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Medium Rings Bearing Bitriazolyls (MRBTs): Easily Accessible Structures with Superior Performance as Cu-catalyst Ligands

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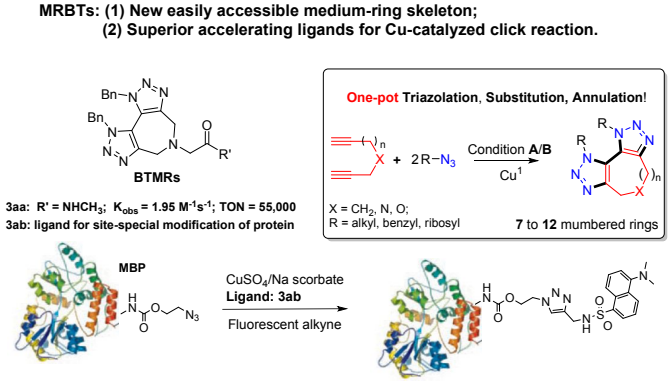


Abstract: Benefiting from their unique properties, developments of structurally novel and easily accessible medium rings are of significant interest in pharmaceutical industry and academic research. However, synthetic access of medium-ring scaffolds is very difficult due to their rigid skeleton and large-angle strains. In this paper, a new class of medium rings bearing bitriazolyls (MRBTs) was designed, synthesized and identified as a promising new-skeleton ligand for Cu(I)-catalyzed click reaction and used in site-special modification of protein. One of MRBTs, **3aa**, exhibited as most as 55,000 turnover number (TON) and dramatically accelerating effects (k_{obs} = 1.95 $M^{-1}s^{-1}$) and ranked among the most efficient CuAAC ligands. Unlike the difficult access to other known medium rings, these 7- to 12-membered MRBTs can be prepared in one-step manner straightforward from structurally diverse linear terminal diynes and azides. The unique

accessibility and intriguing properties therefore imply their broad application perspectives.

Introduction

Medium rings are a class of valuable structural motifs found in natural products and artificial functional materials.[1-4] The unique cyclic frames and conformational constraint provided by medium rings afford them highly attractive bioactivities and physical chemical properties.[2] Screenings based on medium-ring scaffolds have opened intriguing perspectives in the discovery of drug leading compounds, dyes and catalysis ligands.[3] However, synthetic access of medium-ring scaffolds is very difficult due to their rigid skeleton and large-angle strains.[5] Indeed, the scarcity of structural diverse medium rings has been considered one of the main reasons that limited their usages in both of commercial and academic researches. For example, medium rings (8 to 12-membered) are absent among the current top 200 brand-name drugs and top 200 generic drugs, even if their frequent occurrence in many important bioactive natural products.[6] Therefore, developments of easily accessible new- structure medium rings are of significant interest.

1,2,3-Triazole is an unnatural heteroaryl skeleton, which has been witnessed a successful utilization in a wide scope of chemistry and materials science in the past decades.[7,8] Linear or macrocyclic compounds bearing multi/bitriazolyls moieties have been prepared (Figure 1A).[9-12] However, there is little knowledge in the design and applications about medium rings bearing multi/bitriazolyls. Medium-ring skeletons have proved extremely useful to organize spatial presentations of structural moieties for the design of functionalized molecules.[13] On the other hand, synergistic effects provided by sequential assembly of multi/biheteroaryls can effectively enhance their binding affinities.[14] Therefore, equipment of medium rings with multi/bitriazolyls will be interesting to offer a new chemical space with promising functionalities (Figure 1B).

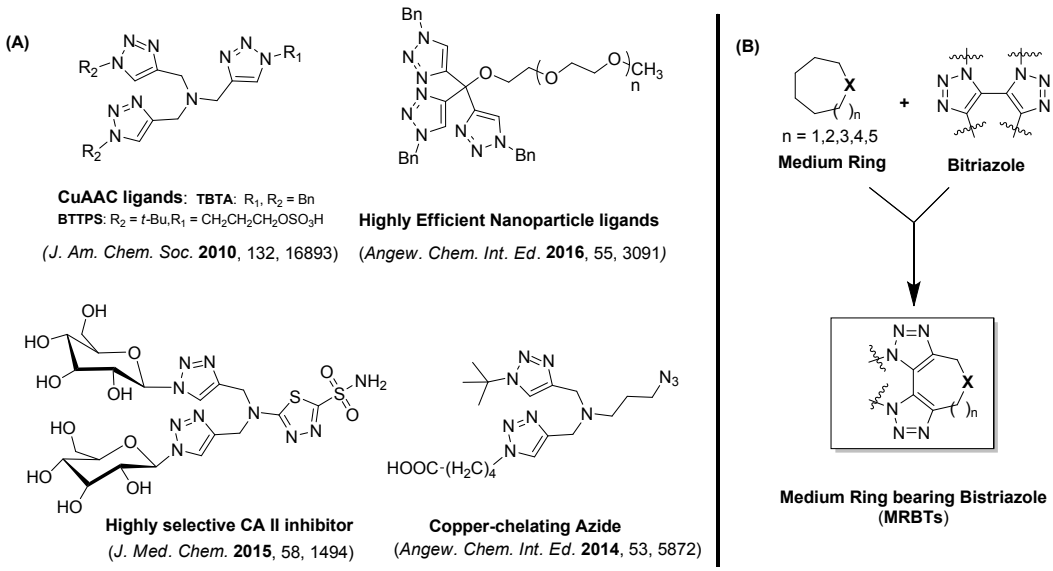


Figure 1 Design of MRBTs and multi/bitriazoles[9-12]

The synthesis of medium ring containing biaryls/biheteroaryls is a long-term challenging task in organic synthesis, which suffered from harsh reaction conditions, multi-step reactions and limited scope of substrates (Figure 2A).[15] Therefore, as the first part of this work, we focused on the development of a facile chemical synthesis of MRBTs. Through a design of *in situ* intramolecular oxidative coupling reaction, MRBTs can be prepared from simple diyne and azide. In contrast to known methods for the preparation of biaryl/biheteroaryl-containing medium rings that proceed through single sp^2 C-C bond-forming transformations, the presented approach involves one-step formation of four C-N bonds and one intramolecular sp^2 C-C bond, leading to the construction of the biheteroaryl core with substitution and annulation all being completed by one time (Figure 2B). This synthesis methodology presents a rare example for one-pot preparation of biaryl/biheteroaryl-containing medium rings direct from linear hydrocarbon.

Following the facile synthetic methodology of MRBTs, we identified 7-memebered MRBTs as the promising new-skeleton ligands for Cu(I)-catalyzed click reaction and in site-special modification of protein (Figure 2C). Through a brand-spectrum screening on the prepared 7-memberd MRBTs and the next structural optimizations, compound **3aa**

was exhibited as most as 55,000 turnover number (TON) and dramatically accelerating effects (k_{obs} = 1.95 $M^{-1}s^{-1}$), ranking among the most efficient CuAAC ligands.

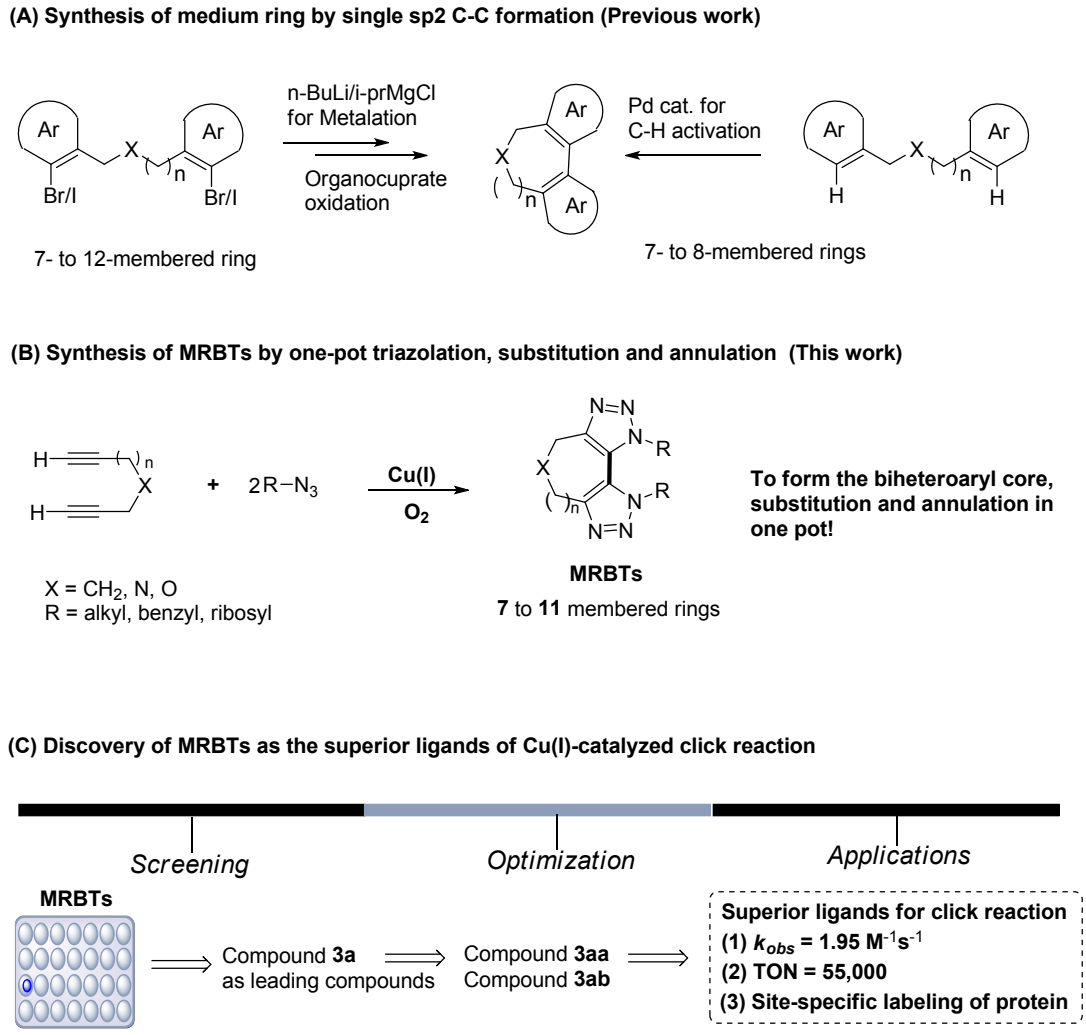


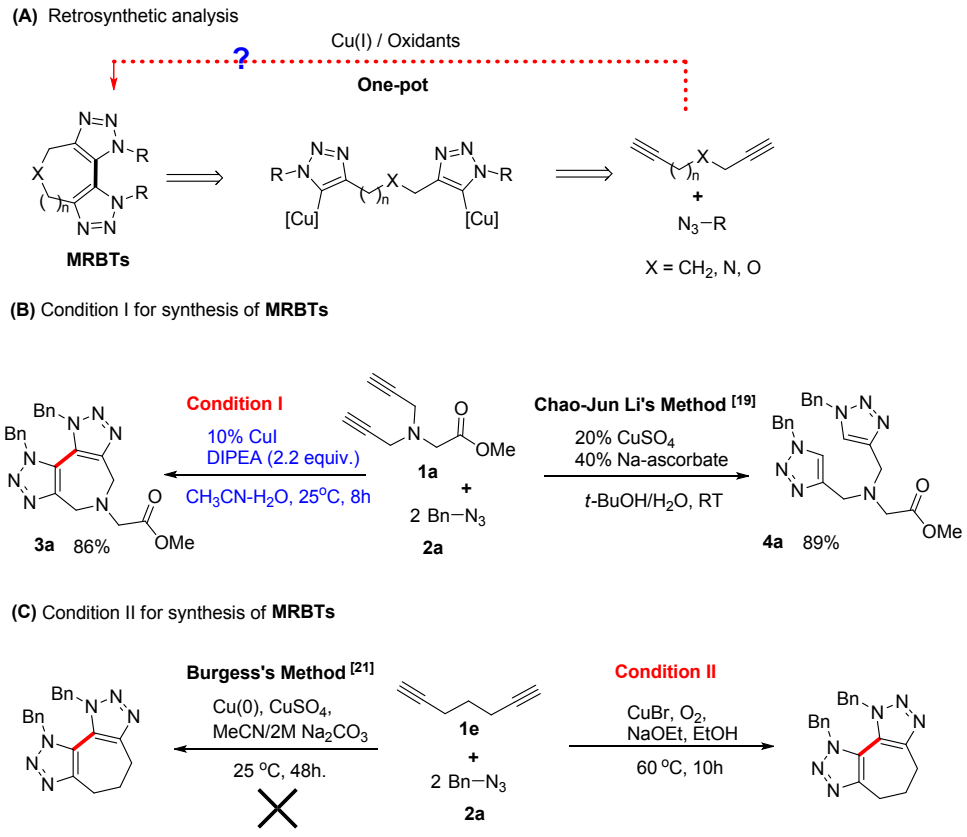
Figure 2 Synthesis and applications of MRBTs

Results and Discussion

Development of a facile synthesis of 7-membered MRBTs.

The structural rigidity imposed on medium rings prevents the use of many well-known biaryl-coupling protocols such as palladium-catalyzed Stille, Suzuki, or Negishi reactions for the construction of intramolecular sp^2 C-C bonds in medium rings.[5] Much efforts have

be made to develop effective methods for the construction of the internal sp^2 C-C bonds in medium rings, among which the strategy based on the organocuprate are used recently.[15] Construction of intramolecular sp2 C-C bonds via oxidation of organocuprate is effective to synthesize biaryl-containing medium rings, however, the preparation of organocuprates usually suffered from extreme reaction conditions and poor functional-group tolerances, which greatly limited the further use of this method in the structurally complicated compounds. Along with our efforts to develop new chemical transformations via copper triazolide intermediates that can be *in situ* prepared from alkyne and azide under very mild conditions,[16,17,18] we here attempted to utilize copper triazolide to realize the effective construction of intramolecular sp^2 C-C bond of MRBTs (Scheme 1A).



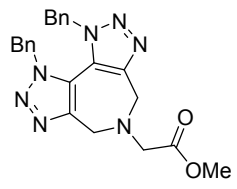
Scheme 1 Synthesis of MRBTs

Compound **1a** was taken as the donor of diyne to investigate our synthetic route of MRBTs (Scheme 1A). Chao-Jun Li group have reported the preparation of compound **1a** and its reaction with azide to give acyclic bistriazole product **4a** with 89% yield (Scheme 1B).[19] Herein, we are interested to explore a new reaction condition for promoting the reaction of **1a** to produce cyclic product **3a**, and then catalysts, solvents, bases were screened and optimized (Supplementary Table S1 in supporting information). We first found that product **3a** was obtained in 31% yield after a mixture of **1a**, **2a** (2.2 equiv), triethylamine (TEA; 2.2 equiv), and CuI (0.1 equiv) in THF was stirred at 25 °C under open air for 6 h. The reactivities of copper triazolide could be regulated by the oxidant systems, which led to different products through different reaction pathways.[20] We thus attempted to investigate roles of air as the oxidant in the cyclization reactions. After being conducted the reaction under nitrogen atmosphere, and the reaction only produced the acyclic bistriazole product **4a** (72% yield), and production of **3a** was completely inhibited. **4a** could not react itself to give **3a** in the presence of CuI and DIPEA under air. The result suggested that the sp^2 C-C bond between triazolyl moieties should form prior to protonation of copper triazolides under the current conditions. We then insert a pure oxygen atmosphere to cyclization reaction. As expected, a mixture of diyne **1a**, azide **2a**, TEA, and CuI in THF under oxygen gave **3a** in a better 71% yield. The type of copper(I) salt catalyst (10 mol %) affected the yield of **3a**, with CuCl giving a 51% yield; CuBr, 69%; Cu_2O, 41%; and CuI, 71%. Screening of solvents showed that the mixture of water and CH_3CN (v/v = 1:1) was the best solvents with a dramatically increasing of cyclic products. When a mixture of **1a** with CuI (0.1 equiv) as the catalyst, **2a** (2.2 equiv), and DIPEA (2.2 equiv) in CH_3CN-H_2O (v/v = 1:1) was stirred under oxygen at 25 °C for 12 h, **3a** was obtained in 86% isolated yield (Condition I in Scheme 1B).

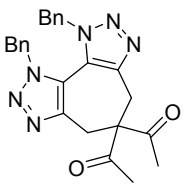
After successful preparation of **3a**, we attempted to apply condition I to other diynes. Unfortunately, no cyclic products could be obtained when 1,6-heptadiyne was used. We tried the conditions that Burgess's group reported for the preparation of linear bistriazoles

(Scheme 1C),[21] however the same results were given without any annulation products of 1,6-heptadiyne and total recovery of starting materials. In both of reaction condition I and Burgess's reaction condition, the diynes used as reactants were found to have heteroatoms (N or O) on the beta-position of alkynyl groups, which might be a reason to facilitate the construction of medium ring. While in the case of 1,6-heptadiyne without N or O on its beta-position, the formation of medium ring would be more difficult. We thus went back to optimize reaction conditions with 1,6-heptadiyne as the starting material. Reaction condition II shown in Scheme 1C was finally built as the optimal one, in which 1,6-heptadiyne reacted smoothly with azides to give target **3b** in the yield of 76% after 10 hours at 60°C with CuBr as the catalyst in the presence of oxygen.

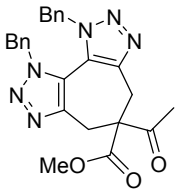
Table 1 Synthesis of seven-membered MRBTs[a,b,]



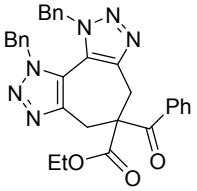
3a (86%)



3b (82%)

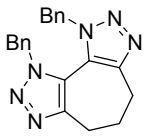


3c (88%)

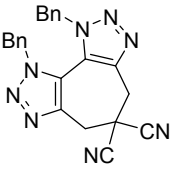


3d (80%)

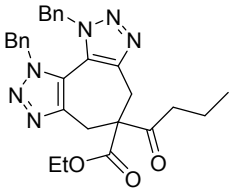
3e (77%)



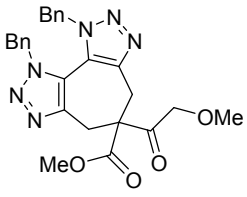
3f (76%)[c]



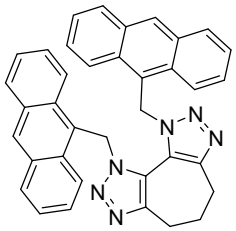
3g (71%)



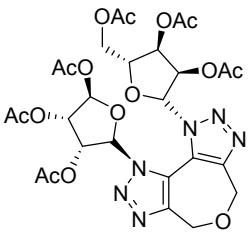
3h (78%)



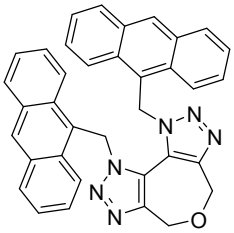
3i (88%)



3j (64%)[c]



3k (55%)



3l (68%)

[a] Reaction Conditions: diyne (0.15 mmol), benzyl azide (0.32 mmol), CuI (0.015 mmol), oxygen balloon and DIPEA (0.3 mmol) were stirred in CH_3CN-H_2O (v/v = 1:1) (3 mL) at room temperature for 12 h. [b] Isolated yield. [c] Reaction Conditions: diyne (0.15 mmol),

benzyl azide (0.32 mmol), CuBr (0.015 mmol), oxygen balloon and NaOEt (0.3 mmol) were stirred in ethanol (3 mL) at 60 °C for 10 h.

Differing from the intermolecular oxidative couplings of copper triazolide, the *intramolecular* cyclizations in medium-ring might be highly unpredictable because medium rings suffer from extra transannular steric interactions that are not present in smaller and larger rings. Furthermore, the cyclization procedures are usually subject to unfavorable entropic effects and enthalpic effects. Additionally, there are two possible competing reactions of the *intramolecular* cyclizations, protonation of copper triazolide and the linear self-couplings during the cyclization reaction. Condition I and II therefore supplied an efficient and concise way to realize *intramolecular* oxidative cyclizations on copper triazolide.

With condition I and II in hand, we then investigated the synthesis of diverse seven-membered MRBTs from different diynes and azides. As shown in Table 1, dialkynyl amines, dialkynyl ethers, and dialkynyl dicarbonyl compounds afforded the corresponding bistriazolyl rings in good to excellent yields (**3a**–**3i**). Various functionalities such as carbonyl, ester, ether, and cyano groups remained intact under the reaction conditions. Anthracenylmethyl azides reacted smoothly with diynes to generate medium rings **3j** and **3l**, in 64% and 68% yields. It is particularly worth noting that a delicate ribosyl azide could also be an effective substrate for the reaction, affording the corresponding seven-membered rings in a moderate yield (Table 1, **3k**).

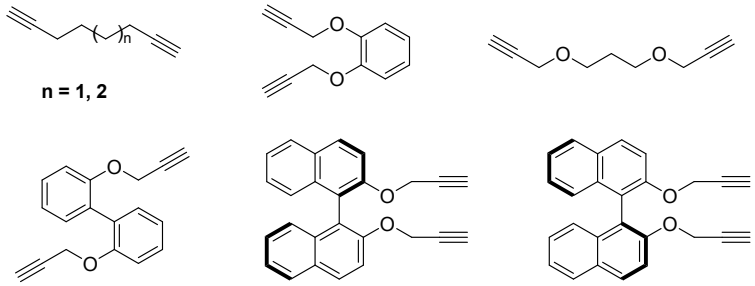
Preparation of 8- to 12-membered MRBTs

Different sizes of medium rings offer different properties, but they often require different synthetic methods.[22] After the facile synthesis and successful applications of our method in 7-membered MRBTs, we turned our attention to developing a general method for preparations of MRBTs with different ring sizes. Eight-membered rings are usually the most difficult medium rings to form, because of energetically unfavorable transannular

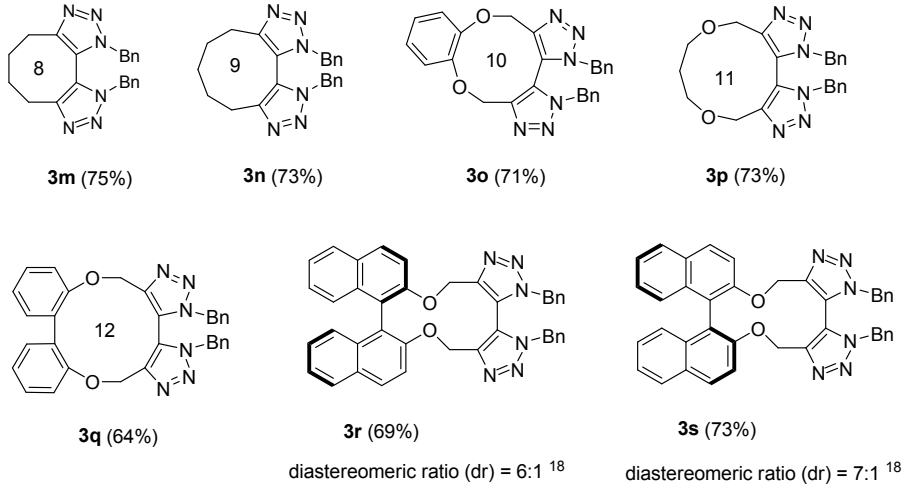
and torsional strain effects in ring-closing reactions.[23] Thus, we tested our method for the preparation of 8-membered rings as shown in Table 2. The reaction of 1,7-octydiyne with benzyl azide proceeded smoothly in the presence of CuBr (0.1 equiv), and NaOEt (2.2 equiv) in ethanol at 60 °C for 10 h, to form eight-membered ring **3m** in 67% yield. Then, the syntheses of MRBTs with 9-membered, 10-membered, 11-membered and 12-membered rings were investigated. The nine-membered carbocycle **3n** was obtained from 1,8-nonadiyne and benzyl azide in 73% yield. Furthermore, 10-, 11-, and 12-membered rings (Table 2, **3o**, **3p**, and **3q**) were synthesized in good yields from the corresponding diynes [1,2-bis(prop-2-yn-1-yloxy) benzene **1l**, 1,3-bis(prop-2-yn-1-yloxy)propane **1p**, and 2,2'-bis(prop-2-yn-1-yloxy)-1,1'-biphenyl **1m**] and benzyl azide. Additionally, the chiral diynes (*R*)-**1n** and (*S*)-**1o**, which were prepared from (*R*)- and (*S*)-binaphthol, respectively, were used as substrates for the synthesis of 12-membered medium rings. Compounds **3r** and **3s** were obtained in yields of 86% and 83%, respectively, from benzyl azide (2.2 equiv), CuI (0.1 equiv), and NaOEt (2.2 equiv) at 60 °C in ethanol for 10 h, with moderate diastereomeric ratios, i.e., 6:1 for **3r** and 7:1 for **3s**.

Table 2 Synthesis of 8 to 11-membered MRBTs[a,b]

The dynes for the synthesis of 8- to 12-membered rings:



8- to 12-Membered MRBTs:



3m (75%) **3n** (73%) **3o** (71%) **3p** (73%)

3q (64%)

3r (69%)

diastereomeric ratio (dr) = 6:1 [18]

3s (73%)

diastereomeric ratio (dr) = 7:1 [18]

[a] Isolated yield. [b]Diyne (0.15 mmol), benzyl azide (0.32 mmol), CuBr (0.015 mmol), oxygen balloon and NaOEt (0.33 mmol) were stirred in ethanol (3 mL) at 60 °C for 10 h.

Identification of MRBTs as the ligands for copper-catalyzed click reaction

An important point of the researches in medium rings is to utilize their unique chemical spaces to discover new functional molecules.[1,3] As a class of remarkable compounds, ligands of copper-catalyzed alkyne and azide cycloaddition (CuAAC) reaction have been shown to improve the biocompatibility of CuAAC reaction[9] as well as enhance the reaction rate,[24] drawing great attention from materials science to biomedical research.[25] Using fluorescent click reaction (Figure 3A) reported by Wang and coworkers,[26] we could investigate the catalytic performances of 7-membered MRBTs. The copper residues of 7-membered MRBTs listed in Table 1 were confirmed by atomic absorption

spectrometer less than 0.5 ppm, and then the compounds were directly used to screen as ligands of CuAAC. Compound **3a** was found to greatly accelerate fluorescent click reaction. In the skeleton of **3a**, two triazolyl moieties and nitrogen atom in the ring might play binding groups to Cu(I), and the ester group outside the ring offered an additional modification site which could be modified readily (Figure 3B). Surprisingly, compound **3aa** obtained by transferring methyl ester of **3a** to methanamide indicated a dramatically increase of catalytic activities. The k_{obs} values was measured and calculated based on reported methods.[9] The k_{obs} of **3aa** was 1.95 $M^{-1}s^{-1}$, which is 5.6 times that of BTTPS[9a] (0.35 $M^{-1}s^{-1}$), one of the best Cu(I) ligands for CuAAC reported to date (Figure 3C, Supplementary Figure S4 and Supplementary Table S5 in the supporting information). This ligand is also 12.5-fold more efficient than the classical TBTA[27] ligand. When increasing the concentration of propargyl alcohol to 300 μM under the same reaction conditions, quantitative conversion was achieved within 5 min by using **3aa** as the ligand (Figure 3D). The catalyst loading and efficiency was then investigated as shown in Table 3. 98% yield was obtained with 0.01 mol % Cu(I) under aqueous conditions (Entry 3 in Table 3). A 55,000 turnover number (TON) was achieved under solvent-free conditions with 10 mmol benzyl azide, 10 mmol ethynylbenzene and 0.001 mol % Cu(I) at room temperature (Entry 5 in Table 3), which makes **3aa** one of the most efficient ligands for copper-catalyzed click reaction (Supplementary Table S6 in the supporting information).

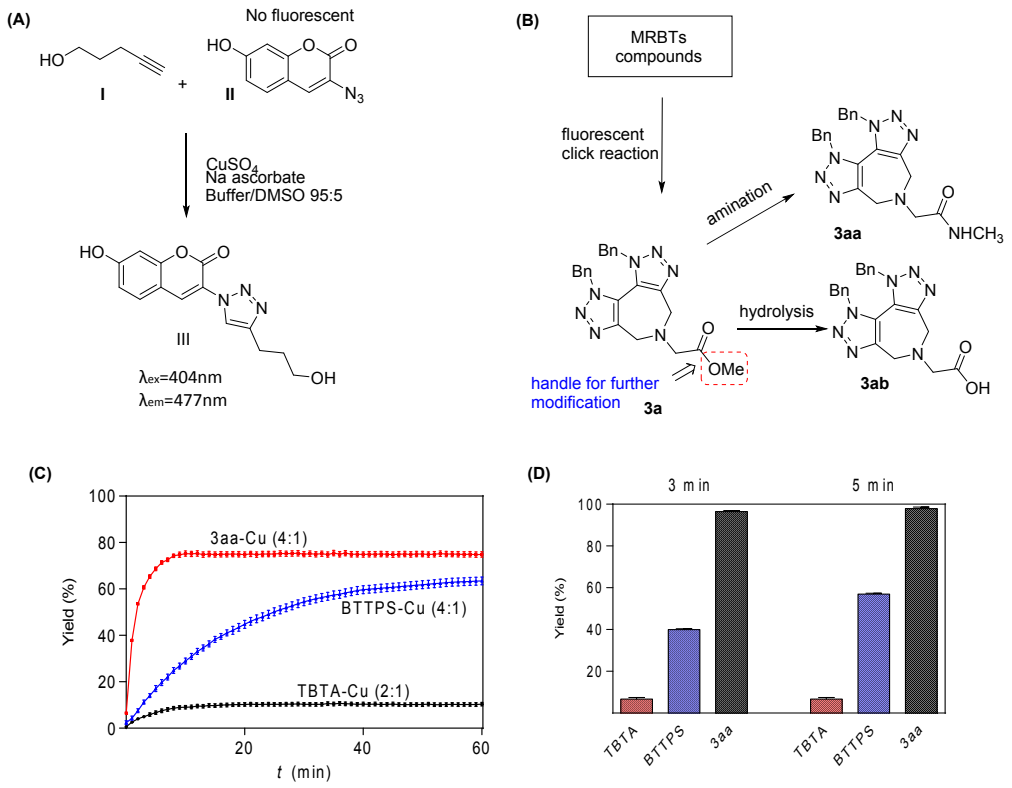
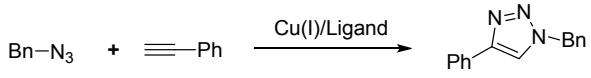


Figure 3 (A) Fluorescent CuAAC reaction; (B) Screening and structural optimization of MRBTs as the ligands of copper-catalyzed click reaction. (C) Kinetics with **3aa**, **BTTPS** and **TBTA** respectively as ligands of copper-catalyzed click reaction. (D) A comparison of the efficiency of the three ligands within 3min and 5min. The reaction conditions: propargyl alcohol (50 μM for C, 300 μM for D), 3-azido-7-hydroxy-coumarin (100 μM), $CuSO_4$ (75 μM), 0.1 M PBS buffer/DMSO (95:5), sodium ascorbate (2.5 mM); **3aa**-Cu (4:1), **BTTPS**-Cu (4:1), **TBTA**-Cu (2:1).

Table 3 Test of catalyst loading of **3aa** (4:1 ratio to Cu) for the reaction of phenylacetylene (0.75 M) with benzyl azide (0.75 M), 3:1 MeOH/water, sodium ascorbate (30 mM), 24°C.

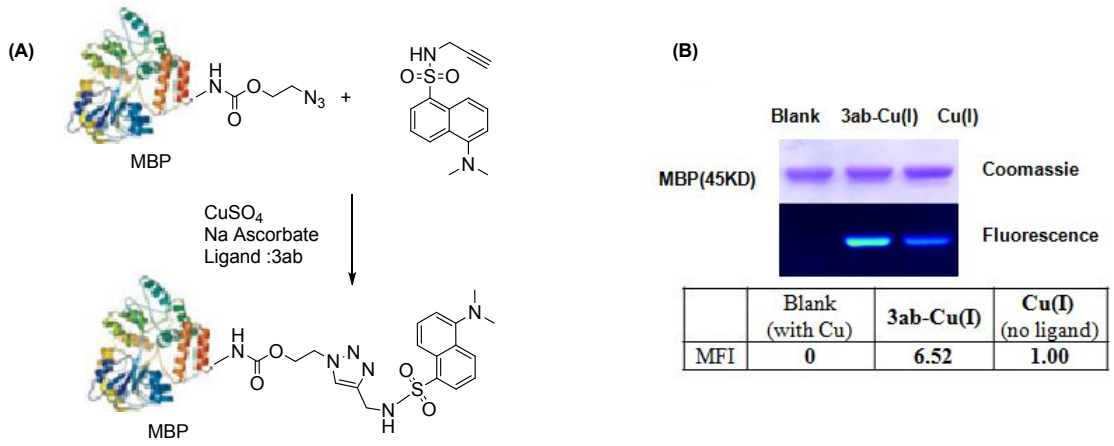


Entry	Cu source	Mol% Cu	Time (h)	Yield[a]	TON
1	$CuSO_4$/ascorbate	1	0.1	99	99
2	$CuSO_4$/ascorbate	0.1	0.4	98	980
3	$CuSO_4$/ascorbate	0.01	16	95	950
4	$CuSO_4$/ascorbate	0.005	54	60	12000

5[b]	CuBr	0.001	24	55	55000
6	--/ascorbate	--	72	<5%	--

[a] Isolated yields. [b] Solvent-free without ascorbate.

After transferring methyl ester to carboxyl group, a more hydrophilic derivative **3ab** could be obtained (Figure 3B), which was then chosen to apply in the bioconjugation of protein. Site-specific inserts of unnatural amino acid (UAA) into proteins have provided a potent tool for the multi-purpose modifications of protein.[28] The use of BTMR ligand in the bioconjugation of protein was explored in this paper, using azide bearing maltose binding protein (MBP-N167-N_3, 45 KDa) (Figure 4A).[29] A total of 100 μL of MBP-N167-N_3 (50 μM) in phosphate buffered saline (PBS) buffer was reacted with 2.0 equivalents of fluorescent alkyne at room temperature for 80 min in the presence of $CuSO_4$ (50 μM), Ligand **3ab** (300 μM), and sodium ascorbate (2.0 mM). The reaction was terminated by the addition of 4 μL ethylenediaminetetraacetic acid (500 mM). The samples were analyzed by SDS-PAGE (12% gel) using fluorescent imaging before Coomassie blue staining. MBP-N167-N_3 was labeled by fluorescent alkyne with **3ab**/Cu(I) as the ligand. The yield of **3ab**-Cu(I) was at least 6-fold higher than that achieved by using the uncoordinated Cu(I) (Figure 4B). Besides, the best ratio of **3ab**/Cu(I) is 6:1 (Supplementary Figure S6 in the supporting information), with a low copper loading preferable for bioconjugation.[30]



	Blank (with Cu)	3ab-Cu(I)	Cu(I) (no ligand)
MFI	0	6.52	1.00

Figure 4. (A) Compound **3ab** as the ligand for site-specific fluorescent labeling of MBP. (B) Images of fluorescent labeling of MBP without Cu (right), with **3ab**-complexed Cu(I) (middle) and with Cu(I) in the absence of ligand (left). MFI, means fluorescence intensity.

Conclusion

In summary, we have reported a novel class of medium rings MRBTs in this paper. Altering from the complex preparative procedures for medium rings, the synthesis of MRBTs were designed to complete by a concise one-pot aerobic oxidative coupling directly from linear diynes and azides. Merits of this method include step- and atom-economy, readily available starting materials, the use of oxygen as a clean oxidant, and the use of only catalytic amounts of Cu(I) salt. In addition, this synthetic methodology could be applied in preparations of 8- to 12-membered medium rings that were not readily available through classical methods.

We then identified one of 7-memebered MRBTs **3a** as the new leading compound for the design of CuAAC ligands by screening, and the following two superior MRBTs **3aa** and **3ab** could be obtained through facile structural modifications. **3aa** and **3ab** demonstrated a higher reaction rate and catalysis efficiency than the well-known BTTPS ligand, and also indicated a low catalyst loading and desirable utility in bioconjugation of the protein. The superior performances of MRBTs as the copper-catalyzed click reaction illustrate the

great practical value of this new medium-ring skeleton, and the further the applications of MRBTs in the design of drug candidates and biomaterials are still undergoing in our lab.

Experimental Section

Materials and Methods. All reactions were run with anhydrous solvents unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium and benzophenone immediately before use. CH_3CN were distilled from CaH_2. Anhydrous dimethylformamide (DMF) was purchased from Aldrich and used as received. MeOH and EtOH were distilled from Mg turnings and iodine immediately before use. Reactions were monitored by thin-layer chromatography (TLC) on silica gel GF254-precoated plates. Compounds were detected under UV light/or visualized by phosphomolybdic acid in ethanol solution. Solvents were evaporated under reduced pressure and below 50 °C (water bath). Mass spectra were obtained on Bruker APEX. High-resolution MS were performed with Bruker BIFLEX III and Bruker Daltonics. Inc. APEX II. ^{1}H NMR and ^{13}C NMR data were recorded with an Avance 400/DPX (Bruker) spectrometer in $CDCl_3$ solutions using the residual solvent signal or TMS as reference. Chemical shifts are reported in parts per million and coupling constants quoted in Hz. Fluorescence spectra were performed on a Cary Eclipse fluorescence spectrophotometer (Varian, America). Intensity data for compound **3d** and **3p** were collected on a Bruker SMART6000 CCD diffractometer.

1,6-heptadiyne(**1e**), Propargyl ether(**1f**), 1,7-octydiyne(**lj**) and 1,8-nonadiyne (**1k**) were purchased from Alfa Aesar China Co. Ltd. (Tianjin) and used as received. Organic azides were prepared based on our previous works or the methods in literature.[18, 31]

General procedure for diyne (1a)

1a was synthesis from methyl 2-(bis(3-(trimethylsilyl)prop-2-yn-1-yl)amino)acetate.[19] Tetrabutylammonium fluoride (507 mg, 1.6 mmol, 2.5 equiv.) was added to methy1 2-(bis(3-trimethylsilyl)prop-2-yn-yl)amino) acetate (200 mg, 0.65 mmol) dissolved in

5mL dry THF. The mixture was reacted with vigorous stirring under room temperature. Upon completion of the reaction (TLC), the mixture was concentrated. The crude mixture was purified by silica gel column chromatography using petroleum ether/ethyl acetate as eluent to give **1a** as a colorless oil (94 mg, 88%).

General procedure for diynes (1b, 1c, 1d, 1g, 1h, 1i)

Potassium carbonate (2.5 equiv.) and tetrabutylammonium iodide (0.1 equiv.) were added to a stirred mixture of 1,3-dicarbonyl compounds/malononitrile (1.0 equiv.) and 3-bromopropyne (2.0 equiv.) dissolved in dry DMF. The mixture was reacted with vigorous stirring at room temperature overnight. Upon completion of the reaction (TLC), the mixture was concentrated. Upon completion of the reaction (TLC), the reaction was diluted with water and extracted with ethyl acetate. The organic fractions were combined, dry over Na_2SO_4, evaporated under reduced pressure. The crude mixture was purified by alumina column chromatography using petroleum ether/ethyl acetate as eluent to give pure products.[32]

General procedure for diynes (1l, 1n, 1o, 1p)

Potassium carbonate (2.5 equiv.) was added to a stirred mixture of diphenol (1 equiv.) and 3-bromopropyne (2 equiv.) dissolved in dry acetone, then the mixture was heated to reflux for 16 hours. Upon completion of the reaction (TLC), the mixture was concentrated. The crude mixture was purified by silica gel column chromatography using petroleum ether/ethyl acetate as eluent to give pure products.[33]

Synthesis of diyne (1m)

NaH (2.5 equiv.) was added to a stirred mixture of 1,3-propylenediol (1 equiv.) and 3-bromopropyne (2 equiv.) dissolved in dry THF, then the mixture was stirred for 24 hours at room temperature. Upon completion of the reaction (TLC), the mixture was concentrated. The crude mixture was purified by silica gel column chromatography using petroleum ether/ethyl acetate as eluent to give pure products.[34]

General procedure for MBTRs (3a-3e, 3g-3i, 3k-3l).

The reaction flask was evacuated three times and then filled with oxygen from oxygen balloon. Under oxygen atmosphere, di-alkynyl ether/di-alkynyl dicarbonyl compounds (0.15 mmol), azides (0.32 mmol, 2.1 equiv.), copper(I) iodide (0.015 mmol, 0.1 equiv.) and N,N-diisoproplyethylamine (DIPEA) (0.3 mmol, 1.2 equiv.) were added into 5 mL dry acetonitrile. The reaction was allowed to stir at room temperature for 12 hours. Upon completion of the reaction (TLC), reaction solvent was evaporated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate. The organic fractions were combined, dry over Na_2SO_4, evaporated under reduced pressure. The crude mixture was purified by silica gel column chromatography using petroleum ether/ethyl acetate as eluent to give target compound.

General procedure for MRBTs (3f, 3j, 3m-3s).

The reaction flask was evacuated three times and then filled with oxygen from oxygen balloon. Under oxygen atmosphere, azides (0.32 mmol, 2.1 equiv.), di-alkynyl ether and di-alkynyl dicarbonyl compounds (0.15 mmol), copper(I) bromide (0.015 mmol, 0.1 equiv.) and NaOEt (0.33 mmol, 2.2 equiv.) were added to dry ethanol. The reaction was heated to 60 ^oC for 10 hours. Upon completion of the reaction (TLC), reaction solvent was evaporated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate. The organic fractions were combined, dry over Na_2SO_4, evaporated under reduced pressure. The crude mixture was purified by silica gel column chromatography using petroleum ether/ethyl acetate as eluent to give target compound.

Synthesis of MRBT 3aa

Compound **3a** 2-(1,9-dibenzyl-1H-bis([1,2,3]triazolo)[4,5-c:4',5'-e]azepin-5(4H, 6H, 9H)-yl)-N-methylacetamide (215 mg, 0.5 mmol) was dissolved in 3 mL of solvent of THF/MeOH/H_2O (v/v/v = 1:1:2). After LiOH (42 mg, 1.0 mmol) was added, the reaction mixture was stirred at room temperature for 1 hour. After volatiles were removed in vacuum, the residue was purified by silica gel column chromatography using

CH_2Cl_2/MeOH as eluent to pure product **3aa** (182 mg, 87% yield).

Synthesis of MRBT 3ab

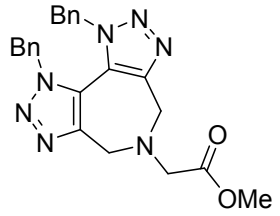
Compound **3a** (215 mg, 0.5 mmol) was dissolved in 3 mL of $MeNH_2$ (33 wt.% in absolute ethanol) and stirring at room temperature for 2 hours. After volatiles were removed in vacuum, the residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate as eluent to pure product **3ab** (200 mg, 93% yield).

X-ray crystallography.

(a) Method. Single crystals of compound **3d** and **3p** suitable for X-ray diffraction analysis were obtained from slow solvent evaporationin in petroleum ether/CH_2Cl_2 solutions at room temperature. No solvent of crystallization was present in the lattice for any of the structures. (b) Crystal parameters. **3d:** $C_{31}H_{28}N_6O_3$; colorless, block; 0.16×0.08×0.03mm; monoclinic, $P2_1/c$; a = 12.6636(2), B = 12.6670(2) and C = 17.6579(3) Å; $\alpha = 90$, $\beta = 109.067(2)$, and $\gamma = 90°$; V = 2677.10(8) $Å^3$; Z = 4; T = 170K; ρ_{calc} = 1.321 g/cm^3; Final R indexes [I> =2σ (I)], R_1 = 0.0562, wR_2 = 0.1742; Final R indexes [all data], R_1 = 0.0841, wR_2 = 0.1789; CCDC no: 1871589. **3p**: $C_{23}H_{24}N_6O_2$; colorless, needle ; 0.28×0.06×0.04 mm; triclinic, P-1; a = 8.2396(2), B = 11.5901(5),and C = 17.6579(3) Å; $\alpha = 107.523(4)$, $\beta = 104.775(3)$, and $\gamma = 90.140(3)°$; V = 1077.91(8) $Å^3$; Z = 2; T = 293K; ρ_{calc} = 1.283; Final R indexes [I> =2σ (I)], R_1 = 0.0549, wR_2 = 0.1661; Final R indexes [all data], R_1 = 0.0738, wR_2 = 0.1740; CCDC no: 1871590. Intensity data for compound **3d** and **3p** were collected on a Bruker SMART6000 CCD diffractometer using mirror-monochromated Cu Kα radiation (λ = 1.54184 Å) at 170K(for **3d**) and 293 K(for **3p**). The frames were integrated with the Bruker APEX2 software package using a narrow-frame algorithm. The data were corrected for decay, Lorentz, and polarization effects as well as absorption and beam corrections based on the multi-scan technique. The structures were solved by a combination of direct methods in SHELXTL and the difference Fourier technique and refined by full-matrix leastsquares procedures.

Characterization of compounds 3a-3l

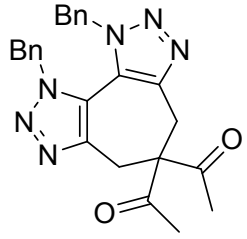
*2-(1,9-Dibenzyl-1H-bis([1,2,3]triazolo)[4,5-c:4',5'-e]azepin-5(4H,6H,9H)-yl)-N-methylacetamide (**3a**)*



3a

The title compound was synthesized according to the general procedure, and isolated as a pale-yellow solid (eluent PE : EtOAc = 1:2 , Rf = 0.3, 55.4 mg, 86% yield). M.p.: 52-53 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.27 (m, 6H), 6.81 – 6.79 (m, 4H), 5.56 (s, 4H), 4.23 (s, 4H), 3.74 (s, 3H), 3.36 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 147.0, 134.1, 129.2, 128.7, 126.2, 123.4, 56.6, 53.4, 52.0, 50.7. HRMS (ESI) *m/z* calculate for ($M+H^+$) $C_{23}H_{24}N_7O_2^+$ 430.1986, Found: 430.1977.

*1,1'-(1,9-Dibenzyl-4,5,6,9-tetrahydro-1H-cyclohepta[1,2-d:3,4-d']bis([1,2,3]triazole)-5,5-diyl)diethanone (**3b**)*

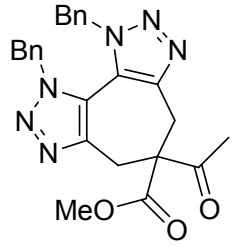


3b

The title compound was synthesized according to the general procedure, and isolated as a pale-yellow solid (General procedure A: eluent PE : EtOAc = 1:1 , Rf = 0.4, 54.2 mg, 82% yield). M.p.: 35-36 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.25 (m, 6H), 6.77 – 6.75 (m, 4H), 5.51 (s, 4H), 3.38 (s, 4H), 2.21 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ

203.3, 145.4, 133.9, 129.1, 128.7, 126.3, 123.3, 74.7, 53.4, 27.7, 26.6. HRMS (ESI) *m/z* calculate for (M+H$^+$) $C_{25}H_{25}N_6O_2^+$ 441.2034, Found: 441.2038.

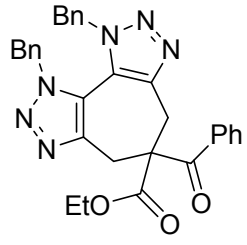
*Methyl 5-acetyl-1,9-dibenzyl-4,5,6,9-tetrahydro-1H-cyclohepta[1,2-d:3,4-d']bis ([1, 2,3]triazole)-5-carboxylate (**3c**)*



3c

The title compound was isolated as a pale-yellow solid (eluent PE:EtOAc = 1:1 , Rf = 0.5, 60.2 mg, 88% yield). M.p.: 34-35 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 –7.25 (m, 6H), 6.80 – 6.77 (m, 4H), 5.51 (s, 4H), 3.74 (s, 3H), 3.37 (s, 4H), 2.23 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 171.3, 145.3, 133.8, 129.1, 128.9, 128.6, 126.3, 123.3, 67.3, 53.4, 53.3, 28.7, 26.0. HRMS (ESI) *m/z* calculate for (M+H$^+$) $C_{26}H_{27}N_6O_3^+$ 471.2139, Found: 471.2164.

*Ethyl 5-benzoyl-1,9-dibenzyl-4,5,6,9-tetrahydro-1H-cyclohepta[1,2-d:3,4-d']bis ([1,2,3]triazole)-5-carboxylate (**3d**)*

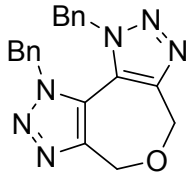


3d

The title compound was synthesized according to the general procedure, and isolated as a white solid (eluent PE : EtOAc = 2:1 , Rf = 0.2, 63.8 mg, 80% yield). M.p.: 148- 149 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.80 (m, 2H), 7.58 – 7.54 (m, 1H), 7.46 – 7.42 (m,

2H), 7.28 – 7.24 (m, 6H), 6.82 – 6.79 (m, 4H), 5.58 – 5.49 (m, 4H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.66 (d, *J* = 15.8 Hz, 2H), 3.46 (d, *J* = 15.8 Hz, 2H), 1.08 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 172.3, 145.6, 134.3, 133.9, 133.4, 129.1, 128.9, 128.8, 128.6, 126.3, 123.3, 65.2, 62.6, 53.4, 30.6, 13.8. HRMS (ESI) *m/z* calculate for ($M+H^+$) $C_{31}H_{29}N_6O_3^+$ 533.2296, Found:533.2308.

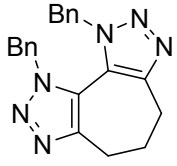
*1,9-Dibenzyl-1,4,6,9-tetrahydrooxepino[3,4-d:5,6-d']bis([1,2,3]triazole) (**3e**)*



3e

The title compound was synthesized according to the general procedure, and isolated as a White solid (eluent PE : EtOAc = 2:1 , Rf = 0.2, 41.4 mg, 77% yield). M. p.: 149- 150 ^{o}C.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 6H), 6.81 – 6.79 (m, 4H), 5.58 (s, 4H), 4.98 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 134.0, 129.2, 128.8, 126.2, 123.4, 65.5, 53.4. HRMS (ESI) *m/z* calculate for ($M+H^+$) $C_{20}H_{19}N_6O^+$ 359.1615 Found: 359.1626.

*1,9-Dibenzyl-4,5,6,9-tetrahydro-1H-cyclohepta[1,2-d:3,4-d']bis([1,2,3]triazole) (**3f**)*

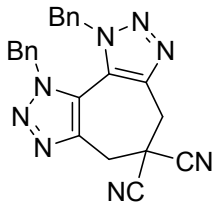


3f

The title compound was synthesized according to the general procedure, and isolated as a yellow solid (eluent PE : EtOAc = 1:1, Rf = 0.5, 40.6 mg, 76% yield). M.p.: 179- 180 ^{o}C.^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 – 7.23 (m, 6H), 6.82 – 6.81 (m, 4H), 5.51 (s, 4H), 2.87 (t, *J* = 6.8 Hz, 4H), 2.21 – 2.16 (m, 2 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.4,

134.3, 129.1, 128.6, 126.4, 123.2, 53.2, 28.2, 23.8. HRMS (ESI) *m/z* calculate for ($M+H^+$) $C_{21}H_{21}N_6^+$ 357.1822, Found: 357.1853. 1

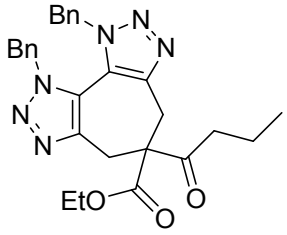
*1,9-Dibenzyl-6,9-dihydro-1H-cyclohepta[1,2-d:3,4-d']bis([1,2,3]triazole)-5,5(4H)-dicarbonitrile (**3g**)*



3g

The title compound was synthesized according to the general procedure, and isolated as a White solid (eluent PE : EtOAc = 2:1, Rf = 0.3, 43.3 mg, 71% yield). M.p.: 75- 76 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 6H), 6.84 – 6.82 (m, 4H), 5.59 (s, 4H), 3.51 (s, 4H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.9, 133.3, 129.4, 129.2, 126.5, 123.8, 114.7, 53.9, 37.4, 33.8. HRMS (ESI) *m/z* calculate for ($M+H^+$) $C_{23}H_{19}N_8^+$ 407.1727, Found: 407.1731.

*Ethyl 1,9-dibenzyl-5-butyryl-4,5,6,9-tetrahydro-1H-cyclohepta[1,2-d:3,4-d']bis([1,2,3]triazole)-5-carboxylate (**3h**)*

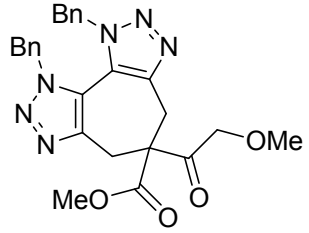


3h

The title compound was synthesized according to the general procedure, and isolated as a White solid (eluent PE : EtOAc = 2:1, Rf = 0.4, 58.3 mg, 78% yield). M.p.: 120- 121 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.25 (m, 6H), 6.79 – 6.77 (m, 4H), 5.51 (s, 4H), 4.18 (q, J = 7.2 Hz, 2H) 3.44 – 3.33 (m, 4H), 2.50 (t, J = 7.2 Hz, 2H), 1.64 – 1.55 (m, 2H),

1.26 (t, J = 6.8 Hz, 3H), 0.90 (t, J = 7.2Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.7, 171.0, 145.5, 133.9, 129.2, 128.7, 126.4, 123.3, 67.0, 62.4, 53.4, 40.3, 28.9, 17.3, 14.1, 13.7. HRMS (ESI) *m/z* calculate for ($M+H^+$) $C_{28}H_{31}N_6O_3^+$ 499.2458, Found:499.2447.

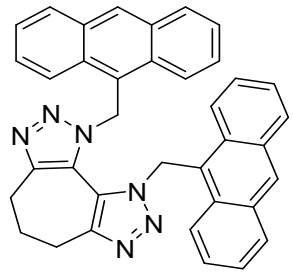
*Methyl 1,9-dibenzyl-5-(2-methoxyacetyl)-4,5,6,9-tetrahydro-1H-cyclohepta[1,2-d:3, 4-d']bis([1,2,3]triazole)-5-carboxylate (**3i**)*



3i

The title compound was synthesized according to the general procedure, and isolated as a Colorless transparent solid (eluent PE : EtOAc = 1:1 , Rf = 0.5, 64.2 mg, 88% yield). M.p.: 68- 69 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.26 (m, 6H), 6.79 – 6.77 (m, 4H), 5.51 (s, 4H), 4.16 (s, 2H), 3.74 (s, 3H), 3.46 (d, J = 16.0 Hz, 2H), 3.40 (s, 3H), 3.35 (d, J = 16.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 170.9, 145.6, 133.9, 129.2, 128.7, 126.3, 123.4, 76.0, 64.9, 59.5, 53.4, 53.0, 28.5. HRMS (ESI) *m/z* calculate for ($M+H^+$) $C_{26}H_{27}N_6O_4^+$ 487.2088, Found: 487.2046.

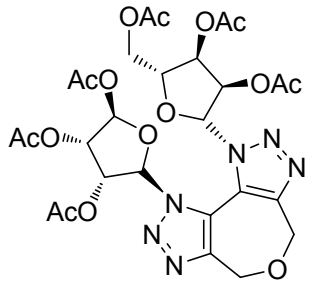
*1,9-Bis(anthracen-9-ylmethyl)-4,5,6,9-tetrahydro-1H-cyclohepta[1,2-d:3,4-d']bis([1,2,3] triazole) (**3j**)*



3j

The title compound was synthesized according to the general procedure, and isolated as a white solid (eluent PE : EtOAc = 2:1 , Rf = 0.3. 53.4 mg, 64% yield). M.p.: 213- 214 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 2H), 8.02 – 8.00 (m, 4H), 7.77 – 7.75 (m, 4H), 7.49 – 7.43 (m, 8H), 6.37 (s, 4H), 2.52 (t, *J* = 6.8 Hz, 4H), 2.01 – 1.95 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 131.4, 130.6, 130.1, 129.7, 127.4, 125.3, 123.7, 123.5, 122.8, 47.5, 28.8, 22.7. HRMS (ESI) *m/z* calculate for (M+H$^+$) $C_{37}H_{29}N_6^+$ 557.2448, Found: 557.2438.

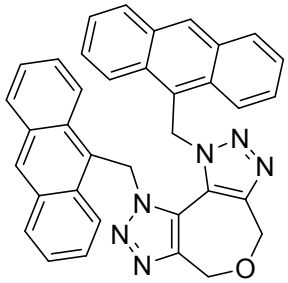
*(2R,3S,4R,5S)-5-(9-((2R,3R,4R,5R)-3,4-Diacetoxy-5-(acetoxymethyl)tetrahydrofuran-2-yl)oxepino[3,4-d:5,6-d']bis([1,2,3]triazole)-1(4H,6H,9H)-yl)tetrahydrofuran-2,3,4-triyl triacetate (**3k**)*



3k

The title compound was synthesized according to the general procedure, and isolated as a colorless oil (eluent PE : EtOAc = 1:2 , Rf = 0.4, 56.1 mg, 55% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (d, *J* = 4.0 Hz, 2H), 6.20 – 6.18 (m, 2H), 5.85 (t, *J* = 5.0 Hz, 2H), 5.19 (d, *J* = 15.3 Hz, 2H), 4.87 (d, *J* = 15.3 Hz, 2H), 4.50 – 4.44 (m, 4H), 4.25 – 4.22 (m, 2H), 2.13 (s, 6H), 2.09 (s, 6H), 2.07 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 169.5, 169.2, 147.8, 122.9, 88.2, 81.9, 74.2, 71.4, 66.3, 62.5, 20.8, 20.6, 20.5. HRMS (ESI) *m/z* calculate for (M+H$^+$) $C_{28}H_{35}N_6O_{15}^+$ 695.2155, Found: 695.2168.

*1,9-Bis(anthracen-9-ylmethyl)-1,4,6,9-tetrahydrooxepino[3,4-d:5,6-d']bis([1,2,3]triazole) (**3l**)*

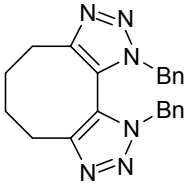


3l

The title compound was synthesized according to the general procedure, and isolated as a yellow solid (eluent PE : EtOAc = 3:1 , Rf = 0.2. 56.9 mg, 68% yield). M.p.: 208- 209 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (s, 2H), 8.05 – 8.03 (m, 4H), 7.75 – 7.73 (m, 4H), 7.47 – 7.45 (m, 8H), 6.52 (s, 4H), 4.65 (s, 4H).^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 131.4, 130.7, 130.4, 129.8, 127.7, 125.4, 123.9, 123.2, 122.6, 63.9, 48.1. HRMS (ESI) *m/z* calculate for ($M+Na^+$) $C_{36}H_{26}N_6NaO^+$ 581.2060, Found: 581.2062.

Characterization of compounds 3m-3s

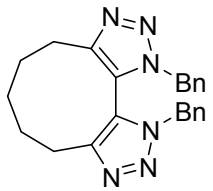
*1,10-Dibenzyl-1,4,5,6,7,10-hexahydrocycloocta[1,2-d:3,4-d']bis([1,2,3]triazole) (**3m**)*



3m

The title compound was synthesized according to the general procedure, and isolated as a pale-yellow solid (eluent PE : EtOAc = 2:1 , Rf = 0.3. 41.6 mg, 75% yield). M.p.: 164-165 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.22 (m, 6H), 6.92 – 6.89 (m, 4H), 5.52 (d, *J* = 15.2 Hz, 2H), 5.17 (d, *J* = 15.2 Hz, 2H), 3.08 – 3.05 (m, 2H), 1.86 – 1.83 (m, 4H), 1.34-1.29 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 133.2, 128.0, 127.8, 126.1, 120.6, 52.2, 26.7, 23.8. HRMS (ESI) *m/z* calculate for ($M+H^+$) $C_{22}H_{23}N_6^+$ Exact Mass: 371.1979, Found: 371.1989.

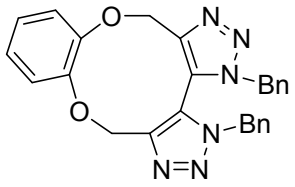
1,11-Dibenzyl-4,5,6,7,8,11-hexahydro-1H-cyclonona[1,2-d:3,4-d']bis([1,2,3]triazole) ***(3n)***



3n

The title compound was synthesized according to the general procedure, and isolated as a white solid (eluent PE : EtOAc = 2:1 , Rf = 0.4. 42.1 mg, 73% yield). M.p.: 145- 146 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.26 (m, 6H), 6.95-6.92 (m,4H), 5.26 (d, *J* = 14.8 Hz, 2H), 4.66 (d, *J* = 14.8 Hz, 2H), 2.72 – 2.64 (m, 2H), 1.76 – 1.73 (m, 2H), 1.38 – 1.28 (m, 2H), 1.27 – 1.23 (m, 2H), 1.19 – 1.11 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.2, 134.3, 129.2, 129.0, 127.9, 121.1, 52.9, 27.4, 26.3, 24.8. HRMS (ESI) *m/z* calculate for ($M+H^+$) $C_{23}H_{25}N_6^+$ 385.2135, Found: 385.2147.

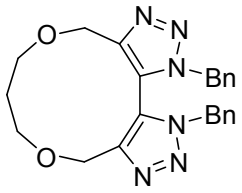
*3,4-Dibenzyl-3,4,7,14-tetrahydrobenzo[2,3][1,4]dioxecino[6,7-d:8,9-d']bis([1,2,3]triazol e) (**3o**)*



3o

The title compound was synthesized according to the general procedure, and isolated as a pale-yellow solid (eluent PE : EtOAc = 2:1 , Rf = 0.3. 47.9 mg, 71% yield). M.p.: 18.-187 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 4H), 7.24 (s, 2H), 6.92 – 6.84 (m, 4H), 6.83 – 6.79 (m, 4H), 5.29 (d, *J* = 14.8 Hz, 2H), 5.07 (d, *J* = 13.2 Hz, 2H), 4.69 (d, *J* = 14.8 Hz, 2H), 4.17 (d, *J* = 13.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 146.7, 132.8, 128.3, 128.2, 126.7, 123.1, 121.5, 120.2, 64.9, 52.2. HRMS (ESI) *m/z* calculate for ($M+H^+$) $C_{26}H_{23}N_6O_2^+$ 451.1877, Found: 451.1856.

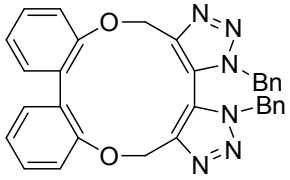
*1,13-Dibenzyl-4,6,7,8,10,13-hexahydro-1H-[1,5]dioxacycloundecino[7,8-d:9,10-d']bis([1,2,3]triazole) (**3p**)*



3p

The title compound was synthesized according to the general procedure, and isolated as a white solid (eluent PE : EtOAc = 2:1 , Rf = 0.4. 45.6 mg, 73% yield). M.p.: 201- 202 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 6H), 6.89-6.87 (m, 4H), 4.94 (d, *J* = 15.0 Hz, 2H), 4.57 (d, *J* = 15.0 Hz, 2H), 4.38 (d, *J* = 14Hz, 2H), 3.79 (d, *J* = 14 Hz, 2H), 3.25 – 3.14 (m, 4H), 1.59 – 1.54 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 133.9, 129.3, 129.1, 127.8, 122.0, 63.5, 62.7, 52.7, 31.0. HRMS (ESI) *m/z* calculate for ($M+H^+$) $C_{23}H_{25}N_6O_2^+$417.2034, Found: 417.2017.

*3,4-Dibenzyl-3,4,7,18-tetrahydrodibenzo[2,3:4,5][1,6]dioxacyclododecino[8,9-d:10,11-d']bis([1,2,3]triazole) (**3q**)*

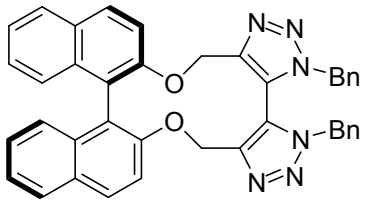


3q

The title compound was synthesized according to the general procedure, and isolated as a white solid (eluent PE : EtOAc = 2:1, Rf = 0.5. 50.5 mg, 64% yield). M.p.: 273- 274 °C. The product as a mixture of two isomers (the ratio is 0.7:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.41 (m, 2H), 7.36 – 7.29 (m, 11H), 7.22 – 7.18 (m, 2H), 7.11 – 7.09 (m, 4H), 6.97 – 6.88 (m, 10H), 6.47 (d, *J* = 8.0 Hz, 2H), 5.30 (d, *J* = 14.8 Hz, 2H), 5.14 (d, *J* = 14.0 Hz, 1.4H), 4.93 (d, *J* = 14.8 Hz, 1.4H), 4.73 (d, *J* = 10.4 Hz, 2H), 4.61 (d, *J* = 14.8

Hz, 2H), 4.47 (d, *J* = 14.8 Hz, 1.4H), 3.88 (d, *J* = 14.4 Hz, 1.4H), 3.54 (d, *J* = 10.4 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.2, 153.9, 146.9, 133.9, 133.4, 132.2, 130.4, 129.4, 129.4, 129.3, 128.6, 128.5, 128.4, 128.2, 128.1, 127.9, 122.8, 122.7, 121.1, 120.9, 110.7, 59.7, 57.4, 53.3, 53.1. HRMS (ESI) *m/z* calculate for (M+H$^+$) $C_{32}H_{27}N_6O_2^+$ 527.2190, Found: 527.2201.

*15,16-Dibenzyl-12,15,16,19-tetrahydrodinaphtho[2',1':2,3;1'',2'':4,5][1,6]dioxacyclododecino[8,9-d:10,11-d']bis([1,2,3]triazole) (**3r**)*



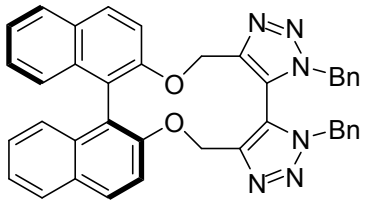
3r

The title compound was synthesized according to the general procedure, and isolated as a white solid. The product as a mixture of two isomers (the ratio is 6:1). (For isomer 1 (**3r**), eluent PE : EtOAc = 2:1 , Rf = 0.4. 55.5 mg, 59% yield). M.p.: 134- 135 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.77 (m, 2H), 7.71 – 7.66 (m, 4H), 7.17 – 7.08 (m, 8H), 7.06 – 7.02 (m, 2H), 6.91 – 6.89 (m, 2H), 6.71 – 6.69 (m, 4H), 5.17 (d, *J* = 14 Hz, 2H), 4.71 (d, *J* = 14.8 Hz, 2H), 4.33 (d, *J* = 14.8 Hz, 2H), 3.77 (d, *J* = 14 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.6, 146.8, 133.9, 133.3, 129.4, 129.2, 129.0, 128.3, 128.2, 126.4, 125.1, 123.5, 122.7, 119.0, 113.9, 58.3, 53.0. HRMS (ESI) *m/z* calculate for (M+H$^+$) $C_{40}H_{31}N_6O_2^+$ 627.2503, Found: 627.2537.

(For isomer 2 (**3r'**), eluent PE : EtOAc = 2:1 , Rf = 0.3. 9.4 mg, 10% yield). M.p.: 134-135 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.76 (m, 4H), 7.48 – 7.44 (m, 2H), 7.38 – 7.34 (m, 4H), 7.25 – 7.20 (m, 2H), 7.09 – 7.05 (m, 2H), 6.90 – 6.87 (m, 6H), 6.84 – 6.82 (m, 2H), 5.26 (d, *J* = 14.8 Hz, 2H), 4.84 (d, *J* = 10.8 Hz, 2H), 4.57 (d, *J* = 14.8 Hz, 2H), 3.66 (d, *J* = 10.8 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.3, 147.0, 134.2, 133.9,

129.5, 129.4, 129.3, 129.1, 128.2, 127.9, 126.4, 126.0, 123.6, 122.5, 118.2, 113.6, 60.8, 53.3. HRMS (ESI) *m/z* calculate for (M+H$^+$) $C_{40}H_{31}N_6O_2^+$ 627.2503, Found: 627.2507.

*15,16-Dibenzyl-12,15,16,19-tetrahydrodinaphtho[2',1':2,3;1'',2'':4,5][1,6]dioxacyclododecino[8,9-d:10,11-d']bis([1,2,3]triazole) (**3s**)*



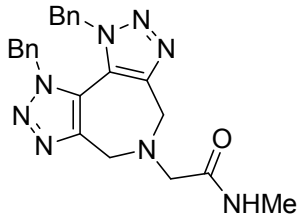
3s

The title compound was synthesized according to the general procedure, and isolated as a white solid. The product as a mixture of two isomers (the ratio is 7:1). (For isomer 1 (**3s**), eluent PE : EtOAc = 2:1 , Rf = 0.3. 60.1 mg, 64% yield). M.p.: 127- 128 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.83 (m, 2H), 7.77 – 7.72 (m, 4H), 7.24 – 7.16 (m, 8H), 7.13 – 7.09 (m, 2H), 6.98 – 6.96 (m, 2H), 6.78 – 6.76 (m, 4H), 5.22 (d, *J* = 14.2 Hz, 2H), 4.77 (d, *J* = 15.2 Hz, 2H), 4.39 (d, *J* = 15.2 Hz, 2H), 3.82 (d, *J* = 14.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.6, 146.8, 133.9, 133.3, 129.4, 129.2, 129.1, 128.3, 128.2, 126.4, 125.1, 123.5, 122.7, 119.1, 113.9, 58.3, 53.1. HRMS (ESI) *m/z* calculate for (M+H$^+$) $C_{40}H_{31}N_6O_2^+$ 627.2503, Found: 627.2536.

(For isomer 2 (**3s'**), eluent PE : EtOAc = 2:1 , Rf = 0.4. 8.5 mg, 9% yield). M.p.: 123-124 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.76 (m, 4H), 7.48 – 7.44 (m, 2H), 7.38 – 7.34 (m, 4H), 7.25 – 7.22 (m, 2H), 7.09 – 7.05 (m, 2H), 6.90 – 6.87 (m, 6H), 6.84 – 6.82 (m, 2H), 5.26 (d, *J* = 14.8 Hz, 2H), 4.84 (d, *J* = 10.8 Hz, 2H), 4.57 (d, *J* = 14.8 Hz, 2H), 3.66 (d, *J* = 10.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 134.2, 133.9, 129.5, 129.4, 129.3, 129.2, 128.2, 127.9, 126.4, 126.0, 123.6, 122.5, 118.2, 113.6, 60.8, 53.3. HRMS (ESI) *m/z* calculate for (M+H$^+$) $C_{40}H_{31}N_6O_2^+$ 627.2503, Found: 627.2541.

Characterization of compounds 3aa and 3ab

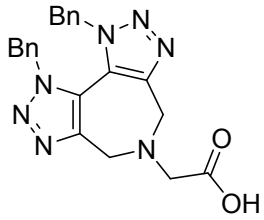
*2-(1,9-Dibenzyl-1H-bis([1,2,3]triazolo)[4,5-c:4',5'-e]azepin-5(4H,6H,9H)-yl)-N-methylacetamide (**3aa**)*



3aa

The title compound was synthesized according to the general procedure, and isolated as a white solid (eluent DCM : MeOH = 20:1 , Rf = 0.4. 182 mg, 87% yield). M.p.: 36-37 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.27 (m, 6H), 6.81 – 6.79 (m, 4H), 5.57 (s, 4H), 4.09 (s, 4H), 3.08 (s, 2H), 2.86 (d, J = 5.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.2, 146.5, 134.0, 129.3, 128.9, 126.2, 123.5, 59.2, 53.5, 51.4, 25.9. HRMS (ESI) *m/z* calculate for ($M+H^+$) $C_{23}H_{25}N_8O^+$ 429.2146, Found: 429.2175.

*2-(1,9-Dibenzyl-1H-bis([1,2,3]triazolo)[4,5-c:4',5'-e]azepin-5(4H,6H,9H)-yl)acetic acid (**3ab**)*



3ab

The title compound was synthesized according to the general procedure, and isolated as a light green solid (eluent DCM : MeOH = 20:1, Rf = 0.5. 200 mg, 93% yield). M.p.: 42-43 ^{o}C. ^{1}H NMR (400 MHz, DMSO) δ 7.27 – 7.25 (m, 6H), 6.96 – 6.94 (m, 4H), 5.78 (s, 4H), 4.04 (s, 4H), 3.15 (s, 2H). ^{13}C NMR (150 MHz, DMSO) δ 171.8, 135.2, 128.8, 128.2, 126.9, 123.2, 99.6, 53.1, 49.7, 22.6. HRMS (ESI) *m/z* calculate for ($M+H^+$) $C_{22}H_{22}N_7O_2^+$ 416.1829, Found: 416.1836.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

X-ray crystallographic data of **3d**

X-ray crystallographic data of **3p**

Optimization of the reaction conditions, chemical structures of diynes, copies of ^{1}H NMR and ^{13}C NMR spectra, kinetics experiments, expression and purification of proteins are included in the supporting information.

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