One-pot click synthesis of 1,2,3-triazole-embedded unsaturated uracil derivatives and hybrids of 1,5- and 2,5-disubstituted tetrazoles and pyrimidines

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Graphical Abstract

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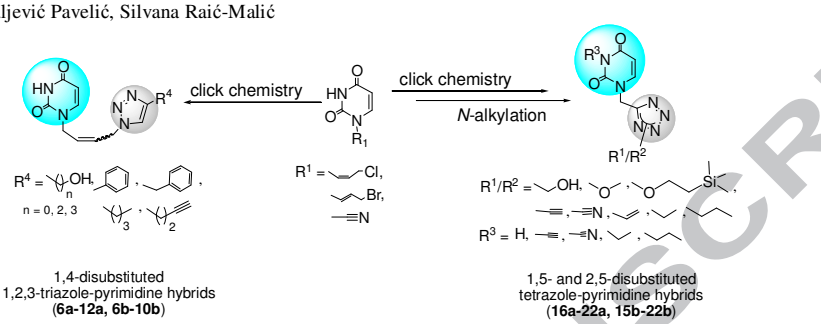

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One-pot click synthesis of 1,2,3-triazole-embedded unsaturated uracil derivatives and hybrids of 1,5- and 2,5-disubstituted tetrazoles and pyrimidines

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ABSTRACT

Novel conformationally restricted pyrimidine derivatives with a 1,2,3-triazolyl scaffold bound *via* *Z*- and *E*-2-butenyl spacers were prepared by Cu(I)-catalyzed click chemistry *via* a one-pot, multi-step reaction under microwave irradiation, while 1,5- and 2,5-disubstituted tetrazoles were synthesized by convenient, environmentally friendly click synthesis and subsequently by *N*-alkylation of 5-substituted 1*H*-tetrazoles. Among all the tested compounds, the *N*-1,*N*-3-disubstituted olefinic uracil derivative showed the highest antiproliferative effects.

Nitrogen-containing five-membered heterocycles are structural motifs that have been extensively studied in designing compounds with diverse biological activities. Thus, a number of modern drugs contain the tetrazole pharmacophore owing to its potential activity profile.[1-5] This scaffold is frequently used as a metabolically stable bioisostere of the carboxylic acid group, but with more favorable pharmacokinetic properties.[1,6] Besides, 1,5-disubstituted tetrazole derivatives have found a wide range of application in medicinal chemistry as surrogates of *cis*-amide bonds and, therefore, have been used as peptidomimetics.[7-10] In contrast to this, 2,5-disubstituted tetrazoles, as pharmacologically active compounds, have been studied less than their 1,5-disubstituted congeners.[11-13]

Similarly, 1,2,3-triazoles and their derivatives have showed varied biological activities, such as anticancer,[14-16] antibacterial and antifungal,[17,18] antitubercular[19-21] and antiviral.[22-24] The 1,2,3-triazole ring displays some similarity with amide bonds, in terms of bond lengths and planarity, and, therefore, a number of bioactive compounds with the 1,2,3-triazole moiety as an amide surrogate demonstrate biological activity.[25-27] Moreover, triazoles have found applications as isosteres of double bonds.[28] Triazole and tetrazole motifs can be easily obtained by click chemistry using 1,3-dipolar cycloaddition reactions (1,3-DCRs). The synthesis of 5-substituted 1*H*-tetrazoles through cycloaddition of azides and nitriles has received significant attention.[29] Since most common methods involve the use of sodium azide, highly dangerous azides and toxic metal residues,[30] safe and efficient transformations of a wide variety of nitriles into the corresponding tetrazoles have been developed.[6] In the field of 1,3-DCRs, copper(I)-catalyzed reactions between terminal alkynes and azides (CuAAC) present a powerful synthetic tool for preparing the 1,2,3-triazole core.[31,32] The discovery that a CuAAC reaction forms efficiently and regioselectively 1,4-disubstituted 1,2,3-triazoles has increased the application of click chemistry in drug discovery, particularly in lead identification and lead optimization processes.[33] This Huisgen-Sharpless cycloaddition approach has also proven to be a very useful tool in nucleoside chemistry for the preparation of 1,2,3-triazole nucleosides, 1,2,3-triazole nucleoside conjugates and 1,2,3-triazole-tethered nucleosides with a 1,2,3-triazole as a linker between nucleobase and sugar.[34-38]

Thus, based on the aforementioned results and in continuation of our search for biologically active acyclic pyrimidine nucleosides,[39-44] a novel class of 1,2,3-triazole/tetrazole-containing *N*-acyclic pyrimidine nucleoside analogues has been designed and synthesized (Figure 1).

Herein, we report the one-pot, multi-step synthesis of conjugates of 1,2,3-triazole and (*Z*)- (**6a–12a**) and (*E*)-olefinic (**6b–10b**) pyrimidine derivatives, and 1,5- (**16a–22a**) and 2,5-disubstituted (**15b–22b**) tetrazole-containing pyrimidines along with an evaluation of their antiproliferative effects and cytotoxicity. As the literature precedents attest, hitherto there are no reports on one-pot, multi-step syntheses of 1,2,3-triazole-embedded unsaturated pyrimidine derivatives and, generally, syntheses of hybrids of tetrazole and *N*-acyclic nucleoside analogues.

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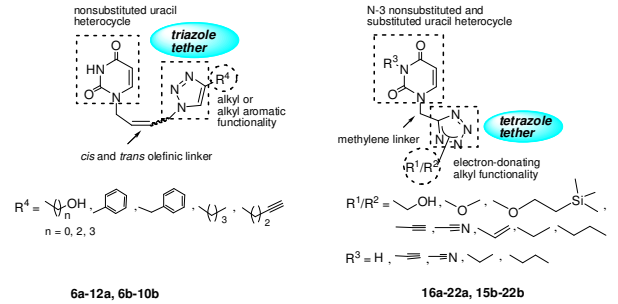
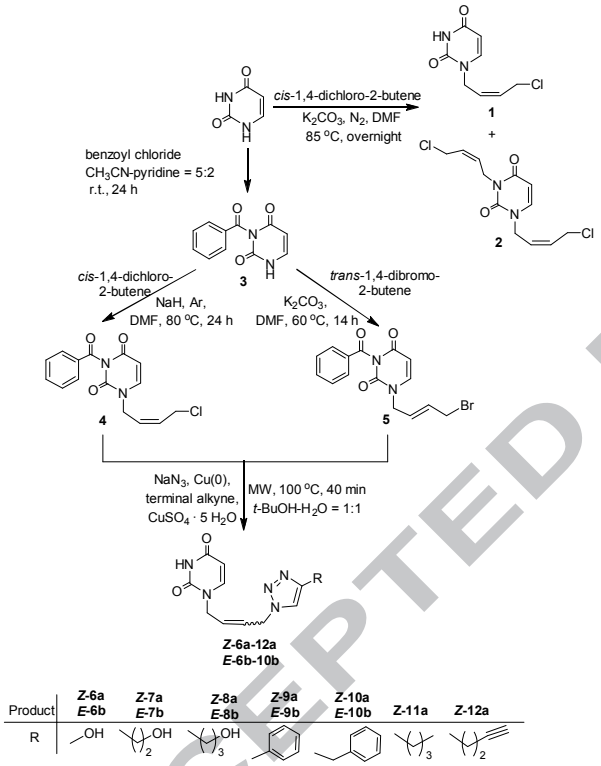


Figure 1. Conformationally constrained 1,4-disubstituted 1,2,3-triazole–pyrimidine (**6a–12a**, **6b–10b**) and 1,5- (**16a–22a**) and 2,5-disubstituted (**15b–22b**) tetrazole–pyrimidine hybrids.

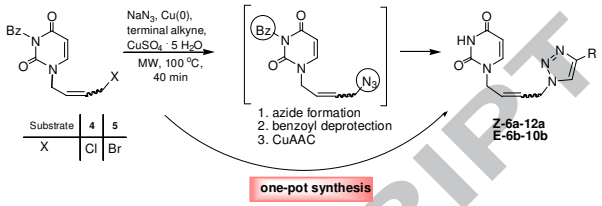
The synthesis of novel *Z*- (**6a–12a**) and *E*-isomers (**6b–10b**) of 1,2,3-triazole-containing *N*-olefinic pyrimidine nucleoside analogues is depicted in the Scheme 1.



Scheme 1. Synthesis of 1,4-regioselective 1,2,3-triazole–pyrimidine hybrids **6a–12a** and **6b–10b**.

N-Alkylation of the potassium salt of uracil with *cis*-1,4-dichloro-2-butene gave a mixture of both *N*-1-substituted **1** and *N*-1,*N*-3-disubstituted **2** olefinic uracil derivatives. Therefore, *N*-3-benzoyl uracil **3** was used as a starting compound for the alkylation to afford (*Z*)-3-benzoyl-1-(4-chloro-2-butenyl)uracil (**4**). (*E*)-3-Benzoyl-1-(4-bromo-2-butenyl)uracil (**5**) was synthesized by *N*-alkylation of the potassium salt of **3** with *trans*-1,4-dibromo-2-butene. Encouraged by the advantages of the application of the one-pot multi-step processes,[45,46] that allows the rapid and convergent construction of complex molecules without the isolation of intermediates, we employed a convenient one-pot, three-step method for the synthesis of 1,4-disubstituted 1,2,3-triazoles *via* the copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition of the generated azides and different terminal alkynes: propargyl alcohol, 4-pentyn-1-ol, 5-hexyn-1-ol, 3-phenyl-1-propyne, 4-phenyl-1-butyne, 1-heptyne and 1,6-heptadiyne (Table 1).

Table 1. One-pot, three-step reactions of *N*-olefinic pyrimidine nucleoside analogues **4** and **5** to give the target *Z*-(**6a–12a**) and *E*-isomers (**6b–10b**) of 1,2,3-triazole-containing uracil derivatives.



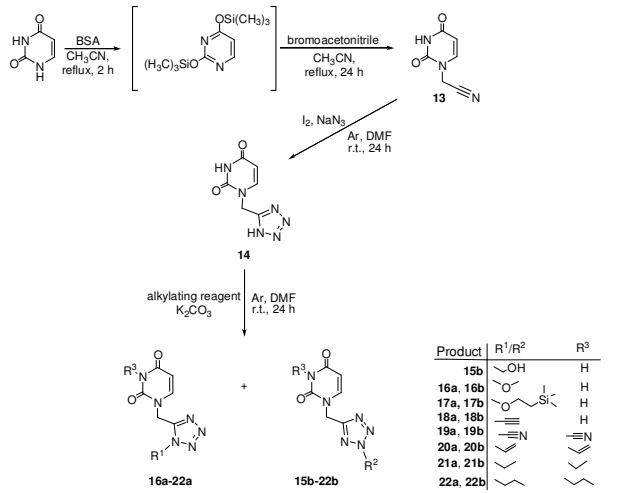
Entry	R	Product	Yield (%)[a]	Product	Yield (%)[b]
1	OH	**Z-6a**	84	***E*-6b**	30
2	OH	**Z-7a**	77	***E*-7b**	26
3	OH	**Z-8a**	83	***E*-8b**	40
4		**Z-9a**	69	***E*-9b**	41
5		**Z-10a**	64	***E*-10b**	38
6		**Z-11a**	37	***E*-11b**	n.r.
7		**Z-12a**	23	***E*-12b**	n.r.

[a] Isolated yield based on **4**. [b] Isolated yield based on **5**. n.r. = no reaction.

Therefore, the target regioselective 1,4-disubstituted 1,2,3-triazoles were prepared by the *in situ* generation of azides *via* reaction of pyrimidine olefinic halides **4** and **5** with sodium azide followed by coupling with a terminal alkyne. Deprotection of *N*-3 benzoyl pyrimidine derivatives in this one-pot process also occurred. Moreover, for environmental reasons, the microwave-assisted reaction was performed over a period of 40 minutes for completion of the reaction.

Generally, the syntheses of the *Z*-isomer series (**6a–12a**) proceeded smoothly and in significantly higher yields than those of the corresponding *E*-isomers. The only exceptions were the cycloaddition reactions of the pyrimidine olefinic chloride **4** with 1-heptyne and 1,6-heptadiyne, which gave the target compounds **11a** and **12a** in somewhat lower yields. Moreover, the reaction of *E*-4-bromo-2-butenyl uracil derivative **5** with the above-mentioned alkynes did not afford conjugates of 1,2,3-triazole and the unsaturated pyrimidine nucleoside, ***E*-11b** and ***E*-12b** (Table 1). In the synthesis of 1,5- and 2,5-disubstituted tetrazoles, 1-(cyanomethyl)uracil (**13**) was used as a precursor, which was prepared by silylation of uracil using *N,O*-bis(trimethylsilyl)acetamide (BSA), and subsequent *in situ* coupling employing bromoacetonitrile to give **13** in an excellent yield of 89% (Scheme 2).

Since the majority of reported methods for the preparation of the tetrazole scaffold have some drawbacks, such as the use of toxic metals and strong Lewis acids, the *in situ* formation of hydrazoic acid, which is toxic and explosive, the application of an alternative method for the synthesis of the target 5-substituted 1*H*-tetrazole **14** was desirable. Therefore, in the area of green synthesis, the environmentally friendly cycloaddition of organic



Scheme 2. Synthesis of 1,5- (**16a**–**22a**) and 2,5- (**15b**–**22b**) disubstituted tetrazole–pyrimidine hybrids.

nitrile **13** and sodium azide in the presence of molecular iodine enabled an advantageous synthesis of 5-substituted-1*H*-tetrazole **14** in a yield of 82%.

N-Alkylation of 5-substituted-1*H*-tetrazole **14** was subsequently carried out using potassium carbonate as the base and various selected alkylating reagents: methoxymethyl chloride, 2-(trimethylsilyl)ethoxymethyl chloride, bromoethanol, propargyl bromide, bromoacetonitrile, allyl bromide, *n*-propyl bromide and *n*-butyl bromide. *N*-Alkylation of **14** with all the halides, except for the alkylation with bromoethanol, gave 1,5- (**16a**–**22a**) and 2,5-disubstituted (**15b**–**22b**) tetrazoles. Furthermore, besides alkylation of the tetrazole moiety, alkylation at *N*-3 of the pyrimidine ring occurred in the reaction of **14** with bromoacetonitrile, allyl bromide, *n*-propyl bromide and *n*-butyl bromide to afford the corresponding *N*-3 substituted tetrazole-containing pyrimidine derivatives **19a,b**–**22a,b**.

The structures of **15b**, **16a**, **19a**, **19b**, **20a**, **20b**, **22a** and **22b** were confirmed by homo- and heteronuclear NMR measurements. The ^{1}H and ^{13}C NMR chemical shifts for all the products are reported in the Supplementary data. In addition, the ^{15}N NMR chemical shifts were assessed for a few selected 1,5- (**19a, 20a, 22a**) and 2,5-disubstituted (**19b, 20b, 22b**) tetrazoles and are presented in Table 2.

Indeed, the ^{1}H–^{15}N correlation signals in the 2D HMBC spectra, together with the characteristic chemical shift of the tetrazole C5' atom allowed us to distinguish between the 1,5- and 2,5-disubstituted regioisomeric pairs. For example, the N1-CH_2 methylene bridge in 1,5-disubstituted tetrazole **20a** showed long-range correlation signals with the N1' and N4' atoms. Correlations were also observed between the N1'-CH_2 methylene protons and the N1' and N2' atoms, which confirmed that for **20a,** *N*-alkylation occurred at N1' of the tetrazole ring. 2,5-Disubstituted tetrazole **20b** also exhibited two sets of ^{1}H–^{15}N correlation signals; correlations were observed between the N1-CH_2 methylene bridge and N1' and N4' atoms as well as between the N1'-CH_2 methylene protons and N1' and N2'. The latter suggested that in case of **20b**, *N*-alkylation proceeded at N2' of the tetrazole ring.

Furthermore, the 1,5- and 2,5-disubstituted regioisomeric pairs could be unequivocally discerned based on the characteristic ^{13}C NMR chemical shift of the tetrazole C5' atom. 2,5-Disubstituted tetrazole compounds **19b**, **20b** and **22b** exhibited ca. 10 ppm more deshielded C5' atoms than their 1,5-disubstituted regioisomers **19a**, **20a** and **22a**.

Table 2. ^{15}N NMR (300 MHz, DMSO-d_6) chemical shifts for **19a, 20a, 22a** and **19b, 20b, 22b**.

Product	N1	N3	N1'	N2'	N3'	N4'	3-CH_2CN	1'/2'-CH_2CN
19a	130	155	221	N/A	N/A	N/A	250	257
19b	130	154	303	272	N/A	334	250	258
20a	129	164	234	372	N/A	328	–	–
20b	130	164	302	287	N/A	330	–	–
22a	129	166	236	371	N/A	327	–	–
22b	131	167	301	289	N/A	328	–	–

N/A - not available due to the lack of long-range ^{1}H-^{15}N correlation signals.

The major differences in the ^{13}C and ^{15}N NMR chemical shifts for the tetrazole regioisomers are presented in Figure 2.

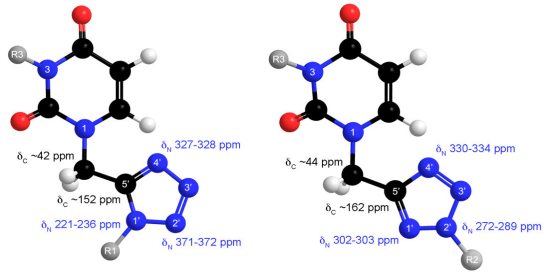


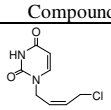
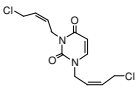
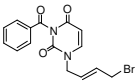
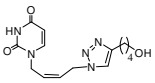
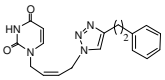
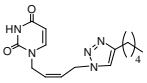
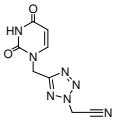
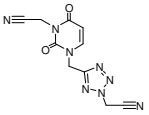
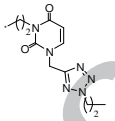
Figure 2. The characteristic ^{13}C and ^{15}N NMR chemical shifts for 1,5- (left) and 2,5-disubstituted tetrazoles (right) with the atom numbering used in the study.

Compounds **1–5**, **6a–12a**, **6b–10b**, **13**, **14**, **16a–22a** and **15b–22b** were evaluated for their antiproliferative activities against human hepatocellular carcinoma (HepG2), metastatic colon carcinoma (SW620) and cervical cancer (HeLa), as well as normal mouse embryonic fibroblast (3T3) cell lines. Their activities were compared with those of 5-fluorouracil (5-FU) (Table 3). Among all the tested compounds, *N*-1,*N*-3-disubstituted olefinic uracil derivative **2** showed the highest antitumor activity against HepG2 and HeLa with IC_{50} values in the low micromolar range (IC_{50} = 8.8 μM and 5.5 μM, respectively). Besides, *N*-1-substituted olefinic uracil derivative **1** exhibited moderate antiproliferative effects against all the tested cell lines in the range of 24.0-44.16 μM. In the series of 1,2,3-triazole–pyrimidine hybrids, *Z*-isomers with hydroxybutyl (**8a**), phenylethyl (**10a**) and pentyl (**11a**) substituents at C-4 of the 1,2,3-triazole ring showed modest antitumor activities (IC_{50} = 34.8-94.2 μM). Among the tetrazole-embedded uracil derivatives, only the 2,5-disubstituted tetrazole–pyrimidine hybrids containing propargyl (**18b**), cyanomethyl (**19b**) and propyl (**21b**) substituents at C-2 of the tetrazole moiety exhibited antiproliferative effects (IC_{50} = 21.15-83.8 μM). Compounds having IC_{50} values more than 100 μM were considered inactive and were not included in Table 3.

In conclusion, by employing a one-pot, multi-step strategy, we have successfully prepared a series of *Z*- (**6a–12a**) and *E*-isomers (**6b–10b**) of 1,2,3-triazole-containing *N*-olefinic pyrimidine nucleoside analogues *via* copper(I)-catalyzed reactions (CuAAC) between the corresponding terminal alkynes and *in situ* generated azide derivatives of unsaturated uracil. Furthermore, an improved and convenient synthesis of 5-substituted 1*H*-tetrazole **14** was applied by cycloaddition of organic nitrile **13** and sodium azide in the presence of molecular iodine, as a useful inexpensive, non-

toxic and eco-friendly catalyst. *N*-Alkylation of **14** subsequently gave 1,5- (**16a–22a**) and 2,5-disubstituted **(15b–22b)** tetrazoles.

Table 3. The growth-inhibition effects of compounds **1**, **2**, **5**, **8a**, **10a**, **11a**, **13**, **18b**, **19b** and **21b** on human hepatocellular carcinoma (HepG2), metastatic colon carcinoma (SW620) and cervical cancer (HeLa), as well as normal mouse embryonic fibroblast (3T3) cell lines.

Compound		IC_{50}[a] (μM) Cell line			
		HepG2	SW620	HeLa	3T3
1		27.94	40.00	24.00	44.16
2		8.80	14.40	5.50	33.70
5		>100	>100	40.00	>100
8a		>100	>100	94.20	>100
10a		56.20	>100	73.40	89.40
11a		>100	87.40	>100	34.80
13		>100	>100	99.00	>100
18b		>100	>100	83.80	>100
19b		48.28	>100	>100	21.15
21b		>100	>100	76.00	>100
5-FU		55.22	0.79	66.5	0.15

[a]IC_{50}: 50% inhibitory concentration or concentration of the compound required to inhibit tumor cell proliferation by 50%. The cell growth rate was evaluated by performing the MTT assay.

The methods described for the regioselective preparation of 1,4-disubstituted 1,2,3-triazoles and 5-substituted 1*H*-tetrazoles show simple, economical and practical advantages over some previously developed methods, and, therefore should be suitable for the preparation of a variety of 1,2,3-triazole and tetrazole structural analogues that could be developed as potential biologically active compounds. Antitumor evaluations showed that, among all the tested compounds, *N*-1,*N*-3-disubstituted olefinic uracil derivative **2** exhibited the highest antiproliferative activity against hepatocellular carcinoma (HepG2, IC_{50} = 5.5 μM) and cervical carcinoma (HeLa, IC_{50} = 8.8μM). Further structural optimization of both *N*-1-substituted **1** and *N*-1,*N*-3-disubstituted **2** olefinic uracil derivatives by inclusion of the 1,2,3-triazole as a double bond bioisostere in *Z*- and *E*-but-2-enyl aliphatic side chain is underway with the aim of improving the cytostatic effects.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found in the online version.

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