Synthesis of 2-Tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*-β-carbolines by a One-Pot Ugi-Azide/Pictet–Spengler Process

Luis E. Cárdenas-Galindo,[a] Alejandro Islas-Jácome,[a] Nancy V. Alvarez-Rodríguez,[a] Laurent El Kaim,*[b] Rocío Gámez-Montaño*[a]

[a] Departamento de Química, División de Ciencias Naturales y Exactas, Universidad de Guanajuato, Noria Alta S/N, Col. Noria Alta, C. P. 36050 Guanajuato, Guanajuato, México
Fax +52(473)7320006 (ext. 8168); E-mail: rociogm@ugto.mx

[b] UMR 7652 (Ecole Polytechnique/ENSTA/CNRS), Laboratoire Chimie et Procédés, Ecole Nationale Supérieure des Techniques Avancées, 32 Bd Victor, 75015 Paris, France
Fax +33(1)45528322; E-mail: laurent.elkaim@ensta.fr

Received: 11.07.2013; Accepted after revision: 03.10.2013

Abstract: A series of novel 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*-β-carbolines were prepared in good to excellent overall yields by an efficient MW-assisted one-pot Ugi-azide/Pictet–Spengler process. This work describes the first synthesis of compounds including both 1,5-disubstituted 1*H*-tetrazole and 2,3,4,9-tetrahydro-1*H*-β-carboline heterocyclic systems.

Key words: tetrazoles, tetrahydro-1*H*-β-carbolines, MCR, Ugi-azide, Pictet–Spengler

Tetrazoles are a privileged class of heterocycles of high interest in medicinal chemistry due to the fact that they are present in various non-natural compounds that show relevant biological activity,[1] which depends mainly on the substitution factor in the aromatic ring system.[2] Tetrazoles can be classified into 1-, 2-, 5-monosubstituted and 1,5-, 2,5-disubstituted tetrazoles[3] (Figure 1).

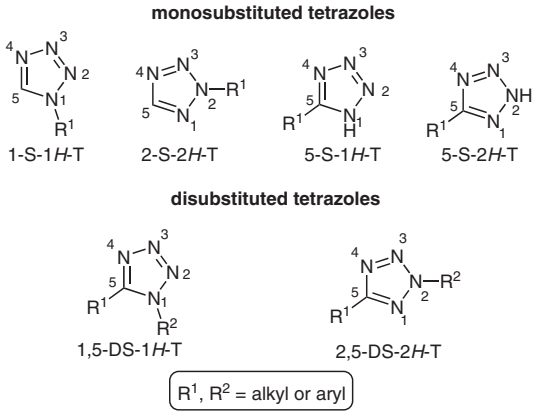


Figure 1 Substituted tetrazoles

In this context, 5-substituted 1*H*-tetrazoles (5-S-1*H*-T) are the most biologically important type of tetrazoles because they are bioisosteres of carboxylic acids.[4] Although, tetrazoles and carboxylic acids are structurally different, both show similar biological activity as a result of the similarities in their physicochemical properties such as acidity and the ability to present tautomeric forms (Figure 2).[5] Losartan (**1**), which is a 5-S-1*H*-T belonging to the family of sartans,[6] shows a vasodilator activity and is an angiotensin II receptor antagonist (Figure 2).[7]

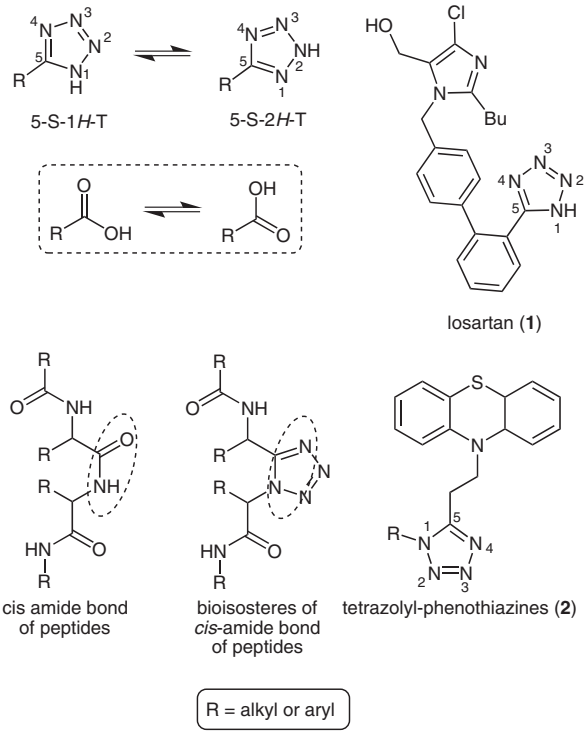


Figure 2 Losartan (**1**) and the phenothiazines **2**

Slightly less important than 5-S-1*H*-T, some 1,5-disubstituted 1*H*-tetrazoles (1,5-DS-1*H*-T) have shown interesting biological activity, since they have proven to be suitable bioisosteres of *cis*-amide bond of peptides because they can adopt their steric conformations (Figure 2).[8] In this context, the 1,5-DS-T-phenothiazines **2** exhibit biological activities such as anti-inflammatory, antiulcer, and analgesic (Figure 2).[9]

Several sophisticated methods have been described for preparing compounds with the 1,5-DS-1*H*-T ring system, among the most important are the click [2,3] dipolar cy-

SYNTHESIS 2014, 46, 0049–0056
Advanced online publication: 23.10.2013
DOI: 10.1055/s-0033-1340051; Art ID: SS-2013-M0475-OP

cloadditions of azides with cyanides.[10] For example, Aldhoun et al. have described a method to prepare 1-glycosylmethyl-5-tosyl-1*H*-tetrazoles using TMSCN and several glycosylmethyl azides as starting materials with good to excellent overall yields.[11] 1,5-DS-1*H*-T can also be prepared using the Ugi-azide reaction, a variant of the Ugi multicomponent process, in which the carboxylic acid is replaced by hydrazoic acid to prepare novel biologically promising 1,5-DS-1*H*-T.[12] The Ugi-azide reaction has been combined with post-condensation processes to prepare a variety of tetrazole containing scaffolds such as benzodiazepine-tetrazoles,[13a] azepine-tetrazoles,[13b] ketopiperazine-tetrazoles,[13c] isoindolinone-tetrazoles,[13d] quinoxalinone-tetrazoles,[13e] bis(pyrrolidinone)-tetrazoles,[13f] indazole-tetrazoles,[13g] and azepinoindolone-tetrazoles.[13h]

To the best of our knowledge, there are still no reports on the preparation of tetrahydro-1*H*-β-carboline-tetrazoles using Ugi-azide/post-condensation processes.

The objective compounds of our work **3a**–**g** (Figure 3) have both the 1,5-DS-1*H*-T and the 2,3,4,9-tetrahydro-1*H*-β-carboline (βTHC) scaffolds. βTHCs are heterocyclic systems present in numerous compounds with biological activity and some of these have been isolated from natural sources such as cocoa and chocolate.[14] In this context, You and co-workers reported that the promising anticancer agent HR22C16 (**4**) proved to be a strong inhibitor of the mitotic kinesin spindle protein.[15] In the same way, it has been reported that woodinine (**5**) presents a potent antibacterial activity.[16] Vajragupta and co-workers theoretically designed the anti-Alzheimer βTHC **6**, which promises to be an excellent BACE1 inhibitor.[17] As can be seen, compound **6** is a 3-methyltriazole analogue of the 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*-β-carbolines **3a**–**g** (Figure 3).

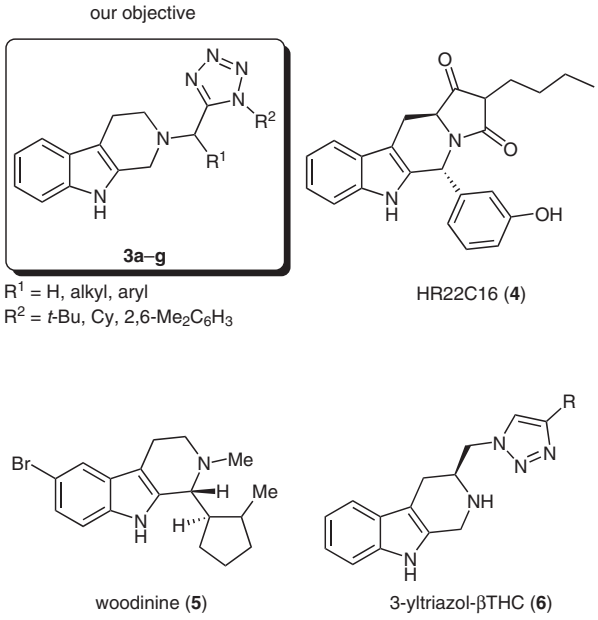
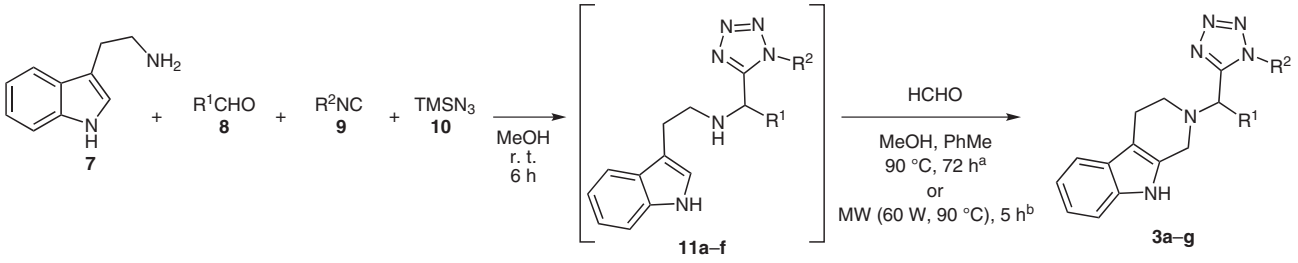


Figure 3 Objective compounds and some βTHCs with biological activity

The Pictet–Spengler (PS) reaction, which is the method of choice for the 1,2,3,4-tetrahydroisoquinoline synthesis from phenethylamine derivatives,[18] is also the method of choice for the preparation of compounds having the βTHC

Table 1 Synthesis of 2-Tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*-β-carbolines **3a**–**g**



Entry	R^1	R^2	Yield of **11a**–**f** (%)[c]	Yield of **3a**–**f** (%)[a,c]	Yield of **3a**–**f** (%)[b,c]	Yield of **3a**–**g** (%)[c,d]
1	Et	*c*-C_6H_{11}	87 (**11a**)	85 (**3a**)	82 (**3a**)	76 (**3a**)
2	*n*-Pr	*t*-Bu	93 (**11b**)	78 (**3b**)	75 (**3b**)	74 (**3b**)
3	4-ClC_6H_4	*t*-Bu	91 (**11c**)	86 (**3c**)	83 (**3c**)	77 (**3c**)
4	4-ClC_6H_4	*c*-C_6H_{11}	90 (**11d**)	86 (**3d**)	82 (**3d**)	77 (**3d**)
5	4-ClC_6H_4	2,6-$Me_2C_6H_3$	89 (**11e**)	80 (**3e**)	74 (**3e**)	71 (**3e**)
6	3-Br-4-$MeOC_6H_3$	2,6-$Me_2C_6H_3$	87 (**11f**)	74 (**3f**)	73 (**3f**)	69 (**3f**)
7	H	2,6-$Me_2C_6H_3$	– (**11g**)	– (**11g**)	– (**11g**)	93 (**3g**)

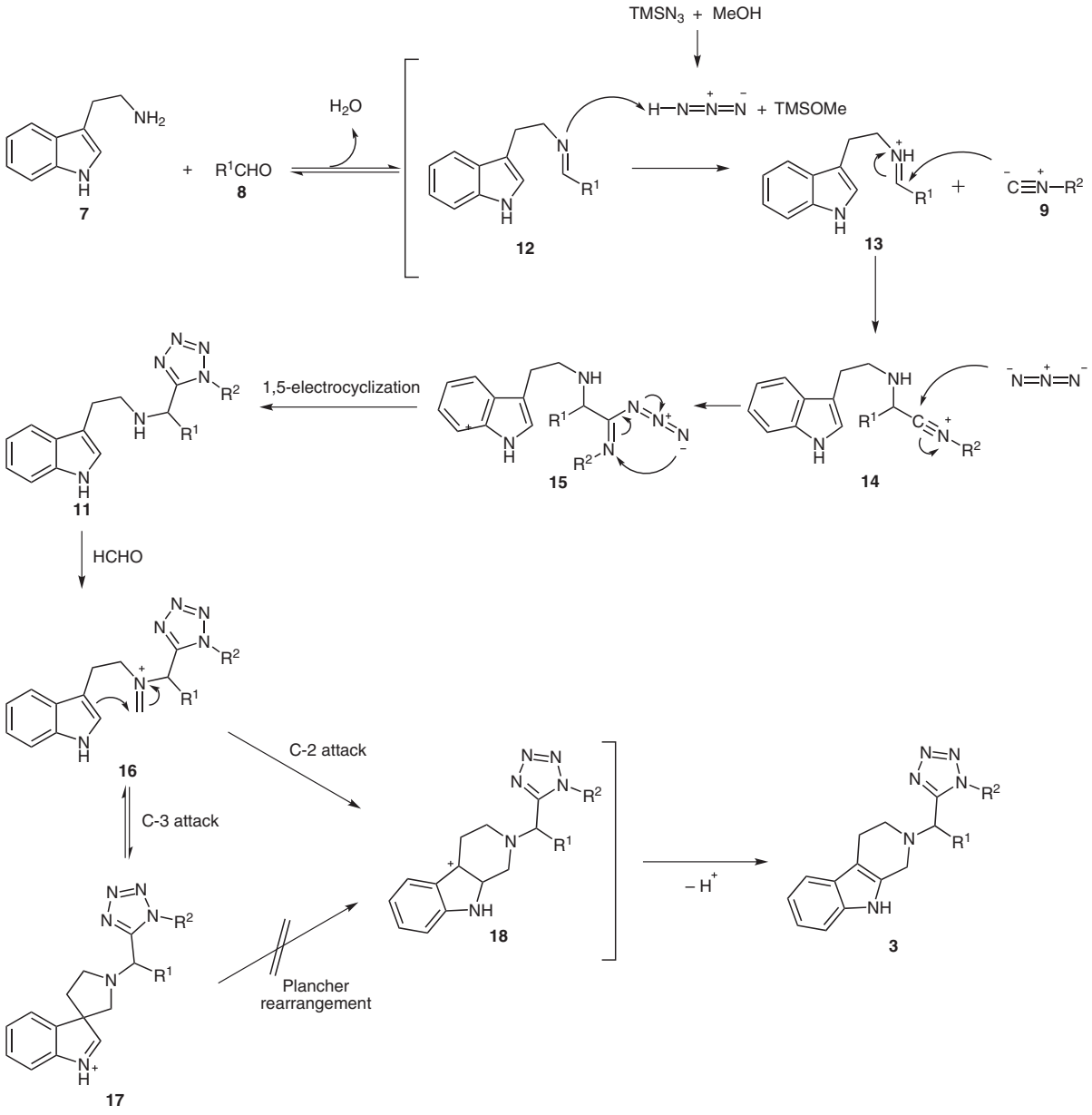
[a] Yields for the conventional heating method from the Ugi adducts **11**.
[b] Yields for the MW heating method from the Ugi adducts **11**.
[c] Yields obtained after a silica gel flash chromatography purification.
[d] Yields of the one-pot process from the starting materials **7**, **8**, **9**, **10** to final product **3**.

moiety from tryptamine derivatives.[19] In this context, methods for the synthesis of βTHC such as the C–C metal-catalyzed coupling reported by Nielsen et al.[20] are considered synthetic variations of the PS reaction.

The stepwise combination of the Ugi reaction with the PS as post-condensation[21] has been used by Dömling and co-workers to prepare a series of polycyclic-fused βTHC with moderate overall yields.[22] In the same way, Orru and co-workers reported the synthesis of pentacyclic-fused diketopiperazine-βTHCs using the stepwise sequence: MAO-N oxidation/Ugi/tandem PS.[23] The MCR/PS method was carried out as a one-pot process by Müller and co-workers to prepare a series of tetracyclic fused βTHCs with moderate yields based on the use of metal catalysis.[24]

In this work, we describe the first one-pot synthesis of βTHCs, which have the 1,5-DS-1*H*-T ring system based on the Ugi-azide/PS method obtaining excellent overall yields. The synthesis started with the sequential combination of the commercially available tryptamine (**7**), aldehydes **8**, isocyanides **9**, and trimethylsilyl azide ($TMSN_3$, **10**) by an Ugi-azide process to prepare the series of 1,5-DS-1*H*-T **11a**–**f** in excellent yields (87–93%) using the Ugi standard conditions (Table 1).

Then, having the compounds **11a**–**f** in our hands, a Pictet–Spengler cyclization was carried out using either, conventional or MW heating methods to obtain the corresponding series of novel 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*-β-carbolines **3a**–**f** in good to excellent yields; 74–86% and 73–83%, respectively (Table 1). Surprisingly, when formaldehyde was used in the Ugi-azide reaction, the corresponding compound **11g** (Table 1, entry 7) could not be isolated because the PS reaction immediately took place



Scheme 1 Plausible reaction mechanism for 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*-β-carbolines **3** formation

to afford the product **3g** through a tandem Ugi-azide/PS process in 93% yield. Based on this idea, the synthesis of final products **3a**–**f** was also performed coupling the Ugi-azide reaction with the PS cyclization under a one-pot process obtaining excellent overall yields (69–77%; Table 1).

In the context of the one-pot chemistry, it has been reported that one-pot processes involving several reactions eventually take place in low yields compared with those involving a minimum of them.[25] In the present case, the conditions for the Ugi-azide process promoted the PS reaction. As can be seen, MeOH was used as solvent in both processes. For this reason, the preparation of a series of final products **3a**–**g** in one pot and with significantly higher overall yields was possible (Table 1).

The plausible reaction mechanism for the 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*-β-carbolines **3** formation is depicted in Scheme 1. A condensation between tryptamine (**7**) and aldehydes **8** occur to give the imines **12**, which were transformed into the corresponding iminium ions **13** by hydrazoic acid. Then, isocyanide **9** reacts with **13** in an α-nucleophilic addition process to produce the nitrilium ions **14**, which are attacked by the azide anion to give the intermediates **15**. Then, a 1,5 dipolar electrocyclization takes place to afford the 1,5-DS-1*H*-T series **11**, which are condensed with formaldehyde to give the iminium ions **16**. At this point, there has been a controversy concerning how the indole-based PS reaction takes place because clearly both C-2 and C-3 attacks are possible.[26] In this context, Hooker et al. performed an isotopic labeling to demonstrate how the reaction occurs[19g] and the answer was according to the expectations, which are supported by thermodynamic studies reported by Kowalski et al., where the Plancher rearrangement was shown to not be possible.[27] Iminium ions **16** initially undergo a rapid C-3 attack[28] to give the spiro-intermediates **17**, which are in chemical equilibrium with the iminium ions **16**. The latter undergo a C-2 attack to give the intermediates **18**, which lose a proton to obtain the thermodynamically stable 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*-β-carbolines **3** (Scheme 1).

In conclusion, this work is the first one-pot synthesis of βTHCs by the Ugi-azide/PS method. As far as we know, there has been no report on one-pot Ugi/PS process. The two reaction steps were performed under a one-pot process, while other synthetic methods involve two or more reaction steps. Our synthesis of the 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*-β-carbolines is a metal-free process. The final products have the 1,5-DS-T and βTHC moieties, which are of high interest in medicinal chemistry, hence our compounds could present biological activity.

An asymmetric version of this methodology is currently being carried out using L-tryptophane as chiral inductor instead of tryptamine to obtain a series of novel optically active 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*-β-carbolines.

Commercially available starting materials were purchased from Sigma-Aldrich and used without further purification. IR spectra were recorded on a PerkinElmer 100FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were acquired using Bruker (400 MHz) and Varian (300 and 200 MHz) spectrometers. $CDCl_3$ was used as the solvent. Chemical shifts are reported in ppm with internal reference to TMS at 0.0 ppm. Coupling constants are reported in Hz. HRMS were recorded on a JEOL JEM-AX505HA spectrometer. Microwave-assisted reactions were performed using a CEM Discover Synthesis™ unit with a monomodal open-vessel system. Reaction progress was monitored by TLC on precoated silica gel (Kieselgel 60 F254) plates. The spots were visualized under UV light (254 nm). Flash column chromatography was conducted using silica gel (230–400 mesh) with different mixtures of solvents as mobile phase. All products were recrystallized using a mixture of CH_2Cl_2–hexanes (1:10, v/v). Melting points were determined on a Fisher–Johns apparatus and are uncorrected.

***N*-[(1*H*-Tetrazol-5-yl)methyl]-2-(1*H*-indol-3-yl)ethanamines 11a–f; General Procedure 1 (GP-1)**

A round-bottomed flask equipped with a magnetic stirring bar was charged with tryptamine (**7**; 1.0 equiv), aldehyde **8** (1.0 equiv), isocyanide **9** (1.0 equiv), and azidotrimethylsilane (**10**; 1.0 equiv) in MeOH (1.0 M). The resulting mixture was stirred for 6 h under N_2 atmosphere at r.t. The solvent was evaporated under reduced pressure. Then, the crude residue was diluted with CH_2Cl_2 (15 mL) and washed with brine (30 mL). The organic layer was dried (Na_2SO_4), evaporated to dryness, and the residue purified by silica gel column chromatography (hexanes–EtOAc, 3:1 v/v).

***N*-[2-(1*H*-Indol-3-yl)ethyl]-1-(1-cyclohexyl-1*H*-tetrazol-5-yl)propan-1-amine (11a)**

According to GP-1, tryptamine (**7**; 500 mg, 3.12 mmol), propionaldehyde (181 mg, 3.12 mmol), cyclohexyl isocyanide (341 mg, 3.12 mmol), and azidotrimethylsilane (360 mg, 3.12 mmol) were reacted together in MeOH (3.1 mL) to afford **11a** (957 mg, 87%) as a white solid; mp 123–125 °C; R_f = 0.36 (hexanes–EtOAc, 3:1 v/v).

FT-IR (ATR): 3303, 3186, 2933, 2860, 1455, 1118, 738 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (s, 1 H, NH), 7.12 (t, *J* = 8.1 Hz, 1 H, H_{Ar}), 7.03 (t, *J* = 7.9 Hz, 2 H, H_{Ar}), 6.92 (d, *J* = 2.2 Hz, 1 H, H_{Ar}), 4.47 (tt, *J* = 3.8 Hz, *J* =11.5 Hz, 1 H, CH), 4.00 (t, *J* = 9.1 Hz, 1 H, CH), 2.86–2.82 (m, 2 H, CH_2), 2.77–2.71 (m, 1 H, 1 H of CH_2), 2.68–2.62 (m, 1 H, 1 H of CH_2), 1.95–1.89 (m, 2 H, CH_2), 1.87–1.73 (m, 6 H, 3 CH_2), 1.69–1.64 (m, 1 H, 1 H of CH_2), 1.50 (s, 1 H, NH), 1.33–1.21 (m, 3 H, CH_2 and 1 H of CH_2), 0.76 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.4 (C-Ar), 136.5 (C-Ar), 127.4 (C-Ar), 122.2 (C-Ar), 121.9 (C-Ar), 119.2 (C-Ar), 118.6 (C-Ar), 113.1 (C-Ar), 111.5 (C-Ar), 58.0 (CH), 55.3 (CH), 47.7 (CH_2), 33.3 (CH_2), 33.1 (CH_2), 27.7 (CH_2), 25.8 (CH_2), 25.4 (CH_2), 24.9 (CH_2), 10.5 (CH_3).

***N*-[2-(1*H*-Indol-3-yl)ethyl]-1-[1-(*tert*-butyl)-1*H*-tetrazol-5-yl]butan-1-amine (11b)**

According to GP-1, tryptamine (**7**; 250 mg, 1.56 mmol), butyraldehyde (113 mg, 1.56 mmol), *tert*-butyl isocyanide (130 mg, 1.56 mmol), and azidotrimethylsilane (180 mg, 1.56 mmol) were reacted together in MeOH (1.6 mL) to afford **11b** (494 mg, 93%) as a white solid; mp 111–113 °C; R_f = 0.43 (hexanes–EtOAc, 3:1 v/v).

FT-IR (ATR): 3289, 3187, 2954, 2875, 1454, 1224, 1120, 1097, 739 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99 (s, 1 H, NH), 7.35 (d, *J* = 7.7 Hz, 1 H, H_{Ar}), 7.18 (d, *J* = 7.6 Hz, 1 H, H_{Ar}), 7.20–7.15 (m, 1 H, H_{Ar}), 7.11–7.06 (m, 1 H, H_{Ar}), 7.00 (d, *J* = 2.2 Hz, 1 H, H_{Ar}), 4.20 (t, *J* = 6.7 Hz, 1 H, CH), 2.94–2.90 (m, 2 H, CH_2), 2.82–2.74 (m, 2 H, CH_2), 1.87–1.75 (m, 3 H, CH_2, NH), 1.68 [s, 9 H, $C(CH_3)_3$], 1.53–1.45 (m, 1 H, 1 H of CH_2), 1.37–1.25 (m, 1 H, 1 H of CH_2), 0.90 (t, *J* = 7.3 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.1 (C-Ar), 136.5 (C-Ar), 127.7 (C-Ar), 122.2 (C-Ar), 122.0 (C-Ar), 119.5 (C-Ar), 118.9 (C-Ar), 113.9 (C-Ar), 111.3 (C-Ar), 61.2 (C quat), 54.5 (CH), 47.8 (CH_2), 38.1 (CH_2), 30.4 [C(CH_3)$_3$], 26.3 (CH_2), 19.7 (CH_2), 14.1 (CH_3).

_N_-{[1-(*tert*-Butyl)-1*H*-tetrazol-5-yl](4-chlorophenyl)methyl}-2-(1*H*-indol-3-yl)ethanamine (11c)

According to GP-1, tryptamine (**7**; 400 mg, 2.50 mmol), 4-chlorobenzaldehyde (351 mg, 2.50 mmol), *tert*-butyl isocyanide (208 mg, 2.50 mmol), and azidotrimethylsilane (288 mg, 2.50 mmol) were reacted together in MeOH (2.5 mL) to afford **11c** (929 mg, 91%) as a white solid; mp 133–134 °C; R_f = 0.39 (hexanes–EtOAc, 3:1 v/v).

IR (ATR): 3286, 3220, 2917, 2846, 1492, 1453, 1230, 1111, 1093, 740 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (s, 1 H, NH), 7.51 (d, J = 7.8 Hz, 1 H, H_{Ar}), 7.35 (d, J = 8.2 Hz, 1 H, H_{Ar}), 7.29–7.23 (m, 2 H, H_{Ar}), 7.20–7.14 (m, 3 H, H_{Ar}), 7.09 (d, J = 8.0 Hz, 1 H, H_{Ar}), 7.05 (s, 1 H, H_{Ar}), 5.24 (s, 1 H, CH), 3.04–2.93 (m, 2 H, CH_2), 2.93–2.82 (m, 2 H, CH_2), 1.58 [s, 9 H, C(CH_3)$_3$], 1.25 (s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7 (C-Ar), 137.6 (C-Ar), 136.6 (C-Ar), 134.5 (C-Ar), 129.6 (C-Ar), 129.3 (C-Ar), 127.6 (C-Ar), 122.3 (C-Ar), 122.1 (C-Ar), 119.6 (C-Ar), 119.0 (C-Ar), 113.8 (C-Ar), 111.4 (C-Ar), 61.6 (C quat), 58.7 (CH), 48.2 (CH_2), 30.2 [C(CH_3)$_3$], 26.2 (CH_2).

_N_-[(4-Chlorophenyl)(1-cyclohexyl-1*H*-tetrazol-5-yl)methyl]-2-(1*H*-indol-3-yl)ethanamine (11d)

According to GP-1, tryptamine (**7**; 500 mg, 3.12 mmol), 4-chlorobenzaldehyde (439 mg, 3.12 mmol), cyclohexyl isocyanide (341 mg, 3.12 mmol), and azidotrimethylsilane (360 mg, 3.12 mmol) were reacted together in MeOH (3.1 mL) to afford **11d** (1.22 g, 90%) as a white solid; mp 125–126 °C; R_f = 0.12 (hexanes–EtOAc, 3:1 v/v).

FT-IR (ATR): 3309, 3169, 2929, 2862, 1486, 1450, 1090, 747 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (s, 1 H, NH), 7.47 (d, J = 7.8 Hz, 1 H, H_{Ar}), 7.29 (d, J = 8.1 Hz, 1 H, H_{Ar}), 7.20 (d, J = 8.6 Hz, 2 H, H_{Ar}), 7.14–7.10 (m, 3 H, H_{Ar}), 7.04–7.01 (m, 1 H, H_{Ar}), 6.96 (d, J = 2.2 Hz, 1 H, H_{Ar}), 5.14 (s, 1 H, CH), 4.12 (tt, J = 3.6, 11.4 Hz, 1 H, CH), 2.94 (dd, J = 6.1, 11.8 Hz, 2 H, CH_2), 2.88–2.78 (m, 2 H, CH_2), 1.99 (s, 1 H, NH), 1.74–1.71 (m, 4 H, 2 CH_2), 1.59 (s, 1 H, 1 H of CH_2), 1.43 (t, J = 14.6 Hz, 2 H, CH_2), 1.17–1.12 (m, 3 H, CH_2 and 1 H of CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.6 (C-Ar), 136.9 (C-Ar), 136.6 (C-Ar), 134.53 (C-Ar), 129.3 (C-Ar), 128.7 (C-Ar), 127.5 (C-Ar), 122.4 (C-Ar), 122.3 (C-Ar), 119.6 (C-Ar), 118.9 (C-Ar), 113.5 (C-Ar), 111.5 (C-Ar), 58.2 (CH), 57.1 (CH), 48.0 (CH_2), 32.8 (CH_2), 25.9 (CH_2), 25.5 (CH_2), 24.9 (CH_2).

_N_-{(4-Chlorophenyl)[1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl]methyl}-2-(1*H*-indol-3-yl)ethanamine (11e)

According to GP-1, tryptamine (**7**; 250 mg, 1.56 mmol), 4-chlorobenzaldehyde (219 mg, 1.56 mmol), 2,6-dimethylphenyl isocyanide (205 mg, 1.56 mmol), and azidotrimethylsilane (180 mg, 1.56 mmol) were reacted together in MeOH (1.6 mL) to afford **11e** (635 mg, 89%) as a white solid; mp 66–68 °C; R_f = 0.57 (hexanes–EtOAc, 3:1 v/v).

FT-IR (ATR): 3406, 3310, 2921, 2848, 1488, 1456, 1275, 1260, 1089, 764, 745 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.07 (s, 1 H, NH), 7.46 (d, J = 7.7 Hz, 1 H, H_{Ar}), 7.41–7.29 (m, 2 H, H_{Ar}), 7.22–7.03 (m, 7 H, H_{Ar}), 6.89 (d, J = 8.4 Hz, 2 H, H_{Ar}), 4.64 (s, 1 H, CH), 3.08–2.69 (m, 4 H, 2 CH_2), 2.26 (s, 1 H, NH), 1.86 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 156.8 (C-Ar), 136.8 (C-Ar), 136.6 (C-Ar), 136.2 (C-Ar), 135.5 (C-Ar), 134.6 (C-Ar), 131.7 (C-Ar), 131.2 (C-Ar), 129.3 (C-Ar), 129.1 (C-Ar), 128.9 (C-Ar), 127.4 (C-Ar), 122.3 (C-Ar), 119.5 (C-Ar), 118.9 (C-Ar), 113.4 (C-Ar), 111.4 (C-Ar), 57.5 (CH), 47.7 (CH_2), 25.8 (CH_2), 17.5 (CH_3), 17.0 (CH_3).

_N_-{(3-Bromo-4-methoxyphenyl)[1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl]methyl}-2-(1*H*-indol-3-yl)ethanamine (11f)

According to GP-1, tryptamine (**7**; 200 mg, 1.25 mmol), 3-bromo-4-methoxybenzaldehyde (268 mg, 1.25 mmol), 2,6-dimethylphenyl isocyanide (164 mg, 1.25 mmol), and azidotrimethylsilane (144 mg, 1.25 mmol) were reacted together in MeOH (1.3 mL) to afford **11f** (577 mg, 87%) as a white solid; mp 120–121 °C; R_f = 0.50 (hexanes–EtOAc, 3:1 v/v).

FT-IR (ATR): 3169, 2929, 2868, 1494, 1450, 1280, 1259, 1011, 741 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (s, 1 H, NH), 7.48 (d, J = 7.7 Hz, 1 H, H_{Ar}), 7.40–7.33 (m, 2 H, H_{Ar}), 7.20–7.15 (m, 2 H, H_{Ar}), 7.10–7.05 (m, 3 H, H_{Ar}), 6.97–6.92 (m, 2 H, H_{Ar}), 6.65 (d, J = 8.1 Hz, 1 H, H_{Ar}), 4.60 (s, 1 H, CH), 3.83 (s, 3 H, OCH_3), 2.99–2.75 (m, 4 H, 2 CH_2), 1.85 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.9 (C-Ar), 156.1 (C-Ar), 136.8 (C-Ar), 136.6 (C-Ar), 135.3 (C-Ar), 132.8 (C-Ar), 131.6 (C-Ar), 131.23 (C-Ar), 131.1 (C-Ar), 129.0 (C-Ar), 128.9 (C-Ar), 127.9 (C-Ar), 127.4 (C-Ar), 122.3 (C-Ar), 122.2 (C-Ar), 119.4 (C-Ar), 118.9 (C-Ar), 113.4 (C-Ar), 112.0 (C-Ar), 111.8 (C-Ar), 111.4 (C-Ar), 57.1 (CH), 56.5 (OCH_3), 47.7 (CH_2), 25.8 (CH_2), 17.5 (CH_3), 17.0 (CH_3).

2-[(1*H*-Tetrazol-5-yl)methyl]-2,3,4,9-tetrahydro-1*H*-β-carbolines 3a–f; General Procedures

General Procedure 2 (GP-2)

In a round-bottomed flask equipped with a magnetic stirring bar, the appropriate *N*-[(1*H*-tetrazol-5-yl)methyl]-2-(1*H*-indol-3-yl)ethanamine **11** (1.0 equiv) and paraformaldehyde (1.5 equiv) were diluted with a mixture of MeOH–toluene (1:1, 0.5 M). The resulting mixture was stirred for 72 h under N_2 atmosphere at 90 °C. The solvent was evaporated under reduced pressure. Then, the crude residue was diluted with CH_2Cl_2 (10 mL) and washed with brine (20 mL). The organic layer was dried (Na_2SO_4), evaporated to dryness, and the residue purified by silica gel column chromatography (hexanes–EtOAc, 3:2 v/v).

General Procedure 3 (GP-3)

In a round-bottomed flask equipped with a magnetic stirring bar, the appropriate *N*-[(1*H*-tetrazol-5-yl)methyl]-2-(1*H*-indol-3-yl)ethanamine **11** (1.0 equiv) and paraformaldehyde (1.5 equiv) were diluted with a mixture of MeOH–toluene (1:1, 0.5 M). The resulting mixture was stirred for 5 h under MW heating conditions at 90 °C (60 W). The solvent was evaporated under reduced pressure. Then, the crude residue was diluted with CH_2Cl_2 (10 mL) and washed with brine (20 mL). The organic layer was dried (Na_2SO_4), evaporated to dryness, and the residue purified by silica gel column chromatography (hexanes–EtOAc, 3:2 v/v).

General Procedure 4 (GP-4)

In a round-bottomed flask equipped with a magnetic stirring bar, tryptamine (**7**; 1.0 equiv), the respective aldehyde **8** (1.0 equiv), the required isocyanide **9** (1.0 equiv), and azidotrimethylsilane (1.0 equiv) were diluted with MeOH (1.0 M). The resulting mixture was stirred for 6 h under N_2 atmosphere at r.t. Then, the solvent was evaporated under reduced pressure. The crude residue was dissolved in a mixture of MeOH–toluene (1:1, 0.5 M) and paraformaldehyde (1.5 equiv) was added. The resulting mixture was stirred for an additional 5 h under MW heating conditions at 90 °C (60 W). The solvent was evaporated under reduced pressure. Then, the crude residue was diluted with CH_2Cl_2 (15 mL) and washed with brine (30 mL). The organic layer was dried (Na_2SO_4), evaporated to dryness, and purified by silica gel column chromatography (hexanes–EtOAc, 3:2 v/v).

2-[1-(1-Cyclohexyl-1*H*-tetrazol-5-yl)propyl]-2,3,4,9-tetrahydro-1*H*-β-carboline (3a)

According to GP-2: Tetrazole **11a** (96 mg, 0.27 mmol) and paraformaldehyde (12 mg, 0.41 mmol) were reacted together in a mix-

ture of MeOH–toluene (1:1, 0.6 mL) to afford **3a** (84 mg, 85%) as a yellow solid.

According to GP-3: Tetrazole **11a** (120 mg, 0.34 mmol) and paraformaldehyde (15 mg, 0.51 mmol) were subjected to MW conditions in a mixture MeOH–toluene 1:1 (0.7 mL) to afford **3a** (102 mg, 82%) as a yellow solid.

According to GP-4: Tryptamine (**7**; 300 mg, 1.87 mmol), propionaldehyde (109 mg, 1.87 mmol), cyclohexyl isocyanide (204 mg, 1.87 mmol), and azidotrimethylsilane (216 mg, 1.87 mmol) were dissolved in MeOH (1.9 mL). After completion of the reaction and workup, the crude residue was diluted with a mixture of MeOH–toluene (1:1, 3.8 mL) and paraformaldehyde (84 mg, 2.81 mmol) was added. The mixture was subjected to MW conditions to afford **3a** (236 mg, 76%) as a yellow solid; mp 102–104 °C; R_f = 0.82 (hexanes–EtOAc, 3:2 v/v).

FT-IR (ATR): 3395, 2933, 2858, 1453, 1275, 1260, 1099, 1060, 748 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.98 (s, 1 H, NH), 7.45 (d, *J* = 7.5 Hz, 1 H, H_{Ar}), 7.29 (dd, *J* = 7.0, 1.4 Hz, 1 H, H_{Ar}), 7.22–7.05 (m, 2 H, H_{Ar}), 4.51–4.41 (m, 1 H, CH), 4.08 (dd, *J* = 10.0, 4.8 Hz, 1 H, CH), 3.84–3.67 (m, 2 H, CH_2), 3.04–2.89 (m, 2 H, CH_2), 2.77 (t, *J* = 5.3 Hz, 2 H, CH_2), 2.36–2.10 (m, 2 H, CH_2), 2.03–1.85 (m, 5 H, 2× CH_2 and 1 H of CH_2), 1.41–1.22 (m, 5 H, 2× CH_2 and 1 H of CH_2), 0.84 (t, *J* = 7.4 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$,): δ = 153.5 (C-Ar), 136.3 (C-Ar), 131.6 (C-Ar), 127.3 (C-Ar), 121.6 (C-Ar), 119.6 (C-Ar), 118.1 (C-Ar), 111.0 (C-Ar), 108.4 (C-Ar), 61.3 (C-H), 58.4 (CH), 49.0 (CH_2), 45.8 (CH_2), 33.5 (CH_2), 33.1 (CH_2), 25.7 (CH_2), 25.1 (CH_2), 22.4 (CH_2), 21.2 (CH_2), 11.7 (CH_3).

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{29}N_6$: 365.2454; found: 365.2459.

2-{1-[1-(*tert*-Butyl)-1*H*-tetrazol-5-yl]butyl}-2,3,4,9-tetrahydro-1*H*-β-carboline (3b)

According to GP-2: Tetrazole **11b** (70 mg, 0.20 mmol) and paraformaldehyde (9 mg, 0.30 mmol) were reacted together in a mixture of MeOH–toluene (1:1, 0.4 mL) to afford **3b** (57 mg, 78%) as a yellow solid.

According to GP-3: Tetrazole **11b** (150 mg, 0.43 mmol) and paraformaldehyde (19 mg, 0.64 mmol) were subjected to MW conditions in a mixture of MeOH–toluene (1:1, 0.9 mL) to afford **3b** (116 mg, 75%) as a yellow solid.

According to GP-4: Tryptamine (**7**; 300 mg, 1.87 mmol), butyraldehyde (135 mg, 1.87 mmol), *tert*-butyl isocyanide (156 mg, 1.87 mmol) and azidotrimethylsilane (216 mg, 1.87 mmol) were dissolved in MeOH (1.9 mL). After completion of the reaction and workup, the crude residue was diluted with a mixture of MeOH–toluene (1:1, 3.8 mL) and paraformaldehyde (84 mg, 2.81 mmol) was added. The mixture was subjected MW conditions to afford **3b** (230 mg, 74%) as a yellow solid; mp 128–130 °C; R_f = 0.52 (hexanes–EtOAc, 3:2, v/v).

FT-IR (ATR): 3245, 2960, 2924, 1456, 1276, 1236, 1120, 747 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.93 (s, 1 H, NH), 7.44 (d, *J* = 7.0 Hz, 1 H, H_{Ar}), 7.29 (dd, *J* = 7.0, 1.4 Hz, 1 H, H_{Ar}), 7.14–7.04 (m, 2 H, H_{Ar}), 4.38 (dd, *J* = 10.5, 3.7 Hz, 1 H, CH), 3.83 (d, *J* = 14.3 Hz, 1 H, 1 H of CH_2), 3.64 (d, *J* = 14.3 Hz, 1 H, 1 H of CH_2), 3.15–3.07 (m, 1 H, 1 H of CH_2), 3.05–2.98 (m, 1 H, 1 H of CH_2), 2.81–2.67 (m, 2 H, CH_2), 2.50–2.37 (m, 1 H, 1 H of CH_2), 2.01–1.90 (m, 1 H, 1 H of CH_2), 1.75 [s, 9 H, $C(CH_3)_3$], 1.71–1.65 (m, 1 H, 1 H of CH_2), 1.43–1.33 (m, 1 H, 1 H of CH_2), 0.98 (t, *J* = 7.3 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.3 (C-Ar), 136.3 (C-Ar), 132.1 (C-Ar), 127.3 (C-Ar), 121.5 (C-Ar), 119.5 (C-Ar), 118.0 (C-Ar), 111.0 (C-Ar), 108.5 (C-Ar), 62.3 (C quat), 60.0 (CH), 48.6 (CH_2), 44.7 (CH_2), 30.0 [$C(CH_3)_3$], 27.9 (CH_2), 22.5 (CH_2), 20.6 (CH_2), 14.2 (CH_3).

HRMS: *m*/*z* $[M - H]^-$ calcd for $C_{20}H_{27}N_6$: 351.2297; found: 351.2303.

2-{[1-(*tert*-Butyl)-1*H*-tetrazol-5-yl](4-chlorophenyl)methyl}-2,3,4,9-tetrahydro-1*H*-β-carboline (3c)

According to GP-2: Tetrazole **11c** (105 mg, 0.26 mmol) and paraformaldehyde (12 mg, 0.39 mmol) were reacted together in a mixture of MeOH–toluene 1:1 (0.5 mL) to afford **3c** (93 mg, 86%) as a pale yellow solid.

According to GP-3: Tetrazole **11c** (175 mg, 0.43 mmol) and paraformaldehyde (19 mg, 0.64 mmol) were subjected to MW conditions in a mixture of MeOH–toluene 1:1 (0.9 mL) to afford **3c** (150 mg, 83%) as a pale yellow solid.

According to GP-4: Tryptamine (**7**; 300 mg, 1.87 mmol), 4-chlorobenzaldehyde (263 mg, 1.87 mmol), *tert*-butyl isocyanide (156 mg, 1.87 mmol), and azidotrimethylsilane (216 mg, 1.87 mmol) were dissolved in MeOH (1.9 mL). After completion of the reaction and workup, the crude residue was diluted with a mixture of MeOH–toluene (1:1, 3.8 mL), and paraformaldehyde (84 mg, 2.81 mmol) was added. The mixture was subjected MW conditions to afford **3c** (607 mg, 77%) as a pale yellow solid; mp 184–186 °C; R_f = 0.73 (hexanes–EtOAc, 3:2, v/v).

FT-IR (ATR): 3231, 2985, 2924, 2852, 1456, 1275, 1240, 1088, 748, 737 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.71 (s, 1 H, NH), 7.43 (d, *J* = 8.5 Hz, 3 H, H_{Ar}), 7.35 (d, *J* = 8.6 Hz, 2 H, H_{Ar}), 7.27 (d, *J* = 3.9 Hz, 1 H, H_{Ar}), 7.14–7.04 (m, 2 H, H_{Ar}), 5.64 (s, 1 H, CH), 4.06 (d, *J* = 14.6 Hz, 1 H, 1 H of CH_2), 3.65 (d, *J* = 14.6 Hz, 1 H, 1 H of CH_2), 3.10–3.03 (m, 1 H, 1 H of CH_2), 2.98–2.90 (m, 1 H, 1 H of CH_2), 2.76 (t, *J* = 5.5 Hz, 2 H, CH_2), 1.69 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.1 (C-Ar), 136.3 (C-Ar), 134.9 (C-Ar), 134.4 (C-Ar), 131.6 (C-Ar), 131.3 (C-Ar), 129.1 (C-Ar), 127.4 (C-Ar), 121.7 (C-Ar), 119.7 (C-Ar), 118.1 (C-Ar), 110.9 (C-Ar), 108.4 (C-Ar), 63.4 (CH), 61.9 (C quat), 48.4 (CH_2), 47.0 (CH_2), 30.5 [$C(CH_3)_3$], 21.8 (CH_2).

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{26}ClN_6$: 421.1907; found: 421.1899.

2-[(4-Chlorophenyl)(1-cyclohexyl-1*H*-tetrazol-5-yl)methyl]-2,3,4,9-tetrahydro-1*H*-β-carboline (3d)

According to GP-2: Tetrazole **11d** (190 mg, 0.44 mmol) and paraformaldehyde (20 mg, 0.66 mmol) were reacted together in a mixture of MeOH–toluene (1:1, 0.9 mL) to afford **3d** (168 mg, 86%) as a yellow solid.

According to GP-3: Tetrazole **11d** (250 mg, 0.57 mmol) and paraformaldehyde (26 mg, 0.86 mmol) were subjected to MW conditions in a mixture of MeOH–toluene (1:1, 1.2 mL) to afford **3d** (211 mg, 82%) as a yellow solid.

According to GP-4: Tryptamine (**7**; 400 mg, 2.50 mmol), 4-chlorobenzaldehyde (351 mg, 2.50 mmol), cyclohexyl isocyanide (273 mg, 2.50 mmol), and azidotrimethylsilane (288 mg, 2.50 mmol) were dissolved in MeOH (2.5 mL). After completion of the reaction and workup, the crude residue was diluted with a mixture of MeOH–toluene (1:1, 5.0 mL), and paraformaldehyde (112 mg, 3.75 mmol) was added. The mixture was subjected to MW conditions to afford **3d** (859 mg, 77%) as a yellow solid; mp 186–188 °C; R_f = 0.82 (hexanes–EtOAc, 3:2, v/v).

FT-IR (ATR): 3298, 2930, 2860, 1490, 1454, 1305, 1239, 1092, 1013, 747 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.69 (s, 1 H, NH), 7.46–7.41 (m, 3 H, H_{Ar}), 7.36–7.32 (m, 2 H, H_{Ar}), 7.28–7.25 (m, 1 H, H_{Ar}), 7.15–7.05 (m, 2 H, H_{Ar}), 5.32 (s, 1 H, CH), 4.55–4.45 (m, 1 H, CH), 3.88 (d, *J* = 14.6 Hz, 1 H, 1 H of CH_2), 3.57 (d, *J* = 14.6 Hz, 1 H, 1 H of CH_2), 3.02–2.94 (m, 1 H, 1 H of CH_2), 2.88–2.83 (m, 1 H, 1 H of CH_2), 2.82–2.73 (m, 2 H, CH_2), 1.98–1.67 (m, 6 H, 3 × CH_2), 1.56–1.50 (m, 2 H, CH_2), 1.31–1.19 (m, 2 H, CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.4 (C-Ar), 136.3 (C-Ar), 134.9 (C-Ar), 134.6 (C-Ar), 131.0 (C-Ar), 131.1 (C-Ar), 129.3 (C-Ar), 127.2 (C-Ar), 121.8 (C-Ar), 119.7 (C-Ar), 118.2 (C-Ar), 111.1 (C-Ar), 108.2 (C-Ar), 63.1 (CH), 58.5 (CH), 49.2 (CH_2), 48.4 (CH_2), 33.1 (CH_2), 25.6 (CH_2), 24.9 (CH_2), 21.3 (CH_2).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{28}ClN_6$: 447.2064; found: 447.2055.

2-{(4-Chlorophenyl)[1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl]methyl}-2,3,4,9-tetrahydro-1*H*-β-carboline (3e)

According to GP-2: Tetrazole **11e** (105 mg, 0.23 mmol) and paraformaldehyde (10 mg, 0.34 mmol) were reacted together in a mixture of MeOH–toluene (1:1, 0.5 mL) to afford **3e** (86 mg, 80%) as a white solid.

According to GP-3: Tetrazole **11e** (300 mg, 0.66 mmol) and paraformaldehyde (30 mg, 0.98 mmol) were subjected to MW conditions in a mixture of MeOH–toluene (1:1, 1.3 mL) to afford **3e** (228 mg, 74%) as a white solid.

According to GP-4: Tryptamine (**7**; 350 mg, 2.18 mmol), 4-chlorobenzaldehyde (307 mg, 2.18 mmol), 2,6-dimethylphenyl isocyanide (287 mg, 2.18 mmol), and azidotrimethylsilane (252 mg, 2.18 mmol) were dissolved in MeOH (2.2 mL). After completion of the reaction and workup, the crude residue was diluted with a mixture of MeOH–toluene (1:1, 4.4 mL), and paraformaldehyde (98 mg, 3.28 mmol) was added. The mixture was subjected to MW conditions to afford **3e** (727 mg, 71%) as a white solid; mp 246–247 °C; R_f = 0.59 (hexanes–EtOAc, 3:2, v/v).

FT-IR (ATR): 3339, 2918, 2850, 1488, 1452, 1262, 1086, 1013, 743 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (s, 1 H, NH), 7.43 (d, *J* = 7.3 Hz, 1 H, H_{Ar}), 7.37 (t, *J* = 7.6 Hz, 1 H, H_{Ar}), 7.28–7.25 (m, 3 H, H_{Ar}), 7.22–7.18 (m, 3 H, H_{Ar}), 7.15–7.05 (m, 3 H, H_{Ar}), 4.73 (s, 1 H, CH), 3.89 (d, *J* = 14.6 Hz, 1 H, 1 H of CH_2), 3.76 (d, *J* = 14.6 Hz, 1 H, 1 H of CH_2), 3.00–2.86 (m, 2 H, CH_2), 2.73 (dd, *J* = 12.4, 6.1 Hz, 2 H, CH_2), 1.92 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.7 (C-Ar), 136.7 (C-Ar), 136.3 (C-Ar), 135.6 (C-Ar), 135.2 (C-Ar), 133.5 (C-Ar), 131.8 (C-Ar), 131.3 (C-Ar), 131.0 (C-Ar), 129.1 (C-Ar), 127.3 (C-Ar), 121.8 (C-Ar), 119.7 (C-Ar), 118.2 (C-Ar), 111.0 (C-Ar), 108.4 (C-Ar), 62.8 (CH), 49.0 (CH_2), 47.8 (CH_2), 29.9 (CH_2), 21.0 (CH_3), 17.0 (CH_3).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{26}ClN_6$: 469.1907; found: 469.1898.

2-{(3-Bromo-4-methoxyphenyl)[1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl]methyl}-2,3,4,9-tetrahydro-1*H*-β-carboline (3f)

According to GP-2: Tetrazole **11f** (95 mg, 0.18 mmol) and paraformaldehyde (8.0 mg, 0.27 mmol) were reacted together in a mixture of MeOH–toluene (1:1, 0.4 mL) to afford **3f** (72 mg, 74%) as a yellow solid.

According to GP-3: Tetrazole **11f** (300 mg, 0.56 mmol) and paraformaldehyde (25 mg, 0.85 mmol) were subjected to MW conditions in a mixture of MeOH–toluene (1:1, 1.1 mL) to afford **3f** (224 mg, 73%) as a yellow solid.

According to GP-4: Tryptamine (**7**; 400 mg, 2.50 mmol), 3-bromo-4-methoxybenzaldehyde (537 mg, 2.50 mmol), 2,6-dimethylphenyl isocyanide (328 mg, 2.50 mmol), and azidotrimethylsilane (288 mg, 2.50 mmol) were dissolved in MeOH (2.5 mL). After completion of the reaction and workup, the crude residue was diluted with a mixture of MeOH–toluene (1:1, 5.0 mL), and paraformaldehyde (112 mg, 3.74 mmol) was added. The mixture was subjected to MW conditions to afford **3f** (936 mg, 69%) as a yellow solid; mp 131–133 °C; R_f = 0.80 (hexanes–EtOAc, 3:2, v/v).

FT-IR (ATR): 3394, 2925, 2842, 1495, 1455, 1283, 1258, 1095, 1054, 1018, 742 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (s, 1 H, NH), 7.39 (dd, *J* = 17.4, 7.7 Hz, 2 H, H_{Ar}), 7.31–7.26 (m, 3 H, H_{Ar}), 7.19 (d, *J* = 7.9 Hz, 1 H, H_{Ar}), 7.14–7.04 (m, 3 H, H_{Ar}), 6.81 (d, *J* = 8.5 Hz, 1 H, H_{Ar}), 4.66 (s, 1 H, CH), 3.99–3.66 (m, 5 H, CH_2 and OCH_3), 3.02–2.85 (m, 2 H, CH_2), 2.83–2.60 (m, 2 H, CH_2), 1.90 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.5 (C-Ar), 155.9 (C-Ar), 136.7 (C-Ar), 136.3 (C-Ar), 135.5 (C-Ar), 134.2 (C-Ar), 131.3 (C-Ar), 131.1 (C-Ar), 129.7 (C-Ar), 129.1 (C-Ar), 128.5 (C-Ar), 121.7 (C-Ar), 119.6 (C-Ar), 118.1 (C-Ar), 112.1 (C-Ar), 111.9 (C-Ar), 111.0 (C-Ar), 108.3 (C-Ar), 62.5 (CH), 56.6 (OCH_3), 49.0 (CH_2), 47.9 (CH_2), 21.0 (CH_2), 17.6 (CH_3), 17.0 (CH_3).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{28}BrN_6O$: 543.1508; found: 543.1521.

2-{[1-(2,6-Dimethylphenyl)-1*H*-tetrazol-5-yl]methyl}-2,3,4,9-tetrahydro-1*H*-β-carboline (3g)

In a round-bottomed flask equipped with a magnetic stirrer bar, tryptamine (**7**; 300 mg, 1.87 mmol, 1.0 equiv) was diluted in MeOH (1.9 mL, 1.0 M), and paraformaldehyde (124 mg, 4.11 mmol, 2.2 equiv), 2,6-dimethylphenyl isocyanide (246 mg, 1.87 mmol, 1.0 equiv), azidotrimethylsilane (216 mg, 1.87 mmol, 1 equiv), and NaOH (22 mg, 0.56 mmol, 0.3 equiv) were added. The resulting mixture was stirred for 6 h under N_2 atmosphere at r.t. The solvent was evaporated under reduced pressure and the crude residue was diluted with CH_2Cl_2 (10 mL) and washed with brine (20 mL). The organic layer was dried (Na_2SO_4), evaporated to dryness, and the residue purified by silica gel column chromatography (hexanes–EtOAc, 4:1, v/v) to afford **3g** (624 mg, 93%) as a white solid; mp 182–184 °C; R_f = 0.64 (hexanes–EtOAc, 3:2, v/v).

FT-IR (ATR): 3148, 3054, 1626, 1474, 1451, 1268, 1108 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.81 (s, 1 H, NH), 7.45–7.41 (m, 1 H, H_{Ar}), 7.37–7.36 (m, 1 H, H_{Ar}), 7.27–7.26 (m, 1 H, H_{Ar}), 7.19 (d, *J* = 7.6 Hz, 2 H, H_{Ar}), 7.14–7.04 (m, 2 H, H_{Ar}), 3.82 (s, 2 H, CH_2), 3.72 (s, 2 H, CH_2), 2.88–2.79 (m, 2 H, CH_2), 2.72–2.62 (m, 2 H, CH_2), 1.93 (s, 6 H, 2 × CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 153.6 (C-Ar), 136.2 (C-Ar), 132.2 (C-Ar), 131.1 (C-Ar), 130.9 (C-Ar), 128.9 (C-Ar), 127.2 (C-Ar), 121.8 (C-Ar), 119.6 (C-Ar), 118.1 (C-Ar), 111.0 (C-Ar), 108.2 (C-Ar), 51.5 (CH_2), 50.2 (CH_2), 49.1 (CH_2), 21.0 (CH_2), 17.6 (2 × CH_3).

Acknowledgment

R.G.-M. acknowledges Instituto de Química-UNAM and Dr. G. Cuevas for technical support with respect to HRMS and X-ray analysis. Financial support from CONACYT (Project 166747 CB-2011-01) is gratefully acknowledged. Post-doctoral scholarship awarded to Dr. Alejandro Islas Jácome (CVU 176745, 290662_UG, 290735_UG) and doctoral scholarships awarded to Luis Edilberto Cárdenas Galindo (CVU 225689, 209242) and Nancy Verónica Álvarez Rodriguez (CVU 425598, 265314) are also gratefully acknowledged.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) Baumann, M.; Baxendale, I. R.; Ley, S. V.; Nikbin, N. *Beilstein J. Org. Chem.* **2011**, *7*, 442.
(2) Myznikov, L. V.; Hrabalek, A.; Koldovskii, G. I. *Chem. Heterocycl. Comp.* **2007**, *43*, 1.
(3) Roh, J.; Vávrová, K.; Hrabálek, A. *Eur. J. Org. Chem.* **2012**, 6101.

(4) Herr, R. J. *Bioorg. Med. Chem.* **2002**, *10*, 3379.
(5) Patani, G. A.; La Voie, E. J. *Chem. Rev.* **1996**, *96*, 3147.
(6) (a) Breschi, M. C.; Calderone, V.; Digiacomo, M.; Martelli, A.; Martinotti, E.; Minutolo, F.; Rapposelli, S.; Balsamo, A. *J. Med. Chem.* **2004**, *47*, 5597. (b) Breschi, M. C.; Calderone, V.; Digiacomo, M.; Macchia, M.; Martelli, A.; Martinotti, E.; Minutolo, F.; Rapposelli, S.; Rosello, A.; Testai, L.; Balsamo, A. *J. Med. Chem.* **2006**, *49*, 2628.
(7) García, G.; Rodríguez-Puyol, M.; Alajarín, R.; Serrano, I.; Sánchez-Alonso, P.; Griera, M.; Vaquero, J.; Rodríguez-Puyol, D.; Alvarez-Builla, J.; Díez-Marques, M. *J. Med. Chem.* **2009**, *52*, 7220.
(8) May, B. C. H.; Abell, D. *Tetrahedron Lett.* **2001**, *42*, 5641.
(9) Rajasekaran, A.; Thampi, P. P. *Eur. J. Med. Chem.* **2004**, *39*, 273.
(10) For reviews, see: (a) Brase, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem. Int. Ed.* **2005**, *44*, 5188. (b) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297.
(11) Aldhoun, M.; Massi, A.; Dondoni, A. *J. Org. Chem.* **2008**, *73*, 9565.
(12) (a) El Kaim, L.; Grimaud, L. *Tetrahedron* **2009**, *65*, 2153. (b) Schaffert, E. S.; Höfner, G.; Wanner, K. T. *Bioorg. Med. Chem.* **2011**, *19*, 6492.
(13) (a) Borisov, R. S.; Polyakov, A. I.; Medvedeva, L. A.; Khrustalev, V. N.; Guranova, N. I.; Voskressensky, L. G. *Org. Lett.* **2010**, *12*, 3894. (b) Nixey, T.; Kelly, M.; Semin, D.; Hulme, C. *Tetrahedron Lett.* **2002**, *43*, 368. (c) Nixey, T.; Kelly, M.; Hulme, C. *Tetrahedron Lett.* **2000**, *41*, 8729. (d) Marcos, C. F.; Marcaccini, S.; Menchi, G.; Pepino, R.; Torroba, T. *Tetrahedron Lett.* **2008**, *49*, 149. (e) Gunawan, S.; Nichol, G.; Hulme, C. *Tetrahedron Lett.* **2012**, *53*, 1664. (f) Gunawan, S.; Petit, J.; Hulme, C. *ACS Comb. Sci.* **2012**, *14*, 160. (g) El Kaim, L.; Grimaud, L.; Purumandla, S. R. *Synlett* **2012**, *23*, 295. (h) Gordillo-Cruz, R.; Rentería-Gómez, A.; Islas-Jácome, A.; Cortes-García, C.; Díaz-Cervantes, E.; Robles, J.; Gámez-Montaño, R. *Org. Biomol. Chem.* **2013**, *11*, 6470.
(14) Herraiz, T. *J. Agric. Food Chem.* **2000**, *48*, 4900.
(15) Liu, F.; Yu, L. Q.; Jiang, C.; Yang, L.; Wu, W. T.; You, Q. D. *Bioorg. Med. Chem.* **2010**, *18*, 4167.
(16) (a) McNulty, J.; Still, I. W. J. *Curr. Org. Chem.* **2000**, *4*, 121. (b) Debitus, C.; Laurent, D.; Païs, M. *J. Nat. Prod.* **1988**, *51*, 799.
(17) Jiaranaikulwanitch, J.; Boonyarat, C.; Fokin, V. V.; Vajragupta, O. *Bioorg. Med. Chem.* **2010**, *20*, 6572.
(18) For reviews, see: (a) Stöckigt, J.; Antonchick, A. P.; Wu, F.; Waldmann, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 8538. (b) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.
(19) (a) Bernhardt, P.; Usera, A. R.; O'Connor, S. E. *Tetrahedron Lett.* **2010**, *51*, 4400. (b) Tang, J. G.; Wang, Y. H.; Wang, R. R.; Dong, Z. J.; Yang, L. M.; Zheng, Y. T.; Liu, J. K. *Chemistry & Biodiversity* **2008**, *5*, 447. (c) Cao, R.; Peng, W.; Wang, Z.; Xu, A. *Curr. Med. Chem.* **2007**, *14*, 479. (d) Guan, H.; Chen, H.; Peng, W.; Ma, Y.; Cao, R.; Liu, X.; Xu, A. *Eur. J. Med. Chem.* **2006**, *41*, 1167. (e) Agafonov, N. E.; Dudin, A. V.; Preobrazhenskii, A. A.; Zhulin, V. M. *Russ. Chem. Bull. Int. Ed.* **2001**, *50*, 560. (f) Pal, B.; Jaisankar, P.; Giri, B. S. *Synth. Commun.* **2003**, *33*, 2339. (g) Hooker, J. M.; Schönberger, M.; Schieferstein, H.; Fowler, J. S. *Angew. Chem. Int. Ed.* **2008**, *47*, 5989. (h) Yu, X.; Lin, W.; Li, J.; Yang, M. *Bioorg. Med. Chem.* **2004**, *14*, 3127. (i) Kuo, F. M.; Tseng, M. C.; Yen, Y. H.; Chu, Y. H. *Tetrahedron* **2004**, *60*, 12075. (j) Burm, B. E. A.; Gremmen, C.; Wanner, M. J.; Koomen, G. J. *Tetrahedron* **2001**, *57*, 2039.
(20) Ascic, E.; Hansen, C. L.; Le Quement, S. T.; Nielsen, T. E. *Chem. Commun.* **2012**, *48*, 3345.
(21) (a) Tyagi, V.; Khan, S.; Chauhan, P. M. S. *Synlett* **2013**, *24*, 1291. (b) Cano-Herrera, M. A.; Miranda, L. D. *Chem. Commun.* **2011**, *47*, 10770. (c) El Kaim, L.; Gageat, M.; Gaultier, L.; Grimaud, L. *Synlett* **2007**, 500.
(22) (a) Wang, W.; Herdtweck, E.; Dömling, A. *Chem. Commun.* **2010**, *46*, 770. (b) Liu, H.; Dömling, A. *J. Org. Chem.* **2009**, *74*, 6895.
(23) Znabet, A.; Zonneveld, J.; Janssen, E.; De Kanter, F. J. J.; Helliwell, M.; Turner, N. J.; Ruijter, E.; Orru, R. V. A. *Chem. Commun.* **2010**, *46*, 7706.
(24) Karpov, A.; Oeser, T.; Müller, T. J. J. *Chem. Commun.* **2004**, 1502.
(25) Zhao, W.; Chen, F. E. *Curr. Org. Synth.* **2012**, *9*, 873.
(26) Jackson, A. H.; Smith, P. *Tetrahedron* **1968**, *24*, 2227.
(27) (a) Kowalski, P.; Bojarski, A. J.; Mokrosz, J. L. *Tetrahedron* **1995**, *51*, 2737. (b) Kowalski, P.; Mokrosz, J. L. *Bull. Soc. Chim. Belg.* **1997**, *106*, 147.
(28) Larghi, E. L.; Amongero, M.; Bracca, A. B. J.; Kaufman, T. S. *ARKIVOC* **2005**, *(xii)*, 98.

