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Full Paper

Design, Synthesis, and the Biological Evaluation of a New Series of Acyclic 1,2,3-Triazole Nucleosides

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A new strategy for the synthesis of N^3-benzoylated- and N^3-benzylated N^1-propargylquinazoline-2,4-diones **30a**–**d** and **31a**–**d** from isatoic anhydride **41** is reported. The alkynes **30a**–**d** and **31a**–**d** were applied in the 1,3-dipolar cycloadditions with azides **27** and **28** to synthesize acyclic 1,2,3-triazole nucleosides. The obtained alkynes and 1,2,3-triazole were evaluated for antiviral activity against a broad range of DNA and RNA viruses. The alkyne **30d** showed activity against adenovirus-2 ($EC_{50} = 8.3\ \mu M$), while compounds **37a** and **37d** were also active toward herpes simplex virus-1 wild-type and thymidine kinase deficient (HSV-1 TK^-) strains (EC_{50} values in the range of 4.6–13.8 μM). In addition, compounds **30a**, **30b**, **37b**, and **37c** exhibited activity toward varicella-zoster virus (VZV) TK^+ and TK^- strains ($EC_{50} = 2.1$–$9.5\ \mu M$). The compound **30b** proved to be the most selective against VZV and displayed marginal activity against human cytomegalovirus (HCMV). Although the compound **30a** had improved anti-HCMV activity, the increase in anti-HCMV activity was accompanied by significant toxicity. Compounds **37a** and **37d** showed inhibitory effects toward the human T lymphocyte (CEM) cell line ($IC_{50} = 21 \pm 7$ and $22 \pm 1\ \mu M$, respectively), while compound **35** exhibited cytostatic activity toward HMEC-1 cells ($IC_{50} = 28 \pm 2\ \mu M$).

Keywords: 1,2,3-Triazoles / Acyclic nucleosides / Antiviral / Cytostatic / Quinazoline-2,4-diones

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Introduction

Acyclic analogs of nucleosides belong to the most important class of compounds showing antiviral and antitumor activities [1, 2]. Among them, acyclovir and penciclovir exhibit activity against herpes viruses including HSV-1, HSV-2, VZV, hepatitis B virus (HBV) [3–7], while ganciclovir [7, 8–10] and valganciclovir – its prodrug with significantly improved oral bioavailability [10–12] – are commonly used as anti-cytomegalovirus agents. However, in most cases, the clinical applications of nucleosides are limited due to the observed side effects. In addition, an important problem in treatment of viral infections is the emergence of drug-resistant mutant viruses. For this reason, the search for new antiviral compounds with improved activity has been continuing for decades. This is not limited to modifications of aliphatic chains, but also includes the introduction of additional groups into the structure of nucleosides with well-documented biological activity. Since the 1,2,3-triazole moiety has been recognized as bioisosteric with the amide function [13, 14], the incorporation of this structural motive has been widely applied and resulted in a broad spectrum of pharmaceutically important molecules. Furthermore, 1,2,3-triazoles are able to form hydrogen bonds, they are not protonated at the physiological pH, and are also stable to oxidation and reduction as well as to many enzymatic reactions [15]. Several compounds of the 1,2,3-triazole family have exhibited a broad spectrum of biological activities, such as anti-inflammatory [16, 17], anticonvulsants [18], antiviral [19–23], anticancer [24–27], antimicrobial agents [28–30], as well as β-lactamase inhibitors [31] and dopamine D2 receptor

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ligands related to schizophrenia [32]. Since 1997, when the first acyclic 1,2,3-triazolenucleosides have been obtained by Lazrek et al. [33, 34], many efforts have been made by several research groups to synthesize more potent antiviral and anticancer nucleoside analogs having both natural and modified nucleobases (Fig. 1) [35–49].

Among various heterocyclic moieties that would serve as modified nucleobase mimetics, substituted quinazoline-2,4-diones are of special interest. This structural motive was successfully attached to various biologically active compounds to provide even more active hybrids (Fig. 2) [50–56].

In continuation of our involvement in the search for new biologically active acyclic nucleoside analogs [57–66], a new series of 1,2,3-triazole nucleosides containing the substituted quinazoline-2,4-dione at C4 was designed (compounds **32–37**, Scheme 1). Based on the previous observations on analogous heterocyclic conjugates **24–26** synthesized in our research group (Fig. 3) [57, 58, 67], functionalized benzyl and benzoyl groups were carefully selected as suitable substituents to be attached at C3 in the quinazolinone-2,4-dione framework. The synthetic strategy for our new series 1,2,3-triazolenucleosides is presented in Scheme 1.

Results and discussion

Chemistry

The starting 3-azidopropanol **27** was prepared from 3-chloropropanol in 90% yield according to the literature procedure [68]. Reaction of 3-azidopropanol **27** with benzyl bromide gave **28** in 80% yield [69, 70]. Initially, we considered the respective N^3-benzoylated quinazoline-2,4-diones as convenient substrates for the preparation of N^3-benzoyl-N^1-propargylquinazoline-2,4-diones **30a** (Scheme 2). The N^3-benzoylquinazoline-2,4-dione **40** was previously obtained from 2-benzoylaminobenzoxazinone, although with low (less than 5%) overall yield [71] Recently, we reported [57] the synthesis of N^3-benzoyl-N^1-propargylquinazoline-2,4-diones **30a** from quinazoline-2,4-dione **38** in 19% overall yield (Scheme 2).

However, this procedure suffers from several steps including benzoylation of **38** to N^1,N^3-dibenzoylquinazoline-2,4-dione **39**, requires a selective N^1-debenzoylation and finally propargylation. Unfortunately, in this method, the selective N^1-debenzoylation step appeared less effective and tedious. For this reason, another strategy for the synthesis of N^3-benzoyl-N^1-propargylquinazoline-2,4-diones **30a** was devised (Scheme 3). It started from propargylation of commercially available isatoic anhydride **41** followed by the reaction of the compound **42** with urea [72] to give N^1-propargylquinazoline-2,4-dione **29**. Finally, the key compound **29** could be transformed into substituted both N^3-benzoyl- and N^3-benzyl-N^1-propargylquinazoline-2,4-diones **30a–d** and **31a–d** via the reaction with the respective benzoyl chlorides and benzyl bromides (Scheme 3).

The standard benzoylation of N^1-propargylquinazoline-2,4-dione **29** with benzoyl chlorides in the presence of triethylamine led to the formation of N^3-benzoylated N^1-propargylquinazoline-2,4-diones **30a–d** in moderate to good yields without formation of by-products. At first, attempts at benzylation of N^1-propargylquinazoline-2,4-dione **29** following the strategy previously described [67] for the synthesis of N^1-allylated N^3-benzoylquinazoline-2,4-dione were undertaken. Treatment of **29** with benzyl bromide in the presence of potassium hydroxide at 105°C for 4 h or 60°C for 48 h led to the formation of ca. a 50:50 mixture of an alkyne **31a** and an allene **43a** in 79% total yield. Unfortunately, several attempts at elaborating the efficient procedure to separate N^3-benzyl-N^1-propargylquinazoline-2,4-diones **31a** from N^3-benzyl-N^1-(propa-1,2-dien-1-yl)quinazoline-2,4-diones **43a** on silica gel columns or by crystallization proved fruitless. Fortunately, we were able to chromatographically isolate a small amount of pure allene **43a**. Attempts to optimize a procedure for benzylation of **29**, thereby avoiding formation of allenes **43** were undertaken. Thus, the treatment of N^1-propargylquinazoline-2,4-dione **29** with benzyl bromide in the presence of potassium carbonate in DMF at room temperature for 48 h afforded pure N^3-benzyl-N^1-propargylquinazoline-2,4-dione **31a** and no traces of the allene **43a** were observed.

The Hüisgen reaction of the azide **27** with the alkyne **29** could be accomplished within 21 days when the reaction mixture was heated at 45°C. However, when the reaction was performed at the same temperature under microwave irradiation, the azide was consumed in less than 30 min. For this reason, all cycloadditions of azides **27** and **28** with N^1-propargylquinazoline-2,4-dione **29**, N^3-benzoylated N^1-propargylquinazoline-2,4-diones **30a–d**, and N^3-benzylated N^1-propargylquinazoline-2,4-diones **31a–d** were carried out in a microwave oven (Scheme 4) and disappearance of the starting azide was monitored by IR spectroscopy. All compounds were purified chromatographically and by crystallization. Structures and purity of all 1,2,3-triazole nucleosides were established by ^{1}H, ^{13}C NMR, and IR techniques as well as by elemental analysis.

Biological evaluation

Antiviral and cytotoxic evaluation

All synthesized compounds were screened for inhibitory activity against a wide variety of DNA and RNA viruses using the following cell-based assays: (i) human embryonic lung (HEL) cells: herpes simplex virus-1 (KOS), herpes simplex virus-2 (G), thymidine kinase deficient (acyclovir resistant) herpes simplex virus-1 (TK$^-$ KOS ACV^r), vaccinia virus, adenovirus-2, human coronavirus (229E), cytomegalovirus (AD-169 strain and Davis strain), varicella-zoster virus (TK$^+$ VZV Oka strain and TK$^-$ VZV 07-1 strain); (ii) HeLa cell cultures: vesicular stomatitis virus, Coxsackie virus B4 and respiratory syncytial virus; (iii) Vero cell cultures: para-influenza-3 virus, reovirus-1, Sindbis virus, Coxsackie virus B4, punta toro virus, yellow fever virus; (iv) MDCK cell cultures: influenza A virus (H1N1 and H3N2 subtypes) and influenza B virus. Ganciclovir, cidofovir,

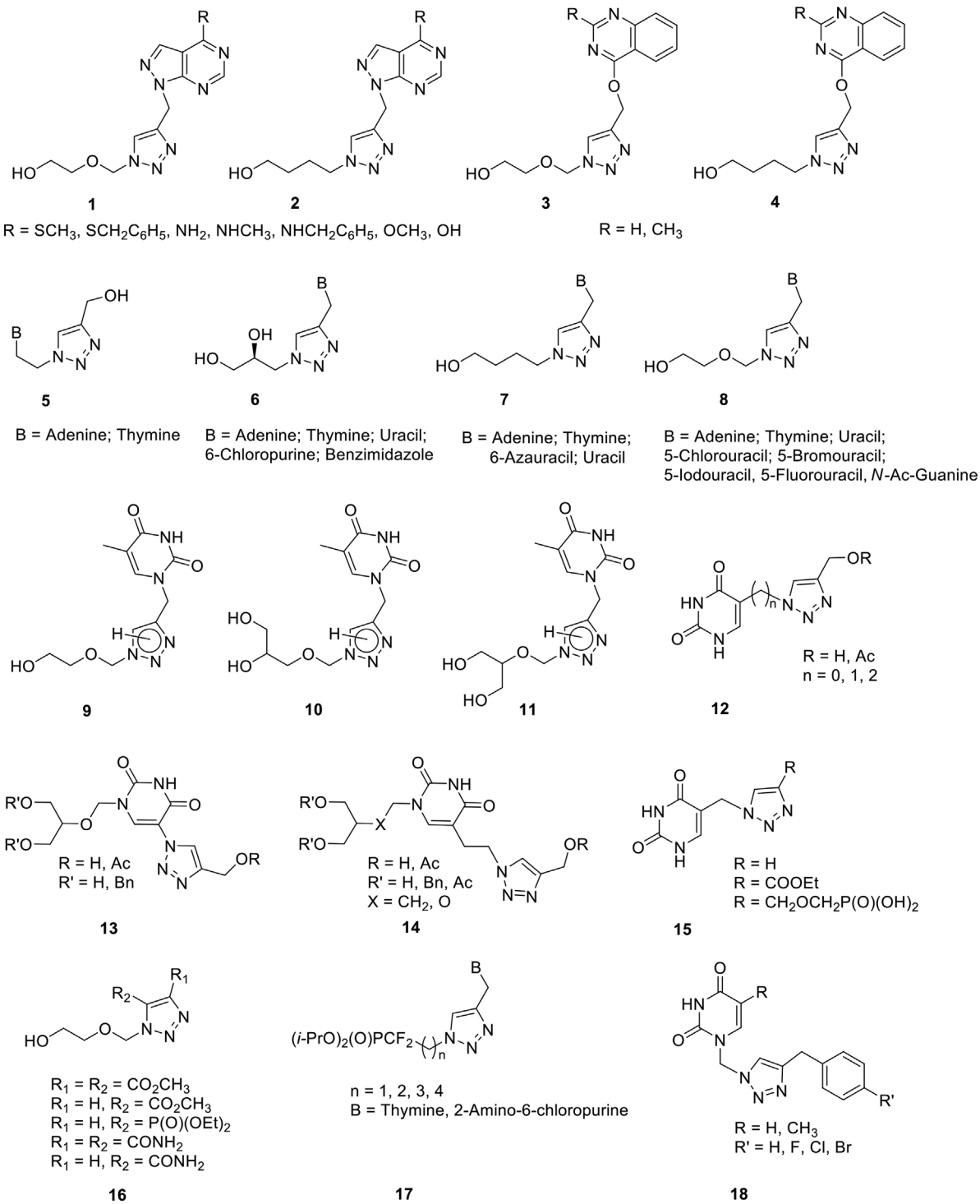

Figure 1. Examples of acyclic nucleoside analogs containing the 1,2,3-triazole moiety.

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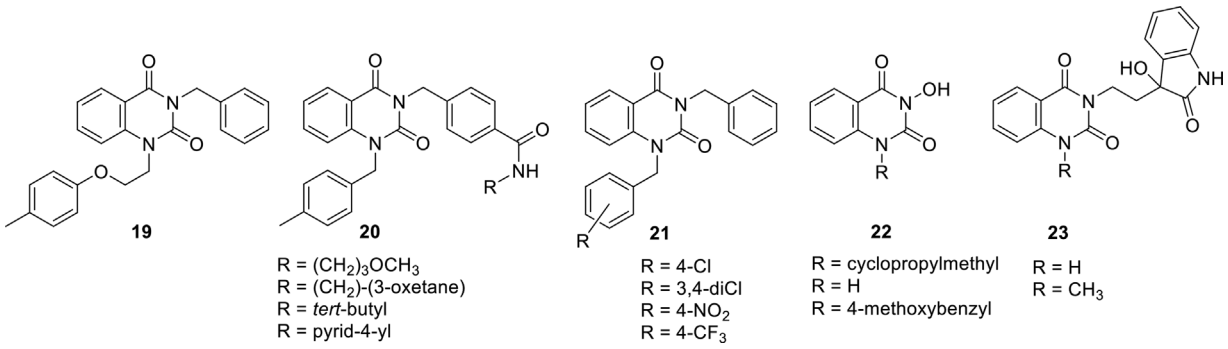
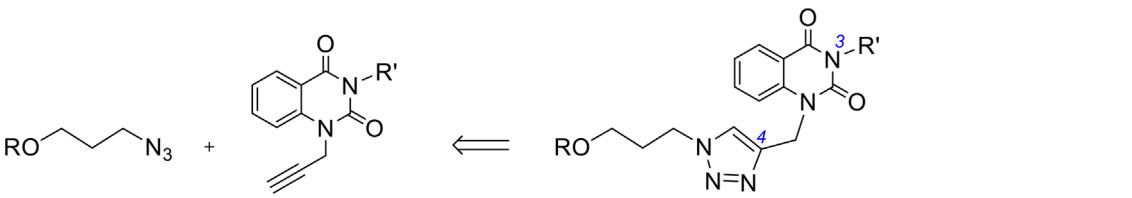


Figure 2. Known quinazoline-2,4-dione derivatives with anticancer and antiviral potency.

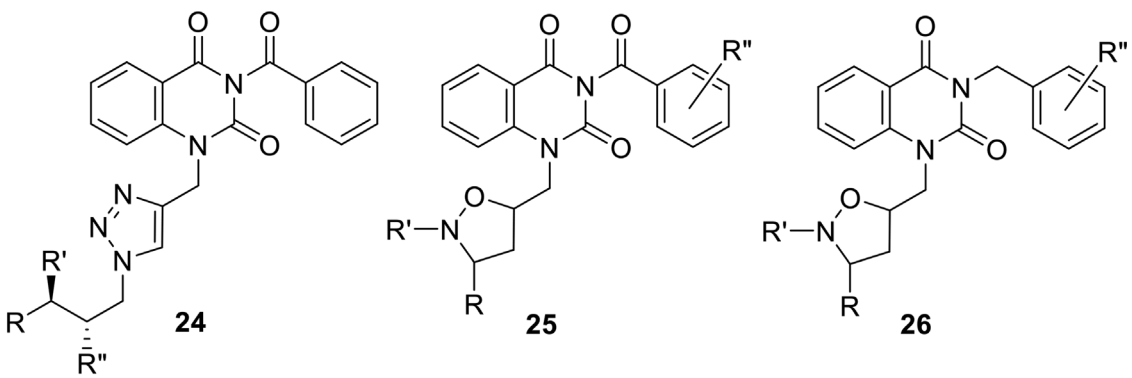


27 R = H,
28 R = Bn

29 R' = H,
30 R' = substituted benzoyl group,
31 R' = substituted benzyl group

32 R = H, R' = H,
33 R = H, R' = substituted benzoyl group,
34 R = H, R' = substituted benzyl group
35 R = Bn, R' = H,
36 R = Bn, R' = substituted benzoyl group,
37 R = Bn, R' = substituted benzyl group

Scheme 1. Retrosynthetic analysis of 1,2,3-triazolenucleosides.

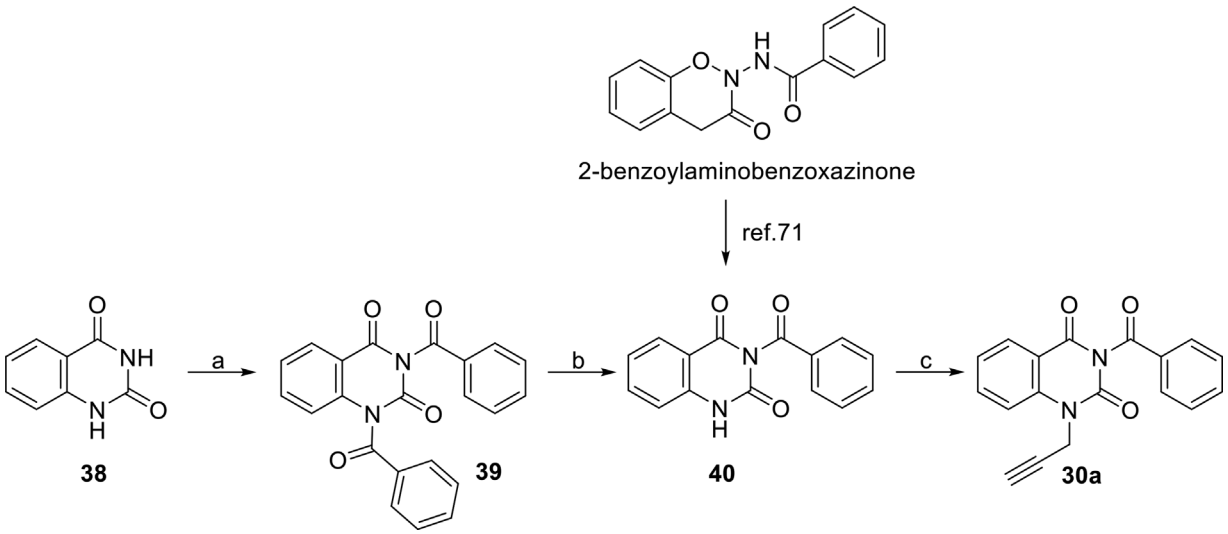


R = $(EtO)_2(O)P$, $(BnO)_2(O)P$,
R' = H, OH
R" = H, OBn

R = $(EtO)_2(O)P$,
R' = CH_3, Bn,
R" = H, F

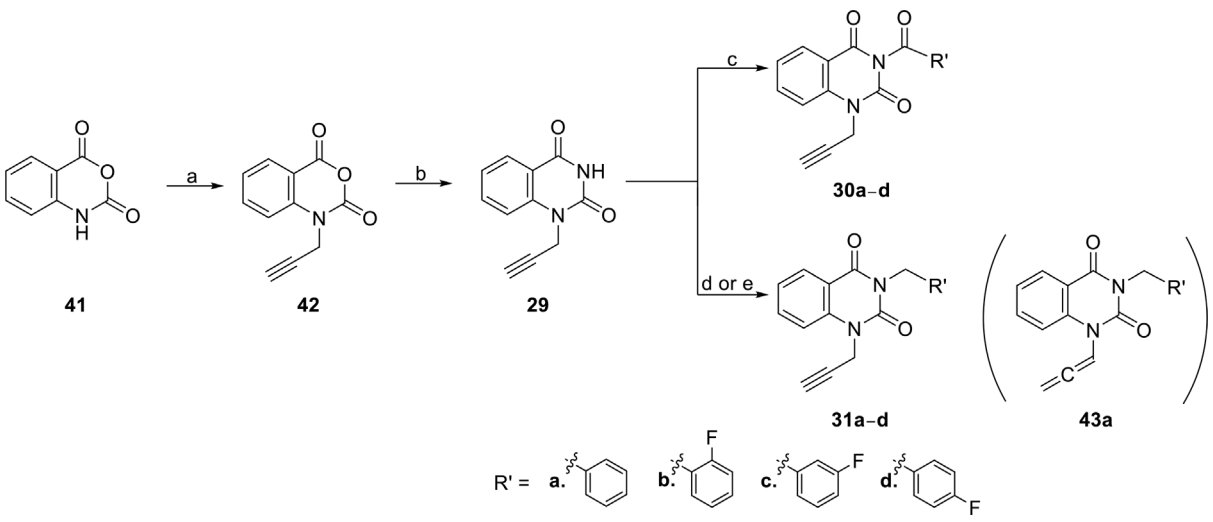
R = $(EtO)_2(O)P$,
R' = CH_3, Bn,
R" = H, F

Figure 3. Quinazoline-2,4-dione nucleoside analogs obtained in our research group.

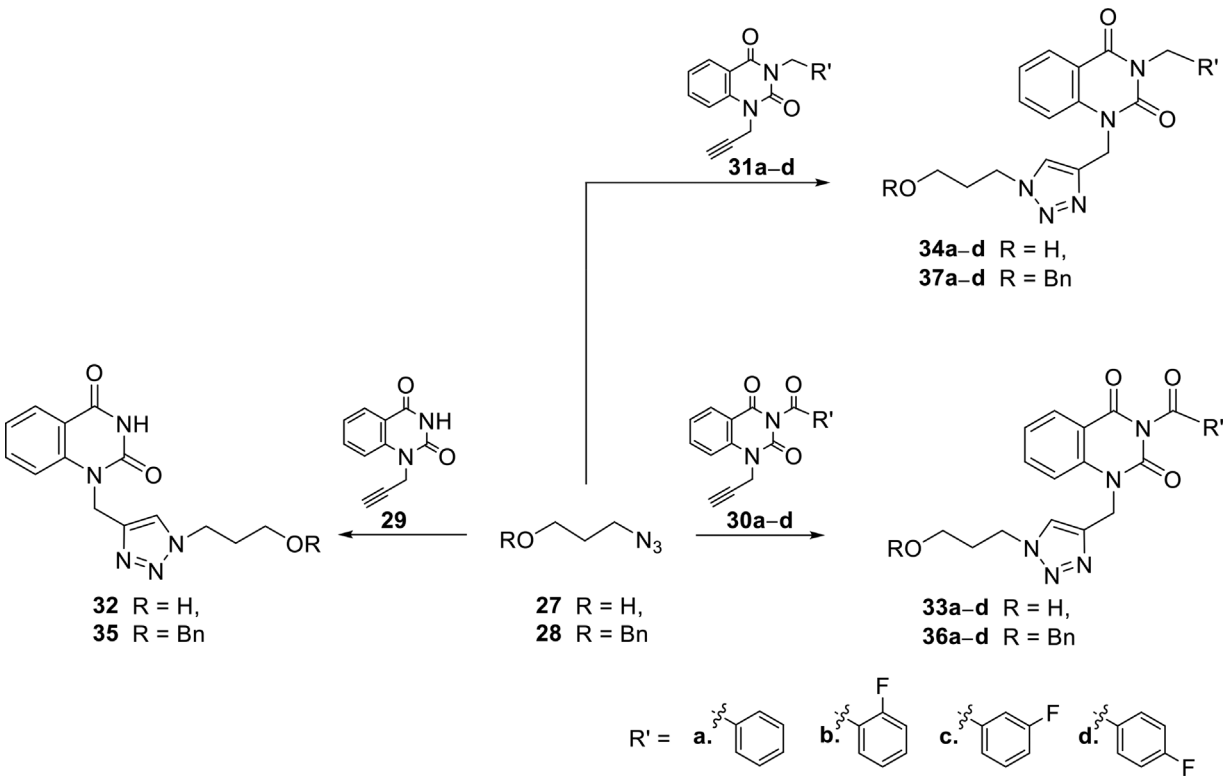


Scheme 2. Synthesis of N^3-benzoyl-N^1-propargylquinazoline-2,4-dione **30a**. Reaction and conditions: (a) Benzoyl chloride, pyridine, acetonitrile, r.t., 48 h; (b) 1 M K_2CO_3, dioxane, r.t., 24 h; (c) propargyl bromide, DMF, K_2CO_3, r.t., 24 h.

acyclovir, brivudin, zalcitabine, zanamivir, alovudine, amantadine, rimantadine, ribavirin, dextran sulfate (molecular weight 10000, DS-10000), mycophenolic acid, and *Urtica dioica* agglutinin (UDA) were used as the reference compounds. The antiviral activity was expressed as the EC_{50}: The effective concentration required to reduce virus plaque formation (VZV, HCMV) by 50% or to reduce virus-induced cytopathogenicity by 50% (other viruses). Among all the tested compounds, only the alkyne **30d** as well as 1,2,3-triazoles **36a** and **36d** exhibited antiviral activity against herpes simplex viruses, adenovirus-2, and human corona virus (229E) in HEL cell cultures (Table 1). It should be noted that these derivatives were equally active against HSV-1 TK^+ and TK^- HSV-1 strains in contrast to the gold standard for therapy of HSV infections [$EC_{50} = 6.6\,\mu M$ (**30d**), $4.6\,\mu M$ (**36a**), and $6.2\,\mu M$ (**36d**) vs. $85\,\mu M$ (acyclovir) for the HSV-1 TK^- strain]. In addition, compound **30d** appeared almost as active toward adenovirus-2 ($EC_{50} = 8.3\,\mu M$) as the reference compounds cidofovir ($EC_{50} = 5.8\,\mu M$), alovudine ($EC_{50} = 5.8\,\mu M$), and zalcitabine ($EC_{50} = 7.2\,\mu M$). A 10-fold lower activity of **36a**



Scheme 3. Synthesis of compounds **30a**–**d** and **31a**–**d**. Reaction and conditions: (a) Propargyl bromide, NaH, DMF, r.t., 24 h; (b) urea, DMF, reflux, 5 h; (c) selected benzoyl chloride, Et_3N, MeCN, r.t., 72 h; (d) benzyl bromide, KOH, MeCN, 105 or 60°C; (e) selected benzyl bromide, K_2CO_3, DMF, r.t., 48 h.



Scheme 4. Synthesis of compounds **33a–d**, **34a–d**, **36a–d**, and **37a–d**. Reaction and conditions: $CuSO_4 \times 5H_2O$, sodium ascorbate, EtOH–H_2O, 35–40°C, 30 min, MW.

Table 1. Antiviral activity and cytotoxicity of the tested compounds in HEL cell cultures.

Compound	Antiviral activity EC_{50} (μM)[a]						Minimum cytotoxic concentration[b] MCC (μM)
	Herpes simplex virus-1 (KOS)	Herpes simplex virus-2 (G)	Herpes simplex virus-1 TK^- KOS ACV^r	Vaccinia virus	Adenovirus-2	Human corona virus (229E)	
30d	13.8 ± 8.8	17.0 ± 4.2	6.6 ± 1.5	>100	8.3 ± 0.9	>100	>100
36a	5.4 ± 2.0	10.5 ± 2.2	4.6 ± 3.2	100	>100	18.5 ± 13.5	≥20
36d	6.8 ± 1.1	11.0 ± 1.4	6.2 ± 0.9	>100	>100	>100	≥20
Brivudin	0.02	146	85	2	ND	ND	>250
Cidofovir	2.8	1.0	1.0	22	5.8	ND	>250
Acyclovir	0.7	0.2	85	>250	ND	ND	>250
Ganciclovir	0.16	0.03	1.0	>100	ND	ND	>100
Zalcitabine	ND	ND	ND	ND	7.2	ND	>250
Alovudine	ND	ND	ND	ND	5.8	ND	>250
UDA	ND	ND	ND	ND	ND	1.8	>100
Ribavirin	ND	ND	ND	ND	ND	>250	>250

ND: not determined.
[a] Required to reduce virus-induced cytopathogenicity by 50%.
[b] Required to cause a microscopically detectable alteration of normal cell morphology.

compared to the reference compound UDA against human corona virus was measured (EC_{50} of 18.5 μM and 1.8 μM, respectively).

Moreover, several synthesized quinazoline-2,4-diones inhibited the replication of both TK^+ and TK^- VZV strains at EC_{50} in the 2–70 μM range (Table 2). In particular, alkynes **30a** (EC_{50} = 6.5 μM), **30b** (EC_{50} = 9.5 μM), and **30d** (EC_{50} = 5.9 μM) as well as 1,2,3-triazoles **36a** (EC_{50} = 5.9 μM), **36b** (EC_{50} = 6.2 μM), **36c** (EC_{50} = 8.3 μM), and **37a** (EC_{50} = 14.2 μM), as well as **37b** (EC_{50} = 8.2 μM) showed marked activity toward TK^- VZV strain, which was higher than that of the reference drugs acyclovir and brivudin (EC_{50} = 40.7 and 32.0 μM, respectively). However, they were significantly less active than the reference anti-VZV drugs against the TK^+ VZV strain Oka. Except for **36c**, these derivatives had a minimum cytotoxic concentration ≥100 μM. However, compounds **30a** (CC_{50} = 11.3 μM) and **30d** (CC_{50} = 9.1 μM) as well as **36a** (CC_{50} = 10.6 μM) and **36b** (CC_{50} = 12.5 μM) reduced cell growth (as measured by the 50% cytostatic concentration, i.e., CC_{50}) at lower concentrations than acyclovir and brivudin (CC_{50} > 350 μM), resulting in low selectivity (ratio CC_{50}/EC_{50}). Interestingly, **30b** emerged as the most selective anti-VZV quinazoline-2,4-diones since it did not inhibit growth of HEL cells up to a concentration of 100 μM.

All synthesized compounds were also subjected to antiviral screening against HCMV, and among them, **36a** (EC_{50} = 10.8–14.5 μM) and **36d** (EC_{50} = 12.6 and 8.9 μM) showed some activity; however, at the same time, **36a** showed cytotoxicity toward HEL cells (CC_{50} = 10.6 μM).

Cytostatic activity

The cytostatic activity of the tested compounds was defined as the 50% cytostatic inhibitory concentration (IC_{50}) causing a 50% decrease in cell proliferation and was determined against the transformed cells murine leukemia L1210, human lymphocyte CEM, human cervix carcinoma HeLa compared to human dermal microvascular endothelial HMEC-1 cells.

In these series, several compounds showed inhibitory activity against the proliferation of tumor cell lines (Table 3). From the entire library of compounds, **36a** and **36d** appeared to be the most inhibitory toward the growth of human T-lymphocyte (CEM) cell line with an inhibitory effect of 21 μM and 22 μM, respectively, comparable to that of the reference drug 5-fluorouracil (IC_{50} = 18 ± 5 μM). **36a** and **36d** weakly inhibited the proliferation of L1210, HeLa, and HMEC-1 cells with IC_{50} values in the range of 83–136 μM and 106–113 μM, respectively. Among all tested compounds, only **35** exhibited cytostatic activity (IC_{50}: 28 ± 2 μM) toward HMEC-1 cell line.

Table 2. Activity of the tested compounds against varicella-zoster virus (VZV) and cytomegalovirus (HCMV) in human embryonic lung (HEL) cells.

Compound	Antiviral activity EC_{50} (μM)[a]				Cytotoxicity (μM)	
	TK^+ VZV strain Oka	TK^- VZV strain 07-1	HCMV strain AD-169	HCMV Davis strain	Cell morphology (MCC)[b]	Cell growth (CC_{50})[c]
30a	5.4 ± 4.1	6.5 ± 5.1	>4	44.7	>100	11.3 ± 2.8
30b	2.8 ± 1.8	9.5 ± 3.5	44.7	63.1	100	>100
30c	17.03	48.12	>100	>100	100	ND
30d	2.7 ± 0.1	5.9 ± 2.7	44.7	44.7	100	9.1 ± 0.1
33a	41.57	49.5	44.7	54.7	>100	ND
33c	43.04	46.35	>20	>100	>100	ND
33d	36.19	48.35	44.7	44.7	>100	ND
34d	42.04	69.95	>100	>100	>100	ND
36a	2.8 ± 0.1	5.9 ± 3.3	10.8 ± 2.6	14.5 ± 7.8	100	10.6 ± 1.6
36b	3.3 ± 0.9	6.2 ± 2.4	20	>20	100	12.5 ± 0.5
36c	2.1	8.3	>20	>20	20	ND
36d	5.03	>4	12.6	8.9	100	ND
37a	>20	14.2	>20	>100	100	ND
37b	6.8	8.2	>4	>4	20	ND
37d	12.3	>20	>20	>100	20	ND
Acyclovir	1.6 ± 1.0	40.7 ± 1.4	ND	ND	>440	>350
Brivudin	0.023 ± 0.001	32.0 ± 16.3	ND	ND	>300	>300
Ganciclovir	ND	ND	16.9 ± 6.9	7.7 ± 0.9	>350	>350
Cidofovir	ND	ND	1.5 ± 0.2	1.7 ± 0.4	>350	>350

ND: not determined.
[a] Effective concentration required to reduce virus plaque formation by 50%. Virus input was 20 plaque-forming units (PFU).
[b] Minimum cytotoxic concentration that causes a microscopically detectable alternation of cell morphology.
[c] Cytotoxic concentration required to reduce cell growth by 50%.

Table 3. Inhibitory effects of the tested compounds against the proliferation of murine leukemia cells (L1210), human T-lymphocyte cells (CEM), human cervix carcinoma cells (HeLa), and human dermal microvascular endothelial cells (HMEC-1).

Compound	IC_{50} (μM)[a]			
	L1210	CEM	HeLa	HMEC-1
29	>250	>250	>250	>250
30a	>250	>250	>250	≥250
30b	>250	52 ± 46	>250	>250
30c	>250	>250	>250	≥250
30d	>250	>250	≥250	≥250
31a	>250	>250	>250	>250
31b	>250	>250	>250	>250
31c	>250	>250	>250	>250
31d	>250	>250	>250	>250
32	>250	>250	>250	>250
33a	≥250	≥250	>250	>250
33b	182 ± 80	≥250	>250	>250
33c	188 ± 60	≥250	>250	>250
33d	≥250	≥250	>250	>250
34a	>250	184 ± 5	>250	>250
34b	>250	165 ± 15	>250	>250
34c	173 ± 42	127 ± 13	>250	>250
34d	156 ± 37	97 ± 79	>250	>250
35	>250	>250	≥250	28 ± 2
36a	83 ± 59	21 ± 7	136 ± 66	119 ± 67
36b	>250	>250	>250	≥250
36c	132 ± 43	137 ± 107	168 ± 39	>250
36d	106 ± 57	22 ± 1	115 ± 31	113 ± 86
37a	93 ± 13	88 ± 39	118 ± 4	143 ± 136
37b	≥250	>250	>250	>250
37c	206 ± 62	88 ± 72	>250	>50
37d	72 ± 14	81 ± 45	65 ± 1	>50
5-Fluorouracil	0.33 ± 0.17	18 ± 5	0.54 ± 0.12	ND

ND, not determined.
[a]50% Inhibitory concentration or compound concentration required to inhibit tumor cell proliferation by 50%.

Conclusion

The N^3-benzoylated- and N^3-benzylated N^1-propargylquinazoline-2,4-diones **30a–d** and **31a–d** were efficiently synthesized from isatoic anhydride **41**.

The copper(I)-catalyzed 1,3-dipolar cycloadditions of the azides **27** and **28** with the selected N^3-benzoylated- and N^3-benzylated N^1-propargylquinazoline-2,4-diones **30a–d** and **31a–d** under microwave irradiation led to the formation of 1,2,3-triazole acyclonucleosides **32**, **35** and **33–34a–d** as well as **36–37a–d** in good yields.

All synthesized compounds were tested for their antiviral activities against DNA and RNA viruses as well as cytostatic activity and cytotoxicity. Among all tested compounds, **30d** (EC_{50} = 7.6 μM) showed activity against adenovirus-2 comparable to that of the reference compounds cidofovir, alovudine, and zalcitabine. Compounds **30d**, **36a,** and **36d** proved equally active against HSV-1 and VZV TK^+ and TK^- strains. In addition, the derivatives **30a**, **30b,** and **36b** were also inhibitory for TK^+ and TK^- VZV strains. The highest selectivity (ratio cytostatic effect [CC_{50}]/antiviral activity [EC_{50}]) was found for the compound **30b** ($CC_{50} \geq 100$ μM and MCC = 100). The selectivity for the compounds **30a**, **30d**, **36a,** and **36b** was low as they reduced cell growth (CC_{50}) at concentrations of 9–12.5 μM. Furthermore, several compounds (**30c** [EC_{50} = 48.12 μM], **33a** [EC_{50} = 49.45 μM], **33c** [EC_{50} = 46.31 μM], and **33d** [EC_{50} = 48.34 μM]) exhibited marginal activity against VZV strains and at the same time, they were not cytotoxic to uninfected HEL cells (MCC ≥ 100 μM).

Among all tested quinazoline-2,4-diones, compounds **36a** and **36d** were the most inhibitory toward the human T-lymphocyte (CEM) cell line and they showed inhibitory effects (IC_{50} = 21 ± 7 and 22 ± 1 μM, respectively) comparable to that of the reference compound 5-fluorouracil (IC_{50} = 18 ± 5 μM). The compound **35** exhibited also cytostatic activity (IC_{50}: 28 ± 2 μM) toward HMEC-1 cell line.

Experimental

Chemistry

General

^{1}H NMR spectra were taken in $CDCl_3$ or DMSO-d_6 on a Bruker Avance III (600 MHz) with TMS as an internal standard; chemical shifts δ are given in ppm with respect to TMS and coupling constants *J* in Hz. ^{13}C NMR spectra were recorded for $CDCl_3$ or DMSO-d_6 solutions on the Bruker Avance III (600 MHz) spectrometer at 151 MHz. IR spectral data were measured on an Infinity MI-60 FT-IR spectrometer. Melting points were determined on a Boetius apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of the Faculty of Pharmacy (Medical University of Lodz) on a Perkin Elmer PE 2400 CHNS analyzer.

The following adsorbents were used: column chromatography, Merck silica gel 60 (70–230 mesh); analytical TLC, Merck TLC plastic sheets silica gel 60 F_{254}. TLC plates were developed in chloroform–methanol solvent systems. Visualization of spots was effected with iodine vapors. All solvents were purified by methods described in the literature.

All microwave irradiation experiments were carried out in a microwave reactor Plazmatronika RM 800.

3-Azidopropan-1-ol **27** [68], (3-azidopropoxy)methylbenzene **28** [69, 70], N^1-(prop-2-yn-1-yl)isatoic anhydride [73], and N^3-benzoyl-N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **30a** [57] were obtained according to the literature procedures.

The InChI codes of the investigated compounds together with some biological activity data are provided as Supporting Information.

*Synthesis of N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **29***

To a solution of the N^1-(prop-2-yn-1-yl)isatoic anhydride **42** (2.46 g, 12.2 mmol) in dry DMF (70 mL), urea (1.38 g, 23.0 mmol) was added and the mixture was heated under reflux for 5 h. Solvent was removed *in vacuo* and the residue was crystallized from ethanol to afford **29** (2.032 g, 83%) as a beige powder. M.p.: 240–245°C; IR (KBr, cm^{-1}) ν_{max}: 3248, 3170, 3046, 2984, 2119, 1711, 1683, 1608, 1501; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 11.69 (s, 1H, NH), 8.04 (dd, *J* = 7.8 Hz, *J* = 1.6 Hz, 1H, H5), 7.82 (ddd, *J* = 8.4 Hz, *J* = 7.8 Hz, *J* = 1.6 Hz, 1H, H7), 7.49 (d, *J* = 8.4 Hz, 1H, H8), 7.33 (t, *J* = 7.8 Hz, 1H, H6), 4.90 (d, *J* = 2.4 Hz, 2H, CH_2C≡CH), 3.29 (t, *J* = 2.4 Hz, 1H, CH_2C≡C*H*); ^{13}C NMR (151 MHz, DMSO-d_6): δ = 160.06 (s, C=O), 150.14 (s, C=O), 140.48, 135.75, 128.09, 123.48, 116.26, 115.44, 79.99, 75.50, 32.32. Anal. calcd. for $C_{11}H_8N_2O_2$: C, 65.99; H, 4.03; N, 14.00. Found: C, 65.76; H, 4.01; N, 14.14.

*General procedure for benzoylation of N^1-(prop-2-yn-1-yl)-quinazoline-2,4-dione **29***

To a suspension of the N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **29** (1.00 mmol) in dry acetonitrile (6 mL), benzoyl chloride (2.20 mmol) and TEA (3.00 mmol) were added. The mixture was stirred at room temperature for 48 h. The solvent was removed and the residue was suspended in dichloromethane (20 mL) and extracted with water (3 × 20 mL). The organic phase was dried ($MgSO_4$), concentrated, and chromatographed and/or crystallized to give pure **30a**–**d**.

*N^3-Benzoyl-N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **30a***

A yellowish solid; 62% yield; m.p.: 178–181°C (lit. m.p.: 180–182°C) [57].

*N^3-(2-Fluorobenzoyl)-N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **30b***

From N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **29** (0.10 g, 0.50 mmol) and 2-fluorobenzoyl chloride (0.13 mL, 1.1 mmol), N^3-(2-fluorobenzoyl)-N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **30b** (0.098 g, 61%) was obtained as a white solid after purification on a silica gel column with dichloromethane and crystallization from a chloroform–diethyl ether mixture. M.p.: 214–217°C; IR (KBr, cm^{-1}) ν_{max}: 3255, 3106, 3080, 3064, 3042, 2979, 2125, 1695, 1656, 1608, 1483, 1105, 757; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.27 (dd, *J* = 7.9 Hz, *J* = 1.4 Hz, 1H, H5), 8.15 (dt, *J* = 9.5 Hz, *J* = 7.7 Hz, *J* = 1.8 Hz, 1H), 7.82 (ddd, *J* = 8.5 Hz, *J* = 7.9 Hz, *J* = 1.4 Hz, 1H, H7), 7.67–7.63 (m, 1H), 7.48 (d, *J* = 8.5 Hz, 1H, H8), 7.39–7.36 (m, 1H), 7.36–7.33 (m, 1H), 7.14 (ddd, *J* = 9.3 Hz, *J* = 8.3 Hz, *J* = 0.8 Hz, 1H), 4.96 (d, *J* = 2.5 Hz, 2H, CH_2C≡CH), 2.36 (t, *J* = 2.5 Hz, 1H, CH_2C≡C*H*); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 164.49 (s, C=O), 162.12 (d, *J* = 259.9 Hz, C2′), 160.61 (s, C=O), 148.66 (s, C=O), 139.57, 136.85 (d, *J* = 9.9 Hz, C1′), 135.90, 133.07, 129.12, 125.00 (d, *J* = 3.6 Hz, C5′), 123.83, 120.47 (d, *J* = 7.9 Hz, C4′), 117.24 (d, *J* = 23.1 Hz, C3′), 115.97, 114.63, 73.65, 32.68. Anal. calcd. for $C_{18}H_{11}FN_2O_3 \times 0.25H_2O$: C, 66.16; H, 3.55; N, 8.57. Found: C, 66.36; H, 3.34; N, 8.68.

*N^3-(3-Fluorobenzoyl)-N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **30c***

According to the general procedure from N^1-(prop-2-yn-1-yl)-quinazoline-2,4-dione **29** (0.10 g, 0.50 mmol) and 3-fluorobenzoyl chloride (0.13 mL, 1.10 mmol), N^3-(3-fluorobenzoyl)-N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **30c** (0.089 g, 55%) was obtained as a white solid after purification on a silica gel column with dichloromethane and crystallization from a chloroform–diethyl ether mixture. M.p.: 197–198°C; IR (KBr, cm^{-1}) ν_{max}: 3262, 3109, 3080, 3055, 2127, 1698, 1660, 1610, 1483, 1025, 893, 793, 775, 759; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.28 (dd, *J* = 7.8 Hz, *J* = 1.5 Hz, 1H, H5), 7.85 (ddd, *J* = 8.7 Hz, *J* = 7.8 Hz, *J* = 1.5 Hz, 1H, H7), 7.79 (dt, *J* = 7.9 Hz, *J* = 2.3 Hz, *J* = 1.2 Hz, 1H), 7.69 (d, *J* = 8.7 Hz, 1H, H8), 7.54–7.50 (m, 2H), 7.42–7.38 (m, 2H), 4.97 (d, *J* = 2.4 Hz, 2H, CH_2C≡CH), 2.39 (t, *J* = 2.4 Hz, 1H, CH_2C≡C*H*); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 167.46 (d, *J* = 3.2 Hz, C=O), 162.93 (d, *J* = 248.7 Hz, C3′), 160.87 (s, C=O), 148.73 (s, C=O), 139.60, 136.14, 133.83 (d, *J* = 7.7 Hz, C1′), 130.90 (d, *J* = 8.2 Hz, C5′), 129.19, 126.23 (d, *J* = 3.3 Hz, C6′), 124.04, 122.21 (d, *J* = 21.8 Hz, C2′), 117.16 (d, *J* = 23.2 Hz, C4′), 115.73, 114.76, 73.89, 32.80. Anal. calcd. for $C_{18}H_{11}FN_2O_3 \times 0.25H_2O$: C, 66.16; H, 3.55; N, 8.57. Found: C, 66.45; H, 3.28; N, 8.82.

*N^3-(4-Fluorobenzoyl)-N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **30d***

According to the general procedure from N^1-(prop-2-yn-1-yl)-quinazoline-2,4-dione **29** (0.10 g, 0.50 mmol) and 4-fluorobenzoyl chloride (0.13 mL, 1.10 mmol), N^3-(4-fluorobenzoyl)-N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **30d** (0.13 g, 81%) was obtained as a white solid after purification on a silica gel column with dichloromethane and crystallization from a chloroform–diethyl ether mixture. M.p.: 160–161°C; IR (KBr, cm^{-1}) ν_{max}: 3264, 3080, 3056, 2982, 2128, 1702, 1595, 1482, 1426, 1057, 1023, 845; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 8.26$ (dd, $J = 7.8$ Hz, $J = 1.3$ Hz, 1H, H5), 8.04–8.01 (m, 2H), 7.84–7.81 (m, 1H, H7), 7.50 (d, $J = 8.5$ Hz, 1H, H8), 7.38 (t, $J = 7.8$ Hz, 1H, H6), 7.21–7.18 (m, 2H), 4.96 (d, $J = 2.4$ Hz, 2H, $CH_2C{\equiv}CH$), 2.38 (t, $J = 2.4$ Hz, 1H, $CH_2C{\equiv}CH$); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 167.18$ (s, C=O), 166.99 (d, $J = 257.9$ Hz, C4′), 160.89 (s, C=O), 148.77 (s, C=O), 139.60, 136.08, 133.40 (d, $J = 9.9$ Hz, C2′, C6′), 129.16, 128.19 (d, $J = 3.3$ Hz, C1′), 123.99, 116.56 (d, $J = 22.0$ Hz, C3′, C5′), 115.76, 114.73, 73.84, 32.78. Anal. calcd. for $C_{18}H_{11}FN_2O_3$: C, 67.08; H, 3.44; N, 8.69. Found: C, 66.78; H, 3.17; N, 8.74.

*General procedure for benzylation of N^1-(prop-2-yn-1-yl)-quinazoline-2,4-dione **29**: Method A*

To a suspension of N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **29** (0.50 mmol) and potassium hydroxide (1.5 mmol) in anhydrous acetonitrile (35 mL), benzyl bromide (0.55 mmol) was added. The mixture was stirred at 105°C for 4 h or 60°C for 48 h, then the solvent was removed by vacuum evaporation. The residue was suspended in dichloromethane and extracted with water (3×20 mL). The organic phase was dried ($MgSO_4$) and concentrated to give a crude product as a mixture of an alkyne **31a** and an allene **43a** (50:50). Then purification on a silica gel column with chloroform and crystallization from a chloroform–diethyl ether mixture gave a mixture of **31a** and **43a** (0.149 g, 53%) and pure **43a** (0.026 g, 9%) as a white powder.

*N^3-Benzyl-N^1-(propa-1,2-dien-1-yl)quinazoline-2,4-dione **43a***

M.p.: 97–100°C; IR (KBr, cm^{-1}) ν_{max}: 3425, 3061, 3027, 3008, 1704, 1664, 1609, 1477, 1432; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 8.26$ (dd, $J = 7.9$ Hz, $J = 1.4$ Hz, 1H, H5), 7.66 (t, $J = 8.5$ Hz, 1H, H7), 7.57 (d, $J = 7.4$ Hz, 2H), 7.49 (d, $J = 8.5$ Hz, 1H, H8), 7.34–7.32 (m, 2H), 7.29–7.27 (m, 2H), 6.63 (t, $J = 6.4$ Hz, 1H, $CHCCH_2$), 5.44 (d, $J = 6.4$ Hz, 2H, $CHC{=}CH_2$), 5.31 (s, 2H, NCH_2Ph); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 207.62$ ($CH{=}C{=}CH_2$), 161.58 (s, C=O), 150.00 (s, C=O), 139.65, 136.83, 134.84, 129.21, 129.13, 128.43, 127.67, 123.40, 115.68, 114.84, 93.78, 84.73, 45.01. Anal. calcd. for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 73.95; H, 4.85; N, 9.45.

*General procedure for benzylation of N^1-(prop-2-yn-1-yl)-quinazoline-2,4-dione **29**: Method B*

To a suspension of N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **29** (0.50 mmol) and anhydrous potassium carbonate (0.50 mmol) in anhydrous DMF (5 mL), substituted benzyl bromide (0.60 mmol) was added. The mixture was stirred at room temperature for 48 h. Then water (10 mL) was added and the mixture was extracted with dichloromethane (3×10 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated. The crude products were purified by chromatography on the silica gel columns and crystallized to give **31a**–**d**.

*N^3-Benzyl-N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **31a***

According to the general procedure (method B) from N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **29** (0.10 g, 0.50 mmol) and benzyl bromide (0.071 mL, 0.60 mmol), the alkyne **31a** (0.12 g, 80%) was obtained as colorless needles after column chromatography with dichloromethane and crystallization from a chloroform–diethyl ether mixture. M.p.: 144–147°C; IR (KBr, cm^{-1}) ν_{max}: 3243, 3070, 3031, 2970, 2117, 1698, 1662, 1610, 1457; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 8.28$ (dd, $J = 7.9$ Hz, $J = 1.6$ Hz, 1H, H5), 7.74–7.71 (m, 1H, H7), 7.56 (d, $J = 7.3$ Hz, 2H), 7.38 (d, $J = 8.4$ Hz, 1H, H8), 7.35–7.32 (m, 3H), 7.30–7.27 (m, 1H), 5.31 (s, 2H, NCH_2Ph), 4.96 (d, $J = 2.4$ Hz, 2H, $CH_2C{\equiv}CH$), 2.33 (t, $J = 2.4$ Hz, 1H, $CH_2C{\equiv}CH$); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 161.58$ (s, C=O), 150.49 (s, C=O), 139.01, 136.82, 135.16, 129.25, 129.13, 128.45, 127.69, 123.42, 115.88, 114.02, 73.32, 45.20, 33.37. Anal. calcd. for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.36; H, 4.60; N, 9.75.

*N^3-(2-Fluorobenzyl)-N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **31b***

According to the general procedure (method B) from N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **29** (0.10 g, 0.50 mmol) and 2-fluorobenzyl bromide (0.073 mL, 0.60 mmol), the alkyne **31b** (0.11 g, 72%) was obtained as a white powder after chromatography on a silica gel column with dichloromethane and crystallization from a chloroform–diethyl ether mixture. M.p.: 151–153°C; IR (KBr, cm^{-1}) ν_{max}: 3272, 3065, 2991, 2964, 2123, 1666, 1655, 1482, 1096, 1059, 1027, 750; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 8.29$ (d, $J = 7.8$ Hz, 1H, H5), 7.77–7.74 (m, 1H, H7), 7.42 (d, $J = 8.5$ Hz, 1H, H8), 7.35–7.31 (m, 2H), 7.27–7.23 (m, 1H), 7.09–7.06 (m, 2H), 5.40 (s, 2H, NCH_2Ph), 4.98 (d, $J = 2.2$ Hz, 2H, $CH_2C{\equiv}CH$), 2.33 (t, $J = 2.2$ Hz, 1H, $CH_2C{\equiv}CH$); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 161.48$ (s, C=O), 160.80 (d, $J = 247.1$ Hz, C2′), 150.35 (s, C=O), 139.07, 135.26, 129.41 (d, $J = 3.9$ Hz, C6′), 129.34, 129.07 (d, $J = 7.9$ Hz, C4′), 124.06 (d, $J = 3.3$ Hz, C5′), 123.72 (d, $J = 14.3$ Hz, C1′), 123.50, 115.77, 115.49 (d, $J = 21.8$ Hz, C3′), 114.10, 73.35, 39.02 (d, $J = 4.9$ Hz, NCH_2Ph), 32.40. Anal. calcd. for $C_{18}H_{13}FN_2O_2$: C, 70.12; H, 4.25; N, 9.09. Found: C, 70.05; H, 4.00; N, 9.19.

*N^3-(3-Fluorobenzyl)-N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **31c***

According to the general procedure (method B) from N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **29** (0.10 g, 0.50 mmol) and 3-fluorobenzyl bromide (0.075 mL, 0.60 mmol), the product **31c** (0.11 g, 73%) was obtained as a white powder after chromatography on a silica gel column with dichloromethane and

crystallization from a chloroform–diethyl ether mixture. M.p.: 167–170°C; IR (KBr, cm^{-1}) ν_{max}: 3246, 3073, 2991, 2972, 2116, 1699, 1663, 1589, 1485, 1078, 1056, 1027, 877, 862, 799, 759; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.28 (dd, *J* = 7.9 Hz, *J* = 1.6 Hz, 1H, H5), 7.74 (ddd, *J* = 8.4 Hz, *J* = 7.9 Hz, *J* = 1.6 Hz, 1H, H7), 7.40 (d, *J* = 8.4 Hz, 1H, H8), 7.34–7.31 (m, 2H), 7.30–7.28 (m, 1H), 7.25–7.23 (m, 1H), 6.99–6.96 (m, 1H), 5.28 (s, 2H, NC*H*$_2$Ph), 4.97 (d, *J* = 2.5 Hz, 2H, C*H*$_2$C≡CH), 2.34 (t, *J* = 2.5 Hz, 1H, CH$_2$C≡C*H*); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.56 (d, *J* = 318.8 Hz, C3′), 161.99 (s, C=O), 150.41 (s, C=O), 139.14 (d, *J* = 7.0 Hz, C1′), 139.02, 135.29, 129.90 (d, *J* = 7.9 Hz, C5′), 129.28, 124.65 (d, *J* = 3.0 Hz, C6′), 123.53, 115.92 (d, *J* = 22.0 Hz, C4′), 115.76, 114.63 (d, *J* = 21.3 Hz, C2′), 114.09, 73.40, 44.69 (d, *J* = 1.7 Hz, NC*H*$_2$Ph), 33.42. Anal. calcd. for $C_{18}H_{13}FN_2O_2$: C, 70.12; H, 4.25; N, 9.09. Found: C, 69.89; H, 3.98; N, 9.18.

N^3-(4-Fluorobenzyl)-*N*^{1}-(prop-2-yn-1-yl)quinazoline-2,4-dione **31d**

According to general procedure (method B) from *N*^{1}-(prop-2-yn-1-yl)quinazoline-2,4-dione **29** (0.10 g, 0.50 mmol) and 4-fluorobenzyl bromide (0.074 mL, 0.60 mmol), the product **31d** (0.13 g, 81%) was obtained as a white powder after chromatography on a silica gel column with dichloromethane and crystallization from a chloroform–diethyl ether mixture. M.p.: 178–181°C; IR (KBr, cm^{-1}) ν_{max}: 3255, 3041, 2974, 2114, 1700, 1664, 1606, 1510, 1481, 1095, 1054, 853, 836; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.28 (dd, *J* = 7.9 Hz, *J* = 1.5 Hz, 1H, H5), 7.74 (ddd, *J* = 8.3 Hz, *J* = 7.9 Hz, *J* = 1.5 Hz, 1H, H7), 7.58–7.55 (m, 2H), 7.39 (d, *J* = 8.3 Hz, 1H, H8), 7.32 (t, *J* = 7.9 Hz, 1H, H6), 7.03–7.00 (m, 2H), 5.26 (s, 2H, NC*H*$_2$Ph), 4.96 (d, *J* = 2.5 Hz, 2H, C*H*$_2$C≡CH), 2.33 (t, *J* = 2.5 Hz, 1H, CH$_2$C≡C*H*); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.36 (d, *J* = 247.2 Hz, C4′), 161.54 (s, C=O), 150.44 (s, C=O), 138.99, 135.23, 132.63 (d, *J* = 3.2 Hz, C1′), 131.17 (d, *J* = 7.9 Hz, C2′, C6′), 129.23, 115.83, 115.24 (d, *J* = 21.2 Hz, C3′, C5′), 114.05, 73.35, 44.45, 33.38. Anal. calcd. for $C_{18}H_{13}FN_2O_2$: C, 70.12; H, 4.25; N, 9.09. Found: C, 70.27; H, 3.99; N, 8.98.

General procedure for the preparation of 1,2,3-triazoles ***32, 33–34a–d*** *and* ***35, 36–37a–d****: Method A*

To a solution of 3-azidopropan-1-ol **27** (0.025 g, 0.25 mmol) in ethanol (3 mL) and H_2O (1 mL), $CuSO_4 \times 5H_2O$ (0.006 g, 0.025 mmol), sodium ascorbate (0.010 g, 0.050 mmol), and *N*^{1}-(prop-2-yn-1-yl)quinazoline-2,4-dione **29** (0.050 g, 0.25 mmol) were added. The mixture was stirred at 45°C for 21 days. After cooling, the solvent was removed by vacuum evaporation. The crude product was purified by crystallization from water to give *N*^{1}-{[1-(3-hydroxypropyl)-1*H*-1,2,3-triazol-4-yl]methyl}quinazoline-2,4-dione **32** (0.065 g, 85%) as colorless needles.

General procedure for the preparation of 1,2,3-triazoles ***32, 33–34a–d*** *and* ***35, 36–37a–d****: Method B*

To a solution of an azide (1.00 mmol) in EtOH (1 mL) and H_2O (1 mL), $CuSO_4 \times 5H_2O$ (0.10 mmol), sodium ascorbate (0.20 mmol), and alkynes (1.00 mmol) were added. The suspension was irradiated in the microwave reactor (Plazmatronika RM800, 800 W) at 40–45°C for 30 min. After cooling, the solvent was removed, the residue was suspended in dry chloroform (3 mL), and filtered through a layer of Celite. The solution was concentrated *in vacuo* and the crude product was purified on a silica gel column with chloroform or chloroform–methanol mixtures (100:1, 50:1 or 25:1, v/v) and crystallized to give the 1,2,3-triazoles **32**, **33–34a–d** and **35**, **36–37a–d**.

N^1-{[1-(3-Hydroxypropyl)-1H-1,2,3-triazol-4-yl]methyl}-quinazoline-2,4-dione **32**

According to general procedure (method B) for the preparation of 1,2,3-triazoles from 3-azidopropan-1-ol **27** (0.051 g, 0.50 mmol) and *N*^{1}-(prop-2-yn-1-yl)quinazoline-2,4-dione **29**, the 1,2,3-triazole **32** (0.14 g, 90%) was obtained as colorless needles after crystallization from water. M.p.: 241–244°C; IR (KBr, cm^{-1}) ν_{max}: 3475, 3086, 3044, 2959, 2928, 1694, 1483, 1317; ^{1}H NMR (600 MHz, DMSO-*d*$_6$): δ = 11.66 (s, 1H, NH), 8.04 (s, 1H, HC5′), 8.02 (d, *J* = 7.8 Hz, 1H, H5), 7.72 (brt, *J* = 8.3 Hz, 1H, H7), 7.53 (d, *J* = 8.3 Hz, 1H, H8), 7.27 (t, *J* = 7.8 Hz, 1H, H6), 5.32 (s, 2H, C*H*$_2$), 4.64 (t, *J* = 5.0 Hz, 1H, O*H*), 4.35 (t, *J* = 7.1 Hz, 2H, NC*H*$_2$CH$_2$CH$_2$OH), 3.38–3.35 (m, 2H, NCH$_2$CH$_2$C*H*$_2$OH), 1.92 (qu, *J* = 7.1 Hz, 2H, NCH$_2$C*H*$_2$CH$_2$OH); ^{13}C NMR (151 MHz, DMSO-*d*$_6$): δ = 162.29 (s, C=O), 150.67 (s, C=O), 142.78, 141.23, 135.65, 127.99, 123.91, 123.17, 116.27, 115.55, 57.91, 47.16, 38.31, 33.29. Anal. calcd. for $C_{14}H_{15}N_5O_3 \times 0.25H_2O$: C, 54.99; H, 5.11; N, 22.90. Found: C, 54.80; H, 4.89; N, 22.78.

N^3-Benzoyl-*N*^{1}-{[1-(3-hydroxypropyl)-1H-1,2,3-triazol-4-yl]-methyl}quinazoline-2,4-dione **33a**

According to general procedure (method B) from 3-azidopropan-1-ol **27** (0.051 g, 0.50 mmol) and *N*^{3}-benzoyl-*N*^{1}-(prop-2-yn-1-yl)quinazoline-2,4-dione **30a**, the 1,2,3-triazole **33a** (0.21 g, 98%) was obtained as a white powder after purification on silica gel with chloroform and crystallization from a chloroform–diethyl ether mixture. M.p.: 156–158°C; IR (KBr, cm^{-1}) ν_{max}: 3546, 3340, 3088, 3061, 2945, 1659, 1608, 1481, 1393; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.23 (dd, *J* = 7.9 Hz, *J* = 1.5 Hz, 1H, H5), 8.01–7.99 (m, 2H), 7.94 (d, *J* = 8.5 Hz, 1H, H8), 7.80 (ddd, *J* = 8.5 Hz, *J* = 7.9 Hz, *J* = 1.5 Hz, 1H, H7), 7.70–7.68 (m, 1H), 7.54–7.52 (m, 2H), 7.34 (dt, *J* = 7.9 Hz, 1H, H6), 5.42 (s, 2H, C*H*$_2$), 4.49 (t, *J* = 6.8 Hz, 2H, C*H*$_2$CH$_2$CH$_2$OH), 3.66–3.63 (m, 2H, CH$_2$CH$_2$C*H*$_2$OH), 2.12 (qu, *J* = 6.8 Hz, 2H, CH$_2$C*H*$_2$CH$_2$OH), 1.86 (t, *J* = 5.0 Hz, 1H, O*H*); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 168.68 (s, C=O), 161.09 (s, C=O), 149.61 (s, C=O), 142.39, 140.28, 136.27, 135.15, 131.70, 130.53, 129.23, 128.96, 124.12, 123.83, 115.61, 115.32, 58.81, 47.14, 38.91, 32.40. Anal. calcd. for $C_{21}H_{19}N_5O_4 \times 0.25H_2O$: C, 61.53; H, 4.79; N, 17.09. Found: C, 61.25; H, 4.50; N, 16.88.

N^3-(2-Fluorobenzoyl)-*N*^{1}-{[1-(3-hydroxypropyl)-1H-1,2,3-triazol-4-yl]methyl}quinazoline-2,4-dione **33b**

According to general procedure (method B) from 3-azidopropan-1-ol **27** (0.031 g, 0.31 mmol) and *N*^{3}-(2-fluorobenzoyl)-*N*^{1}-(prop-2-yn-1-yl)quinazoline-2,4-dione **30b** (0.10 g, 0.31 mmol),

the 1,2,3-triazole **33b** (0.13 g, 99%) was obtained as a white powder after purification on silica gel with chloroform–methanol (50:1 to 25:1, v/v) and crystallization from a chloroform–diethyl ether mixture. M.p.: 148–152°C; IR (KBr, cm^{-1}) ν_{max}: 3332, 3083, 2950, 1662, 1607, 1482, 1456, 1079, 1052, 1033, 758, 696; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 8.21$ (dd, $J = 7.9$ Hz, $J = 1.4$ Hz, 1H, H5), 8.16 (dt, $J = 7.7$ Hz, $J = 1.7$ Hz, 1H), 7.87 (d, $J = 8.5$ Hz, 1H, H8), 7.78 (ddd, $J = 8.5$ Hz, $J = 7.9$ Hz, $J = 1.4$ Hz, 1H, H7), 7.69 (s, 1H, HC5′), 7.68–7.64 (m, 1H), 7.35 (t, $J = 7.4$ Hz, 1H), 7.32 (t, $J = 7.4$ Hz, 1H), 7.14 (dd, $J = 8.5$ Hz, 1H), 4.50 (t, $J = 6.8$ Hz, 2H, $CH_2CH_2CH_2OH$), 3.65 (t, $J = 6.8$ Hz, 2H, $CH_2CH_2CH_2OH$), 2.13 (qu, $J = 6.8$ Hz, 2H, $CH_2CH_2CH_2OH$), 1.75 (brs, 1H, OH); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 164.77$ (s, C=O), 162.09 (d, $J = 259.9$ Hz, C2′), 160.76 (s, C=O), 149.44, 142.57, 140.15, 136.92 (d, $J = 9.8$ Hz, C4′), 136.21, 133.10, 128.89, 125.11 (d, $J = 3.3$ Hz, C5′), 123.82 (d, $J = 20.2$ Hz, C1′), 120.53 (d, $J = 7.8$ Hz, C6′), 117.20 (d, $J = 23.2$ Hz, C3′), 115.72, 115.25, 58.80, 47.12, 38.88, 32.41. Anal. calcd. for $C_{21}H_{18}FN_5O_4 \times 0.25\ H_2O$: C, 58.94; H, 4.36; N, 16.37. Found: C, 59.24; H, 4.05; N, 16.35.

N^3-(3-Fluorobenzoyl)-N^1-{[1-(3-hydroxypropyl)-1H-1,2,3-triazol-4-yl]methyl}quinazoline-2,4-dione ***33c***

According to general procedure (method B) from 3-azidopropan-1-ol **27** (0.031 g, 0.31 mmol) and N^3-(3-fluorobenzoyl)-N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **30c** (0.10 g, 0.31 mmol), the 1,2,3-triazole **33c** (0.12 g, 95%) was obtained as a white powder after purification on silica gel with chloroform–methanol (50:1 to 25:1, v/v) and crystallization from a chloroform–diethyl ether mixture. M.p.: 134–136°C; IR (KBr, cm^{-1}) ν_{max}: 3549, 3351, 3084, 3057, 3042, 2967, 2945, 1657, 1608, 1481, 1442, 1048, 1001, 876, 861, 798, 782, 759; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 8.21$ (dd, $J = 7.9$ Hz, $J = 1.4$ Hz, 1H, H5), 7.94 (d, $J = 8.5$ Hz, 1H, H8), 7.82–7.77 (m, 2H), 7.72 (s, 1H, HC5′), 7.66 (dt, $J = 8.5$ Hz, $J = 1.4$ Hz, 1H, H7), 7.51 (dt, $J = 8.0$ Hz, $J = 5.3$ Hz, 1H), 7.39 (dt, $J = 8.5$ Hz, $J = 2.1$ Hz, 1H), 7.33 (t, $J = 7.9$ Hz, 1H, H6), 4.49 (t, $J = 6.8$ Hz, 2H, $CH_2CH_2CH_2OH$), 3.64 (t, $J = 6.8$ Hz, 2H, $CH_2CH_2CH_2OH$), 2.12 (qu, $J = 6.8$ Hz, 2H, $CH_2CH_2CH_2OH$), 1.96 (brs, 1H, OH); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 167.78$ (d, $J = 2.6$ Hz, C=O), 162.94 (d, $J = 249.4$ Hz, C3′), 161.04 (s, C=O), 149.52 (s, C=O), 142.29, 140.26, 136.42, 133.87 (d, $J = 7.3$ Hz, C1′), 130.96 (d, $J = 7.9$ Hz, C5′), 128.95, 126.23 (d, $J = 2.8$ Hz, C6′), 124.07, 123.95, 122.26 (d, $J = 21.2$ Hz, C2′), 117.11 (d, $J = 23.2$ Hz, C4′), 115.50, 115.41, 58.79, 47.18, 38.92, 32.42. Anal. calcd. for $C_{21}H_{18}FN_5O_4 \times 0.25H_2O$: C, 58.95; H, 4.36; N, 16.37. Found: C, 58.84; H, 4.02; N, 16.28.

N^3-(4-Fluorobenzoyl)-N^1-{[1-(3-hydroxypropyl)-1H-1,2,3-triazol-4-yl]methyl}quinazoline-2,4-dione ***33d***

According to general procedure (method B) from 3-azidopropan-1-ol **27** (0.039 g, 0.39 mmol) and N^3-(4-fluorobenzoyl)-N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **30d** (0.13 g, 0.39 mmol), the 1,2,3-triazole **33d** (0.15 g, 93%) was obtained as a white powder after purification on silica gel with chloroform–methanol (100:1 to 25:1, v/v) and crystallization from a chloroform–diethyl ether mixture. M.p.: 148–150°C; IR (KBr, cm^{-1}) ν_{max}: 3546, 3381, 2961, 2942, 1658, 1598, 1481, 1440, 1011, 848; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 8.21$ (d, $J = 7.8$ Hz, 1H, H5), 8.04–8.02 (m, 2H), 7.94 (d, $J = 8.5$ Hz, 1H, H8), 7.80 (t, $J = 8.5$ Hz, 1H, H7), 7.73 (s, 1H, HC5′), 7.33 (t, $J = 7.8$ Hz, 1H, H6), 7.20 (t, $J = 8.3$ Hz, 2H), 4.50 (t, $J = 6.2$ Hz, 2H, $CH_2CH_2CH_2OH$), 3.65 (t, $J = 6.2$ Hz, 2H, $CH_2CH_2CH_2OH$), 2.12 (qu, $J = 6.2$ Hz, 2H, $CH_2CH_2CH_2OH$), 1.85 (brs, 1H, OH); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 167.49$ (s, C=O), 166.97 (d, $J = 258.8$ Hz, C4′), 161.07 (s, C=O), 149.56 (s, C=O), 140.27, 136.35, 133.40 (d, $J = 9.9$ Hz, C2′, C6′), 128.95, 128.22 (d, $J = 2.8$ Hz, C1′), 123.90, 116.61 (d, $J = 22.3$ Hz, C3′, C5′), 115.54, 115.37, 58.85, 47.18, 38.92, 32.42. Anal. calcd. for $C_{21}H_{18}FN_5O_4 \times 0.25H_2O$: C, 58.95; H, 4.36; N, 16.37. Found: C, 58.79; H, 4.07; N, 16.02.

N^3-Benzyl-N^1-{[1-(3-hydroxypropyl)-1H-1,2,3-triazol-4-yl]-methyl}quinazoline-2,4-dione ***34a***

According to general procedure (method B) from 3-azidopropan-1-ol **27** (0.052 g, 0.52 mmol) and N^3-benzyl-N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **31a** (0.15 g, 0.52 mmol), the 1,2,3-triazole **34a** (0.19 g, 96%) was obtained as white needles after purification on silica gel with chloroform–methanol (50:1 to 25:1, v/v) and crystallization from a chloroform–diethyl ether mixture. M.p.: 121–122°C; IR (KBr, cm^{-1}) ν_{max}: 3486, 2957, 2946, 2928, 1649, 1606, 1482; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 8.24$ (dd, $J = 7.9$ Hz, $J = 1.6$ Hz, 1H, H5), 7.78 (d, $J = 8.5$ Hz, 1H, H8), 7.70 (ddd, $J = 8.5$ Hz, $J = 7.9$ Hz, $J = 1.6$ Hz, 1H, H7), 7.66 (s, 1H, HC5′), 7.54–7.53 (m, 2H), 7.35–7.32 (m, 2H), 7.30–7.26 (m, 2H), 5.41 (s, 2H, CH_2), 5.32 (s, 2H, NCH_2Ph), 4.48 (t, $J = 6.8$ Hz, 2H, $CH_2CH_2CH_2OH$), 3.65–3.62 (m, 2H, $CH_2CH_2CH_2OH$), 2.12 (qu, $J = 6.8$ Hz, 2H, $CH_2CH_2CH_2OH$), 1.75 (brs, 1H, OH); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 161.74$ (s, C=O), 151.16 (s, C=O), 142.98, 139.65, 136.96, 135.40, 129.04, 128.86, 128.44, 127.62, 123.77, 123.31, 115.65, 114.65, 58.81, 47.06, 45.02, 39.53, 32.41. Anal. calcd. for $C_{21}H_{21}N_5O_3$: C, 64.44; H, 5.41; N, 17.89. Found: C, 64.23; H, 5.11; N, 17.75.

N^3-(2-Fluorobenzyl)-N^1-{[1-(3-hydroxypropyl)-1H-1,2,3-triazol-4-yl]methyl}quinazoline-2,4-dione ***34b***

According to general procedure (method B) from 3-azidopropan-1-ol **27** (0.045 g, 0.45 mmol) and N^3-(2-fluorobenzyl)-N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **31b** (0.14 g, 0.45 mmol), the 1,2,3-triazole **34b** (0.18 g, 97%) was obtained as a white powder after purification on silica gel with chloroform and crystallization from a chloroform–diethyl ether mixture. M.p.: 121–123°C; IR (KBr, cm^{-1}) ν_{max}: 3399, 3342, 3072, 2927, 1662, 1606, 1484, 1404, 1097, 1056, 768, 694; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 8.24$ (dd, $J = 7.8$ Hz, $J = 1.0$ Hz, 1H, H5), 7.82 (d, $J = 8.5$ Hz, 1H, H8), 7.74–7.71 (m, 1H, H7), 7.69 (s, 1H, HC5′), 7.31–7.24 (m, 3H), 7.07 (t, $J = 8.4$ Hz, 2H), 5.43 (s, 2H, CH_2), 5.41 (s, 2H, NCH_2Ph), 4.49 (t, $J = 6.4$ Hz, 2H, $CH_2CH_2CH_2OH$), 3.64 (t, $J = 6.4$ Hz, 2H, $CH_2CH_2CH_2OH$), 2.12 (qu, $J = 6.4$ Hz, 2H, $CH_2CH_2CH_2OH$), 1.96 (s, 1H, OH); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 161.70$ (s, C=O), 160.78 (d, $J = 247.6$ Hz, C2′), 151.00 (s, C=O), 139.70, 135.52, 129.31 (d, $J = 4.0$ Hz, C6′), 129.09, 129.04 (d, $J = 8.1$ Hz, C4′), 124.07 (d, $J = 3.4$ Hz, C5′), 123.81 (d, $J = 14.3$ Hz, C1′), 123.39, 115.53, 115.49 (d, $J = 21.8$ Hz, C3′), 114.73, 58.77, 47.08, 39.54, 38.97 (d, $J = 4.6$ Hz, NCH_2Ph), 32.42. Anal. calcd. for

$C_{21}H_{20}FN_5O_3 \times 0.5H_2O$: C, 60.28; H, 5.06; N, 16.74. Found: C, 60.34; H, 4.72; N, 16.39.

N^3-(3-Fluorobenzyl)-N^1-{[1-(3-hydroxypropyl)-1H-1,2,3-triazol-4-yl]methyl}quinazoline-2,4-dione ***34c***

According to general procedure (method B) from 3-azidopropan-1-ol **27** (0.033 g, 0.32 mmol) and N^3-(3-fluorobenzyl)-N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **31c** (0.100 g, 0.32 mmol), the 1,2,3-triazole **34c** (0.12 g, 94%) was obtained as a white powder after purification on silica gel with chloroform and crystallization from a chloroform–diethyl ether mixture. M.p.: 83–85°C; IR (KBr, cm^{-1}) ν_{max}: 3417, 2956, 2926, 1658, 1609, 1484, 1050, 874, 756; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 8.24$ (dd, $J = 7.9$ Hz, $J = 1.4$ Hz, 1H, H5), 7.81 (d, $J = 8.5$ Hz, 1H, H8), 7.74–7.71 (m, 1H, H7), 7.68 (s, 1H, HC5′), 7.31–7.27 (m, 3H), 7.23–7.21 (m, 1H), 7.00–6.96 (m, 1H), 5.43 (s, 2H, CH_2), 5.30 (s, 2H, NCH_2Ph), 4.50 (t, $J = 6.5$ Hz, 2H, $CH_2CH_2CH_2OH$), 3.65 (t, $J = 6.5$ Hz, 2H, $CH_2CH_2CH_2OH$), 2.12 (qu, $J = 6.5$ Hz, 2H, $CH_2CH_2CH_2OH$), 1.79 (s, 1H, OH); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 162.82$ (d, $J = 245.9$ Hz, C3′), 161.65 (s, C=O), 151.10 (s, C=O), 139.65, 139.30 (d, $J = 7.4$ Hz, C1′), 135.54, 129.93 (d, $J = 8.1$ Hz, C5′), 124.48 (d, $J = 2.9$ Hz, C6′), 123.78, 123.42, 115.63 (d, $J = 21.8$ Hz, C4′), 115.54, 114.74, 114.56 (d, $J = 21.1$ Hz, C2′), 58.79, 47.09, 44.51, 39.54, 32.42. Anal. calcd. for $C_{21}H_{20}FN_5O_3 \times 0.25H_2O$: C, 60.94; H, 4.99; N, 16.92. Found: C, 60.88; H, 4,67; N, 16,64.

N^3-(4-Fluorobenzyl)-N^1-{[1-(3-hydroxypropyl)-1H-1,2,3-triazol-4-yl]methyl}quinazoline-2,4-dione ***34d***

According to general procedure (method B) from 3-azidopropan-1-ol **27** (0.033 g, 0.32 mmol) and N^3-(4-fluorobenzyl)-N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **31d** (0.10 g, 0.32 mmol), the 1,2,3-triazole **34d** (0.12 g, 92%) was obtained as a white powder after purification on silica gel with chloroform and crystallization from a chloroform–diethyl ether mixture. M.p.: 107–110°C; IR (KBr, cm^{-1}) ν_{max}: 3330, 2966, 2926, 1699, 1656, 1608, 1486, 1403, 1089, 1058, 1040, 857, 823; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 8.22$ (d, $J = 7.8$ Hz, 1H, H5), 7.76 (d, $J = 8.4$ Hz, 1H, H8), 7.69 (t, $J = 8.4$ Hz, 1H, H7), 7.66 (s, 1H, HC5′), 7.54–7.52 (m, 2H), 7.26 (t, $J = 7.8$ Hz, 1H, H6), 7.00 (t, $J = 8.6$ Hz, 2H), 5.40 (s, 2H, CH_2), 5.25 (s, 2H, NCH_2Ph), 4.48 (t, $J = 6.3$ Hz, 2H, $CH_2CH_2CH_2OH$), 3.64 (t, $J = 6.3$ Hz, 2H, $CH_2CH_2CH_2OH$), 2.11 (qu, $J = 6.3$ Hz, 2H, $CH_2CH_2CH_2OH$), 2.05 (brs, 1H, OH); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 162.31$ (d, $J = 245.9$ Hz, C4′), 161.70 (s, C=O), 151.10 (s, C=O), 139.63, 135.47, 132.76 (d, $J = 3.1$ Hz, C1′), 130.93 (d, $J = 8.0$ Hz, C2′, C6′), 128.99, 123.74, 123.37, 115.59, 115.23 (d, $J = 21.1$ Hz, C3′, C5′), 114.69, 58.78, 47.12, 44.30, 39.53, 32.48. Anal. calcd. for $C_{21}H_{20}FN_5O_3 \times 0.25H_2O$: C, 60.94; H, 4.99; N, 16.92. Found: C, 60.82; H, 4.67; N, 16.67.

N^1-{[1-(3-Benzyloxypropyl)-1H-1,2,3-triazol-4-yl]methyl}-quinazoline-2,4-dione ***35***

According to general procedure (method B) from (3-azidopropoxy)methylbenzene **28** (0.052 g, 0.26 mmol) and N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **29** (0.051 g, 0.26 mmol), pure 1,2,3-triazole **35** (0.091 g, 90%) was obtained as a white powder after purification on silica gel with chloroform and crystallization from a chloroform–diethyl ether mixture. M.p.: 203–205°C; IR (KBr, cm^{-1}) ν_{max}: 3043, 2960, 1682, 1608, 1501, 1482, 1403; ^{1}H NMR (600 MHz, DMSO-d_6): $\delta = 11.64$ (s, 1H, NH), 8.02–8.01 (m, 2H), 7.71–7.68 (m, 1H), 7.52 (d, $J = 8.5$ Hz, 1H, H8), 7.34–7.24 (m, 6H), 5.32 (s, 2H, CH_2), 4.40–4.37 (m, 4H, NCH_2Ph, $NCH_2CH_2CH_2OBn$), 3.39–3.36 (m, 2H, $NCH_2CH_2CH_2OBn$), 2.06 (qu, $J = 6.4$ Hz, 2H, $NCH_2CH_2CH_2OBn$); ^{13}C NMR (151 MHz, DMSO-d_6): $\delta = 162.26$ (s, C=O), 150.66 (s, C=O), 142.79, 141.21, 138.76, 135.56, 128.64, 127.98, 127.89, 127.83, 123.93, 123.10, 116.30, 115.49, 79.61, 79.39, 79.17, 72.44, 66.76, 47.28, 38.31, 30.28. Anal. calcd. for $C_{21}H_{21}N_5O_3 \times 0.25H_2O$: C, 63.71; H, 5.47; N, 17.69. Found: C, 63.53; H, 5.15; N, 17.65.

N^3-Benzoyl-N^1-{[1-(3-benzyloxypropyl)-1H-1,2,3-triazol-4-yl]methyl}quinazoline-2,4-dione ***36a***

According to general procedure (method B) from (3-azidopropoxy)methylbenzene **28** (0.084 g, 0.44 mmol) and N^3-benzoyl-N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **30a** (0.13 g, 0.44 mmol), the 1,2,3-triazole **36a** (0.20 g, 93%) was obtained as a white powder after purification on silica gel with chloroform and crystallization from a chloroform–diethyl ether mixture. M.p.: 111–113°C; IR (KBr, cm^{-1}) ν_{max}: 3065, 3037, 3007, 2965, 2947, 2929, 1700, 1661, 1482; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 8.23$ (dd, $J = 7.9$ Hz, $J = 1.4$ Hz, 1H, H5), 8.00–7.99 (m, 2H), 7.94 (d, $J = 8.5$ Hz, 1H, H8), 7.81–7.78 (m, 1H, H7), 7.68 (t, $J = 7.5$ Hz, 1H), 7.64 (s, 1H, HC5′), 7.52 (t, $J = 7.9$ Hz, 2H), 7.36–7.30 (m, 6H), 5.41 (s, 2H, CH_2), 4.47–4.45 (m, 4H, NCH_2Ph, $NCH_2CH_2CH_2OBn$), 3.46 (t, $J = 6.2$ Hz, 2H, $NCH_2CH_2CH_2OBn$), 2.19 (qu, $J = 6.2$ Hz, 2H, $NCH_2CH_2CH_2OBn$); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 168.66$ (s, C=O), 161.11 (s, C=O), 149.56 (s, C=O), 140.33, 137.93, 136.25, 135.10, 131.76, 130.53, 129.22, 128.93, 128.47, 127.81, 127.76, 123.78, 115.62, 115.37, 73.16, 66.19, 47.67, 38.86, 30.26. Anal. calcd. for $C_{28}H_{25}N_5O_4 \times 0.25H_2O$: C, 67.26; H, 5.14; N, 14.01. Found: C, 67.31; H, 4.86; N, 14.17.

N^1-{[1-(3-Benzyloxypropyl)-1H-1,2,3-triazol-4-yl]methyl}-N^3-(2-fluorobenzoyl)-quinazoline-2,4-dione ***36b***

According to general procedure (method B) from (3-azidopropoxy)methylbenzene **28** (0.065 g, 0.34 mmol) and N^3-(2-fluorobenzoyl)-N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **30b** (0.11 g, 0.34 mmol), the product **36b** (0.16 g, 92%) was obtained as a white powder after purification on silica gel with chloroform and crystallization from a chloroform–diethyl ether mixture. M.p.: 88–90°C; IR (KBr, cm^{-1}) ν_{max}: 3035, 2948, 2929, 1661, 1609, 1482, 1455, 1040, 741, 700; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 8.22$ (d, $J = 7.6$ Hz, 1H, H5), 8.16 (dt, $J = 8.5$ Hz, $J = 7.6$ Hz, $J = 1.1$ Hz, 1H, H7), 7.87 (d, $J = 8.5$ Hz, 1H, H8), 7.77 (t, $J = 7.6$ Hz, 1H, H6), 7.66–7.63 (m, 1H), 7.61 (s, 1H, HC5′), 7.36–7.29 (m, 7H), 7.11 (dd, $J = 8.4$ Hz, 1H), 5.43 (s, 2H, CH_2), 4.48–4.46 (m, 4H, NCH_2Ph, $NCH_2CH_2CH_2OBn$), 3.46 (t, $J = 6.4$ Hz, 2H, $NCH_2CH_2CH_2OBn$), 2.19 (qu, $J = 6.4$ Hz, 2H, $NCH_2CH_2CH_2OBn$); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 164.76$ (s, C=O), 162.07 (d, $J = 259.0$ Hz, C2′), 160.77 (s, C=O), 149.40, 142.42, 140.19, 137.92, 136.88 (d, $J = 9.6$ Hz, C4′), 136.19, 133.10, 128.88, 128.47, 127.81, 127.74, 125.10 (d, $J = 3.6$ Hz,

C5′), 123.74 (d, $J = 10.8$ Hz, C1′), 120.55 (d, $J = 7.8$ Hz, C6′), 117.20 (d, $J = 23.2$ Hz, C3′), 115.73, 115.30, 73.17, 66.16, 47.53, 38.91, 30.30. Anal. calcd. for $C_{28}H_{24}FN_5O_4$: C, 65.49; H, 4.71; N, 13.64. Found: C, 65.16; H, 4.39; N, 13.88.

N^1-{[1-(3-Benzyloxypropyl)-1H-1,2,3-triazol-4-yl]methyl}-N^3-(3-fluorobenzoyl)-quinazoline-2,4-dione ***36c***

According to general procedure (method B) from (3-azidopropoxy)methylbenzene **28** (0.080 g, 0.42 mmol) and N^3-(3-fluorobenzoyl)-N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **30c** (0.14 g, 0.42 mmol), the 1,2,3-triazole **36c** (0.20 g, 93%) was obtained as a white powder after purification on silica gel with chloroform and crystallization from a chloroform–diethyl ether mixture. M.p.: 100–102°C; IR (KBr, cm^{-1}) ν_{max}: 3086, 3036, 2929, 1663, 1483, 1040, 1028, 896, 782; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 8.23$ (d, $J = 7.7$ Hz, 1H, H5), 7.96 (d, $J = 8.5$ Hz, 1H, H8), 7.83–7.78 (m, 2H), 7.68 (d, $J = 8.8$ Hz, 1H), 7.62 (s, 1H, HC5′), 7.52–7.49 (m, 1H), 7.40–7.29 (m, 7H), 5.41 (s, 2H, CH_2), 4.48–4.46 (m, 4H, NCH_2Ph, NCH_2-CH_2CH_2OBn), 3.46 (t, $J = 6.4$ Hz, 2H, $NCH_2CH_2CH_2$OBn), 2.19 (qu, $J = 6.4$ Hz, 2H, $NCH_2CH_2CH_2$OBn); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 167.75$ (d, $J = 3.1$ Hz, CO), 162.95 (d, $J = 249.1$ Hz, C3′), 161.05 (s, C=O), 149.48, 142.14, 140.30, 137.92, 136.40, 133.92 (d, $J = 7.3$ Hz, C1′), 130.94 (d, $J = 7.7$ Hz, C5′), 128.96, 128.47, 127.82, 127.76, 122.22 (d, $J = 21.2$ Hz, C2′), 117.13 (d, $J = 23.2$ Hz, C4′), 115.49 (d, $J = 5.4$ Hz, C6′), 73.17, 66.16, 47.56, 38.93, 30.30. Anal. calcd. for $C_{28}H_{24}FN_5O_4$: C, 65.49; H, 4.71; N, 13.64. Found: C, 65.47; H, 4.66; N, 13.95.

N^1-{[1-(3-Benzyloxypropyl)-1H-1,2,3-triazol-4-yl]methyl}-N^3-(4-fluorobenzoyl)-quinazoline-2,4-dione ***36d***

According to general procedure (method B) from (3-azidopropoxy)methylbenzene **28** (0.080 g, 0.42 mmol) and N^3-(4-fluorobenzoyl)-N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **30d** (0.14 g, 0.42 mmol), the 1,2,3-triazole **36d** (0.20 g, 95%) was obtained as white needles after purification on silica gel with chloroform and crystallization from a chloroform–diethyl ether mixture. M.p.: 103–105°C; IR (KBr, cm^{-1}) ν_{max}: 3069, 3039, 2965, 2948, 2930, 1661, 1482, 1041, 827; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 8.22$ (dd, $J = 7.9$ Hz, $J = 1.6$ Hz, 1H, H5), 8.04–8.02 (m, 2H), 7.96 (d, $J = 8.5$ Hz, 1H, H8), 7.81 (ddd, $J = 8.5$ Hz, $J = 7.9$ Hz, $J = 1.6$ Hz, 1H H7), 7.62 (s, 1H, HC5′), 7.37–7.29 (m, 6H), 7.21–7.18 (m, 2H), 5.40 (s, 2H, CH_2), 4.48–4.46 (m, 4H, NCH_2Ph, NC$H_2CH_2CH_2$OBn), 3.46 (t, $J = 6.4$ Hz, 2H, $NCH_2CH_2CH_2$OBn), 2.19 (qu, $J = 6.4$ Hz, 2H, $NCH_2CH_2CH_2$OBn); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 167.45$ (s, C=O), 166.99 (d, $J = 258.6$ Hz, C4′), 161.08 (s, C=O), 149.52, 142.17, 140.32, 137.90, 136.33, 133.39 (d, $J = 9.9$ Hz, C2′, C6′), 128.94, 128.47, 128.27 (d, $J = 2.9$ Hz, C1′), 127.82, 127.76, 123.97, 123.85, 116.59 (d, $J = 22.2$ Hz, C3′, C5′), 115.55, 115.42, 73.18, 66.16, 47.56, 38.94, 30.30. Anal. calcd. for $C_{28}H_{24}FN_5O_4 \times 0.25$ H_2O: C, 64.91; H, 4.77; N, 13.52. Found: C, 64.97; H, 4.65; N, 13.82.

N^3-Benzyl-N^1-{[1-(3-benzyloxypropyl)-1H-1,2,3-triazol-4-yl]methyl}quinazoline-2,4-dione ***37a***

According to general procedure (method B) from (3-azidopropoxy)methylbenzene **28** (0.025 g, 0.17 mmol) and N^3-benzyl-N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **31a** (0.050 g, 0.17 mmol), the 1,2,3-triazole **37a** (0.076 g, 91%) was obtained as a white powder after purification on silica gel with chloroform–methanol (100:1 to 50:1, v/v) and crystallization from a chloroform–diethyl ether mixture. M.p.: 143–145°C; IR (KBr, cm^{-1}) ν_{max}: 3138, 3086, 3063, 2959, 2931, 1668, 1651, 1612, 1486, 1402; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 8.25$ (dd, $J = 7.9$ Hz, $J = 1.6$ Hz, 1H, H5), 7.78 (d, $J = 8.6$ Hz, 1H, H8), 7.70 (ddd, $J = 8.6$ Hz, $J = 7.9$ Hz, $J = 1.6$ Hz, 1H, H7), 7.58 (s, 1H, HC5′), 7.54 (d, $J = 7.3$ Hz, 2H), 7.38–7.30 (m, 7H), 7.28–7.25 (m, 2H), 5.40 (s, 2H, CH_2), 5.31 (s, 2H, NCH_2Ph), 4.46 (s, 2H, OCH_2Ph), 4.45 (t, $J = 6.8$ Hz, 2H, NC$H_2CH_2CH_2$OBn), 3.45 (t, $J = 6.8$ Hz, 2H, $NCH_2CH_2CH_2$OBn), 2.18 (qu, $J = 6.8$ Hz, 2H, $NCH_2CH_2CH_2$OBn); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 161.76$ (s, C=O), 151.14 (s, C=O), 142.84, 139.69, 137.94, 136.96, 135.38, 129.02, 128.90, 128.48, 128.46, 127.82, 127.73, 127.63, 123.65, 123.27, 115.65, 114.71, 73.17, 66.21, 47.47, 45.03, 39.58, 30.31. Anal. calcd. for $C_{28}H_{27}N_5O_3 \times 0.25$ H_2O: C, 69.19; H, 5.70; N, 14.41. Found: C, 69.22; H, 5.50; N, 14.26.

N^1-{[1-(3-Benzyloxypropyl)-1H-1,2,3-triazol-4-yl]methyl}-N^3-(2-fluorobenzyl)quinazoline-2,4-dione ***37b***

According to general procedure (method B) from (3-azidopropoxy)methylbenzene **28** (0.062 g, 0.32 mmol) and N^3-(2-fluorobenzyl)-N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **31b** (0.10 g, 0.32 mmol), pure product **37b** (0.15 g, 90%) was obtained as a white solid after purification on silica gel with chloroform and crystallization from a chloroform–diethyl ether mixture. M.p.: 103–105°C; IR (KBr, cm^{-1}) ν_{max}: 3337, 3062, 3031, 2927, 1698, 1656, 1486, 1454, 1057, 1024, 757, 694; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 8.25$ (d, $J = 7.9$ Hz, 1H, H5), 7.82 (d, $J = 8.5$ Hz, 1H, H8), 7.72 (t, $J = 8.5$ Hz, 1H, H7), 7.59 (s, 1H, HC5′), 7.37–7.24 (m, 8H), 7.07 (t, $J = 7.3$ Hz, 2H), 5.41 (s, 4H, CH_2, OCH_2Ph), 4.46–4.45 (m, 4H, NCH_2Ph, NC$H_2CH_2CH_2$OBn), 3.45 (t, $J = 6.4$ Hz, 2H, $NCH_2CH_2CH_2$OBn), 2.18 (qu, $J = 6.4$ Hz, 2H, $NCH_2CH_2CH_2$OBn); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 161.71$ (s, C=O), 160.79 (d, $J = 247.2$ Hz, C2′), 150.97 (s, C=O), 142.80, 139.75, 137.94, 135.50, 129.29 (d, $J = 4.0$ Hz, C6′), 129.08, 129.03 (d, $J = 8.0$ Hz, C4′), 128.47, 127.81, 127.72, 124.08 (d, $J = 3.4$ Hz, C5′), 123.84 (d, $J = 14.2$ Hz, C1′), 123.70, 123.34, 115.58, 115.49 (d, $J = 15.8$ Hz, C3′), 114.79, 73.17, 66.21, 47.48, 39.58, 38.96 (d, $J = 4.6$ Hz, NCH_2Ph), 30.30. Anal. calcd. for $C_{28}H_{26}FN_5O_3 \times 0.25H_2O$: C, 66.72; H, 5.30; N, 13.89. Found: C, 66.76; H, 5.24; N, 13.83.

N^1-{[1-(3-Benzyloxypropyl)-1H-1,2,3-triazol-4-yl]methyl}-N^3-(3-fluorobenzyl)quinazoline-2,4-dione ***37c***

According to general procedure (method B) from (3-azidopropoxy)methylbenzene **28** (0.062 g, 0.32 mmol) and N^3-(3-fluorobenzyl)-N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **31c** (0.10 g, 0.32 mmol), the 1,2,3-triazole **37c** (0.15 g, 91%) was obtained as a white solid after purification on silica gel with chloroform and crystallization from a chloroform–diethyl ether mixture. M.p.: 74–76°C; IR (KBr, cm^{-1}) ν_{max}: 3146, 3088, 3077, 3033, 2969, 2923, 1656, 1609, 1485, 1090, 1056, 1023, 892, 789; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 8.24$ (d, $J = 7.9$ Hz, 1H, H5), 7.80 (d, $J = 8.5$ Hz, 1H, H8), 7.71 (t, $J = 8.5$ Hz, 1H, H7), 7.59

(s, 1H, HC5′), 7.38–7.22 (m, 9H), 6.97 (t, $J = 7.3$ Hz, 1H), 5.41 (s, 2H, CH_2), 5.29 (s, 2H, OCH_2Ph), 4.47–4.45 (m, 4H, NCH_2Ph, $NCH_2CH_2CH_2OBn$), 3.46 (t, $J = 6.2$ Hz, 2H, $NCH_2CH_2CH_2OBn$), 2.18 (qu, $J = 6.2$ Hz, 2H, $NCH_2CH_2CH_2OBn$); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 162.83$ (d, $J = 245.6$ Hz, C3′), 161.66 (s, C=O), 151.06 (s, C=O), 142.74, 139.70, 139.31 (d, $J = 7.6$ Hz, C1′), 137.95, 135.51, 129.93 (d, $J = 7.9$ Hz, C5′), 129.04, 128.46, 127.81, 127.72, 124.48 (d, $J = 3.2$ Hz, C6′), 123.64, 123.37, 115.70 (d, $J = 22.0$ Hz, C4′), 115.84, 114.80, 114.58 (d, $J = 21.0$ Hz, C2′), 73.16, 66.22, 47.49, 44.52 (d, $J = 1.9$ Hz, NCH_2Ph), 39.59, 30.30. Anal. calcd. for $C_{28}H_{26}FN_5O_3$: C, 67.32; H, 5.25; N, 14.02. Found: C, 67.27; H, 4.92; N, 13.97.

N^1-{[1-(3-Benzyloxypropyl)-1H-1,2,3-triazol-4-yl]methyl}-N^3-(4-fluorobenzyl)quinazoline-2,4-dione ***37d***

According to general procedure (method B) from (3-azidopropoxy)methylbenzene **28** (0.062 g, 0.32 mmol) and N^3-(4-fluorobenzyl)-N^1-(prop-2-yn-1-yl)quinazoline-2,4-dione **31d** (0.10 g, 0.32 mmol), the 1,2,3-triazole **37d** (0.15 g, 95%) was obtained as a white solid after purification on silica gel with chloroform and crystallization from a chloroform–diethyl ether mixture. M.p.: 96–97°C; IR (KBr, cm^{-1}) ν_{max}: 3331, 3078, 3030, 2999, 2971, 2950, 1653, 1609, 1509, 1485, 1084, 1057, 852, 825; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 8.23$ (dd, $J = 7.9$ Hz, $J = 1.6$ Hz, 1H, H5), 7.77 (d, $J = 8.5$ Hz, 1H, H8), 7.69 (ddd, $J = 8.5$ Hz, $J = 7.9$ Hz, $J = 1.6$ Hz, 1H, H7), 7.58 (s, 1H, HC5′), 7.56–7.53 (m, 2H), 7.38–7.25 (m, 6H), 7.01–6.98 (m, 2H), 5.39 (s, 2H, CH_2), 5.26 (s, 2H, OCH_2Ph), 4.47–4.44 (m, 4H, NCH_2Ph, $NCH_2CH_2CH_2OBn$), 3.46 (t, $J = 6.2$ Hz, 2H, $NCH_2CH_2CH_2OBn$), 2.18 (qu, $J = 6.2$ Hz, 2H, $NCH_2CH_2CH_2OBn$); ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 162.32$ (d, $J = 245.9$ Hz, C4′), 161.71 (s, C=O), 151.07 (s, C=O), 142.76, 139.68, 137.93, 135.45, 132.78 (d, $J = 3.1$ Hz, C1′), 130.98 (d, $J = 7.8$ Hz, C2′, C6′), 128.98, 128.48, 127.83, 127.73, 123.61, 123.32, 115.59, 115.25 (d, $J = 20.8$ Hz, C3′, C5′), 114.76, 73.16, 66.22, 47.49, 44.30, 39.58, 30.31. Anal. calcd. for $C_{28}H_{26}FN_5O_3 \times 0.25H_2O$: C, 66.72; H, 5.30; N, 13.89. Found: C, 66.95; H, 4.95; N, 13.98.

Biological assays

The antiviral assays were based on inhibition of virus-induced cytopathicity or plaque formation in HEL [herpes simplex virus 1 (HSV-1) (KOS), HSV-2 (G), vaccinia virus, vesicular stomatitis virus, cytomegalovirus (HCMV), varicella-zoster virus (VZV), adenovirus-2, and human corona virus (299E)], Vero (parainfluenza-3, reovirus-1, Sindbis virus, and Coxsackie B4), HeLa (vesicular stomatitis virus, Coxsackie virus B4, and respiratory syncytial virus), or MDCK [influenza A (H1N1; H3N2) and influenza B] cell cultures. Confluent cell cultures (or nearly confluent for MDCK cells) 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 with 20 plaque-forming units (PFU). After 1–2 h virus adsorption period, residual virus was removed, and the cell cultures were incubated in the presence of varying concentrations (200, 40, 8, 1.6, 0.32 μM) of the test compounds. Viral cytopathicity 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 concentration required reducing virus-induced cytopathogenicity or viral plaque (VZV) formation by 50%. The minimal cytotoxic concentration (MCC) of the compounds was defined as the compound concentration that caused a microscopically visible alteration of cell morphology. Alternatively, cytotoxicity of the test compounds was measured based on inhibition of cell growth. HEL cells were seeded at a rate of 5×10^3 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 reducing cell proliferation by 50% relative to the number of cells in the untreated controls.

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