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Consecutive Four-Component Coupling-Addition Aza-Anellation *Pictet–Spengler* Synthesis of Tetrahydro-*β*-Carbolines: An Optimized *Michael* Addition and Computational Study on the Aza-Anellation Step

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Abstract: Starting from acid chlorides, alkynes, tryptamines, and acryloyl chloride, 21 densely substituted tetrahydro-*β*-carbolines were prepared in a four-component, one-pot reaction. In this study, the aza-*Michael* addition step to generate intermediate enaminones was optimized in the presence of ytterbium triflate. Moreover, apart from acryloyl chloride, all reactants could be deployed in almost equimolar ratios, which increases the atom economy of the sequence. For mechanistic rationalization, the concluding aza-anellation was investigated by DFT calculations on potential intermediates and corresponding activation energies, revealing that the aza-anellation proceeds via ene reaction rather than via electrocyclization.

Keywords: aza-*Michael* addition; tetrahydro-*β*-carbolines; catalysis; one-pot reaction; multicomponent reaction; ytterbium (III) triflate

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1. Introduction

Increased ecological demands have challenged the chemical industry and have led to a growing interest in conducting chemical reactions as atom economically as possible, i.e., in an environmentally benign manner and with equimolar stoichiometry. Simultaneously, the consumption of chemicals should be reduced while maintaining synthetic efficiency in comparison with established methods [1–4]. One methodological approach for reaching this ambitious goal is provided by multicomponent reactions (MCR), where all reactants are combined in a single vessel either at the beginning of the reaction or successively over time to obtain the desired compounds [5,6]. The intermediates of such one-pot processes are not isolated, but react in situ with the next functionality in a subsequent reaction step, thereby eliminating the consumption of chemicals required for their purification. A major advantage of this approach is the possibility to very quickly create large compound libraries, for example by employing heterocycle synthesis via transition metal catalysis in a diversity-oriented fashion [7], which is of particular interest in the life sciences for obtaining hits of biologically active compounds and for studying modes of action.

A particularly active class of biologically active compounds are tetrahydro-*β*-carbolines (THBC), which represent a structural motif in many naturally occurring indole-based alkaloids [8]. Due to the influence on serotonin uptake in the membrane of nerve endings, they show analgesic, body temperature lowering, and appetite suppressing properties [9]. As PDE-5 inhibitors, they can be used to treat erectile dysfunction and finally exhibit both antiviral and antitumor effects [10–12]. We have previously provided a consecutive four-component synthesis of THBCs via a coupling-addition aza-anellation *Pictet–Spengler* (CAAPS) sequence [13,14]. Herein, we report, after an optimization of the *Michael* addition

step by catalysis with ytterbium triflate, a more efficient, selective generation of a substance library of 21 THBC **5** in a very short time by strictly using almost equimolar amounts of the starting materials.

An open question of the CAAPS sequence is the mechanistic rationalization of the concluding aza-anellation Pictet–Spengler sequel, which is scrutinized by DFT calculations on potential intermediates and transition states starting from the enaminone intermediate herein.

2. Materials and Methods

2.1. General Considerations and Instrumentation

All reactions were performed in Schlenk or multineck flasks under nitrogen atmosphere and using the septum and syringe technique unless otherwise indicated. Dried solvents were taken from the *MB-SPS 800* solvent drying system (*M. Braun*). Triethylamine was freshly distilled according to standard procedure under nitrogen atmosphere with potassium hydroxide and then with calcium hydride. The reaction temperature was adjusted using silicone oil baths preheated to the indicated temperatures or cooling baths (ice/water at 0 °C or dry ice/isopropanol at –78 °C). Column chromatography was performed on silica gel M60 (mesh 230–400, *Macherey-Nagel*, Düren, Germany). The column chromatographic separations were carried out using the flash technique (overpressure of approx. 2 bar compressed air). For the thin layer chromatography, silica-coated aluminum foils (*60 F254 Merck*) were used. The evaluation was performed under UV light (λ = 254 and 356 nm) and staining with iodine.

All commercially available chemicals were obtained from *ABCR*, *ACROS*, *Alfa Aesar*, *Fluorochem*, *Macherey-Nagel*, *Merck*, *Roth*, *Sigma Aldrich*, and *VWR* and were used without further purification. ^{1}H, ^{13}C, and DEPT-135 NMR spectra were recorded at 293 K on *Bruker Avance III 600* (600 MHz), *Bruker Avance DRX 500* (500 MHz), and *Bruker Avance III 300* (300 MHz) instruments unless otherwise noted. Poorly soluble compounds were measured at elevated temperature to increase solubility. $CDCl_3$ and DMSO-d_6 served as solvents. As an internal standard, the residual proton signal of the corresponding solvents was locked when recording the ^{1}H NMR spectra and the ^{13}C NMR spectra ($CDCl_3$, δ_H 7.26, δ_C 77.16; DMSO-d_6, δ_H 2.50, δ_C 39.52). Spin multiplicities were abbreviated as follows: s—singlet; d—doublet, dd—doublet of doublet; ddd—doublet of doublet of doublet; dt—doublet of a triplet; t—triplet; m—multiplet. The quaternary carbon nuclei (C_{quat}) and the carbon nuclei of methine (CH), methylene (CH_2), and methyl (CH_3) groups were assigned based on DEPT-135 spectra. Melting points (uncorrected) were measured on the *Büchi B545* instrument according to the protocol of *Kofler* [15]. EI mass spectra were measured on the *TSQ 7000* triple quadrupole mass spectrometer (Finnigan MAT, Waltham, MA, USA). Indicated were all peaks with an intensity > 10% of the base peak, the mole peak, and any characteristic fragment peaks with an intensity < 10%. ESI mass spectra were measured on the Finnigan LCQ Deca ion-trap *API* mass spectrometer (*Thermo Quest*); HR-ESI mass spectra and HPLC chromatograms were measured on the *UHR-QTOF maXis 4G* mass spectrometer (Bruker Daltonics). IR spectra were measured on the *IRAffinity-1* instrument (Shimadzu) (single reflection ATR unit with diamond ATR crystal, wavenumber range: 4000–600 cm^{-1}). The intensities of the absorption bands were given as s (strong), m (medium), and w (weak). Elemental analyses were measured on the *Perkin Elmer Series II Analyzer 2400* at the Institute of Pharmaceutical Chemistry, Heinrich Heine University. Rotational angle measurements were performed on the *Perkin Elmer 341* polarimeter.

2.2. General Procedure (GP) for the Synthesis of THBC **5**

In a sintered dry screw-cap Schlenk tube with magnetic stir bar under nitrogen atmosphere $PdCl_2(PPh_3)_2$ (42 mg, 0.06 mmol), CuI (22 mg, 0.12 mmol), and acid chloride **1** (if a solid) were suspended in degassed dichloromethane (10 mL) and then stirred at rt for 5 min (for experimental details, see Table 1). Acid chloride **1** (if a liquid), alkyne **2**, and NEt_3 (0.28 mL, 2.00 mmol) were then added sequentially; stirring was performed at rt for

1.5 h. Upon completion of the reaction (TLC control), $Yb(OTf)_3$ (12 mg, 0.02 mmol) was added, followed by tryptamine (**3a**) (320 mg, 2.00 mmol) dissolved in CH_3CN (10 mL). After heating to 80 °C (oil bath) for 16 h, the reaction mixture was allowed to cool to rt, then acryloyl chloride (**4**) was added dropwise and the mixture was heated to 70 °C (oil bath) for 2 h. After cooling to room temp the reaction mixture was diluted with MeOH (5 mL) and the crude product was adsorbed on Celite© under reduced pressure and subsequently purified by chromatography on silica gel to give the analytically pure compound **5**.

Table 1. Experimental data on the CAAPS synthesis of THBCs **5**.

Entry	Acid Chloride 1 (mg) (mmol)	Alkyne 2 (mg) (mmol)	Acryloyl Chloride (4) (mg) (mmol)	Yield THBC 5 (mg) (%)	Eluent [a]
1	293 (2.00) of **1a**	214 (2.60) of **2a**	905 (10.00)	250 (31%) of **5a**	diethyl ether
2	281 (2.00) of **1b**	197 (2.40) of **2a**	905 (10.00)	213 (27%) of **5b**	HE 1:1
3	309 (2.00) of **1c**	197 (2.40) of **2a**	905 (10.00)	150 (18%) of **5c**	HE 1:1
4	341 (2.00) of **1d**	197 (2.40) of **2a**	905 (10.00)	163 (19%) of **5d**	diethyl ether
5	352 (2.00) of **1e**	197 (2.40) of **2a**	905 (10.00)	260 (30%) of **5e**	diethyl ether
6	439 (2.00) of **1f**	197 (2.40) of **2a**	905 (10.00)	385 (40%) of **5f**	HE 1:1
7	319 (2.00) of **1g**	197 (2.40) of **2a**	905 (10.00)	472 (56%) of **5g**	HE 6:4
8	371 (2.00) of **1h**	197 (2.40) of **2a**	905 (10.00)	334 (37%) of **5h**	HE 1:1
9	293 (2.00) of **1a**	197 (2.40) of **2b**	905 (10.00)	210 (25%) of **5i**	diethyl ether
10	341 (2.00) of **1d**	197 (2.40) of **2c**	724 (8.00)	360 (48%) of **5j**	HE 1:2
11	352 (2.00) of **1e**	197 (2.40) of **2b**	905 (10.00)	313 (34%) of **5k**	HE 1:1
12	352 (2.00) of **1e**	197 (2.40) of **2d**	905 (10.00)	160 (19%) of **5l**	HE 1:2
13	293 (2.00) of **1a**	590 (2.00) of **2e**	724 (8.00)	390 (32%) of **5m**	HE 1:1
14	352 (2.00) of **1e**	590 (2.00) of **2e**	724 (8.00)	624 (48%) of **5n**	HE 1:1
15	317 (2.00) of **1g**	590 (2.00) of **2e**	724 (8.00)	332 (26%) of **5o**	HE 1:1
16	439 (2.00) of **1f**	590 (2.00) of **2e**	724 (8.00)	687 (50%) of **5p**	HE 1:1
17	281 (2.00) of **1b**	590 (2.00) of **2e**	724 (8.00)	418 (34%) of **5q**	HE 1:1
18	341 (2.00) of **1d**	590 (2.00) of **2e**	724 (8.00)	423 (33%) of **5r**	HE 1:1
19	309 (2.00) of **1c**	590 (2.00) of **2e**	724 (8.00)	458 (36%) of **5s**	HE 1:1
20 [b]	176 (1.00) of **1e**	99 (1.20) of **2a**	362 (4.00)	198 (20%) of **5t**	HE 1:1
21 [c]	439 (2.00) of **1f**	197 (2.40) of **2a**	724 (8.00)	195 (18%) of **5u**	HE 1:1

[a] HE—*n*-hexane/ethyl acetate. [b] 0.03 mol of $PdCl_2(PPh_3)_2$, 0.06 mol of CuI, and 0.01 mmol of $Yb(OTf)_3$ were employed. A mixture of (*S*)-tryptophan methyl ester (**3b**) (255 mg, 1.00 mmol) and NEt_3 (0.14 mL, 1.00 mmol) in CH_3CN (5 mL) was used instead of tryptamine. [c] A mixture of (*S*)-tryptophan methyl ester (**3b**) (509 mg, 2.00 mmol) and NEt_3 (0.28 mL, 2.00 mmol) in CH_3CN (10 mL) was used instead of tryptamine.

*2.3. rac-12b-Butyl-1-(thiophene-2-carbonyl)-2,3,6,7,12,12b-hexahydroindolo-[2,3-a]quinolizin-(1H)-4-one (**5a**)*

According to the GP, compound **5a** (250 mg, 31%) was isolated as a colorless solid, Mp 245–248 °C (Lit.: 250–251 °C) [13], R_f = 0.25 (diethyl ether). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.84 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.08 (tdd, $^2J_{HH}$ = $^3J_{HH}$ = 12.2 Hz, $^3J_{HH}$ = 9.0 Hz, $^3J_{HH}$ = 5.4 Hz, 1H), 1.25–1.37 (m, 3H), 2.12–2.24 (m, 2H), 2.41 (ddt, $^2J_{HH}$ = 17.3 Hz, $^3J_{HH}$ = 13.8 Hz, $^3J_{HH}$ = 8.3 Hz, 1H), 2.73–2.83 (m, 4H), 2.88 (ddd, $^2J_{HH}$ = 15.2 Hz, $^3J_{HH}$ = 3.8 Hz, $^3J_{HH}$ = 1.6 Hz, 1H), 2.98 (dt, $^2J_{HH}$ = 12.4 Hz, $^3J_{HH}$ = 3.7 Hz, 1H), 3.74 (dd, $^3J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 5.1 Hz, 1H), 5.23 (ddd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 5.0 Hz, $^3J_{HH}$ = 1.6 Hz, 1H), 6.92 (dd, $^3J_{HH}$ = 4.9 Hz, $^3J_{HH}$ = 3.8 Hz, 1H), 7.04–7.11 (m, 2H), 7.14–7.18 (m, 1H), 7.39 (dd, $^3J_{HH}$ = 3.9 Hz, $^4J_{HH}$ = 1.1 Hz, 1H), 7.48 (dd, $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 1.5 Hz, 1H), 7.55 (dd, $^3J_{HH}$ = 4.9 Hz, $^4J_{HH}$ = 0.9 Hz, 1H), 7.94 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 14.12 (CH_3), 21.11 (CH_2), 21.94 (CH_2), 23.47 (CH_2), 27.35 (CH_2), 29.76 (CH_2), 36.10 (CH_2), 40.18 (CH_2), 55.13 (CH), 62.09 (C_{quat}), 111.20 (CH), 111.26 (C_{quat}),118.33 (CH), 119.69 (CH), 122.31 (CH), 126.14 (C_{quat}), 128.64 (CH), 132.68 (CH), 134.05 (C_{quat}), 135.41 (CH), 135.95 (C_{quat}), 144.09 (C_{quat}), 169.75 (C_{quat}), 195.69 (C_{quat}). IR: $\tilde{\nu}$ [cm^{-1}] 3296 (w), 3271 (w), 3202 (w), 3177 (w), 3100 (w), 3057 (w), 3034 (w), 2953 (w), 2928 (w), 2893 (w), 2849 (w), 1655 (w), 1614 (s), 1584 (w), 1518 (w), 1489 (w),1433 (m), 1406 (m), 1352 (w), 1317 (w), 1304 (w), 1290 (w), 1263 (w), 1236 (m), 1219 (w), 1200 (w), 1190 (w), 1146 (w), 1126 (w), 1084 (w), 1059 (w), 1036 (w), 1005 (w), 845 (w), 804 (w), 745

(m), 727 (m), 696 (w), 644 (w). ESI MS: 407 ([M]$^+$). HR-ESI MS calcd. for $C_{24}H_{27}N_2O_2S$: 407.1788; found: 407.1784. HPLC (254 nm): t_R = 4.9 min, 99%.

*2.4. rac-1-Benzoyl-12b-butyl-2,3,6,7,12,12b-hexahydroindolo[2,3-a]quinolizin-4(1H)-on (**5b**)*

According to the GP, compound **5b** (213 mg, 27%) was isolated as a colorless solid, Mp 241–244 °C, R_f = 0.4 (n-hexane/ethyl acetate 1:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.85 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.08–1.14 (m, 1H), 1.27–1.40 (m, 3H), 2.05–2.11 (m, 1H), 2.19–2.34 (m, 2H), 2.75–2.91 (m, 5H), 3.01 (dt, $^2J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 3.8 Hz, 1H), 3.95 (dd, $^3J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 4.7 Hz, 1H), 5.25 (dd, $^2J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 4.4 Hz, 1H), 7.04–7.11 (m, 2H), 7.11–7.16 (m, 1H), 7.29–7.36 (m, 2H), 7.44–7.51 (m, 2H), 7.67 (d, $^3J_{HH}$ = 7.7 Hz, 2H), 7.97 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 14.08 (CH_3), 21.24 (CH_2), 21.79 (CH_2), 23.51 (CH_2), 27.52 (CH_2), 29.89 (CH_2), 36.32 (CH_2), 40.25 (CH_2), 53.55 (CH), 62.41 (C_{quat}), 111.27 (CH), 118.39 (CH), 119.80 (CH), 122.43 (CH), 126.26 (C_{quat}), 128.17 (2 CH), 128.61 (C_{quat}), 128.94 (2 CH), 133.81 (CH), 134.39 (C_{quat}), 136.07 (C_{quat}), 136.94 (C_{quat}), 169.94 (C_{quat}), 203.71 (C_{quat}). IR: $\tilde{\nu}$ [cm^{-1}] 3252 (w), 3246 (w), 3217 (w), 3192 (w), 3159 (w), 3140 (w), 3105 (w), 3084 (w), 3057 (w), 3032 (w), 2953 (w), 2930 (w), 2891 (w), 2870 (w), 2845 (w), 1676 (m), 1614 (s), 1595 (w), 1578 (w), 1489 (w), 1466 (w), 1449 (m), 1433 (m), 1402 (m), 1352 (w), 1302 (w), 1288 (w), 1263 (w), 1223 (m), 1182 (w), 1152 (w), 1123 (w), 1059 (w), 1038 (w), 1026 (w), 1002 (w), 968 (w), 926 (w), 870 (w), 822 (w), 760 (w), 743 (s), 708 (s), 685 (m), 644 (w), 631 (w). ESI MS: 401 ([M]$^+$). HR-ESI MS calcd. for $C_{26}H_{28}N_2O_2$: 401.2224; found: 401.2229. HPLC (254 nm): t_R = 5.1 min, 99%.

*2.5. rac-12b-Butyl-1-(4-methylbenzoyl)-2,3,6,7,12,12b-hexahydroindolo-[2,3-a]quinolizin-4(1H)-one (**5c**)*

According to the GP, compound **5c** (150 mg, 18%) was isolated as a colorless solid, Mp 214–216 °C, R_f = 0.36 (n-hexane/ethyl acetate 1:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.86 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.09–1.16 (m, 1H), 1.29–1.40 (m, 3H), 1.96–2.02 (m, 1H), 2.22 (dddd, $^2J_{HH}$ = 17.9 Hz, $^3J_{HH}$ = 13.7 Hz, $^3J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 5.8 Hz, 2H), 2.35 (s, 3H), 2.68 (ddd, $^2J_{HH}$ = 18.3 Hz, $^3J_{HH}$ = 9.9 Hz, $^3J_{HH}$ = 7.7 Hz, 1H), 2.73–2.92 (m, 4H), 3.01 (td, $^2J_{HH}$ = $^3J_{HH}$ = 12.4 Hz, $^3J_{HH}$ = 3.8 Hz, 1H), 3.75 (dd, $^3J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 4.7 Hz, 1H), 5.23 (ddd, $^2J_{HH}$ = 12.8 Hz, $^3J_{HH}$ = 5.0, $^3J_{HH}$ = 1.5 Hz, 1H), 6.83 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 6.98 (t, $^3J_{HH}$ = 7.6 Hz, 1H), 7.09–7.15 (m, 2H), 7.17–7.23 (m, 2H), 7.23–7.29 (m, 2H, superimposed by $CDCl_3$), 7.51–7.57 (m, 1H), 8.06 (s, 1H).^{13}C NMR (151 MHz, $CDCl_3$): δ 14.17 (CH_3), 20.53 (CH_3), 21.01 (CH_2), 21.18 (CH_2), 23.56 (CH_2), 27.56 (CH_2), 29.88 (CH_2), 36.36 (CH_2), 40.01 (CH_2), 56.88 (CH), 62.07 (C_{quat}), 111.21 (C_{quat}), 111.43 (CH), 118.45 (CH), 119.79 (CH), 122.44 (CH), 126.00 (CH), 126.22 (C_{quat}), 127.43 (CH), 131.63 (CH), 131.84 (CH), 134.62 (C_{quat}), 136.01(C_{quat}), 137.48(C_{quat}), 138.75(C_{quat}), 169.61(C_{quat}), 208.46(C_{quat}). IR: $\tilde{\nu}$ [cm^{-1}] 3231 (w), 3177 (w), 3069 (w), 2951 (w), 2928 (w), 2887 (w), 2870 (w), 2839 (w), 2818 (w), 2359 (w), 2342 (w), 2313 (w), 1967 (w), 1948 (w), 1701 (w), 1672 (m), 1672 (m), 1612 (s), 1599 (m), 1587 (w), 1570 (w), 1522 (w), 1487 (w), 1452 (w), 1429 (m), 1404 (m), 1366 (w), 1354 (w), 1317 (w), 1302 (w), 1281 (w), 1261 (w), 1236 (w), 1217 (w), 1198 (w), 1186 (w), 1165 (w), 1155 (w), 1136 (w), 1121 (w), 1078 (w), 1057 (w), 1036 (w), 1026 (w), 1009 (w), 964 (w), 895 (w), 826 (w), 777 (w), 743 (s), 725 (s), 692 (w), 669 (w), 648 (w). ESI MS: 415 ([M]$^+$). HR-ESI MS calcd. for $C_{26}H_{28}N_2O_2$: 415.2380; found: 415.2385. HPLC (254 nm): t_R = 5.4 min, 99%.

*2.6. rac-12b-Butyl-1-(4-methoxybenzoyl)-2,3,6,7,12,12b-hexahydroindolo-[2,3a]quinolizin-4(1H)-one (**5d**)*

According to the GP, compound **5d** (163 mg, 19%) was isolated as a colorless solid, Mp 207–208 °C (Lit.: 201–202 °C) [13], R_f = 0.24 (diethyl ether). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.84 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.09 (dddd, $^2J_{HH}$ = 12.5 Hz, $^3J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 9.3 Hz, $^3J_{HH}$ = 5.5 Hz, 1H), 1.26–1.39 (m, 3H), 2.03–2.11 (m, 1H), 2.22 (ddd, $^2J_{HH}$ = 14.4 Hz, $^3J_{HH}$ = 12.2 Hz, $^3J_{HH}$ = 4.3 Hz, 1H), 2.30 (ddd, $^2J_{HH}$ = 13.8 Hz, $^3J_{HH}$ = 11.3 Hz, $^3J_{HH}$ = 6.8 Hz, 1H), 2.73–2.90 (m, 5H), 3.00 (td, $^2J_{HH}$ = $^3J_{HH}$ = 12.4 Hz, $^3J_{HH}$ = 3.8 Hz, 1H), 3.78 (s, 3H), 3.89 (dd, $^3J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 4.9 Hz, 1H), 5.25 (ddd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 5.1 Hz, $^3J_{HH}$ = 1.7 Hz, 1H), 6.73–6.82 (m, 2H), 7.03–7.12 (m, 2H), 7.13–7.17 (m, 1H), 7.45–7.52 (m,

1H), 7.63–7.73 (m, 2H), 8.01 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 14.15 (CH_3), 21.13 (CH_2), 21.92 (CH_2), 23.53 (CH_2), 27.50 (CH_2), 29.92 (CH_2), 36.37 (CH_2), 40.08 (CH_2), 52.99 (CH), 55.65 (CH_3), 62.23 (C_{quat}), 111.01 (C_{quat}), 111.27 (CH), 114.09 (2CH), 118.30 (CH), 119.61 (CH), 122.23 (CH), 126.14 (C_{quat}), 129.61 (C_{quat})„ 130.64 (2CH), 134.51 (C_{quat}), 135.92 (C_{quat}), 164.13 (C_{quat}), 169.85 (C_{quat}), 201.95 (C_{quat}). IR: $\widetilde{\nu}$ [cm^{-1}] 3366 (w), 3341 (w), 3319 (w), 3028 (w), 3015 (w), 2955 (w), 2928 (w), 2899 (w), 2866 (w), 2839 (w), 2357 (w), 1653 (w), 1634 (s), 1599 (m), 1576 (m), 1558 (w), 1514 (w), 1456 (w), 1423 (m), 1402 (m), 1377 (w), 1354 (w), 1339 (w), 1304 (m), 1281 (w), 1254 (m), 1231 (m), 1184 (m), 1152 (w), 1115 (w), 1084 (w), 1065 (w), 1040 (m), 1020 (m), 999 (w), 966 (w), 945 (w), 918 (w), 872 (w), 835 (m), 824 (w), 762 (m), 748 (s), 733 (m), 714 (m), 692 (m), 638 (w). ESI MS: 431 ([M]$^+$). Anal. calcd. for $C_{27}H_{30}N_2O_3$ (430.55): C 75.32, H 7.02, N 6.51; found: C 75.02, H 6.88, N 6.42.

*2.7. rac-12b-Butyl-1-(6-chloronicotinoyl)-2,3,6,7,12,12b-hexahydroindolo-[2,3a]quinolizin-4(1H)-one (**5e**)*

According to the GP, compound **5e** (260 mg, 30%) was isolated as a colorless solid, Mp 237–242 °C, R_f = 0.17 (diethyl ether). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.85 (t, $^3J_{HH}$ = 7.04 Hz, 3H), 1.05–1.14 (m, 1H), 1.26–1.39 (m, 3H), 1.98–2.09 (m, 1H), 2.22 (dt, $^2J_{HH}$ = 13.7 Hz, $^3J_{HH}$ = 6.4 Hz, 1H), 2.35 (tt, $^2J_{HH}$ = $^3J_{HH}$ = 14.5 Hz, $^3J_{HH}$ = 8.2 Hz, 1H), 2.63–2.71 (m, 1H), 2.72–2.87 (m, 3H), 2.88–2.94 (m, 1H), 2.96–3.04 (m, 1H), 3.83 (dd, $^3J_{HH}$ = 13.7 Hz, $^3J_{HH}$ = 5.0 Hz, 1H), 5.24 (dd, $^2J_{HH}$ = 13.1 Hz, $^3J_{HH}$ = 4.7 Hz, 1H), 7.05–7.15 (m, 3H), 7.22 (d, $^3J_{HH}$ = 8.2 Hz, 1H), 7.50 (d, $^3J_{HH}$ = 7.1 Hz, 1H), 7.69–7.82 (m, 2H), 8.62 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 14.13 (CH_3), 21.25 ($2CH_2$), 23.45 (CH_2), 27.20 (CH_2), 29.51 (CH_2), 35.84 (CH_2), 40.28 (CH_2), 54.20 (CH), 62.02 (C_{quat}), 111.19 (CH), 111.99 (C_{quat}), 118.59 (CH), 120.16 (CH), 122.79 (CH), 124.52 (CH), 126.21 (C_{quat}), 131.04 (C_{quat}), 133.60 (C_{quat}), 135.89 (C_{quat}), 137.75 (CH), 149.69 (CH), 156.26 (C_{quat}), 169.48 (C_{quat}), 201.35 (C_{quat}). IR: $\widetilde{\nu}$ [cm^{-1}] 3227 (w), 3219 (w), 3167 (w), 3154 (w), 3107 (w), 3059 (w), 2953 (w), 2930 (w), 2847 (w), 1684 (m), 1620 (s), 1578 (m), 1555 (w), 1452 (m), 1433 (m), 1406 (m), 1366 (m), 1352 (m), 1319 (w), 1288 (m), 1263 (m), 1227 (m), 1196 (w), 1148 (w), 1136 (w), 1103 (m), 1034 (w), 1007 (w), 968 (w), 870 (w), 822 (w), 743 (s), 712 (w), 702 (w), 662 (w). ESI MS: 438 ([M(^{37}Cl)$^+$], 436 ([M(^{35}Cl)]$^+$). HR-ESI MS calcd. for $C_{25}H_{27}ClN_3O_2$: 436.1786; found: 436.1786. HPLC (254 nm): t_R = 4.8 min, 99%.

*2.8. rac-1-(4-Bromobenzoyl)-12b-butyl-2,3,6,7,12,12b-hexahydroindolo-[2,3-a]quinolizin-4(1H)one (**5f**)*

According to the GP, compound **5f** (385 mg, 40%) was isolated as a colorless solid, Mp 228–232 °C, R_f = 0.35 (n-hexane/ethyl acetate 1:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.85 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.10 (dddd, $^2J_{HH}$ = 15.7 Hz, $^3J_{HH}$ = 12.4 Hz, $^3J_{HH}$ = 8.7 Hz, $^3J_{HH}$ = 5.4 Hz, 1H), 1.27–1.39 (m, 3H), 2.03 (ddt, $^2J_{HH}$ = 13.7 Hz, $^3J_{HH}$ = 9.1 Hz, $^3J_{HH}$ = 4.6 Hz, 1H), 2.18–2.26 (m, 1H), 2.29 (ddd, $^2J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 9.0, $^3J_{HH}$ = 5.5 Hz, 1H), 2.72–2.82 (m, 4H), 2.89 (ddd, $^2J_{HH}$ = 15.2 Hz, $^3J_{HH}$ = 3.8 Hz, $^3J_{HH}$ = 1.6 Hz, 1H), 3.00 (td, $^2J_{HH}$ = $^3J_{HH}$ = 12.4 Hz, $^3J_{HH}$ = 3.7 Hz, 1H), 3.87 (dd, $^3J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 5.0 Hz, 1H), 5.24 (ddd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 5.1 Hz, $^3J_{HH}$ = 1.6 Hz, 1H), 7.06–7.15 (m, 3H), 7.44 (d, $^3J_{HH}$ = 8.7 Hz, 2H), 7.46–7.53 (m, 3H), 7.86 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 14.14 (CH_3), 21.18 (CH_2), 21.59 (CH_2), 23.50 (CH_2), 27.37 (CH_2), 29.68 (CH_2), 36.13 (CH_2), 40.18 (CH_2), 53.54 (CH), 62.17 (C_{quat}), 111.25 (CH), 111.44 (C_{quat}), 118.40 (CH), 119.87 (CH), 122.51 (CH), 126.15 (C_{quat}), 129.20 (C_{quat}), 129.56 (2CH), 132.21 (2CH), 134.17 (C_{quat}), 135.55 (C_{quat}), 135.92 (C_{quat}), 169.75 (C_{quat}), 202.74 (C_{quat}). IR: $\widetilde{\nu}$ [cm^{-1}] 3225 (w), 3156 (w), 3146 (w), 3105 (w), 3057 (w), 2951 (w), 2927 (w), 2893 (w), 2868 (w), 2361 (w), 1680 (m), 1616 (s), 1585 (m), 1566 (w), 1485 (w), 1449 (w), 1431 (m), 1406 (m), 1352 (w), 1319 (w), 1300 (w), 1283 (m), 1263 (m), 1221 (m), 1179 (w), 1153 (w), 1146 (w), 1121 (w), 1072 (m), 1036 (w), 1009 (m), 966 (w), 926 (w), 912 (w), 870 (w), 837 (w), 820 (w), 760 (w), 741 (s), 683 (w). ESI MS: 481 ([M(^{81}Br)]$^+$), 479 ([M(^{79}Br)]$^+$). HR-ESI MS calcd. for $C_{26}H_{28}BrN_2O_2$: 479.1329; found: 479.1325. HPLC (254 nm): t_R = 5.6 min, 99%.

*2.9. rac-12b-Butyl-1-(2-fluorobenzoyl)-2,3,6,7,12,12b-hexahydroindolo[2,3-a]-quinolizin-4(1H)one (**5g**)*

According to the GP, compound **5g** (472 mg, 56%) was isolated as a colorless solid, Mp 233–236 °C, R_f = 0.21 (n-hexane/ethyl acetate 3:2). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.85 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.12 (tdd, $^2J_{HH}$ = $^3J_{HH}$ = 12.0 Hz, $^3J_{HH}$ = 8.7 Hz, $^3J_{HH}$ = 5.3 Hz, 1H), 1.27–1.39 (m, 3H), 2.13–2.20 (m, 1H), 2.23 (ddt, $^2J_{HH}$ = 16.7 Hz, $^3J_{HH}$ = 12.2 Hz, $^3J_{HH}$ = 2.1 Hz, 2H), 2.72–2.87 (m, 5H), 3.00 (td, $^2J_{HH}$ = $^3J_{HH}$ = 12.4 Hz, $^3J_{HH}$ = 3.8 Hz, 1H), 3.86 (dd, $^3J_{HH}$ = 13.1 Hz, $^3J_{HH}$ = 4.8 Hz, 1H), 5.23 (ddd, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 5.0 Hz, $^3J_{HH}$ = 1.6 Hz, 1H), 7.02 (ddd, $^3J_{HF}$ = 11.5 Hz, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 1.0 Hz, 1H), 7.06–7.11 (m, 1H), 7.13 (tdd, $^3J_{HH}$ = 7.0 Hz, $^5J_{HF}$ = 2.9 Hz, $^4J_{HH}$ = 1.2 Hz, 2H), 7.24 (d, $^3J_{HH}$ = 8.0 Hz, 1H), 7.44 (dddd, $^3J_{HH}$ = 8.6 Hz, $^3J_{HH}$ = 7.0 Hz, $^4J_{HF}$ = 4.9 Hz, $^4J_{HH}$ = 1.8 Hz, 1H), 7.49 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 7.62 (td, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.9 Hz, 1H), 8.11 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 14.13 (CH_3), 21.08 (CH_2), 21.14 (CH_2), 23.53 (CH_2), 27.56 (CH_2), 30.14 (CH_2), 36.75 (CH_2), 40.06 (CH_2), 57.41(d, $^4J_{CF}$ = 6.18 Hz, CH), 62.21 (C_{quat}), 111.25 (CH), 111.29 (C_{quat}), 117.13(d, $^2J_{CF}$ = 23.61 Hz, CH), 118.39 (CH), 119.70 (CH), 122.33 (CH), 124.76(d, $^4J_{CF}$ = 3.27 Hz, CH), 125.93(d, $^2J_{CF}$ = 11.39 Hz, C_{quat}), 126.19 (C_{quat}), 130.52(d, $^3J_{CF}$ = 1.57 Hz, CH), 134.39 (C_{quat}), 135.27(d, $^3J_{CF}$ = 9.27 Hz, CH), 135.98 (C_{quat}), 161.08(d, $^1J_{CF}$ = 255.70 Hz, C_{quat}), 169.77 (C_{quat}), 202.04(d, $^3J_{CF}$ = 4.05 Hz, C_{quat}). IR: $\widetilde{\nu}$ [cm^{-1}] 3250 (w), 3196 (w), 3181 (w), 3109 (w), 3059 (w), 3040 (w), 2955 (w), 2932 (w), 2891 (w), 2872 (w), 2859 (w), 2847 (w), 1682 (w), 1611 (s), 1574 (w), 1557 (w), 1528 (w), 1479 (w), 1450 (m), 1433 (m), 1404 (m), 1362 (w), 1352 (m), 1317 (w), 1269 (m), 1261 (m), 1234 (m), 1213 (m), 1190 (w), 1152 (w), 1123 (w), 1101 (w), 1076 (w), 1061 (w), 1036 (w), 1007 (w), 968 (w), 926 (w), 912 (w), 897 (w), 872 (w), 827 (w), 808 (w), 779 (w), 743 (s), 733 (s), 696 (m), 665 (m), 640 (m), 621 (w). ESI MS: 419 ([M]$^+$). HR-ESI MS calcd. for $C_{26}H_{28}FN_2O_2$: 419.2129; found: 419.2134. HPLC (254 nm): t_R = 5.1 min, 99%.

*2.10. rac-12b-Butyl-1-(4-nitrobenzoyl)-2,3,6,7,12,12b-hexahydroindolo[2,3-a]-quinolizin-4(1H)-one (**5h**)*

According to the GP, compound **5h** (334 mg, 37%) was isolated as a colorless solid, Mp 222–224 °C, R_f = 0.30 (n-hexane/ethyl acetate 1:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.86 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.11 (dtt, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 9.7 Hz, $^3J_{HH}$ = 5.3 Hz, 1H), 1.28–1.41 (m, 3H), 1.98–2.06 (m, 1H), 2.23 (ddd, $^2J_{HH}$ = 14.2 Hz, $^3J_{HH}$ = 13.3 Hz, $^3J_{HH}$ = 4.1 Hz, 1H), 2.30–2.40 (m, 1H), 2.67 (td, $^2J_{HH}$ = $^3J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 3.8 Hz, 1H), 2.82 (ddt, $^2J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 10.5 Hz, $^3J_{HH}$ = 6.0 Hz, 3H), 2.91 (dd, $^2J_{HH}$ = 15.3 Hz, $^3J_{HH}$ = 3.7 Hz, 1H), 3.00 (td, $^2J_{HH}$ = $^3J_{HH}$ = 12.5 Hz, $^3J_{HH}$ = 3.7 Hz, 1H), 3.93 (dd, $^3J_{HH}$ = 13.5 Hz, $^3J_{HH}$ = 4.9 Hz, 1H), 5.26 (dd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 4.6 Hz, 1H), 7.03–7.12 (m, 3H), 7.46–7.54 (m, 1H), 7.70 (d, $^3J_{HH}$ = 8.5 Hz, 2H), 7.74 (s, 1H), 8.09 (d, $^3J_{HH}$ = 8.4 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 14.13 (CH_3), 21.25 (2CH_2), 23.46 (CH_2), 27.19 (CH_2), 29.52 (CH_2), 35.71 (CH_2), 40.30 (CH), 54.28 (CH), 62.12 (C_{quat}), 111.16 (CH), 112.00 (C_{quat}), 118.53 (CH), 120.18 (CH), 122.78 (CH), 123.96 (2CH), 126.22 (C_{quat}), 128.97 (2CH), 133.68 (C_{quat}), 135.88 (C_{quat}), 141.44 (C_{quat}), 150.43 (C_{quat}), 169.49 (C_{quat}), 202.23 (C_{quat}). IR: $\widetilde{\nu}$ [cm^{-1}] 3273 (w), 3221 (w), 3113 (w), 3053 (w), 2978 (w), 2947 (w), 2909 (w), 2868 (w), 2845 (w), 2156 (w), 1971 (w), 1690 (m), 1616 (s), 1582 (w), 1526 (s), 1495 (w), 1452 (m), 1431 (w), 1406 (m), 1383 (w), 1344 (s), 1319 (w), 1302 (w), 1277 (w), 1254 (w), 1233 (m), 1204 (w), 1173 (m), 1150 (w), 1101 (w), 1043 (w), 1032 (w), 1007 (w), 984 (m), 962 (w), 943 (w), 930 (w), 860 (m), 853 (m), 824 (w), 745 (s), 723 (m), 716 (m), 706 (w), 677 (w), 652 (w). ESI MS: 446 ([M]$^+$). HR-ESI MS calcd. for $C_{26}H_{28}N_3O_4$: 446.2074; found: 446.2075. HPLC (254 nm): t_R = 5.1 min, 99%.

*2.11. rac-12b-Phenyl-1-(thiophene-2-carbonyl)-2,3,6,7,12,12b-hexahydro-indolo-[2,3-a]quinolizin-4(1H)-one (**5i**)*

According to the GP, compound **5i** (210 mg, 55%) was isolated as a colorless solid, Mp 302–303 °C (Lit.: 315–316 °C) [13], R_f = 0.24 (diethyl ether). ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.85 (tt, $^2J_{HH}$ = $^3J_{HH}$ = 13.7 Hz, $^3J_{HH}$ = 5.3 Hz, 1H), 1.92–2.01 (m, 1H), 2.27 (dd, $^2J_{HH}$ = 17.7 Hz, $^3J_{HH}$ = 5.7 Hz, 1H), 2.43 (dd, $^2J_{HH}$ = 15.2 Hz, $^3J_{HH}$ = 4.5 Hz, 1H), 2.79 (ddd, $^2J_{HH}$ = 17.7 Hz, $^3J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 6.8 Hz, 1H), 2.92 (ddd, $^2J_{HH}$ = 15.2 Hz, $^3J_{HH}$ =

12.0 Hz, $^3J_{HH}$ = 5.9 Hz, 1H), 3.00 (td, $^2J_{HH}$ = $^3J_{HH}$ = 12.4 Hz, $^3J_{HH}$ = 4.7 Hz, 1H), 4.67 (dd, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 5.8 Hz, 1H), 4.77–4.86 (m, 1H), 7.02 (td, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 2.3 Hz, 2H), 7.09–7.21 (m, 4H), 7.27 (d, $^3J_{HH}$ = 7.8 Hz, 2H), 7.40 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 7.52 (d, $^3J_{HH}$ = 8.1 Hz, 1H), 7.89 (d, $^3J_{HH}$ = 4.9 Hz, 1H), 8.07 (d, $^3J_{HH}$ = 3.8 Hz, 1H), 11.76 (s, 1H).^{13}C NMR (151 MHz, DMSO-d_6): δ 19.79 (CH_2), 21.77 (CH_2), 28.88 (CH_2), 39.00 (CH_2), 47.17 (CH), 66.70 (C_{quat}), 109.47 (C_{quat}), 111.39 (CH), 118.08 (CH), 118.98 (CH), 121.79 (CH), 126.62 (C_{quat}), 126.91 (2 CH), 126.95 (CH), 127.80 (2CH), 128.30 (CH), 134.01 (CH), 135.81 (C_{quat}), 136.05 (CH), 136.16 (C_{quat}), 141.31 (C_{quat}), 144.71 (C_{quat}), 171.69 (C_{quat}), 192.09 (C_{quat}). IR: $\tilde{\nu}$ [cm^{-1}] 3267 (w), 1738 (w), 1651 (m), 1607 (s), 1585 (w), 1574 (w), 1516 (w), 1495 (w), 1454 (w), 1416 (m), 1393 (m), 1377 (w), 1342 (m), 1298 (w), 1283 (w), 1263 (w), 1250 (m), 1231 (m), 1217 (w), 1186 (w), 1153 (w), 1140 (w), 1080 (w), 1065 (w), 1094 (w), 961 (w), 947 (w), 914 (w), 880 (w), 854 (w), 826 (w), 814 (w), 729 (s), 702 (s), 681 (w), 658 (w), 627 (w). MS (ESI): 427 (M^+). ESI MS: 427 ($[M]^+$). HR-ESI MS calcd. for $C_{26}H_{23}N_2O_2S$: 427.1475; found: 427.1479. HPLC (254 nm): t_R = 4.8 min, 99%.

*2.12. rac-1-(4-Methoxybenzoyl)-2,3,6,7,12,12b-hexahydroindolo[2,3-a]quinolizin-4(1H)-one (**5j**)*

According to the GP, compound **5*j*** (360 mg, 48%) was isolated as a colorless solid, Mp 160 °C, R_f = 0.20 (n-hexane/ethyl acetate 1:2). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.94–2.02 (m, 1H), 2.17–2.23 (m, 1H), 2.64 (ddd, $^2J_{HH}$ = 17.9 Hz, $^3J_{HH}$ = 11.9 Hz, $^3J_{HH}$ = 6.0 Hz, 1H), 2.71 (ddd, $^2J_{HH}$ = 17.6 Hz, $^3J_{HH}$ = 5.8 Hz, $^3J_{HH}$ = 2.5 Hz, 1H), 2.76–2.82 (m, 1H), 2.84–2.93 (m, 2H), 3.73 (ddd, $^2J_{HH}$ = 12.8 Hz, $^3J_{HH}$ = 10.1 Hz, $^3J_{HH}$ = 3.1 Hz, 1H), 3.90 (s, 3H), 5.17–5.24 (m, 1H), 5.46–5.51 (m, 1H), 6.99 (d, $^3J_{HH}$ = 8.5 Hz, 2H), 7.06–7.12 (m, 2H), 7.17 (d, $^3J_{HH}$ = 7.9 Hz, 1H), 7.48 (d, $^3J_{HH}$ = 7.6 Hz, 1H), 7.71 (s, 1H), 7.99 (d, $^3J_{HH}$ = 8.5 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 21.37 (CH_2), 25.97 (CH_2), 32.10 (CH_2), 40.96 (CH_2), 48.92 (CH), 55.42 (CH), 55.81 (CH_3), 111.17 (C_{quat}), 111.36 (CH), 114.51 (2CH), 118.36 (CH), 119.94 (CH), 122.41 (CH), 126.61 (C_{quat}), 128.04 (C_{quat}), 131.20 (2CH), 132.81 (C_{quat}), 136.26 (C_{quat}), 164.71 (C_{quat}), 168.54 (C_{quat}), 201.08 (C_{quat}). IR: $\tilde{\nu}$ [cm^{-1}] 3900 (m), 3647 (m), 3005 (w), 2924 (w), 2845 (w), 2438 (w), 2365 (w), 1622 (s), 1616 (m), 1597 (s), 1570 (m), 1506 (m), 1437 (m), 1420 (m), 1373 (w), 1350 (w), 1317 (m), 1304 (m), 1292 (w), 1260 (s), 1234 (m), 1215 (m), 1169 (s), 1155 (m), 1117 (w), 1099 (w), 1053 (w), 1028 (m), 1009 (m), 980 (w), 841 (m), 741 (s), 685 (w), 673 (w), 606 (s). EI MS (70 eV, m/z (%)): 374 (43), 318 ($[C_{20}H_{18}N_2O_2]^{2+}$, 41), 317 (83), 240 (17), 239 ($[C_{15}H_{15}N_2O]^+$, 100), 170 ($[C_{11}H_{10}N_2]^{2+}$, 26), 169 (56), 168 (12), 167 (12), 142 (10), 135 ($[C_8H_7O_2]^+$, 50), 115 (14), 107 ($[C_7H_7O]^+$, 12), 92 (11), 77 (18), 49 (12). HR-ESI MS calcd. for $C_{23}H_{23}N_2O_3$: 375.1703; found: 375.1705. HPLC (254 nm): t_R = 4.3 min, 97%.

*2.13. rac-1-(6-Chloronicotinoyl)-12b-phenyl-2,3,6,7,12,12b-hexahydroindolo-[2,3-a]quinolizin-4(1H)-one (**5k**)*

According to the GP, compound 5k (313 mg, 34%) was isolated as a colorless solid, Mp 233 °C (dec.), R_f = 0.27 (n-hexane/ethyl acetate 1:1). ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.77–1.86 (m, 1H), 2.05 (dd, $^2J_{HH}$ = 14.2 Hz, $^3J_{HH}$ = 6.6 Hz, 1H), 2.29 (dd, $^2J_{HH}$ = 17.8 Hz, $^3J_{HH}$ = 5.9 Hz, 1H), 2.44 (dd, $^2J_{HH}$ = 15.2 Hz, $^3J_{HH}$ = 4.3 Hz, 1H), 2.82 (ddd, $^2J_{HH}$ = 18.7 Hz, $^3J_{HH}$ = 12.8 Hz, $^3J_{HH}$ = 6.9 Hz, 1H), 2.92 (ddd, $^2J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 12.1 Hz, $^3J_{HH}$ = 5.6 Hz, 1H), 2.99 (td, $^2J_{HH}$ = $^3J_{HH}$ = 12.4 Hz, $^3J_{HH}$ = 4.4 Hz, 1H), 4.68 (dd, $^2J_{HH}$ = 12.8 Hz, $^3J_{HH}$ = 5.6 Hz, 1H), 4.88–4.95 (m, 1H), 6.98–7.04 (m, 2H), 7.13 (t, $^3J_{HH}$ = 7.8 Hz, 2H), 7.17 (t, $^3J_{HH}$ = 7.6 Hz, 1H), 7.24 (d, $^3J_{HH}$ = 7.9 Hz, 2H), 7.40 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 7.51 (d, $^3J_{HH}$ = 8.2 Hz, 1H), 7.55 (d, $^3J_{HH}$ = 8.4 Hz, 1H), 8.09 (dd, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 2.4 Hz, 1H), 8.85 (d, $^4J_{HH}$ = 2.4 Hz, 1H), 11.76 (s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 19.84 (CH_2), 21.06 (CH_2), 28.78 (CH_2), 39.00 (CH_2), 46.35 (CH), 66.65 (C_{quat}), 109.63 (C_{quat}), 111.44 (CH), 118.15 (CH), 119.06 (CH), 121.89 (CH), 124.11 (CH), 126.58 (C_{quat}), 126.88 (2CH), 127.15 (CH), 128.10 (2CH), 131.58 (C_{quat}), 135.84 (2C_{quat}), 138.90 (CH), 141.06 (C_{quat}), 150.01 (CH), 153.94 (C_{quat}), 171.71 (C_{quat}), 198.28 (C_{quat}). IR: $\tilde{\nu}$ [cm^{-1}] 3271 (w), 1686 (m), 1630 (m), 1605 (s), 1574 (w), 1555 (w), 1491 (w), 1449 (m), 1423 (w), 1398 (w), 1387 (w), 1364 (w), 1341 (w), 1325 (w), 1290 (w), 1277 (w), 1263 (w), 1221 (w), 1200 (w), 1182 (w), 1138 (w), 1101 (m), 1080 (w), 1047 (w), 986 (w), 947 (w), 901 (w), 835 (w), 779 (w), 758 (s), 743 (m), 704 (s), 685

(m), 656 (w), 625 (m), 607 (s). ESI MS: 458 ([M(^{37}Cl)]$^+$), 456 ([M(^{35}Cl)]$^+$). HR-ESI MS calcd. for $C_{27}H_{23}ClN_3O_2$: 456.1473; found: 427.1475. HPLC (254 nm): t_R = 4.8 min, 99%.

*2.14. rac-1-(6-Chloronicotinoyl)-12b-cyclopropyl-2,3,6,7,12,12b-hexahydroindolo[2,3-a]quinolizin-4(1H)-one (**5l**)*

According to the GP, compound **5l** (160 mg, 19%) was isolated as a colorless solid, Mp 234–236 °C, R_f = 0.21 (n-hexane/ethyl acetate 1:2). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.85–1.92 (m, 1H), 2.05–2.11 (m, 1H), 2.30–2.39 (m, 2H), 2.77–2.85 (m, 3H), 2.88–2.98 (m, 3H), 3.47–3.56 (m, 2H), 3.85 (dd, $^2J_{HH}$ = 13.5 Hz, $^3J_{HH}$ = 5.1 Hz, 1H), 5.26 (dd, $^2J_{HH}$ = 12.5 Hz, $^3J_{HH}$ = 4.7 Hz, 1H), 7.07–7.15 (m, 3H), 7.25 (d, $^3J_{HH}$ = 8.8 Hz, 1H), 7.50 (d, $^3J_{HH}$ = 7.5 Hz, 1H), 7.81 (dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 2.5 Hz, 1H), 7.86 (s, 1H), 8.64 (d, $^4J_{HH}$ = 2.5 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 21.17 (CH_2), 21.27 (CH_2), 28.12 (CH_2), 29.52 (CH_2), 33.49 (CH_2), 40.25 (CH_2), 45.07 (CH_2), 54.14 (CH), 61.57 (C_{quat}), 111.33 (CH), 112.35 (C_{quat}), 118.64 (2CH), 120.29 (CH), 123.03 (CH), 124.61 (CH), 126.10 (C_{quat}), 130.86 (C_{quat}), 132.76 (C_{quat}), 136.03 (C_{quat}), 137.83 (CH), 149.73 (CH), 156.42 (C_{quat}), 169.45 (C_{quat}), 201.17 (C_{quat}). IR: $\tilde{\nu}$ [cm^{-1}] 3582 (w), 3271 (w), 3248 (w), 3171 (w), 3113 (w), 3084 (w), 3055 (w), 2965 (w), 2922 (w), 2891 (w), 2843 (w), 2360 (w), 2008 (w), 1686 (m), 1618 (s), 1578 (m), 1555 (w), 1497 (w), 1433 (m), 1412 (m), 1369 (m) 1350 (w), 1314 (m), 1296 (m), 1283 (m), 1260 (m), 1234 (m), 1223 (m), 1200 (w), 1173 (w), 1157 (w), 1148 (w), 1103 (m), 1078 (w), 1063 (w), 1030 (w), 1003 (w), 964 (w), 920 (w), 907 (w), 891 (w), 878 (w), 845 (w), 833 (w), 818 (w), 772 (w), 745 (s), 731 (m), 708 (m), 679 (w), 656 (w). ESI MS: 422 ([M(^{37}Cl)]$^+$), 420 ([M(^{35}Cl)]$^+$). HR-ESI MS calcd. for $C_{24}H_{22}ClN_3O_2$: 420.1473; found: 420.1480. HPLC (254 nm): t_R = 4.5 min, 97%.

*2.15. rac-1-(Thiophene-2-carbonyl)-12b-(1-tosyl-1H-indol-3-yl)-2,3,6,7,12,12b-hexahydroindolo-[2,3-a]quinolizin-4(1H)-one (**5m**)*

According to the GP, compound **5m** (390 mg, 32%) was isolated as a colorless solid, Mp 314–316 °C, R_f = 0.24 (n-hexane/ethyl acetate 1:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.14–2.22 (m, 1H), 2.34 (s, 3H), 2.55–2.71 (m, 3H), 2.91 (td, $^2J_{HH}$ = $^3J_{HH}$ = 12.5 Hz, $^3J_{HH}$ = 4.2 Hz, 1H), 2.99 (d, $^2J_{HH}$ = 17.5 Hz, 1H), 3.07 (ddd, $^2J_{HH}$ = 16.0 Hz, $^3J_{HH}$ = 12.1 Hz, $^3J_{HH}$ = 5.4 Hz, 1H), 4.08 (d, $^2J_{HH}$ = 11.0 Hz, 1H), 4.94 (dd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 5.3 Hz, 1H), 6.87 (t, $^3J_{HH}$ = 4.1 Hz, 1H), 7.12–7.18 (m, 3H), 7.18–7.28 (m, 4H, superimposed by $CDCl_3$), 7.32–7.36 (m, 1H), 7.39 (d, $^3J_{HH}$ = 8.1 Hz, 1H), 7.48–7.56 (m, 4H), 7.66 (d, $^3J_{HH}$ = 8.0 Hz, 2H), 7.81 (d, $^3J_{HH}$ = 8.3 Hz, 1H), 9.18 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 20.87 (CH_2), 21.77 (CH_3), 23.45 (CH_2), 32.36 (CH_2), 38.81 (CH_2), 55.55 (CH), 62.90 (C_{quat}), 110.30 (C_{quat}), 111.93 (CH), 113.78 (CH), 118.83 (CH), 120.17 (CH), 120.88 (CH), 122.54 (C_{quat}), 122.93 (CH), 124.03 (CH), 124.90 (CH), 126.55 (C_{quat}), 127.16 (2CH), 127.64 (CH), 128.34 (CH), 128.94 (C_{quat}), 130.00 (2CH), 132.46 (CH), 134.94 (C_{quat}), 134.96 (C_{quat}), 135.31 (CH), 135.92 (C_{quat}), 136.03 (C_{quat}), 143.48 (C_{quat}), 145.15 (C_{quat}), 169.45 (C_{quat}), 193.93 (C_{quat}). IR: $\tilde{\nu}$ [cm^{-1}] 3152 (s), 3134 50 (s), 3103 (s), 3063 (s), 2959 (s), 2932 (s), 2916 (s), 2841 (s), 2720 (s), 1672 (m), 1609 (m), 1601 (m), 1445 (m), 1420 (m), 1406 (m), 1391 (m), 1369 (m), 1342 (m), 1329 (s), 1294 (s), 1277 (m), 1263 (s), 1240 (m), 1233 (m), 1217 (s), 1175 (w), 1159 (m), 1140 (m), 1123 (m), 1088 (m), 1040 (m), 1015 (s), 988 (m), 978 (m), 957 (s), 903 (s), 876 (s), 853 (m), 822 (m), 810 (m), 745 (w), 721 (w), 696 (w), 669 (m), 654 (w), 604 (m). EI MS (70 eV, m/z (%)): 619 ([M]$^+$, 26), 465 ([$C_{28}H_{22}N_3O_2S$]$^+$, 17), 464 ([$C_{28}H_{22}N_3O_2S$]$^+$, 52), 439 (15), 438 (28), 327 (21), 326 (87), 323 (13), 298 (24), 285 (16), 284 (42), 283 (31), 282 (26), 281 (11), 269 (22), 257 (24), 256 (61), 255 (29), 155 ([$C_7H_7O_2S$]$^+$, 11), 143 (10), 111 ([C_5H_3OS]$^+$, 100), 91 ([C_7H_7]$^+$, 53), 65 (10). HR-ESI MS calcd. for $C_{35}H_{29}N_3O_4S_2$: 620.1672; found: 620.1675. HPLC (254 nm): t_R = 5.8 min, 99%.

*2.16. rac-1-(6-Chloronicotinoyl)-12b-(1-tosyl-1H-indol-3-yl)-2,3,6,7,12,12b-hexahydroindolo-[2,3-a]quinolizin-4(1H)-one (**5n**)*

According to the GP, compound **5n** (624 mg, 48%) was isolated as a colorless solid, Mp 294–296 °C, R_f = 0.18 (n-hexane/ethyl acetate 1:1). ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.83 (tt, $^2J_{HH}$ = $^3J_{HH}$ = 13.9 Hz, $^3J_{HH}$ = 5.5 Hz, 1H), 2.01 (dd, $^2J_{HH}$ = 15.1 Hz, $^3J_{HH}$ = 6.7 Hz, 1H), 2.27 (s, 3H), 2.30–2.37 (m, 1H), 2.44–2.49 (m, 1H), 2.70 (ddd, $^2J_{HH}$ = 18.6 Hz, $^3J_{HH}$ = 12.8 Hz, $^3J_{HH}$ = 6.6 Hz, 1H), 2.81–2.95 (m, 2H), 4.68–4.74 (m, 1H), 4.98–5.03 (m, 1H), 7.05–7.12 (m,

3H), 7.21–7.30 (m, 3H), 7.45 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 7.50 (d, $^3J_{HH}$ = 10.3 Hz, 2H), 7.55 (d, $^3J_{HH}$ = 8.0 Hz, 2H), 7.59 (d, $^3J_{HH}$ = 8.1 Hz, 1H), 7.62–7.68 (m, 2H), 7.98 (dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 2.6 Hz, 1H), 8.82 (d, ^4J = 2.5 Hz, 1H), 11.76 (s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 19.77 (CH_2), 20.99 (CH_3), 21.30 (CH_2), 28.64 (CH_2), 40.06 (CH_2), 47.49 (CH), 63.04 (C_{quat}), 109.25 (C_{quat}), 111.61 (CH), 112.54 (CH), 118.29 (CH), 119.19 (CH), 122.07 (CH), 122.45 (CH), 123.50 (CH), 124.13 (CH), 124.87 (CH), 125.10 (CH), 125.11 (C_{quat}), 126.32 (2CH), 126.60 (C_{quat}), 127.80 (C_{quat}), 129.92 (2CH), 130.85 (C_{quat}), 133.54 ($_{Cquat}$), 133.55 (C_{quat}), 135.67 (C_{quat}), 136.31 (C_{quat}), 138.74 (CH), 145.30 (C_{quat}), 149.86 (CH), 154.24 (C_{quat}), 170.72 (C_{quat}), 197.1 (C_{quat}). IR: $\widetilde{\nu}$ [cm^{-1}] 3838 (s), 3233 (s), 3194 (s), 3157 (s), 2911 (s), 2847 (s), 1688 (m), 1605 (m), 1582 (m), 1557 (s), 1449 (m), 1420 (s), 1404 (m), 1368 (m), 1348 (m), 1331 (s), 1310 (s), 1298 (s), 1279 (m), 1263 (s), 1231 (m), 1192 (m), 1175 (w), 1142 (m), 1125 (m), 1107 (m), 1086 (m), 1072 (s), 1059 (s), 1028 (s), 988 (m), 959 (s), 893 (s), 874 (s), 827 (s), 804 (m), 777 (m), 750 (w), 702 (m), 677 (m), 656 (m), 633 (m). EI MS (70 eV, m/z (%)): 650 ([M (^{37}Cl)]$^+$, 4), 648 ([M (^{35}Cl)]$^+$, 11), 495 ([$C_{29}H_{22}{}^{37}ClN_4O_2$]$^+$, 16), 494 (15), 493 ([$C_{29}H_{22}{}^{35}ClN_4O_2$]$^+$, 40), 439 (12), 438 (33), 327 (23), 326 (100), 298 (22), 285 (13), 284 (35), 283 (26), 282 (21), 269 (19), 257 (20), 256 (50), 255 (24), 144 (13), 143 (59), 142 ([$C_6H_3{}^{37}ClNO$]$^+$, 11), 140 ([$C_6H_3{}^{35}ClNO$]$^+$, 25), 130 (37), 91 ([C_7H_7]$^+$, 28). Anal. calcd. for $C_{36}H_{29}ClN_4O_4S$ (649.16): C 66.61, H 4.50, N 8.63, S 4.94; found: C 66.34, H 4.55, N 8.47, S 5.19.

*2.17. rac-1-(2-Fluorobenzoyl)-12b-(1-tosyl-1H-indol-3-yl)-2,3,6,7,12,12b-hexahydroindolo-[2,3-a]quinolizin-4(1H)-one (**5o**)*

According to the GP, compound **5o** (332 mg, 26%) was isolated as a colorless solid, Mp 268–270 °C, R_f = 0.26 (n-hexane/ethyl acetate 1:1). ^{1}H NMR (600 MHz, $CDCl_3$,): δ 2.02–2.09 (m, 1H), 2.24–2.33 (m, 4H), 2.60 (dd, $^2J_{HH}$ = 15.5 Hz, $^3J_{HH}$ = 4.2 Hz, 1H), 2.70 (ddd, $^2J_{HH}$ = 18.1 Hz, $^3J_{HH}$ = 10.0 Hz, $^3J_{HH}$ = 6.4 Hz, 1H), 2.78 (td, $^2J_{HH}$ = $^3J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 4.3 Hz, 1H), 2.98–3.08 (m, 2H), 4.09–4.13 (m, 1H), 4.89 (dd, $^2J_{HH}$ = 13.0 Hz, $^3J_{HH}$ = 5.4 Hz, 1H), 6.90 (td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.9 Hz, 1H), 6.94–6.99 (m, 1H), 7.06 (dd, $^3J_{HF}$ = 11.1 Hz, $^3J_{HH}$ = 8.3 Hz, 1H), 7.12–7.22 (m, 4H), 7.25–7.30 (m, 3H, superimposed by $CDCl_3$), 7.38–7.48 (m, 3H), 7.53 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 7.59 (s, 1H), 7.69 (d, $^3J_{HH}$ = 8.3 Hz, 2H), 7.89 (d, $^3J_{HH}$ = 8.3 Hz, 1H), 8.99 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 20.90 (CH_2), 21.73 (CH_3), 22.46 (CH_2), 32.26 (CH_2), 38.85 (CH_2), 56.17(d, $^4J_{CF}$ = 5.93 Hz, CH), 63.39 (C_{quat}), 110.77 (C_{quat}), 111.89 (CH), 113.80 (CH), 116.57(d, $^2J_{CF}$ = 23.1 Hz, CH), 118.85 (CH), 120.19 (CH), 121.09 (CH), 122.60 (C_{quat}), 122.99 (CH), 124.06 (CH), 124.81(d, $^4J_{CF}$ = 3.17 Hz, CH), 124.85 (CH), 126.45(d, $^2J_{CF}$ = 13.7 Hz, C_{quat}), 126.73 (C_{quat}), 127.16 (2CH), 128.29 (CH), 128.99 (C_{quat}), 129.69(d, $^3J_{CF}$ = 2.24 Hz, CH), 129.95 (2CH), 134.51(d, $^3J_{CF}$ = 9.10 Hz, CH), 134.86 (C_{quat}), 134.92 (C_{quat}), 135.70 (C_{quat}), 135.74 (C_{quat}), 145.15 (C_{quat}), 160.00(d, $^1J_{CF}$ = 251 Hz, C_{quat}), 169.37 (C_{quat}), 200.83(d, $^3J_{CF}$ = 3.56 Hz, C_{quat}). IR: $\widetilde{\nu}$ [cm^{-1}] 3981 (w), 3854 (w), 3802 (w), 3736 (w), 3723 (w), 3588 (w), 3524 (w), 3424 (w), 3404 (w), 3271 (w), 3175 (w), 3159 (w), 3136 (w), 3105 (w), 3084 (w), 3067 (w), 3040 (w), 3019 (w), 2974 (w), 2953 (w), 2934 (w), 2913 (w), 2886 (w), 2841 (w), 2810 (w), 2752 (w), 2714 (w), 2695 (w), 2621 (w), 2488 (w), 2359 (w), 2342 (w), 1690 (w), 1609 (s), 1576 (w), 1452 (m), 1410 (m), 1396 (w), 1368 (m), 1350 (m), 1333 (w), 1294 (w), 1277 (m), 1261 (w), 1223 (w), 1213 (w), 1175 (s), 1142 (m), 1123 (m) 1086 (m), 1042 (w), 986 (m), 961 (w), 876 (w), 841 (w), 808 (w), 787 (w), 746 (s), 702 (m), 669 (s), 656 (s), 629 (m). EI MS (70 eV, m/z (%)): 631 ([M]$^+$, 21), 476 ([$C_{30}H_{23}FN_3O_2$]$^+$, 57), 438 ([$C_{26}H_{20}N_3O_2S$]$^+$, 31), 326 ([$C_{21}H_{16}N_3O$]$^{2+}$, 98), 298 ([$C_{19}H_{12}N_3O$]$^{3+}$, 23), 284 ([$C_{19}H_{14}N_3$]$^+$, 51), 256 ([$C_{17}H_{10}N_3$]$^{4+}$, 68), 123 ([C_7H_4FO]$^+$, 100), 91 ([C_7H_7]$^+$, 51). Anal. calcd. for $C_{37}H_{30}FN_3O_4S$ (631.72): C 70.35, H 4.79, N 6.65, S 5.08; found: C 70.24, H 4.87, N 6.38, S 4.97.

*2.18. rac-1-(4-Bromobenzoyl)-12b-(1-tosyl-1H-indol-3-yl)-2,3,6,7,12,12b-hexahydroindolo-[2,3-a]quinolizin-4(1H)-one (**5p**)*

According to the GP, compound **5p** (687 mg, 50%) was isolated as a colorless solid, Mp 290–292 °C, R_f = 0.21 (n-hexane/ethyl acetate 1:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.95–2.03 (m, 1H), 2.28–2.43 (m, 4H), 2.65 (d, $^2J_{HH}$ = 15.2 Hz, 2H), 2.83–2.97 (m, 2H), 3.01–3.10 (m, 1H), 4.07–4.16 (m, 1H), 4.90–4.98 (m, 1H), 7.07–7.12 (m, 2H), 7.13–7.18 (m, 1H), 7.20–7.27

(m, 5H, superimposed by $CDCl_3$), 7.28–7.32 (m, 1H), 7.33–7.41 (m, 3H), 7.44–7.48 (m, 1H), 7.50–7.54 (m, 1H), 7.56 (s, 1H), 7.65 (d, $^3J_{HH}$ = 7.4 Hz, 2H), 7.85–7.92 (m, 1H), 9.11 (s, 1H).^{13}C NMR (151 MHz, $CDCl_3$): δ 20.90 (CH_2), 21.79 (CH_3), 23.22 (CH_2), 32.06 (CH_2), 38.98 (CH_2), 53.55 (CH), 63.10 (C_{quat}), 110.51 (C_{quat}), 111.86 (CH), 113.87 (CH), 118.88 (CH), 120.22 (CH), 120.98 (CH), 122.68 (C_{quat}), 123.01 (CH), 124.18 (CH), 125.04 (CH), 126.60 (C_{quat}), 127.05 (2CH), 127.85 (CH), 128.49 (C_{quat}), 128.90 (C_{quat}), 129.33 (2CH), 129.90 (2CH), 131.98 (2CH), 134.79 (C_{quat}), 134.87 (C_{quat}), 135.83 (C_{quat}), 135.89 (C_{quat}), 135.93 (C_{quat}), 145.26 (C_{quat}), 169.51 (C_{quat}), 201.69 (C_{quat}). IR: $\widetilde{\nu}$ [cm^{-1}] 3244 (w), 3082 (w), 2913 (w), 1676 (w), 1618 (s), 1582 (w), 1489 (w), 1447 (m), 1420 (w), 1398 (m), 1377 (m), 1366 (w), 1342 (w), 1298 (w), 1279 (w), 1265 (w), 1233 (m), 1209 (w), 1175 (s), 1144 (m), 1125 (m), 1092 (m), 1072 (w), 1053 (w), 1009 (w), 988 (m), 955 (w), 890 (w), 878 (w), 810 (m), 746 (s), 719 (w), 691 (w), 675 (s), 656 (m). EI MS (70 eV, m/z (%)): 693 ([^{81}Br-M]$^+$, 3), 692 ([M]$^+$, 3), 691 ([^{79}Br-M]$^+$, 6), 538 ([$C_{30}H_{23}{}^{81}BrN_3O_2$]$^+$, 21), 536 ([$C_{30}H_{23}{}^{79}BrN_3O_2$]$^+$, 22), 439 ([$C_{26}H_{21}N_3O_2S$]$^+$, 13), 438 ([$C_{26}H_{20}N_3O_2S$]$^+$, 30), 327 (25), 326 ([$C_{21}H_{16}N_3O$]$^{2+}$, 100), 298 ([$C_{19}H_{12}N_3O$]$^{4+}$, 21), 285 (20), 284 ([$C_{19}H_{14}N_3$]$^+$, 55), 283 (33), 282 (34), 257 (24), 256 ([$C_{17}H_{10}N_3$]$^{4+}$, 58), 255 (27), 185 ([$C_7H_4{}^{81}BrO$]$^+$, 38), 183 (35, [$C_7H_4{}^{79}BrO$]$^+$, 35), 155 ([$C_7H_7O_2S$]$^+$, 22), 143 (15), 92 (16), 91 ([C_7H_7]$^+$, 51), 65 (22). Anal. calcd. for $C_{37}H_{30}BrN_3O_4S$ (692.63): C 64.16, H 4.37, N 6.07, S 4.63; found: C 64.22, H 4.46, N 5.90, S 4.47.

*2.19. rac-1-Benzoyl-12b-(1-tosyl-1H-indol-3-yl)-2,3,6,7,12,12b-hexahydro-indolo[2,3-a]quinolizin-4(1H)-one (**5q**)*

According to the GP, compound **5q** (418 mg, 34%) was isolated as a colorless solid, Mp 294–297 °C, R_f = 0.22 (n-hexane/ethyl acetate 1:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.01–2.09 (m, 1H), 2.31 (s, 3H), 2.33–2.42 (m, 1H), 2.61–2.75 (m, 2H), 2.85 (td, $^2J_{HH}$ = 12.5 Hz, $^3J_{HH}$ = 4.2 Hz, 1H), 2.95 (ddd, $^2J_{HH}$ = 17.8 Hz, $^3J_{HH}$ = 5.6 Hz, $^3J_{HH}$ = 3.8 Hz, 1H), 3.05 (ddd, $^2J_{HH}$ = 15.4 Hz, $^3J_{HH}$ = 12.1 Hz, $^3J_{HH}$ = 5.5 Hz, 1H), 4.23 (dd, $^2J_{HH}$ = 11.6 Hz, $^3J_{HH}$ = 3.2 Hz, 1H), 4.96 (dd, $^2J_{HH}$ = 12.9 Hz, $^3J_{HH}$ = 5.3 Hz, 1H), 7.10 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 7.15 (t, $^3J_{HH}$ = 7.4 Hz, 1H), 7.19–7.24 (m, 2H), 7.25–7.36 (m, 4H), 7.43 (d, $^3J_{HH}$ = 8.1 Hz, 1H), 7.47–7.55 (m, 4H), 7.60 (s, 1H), 7.67 (d, $^3J_{HH}$ = 8.2 Hz, 2H), 7.89 (d, $^3J_{HH}$ = 8.3 Hz, 1H), 8.98 (s, 1H).^{13}C NMR (151 MHz, $CDCl_3$): δ 20.99 (CH_2), 21.74 (CH_3), 23.25 (CH_2), 32.35 (CH_2), 38.69 (CH_2), 53.47 (CH), 63.16 (C_{quat}), 110.44 (C_{quat}), 111.85 (CH), 113.92 (CH), 118.83 (CH), 120.20 (CH), 120.85 (CH), 122.56 (C_{quat}), 122.96 (CH), 124.10 (CH), 124.83 (CH), 126.52 (C_{quat}), 127.10 (2CH), 127.92 (2CH), 128.24 (CH), 128.89 (2CH), 129.20 (C_{quat}), 129.91 (2CH), 133.43 (CH), 134.90 (C_{quat}), 134.94 (C_{quat}), 135.81 (C_{quat}), 135.87 (C_{quat}), 137.19 (C_{quat}), 145.09 (C_{quat}), 169.22 (C_{quat}), 202.45 (C_{quat}). IR: $\widetilde{\nu}$ [cm^{-1}] 3136 (w), 3132 (w), 3107 (w), 3086 (w), 3067 (w), 3030 (w), 2959 (w), 2934 (w), 2843 (w), 1734 (w), 1686 (w), 1609 (m), 1582 (w), 1545 (w), 1493 (w), 1447 (m), 1408 (m), 1389 (w), 1369 (m), 1350 (w), 1331 (w), 1294 (w), 1275 (w), 1261 (w), 1227 (w), 1211 (w), 1175 (s), 1159 (m), 1140 (m), 1123 (m), 1070 (w), 1047 (w), 986 (m), 959 (w), 903 (w), 876 (w), 829 (w), 810 (w), 797 (w), 746 (s), 712 (m), 692 (w), 671 (m), 656 (s), 627 (w). EI MS (70 eV, m/z (%)): 613 ([M]$^+$, 16), 459 (18), 458 ([$C_{30}H_{24}N_3O_2$]$^+$, 54), 438 ([$C_{26}H_{20}N_3O_2S$]$^+$, 26), 327 (23), 326 ([$C_{21}H_{16}N_3O$]$^{2+}$, 100), 298 (22), 285 (18), 284 ([$C_{19}H_{14}N_3$]$^+$, 46), 283 (31), 282 (26), 269 (18), 257 (25), 256 ([$C_{17}H_{10}N_3$]$^{4+}$, 66), 255 (29), 105 ([C_7H_5O]$^+$, 76), 91 ([C_7H_7]$^+$, 32), 77 (31). HR-ESI MS calcd. for $C_{37}H_{32}N_3O_4S$: 614.2108; Found: 614.2108. HPLC (254 nm): t_R = 5.8 min, 99%. Anal. calcd. for $C_{37}H_{31}N_3O_4S$ (613.73): C 72.41, H 5.09, N 6.85, S 5.22; found: C 71.56, H 5.04, N 6.52, S 4.97.

*2.20. rac-1-(4-Methoxybenzoyl)-12b-(1-tosyl-1H-indol-3-yl)-2,3,6,7,12,12b-hexahydroindolo-[2,3-a]quinolizin-4(1H)-one (**5r**)*

According to the GP, compound **5r** (423 mg, 33%) was isolated as a colorless solid, Mp 273–274 °C, R_f = 0.16 (n-hexane/ethyl acetate 1:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.01–2.07 (m, 1H), 2.32 (s, 3H), 2.36–2.46 (m, 1H), 2.63–2.69 (m, 1H), 2.74 (ddd, $^2J_{HH}$ = 18.0 Hz, $^3J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 6.8 Hz, 1H), 2.84 (td, $^2J_{HH}$ = $^3J_{HH}$ = 12.5 Hz, $^3J_{HH}$ = 4.2 Hz, 1H), 2.97 (ddd, $^2J_{HH}$ = 18.3 Hz, $^3J_{HH}$ = 5.7 Hz, $^3J_{HH}$ = 3.4 Hz, 1H), 3.03 (ddd, $^2J_{HH}$ = 15.4 Hz, $^3J_{HH}$ = 12.1 Hz, $^3J_{HH}$ = 5.5 Hz, 1H), 3.82 (s, 3H), 4.17 (dd, $^2J_{HH}$ = 11.8 Hz, $^3J_{HH}$ = 3.1 Hz, 1H), 4.92–4.98 (m, 1H), 6.78–6.81 (m, 2H), 7.12–7.16 (m, 3H), 7.18–7.23 (m, 2H), 7.24–7.28

(m, 2H, superimposed by $CDCl_3$), 7.30–7.33 (m, 1H), 7.39 (d, $^3J_{HH}$ = 8.1 Hz, 1H), 7.52 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 7.59 (s, 1H), 7.59–7.63 (m, 2H), 7.66–7.70 (m, 2H), 7.86–7.89 (m, 1H), 8.81 (s, 1H).^{13}C NMR (151 MHz, $CDCl_3$): δ 21.02 (CH_2), 21.72 (CH_3), 23.31 (CH_2), 32.32 (CH_2), 38.74 (CH_2), 52.90 (CH), 55.70 (CH_3), 63.30 (C_{quat}), 110.29 (C_{quat}), 111.85 (CH), 113.88 (CH), 114.10 (2CH), 118.80 (CH), 120.17 (CH), 120.82 (CH), 122.62 (C_{quat}), 122.92 (CH), 124.06 (CH), 124.75 (CH), 126.48 (C_{quat}), 127.13 (2CH), 128.20 (CH), 129.30 (C_{quat}), 129.59 (C_{quat}), 129.91 (2CH), 130.62 (2CH), 134.92 (C_{quat}), 134.95 (C_{quat}), 135.81 (C_{quat}), 135.88 (C_{quat}), 145.08 (C_{quat}), 163.99 (C_{quat}), 169.51 (C_{quat}), 200.04 (C_{quat}). IR: $\widetilde{\nu}$ [cm^{-1}] 3298 (w), 3258 (w), 3063 (w), 2947 (w), 2851 (w), 1668 (w), 1618 (m), 1599 (m), 1574 (w), 1508 (w), 1445 (w), 1422 (w), 1395 (m), 1375 (m), 1323 (w), 1300 (w), 1279 (w), 1233 (m), 1209 (w), 1175 (s), 1144 (m), 1124 (m), 1090 (w), 1082 (w), 1051 (w), 1032 (w), 1013 (w), 988 (m), 835 (w), 810 (w), 760 (m), 750 (m), 737 (s), 706 (w), 675 (s), 656 (w), 621 (w). EI MS (70 eV, m/z (%)): 643 ($[M]^+$, 14), 488 ($[C_{31}H_{26}N_3O_3]^+$, 39), 439 ($[C_{26}H_{21}N_3O_2S]^+$, 17), 438 ($[C_{26}H_{20}N_3O_2S]^+$, 21), 326 ($[C_{21}H_{16}N_3O]^{2+}$, 62), 284 ($[C_{19}H_{14}N_3]^+$, 36), 283 (19), 282 (16), 269 (15), 257 (19), 256 ($[C_{17}H_{10}N_3]^{4+}$, 51), 255 (20), 135 (100), 91 ($[C_7H_7]^+$, 20). Anal. Calcd. For $C_{38}H_{33}N_3O_5S$ (643.76): C 70.90, H 5.17, N 6.53, S 4.98; found: C 70.86, H 5.12, N 6.39, S 4.82.

*2.21. rac-1-(4-Methylbenzoyl)-12b-(1-tosyl-1H-indol-3-yl)-2,3,6,7,12,12b-hexahydroindolo-[2,3-a]quinolizin-4(1H)-one (**5s**)*

According to the GP, compound **5s** (458 mg, 36%) was isolated as a colorless solid, Mp 293–296 °C, R_f = 0.29 (n-hexane/ethyl acetate 1:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.01–2.07 (m, 1H), 2.32 (s, 3H), 2.36–2.44 (m, 4H), 2.66 (dd, $^2J_{HH}$ = 15.5 Hz, $^3J_{HH}$ = 4.0 Hz, 1H), 2.72 (ddd, $^2J_{HH}$ = 18.1 Hz, $^3J_{HH}$ = 11.2 Hz, $^3J_{HH}$ = 6.8 Hz, 1H), 2.82 (td, $^2J_{HH}$ = $^3J_{HH}$ = 12.5 Hz, $^3J_{HH}$ = 4.2 Hz, 1H), 2.93 (ddd, $^2J_{HH}$ = 18.2 Hz, $^3J_{HH}$ = 5.7 Hz, $^3J_{HH}$ = 3.1 Hz, 1H), 3.03 (ddd, $^2J_{HH}$ = 15.6 Hz, $^3J_{HH}$ = 12.0 Hz, $^3J_{HH}$ = 5.4 Hz, 1H), 4.15 (dd, $^2J_{HH}$ = 12.1 Hz, $^3J_{HH}$ = 3.0 Hz, 1H), 4.93–4.97 (m, 1H), 7.11–7.16 (m, 5H), 7.17–7.24 (m, 2H), 7.25–7.29 (m, 2H, superimposed by $CDCl_3$), 7.32 (dd, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 1.1 Hz, 1H), 7.38 (d, $^3J_{HH}$ = 8.1 Hz, 1H), 7.47 (d, $^3J_{HH}$ = 8.0 Hz, 2H), 7.52 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 7.59 (d, $^4J_{HH}$ = 1.1 Hz, 1H), 7.67–7.71 (m, 2H), 7.89 (d, $^3J_{HH}$ = 8.3 Hz, 1H), 8.77 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 21.02 (CH_2), 21.75 (CH_3), 21.77 (CH_3), 23.32 (CH_2), 32.46 (CH_2), 38.58 (CH_2), 53.35 (CH), 63.16 (C_{quat}), 110.37 (C_{quat}), 111.85 (CH), 113.93 (CH), 118.82 (CH), 120.18 (CH), 120.79 (CH), 122.55 (C_{quat}), 122.93 (CH), 124.07 (CH), 124.76 (CH), 126.49 (C_{quat}), 127.14 (2CH), 128.19 (2CH), 128.34 (CH), 129.31 (C_{quat}), 129.62 (2CH), 129.90 (2CH), 134.48 (C_{quat}), 134.96 (C_{quat}), 134.98 (C_{quat}), 135.79 (C_{quat}), 135.91 (C_{quat}), 144.66 (C_{quat}), 145.05 (C_{quat}), 169.15 (C_{quat}), 201.80 (C_{quat}). IR: $\widetilde{\nu}$ [cm^{-1}] 3323 (w), 3285 (w), 3238 (w), 1668 (w), 1618 (s), 1580 (w), 1491 (w), 1447 (m), 1420 (w), 1396 (w), 1377 (m), 1344 (w), 1323 (w), 1300 (w), 1279 (w), 1263 (w), 1236 (w), 1209 (w), 1186 (m), 1175 (m), 1144 (m), 1125 (m), 1086 (w), 1053 (w), 1022 (w), 988 (m), 957 (w), 837 (w), 810 (w), 748 (s), 704 (w), 675 (s), 656 (w). EI MS (70 eV, m/z (%)): 627 ($[M]^+$, 14), 473 (15), 472 ($[C_{31}H_{26}N_3O_2]^+$, 47), 438 ($[C_{26}H_{20}N_3O_2S]^+$, 25), 327 (22), 326 ($[C_{21}H_{16}N_3O]^{2+}$, 88), 323 (16), 298 ($[C_{19}H_{12}N_3O]^{4+}$, 20), 285 (20), 284 ($[C_{19}H_{14}N_3]^+$, 55), 283 (31), 282 (25), 269 (19), 257 (28), 256 ($[C_{17}H_{10}N_3]^{4+}$, 75), 255 (30), 119 ($[C_8H_7O]^+$, 100), 91 ($[C_7H_7]^+$, 72). Anal. Calcd. For $C_{38}H_{33}N_3O_4S$ (627.76): C 72.71, H 5.30, N 6.69, S 5.11; found: C 72.91, H 5.34, N 6.55, S 5.03.

*2.22. Methyl (6S)-12b-Butyl-1-(6-chloronicotinoyl)-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo-[2,3-a]quinolizin-6-carboxylate (**5t**)*

According to the GP, compound **5t** (198 mg, 20%) was isolated as a colorless solid, Mp 220–230 °C, R_f = 0.33 (n-hexane/ethyl acetate 5:7). $[\alpha]_D^{25}$: +92° (c = 1 mg/mL, CH_2Cl_2), ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.79 (t, $^3J_{HH}$ = 7.0 Hz, 3H), 1.19–1.25 (m, 4H), 2.57–2.65 (m, 1H), 2.81–2.89 (m, 2H), 3.13 (dd, $^2J_{HH}$ = 16.0 Hz, $^3J_{HH}$ = 6.9 Hz, 1H), 3.47 (dd, $^2J_{HH}$ = 16.0 Hz, $^3J_{HH}$ = 2.7 Hz, 1H), 3.69 (s, 3H), 5.05–5.11 (m, 1H), 5.58 (dd, $^2J_{HH}$ = 6.9 Hz, $^3J_{HH}$ = 2.6 Hz, 1H), 7.08–7.19 (m, 3H), 7.42 (d, $^3J_{HH}$ = 8.4 Hz, 1H), 7.48 (d, $^3J_{HH}$ = 7.7 Hz, 1H), 7.95 (s, 1H), 8.17 (dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 2.5 Hz, 1H), 8.99 (d, $^4J_{HH}$ = 2.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.08 (CH_3), 22.62 (CH_2), 22.67 (CH_2), 22.84 (CH_2), 25.68 (CH_2), 30.08 (CH_2), 37.40 (CH_2), 51.45 (CH), 52.80 (CH_3), 55.10 (CH), 63.05 (C_{quat}), 108.39 (C_{quat}), 111.51

(CH), 118.54 (CH), 120.18 (CH), 122.92 (CH), 124.83 (CH), 125.48 (C_{quat}), 131.34 (C_{quat}), 133.81 (C_{quat}), 136.43 (C_{quat}), 138.54 (CH), 150.61 (CH), 156.80 (C_{quat}), 172.93 (C_{quat}), 173.14 (C_{quat}), 204.15 (C_{quat}). IR: $\tilde{\nu}$ [cm^{-1}] 3377 (w), 3055 (w), 2955 (w), 2926 (w), 2860 (w), 2359 (w), 1726 (m), 1688 (m), 1630 (s), 1574 (w), 1555 (w), 1472 (w), 1445 (w), 1406 (m), 1381 (w), 1354 (w), 1337 (m), 1304 (m), 1288 (w), 1275 (w), 1261 (w), 1224 (m), 1206 (w), 1177 (w), 1148 (w), 1126 (m), 1099 (m), 1067 (w), 1013 (w), 974 (w), 962 (w), 943 (w), 912 (w), 839 (w), 787 (w), 766 (w), 743 (s), 712 (w), 677 (w), 633 (w). EI MS (70 eV, m/z (%)): 495 ([M(^{37}Cl)]$^+$), 493 ([M(^{35}Cl)]$^+$, 4), 438 ([$C_{23}H_{19}{}^{37}ClN_3O_4$]$^+$, 16), (16), 437 (12), 436 ([$C_{23}H_{19}{}^{35}ClN_3O_4$]$^+$, 49), 283 (10), 237 ([$C_{15}H_{13}N_2O$]$^{3+}$, 15), 225 ([$C_{15}H_{17}N_2$]$^{2+}$, 21), 195 (16), 183 (17), 182 (26), 181 ([$C_{12}H_9N_2$]$^{5+}$, 10), 142, ([$C_6H_3{}^{37}ClNO$]$^+$, 33), 140 ([$C_6H_3{}^{25}ClNO$]$^+$, 100), 112 (14). Anal. calcd. for $C_{27}H_{28}ClN_3O_4$ (493.99): C 65.65, H 5.71, N 8.51; found: C 65.43, H 5.51, N 8.23.

*2.23. Methyl (6S)-1-(4-Bromobenzoyl)-12b-butyl-4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo-[2,3-a]quinolizin-6-carboxylate (**5u**)*

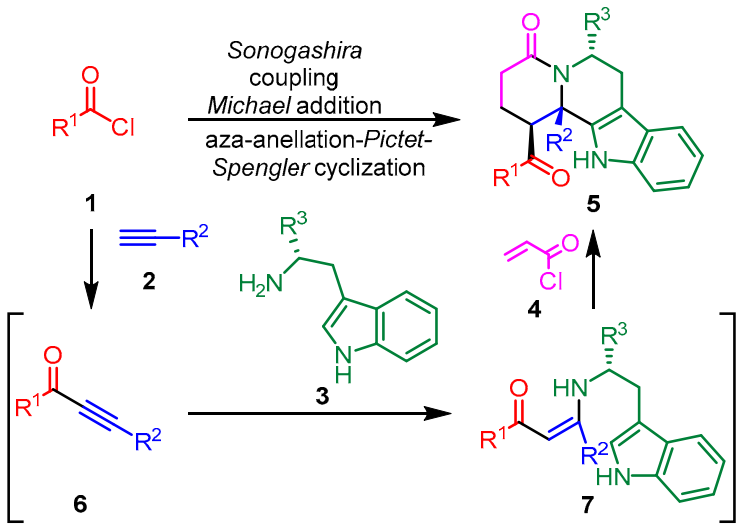
According to the GP, compound **5u** (195 mg, 18%) was isolated as a yellow solid, Mp 245–248 °C, R_f = 0.19 (n-hexane/ethyl acetate 7:3). $[\alpha]_D{}^{25}$: +58° (c = 1 mg/mL, CH_2Cl_2), ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.86 (t, $^3J_{HH}$ = 7.3 Hz, 3H), 1.07–1.15 (m, 1H), 1.17–1.23 (m, 1H), 1.27 1.36 (m, 2H), 2.00–2.08 (m, 1H), 2.30–2.44 (m, 2H), 2.59 (ddd, $^2J_{HH}$ = 14.7 Hz, $^3J_{HH}$ = 12.7 Hz, $^3J_{HH}$ = 4.2 Hz, 1H), 2.85 (ddd, $^2J_{HH}$ = 18.5 Hz, $^3J_{HH}$ = 10.3 Hz, $^3J_{HH}$ = 5.8 Hz, 1H), 2.91–3.00 (m, 2H), 3.61 (s, 4H), 3.83 (dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 5.6 Hz, 1H), 6.08–6.18 (m, 1H), 7.04–7.10 (m, 3H), 7.34–7.46 (m, 4H), 7.50–7.58 (m, 1H), 7.74 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 14.24 (CH_3), 21.36 (CH_2), 21.39 (CH_2), 23.64 (CH_2), 26.72 (CH_2), 29.89 (CH_2), 35.62 (CH_2), 50.73 (CH), 52.36 (CH_3), 53.94 (CH), 62.73 (C_{quat}), 108.69 (C_{quat}), 111.09 (CH), 118.66 (CH), 119.97 (CH), 122.76 (CH), 126.04 (C_{quat}), 129.12 (C_{quat}), 129.33 (2CH), 132.09 (2CH), 132.58 (C_{quat}), 135.54 (C_{quat}), 136.10 (C_{quat}), 171.19 (C_{quat}), 171.39 (C_{quat}), 202.11 (C_{quat}). IR: $\tilde{\nu}$ [cm^{-1}] 3275 (w), 3057 (w), 2953 (w), 2928 (w), 2901 (w), 2870 (w), 2857 (w), 1736 (m), 1672 (m), 1630 (s), 1584 (m), 1566 (w), 1483 (w), 1454 (m), 1435 (m), 1387 (s), 1356 (m), 1327 (m), 1292 (m), 1279 (m), 1254 (m), 1202 (s), 1179 (m), 1167 (m), 1153 (m), 1109 (m), 1070 (m), 1028 (m), 1007 (s), 970 (m), 912 (w), 889 (w), 839 (m), 812 (m), 741 (s), 679 (m). EI MS (70 eV, m/z (%)): 538 ([M(^{81}Br)]$^+$, 3), 536 ([M(^{79}Br)]$^+$, 3), 481 ([$C_{24}H_{20}BrN_2O_4$(^{81}Br)]$^+$, 33), 479 ([$C_{24}H_{20}BrN_2O_4$(^{79}Br)]$^+$, 27), 283 ([$C_{16}H_{15}N_2O_3$]$^{3+}$, 33), 242 (17), 225 ([$C_{15}H_{17}N_2$]$^{2+}$, 33), 201 (13), 195 (13), 185 ([C_7H_4BrO(^{81}Br)]$^+$, 66), 184 (10), 183 ([C_7H_4BrO(^{79}Br)]$^+$, 100), 182 (26), 155 (11), 130 (31). HR-ESI MS calcd. for $C_{28}H_{30}BrN_2O_4$: 537.1383. Found: 537.1375. HPLC (245 nm): t_R = 5.4 min, 99%. Anal. calcd. for $C_{28}H_{29}BrN_2O_4$ (537.45): C 62.57, H 5.44, N 5.21; found: C 61.68, H 5.67, N 4.93.

3. Results and Discussion

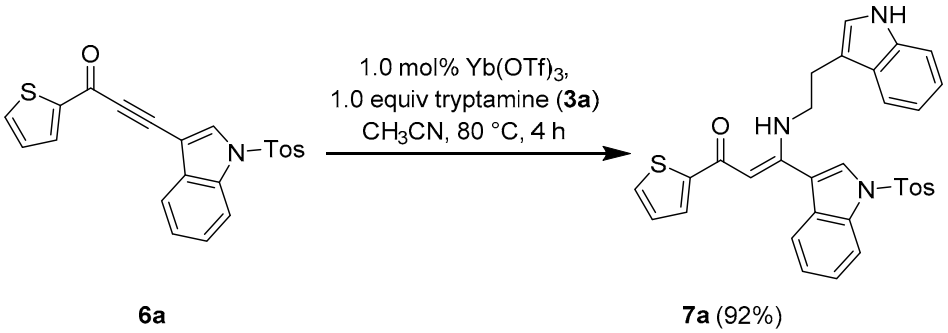
According to Karpov's CAAPS synthesis of THBC, enaminones **7** prepared from acid chlorides **1**, alkynes **2,** and amines **3** via *Sonogashira* alkynylation and *Michael* addition are the second intermediates (Scheme 1) [13,14].

Previous calculations concerning the transition state of the addition of an amine to an acceptor-substituted alkyne strongly support a two-step mechanism, where methanol as a co-additive stabilizes the zwitterion intermediate [16]. However, since acryloyl chloride (**4**) is a reactive electrophile in the further course of the sequence, methanol as a nucleophilic cosolvent turns out to be incompatible. As an alternative to the polar solvent additive, an excess of amine **3** gives reasonable yields of enaminones **7**, but a catalytic approach would be preferable to avoid the use of overstoichiometric reagents [13,17–19]. As described in the literature, bismuth, yttrium, scandium, and ytterbium salts with weakly coordinating counterions have already been successfully employed as catalysts for *Michael* and aldol additions [20–22]. Since ytterbium (III) triflate shows a high tolerance to various solvents, this Lewis acid catalyst was chosen for the *Michael* addition step in the sequence [23]. After a short optimization study with selected ynones **6a** and one equivalent of tryptamine (**3a**) as a model reaction furnished the desired enaminone **7a** in excellent yield using only 1 mol% ytterbium (III) triflate as a catalyst (Scheme 2). It is noteworthy that the

uncatalyzed reactions only showed incomplete conversion after up to 48 h (see Table S1, Supplementary Information).



Scheme 1. Four-component CAAPS synthesis of substituted THBC **5**.



Scheme 2. Optimized model reaction of the ytterbium triflate catalyzed *Michael* addition of ynone **6a** and tryptamine (**3a**) to give enaminone **7a**.

Lewis acid-catalyzed *Michael* additions proceeds smoothly in dichloromethane or acetonitrile as solvents, whereas a much lower conversion is observed in tetrahydrofuran (THF). This observation matches the finding that the catalytic activity of ytterbium triflate is reduced in aldol reactions of silyl enol ethers and formaldehyde [24].

The implementation of the optimized ytterbium triflate catalyzed *Michael* addition to give the central enaminone intermediate in the consecutive four-component CAAPS sequence furnished a library of 21 THBCs **5** in yields of 18–56% in a one-pot process (Figure 1). Since the CAAPS sequence comprises alkynylation, *Michael* addition, aza-anellation, and *Pictet–Spengler* cyclization (which amounts to five bond forming steps), an overall yield within a range between 18 and 56% adds up to 71–89% per bond forming step, which makes the one-pot process quite efficient.

The initial *Sonogashira* coupling of acid chlorides **1** with alkynes **2** proceeded efficiently in dichloromethane as a solvent within 1–2 h by using only a single equivalent of triethylamine as a base. Poor solubility of ytterbium (III) triflate and tryptamine (**3a**) in the *Michael* step (which led to suspensions and prolonged reaction times) was overcome by the addition of acetonitrile as a cosolvent (CH_2Cl_2/CH_3CN 1:1) and by placing the reaction vessel in an oil bath at 80 °C. Acetonitrile, as the sole solvent medium, was discarded due to incomplete conversions of some substrates in the initial *Sonogashira* step. The lower effective concentration in the *Michael* step required a longer reaction time of 16 h for full conversion. The

terminal aza-anellation *Pictet–Spengler* step proceeded at 70 °C in the same reaction vessel to terminate the sequence and to give THBCs **5** after a single chromatographic purification.

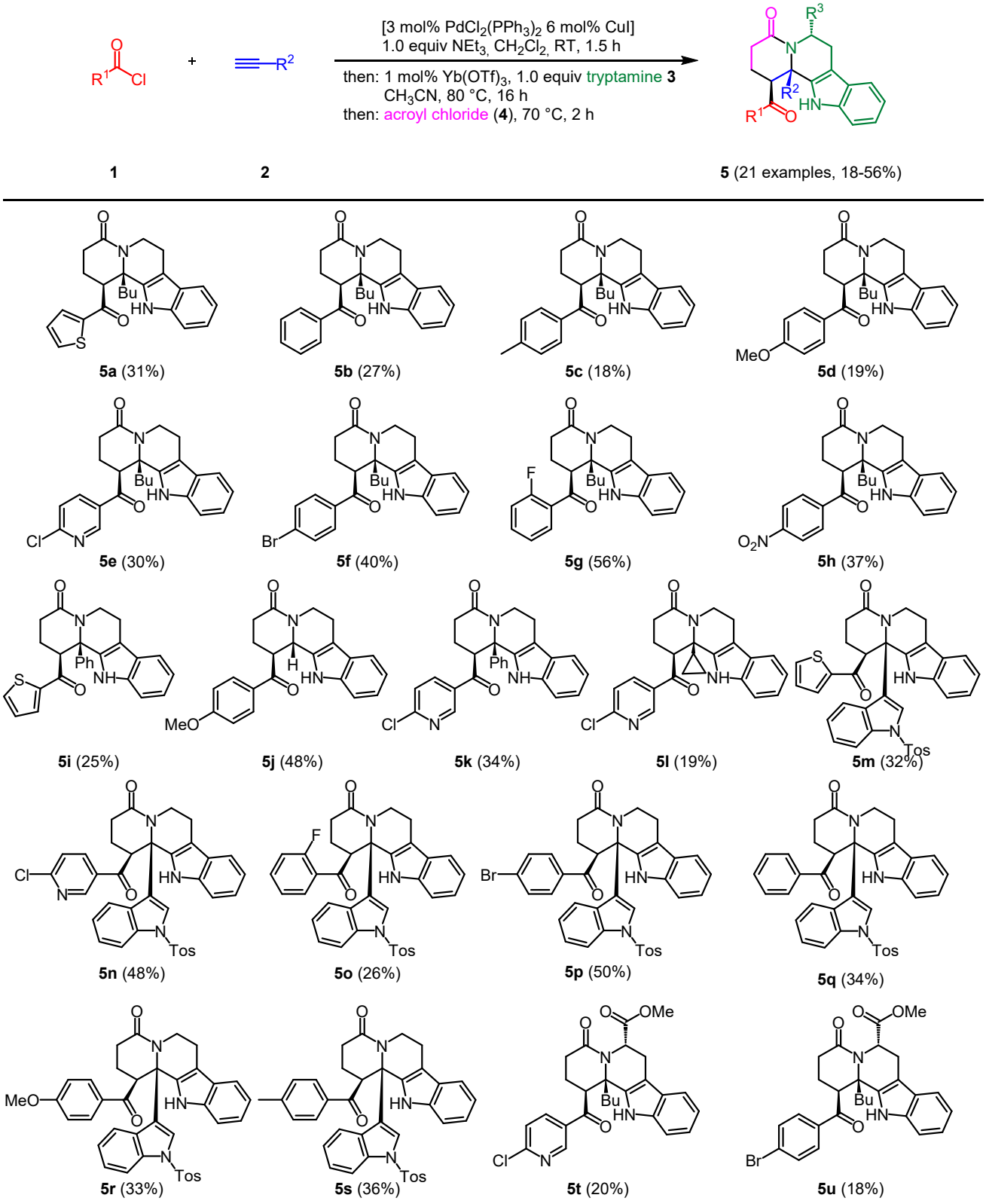


Figure 1. Library of THBC **5** synthesized by modified CAAPS sequence.

The scope of acid chlorides **1** (R^1) allowed for electron-rich and electron-deficient aromatic and heteroaromatic substituents, the alkynes **2** can be aliphatic, aromatic, and heterocyclic substituents (R^2) and, besides tryptamine (**3a**), *L*-tryptophan methyl ester (**3c**) was also well tolerated in the *Michael* addition.

The structures of the THBCs **5** were unambiguously assigned by NMR spectroscopy and mass spectrometry. The occurrence of a single set of signals in the ^{1}H and ^{13}C NMR spectra confirms the highly selective formation of the *syn*-diastereomer. This can be rationalized by a highly diastereofacial formation of the contiguous stereocenters in the aza-anellation *Pictet–Spengler* step [13]. As expected, the products formed from enantiomerically pure *L*-tryptophan were obtained as a single diastereomer [25–27].

In the ^{1}H spectra ($CDCl_3$, 600 MHz), the relevant signals of the protons 1–7 of the quinolizinone core (Figure 2) appeared within the range δ 1.80–6.10 and were split into diastereotopic signals with a characteristic coupling pattern due to the neighboring stereocenters. The assignment of the corresponding protons was performed by HSQC and COSY experiments. The signals that most strongly shifted to low field at δ 4.90–6.10 could be assigned to the protons 7-H_α, which experienced the strongest de-shielding by the adjacent amide nitrogen atom.

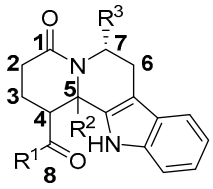


Figure 2. Locant set of hexahydroquinolizinone core of THBC **5** (R^3 = H, CO_2Me).

They usually appeared as a doublet of doublets of doublets, with coupling constants of $^2J_{HH}$ = 12.9–13.0 Hz, $^3J_{HH}$ = 5.0–5.1 Hz, and $^3J_{HH}$ = 1.5–1.7 Hz. In contrast, if the resolution of the 7-H_α signal was too low, only a doublet of doublets with coupling constants of $^2J_{HH}$ = 12.5–13.0 Hz and $^3J_{HH}$ = 4.6–5.4 Hz could be observed. Due to the geminal ester group, the 7-H_α resonance for methyl ester **5t** only appeared as a doublet of doublets, with coupling constants of $^3J_{HH}$ = 6.9 Hz and $^3J_{HH}$ = 2.6 Hz. The signals of the C_4 protons could be readily identified from the HSQC spectra since they exhibited only one CH coupling and were usually found at δ 3.70–4.20. In the case of the indole-substituted hexahydroquinolizinones **5m**-**5s**, they appeared as doublets of doublets, with coupling constants of $^3J_{HH}$ = 11.0–12.1 Hz and $^3J_{HH}$ = 3.0–3.2 Hz, whereas the C_4-H resonances of the remaining THBC **5** could be observed with coupling constants of $^3J_{HH}$ = 13.1–13.6 Hz and $^3J_{HH}$ = 4.7–5.1 Hz. Compounds **5j** and **5t** formed the exception, whose C_4 proton signals were observed deep field shifted at chemical shifts of δ 5.20 and 5.10, respectively. All other proton signals of the quinolizinone nucleus could not always be clearly identified for each spectrum and often overlapped with the signals of the butyl or methyl substituents. However, in the NMR spectrum of THBC **5r**, the aliphatic proton signals were sufficiently separated to make an exemplary assignment. Compared with 7-H_α, the 7-H_β signal was clearly shifted to high field and appeared as a triplet of doublets at δ 2.84, with coupling constants of $^2J_{HH}$ = $^3J_{HH}$ = 12.5 Hz and $^3J_{HH}$ = 4.2 Hz. Proton 2-H_α could be assigned to the resonance at δ 2.97 and presented itself as a doublet of doublets of doublets, with coupling constants of $^2J_{HH}$ = 18.3 Hz, $^3J_{HH}$ = 5.7 Hz, and $^3J_{HH}$ = 3.4 Hz. The signal for 2-H_β appeared at a chemical shift of δ 2.74 and split into a doublet of doublets of doublets, with coupling constants of $^2J_{HH}$ = 18.0 Hz, $^3J_{HH}$ = 10.8 Hz, and $^3J_{HH}$ = 6.8 Hz. Furthermore, the 6-H_α proton signal could be observed at δ 3.03 and appeared as a doublet of doublets of doublets, with coupling constants of $^2J_{HH}$ = 15.4 Hz, $^3J_{HH}$ = 12.1 Hz, and $^3J_{HH}$ = 5.5 Hz. The signal for 6-H_β appeared as a multiplet at δ 2.63–2.69. Of all the diastereotopic protons of the quinolizine core, the 3-H proton signals were most shifted to high field and appeared as multiplets at δ 2.36–2.46 for 3-H_α and δ 2.01–2.07 for 3-H_β.

All the recorded ^{1}H NMR spectra support the strict diastereoselectivity of the presented MCR, forming a single diastereomer of compound **5**. As reported previously, the concluding Pictet–Spengler step, which essentially represents an intramolecular electrophilic aromatic substitution at the pyrrole fragment of the indole core, determines the relative *syn*-relation between the substituents at carbon centers C_4 and C_5 in the pyridone part [13]. The previously observed *syn*-orientation of the substituent at C_3 demands a cyclic rather than an open transition state of the aza-anellation step, which suggests two alternative mechanistic scenarios via pericyclic elementary steps (Figure 3). On the one hand, nitrogen attack of the (*Z*)-configured enaminone **7** on the carbonyl function of acryloyl chloride (**4**) and condensation could result in an azonia hexatriene structure **8**, which could undergo a disrotatory ring closure to the dihydropyridinium enol intermediate **9** (electrocyclization pathway), which could easily tautomerize to the acyliminium ion **11**. The electrophilic iminium moiety in **11** could attack the indole with the face opposite to the adjacent carbonyl substituent, resulting in a *syn*-orientation of carbonyl substituent and R^2 [28].

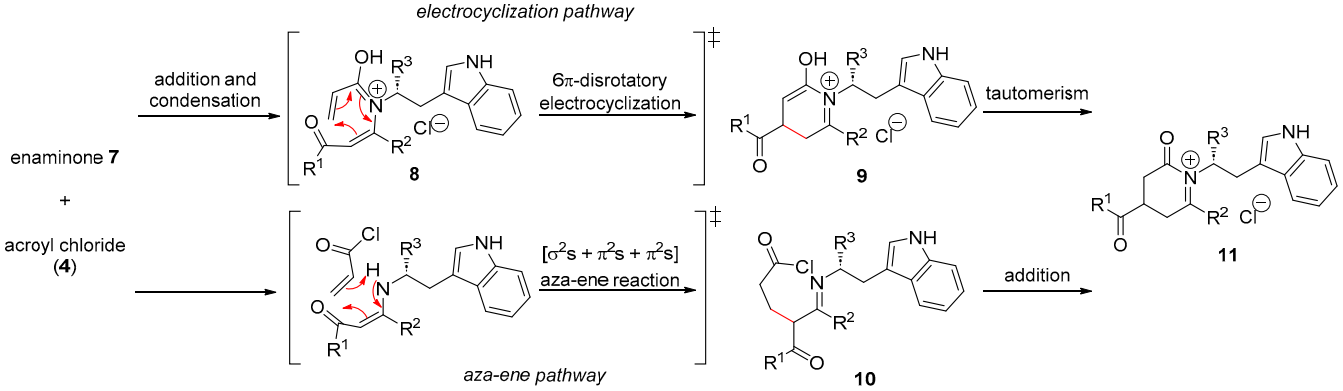


Figure 3. Electrocyclization or aza–ene reaction as proposed mechanisms for the aza-anellation step (red arrows indicate pericyclic movement of electrons in a cyclic transition state).

Alternatively, the aza-anellation [27] could be initiated by ene reaction [29,30] with enaminone **7** as the ene component and acryloyl chloride (**4**) as an enophile (aza–ene pathway), which represents a rare example, as aza–enes are seldom employed in inter- and intramolecular ene reactions [31–33]. The (*Z*)-configured enaminone **7** and acryloyl chloride (**4**) give rise to an envelope conformation of the transition state, leading to the acid chloride **10**, which cyclizes to the acyliminium ion **11** by the intramolecular attack of the imine nitrogen atom on the acid chloride moiety. Thereafter, the acyliminium ion **11** enters the intramolecular electrophilic ring closure with the indole, i.e., the Pictet–Spengler anellation, as already outlined above, to furnish *syn*-configured THBCs **5** [28].

Discrimination between both plausible alternatives for the aza-anellation Pictet–Spengler sequence can be made by calculation of the transition state energies of both pathways, namely via the envisioned initial pericyclic steps. As a computational model, diphenyl-substituted enaminone **7b** and acryloyl chloride (**4**) were chosen as starting points and DFT calculations with *Spartan '18* were performed, employing the standard B3LYP hybrid functional and the 6–31G* basis set using the conductor-like polarizable continuum model (C-PCM) [34] with a dipolar aprotic implicit dielectric medium with a dielectric constant of 37.22 (e.g., DMF) to mimic the mixture of dichloromethane and acetonitrile (Figure 4).

The electrocyclization pathway (in red) commences by condensation of acryloyl chloride (**4**) and enaminone **7b**, giving an azonia hexatriene system **8**. Energetically, the formation of intermediate **8** is endothermic by 27.47 kJ/mol. Disrotatory 6π-electro cyclization proceeds via transition state $\mathbf{TS_{8\rightarrow 9}}$, which lies 140.33 kJ/mol above the starting point, to give the hydroxy dihydropyridinium intermediate **9**, which is formed exothermically and lies energetically close to the aza–ene product **10**. The aza–ene pathway (in green) directly proceeds from acryloyl chloride (**4**) and the enaminone **7b** to exothermically give the aza–

ene product **10**, which lies 18.83 kJ/mol lower in energy with respect to the starting point. With 82.39 kJ/mol, the computed transition state $\mathbf{TS_{(4+7b)\rightarrow 10}}$ of the aza–ene reaction lies almost 58 kJ/mol lower in energy than the transition state $\mathbf{TS_{8\rightarrow 9}}$ of the electrocyclization pathway. This clearly speaks for the aza–ene reaction as the operative mechanism based upon our computational kinetic reasoning. The remainder of the sequence after the exothermic formation of the acyliminium ion **11** represents the Pictet–Spengler anellation, which was also calculated, referencing the energies of the intermediates and transition states to the starting point of acryloyl chloride (**4**) and enaminone **7b**. The intramolecular electrophilic attack of the acyliminium ion **11** on the tethered indole moiety gives slightly exothermically the spirocyclic intermediate **12** via a transition state $\mathbf{TS_{11\rightarrow 12}}$ that lies 68.48 kJ/mol above the acyliminium ion **11**. The subsequent Wagner–Meerwein rearrangement proceeds slightly endothermically to carbenium ion **13** via a transition state $\mathbf{TS_{12\rightarrow 13}}$ that lies 31.55 kJ/mol above the spirocyclic intermediate **12**. Finally, the carbenium ion **13** aromatizes to the indole structure **14**, which lies 79.37 kJ/mol below the starting point and represents the global energy minimum in this calculated scenario.

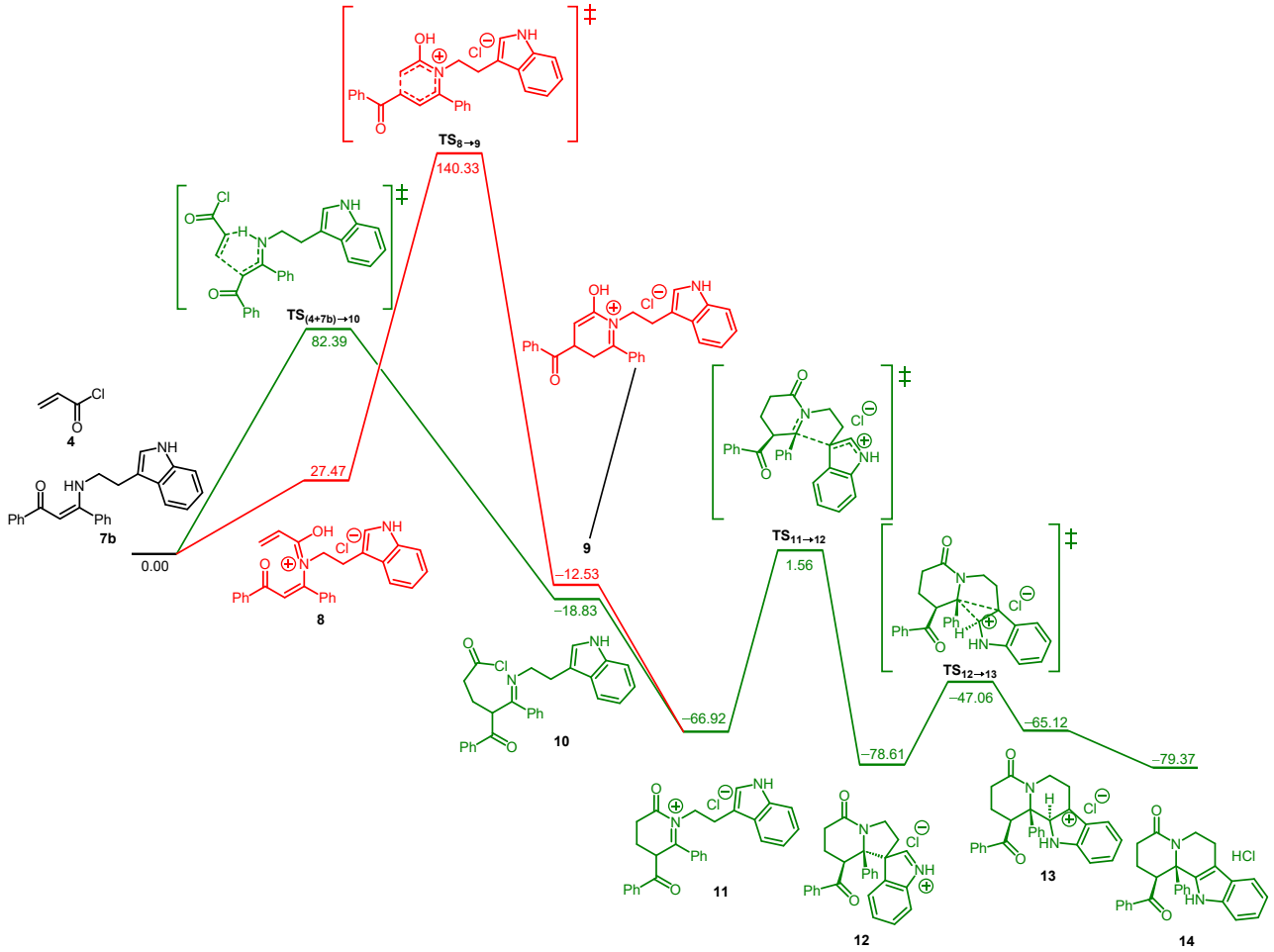


Figure 4. DFT calculations (B3LYP/G-31G*, C-PCM = DMF to mimic CH_2Cl_2/acetonitrile mixtures) of the electrocyclization pathway (red) and aza–ene pathway (green) of the aza-anellation *Pictet–Spengler* sequence of enaminone **7b** and acryloyl chloride (**4**) to give the THBC **14** (dotted lines indicate delocalized electrons in transition states; energies are given in kJ/mol).

Based on the respective activation barriers of the aza–ene reaction (+82.39 kJ/mol) and the electrocyclization (+112.86 kJ/mol), we propose that the aza–ene pathway is the operative mechanism as well as the rate-determining step of the overall sequence, as all subsequent steps possess lower activation barriers.

4. Conclusions

Ytterbium triflate not only efficiently catalyzes the *Michael* addition of tryptamines to ynones to form enaminones, but it can readily be implemented in the four-component CAAPS sequence for the synthesis of tetrahydro-*β*-carbolines. Thereby, acid chlorides, alkynes, tryptamines, and triethylamine could be employed in equistoichiometric amounts to generate the enaminone, which reacted in the terminal step of the sequence with acryloyl chloride to give the desired products. The scope shows that a quite dense and electronically variable substitution could be readily introduced to the central hexahydroquinolizinone core, employing acid chlorides and alkyne substrates as points of diversity.

Mechanistic insight into the aza-anellation *Pictet–Spengler* step was achieved by DFT calculations on two potential pericyclic pathways that can furnish the crucial acyliminium ion intermediate, which terminates the sequence via *Pictet–Spengler* anellation. The computed transition state for the aza–ene reaction lies 30.47 kJ/mol lower in energy than the transition state for electrocyclization and represents the rate determining step of the aza-anellation *Pictet–Spengler* sequence. We therefore propose that a rate determining aza–ene reaction is the operative mechanism of the concluding steps of the CAAPS sequence.

The substance library of THBC analogues might contain potentially biologically active derivatives. Therefore, medicinal chemistry screening for biological activity is currently underway.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/org4030025/s1, Figures S1–S54: ^{1}H and ^{13}CNMR spectra of 3-iodo-1-tosyl-1*H*-indole, 1-tosyl-3-((trimethylsilyl)ethynyl)-1*H*-indole, 3-ethynyl-1-tosyl-1*H*-indole (**2e**), and compounds **3b**, **7a**, **5a–u**. xyz-Coordinates of the DFT computations of the structures (**4** + **7b**), **8–14**, and transition states $\mathbf{TS_{(4+7b)}\rightarrow_{10}}$, $\mathbf{TS_{8}\rightarrow_{9}}$, $\mathbf{TS_{11}\rightarrow_{12}}$, $\mathbf{TS_{12}\rightarrow_{13}}$. References [35–38] are cited in the Supplementary Materials.

Author Contributions: The work consists of parts of the planned Ph D thesis of K.R. and parts of the BSc thesis of F.A.A., which are and were supervised by T.J.J.M.; writing—original draft preparation, K.R.; writing—review and editing, F.A.A. and T.J.J.M.; computations: T.J.J.M.; project administration and funding acquisition was carried out by T.J.J.M. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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