# EFFICIENT ONE-POT SYNTHESIS OF POLYSUBSTITUTED 6-[(1*H*-1,2,3-TRIAZOL-1-YL)METHYL]URACILS THROUGH THE "CLICK" PROTOCOL

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*Dedicated to the 75th anniversary of Professor Antonín Holý's birthday and the 25th anniversary of the discovery of antiviral nucleoside phosphonates.*

The preparation of several triazolo acyclic nucleosides and triazolo acyclic nucleoside phosphonates is described. The synthetic methodology has been developed as an efficient one-pot Cu(I)-catalyzed azide alkyne Huisgen "click" cycloaddition. A novel Cu(I)-catalyzed decarboxylation reaction of 1-substituted 1*H*-1,2,3-triazole-4-carboxylic acids at room temperature was observed and used for the preparation of 1-substituted 1*H*-1,2,3-triazoles. As congeners of TPI (Taiho pharmaceutical inhibitor), the prepared compounds were screened as potential inhibitors of human thymidine phosphorylase, but no inhibitory activity was observed.

**Keywords**: Nucleosides; Nucleotides; Biological activity; Heterocycles; Phosphorus; Click chemistry.

The synthesis of nucleoside or nucleotide analogues with a biomimetically modified 'sugar' moiety is an area of tremendous interest because of their wide range of biological activities, especially antiviral[1], antiparasitic[2] and cytostatic[3]. So-called acyclic nucleosides[4], where the sugar part of the molecule is substituted by an acyclic alkyl or heteroalkyl chain, are very promising and very potent compounds. The biological activity of these compounds with longer chains is negatively influenced by the entropic contribution to the free energy during the interaction of such molecules with the target enzymes or receptors. Long acyclic chains can rotate around



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every single bond. All these free-rotation states are lost after incorporation into the target enzyme, where usually only one rotamer forms a stable complex with the investigated biomolecule. To suppress this negative entropic contribution, the long alkyl chains could be modified by the insertion of double bonds[5] or small 5-membered cycles. The introduction of a 1,2,3-triazole ring by a Cu(I)-catalyzed[6] azide alkyne Huisgen[7] "click" cycloaddition (abbreviated also as "CuAAC") is a very useful tool for freezing the rotation flexibility of the acyclic part of the molecule. Some initial studies describing the possibility of freezing the side-chain flexibility of acyclic nucleosides or acyclic nucleoside phosphonates with the triazole moiety have already been reported[8]. The general impact of the Cu(I)-catalyzed 1,3-dipolar cycloaddition reaction between alkynes and azides on the chemistry of nucleosides and oligonucleotides has been also reviewed[9].

In addition, nucleoside analogues with triazole rings can also act as transition-state analogue inhibitors. This was demonstrated for example for the analogues of the Taiho pharmaceutical inhibitor (TPI) (**1**), which is a very potent thymidine phosphorylase inhibitor, where substituted 6-[(1*H*-imidazol-1-yl)methyl]uracils (**2**) and 6-[(1*H*-1,2,4-triazol-1-yl)methyl]-uracils (**3**) were identified as promising inhibitors of human thymidine phosphorylase (Fig. 1)[10]. Surprisingly, no 6-[(1*H*-1,2,3-triazol-1-yl)methyl]-uracils, which could be also promising inhibitors of human thymidine phosphorylase and are easy to prepare by the Huisgen "click" protocol, have been reported to the best of our knowledge, only base-modified 5-(1,2,3-triazol-1-yl)-2′-deoxyuridines were prepared and studied for their antiviral activities[11].

Due to the high regioselectivity of the CuAAC, only 4′-substituted 6-[(1*H*-1,2,3-triazol-1-yl]methyl)uracils could be selectively prepared. This substituent in the position 4′ can interact with the highly polar phosphate binding site in the molecule of human thymidine phosphorylase[12]. Therefore, 6-[(1*H*-1,2,3-triazol-1-yl)methyl]uracils bearing polar substituent in

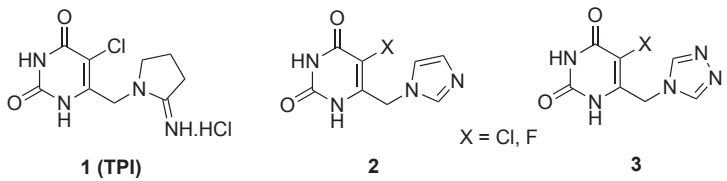



FIG. 1
Structures of the known potent inhibitors of thymidine phosphorylase

the position 4′ can act as transition-state analog inhibitors of human thymidine phosphorylase.

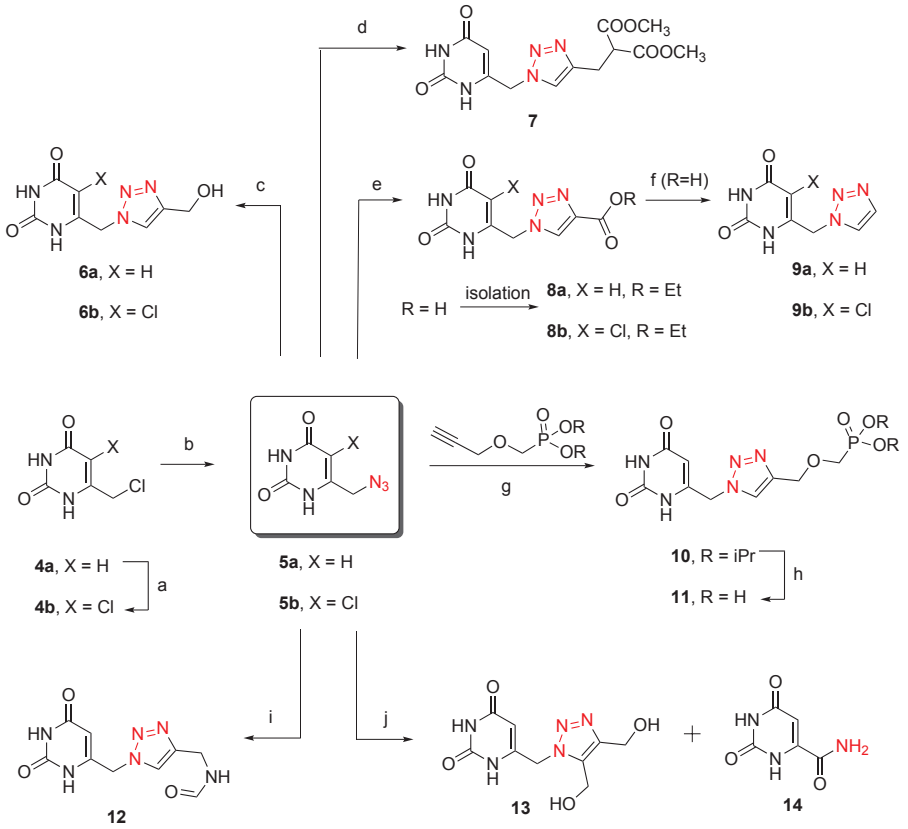
## RESULTS AND DISCUSSION

At first, the key intermediates **5a** and **5b** bearing an azidomethyl group were prepared by the reaction of chloromethyl derivatives **4a** and **4b** with sodium azide in DMF at room temperature (Scheme 1). The conversion to the products of **5** is quantitative and sodium chloride is the only by-product formed. Thus, the reaction mixture containing the compounds of **5** can be used directly in the next step.

The crude intermediates of **5** in DMF were reacted with a wide range of commercially available terminal alkynes under the Cu(I)-catalyzed azide alkyne Huisgen "click" conditions at room temperature to obtain substituted 6-[(1*H*-1,2,3-triazol-1-yl)methyl]uracils (Scheme 1). This reaction was surprisingly very slow when only the catalytic amount (5%) of Cu(I) was used. It was rationalized that the product of the reaction because of its chelate-like structure could form stable complexes with the copper catalyst. This notion was afterwards confirmed during the isolation of the desired product (see below). Therefore, one molar equivalent of Cu(I) was used and the full conversion was obtained within a minute. As expected, the Huisgen "click" reaction with terminal alkynes is fully regiospecific and leads only to the formation of substituted 6-[(1*H*-1,2,3-triazol-1-yl)methyl]-uracils. The acyclic nucleoside phosphonate analogues **10** and **11** were also prepared using diisopropyl [(pro*p*-2-yn-1-yloxy)methyl]phosphonate (Scheme 1), which was prepared according to the literature[7], except that the diisopropyl bromomethylphosphonate[13] reagent was used instead of the tosyloxymethylphosphonate derivative.

Surprisingly, during the formation of 1-substituted 1*H*-1,2,3-triazole-4-carboxylic acids by the reaction of intermediate **5a** or **5b** with acrylic acid, a novel Cu(I)-catalyzed decarboxylation reaction at room temperature was observed. Thus, the prolonged reaction time (5 days) yielded 1-substituted 1*H*-1,2,3-triazoles **9a** and **9b**. This decarboxylation reaction of 1,2,3-triazole-4-carboxylic acids has been already described in the literature but under more drastic conditions, e.g. reflux in concentrated hydrochloric acid[14], thermal decomposition at 160 °C [15], photochemical degradation[16] or in the presence of copper powder at 180 °C [17]. Very recently, a single case of such a decarboxylation reaction has been observed during a Cu(I) catalyzed tandem decarboxylative coupling of alkynoic acids and 1,3-dipolar cycloaddition of azides, which was used for the synthesis of a variety of func-

tionalized 1,2,3-triazoles[18]. The carboxyl function in the molecule of 1,2,3-triazole-4-carboxylic acids was found to be very reactive also in other, different types of reactions. During isolation (see below) on silica gel column chromatography using an eluent containing ethanol, a full conversion into ethyl esters **8a** and **8b** was observed.




SCHEME 1

Conditions: (a) NCS, AcOH, $(Ac)_2O$, 60 °C; (b) $NaN_3$, DMF, r.t.; (c) prop-2-yn-1-ol, DMF, CuI, r.t.; (d) dimethyl 2-(prop-2-yn-1-yl)malonate, DMF, CuI, r.t.; (e) acrylic acid, DMF, CuI, r.t.; (f) DMF, CuI, r.t.; (g) DMF, CuI, r.t.; (h) BTMS, $CH_3CN$, r.t.; (i) prop-2-yn-1-amine, DMF, CuI, r.t.; (j) but-2-yne-1,4-diol, DMF, 120 °C

Another unexpected reaction was observed during the reaction of propargylamine with intermediate **5a** or **5b**, where only an *N*-formyl derivative **12** of the desired product was isolated. It is well known that DMF is a quite reactive solvent and that it can decompose into dimethylamine and

carbon oxide[19], but this formylation at room temperature was truly unanticipated.

The Cu(I)-catalyzed azide alkyne Huisgen "click" cycloaddition could not be used for the preparation of 4- and 5-disubstituted 1,2,3-triazoles. This type of compounds can be prepared by azide alkyne cycloaddition at elevated temperature. Such a reaction was used for the preparation of symmetrical dihydroxymethyl derivative **13**, where a partial degradation of the starting compound **5a** was observed at 120 °C to produce compound **14**.

Finally, the most challenging part of this work was the isolation of the prepared compounds, where the copper catalyst could not be removed by simple column chromatography. Such isolated products were green and according to the X-ray fluorescence method they contained copper. For the most liphophilic compound **7**, a wide range of extraction techniques were applied, such as extraction with aqueous EDTA disodium salt or sodium thiosulfate, but without success. We can speculate that the target compounds form stable complexes with copper owing to their chelate-like structures (Fig. 2). After some optimization, efficient isolation conditions were found. The procedure is based on the low solubility of CuS. Thus, after the complete reaction, 1.5 molar eq. of sodium sulfide were added. The reaction mixture was stirred at room temperature for 10 min while being purged in a slow current of air. A solid dark precipitation was filtered off and the final purification was done using flash chromatography. By this method, all of the prepared 4′-substituted 6-[(1*H*-1,2,3-triazol-1-yl)methyl]-uracils were isolated as pure compounds (copper < 5 ppm) in good to excellent preparative yields of 71–93%. A copper-less process for the preparation of 4′,5′-disubstituted 6-[(1*H*-1,2,3-triazol-1-yl)methyl]uracil **13** provided the product in a 36% yield only.

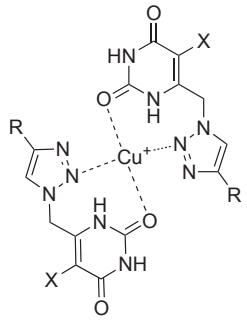



FIG. 2
The proposed structure of the complex of 6-[(1*H*-1,2,3-triazol-1-yl)methyl]uracils with copper

The chemical structure of the prepared compounds and the presence of the 6-[(1*H*-1,2,3-triazol-1-yl)methyl]uracil motive was unambiguously confirmed by solving the X-ray structure of compound **6a** (Fig. 3).

All of the prepared compounds were tested for their *in vitro* inhibition of thymidine phosphorylase. In contrast to active 6-[(1*H*-imidazol-1-yl]-methyl)uracils (**2**) and 6-[(1*H*-1,2,4-triazol-1-yl)methyl]uracils (**3**)[6], none of the prepared compound exhibited any significant inhibitory activity. The inactivity of the tested compounds could be explained for compounds with only a hydrogen atom at position 5 of the uracil ring. It was fully demonstrated that the substituent in position 5 of the uracil ring has a key effect on inhibitory activity where only 5-halo-, 5-alkyl- or 5-aryluracils could act as thymidine phosphorylase inhibitors[20]. Nevertheless, the absence of the biological activity of prepared 5-chlorouracils is really incomprehensible.

All of the prepared compounds (as analogs of nucleic acid components) were also tested for their antiproliferative and antiviral activities. None of the tested compounds exhibited any antiproliferative activity in mouse leukemia L1210 cells, human T-lymphoblastoid CCRF-CEM cell line, human promyelocytic leukemia HL-60 cells, human cervix carcinoma HeLa S3 cells or any antiviral activity against HIV, HCV, RSV, VZV, CMV, HSV-1, HSV-2, Vaccinia virus, Coxsackie B4 virus, Vesicular stomatitis virus, Feline corona virus and Influenza A virus.

In conclusion, an efficient methodology for the preparation and isolation of several triazolo acyclic nucleosides and one triazolo acyclic nucleoside phosphonate was described. The synthetic method has been developed as an efficient one-pot Cu(I)-catalyzed azide alkyne Huisgen "click" cycloaddition. A novel Cu(I)-catalyzed decarboxylation reaction of 1-substituted 1*H*-1,2,3-triazole-4-carboxylic acids at room temperature was observed and used for the preparation of 1-substituted 1*H*-1,2,3-triazoles. As nucleoside

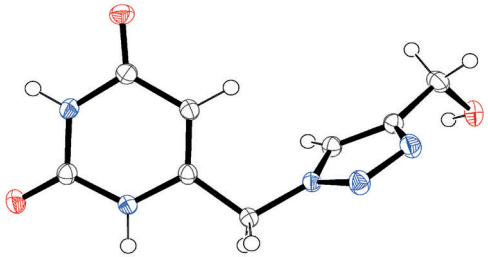


FIG. 3
An ORTEP drawing of **6a**. Thermal ellipsoids are drawn at the 50% probability level

and nucleotide analogues, the prepared compounds were screened for their probable biological activities, but no antiviral, antiproliferative and inhibitory activities towards thymidine phosphorylase were observed.

## EXPERIMENTAL

Unless otherwise stated, the solvents were evaporated at 40 °C/2 kPa and the compounds were dried in vacuo over $P_2O_5$. The NMR spectra were recorded on a Bruker Avance 500 ($^1$H at 500 MHz, $^{13}$C at 125.8 MHz). Chemical shifts, given in ppm (δ-scale), were referenced to the signal of DMSO (δ 2.50 and 39.7) or to dioxane (δ 3.75 and 67.19). Coupling constants (*J*) are given in Hz. The assignment of the carbons was based on C,H-HSQC and C,H-HMBC experiments. The melting points were determined on a Kofler block and are uncorrected. The mass spectra were measured on a LCQ Fleet spectrometer (Thermo Fisher Scientific) using ESI ionization. The high-resolution mass spectra were measured on a LTQ Orbitrap XL spectrometer (Thermo Fisher Scientific) using ESI ionization. The 6-(Chloromethyl)-pyrimidine-2,4(1*H*,3*H*)-dione (**4a**) was purchased from ABCR GmbH & Co.KG (Germany).

The X-ray diffraction data of a single crystal of **6a** (colorless, 0.09 × 0.46 × 0.51 mm) were collected on an Xcalibur X-ray diffractometer with CuKα (λ = 1.54180 Å) at 150 K. The structure was solved by direct methods with SIR92 [21] and refined by the full-matrix, least-squares methods based on *F* with CRYSTALS [22]. The hydrogen atoms were located in a difference map, but those attached to carbon atoms were repositioned geometrically and then refined with riding constraints; the non-hydrogen atoms were refined with anisotropic thermal displacement parameters.

*5-Chloro-6-(chloromethyl)pyrimidine-2,4(1H,3H)-dione* (**4b**) was prepared according to the literature[23]. ESI MS, *m/z* (%): 193.2 (100) [M$^-$]. HR ESI MS: for $C_5H_3Cl_2N_2O_2$ calculated 192.9577; found 192.9577.

### One-Pot Synthesis of Monosubstituted 6-[(1*H*-1,2,3-Triazol-1-yl)methyl]uracils. General Procedure

6-(Chloromethyl)pyrimidine-2,4(1*H*,3*H*)-dione (**4a**) or 5-chloro-6-(chloromethyl)pyrimidine-2,4(1*H*,3*H*)-dione (**4b**) (1 mmol) was added to the suspension of sodium azide (1.05 mmol) in 10 ml of DMF. Full conversion was achieved after stirring at ambient temperature for 2 h according to the TLC (the control sample of the reaction mixture was evaporated in vacuo and the MS spectra of **5a** and **5b** confirmed the presence of the desired product – see below). This reaction mixture containing only sodium chloride, traces of sodium azide and product **5a** or **5b** was pure enough for the next reaction. Therefore, this reaction mixture was injected into the solution containing copper(I) iodide (1 mmol) and the selected alkyne (2 mmol) in 20 ml of DMF under an inert atmosphere of argon. This mixture was stirred at room temperature for 10 min. The reaction was always completed after 1 min according to the TLC. For the synthesis of compounds **9a** and **9b**, the reaction time was prolonged for additional 5 days. For the separation of the copper catalyst, sodium sulfide (1.5 mmol) was added and the reaction mixture was stirred at room temperature for 10 min while being purged in a slow current of air. A solid dark precipitation was filtered off and the final product was isolated by flash chromatography (silica gel, ethyl acetate/acetone/ethanol/water 30:3:4:3).

*6-(Azidomethyl)pyrimidine-2,4(1H,3H)-dione* (**5a**): ESI MS, *m/z* (%): 166.0 (100) [$M^-$]. HR ESI MS: for $C_5H_4N_5O_2$ calculated 166.0365; found 166.0364.

*6-(Azidomethyl)-5-chloropyrimidine-2,4(1H,3H)-dione* (**5b**): ESI MS, *m/z* (%): 200.1 (100) [$M^-$]. HR ESI MS: for $C_5H_3ClN_5O_2$ calculated 199.9981; found 199.9982.

*6-{[4-(Hydroxymethyl)-1H-1,2,3-triazol-1-yl]methyl}pyrimidine-2,4(1H,3H)-dione* (**6a**): Yield 207 mg (93%) of white crystals, m.p. >250 °C. $^1$H NMR (DMSO-$d_6$): 11.13 bs, 1 H and 11.10 bs, 1 H (H-1, H-3); 8.20 s, 1H (H-5′); 5.39 s, 2 H ($NCH_2$); 4.89 s, 1 H (H-5); 4.48 s, 2 H ($OCH_2$). $^{13}$C NMR (DMSO-$d_6$): 163.65 (C-6); 151.40 (C-2); 151.03 (C-4); 145.70 (C-4′); 127.58 (C-5′); 98.51 (C-5); 55.02 ($CH_2OH$); 48.86 ($NCH_2$). ESI MS, *m/z* (%): 222.1 (100) [$M^-$]. HR ESI MS: for $C_8H_8N_5O_3$ calculated 222.0627; found 222.0625. For $C_8H_9N_5O_3$ (223.19) calculated: 43.05% C, 4.06% H, 31.38% N; found: 43.24% C, 4.31% H, 31.19% N.

Crystal data for **6a**: $C_8H_9N_5O_3$, monoclinic, space group $P2_{1/c}$, $a$ = 10.9584(5) Å, $b$ = 10.8983(4) Å, $c$ = 8.2735(4) Å, β = 108.409(5)°, $V$ = 937.53(8) Å$^3$, $Z$ = 4, $M$ = 223.19; 9216 reflections measured, 1976 independent reflections. Final $R$ = 0.043, $wR$ = 0.037, GOF = 1.268 for 1857 reflections with $I > 2\sigma(I)$ and 146 parameters.

CCDC 821669 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

*5-Chloro-6-{[4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl]methyl}pyrimidine-2,4(1H,3H)-dione* (**6b**): Yield 234 mg (91%) of white crystals, m.p. >250 °C. $^1$H NMR (DMSO-$d_6$): 11.50 bs, 1 H (NH); 8.08 s, 1 H (H-5′); 5.40 bs, 2 H ($NCH_2$); 4.51 s, 2 H ($OCH_2$). $^{13}$C NMR (DMSO-$d_6$): 160.35 (C-6); 151.16 (C-2); 148.24 (C-4′); 146.73 (C-4); 123.81 (C-5′); 106.76 (C-5); 55.17 ($CH_2OH$); 48.58 ($NCH_2$). ESI MS, *m/z* (%): 256.1 (100) [$M^-$]. HR ESI MS: for $C_8H_7ClN_5O_3$ calculated 256.0243; found 256.0244. For $C_8H_8ClN_5O_3$ (257.63) calculated: 37.30% C, 3.13% H, 27.18% N; found: 37.15% C, 3.30% H, 27.22% N.

*Dimethyl 2-({1-[(2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)methyl]-1H-1,2,3-triazol-4-yl}-methyl)malonate* (**7**): Yield 278 mg (82%) of white crystals, m.p. >250 °C. $^1$H NMR (DMSO-$d_6$): 11.23 bs, 1 H (H-3); 11.14 bs, 1 H (H-1); 8.00 s, 1 H (H-5′); 5.31 d, 2 H, $J$($CH_2$,5) = 1.2 ($NCH_2$); 4.79 t, 1 H, $J$(5,$CH_2$) = 1.2 (H-5); 3.93 t, 1 H, $J$(CH,$CH_2$) = 7.8 (4′-$CH_2$-CH); 3.64 s, 6 H ($CH_3$); 3.18 d, 2 H, $J$($CH_2$,CH) = 7.8 (4′-$CH_2$). $^{13}$C NMR (DMSO-$d_6$): 168.96 (COO); 163.92 (C-6); 151.40 and 151.13 (C-2, C-4); 143.52 (C-4′); 124.24 (C-5′); 98.22 (C-5); 52.72 ($COOCH_3$); 50.97 (4′-$CH_2$-CH); 48.93 ($NCH_2$); 24.76 (4′-$CH_2$). ESI MS, *m/z* (%): 338.1 (30) [$MH^+$]; 360.2 (100) [$MNa^+$]. ESI MS, *m/z* (%): 337.2 (100) [$M^-$]. HR ESI MS: for $C_{13}H_{14}N_5O_6$ calculated 336.0950; found 336.0940. For $C_{13}H_{15}N_5O_6$ (337.29) calculated: 46.29% C, 4.48% H, 20.76% N; found: 46.11% C, 4.67% H, 20.87% N.

*Ethyl 1-[(2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)methyl]-1H-1,2,3-triazole-4-carboxylate* (**8a**): Yield 214 mg (81%) of white crystals, m.p. >250 °C. $^1$H NMR (DMSO-$d_6$): 11.23 bs, 1 H (H-3); 11.17 bs, 1 H (H-1); 8.87 s, 1 H (H-5′); 5.41 s, 2 H ($NCH_2$); 5.11 s, 1 H (H-5); 4.32 q, 2 H, $J$($CH_2$,$CH_3$) = 7.1 ($OCH_2$); 1.30 t, 3 H, $J$($CH_3$,$CH_2$) = 7.1 ($CH_3$). $^{13}$C NMR (DMSO-$d_6$): 163.91 (C-6); 160.29 (COO); 151.46 (C-2); 149.82 (C-4); 139.16 (C-4′); 130.62 (C-5′); 99.45 (C-5); 60.90 ($OCH_2$); 49.45 ($NCH_2$); 14.38 ($CH_3$). ESI MS, *m/z* (%): 264.2 (100) [$M^-$]. ESI MS, *m/z* (%): 288.2 (22) [$MNa^+$]. HR ESI MS: for $C_{10}H_{10}N_5O_4$ calculated 264.0738; found 264.0735. For $C_{10}H_{11}N_5O_4$ (265.23) calculated: 45.28% C, 4.18% H, 26.41% N; found: 45.41% C, 4.35% H, 26.24% N.

*Ethyl 1-[(5-chloro-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)methyl]-1H-1,2,3-triazole-4-carboxylate* (**8b**): Yield 250 mg (84%) of white crystals, m.p. >250 °C. $^1$H NMR (DMSO-$d_6$):

11.76 bs, 1 H (H-1); 11.61 bs, 1 H (H-3); 8.90 s, 1 H (H-5′); 5.50 s, 2 H ($NCH_2$); 4.31 q, 2 H, $J(CH_2,CH_3)$ = 7.1 ($OCH_2$); 1.30 t, 3 H, $J(CH_3,CH_2)$ = 7.1 ($CH_3$). $^{13}$C NMR (DMSO-$d_6$): 160.29 and 160.06 (C-6, COO); 150.10 (C-2); 144.09 (C-4); 138.94 (C-4′); 130.31 (C-5′); 107.97 (C-5); 60.92 ($OCH_2$); 48.47 ($NCH_2$); 14.40 ($CH_3$). ESI MS, *m/z* (%): 298.1 (100) [$M^-$]. HR ESI MS: for $C_{10}H_9ClN_5O_4$ calculated 298.0343; found 298.0346. For $C_{10}H_{10}ClN_5O_4$ (299.67) calculated: 40.08% C, 3.36% H, 23.37% N; found: 40.31% C, 3.54% H, 23.51% N.

*6-[(1H-1,2,3-Triazol-1-yl)methyl]pyrimidine-2,4(1H,3H)-dione* (**9a**): Yield 137 mg (71%) of white crystals, m.p. >250 °C. $^1$H NMR (DMSO-$d_6$): 11.25 bs, 1 H and 11.15 bs, 1 H (H-1, H-3); 8.25 s, 1 H (H-5′); 7.82 s, 1 H (H-4′); 5.37 s, 2 H ($NCH_2$); 4.90 s, 1 H (H-5). $^{13}$C NMR (DMSO-$d_6$): 163.92 (C-6); 151.43 (C-2); 150.92 (C-4); 133.90 (C-4′); 126.41 (C-5′); 98.62 (C-5); 48.86 ($NCH_2$). ESI MS, *m/z* (%): 192.2 (100) [$M^-$]. HR ESI MS: for $C_7H_6N_5O_2$ calculated 192.0527; found 192.0527. For $C_7H_7N_5O_2$ (193.16) calculated: 43.53% C, 3.65% H, 36.26% N; found: 43.24% C, 3.87% H, 36.09% N.

*6-[(1H-1,2,3-Triazol-1-yl)methyl]-5-chloropyrimidine-2,4(1H,3H)-dione* (**9b**): Yield 175 mg (77%) of white crystals, m.p. >250 °C. $^1$H NMR (DMSO-$d_6$): 11.76 bs, 1 H (H-1); 11.69 bs, 1 H (H-3); 8.26 s, 1 H (H-5′); 7.79 s, 1 H (H-4′); 5.44 s, 2 H ($NCH_2$). $^{13}$C NMR (DMSO-$d_6$): 160.10 (C-6); 150.10 (C-2); 144.88 (C-4); 133.68 (C-4′); 126.14 (C-5′); 107.75 (C-5); 48.00 ($NCH_2$). ESI MS, *m/z* (%): 226.1 (100) [$M^-$]. HR ESI MS: for $C_7H_5ClN_5O_2$ calculated 226.0137; found 226.0139. For $C_7H_6ClN_5O_2$ (227.61) calculated: 36.94% C, 2.66% H, 30.77 N; found: 36.78% C, 2.85% H, 30.64% N.

*Diisopropyl [({1-[(2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)methyl]-1H-1,2,3-triazol-4-yl}methoxy)methyl]phosphonate* (**10**): Yield 340 mg (85%) of colorless oil. ESI MS, *m/z* (%): 400.1 (100) [$M^-$]. ESI MS, *m/z* (%): 402.0 (9) [$MH^+$]; 424.1 (100) [$MNa^+$]. HR ESI MS: for $C_{15}H_{23}N_5O_6P$ calculated 400.1391; found 400.1390. For $C_{15}H_{24}N_5O_6P$ (401.35) calculated: 44.89% C, 6.03% H, 17.45% N; found: 44.97% C, 6.28% H, 17.26% N.

*[({1-[(2,6-Dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)methyl]-1H-1,2,3-triazol-4-yl}methoxy)methyl]phosphonic acid* (**11**): A mixture of diisopropyl ester 200 mg (0.5 mmol), acetonitrile (10 ml), and $BrSiMe_3$ (1 ml) was stirred overnight at room temperature. After evaporation in vacuo and codistillation with acetonitrile, the residue was treated with water and concentrated aqueous ammonia was added to the alkaline reaction. The mixture was evaporated to dryness and the residue was applied on a column of Dowex 50 X 8 ($H^+$-form, 20 ml) and washed with water. Elution with 2.5% aqueous ammonia and evaporation in vacuo afforded a crude product as ammonium salt. This residue in a minimum volume of water was applied on a Dowex 1 X 2 (acetate) (25 ml) column, which was then washed with water followed by a gradient of acetic acid (0–1 M). The main UV-absorbing fraction was evaporated, the residue was codistilled three times with water and crystallized from water–ethanol to afford 110 mg (69%) of the desired product as white crystals, m.p. >250 °C. $^1$H NMR ($D_2O$): 8.20 s, 1 H (H-5′); 5.53 d, 2 H, $J(CH_2,5)$ = 1.0 ($NCH_2$); 5.44 t, 1 H, $J(5,CH_2)$ = 1.0 (H-5); 4.79 s, 2 H (4′-$CH_2$-O); 3.81 d, 2 H, $J$(H,C,P) = 9.1 ($PCH_2$). $^{13}$C NMR ($D_2O$): 167.13 (C-6); 153.27 (C-2); 151.38 (C-4); 144.67 (C-4′); 126.94 (C-5′); 100.66 (C-5); 65.62 d, $J$(C,P) = 159.6 ($PCH_2O$); 65.48 d, $J$(C,O,C,P) = 13.1 (4′-$CH_2$-O); 50.21 (4-$CH_2$-N). ESI MS, *m/z* (%): 316.1 (100) [$M^-$]. ESI MS, *m/z* (%): 318.1 (100) [$MH^+$]. HR ESI MS: for $C_9H_{11}N_5O_6P$ calculated 316.0452; found 316.0442. For $C_9H_{12}N_5O_6P$ (317.20) calculated: 34.08% C, 3.81% H, 22.08% N; found 34.01% C, 4.02% H, 21.94% N.

*N-({1-[(2,6-Dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)methyl]-1H-1,2,3-triazol-4-yl}methyl)formamide* (**12**): Yield 190 mg (76%) of white crystals, m.p. >250 °C. $^1$H NMR (DMSO-$d_6$): 11.25 bs, 1 H and 11.15 bs, 1 H (H-1, H-3); 8.56 bt, 1 H, $J(NH,CH_2)$ = 5.7 ($CH_2NH$); 8.07 s,

2 H (H-5′, CHO); 5.31 d, 2 H, $J(CH_2,5)$ = 1.0 (4-$CH_2$-N); 4.95 bs, 1 H (H-5); 4.35 bd, 2 H, $J(CH_2,NH)$ = 5.9 (4′-$CH_2$-NH). $^{13}$C NMR (DMSO-$d_6$): 164.04 (C-6); 161.39 (CHO); 151.51 (C-2); 150.93 (C-4); 145.08 (C-4′); 124.41 (C-5′); 98.74 (C-5); 49.09 (4-$CH_2$-N); 33.00 (4′-$CH_2$-NH). ESI MS, *m/z* (%): 249.2 (100) [M$^-$]. HR ESI MS: for $C_9H_{11}N_6O_3$ calculated 251.0887; found 251.0886. For $C_9H_{10}N_6O_3$ (250.21) calculated: 43.20% C, 4.03% H, 33.59% N; found: 43.48% C, 4.17% H, 33.42% N.

Preparation of Disubstituted 6-[(1*H*-1,2,3-Triazol-1-yl)methyl]uracils

The reaction mixture containing intermediate **4a** (1 mmol) was injected into the solution of but-2-yn-1,4-diol (2 mmol) in 20 ml of DMF under an inert atmosphere of argon. This mixture was stirred at 120 °C for 3 days to achieve full conversion. The two main products were separated by column chromatography (silica gel, ethyl acetate/acetone/ethanol/water 30:3:4:3).

*6-{[4,5-Bis(hydroxymethyl)-1H-1,2,3-triazol-1-yl]methyl}pyrimidine-2,4(1H,3H)-dione* (**13**): Yield 90 mg (36%) of white crystals, m.p. >250 °C. $^1$H NMR (DMSO-$d_6$): 11.12 bs, 1 H (NH); 5.34 s, 2 H ($NCH_2$); 5.15 bt, 1 H, $J(OH,CH_2)$ = 5.5 (OH); 4.76 s, 1 H (H-5); 4.62 s, 2 H and 4.53 d, 2 H, $J(CH_2,OH)$ = 5.3 ($CH_2OH$). $^{13}$C NMR (DMSO-$d_6$): 163.97 (C-6); 151.43 and 151.24 (C-2, C-4); 145.14 (C-4′); 135.17 (C-5′); 97.96 (C-5); 54.32 and 51.00 ($CH_2OH$); 47.43 ($CH_2N$). ESI MS, *m/z* (%): 252.2 (100) [M$^-$]. HR ESI MS: for $C_9H_{10}N_5O_4$ calculated 252.0738; found 252.0738. For $C_9H_{11}N_5O_4$ (253.21) calculated: 42.69% C, 4.38% H, 27.66% N; found: 42.57% C, 4.58% H, 27.40% N.

*2,6-Dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxamide* (**14**): Yield 65 mg (42%) of white crystals, m.p. >250 °C. $^1$H NMR (DMSO-$d_6$): 11.27 bs, 1 H and 10.57 bs, 1 H (H-1 and H-3); 8.24 bs, 1 H and 8.00 bs, 1 H ($NH_2$); 6.07 s, 1 H (H-5). $^{13}$C NMR (DMSO-$d_6$): 164.55 (C-6); 161.82 ($CONH_2$); 150.96 (C-2); 145.02 (C-4); 100.32 (C-5). ESI MS, *m/z* (%): 154.1 (100) [M$^-$]. HR ESI MS: for $C_5H_4N_3O_3$ calculated 154.0253; found 154.0251. For $C_5H_5N_3O_3$ (155.11) calculated: 38.72% C, 3.25% H, 27.09% N; found: 38.79% C, 4.36% H, 26.87% N.

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