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N-Propargylation and copper(I)-catalyzed azide-alkyne cycloaddition as a convenient strategy for directed post-synthetic modification of 4-oxo-1,4-dihydrocinnoline derivatives

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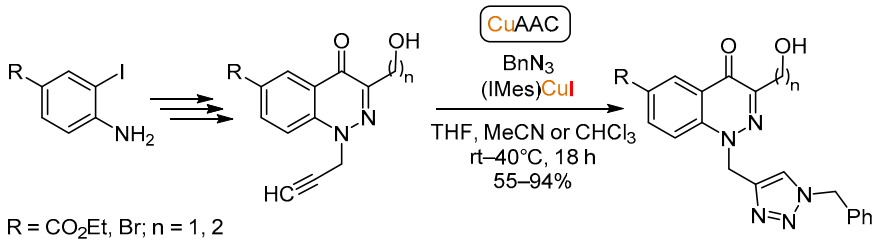


4-Oxo-1,4-dihydrocinnoline derivatives as promising inhibitors of protein tyrosine phosphatase 1B were subjected to post-synthetic modification *via* a sequence of propargylation and copper(I)-catalyzed azide-alkyne cycloaddition reactions. The propargylation of 4-oxo-1,4-dihydrocinnolines with propargyl bromide in the presence of various bases proceeded regioselectively at the cinnolinone N-1 atom. In the cycloaddition reaction of *N*-propargylcinnolinones and benzyl azide, the highest catalytic activity of copper(I) N-heterocyclic carbene complex [(IMes)Cu(Br,I)] was observed, compared to [(IMes)CuCl], [(IPr)Cu(Cl,Br,I)], and CuI.

Keywords: copper(I) N-heterocyclic carbene complexes, anionic effect, copper(I)-catalyzed azide-alkyne cycloaddition, cross coupling, protein tyrosine phosphatase 1B inhibitors, von Richter cyclization.

Diseases caused by changes in the activity of insulin and leptin signaling pathways in the central and peripheral nervous systems have great social impact, since they are often associated with loss of physical function and impaired health-related quality of life. One of the principal factors leading to insulin and leptin resistance is the increase in enzymatic activity of protein tyrosine phosphatase 1B (PTP1B)[1–4] which dephosphorylates insulin and leptin receptors, as well as the associated insulin receptor substrates (IRS proteins), blocking the transmission of insulin and leptin signals into the cell.

A study of bidentate PTP1B ligands derived from 4-oxa-1,4-dihydroquinoline-3-carboxylic acid derivatives **1**[5] (Fig. 1) showed that a hydrophilic substituent at the C-3 atom is required in the quinolone ring together with a hydrophobic substituent at the C-6 atom. The presence of a hydroxy group in the hydroxymethyl substituent at the C-3 atom of ethyl 3-(hydroxymethyl)-4-oxo-1,4-dihydrocinnoline-6-carboxylic acid (**2**) (Fig. 1) affected the desired inhibitory ability, which sharply decreased after methylation of the OH group. We have recently demonstrated the high inhibitory activity of a structural analog of the quinolone-type inhibitors **2** upon treatment of rat models of obesity and metabolic syndrome.[6]

High biological activity and specificity of cinnolinone derivatives **2** (Fig. 1) allow to consider them as lead compounds in the development of PTP1B inhibitors. It is still important to develop an effective strategy for directed

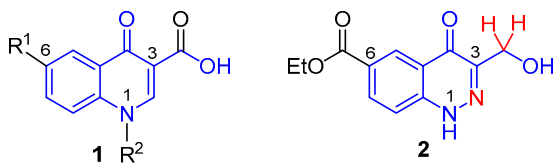
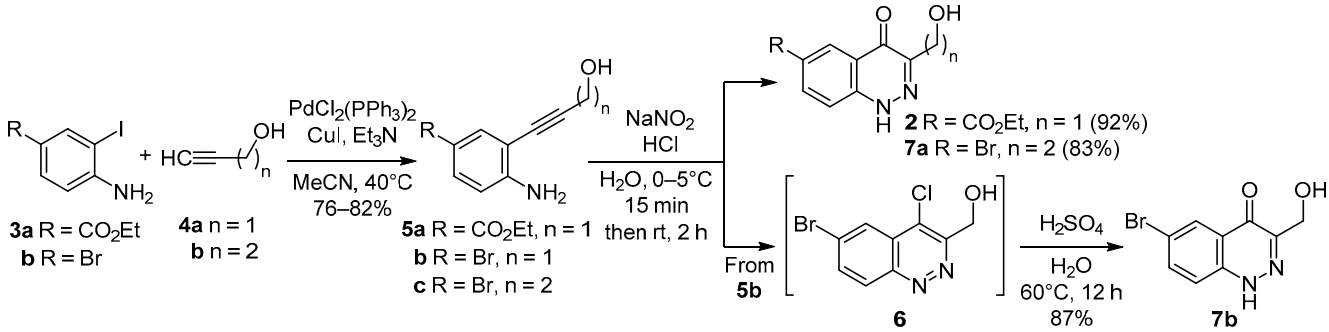


Figure 1. Pharmacophoric structures on the basis of 4-quinolone derivatives **1** and 1,4-dihydrocinnoline derivatives **2**, exhibiting inhibitory activity against PTP1B.

Scheme 1



modification of such compounds for further optimization of their biological activity and for designing molecular probes enabling the visualization of metabolic processes.

The copper(I)-catalyzed azide-alkyne cycloaddition reaction (CuAAC) is often used in the synthesis of various biologically active compounds,[7–9] for example, PTP1B inhibitors[10,11] and biological imaging agents.[12–14]

In the present work, we propose a simple and effective approach for post-synthetic modification of 4-oxo-1,4-dihydrocinnoline derivatives, which includes a propargylation reaction at the cinnolinone N-1 atom, followed by CuAAC reactions of the obtained propargyl derivatives. In order to identify the most effective catalyst for the second step, a series of copper(I) N-heterocyclic carbene complexes were prepared and studied: [(IMes)CuX], [(IPr)CuX] (X = Cl, Br, I), CuI was also tested.

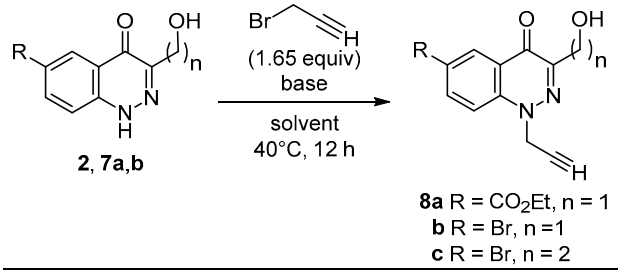
4-Oxo-1,4-dihydrocinnolines containing a hydroxyalkyl group at position 3 and a CO_2Et or Br substituent at position 6 were chosen for the study. The selection of substituents at position 6 was based on their hydrophobic nature, as well as the potential for subsequent functionalization *via* amidation, transesterification,[15] and palladium-catalyzed cross-coupling[16] reactions.

Substituted alkynes are convenient substrates for the synthesis of a wide range of heterocyclic compounds.[17–19] In particular, *ortho*-ethynylated aniline derivatives undergo intramolecular cyclization with the formation of cinnolines under the von Richter cyclization conditions,[20–22] while starting unsymmetrical alkynes can be obtained by using the Sonogashira–Hagihara reaction.[23] For the synthesis of the target compounds, we chose the following reaction sequence: a Sonogashira–Hagihara coupling of acetylenic alcohol with aryl iodides, followed by cyclization of the obtained *ortho*-ethynylated derivatives, providing the corresponding cinnolinones.

The first transformation of substrates **3a**,**b** and **4a**,**b** led to the formation of compounds **5a**–**c** in good yields (76–82%), which under the previously described von Richter cyclization conditions[24] provided cinnolinone derivatives **2** and **7a**,**b** (Scheme 1). In the case of compound **5a**, the cyclization proceeded selectively, with the formation of cinnolinone **2** in a high yield. However, when aniline derivative **5b** containing a bromine substituent at the *para* position was introduced into reaction under the same conditions, a product mixture was obtained, which contained 56% of the target product **7b** and 44% of 6-bromo-4-chloro-3-hydroxymethylcinnoline (**6**) according to ^{1}H NMR data. Such a difference can be associated with the weaker electron-withdrawing properties of the substituent at the C-6 position of cinnolinone, which likely reduced the rate of hydrolysis of the intermediate 6-bromo-4-chloro-3-hydroxymethylcinnoline (**6**). An additional treatment of this mixture with 50% H_2SO_4 led to its complete conversion into the target product **7b** in 87% yield. Remarkably, in the case of homolog **5c**, the formation of the target product **7a** occurred without an impurity of the respective 4-chlorocinnoline. The facile hydrolysis of the intermediate 4-chlorocinnoline in this case was likely associated with the possibility of intramolecular nucleophilic substitution reaction occurring in the first step, which involved the hydroxyethyl group at the C-3 position. The obtained cyclic ester underwent fast hydrolysis with the formation of product **7a**, in agreement with the previously obtained experimental data.[25,26] According to the analysis of ^{1}H NMR spectra, the characteristic shifts of NH protons in compounds **2** and **7a**,**b** were observed at 13.58 ppm (compound **2**), 13.39 and 13.50 ppm (compounds **7a** and **7b**, respectively), which corresponded to the cinnolinone tautomer.

At the next stage of our study, the propargylation reactions of substrates **2** and **7a**,**b** were studied in the presence of K_2CO_3 or NaH (Table 1). The reactions were performed in aprotic solvents: Me_2CO, THF, and DMF. Depending on the reaction conditions, the product yields were 55–86%. It was found that the propargylation reactions proceeded regioselectively at the cinnolinone ring N-1 atom and did not affect the OH group of the substituent at the C-3 position. The most effective reaction conditions were a combination of NaH and DMF (Table 1). According to ^{1}H NMR data, the obtained compounds **8a**–**c** did not exhibit NH proton signals, while the signals of OH protons appeared at 3.28 ppm for compound **8a** (t, J = 6.4 Hz, $CDCl_3$), at 5.10 ppm for compound **8b** (t, J = 5.9 Hz, DMSO-d_6), and at 4.62 ppm for compound **8c** (t, J = 5.5 Hz, DMSO-d_6). Additionally, NOESY spectrum of compound **8c** showed cross peaks of $C\underline{H}_2CCH$ methylene protons at 5.31 ppm and the protons bonded to the cinnolinone ring C-8 atom at 7.76 ppm (d, J = 9.2 Hz). The analysis of compound **8b** by IR spectroscopy confirmed the successful *N*-functionalization of cinnolinone. The characteristic absorption bands due to the stretching vibrations of C≡C and C–H bonds appeared at 2121 and 3246 cm^{-1}, respectively.

Table 1. The yields of compounds **8a**–**c** depending on the propargylation conditions of cinnolinones **2**, **7a**,**b**



Compound	Solvent	Base (amount, equiv)	Yield, %
8a	Me_2CO	K_2CO_3 (3)	55
8a	DMF	NaH (1.05)	86
8b	Me_2CO	K_2CO_3 (3)*	61
8b	DMF	K_2CO_3 (3)*	62
8b	DMF	NaH (1.05)	75
8b	THF	NaH (1.05)	62
8c	DMF	NaH (1.05)	79

* The amount of propargyl bromide was 4 equiv.

The copper(I) carbene complexes employed as catalysts in the azide-alkyne cycloaddition reaction[27] do not usually require the use of an additional external base.[28] 1,3-Bis(2,6-diisopropylphenyl)-imidazol-2-ylidene (IPr) and 1,3-bis-(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes) are the most common ligands used in the catalytic systems for CuAAC due to the high catalytic activity and synthetic availability of the corresponding complexes. It has been previously shown that the reactivity of N-heterocyclic carbene complexes of copper(I) halides under the CuAAC conditions may depend on the nature of the halide anion.[29] That motivated us to study the catalytic activity of the complete series of [(NHC)CuX] complexes, where NHC = IPr, IMes, while X = Cl, Br, I.

The synthesis of imidazolium salts IPr·HCl and IMes·HCl was performed according to a previously described procedure.[30] The preparation of a series of [(IPr)CuX] complexes (X = Cl, Br, I) was achieved starting from the corresponding IPr·HCl salt in aqueous ammonia medium, using CuX(I) as a source of copper(I).[31] The application of these reaction conditions for synthesizing the [(IMes)CuX] complexes (X = Cl, Br, I) was successful only in the presence of CuBr, and the heteroleptic [(IMes)CuBr] complex was isolated in 49% yield.

When CuCl or CuI were used, a mixture of heteroleptic [(IMes)CuX] complex (X = Cl, I) and its homoleptic form $[(IMes)_2Cu]^+Y^-$ was formed, as confirmed by ^1H and ^{13}C NMR data. For this reason, the heteroleptic [(IMes)CuCl] complex was obtained *via* an alternative procedure[32] by a reaction of IMes·HCl with 0.55 equiv of Cu_2O in CH_2Cl_2 medium. Under these conditions, Cu_2O is a base and a Cu(I) source at the same time. The [(IMes)CuCl] complex was obtained by this method in 96% yield. For the synthesis of [(IMes)CuI] complex, we proposed another approach involving the treatment of [(IMes)CuCl] with 2 equiv of NaI in Me_2CO under argon atmosphere. The main product [(IMes)CuI] was formed under these conditions in a mixture with $[(IMes)_2Cu]CuI_2$. The ratio of these complexes varied depending on the order of reagent mixing: after the addition of NaI solution to a suspension of [(IMes)CuCl], the part of homoleptic $[(IMes)_2Cu]CuI_2$ complex in the mixture reached 15%, while the opposite order of mixing led to its increase up to 36%. This observation presumably indicates the critical influence of the iodide concentration on the course of the reaction. Both forms of the obtained complexes were easily resolved in ^1H NMR spectra by the characteristic chemical shifts of the methyl protons in the 2,4,6-trimethylphenyl substituents: 2.12 (*o*-Me) and 2.35 ppm (*p*-Me) for the [(IMes)CuI] complex, 1.69 (*o*-Me) and 2.44 ppm (*p*-Me) for the $[(IMes)_2Cu]CuI_2$ complex (Fig. 2).

Washing the mixture of complexes with MeOH reduced the fraction of $[(IMes)_2Cu]CuI_2$ complex due to its superior solubility. There were no X-ray structural analysis data for [(IMes)CuI] complex available in the Cambridge Crystallographic Data Center (CCDC) database, unlike in the case of [(IMes)Cu(Cl/Br)] complex.[33,34] For the purpose of growing monocrystals, the crystallization was performed in different solvent systems: pentane–CH_2Cl_2, pentane–$CHCl_3$, MeOH–H_2O. In all of the cases, according to the X-ray structural analysis results, only the homoleptic form of $[(IMes)_2Cu]CuI_2$ complex was found (Fig. 3). No suitable crystals of the heteroleptic form [(IMes)CuI] could be obtained. It was concluded that the solution likely contained an equilibrium mixture of the heteroleptic and homoleptic forms. This equilibrium presumably shifted toward the formation of the homoleptic $[(IMes)_2Cu]CuI_2$ complex during the crystallization procedure (Scheme 2). A similar equilibrium in solution was studied earlier in the case of silver(I) halide N-heterocyclic carbene complexes, including the [(IMes)AgCl] complex.[35]

The possibilities of the functionalization of the *N*-propargylated cinnolinones synthesized were initially explored using compound **8a** as a substrate in a CuAAC reaction with benzyl azide as a model compound in $CHCl_3$ medium at room temperature (Table 2).

Under the given conditions, the complexes of [(IPr)CuX] series (X = Cl, Br, I) did not exhibit catalytic

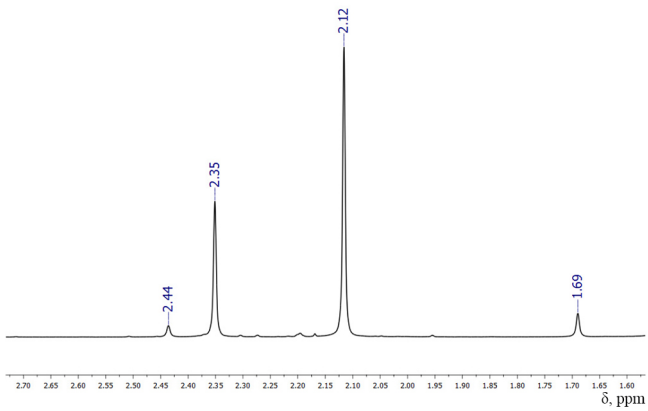


Figure 2. The characteristic chemical shifts of methyl proton signals in ^1H NMR spectrum acquired for a mixture of [(IMes)CuI] and $[(IMes)_2Cu]CuI_2$ complexes.

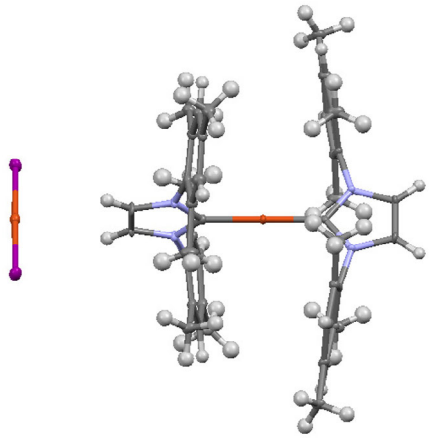
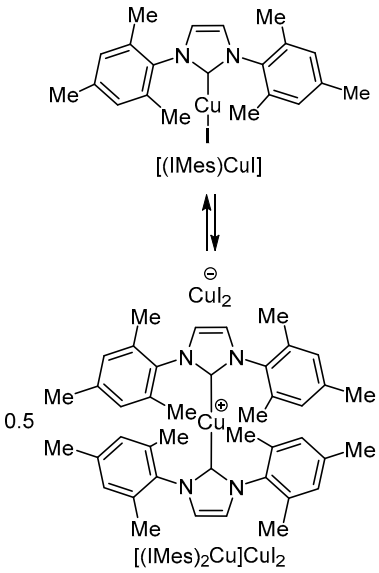


Figure 3. The molecular structure of $[(IMes)_2Cu]CuI_2$ complex with atoms represented by thermal vibration ellipsoids of 50% probability.

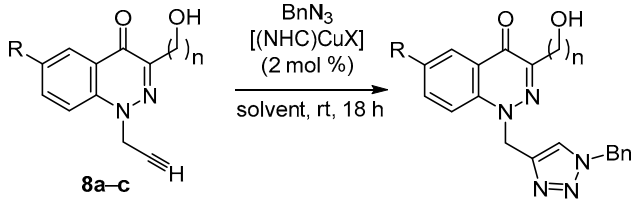
Scheme 2



activity (Table 2). On the other hand, [(IMes)CuX] complexes (X = Cl, Br, I) containing a less sterically hindered ligand showed higher activity under the same reaction conditions. It should be noted that the catalytic activity of [(IMes)CuX] complex depended on the nature of the anion and increased in the order of $Cl^- < Br^- \approx I^-$, leading to an increase in the conversion of the starting compound **8a** to product **9a** from 10% (for X = Cl^-) to 82% (for X = I^-) (Table 2).

It should be also noted that CuI in the absence of ligands and a base under the given conditions did not exhibit any catalytic activity (Table 2). Compounds **8b**,**c** showed lower reactivity in a CuAAC reaction, therefore the reactions were performed at 40°C. When using the [(IMes)CuI] complex, the starting compounds **8b**,**c** formed the reaction products **9b**,**c** with conversion 62% and 50% yields, respectively (Table 2), while product **9b** was isolated in 55% yield. It is likely that the low reactivity of [(IMes)CuI] complex could be attributed to diffusion limitations due to the lower solubility of compounds **8b**,**c** in $CHCl_3$ compared

Table 2. Conversion of compounds **8a**–**c** and the yields of compounds **9a**–**c** depending on the CuAAC reaction conditions



9a R = CO_2Et, n = 1
b R = Br, n = 1
c R = Br, n = 2

Com-pound	[(NHC)CuX]	Solvent	Conversion of compounds **8a**–**c** according to ^{1}H NMR spectrum, %
9a	[(IPr)CuX]*	$CDCl_3$	Trace
9a	[(IMes)CuCl]	$CDCl_3$	10
9a	[(IMes)CuBr]	$CDCl_3$	75
9a	[(IMes)CuI]	$CDCl_3$	82 (75**)
9a	CuI	$CDCl_3$	0
9b***	[(IMes)CuI]*[4]	$CHCl_3$	62 (55**)
9c***	[(IMes)CuI]	$CHCl_3$	50
9c***	[(IMes)CuI]	THF	87
9c***	[(IMes)CuI]	Me_2CO	92
9c***	[(IMes)CuI]	MeCN	99 (94**)

* X = Cl, Br, I.
** Isolated product **9a**–**c** yield.
*** The reaction was performed at 40°C.
*[4] [(IMes)CuI] (4 mol %) was used.

to compound **8a**. We achieved a complete conversion of the starting compound **8b** to product **9b** using MeCN as a solvent (Table 2).

It has been proposed that the most probable intermediates in a CuAAC reaction with terminal acetylenes are binuclear copper(I) clusters containing acetylenide and azide ligands oriented at each other through a metal center.[36–38] A recent study[29] of the reaction between phenylacetylene and benzyl azide, catalyzed by [(NHC)CuX] (NHC = 1-benzyl-3-methylimidazolin-2-ylidene, X = I, Br, Cl, BF_4, PF_6) and $[(NHC)_2CuBr]$ complexes, showed that the strongly basic ligand was capable of deprotonating phenylacetylene, leading to the formation of copper phenylacetylenide **I** with a coordinated halide anion in the form of $PhC{\equiv}CCuX^-$ (Fig. 4) in ionic pair with the corresponding imidazolium cation ($NHC{\cdot}H^+$). A computational study at the level of DFT was used to propose a mechanism for the preparation of triazole **VI** involving a sequence of bimetallic intermediates **II**→**III**→**IV**→**V**$^-$, with protonation of intermediate **V** during the last step and regeneration of the catalyst [(NHC)CuX] (Fig. 4).[29]

At the same time, a study by Titov and coworkers showed the possibility of performing the CuAAC reaction using a trinuclear copper(I) pyrazolate complex *via* the activation of acetylene group in the presence of Cu(I) species, involving the formation of the corresponding π-complex without generation of copper(I) acetylenide.[39]

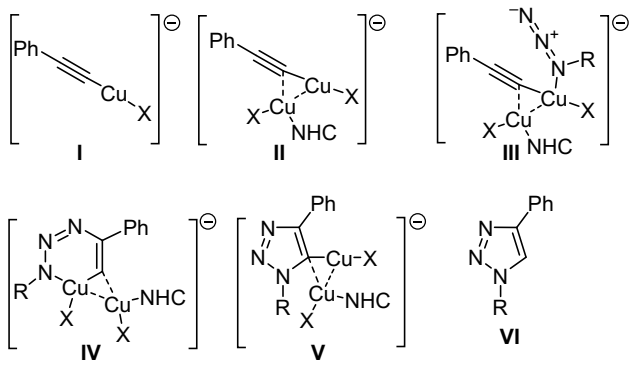


Figure 4. The possible intermediate structures in a CuAAC reaction in the presence of [(NHC)CuX] complex as catalyst.[29]

According to the Dewar–Chatt–Duncanson model, copper(I) compounds can form relatively stable π-complexes with a triple bond,[40] featuring two three-center molecular orbitals. The overlap of unoccupied orbital of Cu(I) and the π-molecular orbital of C≡C bond in these complexes results in an electron donor-acceptor interaction. Some contribution to the bonding is also made by the π-back donation from the occupied d-orbitals of the metal center to the π*-molecular orbital of the C≡C bond. However, the specific activation of acetylene group through Cu(I) in such π-complexes is primarily mediated by electron donor-acceptor interaction[41] and can point to the critical role of Lewis acidity in such activation of the considered Cu(I) complexes. The transfer of π-molecular orbital electrons of C≡C bond to the sp^3-hybrid orbital of Cu(I) center results in decreased electron density on the carbon atoms of C≡C bond, conferring this functional group the properties of a mild electrophile.[42]

Apparently, the studied copper(I) N-heterocyclic carbene complexes can substantially contribute to the activation of C≡C bond *via* π-coordination with free terminal alkynes, as well as with the intermediate Cu acetylenide. Furthermore, the catalytic activity difference in the studied series of [(IMes)CuX] complexes (X = Cl, Br, I) may be associated with the different degrees of C≡C bond activation, depending on the acidity of the complex, which changes depending on the anion. At the same time, the possible presence of an equilibrium (Scheme 2) pointed to the tendency of [(IMes)CuI] complex to the formation of homoleptic form $[(IMes)_2Cu]CuI_2$ in solution, which likely contributed to the observed catalytic activity. This assumption was supported by the observed high activity of homoleptic copper(I) N-heterocyclic complexes $[(NHC)_2CuY]$ (Y = PF_6, BF_4) in the CuAAC reaction.[43]

Thus, the proposed approach to post-synthetic modification of 4-oxo-1,4-dihydrocinnoline derivatives by using the [(IMes)CuI] complex in CuAAC reaction can be recommended for the development of a compound library suitable for molecular structure optimization in the search for biologically active agents.

Experimental

IR spectrum (4000–200 cm^{-1}) of compound **8b** with 1 cm^{-1} resolution was recorded on a Shimadzu IR Prestige-21 spectrometer in KBr pellets. ^{1}H NMR and ^{13}C spectra were acquired on a Bruker Avance III 400 instrument (400 and 101 MHz, respectively) in DMSO-d_6 and $CDCl_3$. The residual proton signals of solvents (DMSO-d_6: 2.50 ppm; $CDCl_3$: 7.26 ppm) were used as internal standards for ^{1}H NMR spectra and deuterated solvent signals (DMSO-d_6: 39.5 ppm; $CDCl_3$: 77.2 ppm) were used as internal standards for ^{13}C NMR spectra. High-resolution mass spectra were recorded in positive ion mode over the *m*/*z* range of 50–1200, using a maXis mass spectrometer with electrospray ionization (ESI-QTOF). The capillary voltage of the ion source was set at 4500 V (ESI+). The nebulizer gas pressure was 0.4 bar and the drying gas flow was 4.0 l/min. The samples were dissolved in MeOH or MeCN. A sodium formate solution was used for mass calibration. The reaction progress was controlled by TLC on Macherey-Nagel plates coated with layer of SIL G/UV254 silica gel (0.2 mm). Preparative column chromatography was performed using silica gel from Macherey-Nagel, with 40–63 μm particle size. In order to exclude the possible influence of catalyst traces remaining on glassware, all reactions intended for the study of catalytic activity were performed in fresh vials, while magnetic stir bars were treated prior to use in a mixture of concd HCl with H_2O_2 for 1 h at 70°C.[44]

Commercially available reagents and solvents were purchased from Sigma-Aldrich, Carl Roth, and abcr GmbH. Compounds **3a**,[45] **3b**,[46] [(IPr)CuX] (X = Cl, Br, I),[31] [(IMes)CuBr],[31] and [(IMes)CuCl][32] were synthesized according to the published procedures. The observed ^{1}H NMR features of the synthesized compounds matched the literature precedents. All solvents were dried prior to use according to standard procedures.

Preparation of propargylanilines 5a–c (General method – a modified literature procedure[47]). A solution of the appropriate aryl iodide **3a**,**b** (9 mmol) in a mixture of Et_3N (15 ml) and MeCN (15 ml) was cooled to 0°C, degassed by bubbling of argon and treated by adding $PdCl_2(PPh_3)_2$ (0.130 g, 0.18 mmol) and CuI (0.034 g, 0.18 mmol), followed by stirring for 5 min. The reaction mixture was then treated by dropwise addition of the appropriate alkyne **4a**,**b** (10.65 mmol). The obtained mixture was stirred at 50°C for 12 h. The reaction mixture was diluted with EtOAc, and the organic layer was washed with saturated aqueous NH_4Cl solution, saturated aqueous NaCl solution, and with H_2O. The organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated at reduced pressure. The obtained residue was purified by the column chromatography, using a 7:1 mixture of CH_2Cl_2–Me_2CO as eluent.

Ethyl 4-amino-3-(3-hydroxyprop-1-yn-1-yl)benzoate (5a).[48] Yield 1.55 g (76%), brown powder. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.99 (1H, d, *J* = 1.9, H-2); 7.81 (1H, dd, *J* = 8.5, *J* = 2.0, H-6); 6.66 (1H, d, *J* = 8.6, H-5); 4.62 (2H, s, $C\underline{H}_2OH(NH_2)$); 4.55 (2H, s, $NH_2(C\underline{H}_2OH)$); 4.31 (2H, q, *J* = 7.1, $CO_2C\underline{H}_2CH_3$); 1.89 (1H, s, OH); 1.36 (3H, t, *J* = 7.1, $CO_2CH_2C\underline{H}_3$).

3-(2-Amino-5-bromophenyl)prop-2-yn-1-ol (5b).[47] Yield 1.62 g (82%), brown powder. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.37 (1H, d, *J* = 2.3, H-6); 7.20 (1H, dd,

J = 8.6, *J* = 2.3, H-4); 6.57 (1H, d, *J* = 8.6 , H-3); 4.53 (2H, s, CH_2); 3.28 (3H, br. s, NH_2, OH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 147.2; 134.5; 132.8; 116.0; 109.2; 109.1; 93.9; 81.2; 51.7.

4-(2-Amino-5-bromophenyl)but-3-yn-1-ol (5c). Yield 1.68 g (78%), brown powder. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.35 (1H, d, *J* = 2.3, H-6); 7.17 (1H, dd, *J* = 8.6, *J* = 2.3, H-4); 6.58 (1H, d, *J* = 8.6, H-3); 3.82 (2H, t, *J* = 6.2, $CH_2C\underline{H}_2OH$); 3.46 (3H, br. s, NH_2, OH); 2.73 (2H, t, *J* = 6.2, $C\underline{H}_2CH_2OH$). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 147.0; 134.3; 132.1; 115.7; 110.3; 109.0; 93.4; 77.8; 61.2; 24.1. Found, *m*/*z*: 240.0021 $[M+H]^+$. $C_{10}H_{11}BrNO$. Calculated, *m*/*z*: 240.0019.

Preparation of 4-oxo-1,4-dihydrocinnolines 2, 7a,b (General method). A suspension of propargylaniline **5a**–**c** (8 mmol) in 2 M HCl (15 ml) was treated by portionwise addition of $NaNO_2$ (0.82 g, 12 mmol) at 0–5°C. The reaction mixture was stirred for 15 min at 0–5°C, then further stirred for 2 h at room temperature. The obtained precipitate was filtered off and washed consistently with H_2O (2×5 ml), MeOH (5 ml), and Et_2O (5 ml).

Ethyl 3-(hydroxymethyl)-4-oxo-1,4-dihydrocinnoline-6-carboxylate (2) was obtained from propargylaniline **5a**. Yield 1.83 g (92%), white powder. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 13.58 (1H, s, NH); 8.60 (1H, d, *J* = 1.8, H-5); 8.22 (1H, dd, *J* = 8.9, *J* = 1.9, H-7); 7.66 (1H, d, *J* = 8.8, H-8); 4.99 (1H, br. s, OH); 4.53 (2H, s, CH_2); 4.35 (2H, q, *J* = 7.1, $CO_2C\underline{H}_2CH_3$); 1.35 (3H, t, *J* = 7.1, $CO_2CH_2C\underline{H}_3$). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 169.6; 164.8; 150.4; 143.3; 132.9; 126.5; 125.2; 121.0; 117.1; 61.1; 58.5; 14.2. Found, *m*/*z*: 271.0692 $[M+Na]^+$. $C_{12}H_{12}N_2NaO_4$. Calculated, *m*/*z*: 271.0689.

6-Bromo-3-(2-hydroxyethyl)cinnolin-4(1*H*)-one (7a) was obtained from propargylaniline **5c**. The product was additionally purified according to the following procedure: the obtained precipitate was dissolved in aqueous 0.3 M NaOH solution (50 ml), the obtained suspension was filtered through a thin layer of Celite, the filtrate was neutralized with aqueous 2 M HCl solution to pH 7. The obtained precipitate was filtered off and washed consistently with H_2O (2×5 ml), MeOH (5 ml), and Et_2O (5 ml). The product was air-dried. Yield 1.79 g (83%), light-brown powder. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 13.39 (1H, s, NH); 8.09 (1H, d, *J* = 2.2, H-5); 7.85 (1H, dd, *J* = 9.0, *J* = 2.3, H-7); 7.51 (1H, d, *J* = 9.0, H-8); 3.71 (2H, t, *J* = 6.9, $CH_2C\underline{H}_2OH$); 2.86 (2H, t, *J* = 6.9, $C\underline{H}_2CH_2OH$). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 168.6; 148.9; 139.9; 136.6; 126.1; 122.3; 119.0; 116.7; 58.7; 33.8. Found, *m*/*z*: 290.9751 $[M+Na]^+$. $C_{10}H_9BrN_2NaO_2$. Calculated, *m*/*z*: 290.9740.

6-Bromo-3-(hydroxymethyl)cinnolin-4(1*H*)-4-one (7b) was obtained from propargylaniline **5b**. The precipitate formed during the reaction was treated with aqueous 15% H_2SO_4 solution (15 ml) at 60°C for 12 h, then dissolved in aqueous 0.3 M NaOH solution (50 ml), the obtained suspension was filtered through a thin layer of Celite, the filtrate was neutralized with aqueous 2 M HCl solution to pH 7. The obtained precipitate was filtered off and washed consistently with H_2O (2×5 ml), MeOH (5 ml), and Et_2O (5 ml). The product was air-dried. Yield 1.77 g (87%), beige powder. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 13.50 (1H, s, NH); 8.12 (1H, d, *J* = 2.2, H-5); 7.88 (1H, dd, *J* = 9.0, *J* = 2.3, H-7); 7.56 (1H, d, *J* = 9.0, H-8); 4.51 (2H, s, CH_2). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 168.3; 149.6; 140.1; 136.4; 126.1; 123.2; 119.2; 117.1; 58.7. Found, *m*/*z*: 276.9591 $[M+Na]^+$. $C_9H_7BrN_2NaO_2$. Calculated, *m*/*z*: 276.9583.

Preparation of *N*-propargylcinnolinones 8a–c (General method). A solution of the appropriate 4-oxo-1,4-dihydrocinnoline **2**, **7a**,**b** (2 mmol) in DMF (4 ml) was stirred and treated by the addition of NaH (60% dispersion in mineral oil) (84 mg, 2.1 mmol), then after 10 min, propargyl bromide (400 mg, 3.3 mmol, 1.65 equiv) was added dropwise. The reaction mixture was heated on oil bath to 40°C and stirred at that temperature for 12 h. The mixture was then poured into H_2O (150 ml), the obtained precipitate was filtered off. The product was air-dried and washed with pentane (3×3 ml). The isolated product was dried at reduced pressure.

Ethyl 3-(hydroxymethyl)-4-oxo-1-(prop-2-yn-1-yl)-1,4-dihydrocinnoline-6-carboxylate (8a). Yield 0.492 g (86%), beige powder. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 9.00 (1H, d, *J* = 1.9, H-5); 8.41 (1H, dd, *J* = 9.1, *J* = 2.0, H-7); 7.63 (1H, d, *J* = 9.1, H-8); 5.17 (2H, d, *J* = 2.5, $C\underline{H}_2C{\equiv}CH$); 4.81 (2H, d, *J* = 6.5, $C\underline{H}_2OH$); 4.43 (2H, q, *J* = 7.1, $CO_2C\underline{H}_2CH_3$); 3.28 (1H, t, *J* = 6.4, OH); 2.52 (1H, t, *J* = 2.5, ≡CH); 1.43 (3H, t, *J* = 7.1, $CO_2CH_2C\underline{H}_3$). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 171.1; 165.3; 149.5; 142.6; 134.5; 128.5; 127.1; 123.1; 115.6; 76.3; 75.7; 61.8; 61.7; 46.6; 14.5. Found, *m*/*z*: 309.0848 $[M+Na]^+$. $C_{15}H_{14}N_2NaO_4$. Calculated, *m*/*z*: 309.0846.

6-Bromo-3-(hydroxymethyl)-1-(prop-2-yn-1-yl)cinnolin-4(1*H*)-one (8b). Yield 0.439 g (75%), beige powder. IR spectrum, ν, cm^{-1}: 2121 (C≡C), 3246 (C(*sp*)–H), 3431 (OH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 8.22 (1H, d, *J* = 2.3, H-5); 8.06 (1H, dd, *J* = 9.2, *J* = 2.4, H-7); 7.80 (1H, d, *J* = 9.2, H-8); 5.34 (2H, d, *J* = 2.3, $C\underline{H}_2C{\equiv}CH$); 5.10 (1H, t, *J* = 5.9, OH); 4.51 (2H, d, *J* = 5.9, CH_2); 3.57 (1H, t, *J* = 2.3, ≡CH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 168.0; 149.3; 139.0; 136.7; 126.9; 124.4; 119.1; 117.8; 77.9; 77.5; 58.4; 45.9. Found, *m*/*z*: 314.9731 $[M+Na]^+$. $C_{12}H_9BrN_2NaO_2$. Calculated, *m*/*z*: 314.9740.

6-Bromo-3-(hydroxyethyl)-1-(prop-2-yn-1-yl)cinnolin-4(1*H*)-one (8c). Yield 0.483 g (79%), beige powder. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 8.19 (1H, d, *J* = 2.2, H-5); 8.01 (1H, dd, *J* = 9.2, *J* = 2.3, H-7); 7.76 (1H, d, *J* = 9.2, H-8); 5.31 (2H, d, *J* = 2.4, $C\underline{H}_2C{\equiv}CH$); 4.62 (1H, t, *J* = 5.5, OH); 3.72 (2H, dd, *J* = 12.1, *J* = 6.6, $CH_2C\underline{H}_2OH$); 3.54 (1H, t, *J* = 2.4, ≡CH); 2.85 (2H, t, *J* = 6.8, $C\underline{H}_2CH_2OH$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 8.46 (1H, d, *J* = 2.3, H-5); 7.83 (1H, dd, *J* = 9.1, *J* = 2.3, H-7); 7.47 (1H, d, *J* = 9.2, H-5); 5.12 (2H, d, *J* = 2.5, $C\underline{H}_2C{\equiv}CH$); 3.99 (2H, dd, *J* = 10.8, *J* = 5.4, $CH_2C\underline{H}_2OH$); 3.07 (2H, t, *J* = 5.6, $C\underline{H}_2CH_2OH$); 2.52 (1H, t, *J* = 2.5, ≡CH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 168.5; 148.8; 138.9; 136.5; 127.0; 123.6; 118.9; 117.5; 77.7; 77.6; 58.5; 45.8; 33.7. Found, *m*/*z*: 328.9899 $[M+Na]^+$. $C_{13}H_{11}BrN_2NaO_2$. Calculated, *m*/*z*: 328.9897.

Preparation of triazole derivatives 9a–c in CuAAC reaction (General method). A vial was charged with the appropriate *N*-propargylcinnolinone **8a**–**c** (0.2 mmol), the appropriate [(NHC)CuX] complex (2 mol %), benzyl azide (30 mg, 0.22 mmol), and 2 ml of the selected solvent ($CDCl_3$, $CHCl_3$, THF, Me_2CO). The reaction mixture was stirred for 18 h at room temperature or with heating to 40°C. In order to determine the product yield from ^{1}H NMR spectral data, an aliquot of the reaction mixture (0.65 ml) was evaporated at reduced pressure and the residue was dissolved in DMSO-d_6. The results are presented in Table 2. In order to determine the isolated product yield, the reaction mixture after evaporation was purified by column chromatography, using a 3:1 mixture of CH_2Cl_2–Me_2CO as eluent.

Ethyl 1-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-3-(hydroxymethyl)-4-oxo-1,4-dihydrocinnoline-6-carboxylate (9a). Yield 0.069 g (75%), beige powder. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 8.95 (1H, d, *J* = 1.9, H Ar); 8.34 (1H, dd, *J* = 9.1, *J* = 2.0, H Ar); 7.91 (1H, d, *J* = 9.1, H Ar); 7.47 (1H, s, H triazole); 7.42–7.32 (3H, m, H Ar); 7.29–7.17 (2H, m, H Ar); 5.68 (2H, s, CH_2); 5.47 (2H, s, CH_2); 4.79 (2H, d, *J* = 6.2, CH_2); 4.41 (2H, q, *J* = 7.1, $CO_2C\underline{H}_2CH_3$); 3.38 (1H, t, *J* = 6.4, OH); 1.41 (3H, t, *J* = 7.1, $CO_2CH_2C\underline{H}_3$). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 171.1; 165.3; 149.3; 143.0; 142.4; 134.5; 134.1; 129.4 (2C); 129.2; 128.3 (3C); 127.0; 123.0; 122.8; 116.1; 62.1; 61.7; 54.6; 52.0; 14.4. Found, *m*/*z*: 420.1668 $[M+H]^+$. $C_{22}H_{22}N_5O_4$. Calculated, *m*/*z*: 420.1666.

1-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-6-bromo-3-(hydroxymethyl)cinnolin-4(1*H*)-one (9b). Yield 0.051 g (55%), beige powder. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 8.21 (1H, s, H Ar); 8.19 (1H, d, *J* = 1.9, H Ar); 7.98–7.90 (2H, m, H Ar, H triazole); 7.46–7.14 (5H, m, H Ar); 5.75 (2H, s, CH_2); 5.55 (2H, s, CH_2); 5.07 (1H, t, *J* = 5.7, OH); 4.51 (2H, d, *J* = 5.7, $C\underline{H}_2OH$). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 168.0; 149.2; 142.1; 139.6; 136.5; 135.9; 128.7 (2C); 128.2; 127.9 (2C); 126.7; 124.4; 123.9; 119.5; 117.6; 58.5; 52.9; 51.1. Found, *m*/*z*: 448.0385 $[M+Na]^+$. $C_{19}H_{16}BrN_5NaO_2$. Calculated, *m*/*z*: 448.0380.

1-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-6-bromo-3-(2-hydroxyethyl)cinnolin-4(1*H*)-one (9c). Yield 0.093 g (94%), beige powder. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 8.20 (1H, s, H Ar); 8.16 (1H, d, *J* = 1.9, H Ar); 7.97–7.82 (2H, m, H Ar, H triazole); 7.45–7.20 (5H, m, H Ar); 5.72 (2H, s, CH_2); 5.55 (2H, s, CH_2); 4.62 (1H, t, *J* = 5.7, OH); 3.73 (2H, dd, *J* = 12.7, *J* = 6.7, $CH_2C\underline{H}_2OH$); 2.87 (2H, t, *J* = 6.9, $C\underline{H}_2CH_2OH$). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 168.3; 148.6; 142.1; 139.4; 136.3; 135.9; 128.7 (2C); 128.1; 127.9 (2C); 126.8; 123.9; 123.6; 119.2; 117.2; 58.6; 52.8; 50.8; 33.7. Found, *m*/*z*: 462.0541 $[M+Na]^+$. $C_{20}H_{18}BrN_5NaO_2$. Calculated, *m*/*z*: 462.0537.

Preparation of the heteroleptic complex [(IMes)CuI]. A solution of NaI (60 mg, 0.4 mmol) in Me_2CO (4 ml) was vigorously stirred while adding a suspension of [(IMes)CuCl] complex (80 mg, 0.2 mmol) in Me_2CO (2 ml). The mixture was stirred at room temperature under argon atmosphere for 1 h (Me_2CO was degassed prior to use). Then Me_2CO was removed by evaporation at reduced pressure, the residue was treated by adding anhydrous CH_2Cl_2 (5 ml), filtered, and the filtrate was evaporated at reduced pressure. The obtained residue was treated with pentane, resulting in a precipitate. The precipitate was separated by decantation and dried at reduced pressure. Yield 160 mg (81%), white powder representing a mixture of [(IMes)CuI] and $[(IMes)_2Cu]CuI_2$. Spectral characteristics are reported for the major component [(IMes)CuI]. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.05 (2H, s, H imidazole); 7.00 (4H, s, H Ar); 2.35 (6H, s, 4-CH_3); 2.12 (12H, s, 2,6-CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 139.5; 135.1; 134.7; 129.5; 122.3; 21.2; 17.9; the carbene carbon atom was not observed.

X-ray structural analysis of the $[(IMes)_2Cu]CuI_2$ complex was performed on a SuperNova (Oxford Diffraction) monocrystal diffractometer with an Atlas two-dimensional CCD detector, microfocus CuKα radiation source (wavelength 1.54184 Å), and a Cryostream crystal thermostat system (Oxford Cryosystems) set at 100 K. The primary processing of experimental data was performed with the CrysAlisPro software suite (Agilent Technologies). A correction for absorption was introduced using the SCALE3 ABSPACK algorithm, integrated in the CrysAlisPro software suite. The crystal structures were solved and refined with the Olex2 program[49] within the SHELX software suite.[50] The crystal had a rhombic syngony, space group *Aea*2, unit cell parameters: *a* 16.669(1), *b* 16.508(1), *c* 15.339(1) Å. The structure was refined by 35447 reflections, including 4005 independent reflections, to R_1 0.024. The complete crystallographic dataset for $[(IMes)_2Cu]CuI_2$ complex was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 2001172).

Supplementary information file containing ^{1}H and ^{13}C NMR spectra of compounds **2**, **5b**,**c**, **7a**,**b**, **8a**–**c**, **9a**–**c**, [(IMes)CuI]], as well as IR spectrum of compound **8b**, is available at the journal website at http://link.springer.com/journal/10593.

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