Synthesis of 2-tetrazolylmethyl-tetrahydro-1*H*-β-carboline methane-linked *bis*-heterocycles via one pot Ugi-azide / Pictet-Spengler process

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Abstract

A series of seven new 2-tetrazolylmethyl-tetrahydro-1*H*-β-carboline methane-linked *bis*-heterocycles including their fluorine-containing analogs were synthesized in good to excellent yields (74-97%) via one pot Ugi-azide / Pictet-Spengler strategy under mild thermal conditions. One intermediate (Ugi-azide product) was isolated and fully characterized in order to confirm the reaction pathway. The products herein described may find application in medicinal chemistry because they are formed by two heterocyclic frameworks (1,5-disubstituted-1*H*-tetrazole and tetrahydro-β-carboline), which are present in a variety of bioactive compounds and drugs. In the same context, it has been reported that fluorine atoms placed suitably into structures of bioactive compounds enhances often very interesting features like bioavailability, lipophilicity and metabolic resistance.

Keywords

One pot, Ugi-azide, Pictet-Spengler, tetrazoles, carbolines, fluorine.

Introduction

Bis-heterocycles are a special class of synthetic or naturally occurring products formed by two heterocyclic moieties in spaced, linked, fused, merged or bound manner,[1] which are of high interest for synthetic chemists because they have proven to be useful in various fields like agrochemistry, optics, material-polymer science, and mainly in medicinal chemistry.[2] In this context, we herein show the synthesis of seven new methane-linked *bis*-heterocycles formed by 1,5-disubstituted-tetrazole (1,5-DS-T) and tetrahydro-1*H*-β-carboline (THβC) moieties, including some fluorine-containing analogs.

It is well documented that addition of fluorine atoms into structure of bioactive molecules often enhance very important features like bioavailability, lipophilicity and metabolic resistance.[3] With respect to the two involved heterocyclic systems (1,5-DS-T and THβC), the first one are bioisosters of *cis*-amide bond in peptides by adopting their bioactive conformations.[4] For this reason, 1,5-DS-T are present in numerous bioactive products and drugs like the Latamoxeb (3rd generation cephalosporin antibiotic).[5] Moreover, 1,5-DS-T's have shown other interesting applications, for example, as prime ligands and chelating agents.[6] On the other hand, THβC are the core of many natural and synthetic products

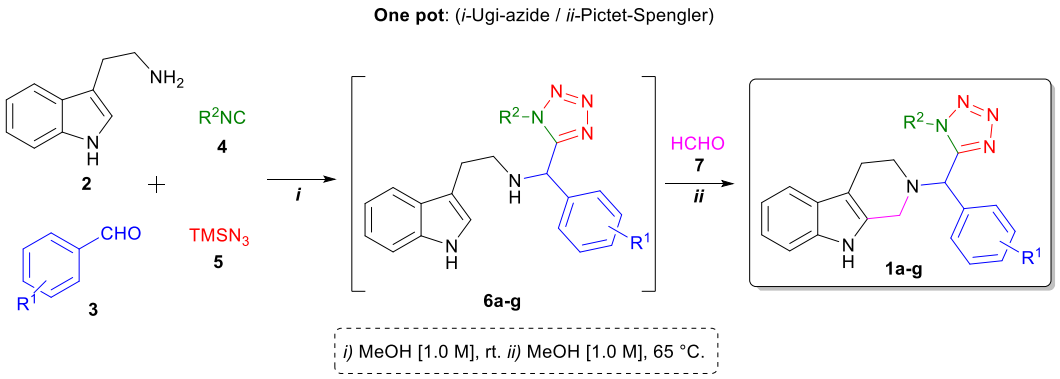
exhibiting a broad spectrum of biological activity, mainly in central nervous system (CNS) related disseases.[7]

1,5-DS-T's are synthesized commonly via click reactions between organic azides and nitriles prepared stepwise.[8] However, the Ugi-azide reaction has become in the current method due to the inherent highlighting features of Multicomponent reactions (MCR) and one pot processes.[9] There are only three reports describing the synthesis of methane-linked *bis*-heterocycles containing the 1,5-DS-T moiety via One pot Ugi-azide based methods.[10] Moreover, THβC are synthesized usually via Pictet-Spengler cyclization from tryptamine derivatives.[11] It is noteworthy that methane-linked *bis*-heterocycles containing 1,5-DS-T and THβC have not been synthesized by others via MRC, one pot or multistep methods.

Results and discussion

Thus, as a part of our ongoing program to develop Ugi-azide based methods to synthesize new methane-linked *bis*-heterocycles containing the 1,5-DS-T moiety,[12] we herein show our most recent results for the synthesis of 2-tetrazolylmethyl-tetrahydro-1*H*-β-carbolines, which must be understood as a smart improvement and extension of our original work 'synthesis of 2,3,4,9-tetrahydro-β-carboline-1,5-1*H*-tetrazoles by a one pot Ugi-azide / Pictet-Spengler process' published in *Synthesis* a couple of years back.[13] As it will be discussed, various aspects were improved with respect to our previous methodology. For example, overall yields were increased, reaction conditions were milder, and substrate scope was enlarged because all products herein described are new, including some novel fluorine-containing analogs. We started the synthesis of *bis*-heterocycles **1a-g** taking the fluorine-containing 2-tetrazolylmethyl-tetrahydro-1*H*-β-carboline **1a** as model to optimize the Ugi-azide/PS process using the conditions previously reported by us as starting point (*i*-MeOH [1.0 M], rt, 6 h; *ii*-MeOH/PhMe 1/1 v/v [1.0 M], MW {90 °C, 60 W}, 5 h).[13] Thus, tryptamine (**2**) was combined sequentially with 2-fluorobenzaldehyde (**3**), *tert*-butyl isocyanide (**4**) and azidotrimethylsilane (**5**) in MeOH [1.0 M] as solvent under room temperature conditions to afford the new Ugi-azide product **6a** in 90% yield after 5 h (Table 1). As seen, the Ugi-azide reaction finished one hour less with respect to our previous results.[13] Then, after various unsuccessful attempts to synthesize the fluorine-containing *bis*-heterocycle **1a**, we decided to use formaldehyde instead paraformaldehyde to avoid harsh conditions needed for its depolymerization MW (5 hours). Compound **6a** reacted with formaldehyde (**7**) via Pictet-Spengler cyclization under conventional heating conditions (65 °C) for 5 hours and the novel product **1a** was isolated in 94% (Table 1). Then, having in hand new optimal conditions for the Ugi-azide/Pictet-Spengler process, we synthesized the full series **1a-g**, but in one pot manner to make more sustainable our MCR-cascade methodology. As seen, good to excellent yields were obtained (74-97%). Besides, good substrate scope was found because benzaldehydes containing one, two, or three fluorine atoms were used. In the same context, benzaldehyde without fluorine atom was used. Moreover, the stereoelectronic nature of isocyanide moiety was explored by using alkyl and aryl isocyanides (*tert*-butyl and 2,6-dimethylphenyl).

Table 1 Substrate scope.



Product	R^1	R^2	Time (h)	Yield[a] (%)
6a	2-F	*t*-Bu	5	90
1a	2-F	*t*-Bu	3	94[b]
1a	2-F	*t*-Bu	8	91
1b	2,3-F	*t*-Bu	8	93
1c	2,3,4-F	*t*-Bu	8	97
1d	H	*t*-Bu	8	92
1e	2-F	2,6-MePh	8	89
1f	2,3-F	2,6-MePh	8	74
1g	2,3,4-F	2,6-MePh	8	nr
1h	H	2,6-MePh	8	90

[a] Measured after purification by silica-gel column chromatography. [b] from **6a**. nr = no reaction

As seen, the product **1g** could not be synthesized may be due to steric hindrance. To test the hypothesis, we calculated its minimal energy conformation by DFT approach using the robust TPSSh/6-311g(d) level of theory, finding a high steric hindrance between its three bulky moieties (THβC, 2,3,4-FPh, and 2,6-MePh), (Fig. 1).

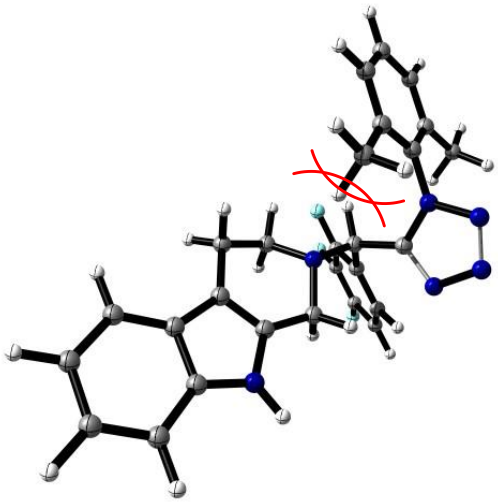


Fig. 1 Steric strain in compound **1g**

Conclusions

This work is a contribution to the synthesis of methane-linked *bis*-heterocycles via Ugi-azide based one pot MCR methodologies as well as to the synthesis of *bis*-heterocycles via MCR/cyclization.[14] An Ugi-azide product was isolated and fully characterized to confirm the reaction pathway. The Pictet-Spengler reaction worked well using formaldehyde instead *para*-formaldehyde becoming milder the reaction conditions. A final *bis*-heterocycle could not be synthesized due to a high steric strain coming from its three bulky moieties. The products herein described may find application in medicinal chemistry because they have two heterocyclic cores (1,5-DS-T and THβC) present in numerous bioactive products and drugs, even contain one or more fluorine atoms, which can be reflected by improving some interesting features like metabolic resistance, lipophilicity, and bioavailability.

Experimental

General Information, software, instrumentation and chemicals

^{1}H and ^{13}C NMR spectra were acquired on Bruker Advance III spectrometer (500 MHz). The solvent for NMR samples were d^{6}-DMSO and $CDCl_3$. Chemical shifts are reported in parts per million (δ/ppm). Internal reference for NMR spectra is TMS at 0.00 ppm. Coupling constants are reported in Hertz (*J*/Hz). Multiplicities of signals are reported using the standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). NMR spectra were analyzed using the MestreNova software (version 6.0.2-5475). IR spectra were recorded on a Perkin Elmer 100 spectrometer by the ATR method using neat compounds. The wavelengths are reported in reciprocal centimeters (ν_{max}/cm^{-1}). FT-IR spectra were analyzed using the Report Builder software (Rev. 2.01). HRMS spectra were acquired on a MaXis-Impact ESI(+)-QqTOF Bruker mass spectrometer. HRMS spectra were analyzed using the data Analysis (Bruker, version 4.1). The reaction progress was monitored by TLC and the spots were visualized under UV light (254 or 365 nm). Flash column chromatography was performed using silica gel (230-400 mesh) and mixtures of hexanes with diethyl ether or Hexanes with AcOEt as mobile phase. Melting points were determined on a Fisher-Johns apparatus and were uncorrected. Commercially available reagents were purchased in Sigma-Aldrich and were used without further purification. Structure names and drawings were done using the ChemBioDraw Ultra software (version 13.0.0.3015).

Synthesis and characterization of the *N*-((1-(*tert*-butyl)-1*H*-tetrazol-5-yl)(2-fluorophenyl) methyl)-2-(1*H*-indol-3-yl)ethan-1-amine (**6a**)

In a vial (10 ml), to a stirred solution of 2-(1*H*-indol-3-yl)ethan-1-amine (387.3 mg, 2.417 mmol, 1.0 equiv.) in anhydrous MeOH [1.0 M] under nitrogen atmosphere at room temperature, the 2-fluorobenzaldehyde (256.0 μL, 2.417 mmol, 1.0 equiv.), *tert*-butyl isocyanide (275.0 μL, 2.417 mmol, 1.0 equiv.) and azidotrimethylsilane (318.0 μL, 2.417 mmol, 1.0 equiv.) were added sequentially. The resulting mixture was stirred at room temperature for 5 hours. Then, the solvent was removed until dryness and the crude was

purified by silica-gel column chromatography using a mixture of Hexane with ethyl acetate (2/1 to 7/3; v/v) as mobile phase to afford the product **6a** (656.6 mg, 90%) as a pale yellow solid; mp = 189 ºC; R_f = 0.23 (Hexane-AcOEt = 7/3; v/v). *Spectral data:* ^{1}H NMR (500 MHz; $CDCl_3$; TMS): δ 8.11 (s, 1H), 7.50–7.48 (m, 1H), 7.34–7.32 (m, 1H), 7.25–7.23 (m, 2H), 7.18–7.15 (m, 1H), 7.07–7.01 (m, 3H), 5.73 (s, 1H), 2.99–2.94 (m, 4H), 2.14 (s, 1H), 1.61 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$; TMS): δ 161.0, 159.9, 155.1, 136.4, 130.0, 129.9, 128.9 (2), 127.3, 126.0, 125.9, 125.0, 124.9, 122.0, 119.3, 118.7, 115.6, 115.4, 113.4, 111.1, 61.5, 50.8, 47.8, 29.7, 25.9 ppm; FT-IR(ATR) ν_{max}/cm^{-1} 3216, 1678, 1223, 738.

Synthesis and characterization of the 2-((1-(*tert*-butyl)-1*H*-tetrazol-5-yl)(2-fluorophenyl)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**1a**). In a vial (10 ml), to a stirred solution of compound **6a** in anhydrous MeOH [1.0 M], the formaldehyde was added. The resulting mixture was stirred at 65 ºC for 3 hours. Then, the solvent was removed until dryness and the crude was purified by silica-gel column chromatography using a mixture of hexane with diethyl ether (1/1 to 2/6; v/v) to afford the product **1a** (193.8 mg, 94%) as a white solid; mp = 234 ºC; R_f = 0.63 (Hexane-diethyl ether = 1/4; v/v). *Spectral data:* ^{1}H NMR (500 MHz; DMSO; TMS): δ 10.63 (s, 1H), 7.65–7.63 (m, 1H), 7.46–7.42 (m, 1H), 7.33–7.26 (m, 3H), 7.22 (d, *J* = 8.0 Hz, 1H), 6.99–6.96 (m, 1H), 6.92–6.89 (m, 1H), 6.07 (s, 1H), 3.93 (d, *J* = 14.4 Hz, 1H), 3.66 (d, *J* = 14.4 Hz, 1H), 3.06–3.01 (m, 1H), 2.87–2.83 (m, 1H), 2.62 (m, 1H), 1.64 (s, 1H); ^{13}C NMR (126 MHz, DMSO; TMS): δ 161.5, 159.6, 154.0, 136.3, 132.6, 132.0 (2), 131.3, 131.2, 127.0, 125.1, 122.9, 122.8, 120.9, 118.8, 117.8, 116.3, 116.1, 111.3, 106.8, 62.4, 55.5, 48.1, 47.1, 29.7, 22.0; FT-IR (ATR)ν_{max}/cm^{-1} 3274, 3059, 1455, 1239, 758; HRMS (ESI) calcd for $C_{23}H_{26}N_6F^+$ $[M+H]^+$ 405.2197, found 405.2210.

One pot synthesis and characterization of the (1*H*-tetrazol-5-yl)(2-fluorophenyl)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indoles **1a-g**

General Procedure (GP). In a vial (10 ml), to a stirred solution of 2-(1*H*-indol-3-yl)ethan-1-amine in anhydrous MeOH [1.0 M] under nitrogen atmosphere at room temperature, the corresponding aldehyde, corresponding isocyanide and azidotrimethylsilane were added sequentially. After 5 hours, formaldehyde was added into same vial. The resulting mixture was stirred at 65 ºC for 3 hours. Then, the solvent was removed until dryness and the crude was purified by silica-gel column chromatography to afford the products **1a-g**.

2-((1-(*tert*-butyl)-1*H*-tetrazol-5-yl)(2-fluorophenyl)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**1a**). According to the GP, to a stirred solution of 2-((1-(*tert*-butyl)-1*H*-tetrazol-5-yl)(2-fluorophenyl)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (348.5 mg, 2.131 mmol, 1.0 equiv.) in anhydrous MeOH (2.1 mL) were sequentially added 2-fluorobenzaldehyde (256.0 μL, 2.345 mmol, 1.1 equiv.), *tert*-butyl isocyanide (248.0 μL, 2.131 mmol, 1.0 equiv.) and azidotrimethylsilane (295.0 μL, 2.131 mmol, 1.0 equiv.). After 5 hours, was added formaldehyde (205.0 μL, 2.77 mmol, 1.2 equiv.). The reaction finished in 3 hours and then, the crude was purified by silica gel column chromatography using a mixture of hexane with diethyl ether (7/3; v/v) to afford the product **1a** (784.3 mg, 91%).

2-((1-(*tert*-butyl)-1*H*-tetrazol-5-yl)(2,3-difluorophenyl)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**1b**). According to the GP, to a stirred solution of 2-((1-(*tert*-butyl)-1*H*-tetrazol-5-yl)(2-fluorophenyl)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (307.5 mg, 1.881 mmol, 1.0 equiv.) in anhydrous MeOH (1.9 mL) were sequentially added 2,3-difluorobenzaldehyde (231.0 μL, 2.069 mmol, 1.1 equiv.), *tert*-butyl isocyanide (219.0 μL, 1.881 mmol, 1.0 equiv.) and azidotrimethylsilane (260.0 μL, 1.881 mmol, 1.0 equiv.). After 5 hours, was added formaldehyde (169.0 μL, 2.260 mmol, 1.2 equiv.). The reaction finished in 3 hours and then, the crude was purified by silica gel column chromatography using a mixture of hexane with diethyl ether (7/3 to 1/1; v/v) to afford the product **1b** (739.1 mg, 93%) as a white solid; mp = 203 ºC; R_f = 0.53 (Hexane-diethyl ether = 3/7; v/v). *Spectral data:* ^{1}H NMR (500 MHz; $CDCl_3$; TMS): δ 7.88 (s, 1H), 7.76–7.73 (m, 1H), 7.42–7.40 (m, 1H), 7.25–7.23 (m, 1H), 7.21–7.12 (m, 2H), 7.11–7.03 (m, 2H), 6.09 (s, 1H), 3.93 (d, *J* = 14.2 Hz, 1H), 3.78 (d, *J* = 14.2 Hz, 1H), 3.11–3.07 (m, 1H), 2.96–2.92 (m, 1H), 2.82–2.76 (m, 1H), 2.73–2.68 (m, 1H), 1.74 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$; TMS): δ 153.3, 151.4, 151.3, 149.9, 149.7, 149.4, 149.3, 147.9, 147.8, 136.1, 131.0, 127.1 (2), 127.0, 124.3 (3), 124.2, 124.0, 123.9, 121.4, 119.3, 117.9, 117.6, 117.5, 110.8, 108.1, 62.1, 54.6, 48.2, 46.8, 30.0, 21.6; FT-IR (ATR)ν_{max}/cm^{-1} 3292, 1456, 1240, 759; HRMS (ESI) calcd for $C_{23}H_{25}N_6F_2^+$ $[M+H]^+$ 423.2103, found 423.2109.

2-((1-(*tert*-butyl)-1*H*-tetrazol-5-yl)(2,3,4-trifluorophenyl)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**1c**). According to the GP, to a stirred solution of 2-((1-(*tert*-butyl)-1*H*-tetrazol-5-yl)(2-fluorophenyl)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (250.2 mg, 1.530 mmol, 1.0 equiv.) in anhydrous MeOH (1.5 mL) were sequentially added 2,3,4-trifluorobenzaldehyde (214.0 μL, 1.836 mmol, 1.2 equiv.), *tert*-butyl isocyanide (178.0 μL, 1.530 mmol, 1.0 equiv.) and azidotrimethylsilane (212.0 μL, 1.530 mmol, 1.0 equiv.). After 5 hours, was added formaldehyde (138.0 μL, 1.836 mmol, 1.2 equiv.). The reaction finished in 3 hours and then, the crude was purified by silica gel column chromatography using a mixture of hexane with diethyl ether (7/3 to 1/1; v/v) to afford the product **1c** (653.7 mg, 97%) as a white solid; mp = 208 ºC; R_f = 0.56 (Hexane-diethyl ether = 1/1; v/v). *Spectral data:* ^{1}H NMR (500 MHz; $CDCl_3$; TMS): δ 7.82–7.77 (m, 1H), 7.74 (s, 1H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.27–7.26 (m, 1H), 7.13–7.10 (m, 1H), 7.08–7.03 (m, 2H), 6.04 (s, 1H), 3.92 (d, *J* = 14.1 Hz, 1H), 3.77 (d, *J* = 14.1 Hz, 1H), 3.10–3.06 (m, 1H), 2.95–2.91 (m, 1H), 2.83–2.70 (m, 2H), 1.75 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$; TMS): δ 152.9, 136.1, 130.8, 127.0, 126.4, 126.3 (3), 126.2, 121.6, 119.5, 112.5, 112.3, 110.7, 108.2, 62.1, 54.4, 48.0, 46.6, 30.0, 21.7; FT-IR (ATR)ν_{max}/cm^{-1} 3263, 1456, 1238, 746; HRMS (ESI) calcd for $C_{23}H_{23}N_6F_3^+$ $[M+H]^+$ 441.2009, found 441.2022.

2-((1-(*tert*-butyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**1d**). According to the GP, to a stirred solution of 2-((1-(*tert*-butyl)-1*H*-tetrazol-5-yl)(2-fluorophenyl)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (377.4 mg, 2.309 mmol, 1.0 equiv.) in anhydrous MeOH (2.3 mL), were added sequentially benzaldehyde (286.0 μL, 2.770 mmol, 1.2 equiv.), *tert*-butyl isocyanide (268.0 μL, 2.309 mmol, 1.0 equiv.) and azidotrimethylsilane (320.0 μL, 2.309 mmol, 1.0 equiv.). After 5 hours, was added

formaldehyde (205.0 μL, 2.770 mmol, 1.2 equiv.). The reaction finished in 3 hours and then, the crude was purified by silica gel column chromatography using a mixture of hexane with diethyl ether (1/1 to 2/6; v/v) to afford the product **1d** (820.9 mg, 92%) as a white solid; mp = 208 ºC; R_f = 0.46 (Hexane-diethyl ether =1/4; v/v). *Spectral data:* ^{1}H NMR (500 MHz; $CDCl_3$; TMS): δ 7.80 (s, 1H), 7.48–7.46 (m, 2H), 7.42–7.41 (m, 1H), 7.38–7.34 (m, 3H), 7.25–7.24 (m, 1H), 7.11–7.04 (m, 2H), 5.65 (s, 1H), 4.06 (d, *J* = 14.5 Hz, 1H), 3.65 (d, *J* = 14.5 Hz, 1H), 3.09–3.04 (m, 1H), 2.97–2.92 (m, 1H), 2.74 (m, 1H), 1.67 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$; TMS): δ 129.8, 128.7 (2), 121.3, 119.3, 117.9, 110.7, 63.8, 48.3, 46.9, 30.2, 21.5; FT-IR (ATR)ν_{max}/cm^{-1} 3244, 3062, 1629, 1239; HRMS (ESI) calcd for $C_{23}H_{27}N_6^+$ $[M+H]^+$ 387.2292, found 387.2303.

2-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)(2-fluorophenyl)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**1e**). According to the GP, to a stirred solution of 2-((1-(*tert*-butyl)-1*H*-tetrazol-5-yl)(2-fluorophenyl)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (348.5 mg, 2.131 mmol, 1.0 equiv.) in anhydrous MeOH (2.1 mL) were sequentially added 2-fluorobenzaldehyde (256.0 μL, 2.345 mmol, 1.1 equiv.), 2,6-dimethylbenzylisocyanide (285.0 mg, 2.131 mmol, 1.0 equiv.) and azidotrimethylsilane (295.0 μL, 2.131 mmol, 1.0 equiv.). After 5 hours, was added formaldehyde (192.0 μL, 2.558 mmol, 1.2 equiv.). The reaction finished in 3 hours and then, the crude was purified by silica gel column chromatography using a mixture of hexane with ethyl acetate (9/1 to 4/1; v/v) to afford the product **1e** (858.5 mg, 89%) as a white solid; mp = 233 ºC; R_f = 0.63 (Hexane-AcOEt = 1/1; v/v). *Spectral data:* ^{1}H NMR (500 MHz; $CDCl_3$; TMS): δ 7.87–7.84 (m, 1H), 7.74 (s, 1H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.37–7.34 (m, 1H), 7.32–7.28 (m, 1H), 7.26–7.25 (m, 1H), 7.20–7.15 (m, 2H), 7.12–7.09 (m, 2H), 7.07–7.04 (m, 1H), 7.00–6.97 (m, 1H), 5.31 (s, 1H), 3.92 (d, *J* = 14.3 Hz, 1H), 3.77 (d, *J* = 14.3 Hz, 1H), 3.05–3.01 (m, 1H), 2.88–2.84 /m, 1H), 2.78–2.72 (m, 1H), 2.69–2.64 (m, 1H), 1.94 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$; TMS): δ 161.7, 159.8, 155.5, 136.1, 135.7, 131.8 (2), 131.4, 131.1, 131.0, 130.6, 130.5, 128.9, 128.8, 127.1, 124.6 (2), 121.4, 121.0, 120.9, 119.3, 117.9, 115.5, 115.3, 110.7, 108.2, 54.1, 48.7, 47.4, 21.3, 17.4, 16.6; FT-IR (ATR)ν_{max}/cm^{-1} 3356, 1450, 1242, 745; HRMS (ESI) calcd for $C_{27}H_{26}N_6F^+$ $[M+H]^+$ 453.2197, found 453.2208.

2-((2,3-difluorophenyl)(1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]in (**1f**). According to the GP, to a stirred solution of 2-((1-(*tert*-butyl)-1*H*-tetrazol-5-yl)(2-fluorophenyl)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (163.5 mg, 1.000 mmol, 1.0 equiv.) in anhydrous MeOH (1.0 mL) were sequentially added 2,3-difluorobenzaldehyde (112.0 μL, 1.000 mmol, 1.0 equiv.), 2,6-dimethylbenzyl isocyanide (134.0 mg, 1.000 mmol, 1.0 equiv.) and azidotrimethylsilane (138.0 μL, 1.000 mmol, 1.0 equiv.). After 5 hours, was added formaldehyde (90.0 μL, 1.200 mmol, 1.2 equiv.). The reaction finished in 3 hours and then, the crude was purified by silica gel column chromatography using a mixture of hexane with ethyl acetate (9/1 to 4/1; v/v) to afford the product **1f** (348.2 mg, 74%) as a white solid; mp = 199 ºC; R_f = 0.63 (Hexane-AcOEt = 3/2; v/v). *Spectral data:* ^{1}H NMR (500 MHz; $CDCl_3$; TMS): δ 7.72–7.66 (m, 2H), 7.42–7.37 (m, 2H), 7.26–7.25 (m, 1H), 7.21–7.20 (m, 1H), 7.16–7.10 (m, 4H), 7.08–7.05 (m, 1H), 5.32 (s,

1H), 3.93 (d, *J* = 14.2 Hz, 1H), 3.76 (d, *J* = 14.2 Hz, 1H), 3.08–3.04 (m, 1H), 2.86–2.82 (m, 1H), 2.77–2.65 (m, 2H), 1.95 (s, 3H), 1.43 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$; TMS): δ 154.8, 136.1, 135.8 (2), 131.3, 131.2, 130.7, 129.0, 128.8, 127.0, 126.5 (2), 124.4 (2), 124.3, 123.3, 123.2, 121.5, 119.4, 118.0, 117.6, 117.5, 110.7, 108.2, 53.9, 48.6, 47.1, 21.4, 17.4, 16.6; FT-IR (ATR)ν_{max}/cm^{-1} 3386, 1456, 1240, 737; HRMS (ESI) calcd for $C_{27}H_{25}N_6F_2^+$ $[M+H]^+$ 471.2103, found 471.2117.

2-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)(phenyl)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**1h**). According to the GP, to a stirred solution of 2-((1-(*tert*-butyl)-1*H*-tetrazol-5-yl)(2-fluorophenyl)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (277.4 mg, 2.309 mmol, 1.0 equiv.) in anhydrous MeOH (2.3 mL), were sequentially added benzaldehyde (286.0 μL, 2.770 mmol, 1.2 equiv.), 2,6-dimethylbenzylisocyanide (309.0 mg, 2.309 mmol, 1.0 equiv.) and azidotrimethylsilane (320.0 μL, 2.309 mmol, 1.0 equiv.). After 5 hours, was added formaldehyde (208.0 μL, 2.770 mmol, 1.2 equiv.). The reaction finished in 3 hours and then, the crude was purified by silica gel column chromatography using a mixture of hexane with ethyl acetate (9/1 to 4/1; v/v) to afford the product **1e** (903.0 mg, 90%) as a white solid; mp = 220 ºC; R_f = 0.60 (Hexane-AcOEt = 1/1; v/v). *Spectral data:* ^{1}H NMR (500 MHz; $CDCl_3$; TMS): δ 7.78–7.70 (m, 1H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.36–7.33 (m, 1H), 7.32–7.17 (m, 7H), 7.12–7.03 (m, 3H), 4.71 (s, 1H), 3.88 (d, *J* = 14.7 Hz, 1H), 3.80 (d, *J* = 14.7 Hz, 1H), 2.98–2.90 (m, 1H), 2.80–2.75 (m, 1H), 2.70–2.67 (m, 1H), 1.92 (s, 1H), 1.15 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$; TMS): δ 156.1, 136.8, 136.0, 135.2, 134.8, 131.6, 131.0, 129.4, 128.9 (2), 128.8, 128.7, 127.1, 121.4, 119.4, 117.9, 110.8, 108.1, 63.6, 48.9, 47.9, 20.7, 17.4, 16.6; FT-IR (ATR)ν_{max}/cm^{-1} 3355, 1455, 1240, 744; HRMS (ESI) calcd for $C_{27}H_{27}N_6^+$ $[M+H]^+$ 435.2291, found 435.2300.

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