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Synthesis of [1,2,3]-triazolo[1,5-*a*][1,4]benzodiazepines via an unprecedented one-pot Cu-catalyzed azidation–cyclization reaction

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ABSTRACT

A novel three-step approach leading to [1,2,3]-triazolo[1,5-*a*][1,4]benzodiazepines in moderate to good yields has been developed. The key step is an unprecedented one-pot Cu-catalyzed azidation–cyclization reaction of *ortho*-bromobenzylpropargylamines.

1. Introduction

Structurally novel and diverse heterocycles are very useful in drug discovery and related fields. Among the large varieties of heterocycles, 1,4-benzodiazepines have been integral parts of many drugs,[1] therapeutic leads,[2] and bioactive naturally occurring substances.[3] This structural moiety is the archetypal privileged structure as defined by Evans in 1988.[4] Compounds possessing the 1,4-benzodiazepine scaffold show a broad range of biological activities. They have been described as mimetics of β-turns[5] and α-helices[6] and they bind to a multitude of targets, as e.g., ligand-gated ion channels, enzymes, and G-protein coupled receptors.[7] The spectrum of therapeutic activities has further been enhanced through the development of heterocyclic fused 1,4-benzodiazepines. This has resulted in the discovery of clinically and commercially successful drugs used for the treatment of diseases of the central nervous system (CNS) and other diseases. The most notable are the triazolobenzodiazepines alprazolam (**1a**), estazolam (**1b**), and triazolam (**1c**) (Fig. 1) showing anxiolytic (**1a**, **b**)[8] or anti-depressant (**1c**)[9] activity.

Recently several articles about protocols leading to nitrogen containing rings fused with triazoles have been published.[10] These protocols are mainly based on the sequential synthesis of the triazole followed by Ullmann coupling. However this strategy is limited to terminal or activated acetylenes. In this paper we describe the first in situ azidation–cyclization process of *ortho*-bromobenzylpropargylamines **7**. The desired starting compounds can easily be generated via A^3-coupling.[11] Based on our previous research[12] we transformed the known literature protocol for the A^3-coupling of bromobenzylamines **6**[13] to a fast MW-assisted protocol (Scheme 1). The implementation of a multi-component reaction allows the rapid construction of a library of diversely substituted propargylamines.[14] The bromobenzylamines **6** are easily accessible via reductive amination of *ortho*-bromoaldehyde **3** and a suitable primary amine **2** (Scheme 1).

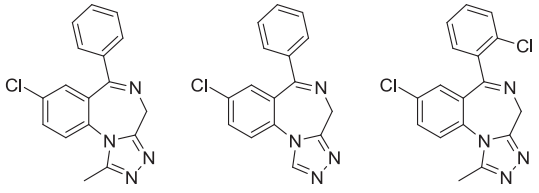

Fig. 1. Drugs containing the [1,2,4]-triazolo-[4,3-*a*][1,4]benzodiazepine scaffold.

2. Results and discussion

A convenient method for the preparation of aryl azides is the Ullmann-type coupling of aryl halides with NaN_3 using CuI as

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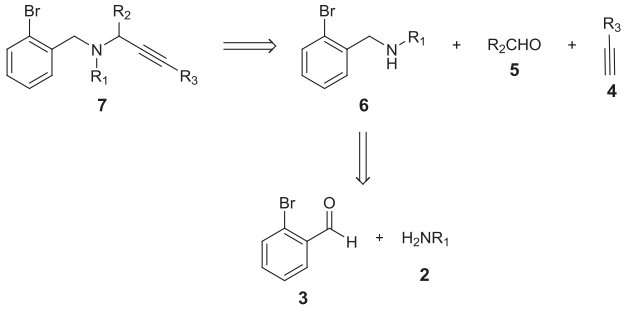


Scheme 1. Retrosynthetical analysis for the starting *ortho*-bromoporpargylamines.

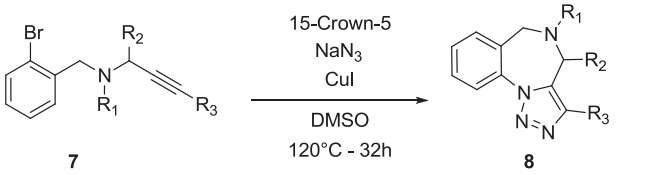
catalyst.[15] Our aim is to perform the azidation of the aryl-bromide and to react the obtained *ortho*-azidobenzylpropargylamine in situ with the acetylene to yield the [1,2,3]-triazolo[1,5-*a*][1,4]benzodiazepines (**8**) (Table 1). The core of this structure has previously been described, although with a limited substitution pattern.[16] Our approach would result in the introduction of various substituents at the triazole ring, the C3- and the N4-position. The optimization of the reaction parameters for the azidation–cyclization process was performed with *ortho*-bromobenzylpropargylamine **7a**, using NaN_3 with CuI as catalyst and DMSO as solvent. The reaction resulted in comparable yields when performed at 120 °C and 150 °C (Table 1, entries 1 and 2). Changing the solvent from DMSO to DMF (Table 1, entry 3) resulted in similar yields, while using NMP gave lower yields (Table 1, entry 4). When the reaction was run for a longer time, the yields dropped (Table 1, entries 5 and 6). Subsequently we screened different copper catalyst as CuCl, CuBr, and Cu(I)OTf. Only CuBr gave similar yields as CuI (Table 1, entries 7–9). This is in accordance with the observations of Shinoda et al.[15] Changing the catalyst loading from 10 mol % to 20 mol % did not alter the yield (Table 2, entry 10). To further improve the reaction we enhanced the nucleophilicity of the azide by addition of 15-crown-5 (2.5 equiv). Performing the reaction at 150 °C resulted in an improved yield (Table 1, entry 11). Though when running the reaction for a longer time the yields dropped (Table 1, entry 13). However, when the reaction was performed at a slightly lower temperature of 120 °C but for a prolonged time (32 h), a good yield of 82% was obtained (Table 1, entry 12). When the reaction was run under microwave irradiation for 3 h the yield was only 28% (Table 1, entry 14). Without any catalyst no desired product is formed (Table 1, entry 15). We conclude that the optimal conditions for the reaction are: sodiumazide (2.5 equiv) at 120 °C for 32 h in DMSO as solvent with CuI (20 mol %) as catalyst and 15-crown-5 (2.5 equiv) as additive.

Table 1
Optimization of the procedure[a]

Entry	Catalyst (mol %)	Solvent	Temp (°C)	Time (h)	Additive	Yield[b]
1	CuI (10)	DMSO	120	24	—	62
2	CuI (10)	DMSO	150	24	—	70
3	CuI (10)	DMF	120	24	—	70
4	CuI (10)	NMP	150	24	—	54
5	CuI (10)	DMF	150	48	—	27
6	CuI (20)	DMSO	150	32	—	40
7	CuCl (10)	DMSO	150	24	—	32
8	CuBr (10)	DMSO	150	24	—	62
9	Cu(I)OTf (10)	DMSO	150	24	—	44
10	CuI (20)	DMSO	150	24	—	71
11	CuI (20)	DMSO	150	12	15-Crown-5[c]	77
12	**CuI (20)**	**DMSO**	**120**	**32**	15-Crown-5[c]	**82**
13	CuI (20)	DMSO	150	24	15-Crown-5[c]	63
14	CuI (20)	DMSO	120	3[d]	15-Crown-5[c]	28
15	—	DMSO	150	24	—	—

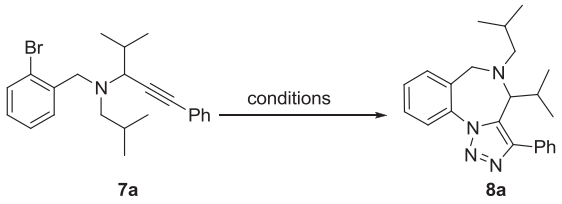
[a] Reactions were run on a 0.25 mmol scale with NaN_3 (2.5 equiv) in the indicated solvent (1 mL).
[b] Isolated yields.
[c] 2.5 equiv were used.
[d] The reaction was run under microwave irradiation at 300 W maximum power.

Table 2
Scope and limitations[a]



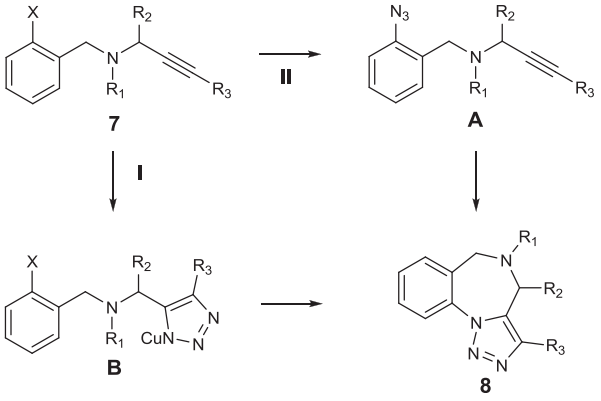
Entry	Compd.	R1	R2	R3	Yield (%)[b]
1	**8a**	^{i}Bu	^{i}Pr	Ph	82
2	**8b**	^{i}Bu	Tolyl	CyPr	49
3	**8c**	Pent	Pent	Hep	53
4	**8d**	Bu	Pr	Bu	49
5	**8e**	Bn	Pr	Ph	58
6	**8f**	Bn	^{i}Pr	Ph	43
7	**8g**	Bn	Et	Ph	48
8	**8h**	Bn	Pent	Ph	40
9	**8i**	PMB	Pr	Ph	54
10	**8j**	Bn	Pr	Tol	45
11	**8k**	PMB	Pr	Tol	77
18	**8l**	Bn	Et	*p*-EtPh	53
13	**8m**	PMB	Pr	*p*-PentPh	71
14	**8n**	PMB	^{i}Bu	Tol	56
15	**8o**	Bn	^{i}Bu	Ph	57
16	**8p**	PMB	Oct	Ph	58
17	**8q**	3,4-diOMeBn	Bu	Ph	58
18	**8r**	Bn	Ph	Ph	—

[a] Reactions were run on a 0.25 mmol scale, employing the optimized conditions.
[b] Isolated yields.



With these conditions in hand we started to explore the scope of our process. A small library of [1,2,3]-triazolo[1,5-*a*][1,4]benzodiazepines was generated. At the amine position we introduced both alkyl (Table 2, entries 1–4) and benzyl (Table 2, entries 5–17) substituents. On the propargylic position the reaction proceeded well with alkyl substituents (Table 2, entries 1, 3, and 5–17) and with a phenyl substituent (Table 2, entry 2 and 4). Regarding the acetylene substituent the reaction is tolerant to both aryl (Table 2, entries 1, 6–17) and alkyl (Table 2, entries 2–4) groups. The desired products are obtained in moderate to good yields as a single diastereoisomer. In the case of a benzyl substituent on the amine position and an aryl residue on both other positions, no desired products was formed and only decomposition was observed (Table 2, entry 18). This could be due to increased sterical hindrance. The chlorine analogue of **7a** failed to react.

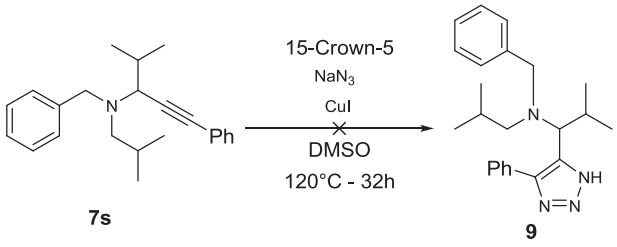
A plausible reaction mechanism is shown in Scheme 2. Following pathway **I** an azide–alkyne [3+2] cycloaddition in the presence of CuI takes place, resulting in the formation of the N–Cu species **B**, which subsequently inserts into the aryl halogen bond via Ullmann coupling leading to the desired product **8**. This pathway occurs in the case of activated or terminal acetylenes[10] and is therefore most probably not operating in our case. Following pathway **II**, the process starts with a copper-catalyzed azidation of



Scheme 2. Plausible reaction pathways.

the aryl-moiety yielding intermediate **A**, followed by an intramolecular thermal [3+2] cycloaddition leading to product **8**.

An indication that the reaction is presumably running via pathway **II** is given by the observation that when compound **7s** (i.e., the debrominated analogue of **7a**) is submitted to the optimized reaction conditions, only starting material was received (Scheme 3).



Scheme 3. No reaction of the benzylpropargylamine lacking the bromide.

3. Conclusion

In conclusion, we have elaborated a novel procedure for the synthesis of a new class of substituted [1,2,3]-triazolo[1,5-*a*][1,4] benzodiazepines employing an azidation–cyclization sequence. The resulting products are obtained in moderate to good yields. Diversity is secured by the generation of the starting *ortho*-bromobenzylpropargylamines via A^3-coupling reaction.

4. Experimental part

4.1. General information

All solvents and reagents were purchased from commercial sources and were used without prior purification. All microwave irradiation experiments were carried out in a monomode microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W. The reactions were carried out in 10 mL glass tubes, sealed with snap caps and placed in the microwave cavity. The reaction mixture was irradiated at a required ceiling temperature using maximum power for the stipulated time, and the reaction mixture temperatures were measured by the external IR sensor. The reaction tube was cooled to ambient temperature with air jet cooling. TLC analysis was performed on aluminum backed plates. The products were purified by silica gel (200–300 mesh) column chromatography. NMR spectra were recorded at 300 MHz (^{1}H and ^{13}C). The ^{1}H and ^{13}C chemical shifts are reported in parts per million relative to tetramethylsilane using the residual solvent signal as the internal reference. The following abbreviation were used to designate chemical shift multiplicities: s=singlet, bs=broad singlet, d=doublet, dd=double doublet, t=triplet, m=multiplet. The ^{13}C NMR spectra are proton decoupled. High-resolution mass spectra were recorded by using double-focusing magnetic sector analyzer and at an ion source temperature 150–250 °C as required. High-resolution EI-mass spectra were performed with a resolution of 10,000. The $[M]^+$ mass for products **7a**–**r** and **8a**–**q** was never observed due to instability of the compound in EI. For all products the $[M-R^2]^+$ fragment was observed.

4.2. General procedure for the MW-assisted synthesis of *ortho*-bromobenzylpropargylamines

To a solution of amine (1 equiv) in toluene (0.5 mL) in a MW vial with magnetic stirrer was added aldehyde (1.1 equiv), terminal alkyne (1.5 equiv) and CuBr (10 mol %). The reaction was irradiated at 100 °C for 30 min. The reaction mixture was directly purified via column chromatography on silica gel using a mixture of ethyl acetate and heptane (5/95) as eluant.

*4.2.1. N-(2-Bromobenzyl)-N-(propan-2-yl)-4-dimethyl-1-phenylpent-1-yn-3-amine (**7a**).* *N*-(2-Bromobenzyl)-2-methylpropan-1-amine (800 mg, 3.32 mmol, 1 equiv), isobutyraldehyde (328 μl, 3.65 mmol, 1.1 equiv), phenylacetylene (554 μl, 4.98 mmol, 1.5 equiv), and CuBr (47.5 mg, 0.332 mmol, 10 mol %). The product was obtained as a yellow oil (1.016 g, 77%). ^{1}H NMR ($CDCl_3$): 7.64 (1H, d, *J*=7.5), 7.50 (3H, m), 7.29 (4H, m), 7.07 (1H, m), 3.80 (2H, m), 3.14 (1H, d, *J*=10.2), 2.49 (1H, dd, J=12.6 and 4.0), 2.18 (1H, m), 1.86 (2H, m), 1.08 (3H, d, *J*=6.4), 1.04 (3H, d, *J*=6.4), 0.98 (3H, d, *J*=6.4), 0.87 (3H, d, *J*=6.8); ^{13}C NMR ($CDCl_3$): 139.1, 132.6, 131.8, 130.8, 128.2, 128.1, 127.7, 127.1, 124.5, 123.7, 87.7, 85.8, 61.1, 59.8, 55.8, 30.9, 26.2, 21.3, 21.04, 20.95, 20.3; HRMS (EI): *m*/*z* calcd for $C_{20}H_{21}NBr$ $[M-CH(CH_3)_2]$: 354.0857; found: 354.0874.

*4.2.2. N-(2-Bromobenzyl)-3-cyclopropyl-N-(propan-2-yl)-1-(4-methylphenyl)prop-2-yn-1-amine (**7b**).* *N*-(2-Bromobenzyl)-2-methylpropan-1-amine (200 mg, 0.83 mmol, 1 equiv), para-tolylaldehyde (108 μl, 0.91 mmol, 1.1 equiv), ethynylcyclopropane (106 μl, 1.25 mmol, 1.5 equiv), and CuBr (11.9 mg, 0.083 mmol, 10 mol %). The product was obtained as a yellow oil (281 mg, 83%). ^{1}H NMR ($CDCl_3$): 7.59 (1H, d, *J*=7.5), 7.48 (3H, d, *J*=7.2), 7.25 (1H, m), 7.07 (3H, m), 4.66 (1H, s), 3.64 (2H, m), 2.41 (1H, dd, *J*=12.6, 4.0), 2.31 (3H, s), 1.99 (1H, dd, *J*=12.2, 10.7), 1.76 (1H, m), 1.39 (1H, m), 0.81 (11H, m); ^{13}C NMR ($CDCl_3$): 139.4, 137.0, 132.9, 131.1, 128.8, 128.7, 128.4, 127.4, 124.8, 91.9, 77.7, 77.3, 76.9, 70.9, 59.0, 56.7, 55.3, 26.3, 21.4, 21.0, 9.00, 8.97, 0.31; HRMS (EI): *m*/*z* calcd for $C_{17}H_{21}NBr$ $[M-(C_6H_5)CH_3]$: 318.0857; found: 318.0835.

*4.2.3. N-(2-Bromobenzyl)-N-pentylpentadec-7-yn-6-amine (**7c**).* *N*-(2-Bromobenzyl)pentan-1-amine (200 mg, 0.78 mmol, 1 equiv), hexanal (106 μl, 0.86 mmol, 1.1 equiv), 1-nonyn (192 μl, 1.172 mmol, 1.5 equiv), and CuBr (11.2 mg, 0.078 mmol, 10 mol %). The product was obtained as a yellow oil (326 mg, 88%). ^{1}H NMR ($CDCl_3$): 7.57 (1H, d, *J*=7.5), 7.49 (1H, m), 7.25 (1H, m), 7.06 (1H, m), 3.69 (2H,m), 3.38 (1H, t, *J*=7.5), 2.46 (2H, m), 2.23 (2H, td, *J*=6.6, 1.9), 1.52 (9H, m), 1.24 (15 H, m), 0.88 (9H, m); ^{13}C NMR ($CDCl_3$): 139.8, 132.5, 130.6, 127.9, 127.0, 124.2, 84.6, 78.7, 55.3, 53.3, 51.6, 34.4, 31.9, 31.5, 29.7, 29.2, 28.9, 28.8, 28.0, 26.4, 22.7, 36.4, 22.7, 22.6, 18.7, 14.12, 14.07; HRMS (EI): *m*/*z* calcd for $C_{22}H_{33}NBr$ $[M-C_5H_{11}]$: 390.1796; found: 390.1790.

*4.2.4. N-(2-Bromobenzyl)-N-(3-ethoxypropyl)-1-(4-fluorophenyl)-pent-2-yn-1-amine (**7d**).* *N*-(2-Bromobenzyl)-3-ethoxypropan-1-amine (200 mg, 0.74 mmol, 1 equiv), 4-fluorobenzaldehyde (200 mg, 0.81 mmol, 1.1 equiv), 1-heptyn (105 mg, 1.1 mmol, 1.5 equiv), and CuBr (10.5 mg, 0.074 mmol, 10 mol %). The product was obtained as a yellow oil (290 mg, 83%). ^{1}H NMR ($CDCl_3$): 7.53 (4H, m), 7.26 (1H, td, *J*=7.4(×2) and *J*=0.9), 7.07 (1H, td, *J*=7.5 (×2)

and J=1.5), 6.98 (2H, t, J=8.7), 4.66 (1H, s), 3.73 (2H, m), 3.33 (4H, m), 2.51 (2H, m), 2.37 (2H, td, J=6.9(×2) and J=2.1), 1.74 (2H, m), 1.63 (2H, m), 1.49 (2H, m), 1.37 (2H, m), 1.09 (3H, t, J=7.0), 0.94 (3H, t, J=7.2); ^{13}C NMR ($CDCl_3$): 163.7, 160.5, 138.7, 135.61, 135.58, 132.8, 131.0, 129.9, 128.4, 127.2, 124.6, 114.7, 114.5, 88.9, 74.9, 68.7, 66.0, 56.1, 55.2, 47.4, 31.2, 28.8, 28.2, 22.3, 18.8, 15.2, 14.1; HRMS: m/z calcd for $C_{15}H_{25}NOBr$ [M−C_5H_4F]: 378.1433; found: 378.1421.

*4.2.5. N-Benzyl-N-(2-bromobenzyl)-4-phenylhex-5-yn-4-amine (**7e**).* *N*-Benzyl-1-(2-bromophenyl)methanamine (400 mg, 1.45 mmol, 1 equiv), butanal (115 mg, 1.6 mmol, 1.1 equiv), phenylacetylene (222 mg, 2.2 mmol, 1.5 equiv), and CuBr (20.7 mg, 0.15 mmol, 10 mol %). The product was obtained as a yellow oil (512 mg, 82%). ^{1}H NMR ($CDCl_3$): 7.63 (1H, m), 7.51 (3H, m), 7.42 (2H, m), 7.29 (7H, m), 7.07 (1H, m), 3.88 (3H, m), 3.58 (2H, m), 1.75 (2H, m), 1.47 (2H, m), 0.83 (3H, m); ^{13}C NMR ($CDCl_3$): 139.9, 139.5, 138.8, 132.7, 132.6, 131.8, 130.5, 128.9, 128.8, 128.3, 128.22, 128.19, 127.9, 127.2, 126.9, 126.8, 124.5, 123.6, 88.0, 85.4, 55.4, 54.5, 52.6, 36.0, 19.8, 19.7, 13.8, 13.7; HRMS: m/z calcd for $C_{23}H_{19}NBr$ [M−C_3H_7]: 388.0701; found: 388.0701.

*4.2.6. N-Benzyl-N-(2-bromobenzyl)-4-methyl-1-phenylpent-1-yn-3-amine (**7f**).* *N*-Benzyl-1-(2-bromophenyl)methanamine (400 mg, 1.45 mmol, 1 equiv), isobutyraldehyde (115 mg, 1.6 mmol, 1.1 equiv), phenylacetylene (222 mg, 2.2 mmol, 1.5 equiv), and CuBr (20.7 mg, 0.15 mmol, 10 mol %). The product was obtained as a yellow oil (330 mg, 67%). ^{1}H NMR ($CDCl_3$): 7.69 (1H, m), 7.52 (3H, m), 7.44 (2H, d, J=7.5), 7.30 (7H, m), 7.08 (1H, m), 3.87 (3H, m), 3.51 (1H, m), 3.14 (1H, m), 2.0 (1H, m), 1.05 (6H, d, J=6.4); ^{13}C NMR ($CDCl_3$): 139.8, 139.4, 138.7, 132.7, 131.8, 130.5, 129.0, 128.9, 1283, 128.2, 128.21, 128.17, 127.8, 127.3, 127.0, 126.8, 124.6, 123.6, 87.3, 86.2, 60.1, 55.6, 54.6, 31.0, 21.0, 20.2; HRMS: m/z calcd for $C_{23}H_{19}NBr$ [M−C_3H_7]: 388.0701; found: 388.0698.

*4.2.7. N-Benzyl-N-(2-bromobenzyl)-4-phenylpent-4-yn-3-amine (**7g**).* *N*-Benzyl-1-(2-bromophenyl)methanamine (200 mg, 0.73 mmol, 1 equiv), propanal (46 mg, 0.8 mmol, 1.1 equiv), phenylacetylene (111 mg, 1.1 mmol, 1.5 equiv), and CuBr (10.4 mg, 0.07 mmol, 10 mol %). The product was obtained as a yellow oil (237 mg, 78%). ^{1}H NMR ($CDCl_3$): 7.64 (1H, m), 7.51 (3H, m), 7.42 (2H, m), 7.29 (7H, m), 7.07 (1H, td, J=7.5, 1.5), 3.88 (3H, m), 3.53 (2H, m), 1.78 (2H, m), 1.00 (3H, t, J=7.3); ^{13}C NMR ($CDCl_3$): 139.9, 139.6, 138.8, 132.6, 131.8, 130.5, 128.84, 128.00, 128.3, 128.22, 128.0, 128.18, 127.9, 127.2, 126.9, 126.8, 124.5, 123.5, 87.8, 85.5, 55.5, 54.7, 54.5, 27.0, 11.4; HRMS: m/z calcd for $C_{23}H_{19}NBr$ [M−C_2H_5]: 388.0701; found: 388.0691.

*4.2.8. N-Benzyl-N-(2-bromobenzyl)-4-phenyloct-7-yn-6-amine (**7h**).* *N*-Benzyl-1-(2-bromophenyl)methanamine (300 mg, 1.086 mmol, 1 equiv), hexanal (120 mg, 1.2 mmol, 1.1 equiv), phenylacetylene (163 mg, 1.6 mmol, 1.5 equiv), and CuBr (16 mg, 0.1086 mmol, 10 mol %). The product was obtained as a yellow oil (434.5 mg, 84%). ^{1}H NMR ($CDCl_3$): 7.63 (1H, m), 7.51 (3H, d, J=6.8), 7.41 (2H, m), 7.28 (7H, m), 7.07 (1H, t, J=2×7.5), 3.87 (3H, m), 3.56 (2H, m), 1.75 (2H, m), 1.46 (2H, m), 1.24 (4H, m), 0.84 (3H, m); ^{13}C NMR ($CDCl_3$): 139.9, 139.6, 138.9, 132.6, 131.8, 128.91, 128.85, 128.3, 127.9, 127.2, 126.9, 123.6, 88.1, 85.4, 55.4, 55.0, 54.6, 52.8, 33.8, 31.4, 26.2, 26.0, 22.6, 14.0; HRMS: m/z calcd for $C_{23}H_{19}NBr$ [M−C_5H_{11}]: 388.0701; found: 388.0695.

*4.2.9. N-(2-Bromobenzyl)-N-(4-methoxybenzyl)-4-phenylhex-5-yn-4-amine (**7i**).* 1-(2-Bromophenyl)-*N*-(4-methoxybenzyl)methanamine (300 mg, 0.98 mmol, 1 equiv), hexanal (77.6 mg, 1.1 mmol, 1.1 equiv), phenylacetylene (143 mg, 1.5 mmol, 1.5 equiv), and CuBr (14.0 mg, 0.1 mmol, 10 mol %). The product was obtained as a yellow oil (364 mg, 80%). ^{1}H NMR ($CDCl_3$): 7.65 (1H, d, J=7.9), 7.50 (3H, m), 7.29 (6H, m), 7.04 (1H, m), 6.84 (2H, m), 3.82 (3H, m), 3.74 (3H, s), 3.63 (1H, t, J=7.5), 3.52 (1H, d, J=13.6), 1.73 (2H, m), 1.46 (2H, m), 0.83 (3H, t, J=7.3); ^{13}C NMR ($CDCl_3$): 158.8, 139.1, 132.8, 132.0, 131.6, 130.7, 130.2, 128.4, 128.3, 128.0, 127.4, 124.7, 123.7, 113.8, 88.3, 85.5, 55.3, 55.0, 54.5, 52.5, 36.1, 20.0, 13.9; HRMS: m/z calcd for $C_{24}H_{21}NOBr$ [M−C_3H_7]: 418.0807; found: 418.0819.

*4.2.10. N-Benzyl-N-(2-bromobenzyl)-4-(4-methylphenyl)hex-5-yn-4-amine (**7j**).* *N*-Benzyl-1-(2-bromophenyl)methanamine (300 mg, 1.1 mmol, 1 equiv), butanal (86 mg, 1.2 mmol, 1.1 equiv), *p*-tolylacetylene (189 mg, 1.6 mmol, 1.5 equiv), and CuBr (15.7 mg, 0.11 mmol, 10 mol %). The product was obtained as a yellow oil (421 mg, 87%). ^{1}H NMR ($CDCl_3$): 7.66 (1H, m), 7.48 (1H, d, J=7.9), 7.41 (4H, d, J=7.9), 7.24 (4H, m), 7.10 (2H, d, J=7.9), 7.03 (1H, m), 3.86 (3H, m), 3.61 (2H, m), 2.32 (3H, m), 1.73 (2H, m), 1.47 (2H, dq, J=14.5, 7), 0.82 (3H, t, J=7.3); ^{13}C NMR ($CDCl_3$): 139.5, 138.9, 137.8, 132.6, 131.7, 130.5, 129.0, 128.8, 128.2, 128.1, 127.2, 126.9, 124.5, 120.5, 87.2, 85.4, 55.4, 54.5, 52.6, 36.0, 21.4; 19.8; 13.8; HRMS: m/z calcd for $C_{24}H_{21}NBr$ [M−C_3H_7]: 402.0857; found: 402.0839.

*4.2.11. N-(2-Bromobenzyl)-N-(4-methoxybenzyl)-4-(4-methylphenyl)hex-5-yn-4-amine (**7k**).* 1-(2-Bromophenyl)-*N*-(4-methoxybenzyl)methanamine (300 mg, 0.98 mmol, 1 equiv), butanal (78 mg, 1.1 mmol, 1.1 equiv), *p*-tolylacetylene (171 mg, 1.5 mmol, 1.5 equiv), and CuBr (14.0 mg, 0.1 mmol, 10 mol %). The product was obtained as a yellow oil (387 mg, 83%). ^{1}H NMR ($CDCl_3$): 7.64 (1H, m), 7.46 (1H, m), 7.41 (2H, d, J=8.3), 7.31 (2H, d, J=8.3), 7.25 (1H, t, J=7.0), 7.09 (2H, d, J=7.9), 7.01 (1H, td, J=5.0, 1.5), 6.82 (2H, d, J=8.7), 3.84 (3H, m), 3.70 (3H, s), 3.63 (1H, t, J=7.5), 3.52 (1H, d, J=13.6), 2.30 (3H, s), 1.73 (2H, m), 1.46 (2H, sxt, J=7.5), 0.82 (3H, t, J=7.3); ^{13}C NMR ($CDCl_3$): 158.6, 139.0, 137.8, 132.6, 131.7, 131.5, 130.5, 130.0, 129.0, 128.1, 127.2, 124.5, 120.5, 113.6, 87.3, 85.4, 55.1, 54.8, 54.3, 52.4, 36.0, 21.4, 19.8, 13.8; HRMS: m/z calcd for $C_{25}H_{23}NOBr$ [M−C_3H_7]: 432.0963; found: 432.0974.

*4.2.12. N-Benzyl-N-(2-bromobenzyl)-4-(2-ethylphenyl)pent-4-yn-3-amine (**7l**).* *N*-Benzyl-1-(2-bromophenyl)methanamine (300 mg, 1.1 mmol, 1 equiv), propanal (70 mg, 1.2 mmol, 1.1 equiv), 2-ethylphenylacetylene (212 mg, 1.6 mmol, 1.5 equiv), and CuBr (15.7 mg, 0.11 mmol, 10 mol %). The product was obtained as a yellow oil (428 mg, 98%). ^{1}H NMR ($CDCl_3$): 7.66 (1H, d, J=7.5), 7.44 (5H, m), 7.26 (3H, m), 7.18 (1H, m), 7.11 (2H, d, J=7.9), 6.99 (1H, m), 3.87 (3H, m), 3.56 (2H, m), 2.59 (2H, q, J=7.5), 1.77 (2H, m), 1.19 (3H, t, J=7.5), 0.98 (3H, t, J=7.3); ^{13}C NMR ($CDCl_3$): 144.4, 139.8, 139.1, 132.9, 132.1, 130.8, 129.1, 128.4, 128.4, 128.1, 127.5, 127.1, 124.6, 121.0, 87.2, 85.9, 55.7, 55.0, 54.8, 29.0, 27.3, 15.7, 11.7; HRMS: m/z calcd for $C_{25}H_{23}NBr$ [M−C_2H_5]: 416.1014; found: 416.1007.

*4.2.13. N-(2-Bromobenzyl)-N-(4-methoxybenzyl)-4-(2-pentylphenyl)hex-5-yn-4-amine (**7m**).* 1-(2-Bromophenyl)-*N*-(4-methoxybenzyl)methanamine (300 mg, 0.98 mmol, 1 equiv), butanal (78 mg, 1.1 mmol, 1.1 equiv), 2-pentylphenylacetylene (253 mg, 1.5 mmol, 1.5 equiv), and CuBr (14.0 mg, 0.1 mmol, 10 mol %). The product was obtained as a yellow oil (434.6 mg, 83%). ^{1}H NMR ($CDCl_3$): 7.64 (1H, m), 7.48 (1H, d, J=7.9, 7.43 (2H, d, J=7.9), 7.30 (2H, m), 7.25 (1H, m), 7.12 (2H, d, J=8.3), 7.04 (1H, td, J=7.6, 1.3), 6.83 (2H, d, J=8.7), 3.82 (3H, m), 3.74 (3H, s), 3.62 (1H, t, J=7.5), 3.52 (1H, d, J=13.6), 2.58 (1H, t, J=7.7), 1.75 (2H, m), 1.57 (2H, m), 1.45 6H, m), 1.29 (12H, m), 0.88 (3H, t, J=6.8), 0.82 (3H, t, J=7.3); ^{13}C NMR ($CDCl_3$): 158.6, 142.9, 139.0, 123.6, 131.7, 131.5, 130.5, 130.0, 128.4, 1128.1, 127.2, 124.5, 120.7, 113.6, 87.3, 85.4, 55.1, 54.8, 54.4, 52.4, 36.1, 35.8, 31.4, 31.0, 22.5, 19.8, 14.0, 13.8; HRMS: m/z calcd for $C_{29}H_{31}NOBr$ [M−C_3H_7]: 488.1589; found: 488.1608.

*4.2.14. N-(2-Bromobenzyl)-N-(4-methoxybenzyl)-5-methyl-1-(4-methylphenyl)hex-1-yn-3-amine (**7n**).* 1-(2-Bromophenyl)-*N*-(4-

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methoxybenzyl)methanamine (300 mg, 0.98 mmol, 1 equiv), isobutyraldehyde (93 mg, 1.1 mmol, 1.1 equiv), *p*-tolylacetylene (171 mg, 1.5 mmol, 1.5 equiv), and CuBr (14.0 mg, 0.1 mmol, 10 mol %). The product was obtained as a yellow oil (408 mg, 85%). ^{1}H NMR ($CDCl_3$): 7.63 (1H, dd, *J*=7.7, 1.3), 7.49 (1H, d, *J*=7.9), 7.41 (2H, d, *J*=7.9), 7.31 (2H, d, *J*=8.7), 7.25 (1H, m), 7.11 (2H, *J*=7.9), 7.04 (1H, td, *J*=7.7, 1.5), 6.83 (2H, d, *J*=8.7), 3.83 (2H, d, *J*=3.0), 3.71 (5H, m), 3.50 (1H, d, *J*=13.6), 2.33 (3H, s), 1.89 (1H, m), 1.70 (1H, m), 1.55 (1H, m), 0.81 (3H, d, *J*=6.8), 0.73 (3H, d, *J*=6.8); ^{13}C NMR ($CDCl_3$): 158.6, 139.0, 137.9, 132.6, 131.7, 131.5, 130.7, 130.1, 129.0, 128.2, 127.2, 124.6, 120.5, 113.6, 87.4, 85.3, 65.9, 55.2, 54.8, 54.4, 50.6, 43.0, 24.8, 22.7, 22.2, 21.5, 15.3; HRMS: *m*/*z* calcd for $C_{25}H_{23}NOBr$ [M−C_4H_9]: 432.0963; found: 432.0960.

*4.2.15. N-Benzyl-N-((2-bromobenzyl)-5-methyl-1-phenyl)hex-1-yn-3-amine (**7o**).* *N*-Benzyl-1-(2-bromophenyl)methanamine (300 mg, 1.1 mmol, 1 equiv), isobutyraldehyde (102 mg, 1.2 mmol, 1.1 equiv), phenylacetylene (167 mg, 1.6 mmol, 1.5 equiv), and CuBr (15.7 mg, 0.11 mmol, 10 mol %). The product was obtained as a yellow oil (467 mg, 96%). ^{1}H NMR ($CDCl_3$): 7.64 (1H, d, *J*=7.5), 7.51 (3H, m), 7.41 (2H, m), 7.26 (7H, m), 7.03 (1H, td, *J*=7.6, 1.3), 3.87 (3H, m), 3.70 (1H, t, *J*=7.3), 3.58 (1H, d, *J*=13.6), 1.91 (1H, m), 1.71 (1H, m), 1.57 (1H, m), 0.81 (3H, d, *J*=6.8), 0.73 (3H, d, *J*=6.8); ^{13}C NMR ($CDCl_3$): 139.5, 138.8, 132.6, 131.8, 130.7, 129.0, 128.2, 127.9, 127.2, 127.0, 124.6, 123.6, 88.1, 85.3 65.9, 55.5, 54.6, 50.8, 433.0, 24.8, 22.7, 22.2, 15.3; HRMS: *m*/*z* calcd for $C_{23}H_{19}NOBr$ [M−C_4H_9]: 388.0701; found: 388.0691.

*4.2.16. N-(2-Bromobenzyl)-N-(4-methoxybenzyl)-4-phenylundec-10-yn-9-amine (**7p**).* 1-(2-Bromophenyl)-*N*-(4-methoxybenzyl)methanamine (300 mg, 0.98 mmol, 1 equiv), nonal (153 mg, 1.1 mmol, 1.1 equiv), phenylacetylene (143, 1.5 mmol, 1.5 equiv), and CuBr (14.0 mg, 0.1 mmol, 10 mol %). The product was obtained as a yellow oil (348 mg, 67%). ^{1}H NMR ($CDCl_3$): 7.64 (1H, d, *J*=7.5), 7.50 (3H, m), 7028 (6H, m), 7.04 (1H, m), 6.83 (2H, d, *J*=8.7), 3.82 (3H, m), 3.74 (3H, s), 3.61 (1H, t, *J*=7.5), 3.52 (1H, d, *J*=13.6), 1.75 (2H, m), 1.44 (2H, m), 1.24 (10H, m), 0.87 (3H, t, *J*=6.8); ^{13}C NMR ($CDCl_3$): 158.8, 139.1, 132.7, 131.9, 131.6, 130.7, 130.1, 128.4, 128.2, 127.9, 127.3, 124.6, 123.7, 88.3, 85.4, 55.3, 54.9, 54.5, 52.7, 33.9, 32.0, 29.6, 29.4, 29.3, 26.6, 22.8, 14.2; HRMS: *m*/*z* calcd for $C_{24}H_{22}NOBr$ [M−C_8H_{17}]: 418.0807; found: 418.0819.

*4.2.17. N-(2-Bromobenzyl)-N-(3,4-dimethoxybenzyl)-4-phenylhept-6-yn-5-amine (**7q**).* 1-(2-Bromophenyl)-*N*-(3,4-dimethoxybenzyl) methanamine (300 mg, 0.91 mmol, 1 equiv), hexanal (86 mg, 1.0 mmol, 1.1 equiv), phenylacetylene (139 mg, 1.4 mmol, 1.5 equiv), and CuBr (13.0 mg, 0.09 mmol, 10 mol %). The product was obtained as a yellow oil (414 mg, 90%). ^{1}H NMR ($CDCl_3$): 7.63 (1H, dd, *J*=7.5, 1.5), 7.51 (3H, m), 7.31 (4H, m), 7.09 (1H, td, *J*=7.5, 1.5), 6.98 (1H, d, *J*=1.5), 6.92 (1H, m), 6.80 (1H, m), 3.87 (3H, s), 3.86 (3H, s), 3.82 (3H, m), 3.62 (1H, t, *J*=7.5), 3.52 (1H, d, *J*=13.9), 1.78 (2H, m), 1.45 (2H, m), 1.26 (2H, m), 0.86 (3H, t, *J*=7.3); ^{13}C NMR ($CDCl_3$): 148.8, 148.0, 138.9, 132.7, 132.2, 131.8, 130.7, 128.3, 127.9, 127.2, 124.6, 123.6, 120.8, 112.0, 110.9, 88.1, 85.3, 55.9, 55.8, 55.1, 54.7, 53.0, 33.6, 28.9, 22.4, 14.1; HRMS: *m*/*z* calcd for $C_{25}H_{23}NO_2Br$ [M−C_4H_9]: 448.0912; found: 448.0880.

*4.2.18. N-Benzyl-N-(2-bromobenzyl)- 1,3-diphenylprop-2-yn-1-amine (**7r**).* *N*-Benzyl-1-(2-bromophenyl)methanamine (300 mg, 1.1 mmol, 1 equiv), benzaldehyde (173 mg, 1.6 mmol, 1.5 equiv), phenylacetylene (167 mg, 1.6 mmol, 1.5 equiv), and CuBr (15.6 mg, 0.11 mmol, 10 mol %). The product was obtained as a yellow oil (424 mg, 85%). ^{1}H NMR ($CDCl_3$): 7.73 (1H, d, *J*=7.5), 7.64 (3H, m), 7.50 (1H, d, *J*=7.9), 7.32 (12H, m), 7.08 (1H, m), 4.94 (1H, s), 4.0 (1H, d, *J*=14.3), 3.70 (3H, m); ^{13}C NMR ($CDCl_3$): 139.2, 138.9, 138.5, 132.7, 132.0, 130.8, 129.0, 128.40, 128.36, 128.29, 128.26, 128.1, 127.6, 127.3, 127.1, 124.7, 123.3, 88.8, 84.7, 56.5, 55.0, 54.0; HRMS: *m*/*z* calcd for $C_{23}H_{19}NOBr$ [M−C_6H_5]: 388.0701; found: 388.0691.

4.3. General procedure for the azidation−cyclization reaction

An oven-dried 10 mL screwcap reaction vial was loaded with *ortho*-bromobenzylpropargylamine (1 equiv), sodiumazide (2.5 equiv), 15-crown-5 (2.5 equiv), CuI (20 mol %), DMSO (1 mL), and a magnetic stirring bar. The vial was evacuated and then put under Argon atmosphere. The reaction was heated in oilbath at 120 °C for 32 h. After cooling down to ambient temperature diethylether (25 mL) was added. The resulting mixture was washed with water (3×25 mL) and brine (25 mL), dried over MgSO4, filtered and concentrated in vacuo. The crude product was purified via Silica gel column chromatography using a mixture of heptane/ethyl acetate (8/2) as eluant.

*4.3.1. 3-Phenyl-5-(2-methylpropyl)-4-(propan-2-yl)-5,6-dihydro-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepine (**8a**).* *ortho*-Bromobenzylpropargylamine **7a** (100 mg, 0.251 mmol, 1 equiv), sodiumazide (40.7 mg, 0.63 mmol, 2.5 equiv), 15-crown-5 (138.0 mg, 0.63 mmol, 2.5 equiv), and CuI (9.5 mg, 0.05 mmol, 20 mol %). The product was obtained as an orange oil (81.9 mg, 82%). ^{1}H NMR ($CDCl_3$): 7.90 (1H, d, *J*=7.9), 7.74 (2H, m), 7.47 (6H, m), 3.75 (1H, d, *J*=11.7), 3.58 (1H, d, *J*=10.5), 3.19 (1H, d, *J*=11.7), 2.59 (1H, dd, *J*=11.9 and 6.6), 2.37 (1H, dd, *J*=12.1 and 7.9), 1.84 (1H, m), 1.06 (1H, m), 0.97 (6H, d, *J*=6.4), 0.89 (3H, d, *J*=6.4), 0.22 (3H, d, *J*=6.8); ^{13}C NMR ($CDCl_3$): 147.2, 137.8, 133.0, 131.0, 129.0, 128.7, 128.1, 121.7, 77.5, 76.6, 67.8, 65.0, 54.7, 33.2, 26.7, 21.1, 19.4; HRMS (EI): *m*/*z* calcd for $C_{20}H_{21}N_4$ [M−$CH(CH_3)_2$]: 317.1766; found: 317.1770.

*4.3.2. 3-Cyclopropyl-4-(4′-methylphenyl)-5-(2-methylpropyl)-5,6-dihydro-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepine (**8b**).* *ortho*-Bromobenzylpropargylamine **7b** (100 mg, 0.244 mmol, 1 equiv), sodiumazide (39.7 mg, 0.61 mmol, 2.5 equiv), 15-crown-5 (134.2 mg, 0.61 mmol, 2.5 equiv), and CuI (9.5 mg, 0.05 mmol, 20 mol %). The product was obtained as an orange oil (51.2 mg, 49%). ^{1}H NMR ($CDCl_3$): 7.85 (1H, d, *J*=7.5), 7.37 (1H, m), 7.29 (2H, m), 7.12 (2H, m), 6.99 (2H, d, *J*=7.5); 4.83 (1H, s), 3.72 (2H, m), 2.39 (1H, m), 2.26 (4H, m), 1.95 (1H, m), 1.21 (1H, ddd, *J*=13.0, 8.5, 4.9), 0.98 (4H, d, *J*=6.4), 0.91 (4H, d, *J*=6.4), 0.74 (2H, m); ^{13}C NMR ($CDCl_3$): 147.3, 137.1, 136.92, 136.90, 133.9, 130.3, 129.5, 128.8, 128.4, 128.2, 127.9, 122.2, 32.1, 60.9, 52.7, 26.5, 21.03, 21.00, 7.22, 7.19, 5.9.; HRMS (EI): *m*/*z* calcd for $C_{17}H_{21}N_4$ [M−$C_6H_5CH_3$]$^+$: 281.1766; found: 281.1742.

*4.3.3. 3-Heptyl-4-pentyl-5-pentyl-5,6-dihydro-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepine (**8c**).* *ortho*-Bromobenzylpropargylamine **7c** (100 mg, 0.216 mmol, 1 equiv), sodiumazide (35.1 mg, 0.54 mmol, 2.5 equiv), 15-crown-5 (118.8 mg, 0.54 mmol, 2.5 equiv), and CuI (8.2 mg, 0.043 mmol, 20 mol %). The product was obtained as an orange oil (48.8 mg, 53%). ^{1}H NMR ($CDCl_3$): 7.86 (1H, d, *J*=7.9), 7.45 (3H, m), 3.86 (1H, br s), 3.72 (1H, d, *J*=11.7), 3.30 (1H, d, *J*=12.4), 2.66 (4H, m), 1.74 (3H, m), 1.34 (13H, m), 1.05 (6H, m), 0.91 (7H, m), 0.75 (4H, t, *J*=2×7.0); ^{13}C NMR ($CDCl_3$): 137.5, 130.7, 129.3, 128.8, 121.7, 58.1, 56.1, 55.0, 31.8, 31.2, 30.2, 29.5, 29.1, 27.4, 26.0, 25.0, 22.7, 22.6, 22.3, 14.1, 13.9; HRMS (EI): *m*/*z* calcd for $C_{22}H_{33}N_4$ [M−C_5H_{11}]$^+$: 353.2705; found: 353.2696.

*4.3.4. 3-Pentyl-4-(4′-fluorophenyl)-5-(3′-ethoxypropyl)-5,6-dihydro-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepine (**8d**).* *ortho*-Bromobenzylpropargylamine **7d** (100 mg, 0.21 mmol, 1 equiv), sodiumazide (34.5 mg, 0.53 mmol, 2.5 equiv), 15-crown-5 (117 mg, 0.53 mmol, 2.5 equiv), and CuI (8.0 mg, 0.04 mmol, 20 mol %). The product was obtained as an orange oil (38.5 mg, 49%). ^{1}H NMR ($CDCl_3$): 7.77 (1H, d, *J*=7.9), 7.38 (1H, m), 7.31 (2H, d, *J*=4.1), 7.14 (2H, dd, *J*=8.3 and *J*=5.7), 6.86 (2H, m), 4.76 (1H, s), 3.78 (1H, d, *J*=13.6), 3.49 (4H, m), 2.65 (2H, t,

J=7.2), 2.40 (1H, m), 2.23 (1H, m), 1.88 (2H, quin, *J*=6.7), 1.59 (2H, m), 1.29 (4H, m), 0.18 (3H, t, *J*=7.0), 0.87 (3H, t, *J*=7.0); ^{13}C NMR ($CDCl_3$): 160.3, 146.8, 137.0, 135.6, 135.5, 132.5, 130.4, 129.3, 129.2, 128.6, 122.3, 115.0, 114.7, 68.2, 66.3, 59.7, 52.8, 51.3, 31.7, 19.9, 28.4, 25.0, 22.4, 15.2, 14.0; HRMS (EI): *m*/*z* calcd for $C_{21}H_{29}N_4O$ $[M-C_6H_4F]^+$: 353.2341; found: 353.2352.

*4.3.5. 3-Phenyl-4-propyl-5-benzyl-5,6-dihydro-4H-[1,2,3]triazolo [1,5-a][1,4]benzodiazepine (**8e**).* *ortho*-Bromobenzylpropargylamine **7e** (100 mg, 0.23 mmol, 1 equiv), sodiumazide (38 mg, 0.58 mmol, 2.5 equiv), 15-crown-5 (127 mg, 0.58 mmol, 2.5 equiv), and CuI (8. mg, 0.046 mmol, 20 mol %). The product was obtained as an orange oil (53.7 mg, 58%). ^{1}H NMR ($CDCl_3$): 7.94 (1H, d, *J*=7.9), 7.66 (2H, dd, *J*=7.9, 1.5), 7.47 (6H, m), 7.25 (5H, m), 4.23 (1H, t, *J*=7.5), 3.83 (2H, m), 3.67 (1H, m), 3.40 (1H, d, *J*=12.4), 1.28 (1H, m), 1.01 (2H, m), 0.80 (1H, m), 0.47 (3H, t, *J*=7); ^{13}C NMR ($CDCl_3$): 146.3, 138.2, 137.6, 133.5, 130.9, 130.7, 129.3, 129.1, 129.0, 128.7, 128.4, 128.2, 127.5, 122.0, 62.2, 55.0, 54.8, 38.0, 19.3, 13.4; HRMS (EI): *m*/*z* calcd for $C_{23}H_{19}N_4$ $[M-C_3H_7]^+$: 351.1610; found: 351.1610.

*4.3.6. 3-Phenyl-4-(propan-2-yl)-5-benzyl-5,6-dihydro-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepine (**8f**).* *ortho*-Bromobenzylpropargylamine **7f** (100 mg, 0.23 mmol, 1 equiv), sodiumazide (38 mg, 0.58 mmol, 2.5 equiv), 15-crown-5 (127 mg, 0.58 mmol, 2.5 equiv), and CuI (8.8 mg, 0.046 mmol, 20 mol %). The product was obtained as an orange oil (39.2 mg, 43%). ^{1}H NMR ($CDCl_3$): 7.9 (1H, d, *J*=7.9), 7.73 (2H, dd, *J*=8.1, 1.3), 7.37 (11H, m), 3.78 (4H, m), 3.24 (1H, d, *J*=11.7), 1.13 (1H, m), 0.83 (3H, d, *J*=6.4), 0.27 (3H, d, *J*=6.4); ^{13}C NMR ($CDCl_3$): 147.3, 138.3, 137.8, 132.9, 131.0, 132.9, 131.0, 130.8, 130.4, 129.34, 129.27, 128.8, 128.4, 128.30, 128.25, 127.5, 121.8, 63.6, 63.0, 54.6, 33.2, 20.8, 19.5; HRMS (EI): *m*/*z* calcd for $C_{23}H_{19}N_4$ $[M-CH(CH_3)_2]^+$: 351.1610; found: 351.1659.

*4.3.7. 3-Phenyl-4-ethyl-5-benzyl-5,6-dihydro-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepine (**8g**).* *ortho*-Bromobenzylpropargylamine **7f** (100 mg, 0.24 mmol, 1 equiv), sodiumazide (39 mg, 0.60 mmol, 2.5 equiv), 15-crown-5 (132 mg, 0.6 mmol, 2.5 equiv), and CuI (9.1 mg, 0.048 mmol, 20 mol %). The product was obtained as an orange oil (43.2 mg, 48%). ^{1}H NMR ($CDCl_3$): 7.94 (1H, d, *J*=7.9), 7.66 (2H, m), 7.46 (6H, m), 7.24 (5H, m), 4.14 (1H, t, *J*=7.9), 3.83 (2H, m), 3.67 (1H, m), 3.40 (1H, d, *J*=12.1), 1.28 (1H, m), 1.08 (1H, m), 0.48 (3H, t, *J*=7.3); ^{13}C NMR ($CDCl_3$): 146.6, 138.2, 137.6, 133.3, 130.9, 130.7, 130.5, 129.3, 129.0, 128.8, 128.4, 128.3, 127.5, 122.0, 62.4, 56.8, 55.0, 29.0, 10.9; HRMS (EI): *m*/*z* calcd for $C_{23}H_{19}N_4$ $[M-C_2H_6]^+$: 351.1610; found: 351.1575.

*4.3.8. 3-Phenyl-4-pentyl-5-benzyl-5,6-dihydro-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepine (**8h**).* *ortho*-Bromobenzylpropargylamine **7h** (100 mg, 0.22 mmol, 1 equiv), sodiumazide (35 mg, 0.54 mmol, 2.5 equiv), 15-crown-5 (119 mg, 0.54 mmol, 2.5 equiv), and CuI (8.2 mg, 0.043 mmol, 20 mol %). The product was obtained as an orange oil (36.7 mg, 40%). ^{1}H NMR ($CDCl_3$): 7.94 (1H, d, *J*=7.5), 7.65 (2H, d, *J*=7.5), 7.47 (6H, m), 7.24 (5H, m), 4.20 (1H, m), 3.83 (2H, m), 3.67 (1H, m), 3.41 (1H, d, *J*=12.1), 1.28 (2H, m), 0.98 (4H, m), 0.75 (2H, m), 0.64 (3H, m); ^{13}C NMR ($CDCl_3$): 146.4, 138.2, 137.6, 133.5, 130.9, 130.7, 130.5, 129.3, 129.1, 129.0, 128.7, 128.3, 128.2, 127.5, 62.2, 55.1, 54.9, 35.6, 30.9, 25.6, 22.2, 13.8; HRMS (EI): *m*/*z* calcd for $C_{23}H_{19}N_4$ $[M-C_5H_{11}]^+$: 351.1610; found: 351.1628.

*4.3.9. 3-Phenyl-4-propyl-5-(4′-methoxybenzyl)-5,6-dihydro-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepine (**8i**).* *ortho*-Bromobenzylpropargylamine **7i** (100 mg, 0.22 mmol, 1 equiv), sodiumazide (35.1 mg, 0.54 mmol, 2.5 equiv), 15-crown-5 (119 mg, 0.54 mmol, 2.5 equiv), and CuI (8.2 mg, 0.043 mmol, 20 mol %). The product was obtained as an orange oil (50.0 mg, 54%). ^{1}H NMR ($CDCl_3$): 7.93 (1H, d, *J*=7.5), 7.66 (2H, dd, *J*=7.9, 1.5), 7.47 (6H, m), 7.1 (2H, d, *J*=8.7), 6.8 (2H, d, *J*=8.7), 4.23 (1H, t, *J*=7.5), 3.79 (5H, m), 3.58 (1H, d, *J*=12.8), 3.37 (1H, d, *J*=12.1), 12.7 (1H, m), 1.02 (2H, m), 0.81 (1H, m), 0.48 (3H, t, *J*=7.0); ^{13}C NMR ($CDCl_3$): 158.9, 146.3, 137.6, 133.6, 130.9, 130.7, 130.3, 130.2, 129.2, 129.0, 128.7, 128.23, 128.20, 122.0, 113.7, 61.6, 55.2, 55.0, 54.4, 38.0, 19.3, 13.4; HRMS (EI): *m*/*z* calcd for $C_{24}H_{21}N_4O$ $[M-C_3H_7]^+$: 381.1715; found: 381.1738.

*4.3.10. 3-(4′-Methylphenyl)-4-propyl-5-benzyl-5,6-dihydro-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepine (**8j**).* *ortho*-Bromobenzylpropargylamine **7j** (100 mg, 0.23 mmol, 1 equiv), sodiumazide (36 mg, 0.56 mmol, 2.5 equiv), 15-crown-5 (124 mg, 0.56 mmol, 2.5 equiv), and CuI (8.6 mg, 0.045 mmol, 20 mol %). The product was obtained as an orange oil (41.4 mg, 45%). ^{1}H NMR ($CDCl_3$): 7.94 (1H, d, *J*=7.9), 7.52 (3H, m), 7.41 (2H, m), 7.26 (7H, m), 4.22 (1H, t, *J*=7.5), 3.82 (2H, m), 3.68 (1H, m), 3.39 (1H, d, *J*=12.4), 2.43 (3H, s), 1.28 (2H, m), 1.0 (2H, m), 0.83 (2H, m), 0.47 (3H, t, *J*=7); ^{13}C NMR ($CDCl_3$): 146.4, 138.3, 137.6, 133.3, 130.6, 130.4, 129.4, 129.3, 129.1, 128.9, 128.3, 128.1, 128.0, 127.4, 122.0, 62.3, 55.00, 54.96, 38.0, 35.4, 21.3, 19.3, 13.8; HRMS (EI): *m*/*z* calcd for $C_{24}H_{21}N_4$ $[M-C_3H_7]^+$: 365.1766; found: 365.1763.

*4.3.11. 3-(4′-Methylphenyl)-4-propyl-5-(4′-methoxybenzyl)-5,6-dihydro-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepine (**8k**).* *ortho*-Bromobenzylpropargylamine **7k** (100 mg, 0.21 mmol, 1 equiv), sodiumazide (34 mg, 0.53 mmol, 2.5 equiv), 15-crown-5 (116 mg, 0.53 mmol, 2.5 equiv), and CuI (8.0 mg, 0.042 mmol, 20 mol %). The product was obtained as an orange oil (71.3 mg, 77%). ^{1}H NMR ($CDCl_3$): 7.93 (1H, d, *J*=7.9), 7.51 (2H, m), 7.40 (2H, m), 7.27 (2H, d, *J*=7.9), 7.12 (2H, d, *J*=8.7), 6.80 (2H, d, *J*=8.7), 4.22 (1H, t, *J*=7.5), 3.78 (5H, m), 3.60 (1H, m), 3.36 (1H, d, *J*=12.4), 2.43 (3H, s), 1.25 (1H, m), 1.01 (2H, m), 0.82 (1H, m), 0.48 (3H, t, *J*=7.0); ^{13}C NMR ($CDCl_3$): 158.9, 146.3, 138.0, 137.6, 133.3, 130.7, 130.4, 130.3, 129.4, 129.2, 128.9, 128.1, 128.0, 121.9, 113.7, 61.6, 55.2, 54.9, 54.5, 38.0, 21.3, 19.3, 13.4; HRMS (EI): *m*/*z* calcd for $C_{25}H_{23}N_4O$ $[M-C_3H_7]^+$: 395.1872; found: 395.1875.

*4.3.12. 3-(4′-Ethyl-phenyl)-4-propyl-5-benzyl-5,6-dihydro-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepine (**8l**).* *ortho*-Bromobenzylpropargylamine **7l** (100 mg, 0.22 mmol, 1 equiv), sodiumazide (36 mg, 0.56 mmol, 2.5 equiv), 15-crown-5 (123 mg, 0.56 mmol, 2.5 equiv), and CuI (8.6 mg, 0.045 mmol, 20 mol %). The product was obtained as an orange oil (48.3 mg, 53%). ^{1}H NMR ($CDCl_3$): 7.93 (1H, d, *J*=7.9), 7.58 (2H, d, *J*=7.9), 7.51 (1H, m), 7.4 (2H, m), 7.26 (7H, m), 4.13 (1H, t, *J*=8.1), 3.82 (2H, m), 3.68 (1H, m), 3.39 (1H, d, *J*=12.1), 2.73 (2H, q, *J*=7.5), 1.31 (4H, m), 1.07 (1H, dt, *J*=14.1, 7.3), 0.49 (3H, t, *J*=7.3); ^{13}C NMR ($CDCl_3$): 146.6, 144.4, 138.3, 137.6, 133.0, 130.7, 130.4, 129.3, 129.1, 128.9, 128.3, 128.31, 128.25, 128.20, 127.4, 122.0, 62.3, 56.8, 54.9, 29.0, 28.7, 15.6, 10.9; HRMS (EI): *m*/*z* calcd for $C_{25}H_{23}N_4$ $[M-C_2H_5]^+$: 379.1923; found: 379.1949.

*4.3.13. 3-(4′-Pentyl-phenyl)-4-propyl-5-(4′-methoxybenzyl)-5,6-dihydro-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepine (**8m**).* *ortho*-Bromobenzylpropargylamine **7m** (100 mg, 0.19 mmol, 1 equiv), sodiumazide (31 mg, 0.47 mmol, 2.5 equiv), 15-crown-5 (103 mg, 0.47 mmol, 2.5 equiv), and CuI (7.2 mg, 0.038 mmol, 20 mol %). The product was obtained as an orange oil (65.6 mg, 71%). ^{1}H NMR ($CDCl_3$): 7.93 (1H, d, *J*=7.5), 7.57 (2H, d, *J*=7.9), 7.50 (1H, m), 7.27 (2H, m), 7.1 (2H, d, *J*=8.3), 6.80 (2H, d, *J*=8.7), 4.22 (1H, t, *J*=7.3), 3.77 (5H, m), 3.58 (1H, d, *J*=12.8), 3.36 (1H, d, *J*=12.1), 2.69 (2H, t, *J*=7.7), 1.69 (2H, m), 1.38 (4H, m), 1.25 (1H, m), 1.01 (2H, m), 0.92 (3H, t, *J*=6.6), 0.81 (1H, m), 0.48 (3H, t, *J*=7.0); ^{13}C NMR ($CDCl_3$): 158.9, 146.4, 143.1, 137.7, 133.3, 130.7, 130.5, 130.4, 130.3, 129.2, 128.9, 128.8, 128.2, 128.1, 122.0, 113.7, 61.6, 55.2, 55.0, 54.4, 38.0, 35.7, 31.5, 31.2, 22.6, 19.3, 14.1, 13.4; HRMS (EI): *m*/*z* calcd for $C_{29}H_{31}N_4O$ $[M-C_3H_7]^+$: 451.2498; found: 451.2540.

4.3.14. 3-(4′-Methyl-phenyl)-4-(2′-metylpropyl)-5-(4′-methoxybenzyl)-5,6-dihydro-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepine

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(***8n***). *ortho*-Bromobenzylpropargylamine **7n** (100 mg, 0.20 mmol, 1 equiv), sodiumazide (33 mg, 0.51 mmol, 2.5 equiv), 15-crown-5 (112 mg, 0.51 mmol, 2.5 equiv), and CuI (7.6 mg, 0.04 mmol, 20 mol %). The product was obtained as an orange oil (51.5 mg, 56%). ^{1}H NMR ($CDCl_3$): 7.94 (1H, d, J=7.5), 7.52 (3H, m), 7.41 (2H, d), 7.27 (2H, d, J=8.3); 7.13 (2H, d, J=8.7), 6.83 (2H, m), 4.28 (1H, t, J=7.5), 3.8 (5H, m), 3.62 (1H, m), 3.39 (1H, d, J=12.4), 2.44 (3H, s), 1.20 (3H, m), 0.88 (1H, m), 0.44 (3H, d, J=2.3), 0.42 (3H, d, J=2.3); ^{13}C NMR ($CDCl_3$): 159.0, 146.2, 138.0, 133.6, 130.7, 130.4, 130.33, 130.27, 129.4, 129.2, 128.9, 128.0, 128.2, 122.0, 113.7, 61.5, 55.3, 55.0, 52.9, 45.0, 24.5, 22.4, 22.0, 21.3; HRMS (EI): m/z calcd for $C_{25}H_{23}N_4O$ $[M-CH_2CH(CH_3)]^+$: 395.1872; found: 395.1897.

4.3.15. 3-Phenyl-4-(2′metylpropyl)-5-benzyl-5,6-dihydro-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepine (***8o***). *ortho*-Bromobenzylpropargylamine **7o** (100 mg, 0.22 mmol, 1 equiv), sodiumazide (36 mg, 0.56 mmol, 2.5 equiv), 15-crown-5 (123 mg, 0.56 mmol, 2.5 equiv), and CuI (8.5 mg, 0.045 mmol, 20 mol %). The product was obtained as an orange oil (59.4 mg, 57%). ^{1}H NMR ($CDCl_3$): 7.95 (1H, d, J=7.5), 7.66 (2H, m), 7.46 (6H, m), 7.25 (5H, m), 4.28 (1H, t, J=7.5), 3.85 (2H, m), 3.68 (1H, m), 3.42 (1H, d, J=12.4), 1.20 (2H, m), 0.92 (1H, m), 0.41 (3H, s), 0.389 (3H, s); ^{13}C NMR ($CDCl_3$): 146.2, 138.1, 133.7, 130.9, 130.6, 130.5, 129.3, 123.2, 128.9, 128.8, 128.3, 128.24, 128.17, 127.5, 62.1, 55.1, 23.0, 44.9, 24.5, 22.6, 21.9; HRMS (EI): m/z calcd for $C_{23}H_{19}N_4$ $[M-CH_2CH(CH_3)]^+$: 351.1610; found: 351.1599.

4.3.16. 3-Phenyl-4-octyl-5-(4′-methoxybenzyl)-5,6-dihydro-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepine (***8p***). *ortho*-Bromobenzylpropargylamine **7p** (100 mg, 019 mmol, 1 equiv), sodiumazide (31 mg, 0.47 mmol, 2.5 equiv), 15-crown-5 (103 mg, 0.47 mmol, 2.5 equiv), and CuI (6.9 mg, 0.036 mmol, 20 mol %). The product was obtained as an orange oil (53.7 mg, 58%). ^{1}H NMR ($CDCl_3$): 7.93 (1H, d, J=7.9), 7.66 (2H, dd, J=7.7, 1.3), 7.52 (1H, m), 7.46 (2H, d, J=7.5), 7.42 (2H, m), 7.10 (2H, d, J=8.7), 6.80 (2H, d, J=8.7), 4.21 (1H, m), 3.79 (5H, m), 3.58 (1H, d, J=12.4), 1.22 (3H, m), 1.01 (8H, m), 0.8 (7H, m); ^{13}C NMR ($CDCl_3$): 158.9, 146.4, 137.6, 133.5, 131.0, 130.8, 130.5, 130.3, 130.2, 129.2, 129.0, 128.7, 128.3, 128.2, 122.0, 113.7, 61.5, 55.2, 55.0, 54.4, 35.6, 31.7, 29.1, 29.0, 28.7, 25.9, 22.6, 14.0; HRMS (EI): m/z calcd for $C_{24}H_{21}N_4O$ $[M-C_8H_{17}]^+$: 381.1715; found: 381.1693.

4.3.17. 3-Phenyl-4-butyl-5-(3′,4′-dimethoxybenzyl)-5,6-dihydro-4H-[1,2,3]triazolo[1,5-a][1,4]benzodiazepine (***8q***). *ortho*-Bromobenzylpropargylamine **7q** (100 mg, 0.20 mmol, 1 equiv), sodiumazide (32 mg, 0.50 mmol, 2.5 equiv), 15-crown-5 (109 mg, 0.50 mmol, 2.5 equiv), and CuI (7.6 mg, 0.04 mmol, 20 mol %). The product was obtained as an orange oil (53.6 mg, 58%). ^{1}H NMR ($CDCl_3$) 7.94 (1H, d, J=7.5), 7.65 (2H, m), 7.52 (1H, m), 7.46 (1H, m), 7.43 (3H, m), 6.89 (1H, d, J=1.5), 6.74 (1H, m), 6.64 (1H, m), 4.22 (1H, m), 3.88 (3H, s), 3.82 (5H, m), 3.58 (1H, d, J=12.8), 3.40 (1H, d, J=12.1), 1.28 (1H, m), 1.03 (2H, m), 0.86 (2H, m), 0.73 (1H, m), 0.58 (3H, t, J=7.9); ^{13}C NMR ($CDCl_3$): 7.94 (1H, d, J=7.5), 7.65 (2H, m), 7.47 (6H, m), 6.89 (1H, d, J=1.5), 6.64 (1H, m), 4.22 (1H, m), 3.83 (8H, m), 3.58 (1H, d, J=12.1), 1.28 (1H, m), 1.03 (2H, m), 0.88 (2H, m), 0.73 (1H, m), 0.58 (3H, m); HRMS (EI): m/z calcd for $C_{25}H_{23}N_4O_2$ $[M-C_4H_9]^+$: 411.1821; found: 411.1814.

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Supplementary data

Characterization for all compounds. Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2013.03.031.

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