

Synthesis of 2-Azidomethyl-5-ethynylfuran: A New Bio-Derived Self-Clickable Building Block

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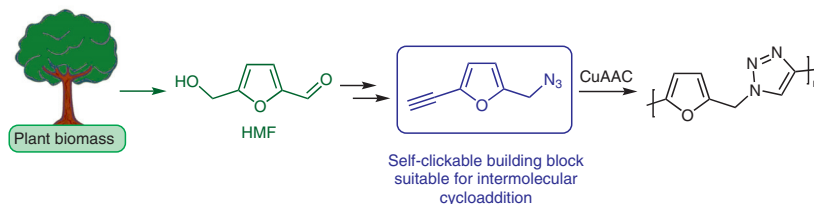
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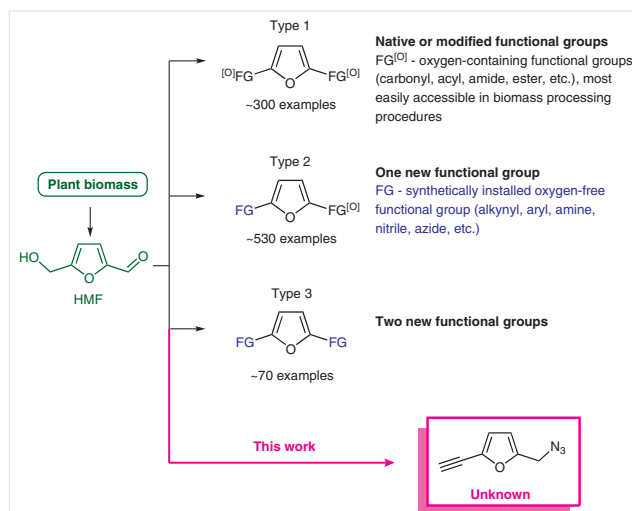
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Abstract 2-Azidomethyl-5-ethynylfuran, a new ambivalent compound with both azide and alkyne moieties that can be used as a self-clickable monomer, is synthesized starting directly from renewable biomass. The reactivity of the azide group linked to furfural is tested via the efficient preparation of a broad range of furfural-containing triazoles in good to excellent yields using a ‘green’ copper(I)-catalyzed azide-alkyne cycloaddition procedure. Access to new bio-based chemicals and oligomeric materials via a click-chemistry approach is also demonstrated using this bio-derived building block.

Key words 5-(hydroxymethyl)furfural, click chemistry, biomass conversion, triazoles, oligomers

The production and conversion of bio-derived platform chemicals and building blocks has received significant attention in order to meet the demands of sustainable development and green chemistry concepts.¹ 5-(Hydroxymethyl)furfural (HMF), produced by catalytic dehydration of hexose carbohydrates, has been recently nominated as a ‘sleeping giant’² of sustainable chemistry, possessing numerous applications especially in the production of biofuels,³ polymers⁴ and fine chemicals.⁵ However, most of the described HMF derivatives were afforded by various redox processes and therefore comprise one or two oxygen-containing functional groups (Scheme 1, Types 1 and 2), whereas literature reports on bio-based furans with two oxygen-free functional groups (Scheme 1, Type 3) are less prominent. Furthermore, the vast majority of HMF-based materials are either polyesters or polyamides.⁴ Examples of HMF-based polymers with other types of backbone remain quite rare.



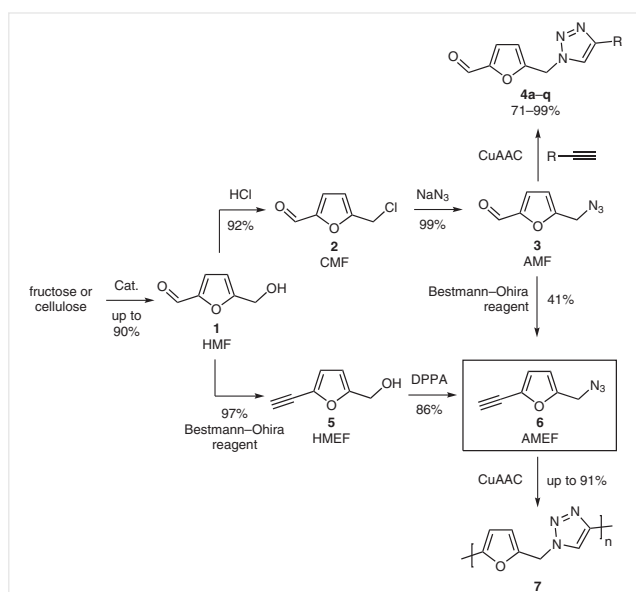
Scheme 1 Three types of HMF derivatives (according to a literature search;⁶ for representative examples see the reviews^{1a,b})

The introduction of two oxygen-free functional groups into bio-derived sustainable building blocks is currently one of the key research directions. This problem is especially challenging for the cases of two mutually reactive functional groups, for example, azide and alkyne fragments that are able to quickly combine into a triazole via a Huisgen dipolar cycloaddition.⁷ A catalytic modification of this reaction, the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC), has proved to be one of the most important linking reactions for click-chemistry applications.⁸ It usually proceeds under mild conditions with high yields and regioselectivity and has numerous advantages for use in materials science,⁹ drug development¹⁰ and other fields of organic, bioorganic and medicinal chemistry.¹¹

Indeed, among a small number of HMF derivatives with two oxygen-free functional groups there is only one example each of the synthesis of alkyne- or azide-containing furan-yls: 2,5-diethynylfuran¹² and 2,5-bis(azidomethyl)furan,¹³ but there are no examples of combining these moieties in one molecule. More generally, only a few azide¹⁴ and alkyne¹⁵ derivatives have been synthesized from biomass-derived furans, despite their unquestionable relevance for the easy and rapid 'click' synthesis of triazoles,¹⁶ which are themselves reported to have antitubercular¹⁷ and anticancer¹⁸ activity.

In this work, we report a synthetic route to the new, 'self-clickable' building block, 2-azidomethyl-5-ethynylfuran (AMEF) (**6**). The term 'self-clickable' describes an ambivalent reactivity and ability to engage in intermolecular cycloaddition related to the presence of both azide and alkyne moieties. This duality allows 'click' polycondensation¹⁹ to be carried out under mild conditions leading to heterocyclic furan-triazole oligomers. In addition, a number of new bio-based triazoles were obtained via a model reaction involving the precursor of AMEF, 5-(azidomethyl)furfural (AMF) (**3**), following classical CuAAC methodology under mild conditions. To implement the bio-derived strategy, the available bulk constituents of natural biomass (cellulose and fructose) were tested as the feedstock for this synthesis.

The synthesis of compounds **3** and **6** was carried out using renewable resources as starting materials (Scheme 2). In the first stage, we conducted the Lewis or Brønsted acid catalyzed dehydration of natural carbohydrates (cellulose or fructose, respectively) into HMF (**1**), which was isolated in a pure crystalline form, as described previously.²⁰



Scheme 2 A proposed synthetic strategy affording new bio-based building blocks and oligomers via click-chemistry approach

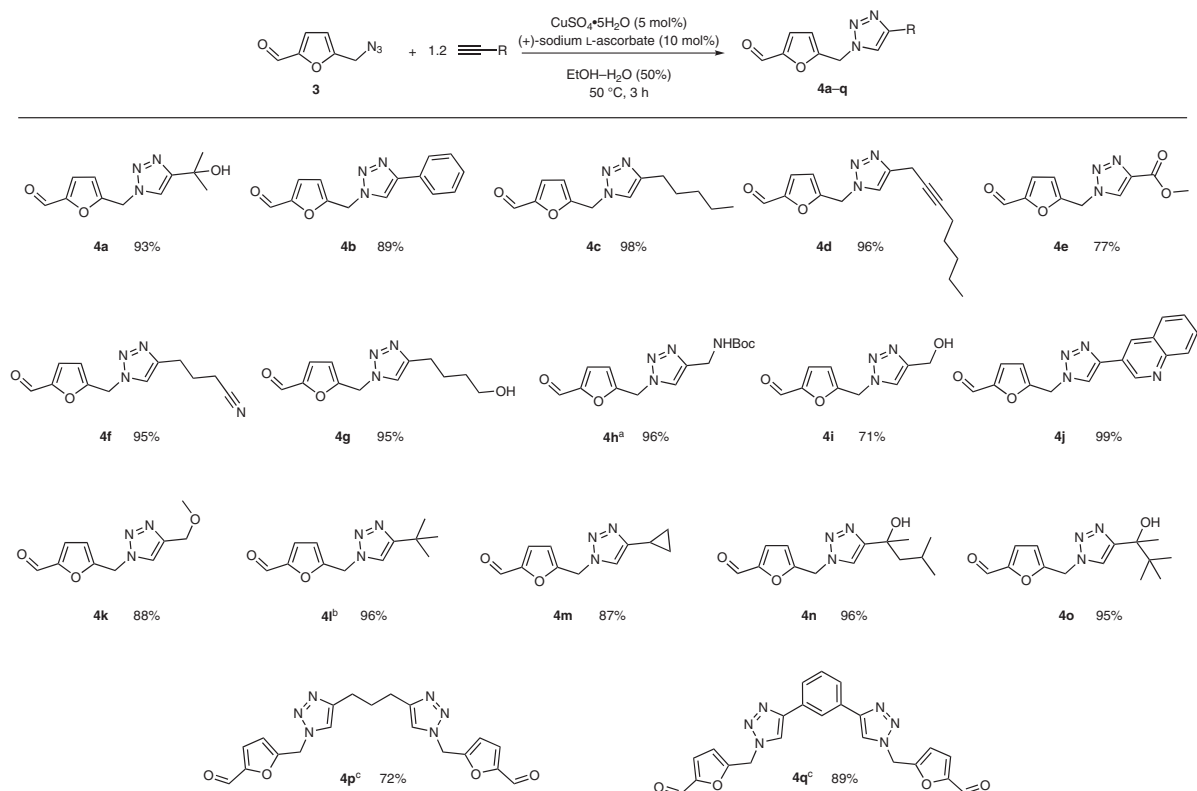
In the next stage, HMF was converted into 5-(chloromethyl)furfural (CMF) (**2**) using hydrogen chloride in a biphasic system, with the product being obtained in 92% yield. It should be noted that CMF itself can be discussed as a platform chemical since it can be obtained directly from biomass in good yield.²¹ Subsequent nucleophilic substitution of the chlorine in CMF with sodium azide under mild conditions afforded AMF (**3**) with almost complete conversion.

To probe the reactivity of the azide group linked to a furfural moiety, AMF was subsequently utilized in a series of CuAAC reactions with various alkynes. A range of new bi-heterocyclic compounds **4a–q** was synthesized in good to excellent yields in these experiments (Scheme 3). All reactions were carried out under mild conditions in the presence of air, using aqueous ethanol as the solvent and with almost stoichiometric ratios of reagents without any purification of products. The use of classic CuAAC methodology is nicely compatible with a wide range of terminal alkynes in this cycloaddition reaction. Nevertheless, it is known that alkynes with internal triple bonds are significantly less reactive; for example, the reaction of AMF with deca-1,4-diyne resulted in the formation of only one product **4d** without involving the internal triple bond in the cycloaddition. In spite of the high practical interest of biomass conversion and furan-based platform chemicals, this work represents the first study of the reactivity of HMF-derived azide **3** in CuAAC reactions and the preparation of new compounds **4a–q**.⁶

The synthesis of reactive self-clickable AMEF (**6**) was performed by two methods. The more efficient approach was a two-stage process starting with substitution of the aldehyde fragment in HMF with an acetylenic moiety using the Bestmann–Ohira reagent (dimethyl 1-diazo-2-oxopropylphosphonate). The formation of 2-hydroxymethyl-5-ethynylfuran (HMEF) (**5**) in 97% yield was followed by substitution of the hydroxy group with an azide moiety from diphenylphosphoryl azide (DPPA) in the presence of DBU. The yield after chromatography was 86%; thus utilization of this methodology resulted in an overall yield of AMEF of 83% from HMF.

Another method for the synthesis of AMEF involves the introduction of an acetylenic moiety on AMF via alkynylation of the aldehyde group by using potassium carbonate and the Bestmann–Ohira reagent. The target product **6** was isolated by column chromatography on silica gel in a moderate 41% yield (37% overall yield from HMF) and showed relatively good stability at reduced temperatures (below -5°C).

To evaluate the synthetic potential of AMEF as a monomer, we conducted a study of its 'click' polycondensation using different Cu-based catalytic systems: aqueous ethanol as a green solvent with the classic copper(II) sulfate and sodium ascorbate couple, being an alternative to polycondensation in DMF with copper(I) bromide in the presence



Scheme 3 Synthesis of triazole derivatives of AMF (isolated yields are shown); ^a 1.05 equiv of the corresponding alkyne was used; ^b 1.5 equiv of the corresponding alkyne was used; ^c 0.45 equiv of the corresponding alkyne was used

of different ligands (Table 1). The best performance was shown in the case of the CuBr/PMDETA system (Table 1, entry 1).

Table 1 Cu-Catalyzed Polymerization of AMEF Using Different Catalytic Systems

Entry	Catalyst	Solvent	Yield
1	CuBr/PMDETA	DMF	91%
2	CuBr/TEEDA	DMF	84%
3	CuBr/bipy	DMF	76%
4	CuBr/phen	DMF	79%
5	CuSO ₄ /sodium ascorbate	EtOH/H ₂ O	70%

As a result of polycondensation, oligomers were obtained as colored solids (the color depended on the catalytic system used) that were slightly soluble in dipolar aprotic solvents such as DMF and DMSO. The number-average molecular weight of the oligomers was estimated roughly as 4100 g/mol by integration of the terminal azide end-group signal (4.51 ppm) relative to the signals of the rest of the chain in the ¹H NMR spectra. The oligomers were found to be thermally transformable. This finding was confirmed by

DSC measurements (see the Supporting Information), as all of the oligomer samples showed strong exothermic effects at temperatures above 200 °C. Apparently, this is due to the presence of relatively energy-rich azide fragments in the material.

The microstructures of the prepared oligomer samples were studied by means of scanning electron microscopy (FE-SEM) (Figure 1). The substances had similar morphologies of sharp-edged particles whenever DMF was used as the solvent. Thus, the sample morphologies were almost independent of the used catalytic system and were tolerant to variations in the catalyst (Figure 1, A–D). To modify the morphology, aqueous ethanol was used as the reaction medium, leading to the formation of larger particles with smooth edges (Figure 1, E and F).

In conclusion, we have, for the first time, synthesized an ambivalent compound with both azide and alkyne moieties from renewable sources. The synthesis provides an access to a new type of biheterocyclic oligomers under mild conditions following classical click-chemistry methodology. The oligomers were characterized by NMR, IR, DSC and FE-SEM studies. In addition, a broad range of triazoles with a furfural moiety was prepared in good to excellent yields in accordance with green chemistry requirements. The approach paves the way for the application of Cu-catalyzed

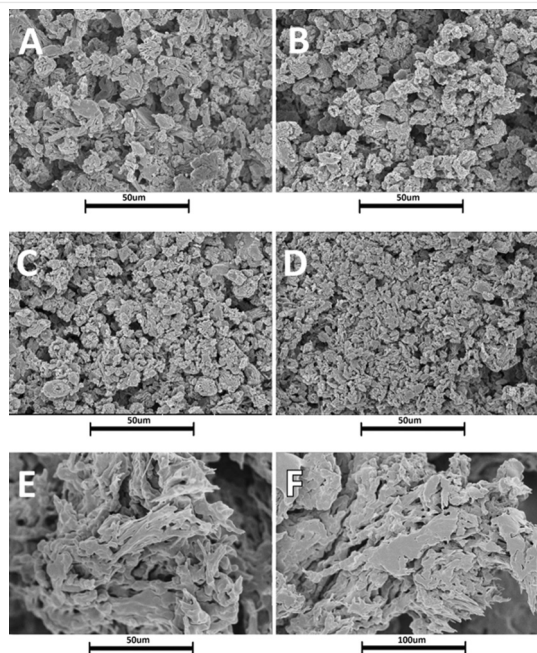


Figure 1 Field-emission scanning electron microscopy (FE-SEM) images of the synthesized oligomers prepared from AMEF (**6**) using the catalytic systems listed in Table 1 (entries 1–5): 1 (A), 2 (B), 3 (C), 4 (D) and 5 (E and F); 50 μm scale bars are shown below images A–E and a 100 μm scale bar is shown below image F.

systems for the construction of bio-based biheterocyclic compounds and is expected to provide attractive solutions for the development of new building blocks and the design of bio-based organic materials. The direct involvement of natural biomass as a sustainable source of chemicals is one of the most promising trends in synthetic chemistry and more detailed studies on the subject are to be anticipated in the near future.

Caution! Sodium azide is highly toxic and should be handled with extreme care. All reagents from commercial sources were checked by NMR before use or were purified by standard methods.²² HMF (**1**),²⁰ CMF (**2**),^{5c} *N*-Boc-propargylamine,²³ HMEF (**5**),¹² diphenylphosphoryl azide (DPPA)²⁴ and dimethyl 1-diazo-2-oxopropylphosphonate (Bestmann–Ohira reagent)²⁵ were prepared according to the published procedures. All reactions were performed in oven-dried (120 °C) glassware. Chromatographic separations were performed on silica gel (Kieselgel, 230–400 mesh, Merck Schuchardt) with analytical grade solvents. Analytical TLC was performed on Merck silica gel plates with QF-254 indicator. Visualization was accomplished with UV light (254 nm). Melting points were determined using a 1101D Mel-Temp apparatus and are uncorrected. IR spectra were recorded on a Bruker Alpha-T spectrophotometer. NMR spectra were recorded using a Bruker Fourier 300 HD spectrometer at frequencies of 300.1 MHz (¹H) and 75.5 MHz (¹³C) with the residual solvent peak as an internal standard. Unless otherwise noted, NMR spectra were recorded at room temperature. The spectra were processed using MestReNova software. The ¹³C NMR spectra of compounds **4a**, **4c**, **4f**, **4i**, **4k**, **4m** and **4n** were

also recorded at –60 °C (Bruker Avance 600 NMR spectrometer, 151 MHz), since at room temperature two of the signals were rather broad and difficult to detect, most likely due to dynamic or relaxation properties (see the Supporting Information). Electrospray ionization mass spectrometry (ESI-MS) was performed on a high-resolution time-of-flight Bruker maXis instrument. The spectra were processed using the Bruker Data Analysis 4.0 software package. Analysis of sample morphology was carried out using a Hitachi SU8000 field-emission scanning electron microscope. DSC analysis was performed on a Mettler Toledo DSC823e calorimeter equipped with an FSR 5 thermocouple and a liquid nitrogen cooling block. The samples were placed in 40 μL aluminum crucibles with perforated caps. Perforation allowed free atmosphere exchange with the oven to obtain results at a constant pressure. The samples were heated under an argon atmosphere (flow: 70 mL/min). Data processing was performed using the STARE service program.

5-(Azidomethyl)furfural (AMF) (**3**)

Sodium azide (4.5 g, 69.2 mmol) was added to a solution of 5-(chloromethyl)furfural (5.0 g, 34.6 mmol) in acetonitrile (100 mL). The mixture was stirred for 6 h at room temperature, filtered through Celite, and the filtrate was evaporated at 30 °C. The residue was dissolved in diethyl ether and refiltered through Celite to remove inorganic impurities. After evaporation, 5-(azidomethyl)furfural (**3**) was obtained as a yellow oil (5.18 g, 99%).

IR (KBr): 3123, 2838, 2101, 1678, 1522, 1402, 1275, 1024, 810 cm^{-1} .

¹H NMR (300 MHz, CDCl_3): δ = 4.40 (s, 2 H), 6.54 (d, J = 3.5 Hz, 1 H), 7.21 (d, J = 3.5 Hz, 1 H), 9.62 (s, 1 H).

¹³C NMR (75 MHz, CDCl_3): δ = 47.1, 111.5, 121.9, 153.1, 155.4, 177.7.

HRMS (ESI): m/z [$M + \text{Na}$]⁺ calcd for $\text{C}_6\text{H}_5\text{N}_3\text{O}_2\text{Na}$: 174.0274; found: 174.0279.

Dipolar Cycloaddition of 5-(Azidomethyl)furfural (**3**) to Alkynes; General Procedure

5-(Azidomethyl)furfural (**3**) (200 mg, 1.32 mmol) in an 8 mL glass vial was dissolved in 50% aqueous ethanol (3 mL) followed by the addition of copper sulfate pentahydrate (16 mg, 0.07 mmol) and sodium ascorbate (26 mg, 0.13 mmol). Next, an appropriate amount of alkyne (typically 1.58 mmol; 1.38 mmol of *N*-Boc-propargylamine; 1.98 mmol of 3,3-dimethylbut-1-yne) was added, and the reaction mixture was stirred at 50 °C for 3 h. For triazoles insoluble in aqueous ethanol (**4b**, **4e**, **4j**), the reaction mixture was diluted with water (10 mL) and the precipitate was filtered, washed with water and dried under vacuum. Drying was completed in a desiccator over phosphorus pentoxide. For triazoles soluble in aqueous ethanol (**4a**, **c**, **d**, **f**, **i**, **k**–**o**), the solvent was evaporated under vacuum, the residue dissolved in chloroform and filtered through Celite. Subsequent evaporation under vacuum at 50 °C yielded the pure triazoles.

5-[[4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl]methyl]furfural (**4a**)

Yield: 288 mg (93%); yellowish-brown crystals; mp 85–88 °C.

IR (KBr): 3322, 3139, 1668, 1527, 1403, 1019, 977, 792 cm^{-1} .

¹H NMR (300 MHz, CD_2Cl_2): δ = 1.58 (s, 6 H), 5.62 (s, 2 H), 6.63 (d, J = 3.5 Hz, 1 H), 7.22 (d, J = 3.5 Hz, 1 H), 7.68 (br s, 1 H), 9.58 (s, 1 H).

¹³C NMR (151 MHz, CDCl_3 , –60 °C): δ = 29.9, 46.3, 67.8, 112.9, 120.0, 125.6, 152.1, 153.6, 156.1, 177.8.

HRMS (ESI): m/z [$M + \text{Na}$]⁺ calcd for $\text{C}_{11}\text{H}_{13}\text{N}_3\text{O}_3\text{Na}$: 258.0849; found: 258.0845.

5-[[4-(4-Phenyl-1H-1,2,3-triazol-1-yl)methyl]furfural (4b)

Yield: 298 mg (89%); yellow crystals; mp 122–125 °C.

IR (KBr): 3116, 1676, 1525, 1195, 1027, 765, 693 cm⁻¹.¹H NMR (300 MHz, CDCl₃): δ = 5.68 (s, 2 H), 6.63 (d, *J* = 3.6 Hz, 1 H), 7.23 (d, *J* = 3.6 Hz, 1 H), 7.32–7.37 (m, 1 H), 7.41–7.46 (m, 2 H), 7.81–7.84 (m, 2 H), 7.90 (s, 1 H), 9.65 (s, 1 H).¹³C NMR (75 MHz, CDCl₃): δ = 46.9, 112.5, 120.0, 122.1, 126.0, 128.6, 129.1, 130.2, 148.7, 153.3, 153.5, 177.7.HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₄H₁₂N₃O₂: 254.0924; found: 254.0930.**5-[[4-(4-Pentyl-1H-1,2,3-triazol-1-yl)methyl]furfural (4c)**

Yield: 320 mg (98%); yellowish-green crystals; mp 63–66 °C.

IR (KBr): 3065, 2927, 1674, 1532, 1266, 1018, 977, 799 cm⁻¹.¹H NMR (300 MHz, CDCl₃): δ = 0.88 (t, *J* = 6.6 Hz, 3 H), 1.32–1.34 (m, 4 H), 1.67–1.71 (m, 2 H), 2.70 (br s, 2 H), 5.60 (s, 2 H), 6.56 (d, *J* = 3.5 Hz, 1 H), 7.20 (d, *J* = 3.5 Hz, 1 H), 7.49 (br s, 1 H), 9.62 (s, 1 H).¹³C NMR (151 MHz, CDCl₃, –60 °C): δ = 14.3, 22.5, 25.5, 29.1, 31.4, 46.3, 112.5, 121.3, 125.5, 149.2, 152.0, 153.9, 177.6.HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₃H₁₈N₃O₂: 248.1394; found: 248.1392.**5-[[4-(4-Oct-2-yn-1-yl)-1H-1,2,3-triazol-1-yl]methyl]furfural (4d)**

Yield: 362 mg (96%); brown oil.

IR (KBr): 3128, 2930, 1681, 1523, 1403, 1024, 790 cm⁻¹.¹H NMR (300 MHz, CDCl₃): δ = 0.88 (t, *J* = 7.0 Hz, 3 H), 1.29–1.36 (m, 4 H), 1.45–1.54 (m, 2 H), 2.14–2.20 (m, 2 H), 3.67 (s, 2 H), 5.60 (s, 2 H), 6.58 (d, *J* = 3.5 Hz, 1 H), 7.20 (d, *J* = 3.5 Hz, 1 H), 7.60 (s, 1 H), 9.62 (s, 1 H).¹³C NMR (75 MHz, CDCl₃): δ = 14.1, 16.8, 18.9, 22.3, 28.6, 31.2, 46.8, 75.6, 82.7, 112.4, 122.0, 146.1, 153.2, 153.6, 177.7.HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₆H₂₀N₃O₂: 286.1550; found: 286.1551.**5-[[4-(4-Methoxycarbonyl-1H-1,2,3-triazol-1-yl)methyl]furfural (4e)**

Yield: 240 mg (77%); red crystals; mp 125–127 °C.

IR (KBr): 3123, 2838, 1727, 1674, 1548, 1333, 1241, 1017, 813 cm⁻¹.¹H NMR (300 MHz, DMSO-*d*₆): δ = 3.84 (s, 3 H), 5.88 (s, 2 H), 6.83 (d, *J* = 3.6 Hz, 1 H), 7.53 (d, *J* = 3.6 Hz, 1 H), 8.88 (s, 1 H), 9.57 (s, 1 H).¹³C NMR (75 MHz, DMSO-*d*₆): δ = 46.1, 51.8, 112.6, 123.9, 129.5, 138.8, 152.5, 153.9, 160.5, 178.4.HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₀H₁₀N₃O₄: 236.0666; found: 236.0667.**5-[[4-(3-Cyanopropyl)-1H-1,2,3-triazol-1-yl]methyl]furfural (4f)**

Yield: 306 mg (95%); brown crystals; mp 70–74 °C.

IR (KBr): 3113, 2243, 1675, 1530, 1270, 972, 795 cm⁻¹.¹H NMR (300 MHz, CDCl₃): δ = 2.06 (br s, 2 H), 2.40–2.44 (m, 2 H), 2.86 (br s, 2 H), 5.61 (s, 2 H), 6.58 (d, *J* = 3.5 Hz, 1 H), 7.20 (d, *J* = 3.5 Hz, 1 H), 7.61 (br s, 1 H), 9.59 (s, 1 H).¹³C NMR (151 MHz, CDCl₃, –60 °C): δ = 16.6, 24.0, 24.5, 46.4, 112.7, 119.9, 122.0, 125.5, 146.2, 152.1, 153.5, 177.7.HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₂H₁₃N₄O₂: 245.1033; found: 245.1037.**5-[[4-(4-Hydroxybutyl)-1H-1,2,3-triazol-1-yl]methyl]furfural (4g)**

Yield: 314 mg (95%); yellow crystals; mp 60–63 °C.

IR (KBr): 3344, 3118, 2934, 1681, 1525, 1264, 1027, 774 cm⁻¹.¹H NMR (300 MHz, CDCl₃): δ = 1.57–1.66 (m, 2 H), 1.70–1.80 (m, 2 H), 1.95 (br s, 1 H), 2.74 (t, *J* = 7.4 Hz, 2 H), 3.65 (t, *J* = 6.3 Hz, 2 H), 5.58 (s, 2 H), 6.55 (d, *J* = 3.6 Hz, 1 H), 7.20 (d, *J* = 3.6 Hz, 1 H), 7.44 (s, 1 H), 9.60 (s, 1 H).¹³C NMR (75 MHz, CDCl₃): δ = 25.4, 25.6, 32.2, 46.7, 62.4, 112.3, 121.2, 122.2, 148.9, 153.1, 153.8, 177.7.HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₂H₁₆N₃O₃: 250.1186; found: 250.1186.**5-[[4-(*N*-Boc-aminomethyl)-1H-1,2,3-triazol-1-yl]methyl]furfural (4h)**

Yield: 388 mg (96%); yellow crystals; mp 106–110 °C.

IR (KBr): 3403, 1683, 1512, 1272, 1169, 793 cm⁻¹.¹H NMR (300 MHz, CDCl₃): δ = 1.41 (s, 9 H), 4.38 (d, *J* = 5.9 Hz, 2 H), 5.15 (br s, 1 H), 5.59 (s, 2 H), 6.56 (d, *J* = 3.2 Hz, 1 H), 7.20 (d, *J* = 3.4 Hz, 1 H), 7.63 (s, 1 H), 9.62 (s, 1 H).¹³C NMR (75 MHz, CDCl₃): δ = 28.5, 36.2, 46.8, 79.9, 112.5, 121.8, 122.3, 146.5, 153.3, 153.4, 155.9, 177.7.HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₄H₁₉N₄O₄: 307.1401; found: 307.1401.**5-[[4-(4-Hydroxymethyl-1H-1,2,3-triazol-1-yl)methyl]furfural (4i)**

Yield: 195 mg (71%); yellow crystals; mp 75–79 °C.

IR (KBr): 3370, 1662, 1528, 1267, 1133, 1013, 795 cm⁻¹.¹H NMR (300 MHz, CDCl₃): δ = 2.59 (br s, 1 H), 4.79 (br s, 2 H), 5.61 (s, 2 H), 6.59 (d, *J* = 3.5 Hz, 1 H), 7.20 (d, *J* = 3.5 Hz, 1 H), 7.77 (br s, 1 H), 9.60 (s, 1 H).¹³C NMR (151 MHz, CDCl₃, –60 °C): δ = 46.5, 54.9, 112.9, 122.9, 125.5, 148.2, 152.1, 153.4, 177.7.HRMS (ESI): *m/z* [M + H]⁺ calcd for C₉H₁₀N₃O₃: 208.0717; found: 208.0715.**5-[[4-(4-Quinolin-3-yl)-1H-1,2,3-triazol-1-yl]methyl]furfural (4j)**

Yield: 398 mg (99%); orange crystals; mp 179–183 °C.

IR (KBr): 3424, 3130, 1680, 1497, 1030, 827, 786, 759 cm⁻¹.¹H NMR (300 MHz, DMSO-*d*₆): δ = 5.94 (s, 2 H), 6.90 (d, *J* = 3.5 Hz, 1 H), 7.57 (d, *J* = 3.5 Hz, 1 H), 7.61–7.66 (m, 1 H), 7.77 (t, *J* = 7.3 Hz, 1 H), 8.06 (d, *J* = 8.0 Hz, 2 H), 8.82 (s, 1 H), 8.91 (s, 1 H), 9.44 (br s, 1 H), 9.59 (s, 1 H).¹³C NMR (151 MHz, DMSO-*d*₆): δ = 46.2, 112.7, 122.7, 123.7, 124.0, 127.2, 127.6, 128.3, 128.8, 129.7, 131.1, 144.2, 147.1, 148.2, 152.6, 154.3, 178.5.HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₇H₁₃N₄O₂: 305.1033; found: 305.1032.**5-[[4-(4-Methoxymethyl-1H-1,2,3-triazol-1-yl)methyl]furfural (4k)**

Yield: 257 mg (88%); brown oil.

IR (KBr): 3126, 2932, 1681, 1524, 1402, 1274, 1195, 1094, 793 cm⁻¹.¹H NMR (300 MHz, CDCl₃): δ = 3.40 (s, 3 H), 4.54 (s, 2 H), 5.61 (s, 2 H), 6.56 (d, *J* = 3.5 Hz, 1 H), 7.19 (d, *J* = 3.5 Hz, 1 H), 7.78 (br s, 1 H), 9.60 (s, 1 H).

^{13}C NMR (151 MHz, CDCl_3 , -60°C): δ = 29.9, 46.3, 67.8, 112.9, 120.0, 125.6, 152.1, 153.6, 156.1, 177.8.

HRMS (ESI): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{10}\text{H}_{12}\text{N}_3\text{O}_3$: 222.0873; found: 222.0876.

5-[[4-(*tert*-Butyl)-1*H*-1,2,3-triazol-1-yl]methyl]furfural (4l)

Yield: 298 mg (96%); yellow crystals; mp 98–101 $^\circ\text{C}$.

IR (KBr): 3123, 2966, 1674, 1526, 1221, 1050, 763 cm^{-1} .

^1H NMR (300 MHz, CDCl_3): δ = 1.33 (s, 9 H), 5.57 (s, 2 H), 6.55 (d, J = 3.5 Hz, 1 H), 7.20 (d, J = 3.5 Hz, 1 H), 7.36 (s, 1 H), 9.62 (s, 1 H).

^{13}C NMR (75 MHz, CDCl_3): δ = 30.4, 30.9, 46.6, 112.3, 118.9, 122.2, 153.1, 154.0, 158.6, 177.7.

HRMS (ESI): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{12}\text{H}_{16}\text{N}_3\text{O}_2$: 234.1237; found: 234.1235.

5-[[4-(Cyclopropyl)-1*H*-1,2,3-triazol-1-yl]methyl]furfural (4m)

Yield: 250 mg (87%); yellow crystals; mp 99–102 $^\circ\text{C}$.

IR (KBr): 3088, 1673, 1525, 1016, 976, 765 cm^{-1} .

^1H NMR (300 MHz, CDCl_3): δ = 0.83–0.94 (m, 4 H), 1.93 (br s, 1 H), 5.55 (s, 2 H), 6.54 (d, J = 3.5 Hz, 1 H), 7.19 (d, J = 3.5 Hz, 1 H), 7.45 (br s, 1 H), 9.60 (s, 1 H).

^{13}C NMR (151 MHz, CDCl_3 , -60°C): δ = 6.7, 8.3, 46.3, 112.5, 120.3, 125.6, 151.0, 152.0, 153.9, 177.7.

HRMS (ESI): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{11}\text{H}_{12}\text{N}_3\text{O}_2$: 218.0924; found: 218.0927.

5-[[4-(2-Hydroxy-4-methylpentan-2-yl)-1*H*-1,2,3-triazol-1-yl]methyl]furfural (4n)

Yield: 352 mg (96%); brown oil.

IR (KBr): 3409, 2956, 1681, 1523, 1195, 1049, 789 cm^{-1} .

^1H NMR (300 MHz, CDCl_3): δ = 0.80 (d, J = 5.5 Hz, 3 H), 0.85 (d, J = 5.5 Hz, 3 H), 1.58 (s, 3 H), 1.68–1.80 (m, 3 H), 2.61 (br s, 1 H), 5.60 (s, 2 H), 6.55 (d, J = 1.6 Hz, 1 H), 7.20 (d, J = 2.1 Hz, 1 H), 7.60 (br s, 1 H), 9.60 (s, 1 H).

^{13}C NMR (151 MHz, CDCl_3 , -60°C): δ = 24.28, 24.29, 24.34, 28.4, 46.4, 50.8, 71.1, 112.7, 120.4, 125.6, 152.1, 153.7, 155.9, 177.7.

HRMS (ESI): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{14}\text{H}_{20}\text{N}_3\text{O}_3$: 278.1499; found: 278.1501.

5-[[4-(2-Hydroxy-3,3-dimethylbutan-2-yl)-1*H*-1,2,3-triazol-1-yl]methyl]furfural (4o)

Yield: 349 mg (95%); brown crystals; mp 96–99 $^\circ\text{C}$.

IR (KBr): 3426, 2965, 1681, 1523, 1376, 1210, 1071, 774 cm^{-1} .

^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ = 0.85 (s, 9 H), 1.44 (s, 3 H), 4.88 (br s, 1 H), 5.76 (s, 2 H), 6.74 (d, J = 3.5 Hz, 1 H), 7.52 (d, J = 3.5 Hz, 1 H), 7.89 (s, 1 H), 9.56 (s, 1 H).

^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ = 23.6, 25.3, 37.3, 45.6, 74.0, 112.1, 123.0, 124.1, 152.3, 154.4, 155.0, 178.3.

HRMS (ESI): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{14}\text{H}_{20}\text{N}_3\text{O}_3$: 278.1499; found: 278.1495.

Dipolar Cycloaddition of 5-(Azidomethyl)furfural (3) to Compounds with Two Terminal Alkyne Moieties

5-(Azidomethyl)furfural (**3**) (200 mg, 1.32 mmol) in an 8 mL glass vial was dissolved in 50% aqueous ethanol (3 mL) and then copper sulfate pentahydrate (16 mg, 0.07 mmol) and sodium ascorbate (26 mg, 0.13

mmol) were added. Next, the corresponding alkyne (0.60 mmol) was added and the reaction mixture was stirred at 50 $^\circ\text{C}$ for 3 h. The mixture was diluted with water (10 mL) and the precipitate was filtered, washed with water and dried under vacuum. Drying was completed in a desiccator over phosphorus pentoxide.

5,5'-[[Propane-1,3-diylbis(1*H*-1,2,3-triazole-4,1-diyl)]bis(methylene)]bis(furfural) (4p)

Yield: 171 mg (72%); white crystals; mp 141–144 $^\circ\text{C}$.

IR (KBr): 3063, 1673, 1532, 1221, 1018, 797 cm^{-1} .

^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ = 1.91 (quin, J = 7.7 Hz, 2 H), 2.66 (t, J = 7.6 Hz, 4 H), 5.75 (s, 4 H), 6.76 (d, J = 3.6 Hz, 2 H), 7.51 (d, J = 3.6 Hz, 2 H), 7.95 (s, 2 H), 9.56 (s, 2 H).

^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ = 24.4, 28.6, 45.7, 112.2, 122.4, 124.0, 146.9, 152.4, 154.9, 178.4.

HRMS (ESI): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{19}\text{H}_{19}\text{N}_6\text{O}_4$: 395.1462; found: 395.1461.

5,5'-[[1,3-Phenylenebis(1*H*-1,2,3-triazole-4,1-diyl)]bis(methylene)]bis(furfural) (4q)

Yield: 229 mg (89%); pale yellow crystals; mp 136–139 $^\circ\text{C}$.

IR (KBr): 3449, 3122, 1685, 1655, 1524, 1193, 1025, 787 cm^{-1} .

^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ = 5.88 (s, 4 H), 6.86 (d, J = 3.5 Hz, 2 H), 7.50–7.56 (m, 3 H), 7.84 (dd, J = 7.7, 1.2 Hz, 2 H), 8.37 (s, 1 H), 8.73 (s, 2 H), 9.58 (s, 2 H).

^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ = 46.1, 112.5, 121.9, 122.0, 123.9, 124.8, 129.6, 131.0, 146.4, 152.5, 154.4, 178.4.

HRMS (ESI): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{22}\text{H}_{17}\text{N}_6\text{O}_4$: 429.1306; found: 429.1303.

2-Azidomethyl-5-ethynylfuran (AMEF) (6)

From 2-hydroxymethyl-5-ethynylfuran (HMEF) (**5**): Diphenylphosphoryl azide (0.84 g, 3.0 mmol) was added under an argon atmosphere to an ice-cold solution of 2-hydroxymethyl-5-ethynylfuran (**5**) (0.25 g, 2.0 mmol) in acetonitrile (10 mL), followed by the addition of DBU (0.45 mL, 3.0 mmol). The reaction mixture was stirred for 10 h and concentrated under vacuum. The residue was diluted with water (10 mL) and dichloromethane (10 mL) and acidified with dilute hydrochloric acid. The aqueous layer was separated and extracted with dichloromethane (2 to 10 mL). The organic fractions were combined, dried over anhydrous magnesium sulfate and evaporated at 30 $^\circ\text{C}$. The residue was purified by column chromatography on silica gel to afford **6** as a yellow liquid (0.26 g, 86%). R_f = 0.45 (hexanes/EtOAc, 4:1).

From 5-(azidomethyl)furfural (AMF) (**3**): Potassium carbonate (1.8 g, 13.2 mmol) was placed in a 100 mL Schlenk flask. A vacuum was applied and then the flask was repeatedly flushed with argon. A solution of 5-(azidomethyl)furfural (**3**) (1.0 g, 6.6 mmol) in absolute methanol (50 mL) was added, the mixture was stirred under an argon atmosphere for 10 min at room temperature and then Bestmann–Ohira reagent (1.2 mL, 7.9 mmol) was added dropwise. The mixture was stirred overnight at room temperature, diluted with dichloromethane (100 mL), washed with water (100 mL) and brine (2 \times 50 mL), and dried over anhydrous magnesium sulfate. The solvent was removed at 30 $^\circ\text{C}$ under reduced pressure and the residue was purified by column chromatography on silica gel to afford **6** as a yellow liquid (0.40 g, 41%). R_f = 0.45 (hexanes/EtOAc, 4:1).

IR (KBr): 3290, 3127, 2098, 1404, 1203, 1019, 798 cm^{-1} .

¹H NMR (300 MHz, CDCl₃): δ = 3.41 (s, 1 H), 4.28 (s, 2 H), 6.34 (d, *J* = 3.4 Hz, 1 H), 6.62 (d, *J* = 3.4 Hz, 1 H).

¹³C NMR (75 MHz, CDCl₃): δ = 47.1, 73.7, 82.5, 110.4, 117.1, 137.0, 150.5.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₇H₆N₃O: 148.0505; found: 148.0511.

Synthesis of Oligomers from 2-Azidomethyl-5-ethynylfuran (**6**)

With dimethylformamide as the solvent: Copper(I) bromide (7.2 mg, 0.05 mmol) in an 8 mL glass vial was dissolved in DMF (2 mL) under an argon atmosphere. The corresponding ligand (0.10 mmol) was added and the mixture was stirred for 5 min. 2-Azidomethyl-5-ethynylfuran (**6**) (74.0 mg, 0.50 mmol) was added and the mixture was stirred overnight at room temperature. The oligomer was precipitated by addition of methanol (7 mL), filtered, washed with diethyl ether and dried under vacuum. The yield ranged from 76–91% depending on the ligand used.

With aqueous ethanol as the solvent: Catalytic amounts of copper sulfate pentahydrate (20.4 mg, 0.08 mmol) and sodium ascorbate (20.2 mg, 0.10 mmol) were added to a solution of 2-azidomethyl-5-ethynylfuran (**6**) (100.0 mg, 0.68 mmol) in 50% aqueous ethanol (10 mL) and the mixture was stirred overnight. The precipitate that formed was filtered, washed with 50% aqueous ethanol and ethyl acetate and then dried in a desiccator over phosphorus pentoxide. The product weight was 70.3 mg (70%).

IR (KBr): 3424, 3144, 1655, 1449, 1343, 1229, 1047, 769 cm⁻¹.

¹H NMR (300 MHz, DMSO-*d*₆): δ = 5.68–5.75 (m, 2 H), 6.67–6.71 (m, 1 H), 6.76–6.79 (m, 1 H), 8.37–8.44 (m, 1 H).

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Supporting Information

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