1, 125.1, 115.1, 110.2, 61.4, 53.7, 53.4, 30.6, 19.3 ppm. HRMS: Calcd. for $C_{23}H_{23}N_5O_3$ [M + H^+] 418.1874; found 418.1873.

5-Acetyl-4-{4-[(1-(4-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl]methoxy)phenyl}-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one 6d:

Yield 97%, yellow Solid, mp 181 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 9.14 (s, 1H, NH), 8.35 (s, 1H, H_{Ar}), 8.22 (d, 2H, *J* = 8.8 Hz, 2 H_{Ar}), 7.76 (s, 1H, NH), 7.52 (d, 2H, *J* = 8.8 Hz, 2 H_{Ar}), 7.14 (d, 2H, *J* = 8.6 Hz, 2 H_{Ar}), 6.96 (d, 2H, *J* = 8.6 Hz, 2 H_{Ar}), 5.79 (s, 2H, CH_2), 5.19 (s, 1H, CH), 5.12 (s, 2H, CH_2), 2.27 (s, 3H, CH_3), 2.07 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 194.8, 157.7, 152.6, 148.4, 147.8, 143.9, 143.7, 137.3, 129.6, 129.6, 128.1, 128.1, 125.5, 124.4, 124.4, 115.1, 115.1, 110.1, 61.5, 53.7, 52.4, 31.2, 19.3 ppm. HRMS: Calcd. for $C_{23}H_{22}N_6O_5$ [M + H^+] 463.1724 found 463.1724.

General procedure for the synthesis of the bis-1, 2, 3-triazole analogues of DHPMs 7a-d, 8a-d:

A solution of bis-propargylated compounds **3a-d** (1 equiv), sodium azide (5 equiv, 5 mmol, 325 mg), alkyl halide (5 equiv), Et_3N (1.5 equiv, 1.5 mmol, 0.2 mL), CuI (0.1 equiv, 0.1 mmol, 19 mg) in water/acetonitrile mixture (10 mL, v/v) was irradiated in the microwave oven at 100 °C for 5 min. The reaction mixture was diluted with 25 mL of water at 0 °C and extracted with ethyl acetate (3 x 25 mL). The combined organic layers were dried with Na_2SO_4, concentrated and the crude product was purified by column chromatography using CH_2Cl_2/MeOH mixture (99:1, *v/v*) as eluent.

5-Acetyl-1,3-bis[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one 7a:

Yield 96%, yellow Solid, mp 59 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 8.02 (s, 1H, H_{Ar}), 7.99 (s, 1H, H_{Ar}), 7.15-7.35 (m, 15H, 15 H_{Ar}), 5.57 (s, 2H, CH_2), 5.54 (s, 2H, CH_2), 5.31 (s, 1H, CH), 5.15 (d, 1H, *J* = 15.2 Hz, CH_2), 4.83-4.96 (m, 2H, CH_2), 3.97 (d, 1H, *J* = 15.2 Hz, CH_2), 2.49 (s, 3H, CH_3), 2.03 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 196.2, 166.4, 156.4, 152.6, 150.8, 147.5, 144.5, 143.5, 142.9, 140.5, 139.1, 136.4, 134.7, 129.4, 129.2, 129.2, 128.5, 128.5, 128.3, 128.3, 127.4, 124.4, 124.2, 122.7, 121.9, 114.5, 58.0, 53.3, 53.3, 41.0, 39.1, 30.1, 17.3 ppm. HRMS: Calcd. for $C_{33}H_{32}N_8O_2$ [M + H^+] 573.2721 found 573.2719.

5-Acetyl-6-methyl-1,3-bis{[1-(4-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl]methyl}-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one 8a:

Yield 95, yellow solid, mp 80 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.96-8.10 (m, 4H, 4 H_{Ar}), 7.38 (s, 1H, H_{Ar}), 7.21-7.28 (m, 5H, 5 H_{Ar}), 7.14 (s, 1H, H_{Ar}), 7.07 (m, 4H, 4 H_{Ar}), 5.45 (s, 4H, 2 CH_2), 5.29 (s, 1H, CH), 4.83-499 (m, 3H, CH_2, H-CH_2), 4.11 (d, 1H, *J* = 15.3 Hz, CH_2), 2.43 (s, 3H, CH_3), 1.99 (s, 3H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 196.3, 153.1, 147.8, 146.6, 145.4, 145.1, 141.5, 139.9, 128.9, 128.9, 128.9, 128.6, 128.6 128.6 128.6, 127.3, 127.3, 127.3, 124.3, 124.3, 124.3, 124.3, 124.3, 123.7, 122.9, 114.8, 59.0, 53.2, 53.2, 41.2, 39.2, 30.8, 17.4 ppm. HRMS: Calcd. for $C_{33}H_{30}N_{10}O_6$ [M + H^+] 663.2423 found 663.2421.

5-Acetyl-1,3-bis[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-4-(2,5-dimethoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one 7b:

Yield 98, yellow Solid, mp 99 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 7.99 (s, 1H, H_{Ar}), 7.95 (s, 1H, H_{Ar}), 7.25-7.36 (m, 10H, 10 H_{Ar}), 6.78-6.89 (m, 2H, 2 H_{Ar}), 6.52 (s, 1H, H_{Ar}), 5.62 (s, 1H, CH), 5.55 (s, 4H, 2 CH_2), 4.06-5.11 (d, 1H, *J* = 16.1 Hz, CH_2), 4.81-4.99 (m, 2H, CH_2), 3.94-3.99 (d, 1H, *J* = 15.3 Hz, CH_2), 3.60 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 2.39 (s, 3H, CH_3), 1.92 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 196.1, 153.4, 152.2, 150.0, 145.4, 136.1, 128.9, 128.7, 128.7, 128.7, 128.7, 128.7, 127.9, 127.9, 127.9, 127.9, 127.8, 127.8, 127.8, 127.8, 123.8, 123.5, 113.6, 113.4, 112.8, 112.4, 55.7, 55.2, 52.7, 52.7, 52.0, 40.5, 38.4, 29.3, 16.2 ppm. HRMS: Calcd. for $C_{35}H_{36}N_8O_4$ [M + H^+] 633.2932 found 633.2933.

5-Acetyl-4-(2,5-dimethoxyphenyl)-6-methyl-1,3-bis{[1-(4-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl]methyl}-3,4-dihydropyrimidin-2(1*H*)-one 8b:

Yield 96, yellow solid, mp 113 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 8.20-8.23 (m, 4H, 4 H_{Ar}), 8.09 (s, 1H, H_{Ar}), 8.02 (s, 1H, H_{Ar}), 7.46-7.52 (m, 4H, 4 H_{Ar}), 6.87 (dd, 1H, *J* = 2.7, 8.9 Hz, H_{Ar}), 6.76-6.80 (m, 1H, H_{Ar}), 6.52 (d, 1H, *J* = 2.5 Hz, H_{Ar}), 5.74 (s, 4H, 2 CH_2), 5.67 (s, 1H, CH), 5.09 (d, 1H, *J* = 16.0 Hz, CH_2), 4.85-4.99 (m, 2H, CH_2), 4.02 (d, 1H, *J* = 15.2 Hz, CH_2), 3.65 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 2.41 (s, 3H, CH_3), 2.07 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 197.3, 153.1, 152.4, 149.9, 147.1, 147.1, 145.6, 142.9, 142.9, 128.9, 128.9, 128.9, 128.9, 128.9, 128.9, 128.9, 128.6, 123.7, 123.7, 123.7, 123.7, 123.7, 123.7, 113.8, 113.1, 112.4, 55.6, 55.1, 52.6, 52.1, 51.9, 40.8, 38.1, 30.5, 16.2 ppm. HRMS: Calcd. for $C_{35}H_{34}N_{10}O_8$ [M + H^+] 723.2634 found 723.2631.

5-Acetyl-1,3-bis[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-4-[4-(dimethylamino)phenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one 7c:

Yield 97%, yellow solid, mp 113 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 1.96 (s, 3H, CH_3), 2.07 (s, 1H, CH_2), 2.49 (s, 3H, CH_3), 2.84 (s, 6H, $N(CH_3)_2$), 3.93 (d, 1H, *J* = 14.9 Hz, CH_2), 4.82-4.94 (m, 2H, CH_2), 5.16 (s, 1H, CH), 5.55 (s, 2H, CH_2), 5.58 (s, 2H, CH_2), 6.52 (d, 2H, *J* = 8.5 Hz, 2 H_{Ar}), 7.00 (d, 2H, *J* = 8.4 Hz, 2 H_{Ar}), 7.25-7.35 (m, 10H, 10 H_{Ar}), 8.00 (s, 1H, H_{Ar}), 8.05 (s, 1H, H_{Ar}) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 196.4, 152.6, 150.6, 146.7, 136.5, 136.4, 129.3, 129.2, 129.2, 129.2, 129.2, 129.2, 129.2, 128.7, 128.6, 128.6, 128.5, 128.4, 128.4, 128.4, 128.3, 128.3, 128.2, 127.4, 114.3, 112.6, 112.5, 111.5, 57.8, 53.3, 53.3, 40.4, 39.2, 31.2, 17.1. HRMS: Calcd. for $C_{35}H_{37}N_9O_2$ [M + H^+] 616.3143 found 616.3146.

5-Acetyl-4-[4-(dimethylamino)phenyl]-6-methyl-1,3-bis{[1-(4-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl]methyl}-3,4-dihydropyrimidin-2(1*H*)-one 8c:

Yield 94%, yellow solid, mp 121 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 8.28 (d, 2H, *J* = 8.6 Hz, 2 H_{Ar}), 8.18-8.22 (m, 3H, 3 H_{Ar}), 7.96 (d, 2H, *J* = 8.6 Hz, 2 H_{Ar}), 7.53 (s, 1H, H_{Ar}), 7.32-7.36 (m, 2H, 2 H_{Ar}), 7.05 (d, 2H, *J* = 8.3 Hz, 2 H_{Ar}), 6.58 (d, 2H, *J* = 8.3 Hz, 2 H_{Ar}), 5.57 (s, 4H, 2 CH_2), 5.25 (s, 1H, CH), 4.85-5.00 (m, 3H, H-(CH_2), 4.27 (d, 1H, *J* = 14.9 Hz, CH_2), CH_2), 2.89 (s, 6H , $N(CH_3)_2$), 2.25 (s, 3H, CH_3), 2.05 (s, 3H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 195.8, 166.0, 152.0, 147.1, 145.0, 140.5, 138.3, 138.1, 138.1, 127.6, 127.6, 127.6, 127.6, 127.6, 126.6, 123.3, 123.3, 123.3, 123.3, 122.9, 122.9, 122.9, 122.9, 122.9, 113.1, 113.1, 60.9, 57.9, 52.1, 52.1, 40.1, 39.4, 38.1, 21.7, 16.2 ppm. HRMS: Calcd. for $C_{35}H_{35}N_{11}O_6$ [M + H^+] 706.2845 found 706.2850.

5-Acetyl-4-{4-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]phenyl}-1-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one 7d:

Yield 99, yellow Solid, mp 169 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 8.26 (s, 1H, H_{Ar}), 8.00 (d, 1H, *J* = 3.4 Hz, 1 H_{Ar}), 7.87 (s, 1H, NH), 7.25-7.36 (m, 10H, 10 H_{Ar}), 7.10 (d, 2H, *J* = 8.6 Hz, 2 H_{Ar}), 6.87-6.90 (d, 2H, *J* = 8.6 Hz, 2 H_{Ar}), 5.60 (s, 2H, CH_2), 5.55 (s, 2H, CH_2), 5.14 (d, 1H, *J* = 3.1 Hz, CH), 5.08 (s, 2H, CH_2), 4.78-5.02 (m, 2H, CH_2), 2.51 (s, 3H, CH_3), 2.04 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 197.3, 157.8, 152.9, 148.4, 144.9, 143.5, 136.2, 136.2, 136.0, 129.3, 129.3, 129.3, 129.3, 129.3, 128.8, 128.8, 128.4, 128.4, 128.3, 128.3, 128.3, 128.3, 125.1, 123.8, 115.2, 113.5, 61.3, 60.5, 53.3, 52.9, 38,4, 31.1, 17.1 ppm. HRMS: Calcd. for $C_{33}H_{32}N_8O_3$ [M + H^+] 589.2670 found 589.2670.

5-Acetyl-4-{4-[(1-(4-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy]phenyl}-1-{[1-(4-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl]methyl}-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one 8d:

Yield 99%, yellow Solid, mp 139 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 8.33 (s, 1H, H_{Ar}), 8.19-8.24 (m, 4H, 4 H_{Ar}), 8.01 (d, 1H, *J* = 3.4 Hz, H_{Ar}), 7.99 (s, 1H, NH), 7.48-7.54 (m, 4H, 4 H_{Ar}), 7.11 (d, 2H, *J* = 8.6 Hz, 2 H_{Ar}), 6.88 (d, 2H, *J* = 8.6 Hz, 2 H_{Ar}), 5.79 (s, 2H, CH_2), 5.75 (s, 2H, CH_2), 5.15 (d, 1H, *J* = 3.1 Hz, CH), 5.10 (s, 2H, CH_2), 4.82-5.04 (m, 2H, CH_2), 2.52 (s, 3H, CH_3), 2.05 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 196.6, 157.9, 152.8, 148.2, 147.7, 145.1, 143.8, 143.6, 136.3, 129.5, 129.5, 129.5, 129.5, 129.5, 129.5, 128.4, 128.4, 125.5, 124.4, 124.4, 124.4, 124.4, 124.4, 124.4, 115.1, 113.3, 61.6, 55.4, 53.1, 52.4, 38.2, 31.2, 17.1 HRMS: Calcd. for $C_{33}H_{30}N_{10}O_7$ [M + H^+] 679.2372 found 679.2371.

General procedure for the synthesis of tri-1,2,3-triazole analogues of DHPMs 9d and 10d

A mixture of *O*-*N*-1,*N*-3-tri-propargylated compound **4d** (1 mmol), sodium azide (5 equiv, 5 mmol, 325 mg), alkyl halide (5 equiv), Et_3N (1.5 equiv, 1.5 mmol, 0.2 mL), CuI (0.1 equiv, 0.1 mmon, 19 mg) in 10 mL of water/acetonitrile mixture (v/v) was irradiated in the microwave oven at 100 °C for 5 min. The reaction mixture was diluted with 25 mL of water, and extracted with ethyl acetate (3 x 25 mL). The organic layer was dried over Na_2SO_4, evaporated under vacuum and the crude product was purified by column chromatography using CH_2Cl_2/MeOH mixture (99:1, *v/v*) as eluent.

5-Acetyl-4-{4-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]phenyl}-1,3-bis[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one 9d:

Yield 95%, yellow Solid, mp 81 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 8.27 (s, 1H, H_{Ar}), 8.05 (s, 1H, H_{Ar}), 8.01 (s, 1H, H_{Ar}), 7.24-7.34 (m, 15H, 15 H_{Ar}), 7.11 (d, 2H, *J* = 8.2 Hz, 2 H_{Ar}), 6.83 (d, 2H, *J* = 8.2 Hz, 2 H_{Ar}), 5.61 (s, 2H, CH_2), 5.57 (s, 2H, CH_2), 5.55 (s, 2H, CH_2), 5.25 (s, 1H, CH), 5.11 (d, 1H, *J* = 15.2 Hz, CH_2), 5.08 (s, 2H, CH_2), 4.83-4.95 (m, 2H, CH_2), 3.95 (d, 1H, *J* = 15.2 Hz, CH_2), 2.49 (s, 3H, CH_3), 2.00 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 196.1, 158.2, 152.8, 152.6, 147.7, 147.7, 147.1, 144.1, 143.8, 143.8, 143.8, 143.6, 133.0, 129.5, 129.5, 129.5, 129.5, 129.5, 129.3, 129.3, 129.3, 129.3, 129.0, 129.0, 125.0, 124.8, 124.4, 124.4, 124.4, 124.4, 124.4, 124.4, 115.2, 114.5, 61.5, 57.6, 55.4, 52.4, 52.4, 39.9, 39.7, 31.2, 17.3 ppm. HRMS: Calcd. for $C_{43}H_{41}N_{11}O_3$ [M + H^+] 760.3467 found 760.3469.

5-Acetyl-6-methyl-4-{4-[(1-(4-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy]phenyl}-1,3-bis{[1-(4-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl]methyl}-3,4-dihydropyrimidin-2(1*H*)-one 10d:

Yield 96%, yellow solid, mp 119 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ = 8.32 (s, 1H, H_{Ar}), 8.22-8.26 (m, 6H, 6 H_{Ar}), 8.19 (s, 1H, H_{Ar}), 8.11 (s, 1H, H_{Ar}), 7.45-7.56 (m, 6H, 6 H_{Ar}), 7.12 (d, 2H, *J* = 7.6 Hz, 2 H_{Ar}), 6.86 (d, 2H, *J* = 7.8 Hz, 2 H_{Ar}), 5.79 (s, 2H, CH_2), 5.76 (s, 2H, CH_2), 5.74 (s, 2H, CH_2), 5.28 (s, 1H, CH), 5.14-5.20 (d, 1H, *J* = 15.2 Hz, CH_2), 5.10 (s, 2H, CH_2), 4.87-4.95 (m, 2H, CH_2), 4.00 (d, 1H, *J* = 15.2 Hz, CH_2), 2.49 (s, 3H, CH_3), 2.02 (s, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz) δ = 195.5, 157.7, 152.1, 147.2, 147.2, 147.2, 147.1, 144.2,

143.4, 143.3, 143.3, 143.3, 143.1, 132.5, 129.0, 129.0, 129.0, 129.0, 129.0, 128.8, 128.8, 128.8, 128.8, 128.5, 124.5, 124.3, 123.9, 123.9, 123.9, 123.9, 123.9, 123.8, 114.6, 113.9, 61.1, 57.1, 54.9, 51.9, 51.9, 39.7, 39.5, 30.7, 16.7 ppm. HRMS: Calcd. for $C_{43}H_{38}N_{14}O_9$ [M + H^+] 895.3019 found 895.3021.

Antiviral activity assays

The antiviral assays were based on inhibition of virus-induced cytopathicity or plaque formation in human embryonic lung (HEL) cells against varicella-zoster virus (VZV) (thymidine kinase wild-type (TK+) (Oka strain) and TK-deficient (TK^-) (07-1 strain) and against human cytomegalovirus (HCMV) AD-169 and Davis strains. Confluent cell cultures in microtiter 96-well plates were infected with 100 (for human cytomegalovirus, HCMV) or with 20 plates forming units (PFU) for VZV.
After 2 h adsorption, the viral inoculum was removed and the cell cultures were incubated with fresh medium in the presence of varying concentrations of the test compounds. Viral plaque formation for VZV or viral cytopathic effect (for HCMV) was recorded after, respectively, 5 and 7 days post-infection. Antiviral activity was expressed as the EC_{50} or compound concentration required to reduce viral cytopathic effect (HCMV) or viral plaque formation (VZV) by 50%.
Alternatively, the cytostatic activity of the test compounds was measured based on 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 proliferate for 24 h. Then, medium containing different concentrations of the test compounds was added. After 3 days of 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 to reduce cell proliferation by 50% relative to the number of cells in the untreated controls.

Acknowledgements

H. Kaoukabi is grateful to the ERASMUS program (University Autonoma, laboratory Organic-Inorganic Solids and Luminiscent Probes (M01-L207), Madrid, Spain) for financial support in the form of a fellowship. We gratefully acknowledge the invaluable technical help received from the staff of the CAC (center for analysis and characterization) at Cadi Ayyad University. We are also grateful to Ellen De Waegenaere for assisting with the biological assays.

References

[1] A. Arvin, G. Campadelli-Fiume, E. Mocarski , P.S. Moore, B. Roizman , R. Whitley , K Yamanishi . Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis. Editors Cambridge: Cambridge University Press. (2007).

[2] A.Wald, K. Link. Risk of human immunodeficiency virus infection in herpes simplex virus type 2-seropositive persons: a meta-analysis. *J Infect Dis*. 185 (2002) 45-52.

[3] S. Barton, C. Celum , T.W .Shacker . The role of anti-HSV therapeutics in the HIV-infected host and in controlling the HIV epidemic. *Herpes*. 12 (2005) 15-21.

[4] M. U. Rahman, A. Rathore, A. A. Siddiqui, G. Parveen, M. Shahar Yar. Synthesis and characterization of quinazoline derivatives: search for hybrid molecule as diuretic and antihypertensive agents. *J. Enzyme Inhib. Med. Chem*. 29 (2014) 733–743.

[5] A. Müller-Schiffmann, H. Sticht, C. Korth . Hybrid compounds: from simple combinations to nanomachines. *BioDrugs*. 26 (2012) 21-31.

[6] A. Husain, M. Rashid, R. Mishra , S. Parveen, D.S. Shin, D. Kumar. Benzimidazole bearing oxadiazole and triazolo-thiadiazoles nucleus: design and synthesis as anticancer agents. *Bioorg Med Chem Lett*. 22 (2012) 5438-5444.

[7] a) D. Dheer , V. Singh , R. Shankar. Medicinal attributes of 1,2,3-triazoles: Current developments. *Bioorg. Chem.* 71 (2017) 30–54. B) Y.-W. He, C.-Z. Dang, J.-Y. Zhao, L.-L. Ma, Y.-H. Li, H.A. Aisa. 1,2,3-triazole-containing derivatides of rupestonic acid : Click-chemical synthesis and antiviral activities against influenza viruses. *Eur. J. Med. Chem.*76 (2014) 245-255. c) M. de Lourdes, G. Ferreira, L.C.S. Pinheiro, O.A. Santos-Filho, M.D.S. Pecanha, C.Q. Sacramento, V. Machado, V.F. Ferreira, T.M.L. Souza, N. Boechat. Design, synthesis, and antiviral activity of new 1H-1,2,3-triazole nucleoside ribavirin analogs. *Med. Chem. Res.* 23

(2014) 1501–1511. d) Y.N. Wen, Z.F. Zhang, N.N. Liu, Y.H. Xiang, Z.Y. Zhang, G.A. Andrei, R. Snoeck, D. Schols, Q.S. Zhanga, Q.P. Wu. Synthesis and Bioactivity of Novel Trisubstituted Triazole Nucleosides. Nucl. *Nucleot. Nucl. Acids* 35 (2016) 147–160. e) A.K. Jordao, V.F. Ferreira, T.M.L. Souza, G.G. de Souza Faria, V. Machado, J. L. Abrantes, M.C.B.V. de Souza, A. C. Cunha. Synthesis and anti-HSV-1 activity of new 1,2,3-triazole derivatives. *Bioorg. Med. Chem.*19 (2011) 1860-1865.

[8] a) L H.S. Matos, F.T. Masson, L.A. Simeoni, M. Homen-de-Mello. Biological activity of dihydropyrimidinone (DHPM) derivatives: A systematic review. *Eur. J. Med. Chem.* 143 (2018) 1779-1789. b) R. Kaur, S. Chaudhary, K. Kumar, M.K. Gupta, R.K. Rawal. Recent synthetic and medicinal perspectives of dihydropyrimidinones. A review, *Eur. J. Med. Chem.* 132 (2017) 108-134. c) C. McGuigan, H. Barucki, S. Blewett, A. Carangio, J.T. Erichsen, G. Andrei, R. Snoeck, E. De Clercq, J. Balzarini. Highly Potent and Selective Inhibition of Varicella-Zoster Virus by Bicyclic Furopyrimidine Nucleosides Bearing an Aryl Side Chain. *J. Med. Chem.* 43 (2000) 4993-4997. d) J. Kim, T. Ok, C. Park, W. So, M. Jo, Y. Kim, M. Seo, D. Lee, S. Jo, Y. Ko, I. Choi, Y. Park, J. Yoon, M.K. Ju, J. Ahn, J. Kim, S.-J. Han, T.-H. Kim, J. Cechetto, J. Nam, M. Liuzzi, P. Sommer. A novel 3,4-dihydropyrimidin-2(1H)-one: HIV-1 replication inhibitors with improved metabolic stability. *Bioorg. Med. Chem. Lett.* 22 (2012) 2522-2526.

[9] P. Biginelli. Ueber Aldehyduramide des Acetessigäthers. II. Eur. J. Inorg. Chem. 24(1891) 1317–1319.

[10] M. Taourirte, T. Oulih, H.B. Lazrek, J.L. Barascut, J.L. Imbach, N. A. Almasoudi. Synthesis of 3′-Deoxy-3′-[4-(pyrimidin-1-yl) methyl-1,2,3-triazol-1-yl]thymidine via 1,3-Dipolar Cycloaddition. *Nucleosides Nucleotides Nucleic Acids.* 22 (2003) 1985–1993.

[11] A. Debache, B. Boumoud, M. Amimour, A. Belfaitah, S. Rhouati, B. Carboni. Phenylboronic acid as a mild and efficient catalyst for Biginelli reaction. *TetrahedronLett.* 47 (2006) 5697-5699. b) JS Yadav, S Praveen Kumar, G Kondaji, R Srinivasa Rao, K Nagaiah. A Novel L-Proline Catalyzed Biginelli Reaction: One-Pot Synthesis of 3, 4-Dihydropyrimidin-2 (1 H)-ones under Solvent-Free Conditions. *Chem. Lett.* 33 (2004) 1168-1169. c) S. Tu, F. Fang, C. Miao, H. Jiang, Y. Feng, D. Shi, X. Wang. One-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones using boric acid as catalyst. *Tetrahedron Lett.* 44 (2003) 6153-6155.

[12] a) H. El Badaoui, F. Bazi, S. Tamani, S. Boulaajaj, M. Zahouily, H.B. Lazrek, S. Sebti . Lewis Acid–Doped Natural Phosphate: New Catalysts for the One-Pot Synthesis of 3,4-Dihydropyrimdin-2(1H)-one. *Synt. Commun.* 35 (2005) 2561–2568. b) H. El Badaoui,F. Bazi, S. Sokori, S. Boulaajaj, H.B. Lazrek, S. Sebti . One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones Using $ZnCl_2$, $CuCl_2$, $NiCl_2$ and $CoCl_2$ Doped Hydroxyapatite. *Lett. Org. Chem.* 2 (2005) 561-565. c)H. El Badaoui, F. Bazi, R. Tahir, H.B. Lazrek, S. Sebti, Synthesis of 3,4-dihydropyrimidin-2-ones catalysed by fluorapatite doped with metal halides. *Catal. Communi*. 6 (2005). 455-458.

[13] a) H. Kaoukabi, M. Taourirte, M. El Azhari, H.B. Lazrek, M. Saadi, L. El Ammari. 5-Acetyl-4-(2,5-dimethoxyphenyl)-6-methyl-1-(prop-2-ynyl)-3,4-dihydropyrimidin-2(1H)-one. *IUCrData*. (2017). 2, x170816. b) H. Kaoukabi, M. Taourirte, H.B. Lazrek, M. El Azhari, M. Saadi, L. El Ammari. 5-Acetyl-6-methyl-4-phenyl-1-(prop-2-ynyl)-3,4-dihydropyrimidin-2(1H)-one. *IUCrData*. (2017). 2, x171802.

[14] D. G. Blackmond. Chiral amnesia" as a driving force for solid-phase homochirality. *Chem. Eur. J.* 13 (2007) 3290-3295

[15] a) H. Elayadi , M. Smietana, J.J. Vasseur, J. Balzarini, H.B. Lazrek . Synthesis of 1,2,3-triazolyl nucleoside analogs as potential anti-influenza A (H_3N_2 subtype) virus agents. *Pharm. Chem. Life Sci*. 347 (2014) 135–141. b) K. El Akri, K. Bougrin, B.J. Balzarini, A. Faraj, R. Benhida. Efficient synthesis and in vitro cytostatic activity of 4-substituted triazolyl-nucleosides. Bioorg. *Med. Chem. Lett.* 17 (2007) 6656-6659.

[16] L.Y. Ma, B.Wang, L.P. Pang, M. Zhang, S.Q. Wang, Y.C Zheng, K.P. Shao, D.Q. Xue, H.M. Liu. Design and synthesis of novel 1,2,3-triazole-pyrimidine-urea hybrids as potential anticancer agents. *Bioorg. Med. Chem. Lett*. 25 (2015) 1124–1128.

[17] E. De Clercq. Selective anti-herpesvirus agents. *Antivir. Chem. Chemother*. 23 (2013) 93-101.

Highlights:

- Synthesis of new dihydropyrimidinone derivatives with valuable antiviral activities
- Synthesis of dihydropyrimidinone derivatives using Biginelli and 1,3-dipolar cycloadditions reactions.
- Interesting antiviral activities against VZV TK+ and VZV TK- strains were observed
- No measurable cell-growth inhibition for the active compounds