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# 2,6-Bis[4-(4-butylphenyl)-1*H*-1,2,3-triazol-1-yl]-9-dodecyl-9*H*-purine

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**Abstract:** Target 2,6-bis[4-(4-butylphenyl)-1*H*-1,2,3-triazol-1-yl]-9-dodecyl-9*H*-purine has been prepared via a Cu(I)-catalyzed azide-alkyne 1,3-dipolar cycloaddition reaction between 2,6-diazido-9-dodecyl-9*H*-purine and 4-*n*-butyl(phenylacetylene) in a 29% yield. The obtained compound was fully characterized by NMR, IR and HRMS.

**Keywords:** purines; bis(triazolyl)purines; *N*(9)-alkylated purines; CuAAC

## 1. Introduction

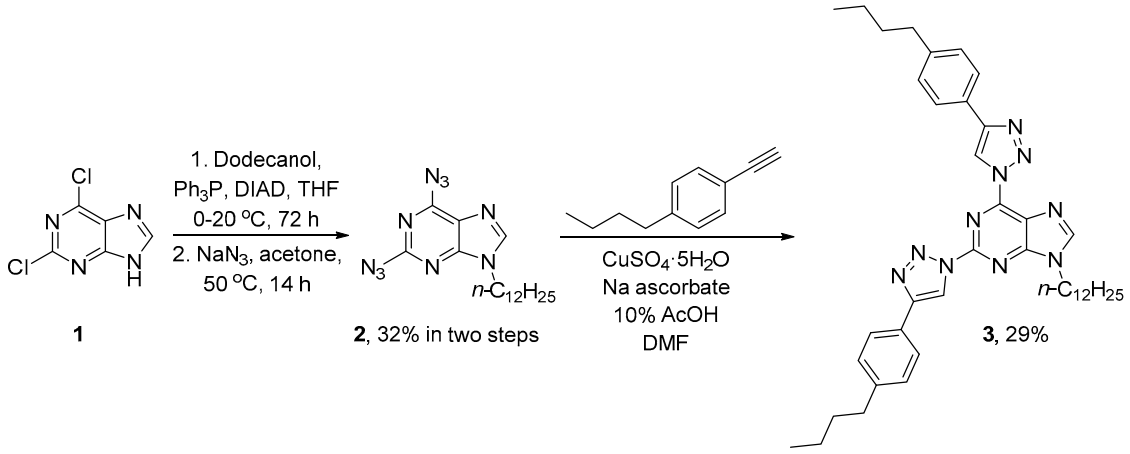
Purine derivatives are widely studied due to their extensive applications in biology, biochemistry and medicine. Purine and purine nucleosides are applicable in anticancer therapy [1–3], as antivirals [4–6] and as agonists and antagonists of adenosine receptors [7,8]. As a result, the development of novel purine derivatives is very in demand.

In 2013, we developed a method for the synthesis of 2,6-bis(triazolyl)purine nucleosides, which contained ribose, arabinopyranose and arabinofuranose as sugar moieties [9]. We successfully showed that these 2,6-bis(triazolyl)purine nucleosides participate in aromatic nucleophilic reactions with different *N*- and *S*-nucleophiles and that the triazolyl ring in purine *C6* positions acts as a good leaving group [9,10].

With this information in hand, we decided to adapt the discovered conditions to synthesize 2,6-bis(triazolyl)purine derivatives with different alkyl groups in the *N9* position of purine. We replaced the monosaccharide moiety with the simple alkylgroups and avoided the unwanted deprotection of acetyl protecting groups from hydroxyl moieties during chemical transformations.

## 2. Results and Discussion

The target product was obtained in three steps from 2,6-dichloropurine (**1**) (Scheme 1). Firstly, the Mitsunobu reaction between 2,6-dichloropurine and dodecanol was used for the synthesis of 2,6-dichloro-9-dodecyl-9*H*-purine. The latter was obtained in 72 h with a 48% yield. Next, chloro substituents were exchanged with azides in a nucleophilic aromatic substitution reaction yielding compound **2** in a 32% yield over two steps [11]. Then, 2,6-diazido-9-dodecyl-9*H*-purine **2** was used in a CuAAC reaction with 4-*n*-butyl(phenylacetylene). $CuSO_4 \cdot 5H_2O$ and sodium ascorbate as a catalytic system was used in the presence of 10% AcOH aq. solution. The reaction was carried out in DMF at 60 °C for 11 h, in a flask covered from light. Purification of product **3** by silicagel column chromatography using gradient of 1%→10% of MeCN/$CHCl_3$ mixture gave a light yellow solid in a 29% yield. Product **3** was fully characterized by IR and $^1$H- and $^{13}$C-NMR (Figures 1–3).




**Scheme 1.** Synthesis of 2,6-bis(triazolyl)purine derivative **3**.

The obtained compound **3** can be further exploited in aromatic nucleophilic substitution reactions with different nucleophiles such as *N*-, *S*- and *O*-nucleophiles.

## 3. Materials and Methods

### *3.1. General Information*

Reactions and purity of the synthesized compounds were monitored by TLC using Silicagel 60 $F_{254}$ aluminum plates (Merck, Darmstadt, Germany). Visualization was accomplished by UV light. Column chromatography was performed using Silicagel 60 (0.040–0.063 mm) (Merck). Yields of products refer to chromatographically and spectroscopically homogeneous materials. Anhydrous dimethylformamide was obtained by distillation over $CaH_2$, tetrahydrofuran was obtained by distillation over sodium. Commercial reagents were used as received.

NMR spectra were recorded on Bruker Avance 300 (300 MHz for $^1$H and 75.5 MHz for $^{13}$C, respectively). The proton signal for residual non-deuterated solvent (δ 7.26 ppm for $CDCl_3$) and carbon signal (δ 77.1 ppm for $CDCl_3$) were used as an internal reference for $^1$H-NMR and $^{13}$C-NMR spectra, respectively. Coupling constants are reported in Hz. Chemical shifts of signals are given in ppm and multiplicity assigned as s: singlet; d: doublet; t: triplet; m: multiplet.

The infrared spectra were recorded on a Perkin Elmer Spectrum BX. Wavelengths are given in $cm^{-1}$. High resolution mass spectrometry (HRMS) analyses were carried out on a Dual-ESI Q-TOF 6520 (Agilent Technologies, Foster City, CA, USA) mass spectrometer and Agilent 1290 Infinity series UPLC system equipped with column Extend C18 RRHD 2.1 × 50 mm, 1.8 μm connected to an Agilent 6230 TOF LC/MS mass spectrometer.

For HPLC analysis we used an Agilent Technologies 1200 Series chromatograph equipped with an Agilent XDB-C18 (4.6 × 50 mm, 1.8 μm) column and Phenomenex Gemini NX (4.6 × 100 mm, 3 μm) column. Eluent A: 0.01 M $KH_2PO_4$ solution with 6% *v*/*v* MeCN added; eluent B: 0.1% TFA solution with 5% *v*/*v* MeCN added; eluent C: MeCN.

### *3.2. Synthesis of 2,6-Bis[4-(4-butylphenyl)-1H-1,2,3-triazol-1-yl]-9-dodecyl-9H-purine* (**3**)

In a flask protected from daylight, 10% AcOH aq. solution (1.0 mL), $CuSO_4·5H_2O$ (24 mg, 0.096 mmol, 8 mol %) and sodium ascorbate (37 mg, 0.19 mmol, 15 mol %) were added to a solution of 2,6-diazido-9-dodecyl-9*H*-purine **2** (471 mg, 1.27 mmol, 1.0 equiv.) and 4-*n*-butyl(phenylacetylene) (1.00 mL, 5.73 mmol, 4.5 equiv.) in DMF (10 mL) and stirred for 11 h at 60 °C. The reaction mixture was evaporated under the reduced pressure and the residue was dissolved in DCM (20 mL); the organic phase was washed with brine (5 × 10 mL) and subsequently dried over anh. $Na_2SO_4$ and evaporated. Silicagel column chromatography ($CHCl_3$/MeCN, gradient 1%→10%) provided desired compound.

Yield 250 mg, 29%.
Light yellow solid, $R_f$ = 0.18 ($CHCl_3$/MeCN = 20/1).
mp = 205–208 °C (decomposes).
IR (KBr) ν ($cm^{-1}$): 2924, 2853, 1607, 1590.

$^1$H-NMR (300 MHz, $CDCl_3$) δ (ppm): 9.24 (s, 1H, H-C(triazole)), 8.88 (s, 1H, H-C(triazole)), 8.28 (s, 1H, H-C(8)), 7.96–7.84 (m, 4H, Ar), 7.32–7.26 (m, 4H, Ar), 4.42 (t, 2H, $^3J$ = 7.2 Hz, (-$CH_2$-)), 2.66 (t, 4H, $^3J$ = 7.6 Hz, 2 × (-$CH_2$-)), 2.01 (quintet, 2H, $^3J$ = 6.7 Hz, (-$CH_2$-)), 1.64 (quintet, 4H, $^3J$ = 7.8 Hz, 2 × (-$CH_2$-)), 1.48–1.31 (m, 8H, 4 × (-$CH_2$-)), 1.31–1.16 (m, 14H, 7 × (-$CH_2$-)), 0.95 (t, 6H, $^3J$ = 7.3 Hz, 2 × (-$CH_3$)), 0.86 (t, 3H, $^3J$ = 6.6 Hz, (-$CH_3$)).

$^{13}$C-NMR (75.5 MHz, $CDCl_3$) δ (ppm): 155.9, 148.7, 148.5, 148.3, 147.2, 145.4, 144.1, 143.8, 129.1 (2C), 127.3, 127.0, 126.3, 126.1, 122.2, 119.2, 118.6, 44.9, 35.6 (2C)*, 33.7 (2C)*, 32.0, 29.9, 29.7 (2C)*, 29.6 (2C), 29.4, 29.2, 26.8, 22.8, 22.5 (2C)*, 14.2, 14.1 (2C). (* The signal was assigned from HSQC spectrum.)
HRMS (ESI): calcd for [$C_{41}H_{54}N_{10}$ + $Na^+$] 709.4431, found 709.4417.

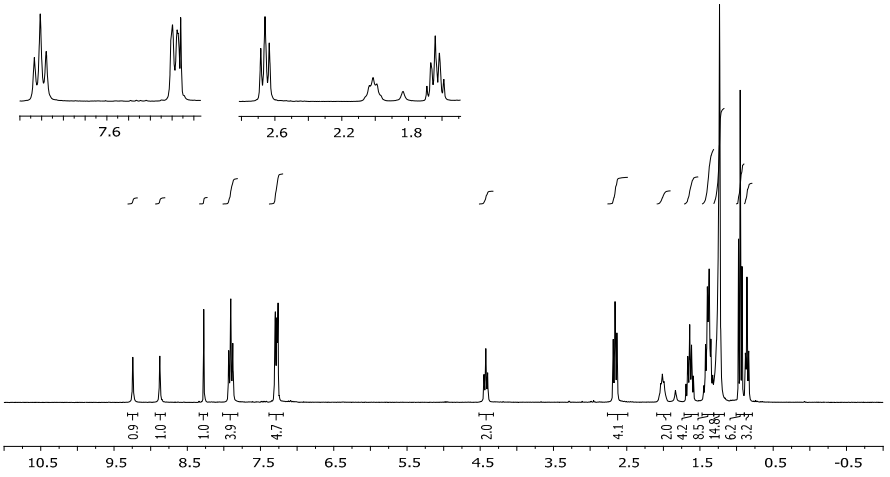


**Figure 1.** $^1$H-NMR (300 MHz, $CDCl_3$) spectrum.

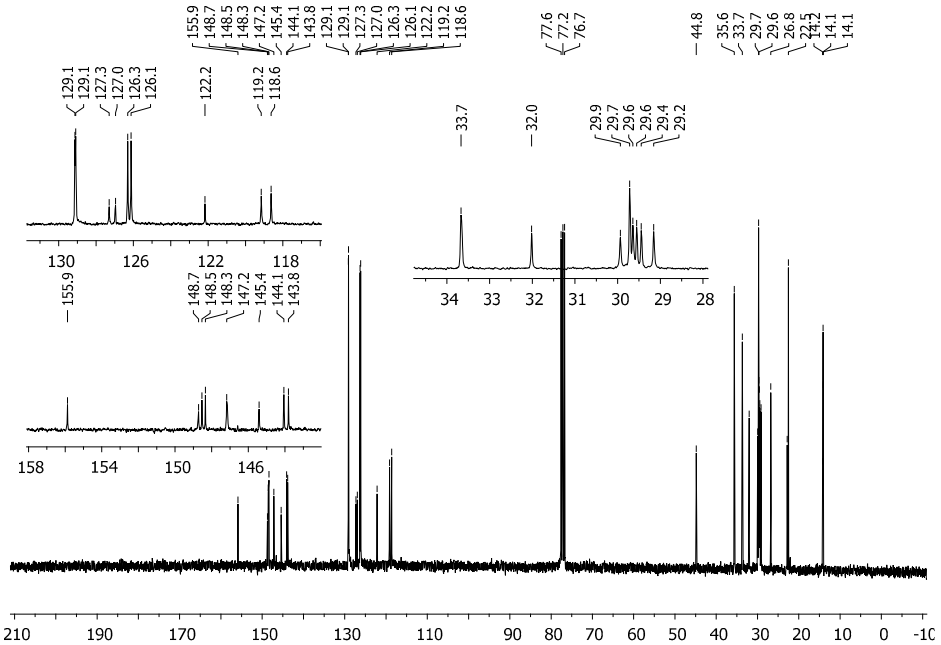


**Figure 2.** $^{13}$C-NMR (75.5 MHz, $CDCl_3$) spectrum.

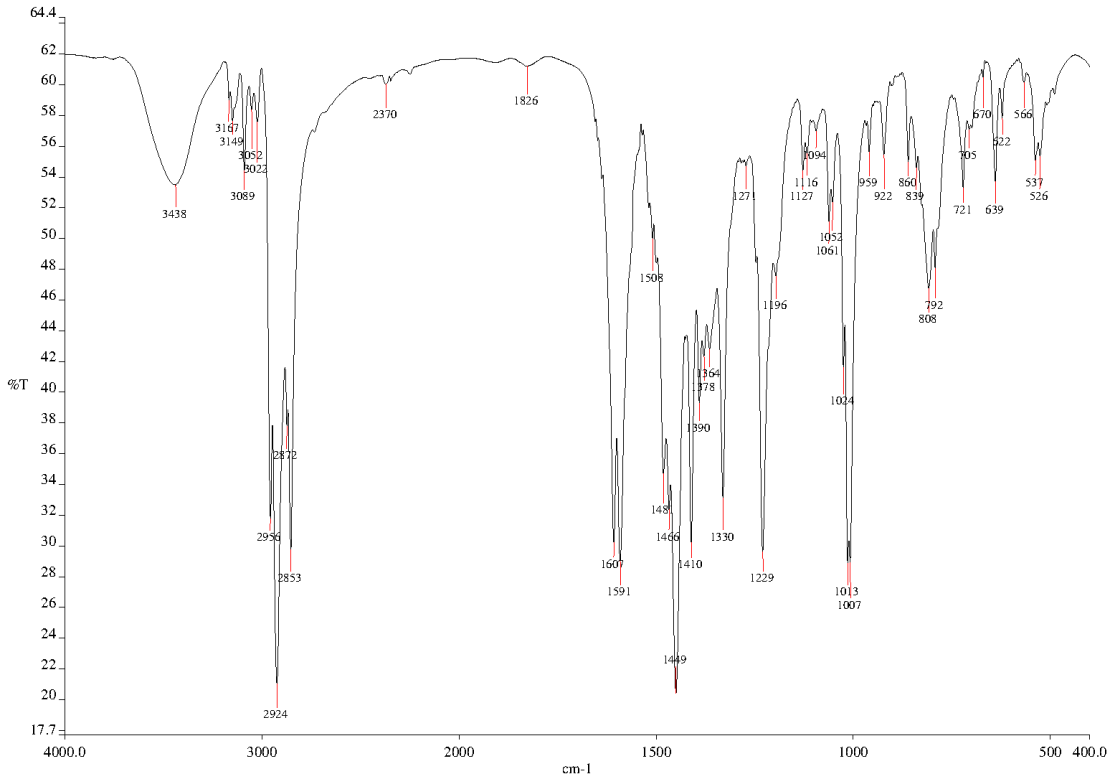



**Figure 3.** IR spectrum (KBr) ν ($cm^{-1}$).

**Author Contributions:** M.T. and Ē.B. designed the experiments; A.Š. performed the experiments; A.Š., I.N., Ē.B. and M.T. analyzed the IR, HRMS and NMR spectral data and wrote the manuscript. All authors read and approved the final manuscript.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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