Article

Consecutive four-component coupling-addition-aza-anellation-*Pictet-Spengler* synthesis of tetrahydro-*β*-carbolines – Optimized Michael addition and computational study on the aza-anellation step

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Abstract: Starting from acid chlorides, alkynes, tryptamines, and acroyl chloride, 21 densely substituted tetrahydro-*β*-carbolines are prepared in a four-component one-pot reaction. In this study, the aza-*Michael* addition step to generate intermediate enaminones is optimized in the presence of ytterbium triflate. Moreover, apart from acroyl chloride, all reactants can 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 rather proceeds via ene-reaction than via electrocyclization.

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

1. Introduction

Increased ecological demands challenge the chemical industry and lead to a growing interest to conduct 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 reacted *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 create very quickly 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.

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2. Materials and Methods

2.1. General Considerations and Instrumentation

All reactions were performed in Schlenk or multi-neck 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 for 0 °C or dry ice/isopropanol for –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 ^{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 are abbreviated as follows: s: singlet; d: doublet, dd: doublet of doublet; ddd: doublet of doublet of doublet; dt: doublet of a triplet; t: triplet; and 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*). Indicated are 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*), and 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 are 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, and 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 acroyl chloride (**4**) was added dropwise, and the mixture was heated at 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**.

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

entry	acid chloride 1 [mg] (mmol)	alkyne 2 [mg] (mmol)	acroyl 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[b]	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 imployed. 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%.

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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: $\tilde{\nu}$ [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.

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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: $\tilde{\nu}$ [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: $\tilde{\nu}$ [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: $\tilde{\nu}$ [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),

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696 (m), 665 ( ), 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: $\tilde{\nu}$ [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 **5j** (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%.

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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)-on (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, ücalclagert von $CDCl_3$), 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%.

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2.16. rac-1-(6-Chloronicotinoyl)-12b-(1-tosyl-1H-indol-3-yl)-2,3,6,7,12,12b-hexa-hydroindolo[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, ^{4}J = 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 (C_{quat}), 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: $\tilde{\nu}$ [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-hexa- hydroindolo[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, ^{3}jHH = 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: $\tilde{\nu}$ [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),

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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: $\tilde{\nu}$ [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: $\tilde{\nu}$ [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: $\tilde{\nu}$ [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.

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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: $\tilde{\nu}$ [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

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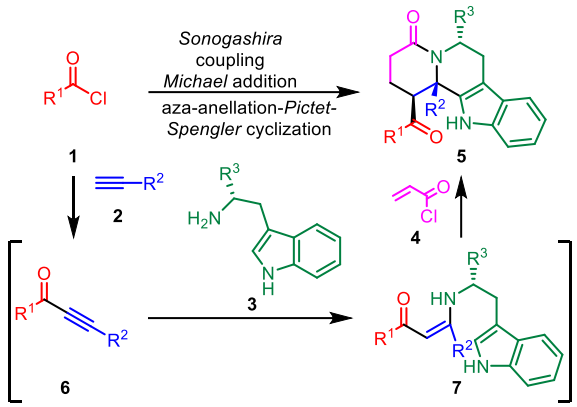
([$C_{24}H_{20}BrN_2O_4(^{79}Br)$]$^+$, 27), 283 ([$C_{16}H_{15}N_2O_3$]$^{3+}$, 33), 242 (17), 225 ([$C_{15}H_{17}N_2$]$^{2+}$, 33), 201 (13), 195 (13), 185 ([$C_7H_4BrO(^{81}Br)$]$^+$, 66), 184 (10), 183 ([$C_7H_4BrO(^{79}Br)$]$^+$, 100), 182 (26), 155 (11), 130 (31). HR-ESI MS calcd. for $C_{28}H_{30}BrN_2O_4$: 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.

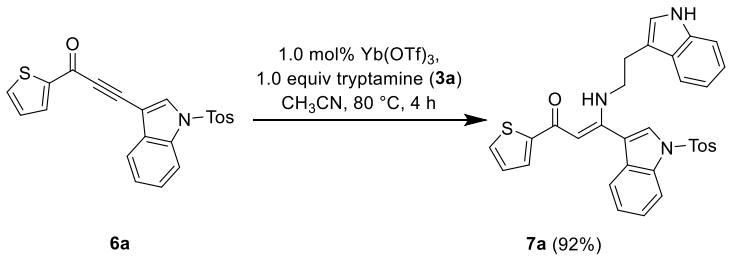
3. Results and Discussion

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].



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

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 coadditive stabilizes the zwitterion intermediate [16]. However, since acroyl 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 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]. In particular, 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 show incomplete conversion after up to 48 h (see Table S1, supplementary information).



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 proceed smoothly in dichloromethane or acetonitrile as solvents, whereas much lower conversion was observed in tetrahydrofuran (THF). This observation matches with 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 furnishes 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,

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and *Pictet-Spengler* cyclization, which amount to five bond forming steps, an overall yield in a range between 18-56% 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** proceeds 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 leads to suspensions and prolonged reaction times, is overcome by addition of acetonitrile as a cosolvent (CH_2Cl_2/CH_3CN 1:1) and placing the reaction vessel in an oil bath of 80 °C. Acetonitrile as the sole solvent medium has been discarded due to incomplete conversions of some substrates in the initial *Sonogashira* step. The lower effective concentration in the Michael step requires a longer reaction time of 16 h for full conversion. The terminal aza-anellation-*Pictet-Spengler* step proceeds at 70 °C in the same reaction vessel to terminate the sequence and to give after a single chromatographic purification the THBCs **5**.

The scope of acid chlorides **1** (R^1) allows 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**) also *L*-tryptophan methyl ester (**3c**) is well tolerated in the *Michael* addition.

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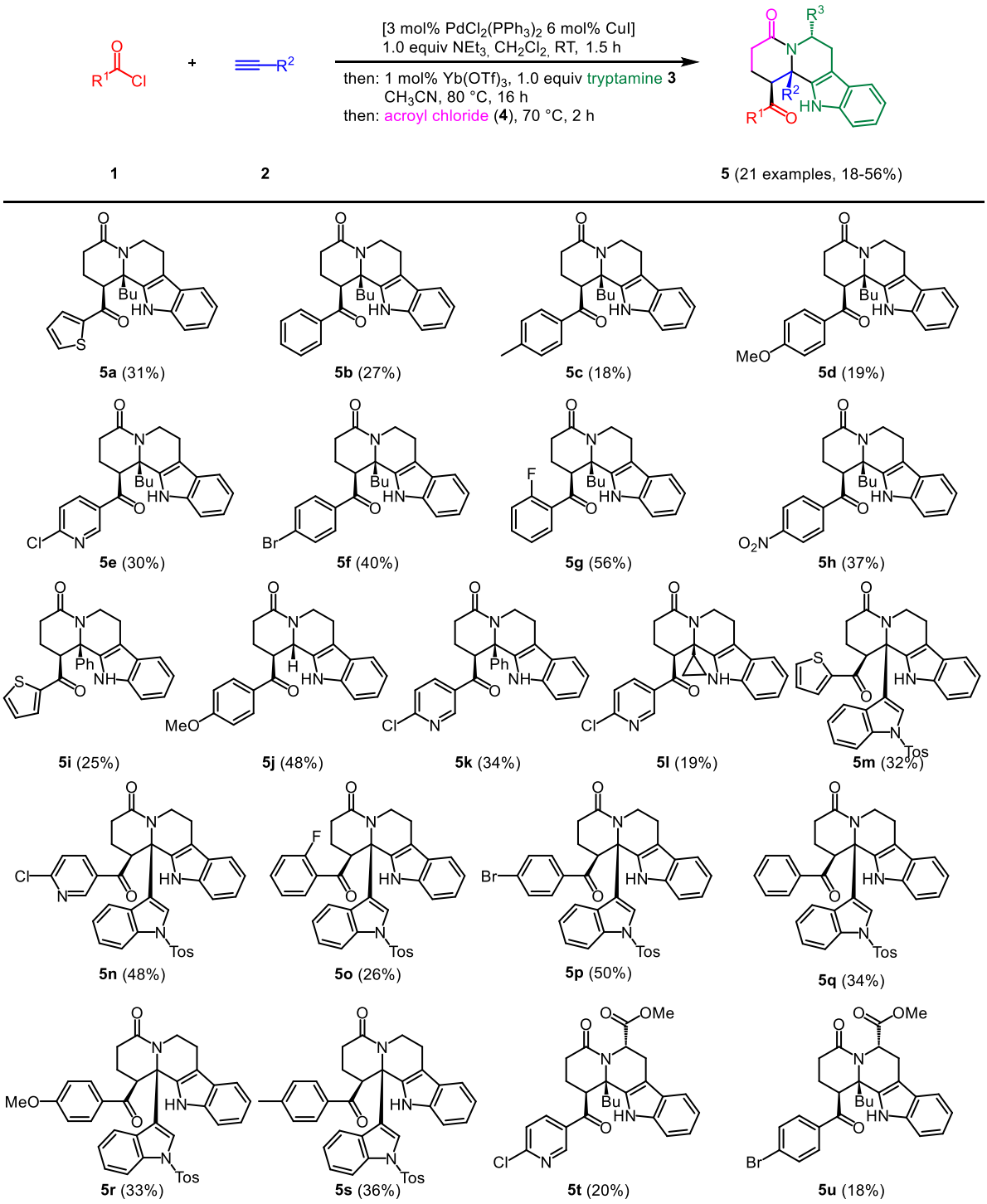

Figure 1. Library of THBC **5** synthesized by modified CAAPS sequence.

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 accounts for the highly selective formation of the *syn*-diastereomer. This can be rationalized by a highly diastererofacial 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.

In the ^{1}H spectra ($CDCl_3$, 600 MHz), the relevant signals of the protons 1-7of the quinolizinone core (Figure 2) appear in the range δ 1.8-6.1 and split into diastereotopic signals with characteristic coupling pattern due to the neighboring stereocenters. The assignment of the corresponding protons is done by HSQC and COSY experiments. The signals most strongly shifted to low field at δ 4.9-6.1 can be assigned to the protons 7-H_α, which experience the strongest deshielding by the adjacent amide nitrogen atom.

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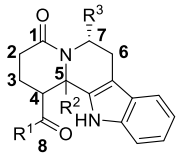

Figure 2. Locant set of hexahydroquinolizinone-core of THBC **5** (R^3 = H, CO_2Me).

They appear usually 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 is 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 can be observed. Due to the geminal ester group the 7-H_α resonance for methyl ester **5t** only appears 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 can be readily identified from the HSQC spectra since they exhibit only one CH coupling and are usually found at δ 3.7-4.2. In the case of the indole-substituted hexahydroquinolizinones **5m**-**5s**, they appear 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** can 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** form the exception, whose C_4 proton signals are observed deep field shifted at chemical shifts of δ 5.2 and 5.1 respectively. All other proton signals of the quinolizinone nucleus cannot always be clearly identified for each spectrum and often overlap with the signals of the butyl- or methyl substituents. However, in the NMR spectrum of THBC **5r**, the aliphatic proton signals are sufficiently separated to make an exemplary assignment. Compared to 7-H_α, the 7-H_β signal is clearly shifted to high field and appears 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 can be assigned to the resonance at δ 2.97 and presents 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 appears at a chemical shift of δ 2.74 and splits 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 can be observed at δ 3.03 and appears 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 appears as a multiplet at δ 2.63-2.69. Of all the diastereotopic protons of the quinolizine core the 3-H proton signals are most shifted to high field and appear 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 acroyl chloride (**4**) and condensation may result in an azonia-hexatriene structure **8**, which might undergo a disrotatory ring closure to the dihydropyridinium enol intermediate **9** (electrocyclization pathway), which can easily tautomerize to the acyliminium ion **11**. The electrophilic iminium moiety in **11** can attack the indole with the face opposite to the adjacent carbonyl substituent resulting in a *syn*-orientation of carbonyl substituent and R^2 [25].

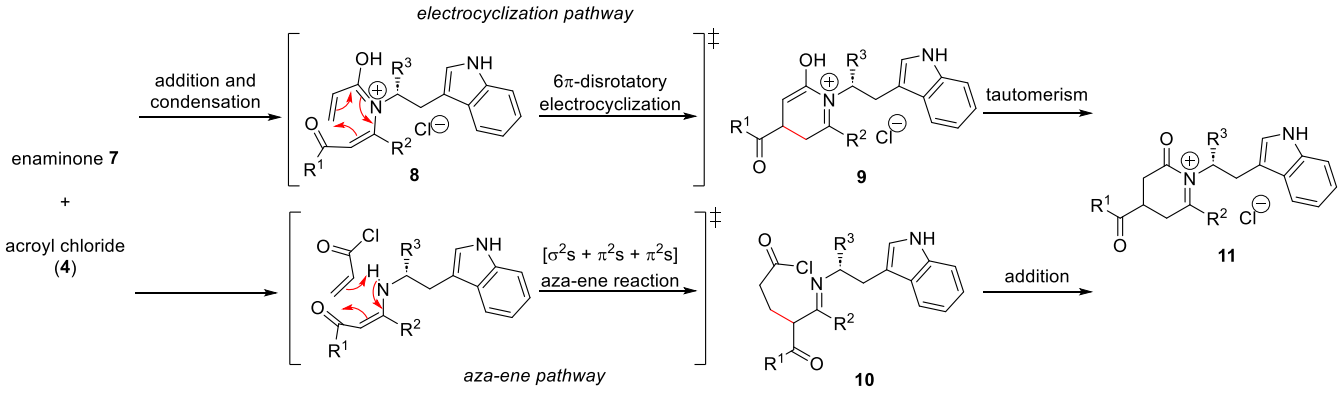

Figure 3. Electrocyclization or aza-ene reaction as proposed mechanisms for the aza-anellation step.

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Altenatively, the aza-anellation [26] can be initiated by ene reaction [27,28] with enaminone **7** as the ene component and acroyl chloride (**4**) as an enophile (aza-ene pathway), which represents a rare example as aza-enes are only infrequently employed in inter- and intramolecular ene reactions [29-31]. The (*Z*)-configured enaminone **7** and acroyl 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 intramolecular attack by 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** [26].

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 by the envisioned initial pericyclic steps. As a computational model diphenyl-substituted enaminone **7b** and acroyl chloride (**4**) were chosen as starting points and DFT calculations were performed employing the standard B3LYP hybrid functional and the G-31G* basis set using the conductor-like polarizable continuum model (C-PCM) [32] 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 acroyl 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 forms exothermically and lies energetically close to the aza-ene product **10**. The aza-ene pathway (in green) directly proceeds from acroyl 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 acroyl 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.

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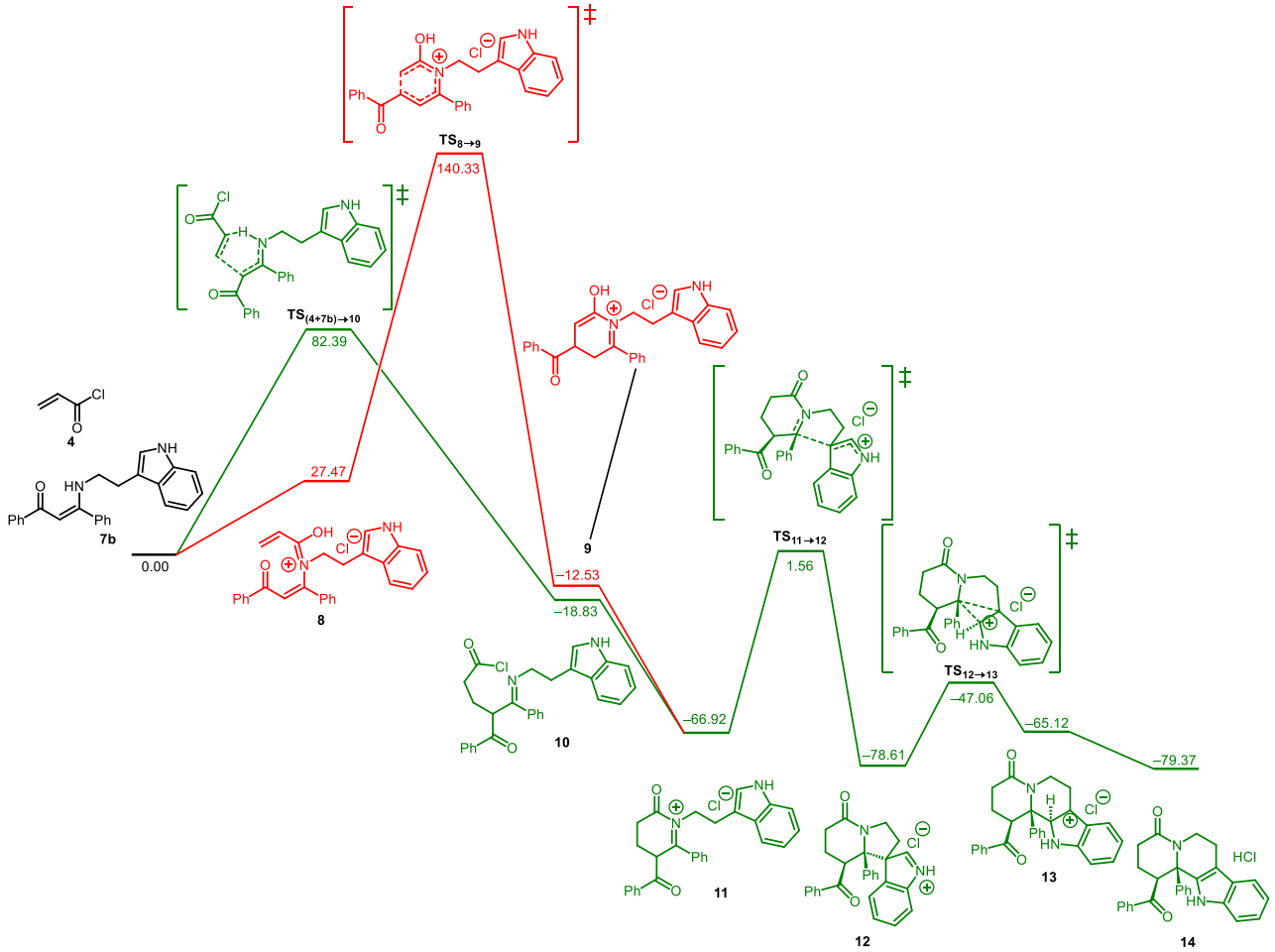

Figure 4. DFT calculations (B3LYP/G-31G*, C-PCM = DMF to mimic CH_2Cl_2/acetonitrile mixtures) of the electrocyclization pathway (red) and aza-ene pathway (green) of the aza-anellation *Pictet-Spengler* sequence of enaminone **7b** and acroyl chloride (**4**) to give the THBC **14** (energies are given 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 can be employed in equistoichiometric amounts to generate the enaminone, which reacts in the terminal step of the sequence with acroyl chloride to give the desired products. The scope shows that quite dense and electronically variable substitution can be readily introduced on 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 might 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 the website of this paper posted on Preprints.org, Figures S1-54: ^{1}H and ^{13}CNMR spectra of 3-iodo-1-tosyl-1*H*-

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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 $\mathbf{TS}_{(4+7b)\rightarrow 10}$, $\mathbf{TS}_{8\rightarrow 9}$, $\mathbf{TS}_{11\rightarrow 12}$, $\mathbf{TS}_{12\rightarrow 13}$.

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

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