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An easy access to 4-(1,2,3-triazolylalkyl)-1,2,3-triazole-fused dihydroisoquinolines and dihydroisoindoles

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ABSTRACT

A convenient synthesis of 4-(1,2,3-triazolylalkyl)-1,2,3-triazole fused dihydroisoquinolines and dihydroisoindoles is reported, starting from easily available (2-iodoaryl)alkyl azides and terminal alkynols. The procedure is based upon transition-metal catalyzed coupling reactions followed by iterative cycloaddition reactions.

1. Introduction

The 1,2,3-triazole ring is considered an important pharmacophore in drug discovery research, and is common amongst various compounds of biological significance.[1] These compounds were traditionally synthesized by the Huisgen's thermal 1,3-dipolar [3+2]-cycloaddition of azides with alkynes,[2] but the original reactions were seriously limited by the high reaction temperature and by the low regioselectivity leading to 1,4- and 1,5-substituted-1,2,3-triazoles. Significant advances have been obtained in this field by the copper(I)-catalyzed 1,3-dipolar cycloaddition reaction of azides with alkynes (CuAAC), the most prominent example of 'click chemistry', developed by the groups of Sharpless[3] and Meldal.[4] Mild, efficient metal catalyzed variants for both terminal- and internal alkynes are now available.[5] These reactions can be conducted at room temperature and are highly regioselective, leading exclusively to 4-substituted-1,2,3-triazoles. The extraordinary success of click chemistry has led to a wide number of publications over the last few years.[6,7] In particular, this methodology has been used by many research groups for the synthesis of several bicyclic, as well as polycyclic fused triazoles heterocycles,[8] compounds of great interest for their various biological and pharmacological activities.[8,9] Generally, fused triazoles are prepared by an intramolecular 1,3-dipolar cycloaddition between azides and alkynes[8a,c,j] and a one-pot copper-[8d] or palladium-catalyzed[8f,g] coupling reaction followed by a [3+2] cycloaddition.

In connection with our continuing interest in the development of novel heterocyclic ring structures of biological signficance,[10] we have recently developed a general approach to novel unsymmetrically substituted 4,4′-bi-1,2,3-triazoles,[11a] an easy synthesis of 1,2,3-triazole-fused heterocycles[11b] and N–C linked 1,2,3-triazole oligomers,[11c] and a general procedure for the synthesis of 1,2,3-triazole-fused dihydroisoquinolines.[11d] On the basis of these results, we now report the extensions of our initial discovery dealing with 1,2,3-triazole fused-heterocycles, that have led to the facile synthesis of 4-(1,2,3-triazolylakyl)-1,2,3-triazole-fused-heterocycles and of more complex derivatives containing additional triazole rings. The methodology is based on the use of easily available azides subjected to coupling reactions with several alkynols, leading to difunctional compounds bearing a hydroxyl group as the site for azide substitution, followed by an iterative formation of triazole rings.

2. Results and discussion

Our strategy is outlined in Scheme 1. We started with the coupling reactions between 2-(2-iodoaryl)alkylazides **1**, 2-iodobenzylazide (m=0) and 2-(2-iodophenyl)ethyl azide (m=1) with several terminal alkynols **2** (n=1,2,3) leading to the corresponding coupled products **3** that were easily transformed into the fused triazoles **4** by means of a thermal intramolecular [3+2] cycloaddition reaction in toluene, without a catalyst. In order to obtain the desired final products **8** it was necessary to convert the fused triazoles alcohols **4** into the corresponding azides **7**. Thus the compounds **4** were easily

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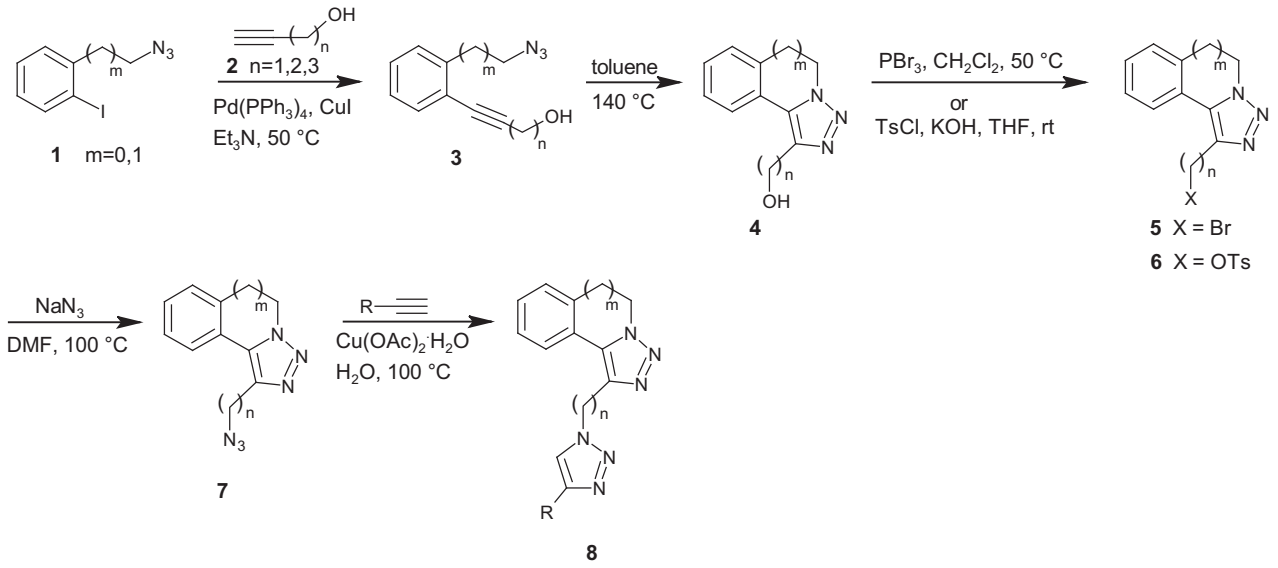


Scheme 1.

transformed into bromoderivatives **5** or tosyl derivative **6**, that, by reaction with NaN_3 in DMF led to the azides **7**. The final cycloaddition reaction of the azides **7** with several aryl- and alkylalkynes afforded the 4-(1,2,3-triazolylalkyl)-substituted-1,2,3-triazole-fused dihydroisoquinolines and dihydroisoindoles **8**.

All results are depicted in Table 1. The products **3**–**7** were obtained in fair to good yields. High yields were obtained in the cycloaddition reactions, compounds **8a**,**b**,**d**,**f**, (80–95%), whereas fair to good yields (49–82%) were obtained for compounds **8c**,**e**,**g**.

In order to demonstrate the versatility of our strategy, we decided to increase the number of triazole rings linked to the fused heterocycles by simple variation of the alkyne in the cyclization reaction involving compound **7**. As reported in Scheme 2, starting from compound **7c** and employing 4-bromo-1-butyne, the resulting product **9**, obtained in 71% yield, was easily transformed into azide **10** (98% yield) that was subjected to the cycloaddition reaction with two alkynes leading to products **11a**,**b** in high yields (85% and 90%). It is worth noting that, following the same approach, but starting from compound **10** and employing, in the cycloaddition reaction, instead of a simple alkyne, the bromoalkyne, we can, in principle, considerably increase the number of triazole rings linked to the fused heterocycles.

3. Conclusion

In summary, we have described an efficient and easy method for the synthesis of 4-(1,2,3-triazolylakyl)-1,2,3-triazole-fused-heterocycles **8**, starting from readily available terminal alkynols and azides and employing simple coupling reactions and appropriate transformation of the alcoholic group in the azide function to obtain the title compounds. Moreover, this procedure is greatly versatile, as demonstred by the synthesis of compounds **11**, with additional triazole rings linked to the fused heterocycles.

4. Experimental section

4.1. General

Macherey–Nagel silica gel (60, particle size 0.040–0.063 mm) for column chromatography and Macherey–Nagel aluminum sheets with silica gel 60 F_{254} for TLC were used. GC analysis was performed on a Varian 3900 gas chromatograph equipped with a Supelco SLB™-5 ms capillary column (30 m×0.25 mm id). GC/mass-spectrometry analysis was performed on a Shimadzu GC–MS-QP5000 gas chromatograph-mass spectrometer equipped with a Supelco SLB™-5 ms capillary column (30 m×0.25 mm id). ^1H NMR spectra were recorded in deuterochloroform or DMSO-d_6 on a Varian Inova at 400 MHz. ^{13}C NMR spectra were recorded in deuterochloroform or DMSO-d_6 on a Varian Inova at 100.6 MHz. IR spectra were recorded on a Perkin–Elmer FT-IR Spectrum Bx. Elemental analyses were recorded on a Carlo Erba EA 1108 elemental analyzer. Melting points were determined on a Stuart Scientific Melting point apparatus SMP3. Tetrahydrofuran was distilled from sodium, *N*,*N*-dimethylformamide, toluene, and triethylamine were used as supplied.

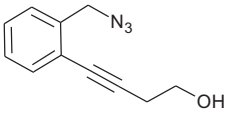
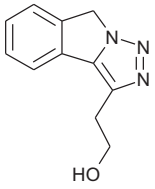
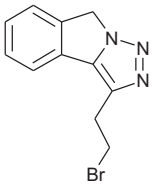
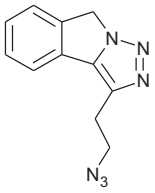
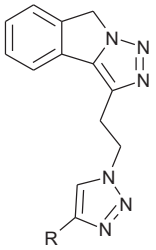
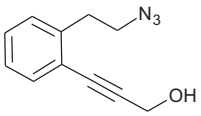
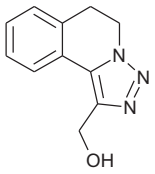
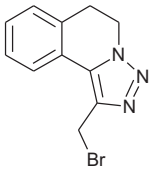
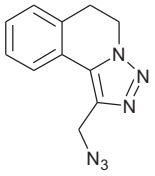
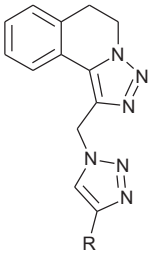
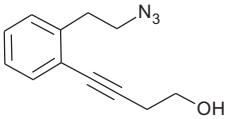
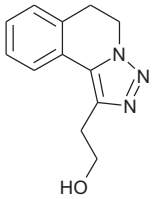
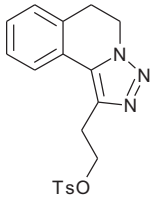
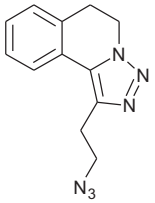
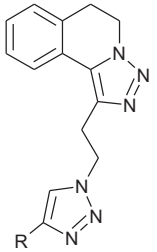
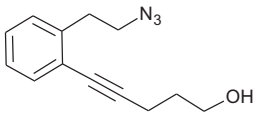
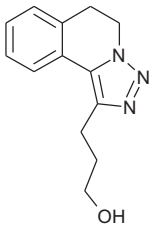
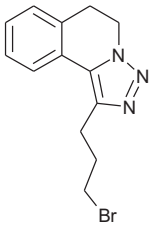
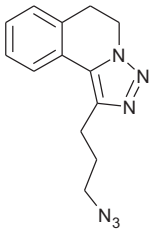
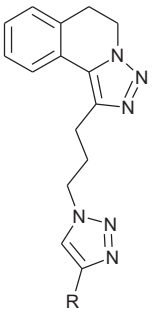
4.2. General procedure for the synthesis of compounds 3

Alkyn-1-ol (2 equiv) was added at room temperature under nitrogen to a stirred suspension (0.25–0.29 M) of 2-(2-iodophenyl) ethylazide or 2-iodobenzylazide (1 equiv), $Pd(PPh_3)_4$ (0.04 equiv), CuI (0.08 equiv) in Et_3N. The mixture was heated at 50 °C for 2 h, then quenched with a saturated aqueous solution of NH_4Cl (50 mL) and extracted with ethyl acetate (3×60 mL). The organic extracts were washed with an aqueous solution of NaCl (3×50 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography.

*4.2.1. 4-[2-(Azidomethyl)phenyl]but-3-yn-1-ol (**3a**).* Compound **3a** was prepared from but-3-yn-1-ol (0.811 g, 11.58 mmol) and 2-iodobenzylazide (1.500 g, 5.79 mmol) in accordance with the general procedure. Purification by column chromatography, R_f (silica gel, 30% ethyl acetate/hexane) 0.41, afforded 0.570 g of compound **3a** (49% yield) as a yellow-orange oil. [Found: C, 65.70; H, 5.48; N, 20.93. $C_{11}H_{11}N_3O$ requires C, 65.66; H, 5.51; N, 20.88%]. ν_{max} (neat) 3365, 3065, 2936, 2882, 2090, 1481, 1446, 1381, 1343, 1262, 1191, 1046, 760; δ_H (400 MHz, $CDCl_3$) 7.44 (dd, *J*=6.2, 1.8 Hz, 1H), 7.30–7.22 (m, 3H), 4.45 (s, 2H), 3.80 (t, *J*=6.4 Hz, 2H), 2.75 (br s, 1H), 2.69 (t, *J*=6.4 Hz, 2H); δ_C (100.6 MHz, $CDCl_3$) 137.1, 132.4, 128.6, 128.2, 128.1, 123.2, 92.3, 79.7, 61.0, 53.5, 23.9; MS *m*/*z* 201 (M^+, 14), 172 (29), 154 (25), 144 (90), 143 (71), 128 (18), 127 (19), 118 (100), 115 (85), 102 (12), 90 (77), 89 (52), 77 (24), 63 (36), 51 (26), 39 (66%).

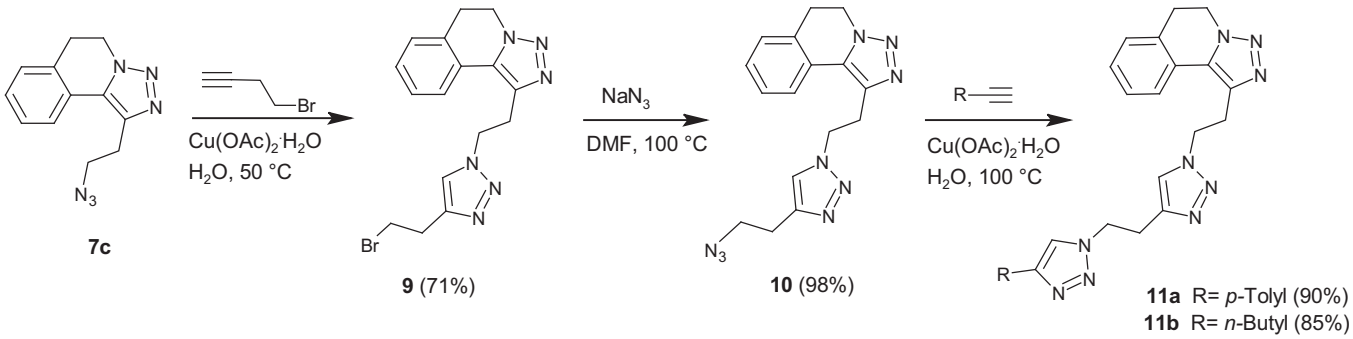
*4.2.2. 3-[2-(2-Azidoethyl)phenyl]prop-2-yn-1-ol (**3b**).* Compound **3b** was prepared from prop-2-yn-1-ol (0.617 g, 10.99 mmol) and 2-

Table 1
Synthesis of compounds **8** according to Scheme 1

m	*n*	**3** Yield (%)	**4** Yield (%)	**5** Yield (%)	**6** Yield (%)	**7** Yield (%)	**8** Yield (%)
0	2	 **3a** (49)	 **4a** (46)	 **5a** (41)		 **7a** (82)	 **8a** R = Ph (80)
1	1	 **3b** (58)	 **4b** (86)	 **5b** (61)		 **7b** (89)	 **8b** R = *p*-Anisyl (87) **8c** R = Cyclohexyl (49)
1	2	 **3c** (58)	 **4c** (63)		 **6c** (82)	 **7c** (96)	 **8d** R = Ph (81) **8e** R = *n*-Pentyl (82)
1	3	 **3d** (59)	 **4d** (78)	 **5d** (46)		 **7d** (82)	 **8f** R = *p*-Tolyl (95) **8g** R = *n*-Pentyl (77)

(2-iodophenyl)ethylazide (1.500 g, 5.50 mmol) in accordance with the general procedure. Purification by column chromatography, R_f (silica gel, 30% ethyl acetate/hexane) 0.60, afforded 0.641 g of compound **3b** (58% yield) as a yellow oil. [Found: C, 65.71; H, 5.52; N, 20.85. $C_{11}H_{11}N_3O$ requires C, 65.66; H, 5.51; N, 20.88%]. ν_{max} (neat) 3363, 3063, 2927, 2866, 2090, 1481, 1449, 1349, 1294, 1260, 1025, 953, 761; δ_H (400 MHz, $CDCl_3$) 7.41 (d, J=7.2 Hz, 1H), 7.26–7.20 (m, 1H), 7.19–7.11 (m, 2H), 4.50 (s, 2H), 3.46 (t, J=7.2 Hz, 2H), 3.37 (br s, 1H), 3.02 (t, J=7.2 Hz, 2H); δ_C (100.6 MHz, $CDCl_3$) 139.6, 132.4, 129.1, 128.5, 126.6, 122.2, 91.4, 83.1, 51.2, 51.0, 33.8; MS *m*/*z* 201 (M^+, 54), 172 (67), 156 (19), 144 (68), 130 (41), 115 (100), 103 (34), 89 (24), 77 (58), 63 (31), 58 (24), 51 (39), 39 (57%).

*4.2.3. 4-[2-(2-Azidoethyl)phenyl]but-3-yn-1-ol (**3c**).* Compound **3c** was prepared from but-3-yn-1-ol (0.770 g, 10.99 mmol) and 2-(2-iodophenyl)ethylazide (1.500 g, 5.50 mmol) in accordance with the general procedure. Purification by column chromatography, R_f (silica gel, 30% ethyl acetate/hexane) 0.48, afforded 0.685 g of compound **3c** (58% yield) as a yellow oil. [Found: C, 67.00; H, 6.12; N, 19.63. $C_{12}H_{13}N_3O$ requires C, 66.96; H, 6.09; N, 19.52%]. ν_{max}



Scheme 2.

(neat) 3365, 3062, 2930, 2879, 2101, 1481, 1444, 1288, 1259, 1044, 757; δ_H (400 MHz, $CDCl_3$) 7.42–7.37 (m, 1H), 7.25–7.13 (m, 3H), 3.81 (t, *J*=6.4 Hz, 2H), 3.49 (t, *J*=7.4 Hz, 2H), 3.04 (t, *J*=7.4 Hz, 2H), 2.70 (t, *J*=6.4 Hz, 2H), 2.30 (br s, 1H); δ_C (100.6 MHz, $CDCl_3$) 139.6, 132.4, 129.2, 128.1, 126.7, 123.2, 90.9, 80.3, 61.2, 51.5, 34.2, 23.8; MS *m*/*z* 215 (M^+, 25), 185 (100), 158 (41), 156 (39), 154 (19), 141 (18), 130 (63), 129 (55), 128 (62), 115 (59), 104 (21), 103 (21), 91 (11), 89 (11), 77 (51), 63 (18), 51 (26), 39 (28%).

*4.2.4. 5-[2-(2-Azidoethyl)phenyl]pent-4-yn-1-ol (**3d**).* Compound **3d** was prepared from pent-4-yn-1-ol (0.925 g, 11.00 mmol) and 2-(2-iodophenyl)ethylazide (1.500 g, 5.50 mmol) in accordance with the general procedure. Purification by column chromatography, R_f (silica gel, 30% ethyl acetate/hexane) 0.40, afforded 0.743 g of compound **3d** (59% yield) as a yellow oil. [Found: C, 68.15; H, 6.63; N, 18.43. $C_{13}H_{15}N_3O$ requires C, 68.10; H, 6.59; N, 18.33%]. ν_{max} (neat) 3365, 3062, 2931, 2872, 2085, 1481, 1442, 1381, 1349, 1294, 1261, 1052, 757; δ_H (400 MHz, $CDCl_3$) 7.40–7.34 (m, 1H), 7.23–7.12 (m, 3H), 3.78 (t, *J*=6.2 Hz, 2H), 3.47 (t, *J*=7.4 Hz, 2H), 3.03 (t, *J*=7.4 Hz, 2H), 2.55 (t, *J*=7.0 Hz, 2H), 2.28 (br s, 1H), 1.89–1.80 (m, 2H); δ_C (100.6 MHz, $CDCl_3$) 139.2, 132.3, 129.2, 127.9, 126.6, 123.3, 93.6, 78.9, 61.4, 51.3, 34.1, 31.3, 15.9; MS *m*/*z* 229 (M^+, 14), 199 (43), 198 (32), 185 (100), 172 (24), 170 (25), 156 (40), 145 (36), 144 (36), 130 (52), 129 (42), 128 (56), 115 (70), 103 (23), 91 (17), 89 (16), 77 (56), 63 (19), 51 (31), 39 (48%).

4.3. General procedure for the synthesis of compounds 4

A solution (0.23–0.50 M) of compound **3** in toluene was heated at 140 °C for 24–30 h in a capped flask. Compound **4b** was recovered by filtration, then purified by crystallization. For compounds **4a**,**c**,**d**, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (30 mL) and extracted with ethyl acetate (3×40 mL). The organic extracts were washed with an aqueous solution of NaCl (3×30 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography.

*4.3.1. 2-(8H-[1,2,3]Triazolo[5,1-a]isoindol-3-yl)ethanol (**4a**).* Compound **4a** was prepared from **3a** (0.509 g, 2.53 mmol) in accordance with the general procedure. Purification by column chromatography, R_f (silica gel, ethyl acetate) 0.23, afforded 0.234 g of compound **4a** (46% yield). After crystallization from ethyl acetate, compound **4a** was obtained as a white solid, mp=130–132 °C. [Found: C, 65.73; H, 5.54; N, 20.93. $C_{11}H_{11}N_3O$ requires C, 65.66; H, 5.51; N, 20.88%]. ν_{max} (KBr) 3306, 2924, 2858, 1446, 1440, 1429, 1408, 1145, 1047, 1010, 768, 731; δ_H (400 MHz, $CDCl_3$+D_2O) 7.63 (d, *J*=7.6 Hz, 1H), 7.48–7.38 (m, 2H), 7.37–7.31 (m, 1H), 5.23 (s, 2H), 4.01 (t, *J*=6.0 Hz, 2H), 3.13 (t, *J*=6.0 Hz, 2H); δ_C (100.6 MHz, $CDCl_3$) 140.5, 140.1, 136.2, 128.7, 128.1, 127.9, 124.0, 121.0, 61.4, 51.0, 28.9; MS *m*/*z* 201 (M^+, 14), 172 (24), 154 (19), 144 (84), 143 (64), 130 (20), 118 (100), 115 (85), 90 (71), 77 (22), 63 (36), 51 (26), 39 (64%).

*4.3.2. (5,6-Dihydro-[1,2,3]triazolo[5,1-a]isoquinolin-1-yl)methanol (**4b**).* Compound **4b** was prepared from **3b** (0.637 g, 3.17 mmol) in accordance with the general procedure. The reaction mixture was cooled and crude product was recovered by filtration under vacuum. Purification by crystallization from ethyl acetate/hexane afforded 0.547 g of compound **4b** (86% yield) as a white solid, mp=137–139 °C. [Found: C, 65.68; H, 5.47; N, 20.91. $C_{11}H_{11}N_3O$ requires C, 65.66; H, 5.51; N, 20.88%]. ν_{max} (KBr) 3255, 3047, 2934, 2856, 1483, 1430, 1341, 1188, 1150, 1116, 1034, 1022, 758, 729, 677, 629; δ_H (400 MHz, $CDCl_3$+D_2O) 7.86 (d, *J*=7.6 Hz, 1H), 7.39–7.22 (m, 3H), 4.92 (s, 2H), 4.48 (t, *J*=6.8 Hz, 2H), 3.14 (t, *J*=6.8 Hz, 2H); δ_C (100.6 MHz, $CDCl_3$) 142.1, 132.3, 131.2, 129.2, 128.2, 128.1, 125.8, 124.5, 56.4, 44.8, 29.0; MS *m*/*z* 201 (M^+, 56), 172 (69), 156 (19), 144 (68), 130 (41), 115 (100), 103 (35), 89 (23), 77 (60), 63 (31), 57 (24), 51 (40), 39 (57%).

*4.3.3. 2-(5,6-Dihydro-[1,2,3]triazolo[5,1-a]isoquinolin-1-yl)ethanol (**4c**).* Compound **4c** was prepared from **3c** (0.683 g, 2.19 mmol) in accordance with the general procedure. Purification by column chromatography, R_f (silica gel, 10% hexane/ethyl acetate) 0.34, afforded 0.430 g of compound **4c** (63% yield). After crystallization from ethyl acetate, compound **4c** was obtained as a white solid, mp=99–101 °C. [Found: C, 66.98; H, 6.13; N, 19.53. $C_{12}H_{13}N_3O$ requires C, 66.96; H, 6.09; N, 19.52%]. ν_{max} (KBr) 3304, 2946, 2914, 2861, 1469, 1434, 1191, 1151, 1047, 1017, 776, 742, 682; δ_H (400 MHz, $CDCl_3$+D_2O) 7.60 (d, *J*=7.6 Hz, 1H), 7.32–7.21 (m, 3H), 4.45 (t, *J*=6.8 Hz, 2H), 4.02 (t, *J*=6.2 Hz, 2H), 3.20–3.07 (m, 4H); δ_C (100.6 MHz, $CDCl_3$) 140.4, 132.3, 129.7, 128.7, 128.4, 127.6, 124.9, 124.1, 60.8, 44.6, 29.3, 29.0; MS *m*/*z* 215 (M^+, 22), 185 (100), 158 (38), 156 (37), 154 (17), 141 (16), 130 (59), 129 (53), 128 (59), 115 (57), 104 (20), 103 (20), 91 (11), 89 (10), 77 (44), 63 (18), 51 (25), 39 (23%).

*4.3.4. 3-(5,6-Dihydro-[1,2,3]triazolo[5,1-a]isoquinolin-1-yl)propan-1-ol (**4d**).* Compound **4d** was prepared from **3d** (0.743 g, 3.25 mmol) in accordance with the general procedure. Purification by column chromatography, R_f (silica gel, ethyl acetate) 0.27, afforded 0.580 g of compound **4d** (78% yield). After crystallization from ethyl acetate/hexane, compound **4d** was obtained as a pale yellow solid, mp=71–72 °C. [Found: C, 68.16; H, 6.61; N, 18.37. $C_{13}H_{15}N_3O$ requires C, 68.10; H, 6.59; N, 18.33%]. ν_{max} (KBr) 3395, 3193, 2929, 2863, 1470, 1442, 1372, 1346, 1193, 1150, 1058, 1044, 764, 734; δ_H (400 MHz, $CDCl_3$+D_2O) 7.57 (d, *J*=7.6 Hz, 1H), 7.30–7.18 (m, 3H), 4.43 (t, *J*=6.8 Hz, 2H), 3.67 (t, *J*=6.0 Hz, 2H), 3.10 (t, *J*=6.8 Hz, 2H), 3.01 (t, *J*=7.4 Hz, 2H), 2.04–1.95 (m, 2H); δ_C (100.6 MHz, $CDCl_3$) 142.5, 132.3, 129.0, 128.5, 128.3, 127.6, 125.1, 124.1, 61.4, 44.6, 31.2, 29.0, 22.8; MS *m*/*z* 229 (M^+, 14), 199 (43), 198 (32), 185 (100), 172 (24), 170 (26), 156 (40), 145 (37), 144 (37), 130

(57), 129 (42), 128 (58), 115 (76), 103 (24), 91 (15), 89 (16), 77 (57), 63 (20), 51 (31), 39 (48%).

4.4. General procedure for the synthesis of compounds 5a,b,d

PBr_3 (2 equiv) was added at room temperature to a solution (0.20–0.35 M) of compounds **4a**,**b**,**d** (1 equiv) in CH_2Cl_2. The mixture was heated at 50 °C and, after completion (2–5 h), was quenched with a saturated aqueous solution of $NaHCO_3$ (30 mL) and extracted with ethyl acetate (3×40 mL). The organic extracts were washed with an aqueous solution of NaCl (3×30 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by percolation.

*4.4.1. 3-(2-Bromoethyl)-8H-[1,2,3]triazolo[5,1-a]isoindole (**5a**).* Compound **5a** was prepared from **4a** (0.234 g, 1.17 mmol) and PBr_3 (0.638 g, 2.34 mmol) in accordance with the general procedure. Purification by percolation, R_f (florisil, ethyl acetate) 0.68, afforded 0.127 g of compound **5a** (41% yield). After crystallization from ethyl acetate/hexane, compound **5a** was obtained as a white solid, mp=131–132 °C. [Found: C, 50.15; H, 3.90; N, 15.94. $C_{11}H_{10}BrN_3$ requires C, 50.02; H, 3.82; N, 15.91%]. ν_{max} (KBr) 3069, 2958, 2856, 1454, 1429, 1273, 1256, 1272, 1256, 1166, 1092, 1165, 1092, 1023, 771, 726; δ_H (400 MHz, $CDCl_3$) 7.64 (d, *J*=7.6 Hz, 1H), 7.48–7.39 (m, 2H), 7.35 (td, *J*=7.6, 1.0 Hz, 1H), 5.24 (s, 2H), 3.73 (t, *J*=7.0 Hz, 2H), 3.46 (t, *J*=7.0 Hz, 2H); δ_C (100.6 MHz, $CDCl_3$) 140.7, 140.3, 135.5, 128.7, 128.1, 127.8, 124.1, 121.1, 51.0, 31.7, 29.6.

*4.4.2. 1-(Bromomethyl)-5,6-dihydro-[1,2,3]triazolo[5,1-a]isoquinoline (**5b**).* Compound **5b** was prepared from **4b** (0.547 g, 2.72 mmol) and PBr_3 (1.484 g, 5.44 mmol) in accordance with the general procedure. Purification by percolation, R_f (florisil, 50% ethyl acetate/CH_2Cl_2) 0.73, afforded 0.440 g of compound **5b** (61% yield) as a white solid, mp=93–95 °C. [Found: C, 50.10; H, 3.88; N, 15.95. $C_{11}H_{10}BrN_3$ requires C, 50.02; H, 3.82; N, 15.91%]. ν_{max} (KBr) 2952, 2921, 2851, 1469, 1425, 1260, 1194, 1094, 1034, 1017, 768, 733, 677, 582; δ_H (400 MHz, $CDCl_3$) 7.76 (d, *J*=8.0 Hz, 1H), 7.44–7.38 (m, 1H), 7.37 (m, 2H), 4.80 (s, 2H), 4.53 (t, *J*=6.8 Hz, 2H), 3.18 (t, *J*=6.8 Hz, 2H); δ_C (100.6 MHz, $CDCl_3$) 139.0, 132.7, 130.8, 129.5, 128.5, 128.1, 125.4, 124.0, 44.7, 28.9, 23.5.

*4.4.3. 1-(3-Bromopropyl)-5,6-dihydro-[1,2,3]triazolo[5,1-a]isoquinoline (**5d**).* Compound **5d** was prepared from **4d** (0.580 g, 2.53 mmol) and PBr_3 (1.380 g, 5.06 mmol) in accordance with the general procedure. Purification by percolation, R_f (florisil, ethyl acetate) 0.73, afforded 0.338 g of compound **5d** (46% yield) as a pale yellow viscous oil. [Found: C, 53.40; H, 4.88; N, 14.43. $C_{13}H_{14}BrN_3$ requires C, 53.44; H, 4.83; N, 14.38%]. ν_{max} (neat) 3053, 2952, 2930, 2856, 1480, 1434, 1370, 1243, 1195, 1045, 770; δ_H (400 MHz, $CDCl_3$) 7.61 (d, *J*=7.6 Hz, 1H), 7.36–7.23 (m, 3H), 4.49 (t, *J*=6.8 Hz, 2H), 3.51 (t, *J*=6.6 Hz, 2H), 3.15 (t, *J*=6.8 Hz, 2H), 3.10 (t, *J*=7.4 Hz, 2H), 2.40–2.31 (m, 2H); δ_C (100.6 MHz, $CDCl_3$) 141.2, 132.4, 129.2, 128.6, 128.4, 127.7, 125.1, 124.0, 44.6, 33.3, 31.3, 29.1, 24.8.

4.5. Synthesis of compound 6c

*4.5.1. 2-(5,6-Dihydro-[1,2,3]triazolo[5,1-a]isoquinolin-1-yl)ethyl 4-methylbenzenesulfonate (**6c**).* A solution of compound **4c** (0.364 g, 1.69 mmol) in THF (15 mL) was added at room temperature under a nitrogen atmosphere to KOH (0.182 g, 5.08 mmol), followed by the addition of tosyl chloride (0.644 g, 3.38 mmol) in one portion. The mixture was stirred at room temperature for 16 h, then quenched with a saturated aqueous solution of NH_4Cl (30 mL) and extracted with ethyl acetate (3×40 mL). The organic extracts were washed with an aqueous solution of NaCl (3×30 mL), dried over Na_2SO_4, and concentrated under vacuum. Purification by column chromatography, R_f (silica gel, 30% hexane/ethyl acetate) 0.50, afforded 0.512 g of compound **6c** (82% yield). After crystallization from ethyl acetate/hexane, compound **6c** was obtained as a white solid, mp=105–106 °C. [Found: C, 61.80; H, 5.23; N, 11.43; S, 8.75. $C_{19}H_{19}N_3O_3S$ requires C, 61.77; H, 5.18; N, 11.37; S, 8.68%]. ν_{max} (KBr) 3042, 2957, 2915, 1591, 1481, 1352, 1169, 1096, 978, 857, 767, 662, 548; δ_H (400 MHz, $CDCl_3$) 7.67 (d, *J*=8.0 Hz, 2H), 7.52 (d, *J*=7.2 Hz, 1H), 7.34–7.21 (m, 5H), 4.45 (t, *J*=6.8 Hz, 2H), 4.40 (t, *J*=7.2 Hz, 2H), 3.30 (t, *J*=7.2 Hz, 2H), 3.11 (t, *J*=6.8 Hz, 2H), 2.36 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 144.9, 137.5, 133.3, 132.8, 130.4, 130.0, 129.2, 128.8, 128.1, 128.0, 125.0, 124.3, 68.8, 45.0, 29.4, 26.8, 21.7; MS *m*/*z* 281 (4), 207 (10), 197 (36), 168 (100), 154 (39), 141 (35), 127 (21), 115 (70), 103 (8), 89 (13), 84 (50), 77 (24), 70 (23), 63 (15), 51 (16), 39 (31%).

4.6. General procedure for the synthesis of compounds 7

Sodium azide (1.2 equiv) was added to a solution (0.17–0.29 M) of compounds **5a**,**b**,**d** or **6c** (1 equiv) in DMF. The mixture was warmed to 100 °C for 2–5 h, then quenched with an aqueous solution of NaCl (40 mL) and extracted with ethyl acetate (3×50 mL). The organic extracts were washed with an aqueous solution of NaCl (3×40 mL) and dried over Na_2SO_4. After evaporation of the solvent at reduced pressure, pure azides were isolated.

*4.6.1. 3-(2-Azidoethyl)-8H-[1,2,3]triazolo[5,1-a]isoindole (**7a**).* Compound **7a** was prepared from **5a** (0.120 g, 0.455 mmol) and sodium azide (0.036 g, 0.55 mmol) in accordance with the general procedure leading to 0.084 g (82% yield) of azide **7a** as a viscous pale yellow oil. [Found: C, 58.43; H, 4.50; N, 37.10. $C_{11}H_{10}N_6$ requires C, 58.40; H, 4.46; N, 37.15%]. ν_{max} (neat) 3059, 2932, 2861, 2095, 1459, 1442, 1365, 1296, 1270, 1170, 1087, 1023, 779, 729; δ_H (400 MHz, $CDCl_3$) 7.65 (d, *J*=7.6 Hz, 1H), 7.50–7.41 (m, 2H), 7.37 (t, *J*=7.6 Hz, 1H), 5.27 (s, 2H), 3.71 (t, *J*=6.8 Hz, 2H), 3.18 (t, *J*=6.8 Hz, 2H); δ_C (100.6 MHz, $CDCl_3$) 140.7, 140.4, 134.8, 128.8, 128.1, 127.9, 124.1, 120.9, 51.0, 50.9, 26.0; MS *m*/*z* 226 (M^+, 13), 169 (33), 143 (54), 142 (92), 116 (61), 115 (100), 89 (50), 77 (16), 71 (26), 63 (36), 57 (17), 51 (24), 39 (66%).

*4.6.2. 1-(Azidomethyl)-5,6-dihydro-[1,2,3]triazolo[5,1-a]isoquinoline (**7b**).* Compound **7b** was prepared from **5b** (0.440 g, 1.67 mmol) and sodium azide (0.130 g, 2.00 mmol) in accordance with the general procedure leading to 0.337 g (89% yield) of azide **7b** as a viscous yellow oil. [Found: C, 58.45; H, 4.52; N, 37.18. $C_{11}H_{10}N_6$ requires C, 58.40; H, 4.46; N, 37.15%]. ν_{max} (neat) 3058, 2952, 2926, 2090, 1480, 1470, 1465, 1454, 1441, 1432, 1380, 1302, 1255, 1089, 1039, 1020, 802, 774; δ_H (400 MHz, $CDCl_3$) 7.68–7.63 (m, 1H), 7.40–7.31 (m, 3H), 4.65 (s, 2H), 4.56 (t, *J*=6.8 Hz, 2H), 3.20 (t, *J*=6.8 Hz, 2H); δ_C (100.6 MHz, $CDCl_3$) 137.0, 132.6, 131.4, 129.5, 128.5, 128.0, 125.0, 124.0, 46.0, 44.8, 28.9; MS *m*/*z* 226 (M^+, 41), 184 (41), 156 (91), 142 (24), 130 (85), 129 (63), 128 (49), 115 (100), 103 (54), 89 (27), 77 (83), 63 (43), 51 (55), 39 (75%).

*4.6.3. 1-(2-Azidoethyl)-5,6-dihydro-[1,2,3]triazolo[5,1-a]isoquinoline (**7c**).* Compound **7c** was prepared from **6c** (0.800 g, 2.17 mmol) and sodium azide (0.169 g, 2.60 mmol) in accordance with the general procedure leading to 0.500 g (96% yield) of azide **7c** as a pale yellow oil. [Found: C, 60.03; H, 5.10; N, 34.90. $C_{12}H_{12}N_6$ requires C, 59.99; H, 5.03; N, 34.98%]. ν_{max} (neat) 3053, 2931, 2872, 2107, 1480, 1434, 1374, 1341, 1291, 1256, 1196, 771, 732; δ_H (400 MHz, $CDCl_3$) 7.59 (d, *J*=7.2 Hz, 1H), 7.36–7.26 (m, 3H), 4.49 (t, *J*=6.8 Hz, 2H), 3.73 (t, *J*=7.2 Hz, 2H), 3.20 (t, *J*=7.2 Hz, 2H), 3.15 (t, *J*=6.8 Hz, 2H); δ_C (100.6 MHz, $CDCl_3$) 138.9, 132.6, 129.9, 128.8, 128.5, 127.7, 125.0, 123.9, 50.1, 44.7, 29.1, 26.5; MS *m*/*z* 240 (M^+, 8), 212 (20), 185 (34), 156 (100), 141 (10), 130 (33), 129 (35), 128 (42), 115 (27), 103 (19), 89 (9), 77 (39), 63 (20), 51 (29), 39 (29%).

*4.6.4. 1-(3-Azidopropyl)-5,6-dihydro-[1,2,3]triazolo[5,1-a]isoquinoline (**7d**).* Compound **7d** was prepared from **5d** (0.338 g, 1.16 mmol)

and sodium azide (0.091 g, 1.39 mmol) in accordance with the general procedure leading to 0.242 g (82% yield) of azide **7d** as a pale yellow oil. [Found: C, 61.45; H, 5.52; N, 33.18. $C_{13}H_{14}N_6$ requires C, 61.40; H, 5.55; N, 33.05%]. ν_{max} (neat) 2928, 2867, 2102, 1480, 1469, 1450, 1444, 1348, 1262, 1193, 1017, 771; δ_H (400 MHz, $CDCl_3$) 7.56 (d, J=7.6 Hz, 1H), 7.36–7.22 (m, 3H), 4.48 (t, J=6.8 Hz, 2H), 3.39 (t, J=6.8 Hz, 2H), 3.14 (t, J=6.8 Hz, 2H), 3.02 (t, J=7.4 Hz, 2H), 2.12–2.02 (m, 2H); δ_C (100.6 MHz, $CDCl_3$) 141.4, 132.4, 129.1, 128.6, 128, 127.7, 125.1, 123.9, 50.7, 44.6, 29.1, 27.7, 23.4; MS m/z 226 (53), 199 (59), 198 (100), 197 (66), 182 (20), 170 (27), 156 (26), 154 (24), 141 (24), 130 (78), 128 (66), 115 (74), 103 (43), 89 (24), 77 (85), 63 (31), 51 (50), 42 (44), 41 (45), 39 (77%).

4.7. General procedure for the synthesis of compounds 8

Alkyne (1.2 equiv) and azide (1 equiv) were added at room temperature to a solution (0.03–0.06 M) of $Cu(OAc)_2 \cdot H_2O$ (0.2 equiv) in H_2O in a capped flask. The mixture was warmed to 100 °C and, after completion (1–5 h), was quenched with a saturated aqueous solution of NH_4Cl (30 mL) and extracted with ethyl acetate or CH_2Cl_2 (3×50 mL). The organic extracts were washed with an aqueous solution of NaCl (3×30 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography on silica gel and by crystallization.

*4.7.1. 3-[2-(4-Phenyl-1H-1,2,3-triazol-1-yl)ethyl]-8H-[1,2,3]triazolo [5,1-a]isoindole (**8a**).* Compound **8a** was prepared from **7a** (0.084 g, 0.37 mmol) and phenylacetylene (0.046 g, 0.45 mmol) and the reaction was performed at 100 °C in accordance with the general procedure. Purification by column chromatography, R_f (silica gel, ethyl acetate) 0.41, afforded 0.097 g of compound **8a** (80% yield). After crystallization from ethyl acetate/hexane, compound **8a** was obtained as a pale brown solid, mp=173–175 °C. [Found: C, 69.45; H, 4.95; N, 25.68. $C_{19}H_{16}N_6$ requires C, 69.50; H, 4.91; N, 25.59%]. ν_{max} (KBr) 3132, 3053, 2941, 1455, 1448, 1426, 1350, 1216, 1177, 1036, 760, 686; δ_H (400 MHz, $CDCl_3$) 7.70 (s, 1H), 7.68–7.62 (m, 2H), 7.46–7.22 (m, 7H), 5.21 (s, 2H), 4.89 (t, J=6.0 Hz, 2H), 3.59 (t, J=6.0 Hz, 2H); δ_C (100.6 MHz, $CDCl_3$) 147.4, 140.5, 130.4, 128.8, 128.6, 128.2, 127.9, 127.3, 125.6, 124.0, 120.9, 120.6, 51.1, 49.2, 26.9 (two coincident peaks not observed).

*4.7.2. 5,6-Dihydro-1-{[4-(4-methoxyphenyl)-1H-1,2,3-triazol-1-yl] methyl}-[1,2,3]triazolo[5,1-a]isoquinoline (**8b**).* Compound **8b** was prepared from **7b** (0.120 g, 0.53 mmol) and *p*-methoxyphenylacetylene (0.084 g, 0.64 mmol) and the reaction was performed at 100 °C in accordance with the general procedure. Purification by column chromatography, R_f (silica gel, ethyl acetate) 0.64, afforded 0.166 g of compound **8b** (87% yield). After crystallization from ethyl acetate/hexane, compound **8b** was obtained as a white solid, mp=178–180 °C. [Found: C, 66.98; H, 4.99; N, 23.50. $C_{20}H_{18}N_6O$ requires C, 67.02; H, 5.06; N, 23.45%]. ν_{max} (KBr) 3132, 3013, 2968, 2936, 2895, 2824, 1614, 1556, 1492, 1457, 1246, 1172, 1022, 787, 759; δ_H (400 MHz, $CDCl_3$) 7.86–7.81 (m, 2H), 7.69–7.62 (m, 2H), 7.35 (td, J=7.6, 1.6 Hz, 1H), 7.32–7.23 (m, 2H), 6.89–6.82 (m, 2H), 5.86 (s, 2H), 4.52 (t, J=6.8 Hz, 2H), 3.75 (s, 3H), 3.15 (t, J=6.8 Hz, 2H); δ_C (100.6 MHz, $CDCl_3$) 159.5, 148.1, 136.1, 132.6, 131.8, 129.8, 128.4, 128.3, 126.8, 125.5, 123.5, 123.0, 118.7, 114.1, 55.2, 45.7, 44.8, 28.9.

*4.7.3. 1-[(4-Cyclohexyl-1H-1,2,3-triazol-1-yl)methyl]-5,6-dihydro-[1,2,3]triazolo[5,1-a]isoquinoline (**8c**).* Compound **8c** was prepared from **7b** (0.217 g, 0.96 mmol) and cyclohexylacetylene (0.125 g, 1.15 mmol) and the reaction was performed at 100 °C in accordance with the general procedure. Purification by column chromatography, R_f (silica gel, ethyl acetate) 0.61, afforded 0.157 g of compound **8c** (49% yield). After crystallization from ethyl acetate/hexane, compound **8c** was obtained as a white solid, mp=168–169 °C. [Found: C, 68.30; H, 6.59; N, 25.18. $C_{19}H_{22}N_6$ requires C, 68.24; H, 6.63; N, 25.13%]. ν_{max} (KBr) 3117, 3061, 2920, 2844, 1480, 1442, 1256, 1207, 1161, 1046, 812, 759, 726, 678; δ_H (400 MHz, $CDCl_3$) 7.77 (d, J=7.2 Hz, 1H), 7.38 (s, 1H), 7.34–7.22 (m, 3H), 5.76 (s, 2H), 4.50 (t, J=6.8 Hz, 2H), 3.14 (t, J=6.8 Hz, 2H), 2.69–2.55 (m, 1H), 1.99–1.86 (m, 2H), 1.75–1.55 (m, 3H), 1.36–1.20 (m, 4H), 1.19–1.05 (m, 1H); δ_C (100.6 MHz, $CDCl_3$) 154.1, 136.1, 132.5, 131.6, 129.6, 128.3, 128.2, 125.4, 123.5, 119.2, 45.4, 44.7, 35.1, 32.6, 28.8, 25.9, 25.8; MS m/z 334 (M^+, 3), 306 (4), 185 (49), 156 (100), 130 (51), 129 (82), 128 (36), 103 (16), 77 (25), 41 (28), 39 (23%).

*4.7.4. 5,6-Dihydro-1-[2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethyl]-[1,2,3]triazolo[5,1-a]isoquinoline (**8d**).* Compound **8d** was prepared from **7c** (0.074 g, 0.31 mmol) and phenylacetylene (0.038 g, 0.37 mmol) and the reaction was performed at 100 °C in accordance with the general procedure. Purification by column chromatography, R_f (silica gel, 10% hexane/ethyl acetate) 0.56, afforded 0.085 g of compound **8d** (81% yield). After crystallization from ethyl acetate/hexane, compound **8d** was obtained as a white solid, mp=149–150 °C. [Found: C, 70.08; H, 5.33; N, 24.48. $C_{20}H_{18}N_6$ requires C, 70.16; H, 5.30; N, 24.54%]. ν_{max} (KBr) 3128, 3095, 3044, 2952, 1609, 1469, 1448, 1427, 1374, 1225, 1193, 1077, 1049, 913, 769, 747, 725, 691; δ_H (400 MHz, $CDCl_3$) 7.78 (s, 1H), 7.71–7.67 (m, 2H), 7.42 (d, J=7.2 Hz, 1H), 7.34–7.18 (m, 6H), 4.91 (t, J=6.8 Hz, 2H), 4.44 (t, J=6.8 Hz, 2H), 3.56 (t, J=6.8 Hz, 2H), 3.07 (t, J=6.8 Hz, 2H); δ_C (100.6 MHz, $CDCl_3$) 147.3, 138.1, 132.4, 130.6, 130.1, 128.9, 128.5, 128.4, 127.8, 127.8, 125.5, 124.5, 123.9, 120.5, 48.5, 44.7, 29.0, 27.6; MS m/z 342 (M^+, 39), 285 (57), 258 (67), 197 (25), 185 (65), 170 (55), 156 (35), 154 (29), 143 (23), 141 (27), 130 (94), 128 (83), 115 (57), 103 (85), 89 (42), 77 (100), 63 (35), 51 (42), 39 (51%).

*4.7.5. 5,6-Dihydro-1-[2-(4-pentyl-1H-1,2,3-triazol-1-yl)ethyl]-[1,2,3] triazolo[5,1-a]isoquinoline (**8e**).* Compound **8e** was prepared from **7c** (0.072 g, 0.30 mmol) and 1-heptyne (0.035 g, 0.36 mmol) and the reaction was performed at 100 °C in accordance with the general procedure. Purification by column chromatography, R_f (silica gel, 10% hexane/ethyl acetate) 0.45, afforded 0.083 g of compound **8c** (82% yield). After crystallization from ethyl acetate/hexane, compound **8c** was obtained as a white solid, mp=94–95 °C. [Found: C, 67.90; H, 7.23; N, 24.91. $C_{19}H_{24}N_6$ requires C, 67.83; H, 7.19; N, 24.98%]. ν_{max} (KBr) 3120, 3069, 2952, 2927, 2854, 1457, 1374, 1339, 1214, 1128, 1049, 771; δ_H (400 MHz, $CDCl_3$) 7.36–7.32 (m, 1H), 7.30–7.23 (m, 3H), 7.20 (s, 1H), 4.80 (t, J=7.0 Hz, 2H), 4.48 (t, J=7.0 Hz, 2H), 3.51 (t, J=7.0 Hz, 2H), 3.12 (t, J=7.0 Hz, 2H), 2.54 (t, J=7.6 Hz, 2H), 1.49 (quintet, J=7.6 Hz, 2H), 1.28–1.14 (m, 4H), 0.79 (t, J=7.0 Hz, 3H); δ_C (100.6 MHz, $CDCl_3$) 148.1, 138.2, 132.3, 130.1, 129.0, 128.4, 127.9, 124.4, 123.9, 121.3, 48.4, 44.7, 31.2, 29.0, 28.9, 27.7, 25.4, 22.2, 13.8; MS m/z 336 (M^+, 12), 251 (15), 223 (31), 208 (14), 197 (100), 185 (49), 170 (38), 169 (35), 168 (35), 156 (21), 154 (21), 143 (14), 141 (16), 130 (48), 128 (50), 124 (58), 115 (31), 103 (29), 77 (33), 68 (19), 55 (20), 42 (30), 41 (88), 39 (41%).

*4.7.6. 5,6-Dihydro-1-[3-(4-p-tolyl-1H-1,2,3-triazol-1-yl)propyl]-[1,2,3]triazolo[5,1-a]isoquinoline (**8f**).* Compound **8f** was prepared from **7d** (0.102 g, 0.40 mmol) and *p*-tolylacetylene (0.056 g, 0.48 mmol) and the reaction was performed at 100 °C in accordance with the general procedure. Purification by column chromatography, R_f (silica gel, ethyl acetate) 0.42, afforded 0.141 g of compound **8f** (95% yield). After crystallization from ethyl acetate/hexane, compound **8f** was obtained as a white solid, mp=119–120 °C. [Found: C, 71.28; H, 5.93; N, 22.63. $C_{22}H_{22}N_6$ requires C, 71.33; H, 5.99; N, 22.69%]. ν_{max} (KBr) 3086, 3038, 2920, 2856, 1493, 1471, 1454, 1437, 1344, 1217, 1182, 1046, 816, 763; δ_H (400 MHz, $CDCl_3$) 7.80 (s, 1H), 7.64 (d, J=8.0 Hz, 2H), 7.39–7.34 (m, 1H), 7.26–7.19 (m, 3H), 7.14 (d, J=8.0 Hz, 2H), 4.48 (t, J=6.8 Hz, 2H), 4.43 (t, J=6.8 Hz,

2H), 3.09 (t, J=6.8 Hz, 2H), 2.97 (t, J=6.8 Hz, 2H), 2.43 (quintet, J=6.8 Hz, 2H), 2.29 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 147.4, 140.9, 137.6, 132.3, 129.2, 128.6, 128.4, 127.7, 125.4, 124.8, 123.8, 119.7, 49.2, 44.6, 28.9, 28.7, 23.0, 21.1 (two coincident peaks not observed); MS m/z 370 (M^+, 17), 313 (21), 212 (100), 198 (43), 185 (16), 182 (15), 169 (18), 168 (18), 156 (17), 141 (16), 130 (39), 128 (32), 115 (41), 103 (28), 91 (15), 77 (43), 65 (12), 63 (12), 51 (16), 39 (27%).

*4.7.7. 5,6-Dihydro-1-[3-(4-pentyl-1H-1,2,3-triazol-1-yl)propyl]-[1,2,3]triazolo[5,1-a]isoquinoline (**8g**).* Compound **8g** was prepared from **7d** (0.182 g, 0.72 mmol) and 1-heptyne (0.084 g, 0.87 mmol) and the reaction was performed at 100 °C in accordance with the general procedure. Purification by column chromatography, R_f (silica gel, ethyl acetate) 0.43, afforded 0.194 g of compound **8g** (77% yield). After crystallization from ethyl acetate/hexane, compound **8g** was obtained as a white solid, mp=114–115 °C. [Found: C, 68.50; H, 7.53; N, 24.00. $C_{20}H_{26}N_6$ requires C, 68.54; H, 7.48; N, 23.98%]. ν_{max} (KBr) 3125, 3063, 2947, 2920, 2852, 1544, 1471, 1464, 1440, 1360, 1340, 1211, 1046, 1015, 823, 808, 767, 726; δ_H (400 MHz, $CDCl_3$) 7.40–7.34 (m, 2H), 7.30–7.23 (m, 3H), 4.48 (t, J=7.0 Hz, 2H), 4.42 (t, J=7.0 Hz, 2H), 3.14 (t, J=7.0 Hz, 2H), 2.93 (t, J=7.0 Hz, 2H), 2.63 (t, J=7.7 Hz, 2H), 2.38 (quintet, J=7.0 Hz, 2H), 1.59 (quintet, J=7.7 Hz, 2H), 1.32–1.20 (m, 4H), 0.81 (t, J=7.2 Hz, 3H); δ_C (100.6 MHz, $CDCl_3$) 148.1, 141.0, 132.3, 129.2, 128.7, 128.4, 127.7, 124.8, 123.8, 120.9, 49.0, 44.6, 31.2, 29.0, 29.0, 28.8, 25.4, 23.0, 22.2, 13.8; MS m/z 350 (M^+, 7), 212 (23), 198 (100), 185 (18), 168 (9), 156 (9), 130 (14), 128 (15), 103 (10), 77 (14), 68 (10), 54 (9), 41 (44%).

4.8. Synthesis of compounds 11 according to Scheme 2

*4.8.1. 1-{2-[4-(2-Bromoethyl)-1H-1,2,3-triazol-1-yl]ethyl}-5,6-dihydro-[1,2,3]triazolo[5,1-a]isoquinoline (**9**).* 4-Bromo-1-butyne (0.213 g, 1.60 mmol) and azide **7c** (0.320 g, 1.33 mmol) were added at room temperature to a solution of $Cu(OAc)_2 \cdot H_2O$ (0.054 g, 0.27 mmol) in H_2O (5 mL). The mixture was warmed at 50 °C for 1 h in a capped flask, then quenched with a saturated aqueous solution of NH_4Cl (40 mL) and extracted with ethyl acetate (3×50 mL). The organic extracts were washed with an aqueous solution of NaCl (3×40 mL), dried over Na_2SO_4, and concentrated under vacuum. Purification by column chromatography, R_f (silica gel, 10% hexane/ethyl acetate) 0.32, afforded 0.353 g of compound **9** (71% yield). After crystallization from ethyl acetate/hexane, compound **9** was obtained as a white solid, mp=110–111 °C. [Found: C, 51.53; H, 4.55; N, 22.57. $C_{16}H_{17}BrN_6$ requires C, 51.49; H, 4.59; N, 22.52%]. ν_{max} (KBr) 3132, 3081, 2952, 2904, 1555, 1476, 1426, 1253, 1212, 1166, 1124, 1053, 1014, 915, 823, 763, 724; δ_H (400 MHz, $CDCl_3$) 7.39 (s, 1H), 7.32–7.22 (m, 4H), 4.84 (t, J=6.8 Hz, 2H), 4.47 (t, J=6.8 Hz, 2H), 3.51 (t, J=6.8 Hz, 2H), 3.45 (t, J=6.8 Hz, 2H), 3.12 (t, J=6.8 Hz, 4H); δ_C (100.6 MHz, $CDCl_3$) 144.4, 138.1, 132.3, 130.1, 128.9, 128.4, 127.8, 124.5, 123.8, 122.4, 48.6, 44.7, 31.3, 29.2, 29.0, 27.6.

*4.8.2. 1-{2-[4-(2-Azidoethyl)-1H-1,2,3-triazol-1-yl]ethyl}-5,6-dihydro-[1,2,3]triazolo[5,1-a]isoquinoline (**10**).* Sodium azide (0.096 g, 1.48 mmol) was added to a solution of compound **9** (0.461 g, 1.24 mmol) in DMF (9 mL). The mixture was warmed to 100 °C for 3 h, then quenched with an aqueous solution of NaCl (30 mL) and extracted with ethyl acetate (3×40 mL). The organic extracts were washed with an aqueous solution of NaCl (3×30 mL) and dried over Na_2SO_4. After evaporation of the solvent at reduced pressure, 0.407 g of pure azide **10** (98% yield) were isolated. After crystallization from ethyl acetate/hexane, compound **10** was obtained as a white solid, mp=84–85 °C. [Found: C, 57.28; H, 5.19; N, 37.63. $C_{16}H_{17}N_9$ requires C, 57.30; H, 5.11; N, 37.59%]. ν_{max} (KBr) 3117, 3064, 2938, 2869, 2095, 1542, 1470, 1431, 1379, 1349, 1305, 1212, 1115, 1049, 1011, 964, 808, 771, 729, 676; δ_H (400 MHz, $CDCl_3$) 7.36 (s, 1H), 7.32–7.28 (m, 1H), 7.26–7.19 (m, 3H), 4.80 (t, J=6.8 Hz, 2H), 4.44 (t, J=6.8 Hz, 2H), 3.48 (t, J=6.8 Hz, 2H), 3.40 (t, J=6.8 Hz, 2H), 3.09 (t, J=6.8 Hz, 2H), 2.80 (t, J=6.8 Hz, 2H); δ_C (100.6 MHz, $CDCl_3$) 143.6, 138.0, 132.3, 130.0, 128.8, 128.3, 127.7, 124.4, 123.7, 122.3, 50.3, 48.4, 44.6, 28.9, 27.5, 25.3.

*4.8.3. 5,6-Dihydro-1-(2-(4-(2-(4-p-tolyl-1H-1,2,3-triazol-1-yl)ethyl)-1H-1,2,3-triazol-1-yl)ethyl)-[1,2,3]triazolo[5,1-a]isoquinoline (**11a**).* Compound **10** (0.154 g, 0.46 mmol) and p-tolylacetylene (0.064 g, 0.55 mmol) were added at room temperature to a solution of $Cu(OAc)_2 \cdot H_2O$ (0.018 g, 0.09 mmol) in H_2O (3 mL) in a capped flask. The mixture was warmed to 100 °C and, after completion (1 h), was quenched with a saturated aqueous solution of NH_4Cl (30 mL) and extracted with CH_2Cl_2 (3×40 mL). The organic extracts were washed with an aqueous solution of NaCl (3×30 mL), dried over Na_2SO_4, and concentrated under vacuum. Purification by column chromatography, R_f (silica gel, 10% CH_3OH/CH_2Cl_2) 0.46, afforded 0.187 g of compound **11a** (90% yield). After crystallization from CH_2Cl_2/hexane, compound **11a** was obtained as a white solid, mp=213–214 °C. [Found: C, 66.58; H, 5.53; N, 27.90. $C_{25}H_{25}N_9$ requires C, 66.50; H, 5.58; N, 27.92%]. ν_{max} (KBr) 3127, 3063, 2946, 2917, 1545, 1474, 1448, 1434, 1380, 1218, 1053, 819, 764, 727; δ_H (400 MHz, DMSO-d_6) 8.47 (s, 1H), 7.91 (s, 1H), 7.70 (d, J=8.2 Hz, 2H), 7.58–7.53 (m, 1H), 7.45–7.41 (m, 1H), 7.39–7.33 (m 2H), 7.22 (d, J=8.2 Hz, 2H), 4.74 (t, J=7.4 Hz, 2H), 4.61 (t, J=7.4 Hz, 2H), 4.51 (t, J=6.8 Hz, 2H), 3.47 (t, J=7.4 Hz, 2H), 3.22 (t, J=7.4 Hz, 2H), 3.16 (t, J=6.8 Hz, 2H), 2.31 (s, 3H); δ_C (100.6 MHz, DMSO-d_6) 146.2, 142.6, 138.0, 137.0, 133.1, 129.3, 129.3, 128.7, 128.6, 128.0, 127.5, 125.0, 124.3, 123.8, 123.0, 120.9, 48.9, 48.1, 44.2, 28.3, 27.0, 26.1, 20.8.

*4.8.4. 1-(2-(4-(2-(4-Butyl-1H-1,2,3-triazol-1-yl)ethyl)-1H-1,2,3-triazol-1-yl)ethyl)-5,6-dihydro-[1,2,3]triazolo[5,1-a]isoquinoline (**11b**).* Compound **10** (0.120 g, 0.36 mmol) and 1-hexyne (0.036 g, 0.43 mmol) were added at room temperature to a solution of $Cu(OAc)_2 \cdot H_2O$ (0.014 g, 0.07 mmol) in H_2O (3 mL) in a capped flask. The mixture was warmed to 100 °C and, after completion (2 h), was quenched with a saturated aqueous solution of NH_4Cl (30 mL) and extracted with CH_2Cl_2 (3×40 mL). The organic extracts were washed with an aqueous solution of NaCl (3×30 mL), dried over Na_2SO_4, and concentrated under vacuum. Purification by column chromatography, R_f (silica gel, 5% CH_3OH/CH_2Cl_2) 0.28, afforded 0.127 g of compound **11b** (85% yield). After crystallization from ethyl acetate, compound **11b** was obtained as a white solid, mp=148–149 °C. [Found: C, 63.35; H, 6.53; N, 30.12. $C_{22}H_{27}N_9$ requires C, 63.29; H, 6.52; N, 30.19%]. ν_{max} (KBr) 3135, 3067, 2941, 2925, 2861, 1546, 1476, 1453, 1435, 1382, 1212, 1130, 1052, 1044, 846, 766; δ_H (400 MHz, $CDCl_3$) 7.39–7.34 (m, 1H), 7.32–7.25 (m, 3H), 7.20 (s, 1H), 7.14 (s, 1H), 4.80 (t, J=7.0 Hz, 2H), 4.54 (t, J=7.0 Hz, 2H), 4.50 (t, J=7.0 Hz, 2H), 3.50 (t, J=7.0 Hz, 2H), 3.19 (t, J=7.0 Hz, 2H), 3.15 (t, J=7.0 Hz, 2H), 2.59 (t, J=7.6 Hz, 2H), 1.54 (quintet, J=7.6 Hz, 2H), 1.34–1.22 (m, 2H), 0.84 (t, J=7.2 Hz, 3H); δ_C (100.6 MHz, $CDCl_3$) 148.1, 142.9, 138.0, 132.4, 130.1, 129.0, 128.5, 127.8, 124.5, 123.8, 122.6, 121.0, 49.0, 48.5, 44.7, 31.4, 29.0, 27.6, 26.6, 25.1, 22.1, 13.7.

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References and notes

1. (a) Stefani, H. A.; Silva, N. C. S.; Manarin, F.; Lüdtke, D. S.; Zukerman-Schpector, J.; Madureira, L. S.; Tiekink, E. R. T. *Tetrahedron Lett.* **2012**, *53*, 1742–1747; (b) Deobald, A. M.; Camargo, L. R. S.; Alves, D.; Zukerman-Schpector, J.; Correa, A. G.; Paixao, M. V. *Synthesis* **2011**, 4003–4010; (c) Kumar, K. K.; Seenivasan, S. P.; Kumar, V.; Das, T. M. *Carbohydr. Res.* **2011**, *346*, 2084–2090; (d) Song, Z.; He, X. P.; Jin, X. P.; Gao, L. X.; Sheng, L.; Zhou, Y. B.; Li, J.; Chen, G. R. *Tetrahedron Lett.* **2011**, *52*, 894–898; (e) Zeng, Q.; Saha, S.; Lee, L. A.; Barnhill, H.; Oxsher, J.; Dreher, T.;

Wang, Q. *Bioconjugate Chem.* **2011**, *22*, 58–66; (f) Saikia, B.; Saikia, P. P.; Goswami, A.; Barua, N. C.; Saxena, A. K.; Suri, N. *Synthesis* **2011**, 3173–3179; (g) He, R.; Yu, Z.; He, Y.; Zeng, L. F.; Xu, J.; Wu, L.; Gunawan, A. M.; Wang, L.; Jiang, Z. X.; Zhang, Z. Y. *ChemMedChem* **2010**, *5*, 2051–2056; (h) Aragão-Leoneti, V.; Campo, V. L.; Gomes, A. S.; Field, R. A.; Carvalho, I. *Tetrahedron* **2010**, *66*, 9475–9492; (i) Holub, J. M.; Kirshenbaum, K. *Chem. Soc. Rev.* **2010**, *39*, 1325–1337; (j) Mamidyala, S. K.; Finn, M. G. *Chem. Soc. Rev.* **2010**, *39*, 1252–1261; (k) El-Sagheer, A. H.; Brown, T. *Chem. Soc. Rev.* **2010**, *39*, 1388–1405.

2. (a) Huisgen, R. *Pure Appl. Chem.* **1989**, *61*, 613–628; (b) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, NY, 1984; pp 1–176.
3. (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021; (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599.
4. Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.
5. (a) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952–3015; (b) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51–68.
6. Selected reviewes: (a) Amblard, F.; Cho, J. H.; Schinazi, R. F. *Chem. Rev.* **2009**, *109*, 4207–4220; (b) Gil, M. V.; Arévalo, M. J.; López, Ó. *Synthesis* **2007**, 1589–1620.
7. (a) Ladouceur, S.; Soliman, A. M.; Zysman-Colman, E. *Synthesis* **2011**, 3604–3611; (b) James, D.; Escudier, J. M.; Amigues, E.; Schulz, J.; Vitry, C.; Bordenave, T.; Slozek-Pinaud, M.; Fouquet, E. *Tetrahedron Lett.* **2010**, *51*, 1230–1232; (c) Montagnat, O. D.; Lessene, G.; Hughes, A. B. *J. Org. Chem.* **2010**, *75*, 390–398; (d) Cravotto, G.; Fokin, V. V.; Garella, D.; Binello, A.; Boffa, L.; Barge, A. *J. Comb. Chem.* **2010**, *12*, 13–15; (e) Jurícek, M.; Kouwer, P. H. J.; Rehák, J.; Sly, J.; Rowan, A. E. *J. Org. Chem.* **2009**, *74*, 21–25; (f) Xia, Y.; Liu, Y.; Wan, J.; Wang, M.; Rocchi, P.; Qu, F.; Iovanna, J. L.; Peng, L. *J. Med. Chem.* **2009**, *52*, 6083–6096; (g) Broggi, J.; Díez-González, S.; Petersen, J. L.; Berteina-Raboin, S.; Nolan, S. P.; Agrofoglio, L. A. *Synthesis* **2008**, 141–148; (h) Li, P.; Wang, L.; Zhang, Y. *Tetrahedron* **2008**, *64*, 10825–10830; (i) Jlalia, I.; Elamari, H.; Meganem, F.; Herscovici, J.; Girard, C. *Tetrahedron Lett.* **2008**, *49*, 6756–6758; (j) Wang, Z.-X.; Zhao, Z.-G. *J. Heterocycl. Chem.* **2007**, *44*, 89–92; (k) Chassaing, S.; Kumarraja, M.; Sido, A. S. S.; Pale, P.; Sommer, J. *Org. Lett.* **2007**, *9*, 883–886; (l) Yoo, E. J.; Ahlquist, M.; Kim, S. H.; Bae, I.; Fokin, V. V.; Sharpless, K. B.; Chang, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 1730–1733; (m) Bertrand, P.; Gesson, J. P. *J. Org. Chem.* **2007**, *72*, 3596–3599.
8. (a) Majumdar, K. C.; Ray, K. *Synthesis* **2011**, 3767–3783; (b) Brawn, R. A.; Welzel, M.; Lowe, J. T.; Panek, J. S. *Org. Lett.* **2010**, 336–339; (c) Majumdar, K. C.; Ray, K.; Ganai, S.; Ghosh, T. *Synthesis* **2010**, 858–862; (d) Hu, Y. Y.; Hu, J.; Wang, X. C.; Guo, L. N.; Shu, X. Z.; Niu, Y. N.; Liang, Y. M. *Tetrahedron* **2010**, *66*, 80–86; (e) Chowdhury, C.; Mukherjee, S.; Das, B.; Achari, B. *J. Org. Chem.* **2009**, *74*, 3612–3615; (f) Chowdhury, C.; Sasmal, A. K.; Dutta, P. K. *Tetrahedron Lett.* **2009**, *50*, 2678–2681; (g) Mohapatra, D. K.; Maity, P. K.; Shabab, M.; Khan, M. I. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5241–5245; (h) Laleu, B.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 9164–9167; (i) Chen, W. L.; Su, C. L.; Huang, X. *Synlett* **2006**, 1446–1448; (j) Dolhem, F.; Thali, F. A.; Lièvre, C.; Demailly, G. *Eur. J. Org. Chem.* **2005**, 5019–5023; (k) Chowdhury, C.; Mandal, S. B.; Achari, B. *Tetrahedron Lett.* **2005**, *46*, 8531–8534.
9. Shafran, E. A.; Bakulev, V. A.; Rozin, Y. A.; Shafran, Y. M. *Chem. Heterocycl. Compd.* **2008**, *44*, 1040–1069.
10. (a) Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A.; Quarta, M. R.; Fittipaldi, M. *Synthesis* **2009**, 3853–3859; (b) Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A. *Tetrahedron* **2008**, *64*, 7301–7306; (c) Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A. *Tetrahedron* **2008**, *64*, 53–60.
11. (a) Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A.; Capuzzolo, F. *Tetrahedron* **2009**, *65*, 10573–10580; (b) Fiandanese, V.; Marchese, G.; Punzi, A.; Iannone, F.; Rafaschieri, G. G. *Tetrahedron* **2010**, *66*, 8846–8853; (c) Fiandanese, V.; Iannone, F.; Marchese, G.; Punzi, A. *Tetrahedron* **2011**, *67*, 5254–5260; (d) Fiandanese, V.; Maurantonio, S.; Punzi, A.; Rafaschieri, G. G. *Org. Biomol. Chem.* **2012**, *10*, 1186–1195.