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Total synthesis of new indolo[2,3-*a*]quinolizine alkaloids sempervirine type, potential pharmaceuticals☆

Teodozja M. Lipińska*

Institute of Chemistry, University of Podlasie, 3 Maja 54, 08-110 Siedlce, Poland

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Abstract—Total synthesis of the two series of new pentacycilc cycloalk[*g*]indolo[2,3-*a*]quinolizine alkaloids (modified sempervirine possessing the wide range of activity), has been elaborated in five steps from 5-acetyl-3-methylthio-1,2,4-triazine (obtained from the simple acyclic materials). In the two key steps: inverse electron demand Diels–Alder reaction of precursor with cyclic enamines and the following Fischer indolization of 3-acetyl-1-methylthiocycloalka[*c*]pyridines, the AB–DE synthons, has been obtained. The final stages: desulfuration, and formation of the C-ring via the Gribble method have led to the expected zwitterionic alkaloids. Model syntheses of the indolopyridocoline and its methoxy analogue from 2-acetylpyridine have been performed for investigation of the microwave-induced Fischer synthesis of sensitive indoles and for obtaining compounds for comparative study of spectroscopic data.

1. Introduction

In recent years, there has been a growing interest in the synthesis of bioactive molecules and their non-natural analogues in the field of organic chemistry as a result of the new synthetic methods and techniques, which enable creating new medicaments. Sempervirine and other indolo[2,3-*a*]quinolizine alkaloids (alstonine, flavopereirine), were first known as cardiac species,[2] but recently their anticancer[3] (as DNA intercalating agent),[4] immunostimulative[3d,5] and anti-HIV,[3d] sedative and antipsychotic[5a,6] activities have been discovered. Just recently, it has been shown that sempervirine and other indole alkaloids (vinblastine, vincamine, ajmalicine, harmaline) can act as inhibitors of the enzyme CYP2D6 (it might exists as various polymorphic genotypes), giving a wide range of clinical effects, depending on individual organism.[7] Sempervirine, as indolo[2,3-*a*]quinolizinium type of molecule, can exist in acidic and neutral medium as a cation and in alkaline medium it has a conjugated zwitterionic structure, where one neutral canonical structure can be drawn[8,9] (Fig. 1). Since trace amounts of sempervirine exist in a natural resource, the rhizome and roots of *Gelsemium sempervirens*,[10] many methods have already been developed for its total synthesis involving various strategies for construction of the 1,2,3,4-tetrahydrobenz[*g*]indolo[2,3-*a*]quinolizine ring system.[8,11] Among them, the conception of the construction of pentacyclic ring system via a AB–DE synthon was developed,[12,13] as it is shown in Figure 2. This 2-(2-pyridyl)indole-type synthon was obtained by Stevens and co-workers[12] in the Fischer synthesis from 3-acetyl-5,6,7,8-tetrahydroisoquinoline

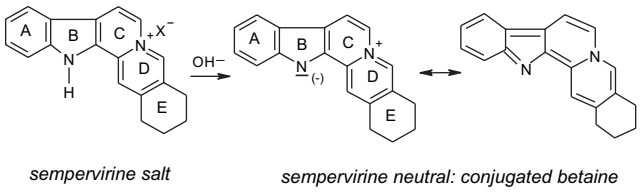

Figure 1.

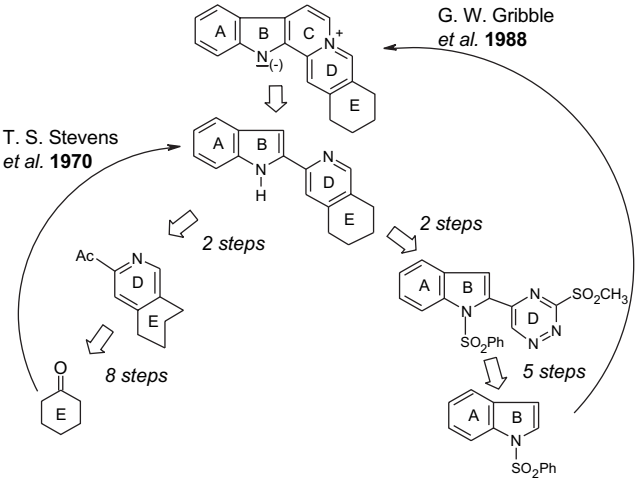

Figure 2.

☆ See Ref. 1.
Keywords: Total synthesis; Pentacyclic indole alkaloids; Zwitterions; DNA intercalators-anticancer agents.
* Tel.: +48 25 6431013; fax: +48 25 6442045; e-mail: tlip@ap.siedlce.pl

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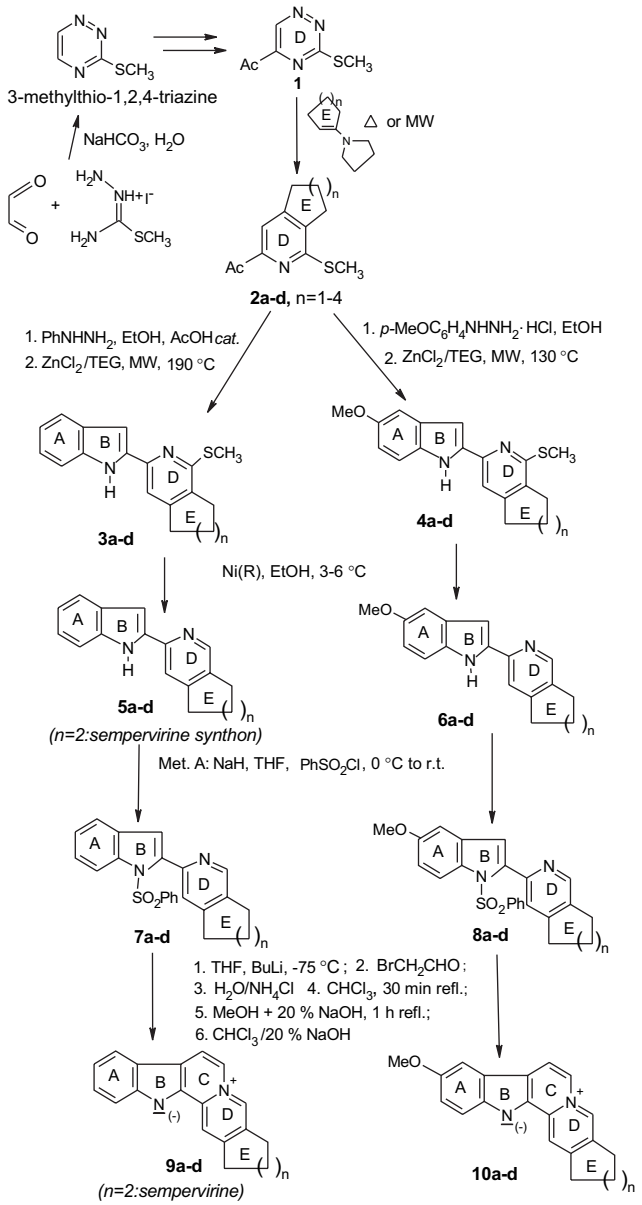
prepared in eight steps from cyclohexanone. The second synthesis by Gribble and co-workers[13] formed the AB–CD synthon in eight steps from *N*-phenylsulfonylindole, which was functionalized in C2 position for construction of the 1,2,4-triazine ring, next transformed by Diels–Alder reaction with the 1-(1-pyrrolidine)cyclohexene. The latter investigators successfully formed the middle C-ring via the indole *N*-protection, direct metalation and reaction with bromoacetaldehyde as a 1,2-dielectrophile. We took some advantage of these two developments and elaborated a novel total synthesis strategy, not only to improve the yield of sempervirine, but also to gain access to its new analogues for biological evaluation.

In present paper, we describe the scope and limitations of our method (see Scheme 1) and, report the full experimental details after optimization of its key steps and give the characterization data of the intermediates and final products.



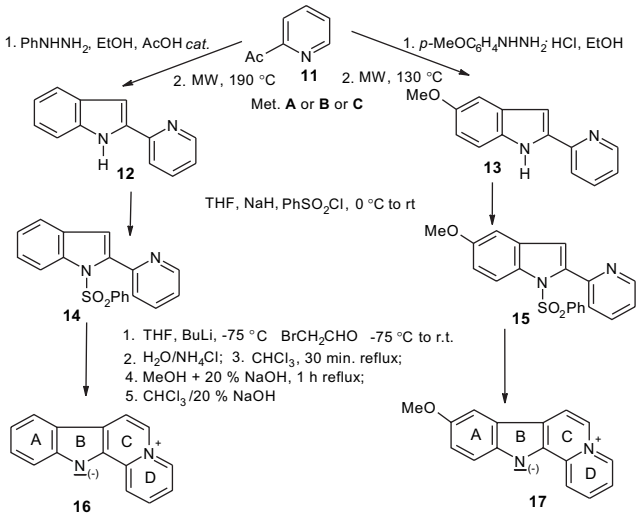
Scheme 1. Synthesis of the two series of modified sempervirine.

2. Results and discussion

2.1. Synthetic strategy

Our total synthesis strategy is based on the availability of the 5-acetyl-3-methylthio-1,2,4-triazine **1**[14] and the possibility of its transformation into 3-acetyl-1-methylthiocycloalka[*c*]pyridines **2a–d** by the Diels–Alder reaction with cyclic enamines.[15] Thus, we envisioned and discovered that the AB–DE sempervirine synthon **5b**[14b] as well as other 2-(2-pyridyl)indoles could be constructed in the Fischer indolization, thanks to the presence of the acetyl group in the molecules **2a–d** (see Scheme 1). With this perspective in mind, we planned the synthesis of **3a–d**[15b] and **4a–d**,[16] and next the AB–CD synthons **5a–d** and **6a–d**. The latter can be transformed into pentacyclic indolo[2,3-*a*]quinolizine alkaloids via the Gribble method.[13]

The starting material, 5-acetyl-3-methylthio-1,2,4-triazine **1**, was prepared in 40% yield in two-step synthesis[14] from 3-methylthio-1,2,4-triazine,[17] which can be obtained on a large laboratory-scale (up to 100 g) from the glioxal and *S*-methylthiosemicarbazide hydroiodide. Syntheses of **2a–d** via inverse electron demand Diels–Alder reaction of the **1** with cyclic enamines have been optimized recently.[18] The acetyl group remains in compounds **2a–d**, which gives access to the construction of the indole moiety via the Fischer synthesis. Initially, we obtained **3b** in conventional conditions;[14b] in a medium of excess molten zinc chloride and methylnaphthalene at temperature 200–220 °C, according to the Steven's method.[12] We chose this procedure from the two classic methods for performing the difficult Fischer synthesis. However, this procedure was inconvenient and non-ecological and gave rather low and non-reproducible 25–55% yield. The second method for performing difficult Fischer synthesis, described as efficient for transformation of 2-acetylpyridine **11** into 2-(2-pyridyl)indole **12** (see Scheme 2), involves using the polyphosphoric acid as a reaction medium.[19] However, we observed that this procedure gave the overall degradation of more complicated molecules like the **2a–d** phenylhydrazones. Having observed this, we had to search for another, more efficient



Scheme 2. Model synthesis of the indolopyridocoline **16** and its methoxy analogue **17**.

and ecological-friendly Fischer synthesis procedure, without the use of the protic acids.

2.2. Model synthesis

In order to investigate novel procedures for the difficult Fischer synthesis of sensitive indoles **3a–d** and **4a–d**, the key step in our total synthesis, we first carried out model syntheses, using the 2-acetypyridine **11** as a starting material (see Scheme 2). We investigated parallelly the syntheses towards the indolopyridocoline **16** and its unknown methoxy analogue **17**, as a model synthesis towards the methoxy analogues of sempervirine (**10a–d**). We noticed that the difference between them was only visible in the first, Fischer indolization step.[16] We confirmed that both conventional procedures were suitable for the indole **12** synthesis, they are not proper for obtaining 6-methoxy-2-(2-pyridyl)indole **13**, due to degradation processes. We investigated the three microwave-induced Fischer indolization procedures (methods *A*, *B* and *C*, see Scheme 2 and Table 1) as suitable for the difficult processes with acid-catalysis and high-temperature requirements.

The first investigated method (method *A*) involved the temperature-controlled microwave irradiation of the mixture of the 2-acetylpyridine **11** phenylhydrazone with an excess of the polyphosphoric acid (PPA) at 190 °C for 4 min. The indole **12** can be obtained in 60% yield in scale up to 5 g. However, in the case of microwave irradiation of the 2-acetylpyridine **11** *p*-methoxy-phenylhydrazone in this medium at temperature 120 °C for 4 min degradation was observed and only trace of the 6-methoxyindole was isolated **13** (see Table 1).

Next, we elaborated more ecological Fischer synthesis procedure, where the 2-acetylpyridine **11** phenylhydrazone is adsorbed on montmorillonite K10 modified by zinc chloride (MK10/$ZnCl_2$) and irradiated by microwaves without a solvent at controlled temperature (method *B*).[20] Finally, in this procedure, synthesis of 2-(2-pyridyl)indole **12** ran at 160 °C for 6 min in 45% yield. The 5-methoxy-2-(2-pyridyl)indole **13** was obtained in yield of 40–43% by this method[16] at temperature 130 °C from 2-acetylpyridine **11** via its *p*-methoxyphenylhydrazone hydrochloride.

Recently, we have discovered a new microwave-assisted procedure, where controlled microwave irradiation of the 2-acetylpyridine **11** phenylhydrazone was performed in the medium of the anhydrous zinc chloride solution (0.16 M) in dry triethylene glycol: $ZnCl_2$/TEG-mediated method *C*.[21] Only catalytic quantity of zinc chloride (0.1 equiv) was used in the reaction mixture. 2-(2-Pyridyl)indole **12** was isolated in 65% yield by column chromatography of the dichloromethane extracts, obtained by treatment with this solvent the reaction mixture, prior diluted with the cooled 5% sodium hydroxide. The Fischer synthesis of 5-methoxy-2-(2-pyridyl)indole **13** was established in yield 63% at the lower programmed temperature then the indole **12** (see, Table 1).

Table 1. Comparison of the 2-acetylpyridine **11** Fischer indolization yields into **12** and **13** via three microwave-assisted methods

Indole	Method	Conditions under MW	Yield (%)
12	*A*[a]	PPA, 190 °C, 4 min	60
12	*B*[b]	MK10/$ZnCl_2$, solvent free 190 °C, 4 min	45
12	*C*[c]	$ZnCl_2$/TEG, 190 °C, 8 min	65
13	*A*[a]	PPA, 130 °C, 4 min	Trace
13	*B*[b]	MK10/$ZnCl_2$, solvent free 130 °C, 4 min	43
13	*C*[c]	$ZnCl_2$/TEG, 130 °C, 5 min	63

[a] Irradiation of a crude phenylhydrazone with an excess PPA.
[b] Irradiation of a solid-supported phenylhydrazone without solvent.
[c] Irradiation of the mixture 0.5 mmol substrate with a 0.33 mL, 0.16 M, zinc chloride solution in triethylene glycol ($ZnCl_2$/TEG).

Comparison of the yields of **12** and **13** obtained by the Fischer transformation of the 2-acetylpyridine **11** via the methods *A*, *B* and *C* is shown in Table 1. Next, construction of the C-ring by using the Gribble method: *N*-protection of indole, direct metalation with *n*-butyllithium and reaction with dry solution of bromoacetaldehyde (Scheme 2), resulted in the formation of **16** and **17**. Both products were obtained in overall yields of 24–29% from **11**.

2.3. Synthesis of the sempervirine and its analogues

The two key steps in our total synthetic strategy (see Scheme 1) consist of the synthesis of the acetyl derivatives of cycloalka[*c*]pyridine **2a–d** and their transformation via the Fischer reaction towards the indoles **3a–d** and 5-methoxyindoles **4a–d**. Optimization of both these stages was necessary to obtain the final products in high enough quantities for biological investigations. Recently, we have published the results of the experimental and theoretical studies towards optimization of the synthesis of **2a–d**.[18] Thus, we arrived at 75% yield of **2a** (n=1), 65% of **2b** (n=2), 54% of **2c** (n=3) and 30% of **2d** (n=4) in the conventional heating of **1** and appropriate enamine with anhydrous ethanol. Better yield of **2d**, 45%, was obtained when high concentration reaction mixture **1** and 1-pyrrolidine-1-cyclooctanone in chlorobenzene was irradiated by microwaves at the controlled temperature of 110 °C. The Fischer indolization was previously performed by conventional method with an excess of zinc chloride.[14b] Next, we applied our microwave-induced solid-supported procedure (method *B*) with the use of the montmorillonite K10 modified with zinc chloride (MK10/$ZnCl_2$)[15,16] as the extension of the model reactions **11**→**12**[20] and **11**→**13**[16] (see Scheme 2). However, the yields of products were dissatisfying: 26–29% of **3a–d** and 38–43% of **4a–d**, due to overheating and following degradation processes of irradiated reactants on the solid support. Just recently, we have updated this crucial step by application of our new, $ZnCl_2$/TEG-mediated microwave-induced methodology (method *C*).[21] The Fischer transformations of the **2a–d** phenylhydrazones into **3a–d** required microwave irradiation of the reaction mixture (0.5 mmol substrate with the 0.33 mL of the 0.16 M zinc chloride solution in triethylene glycol ($ZnCl_2$/TEG)) at 180 °C the temperature programed for 7 min. The 5-methoxyindoles **4a–d** were formed at 130 °C for 5 min of irradiation of the *p*-methoxyphenylhydrazones in $ZnCl_2$/TEG medium. This one pot procedure (without isolation of phenylhydrazones) gave almost double increase in yields in comparison to method *B*. After an aqueous workup of the reaction mixture and isolation by column chromatography, the indoles **3a–d** were obtained in yields of 50–53% and the 5-methoxyindoles **4a–d** in yields of 60–63%.[21] These were good results for the difficult Fischer syntheses of the sensitive indoles.

Next step in our total synthesis, removal of the methylthio group in indoles **3a–d** and 5-methoxyindoles **4a–d**, was successfully carried out with the W2 Raney nickel in ethanol at 3–6 °C. We observed that in higher temperature the reaction ran less selectively (with reduction of the pyridine ring) and the yield of products decreased, but in lower temperature the desulfurization process was inhibited. As the crude products were partially bonded in nickel-complexed forms, the workup with EDTA was necessary. The synthons **5a–d** and **6a–d** were obtained in 60–70% yields and were converted to their *N*-phenylsulfonyl derivatives **7a–d** and **8a–d**. Subsequent formation of the C-ring according to the Gribble method[13] led to the sempervirine **9b**, its three analogues with different E-ring **9a**, **9c**,**d** and four alkaloids with methoxy group **10a–d**. Unfortunately, the yields of the two final steps were moderate. We observed incomplete conversion of the substrate in the process of *N*-protection of the indole with phenylsulfonyl chloride in the presence of sodium hydride. It resulted in troublesome isolation of **7a–d** (55–60%) and **8a–d** (52–57%) by column chromatography, because their R_f are lower then R_f of the substrates **5a–d** and **6a–d** (see, Table 2), which were recovered in 15–25% yields. The one pot process of the C ring construction, started when the excess of the bromoacetaldehyde (6 equiv) was added to the cooled (−78 °C) reaction mixture containing the substrate **7a–d** or **8a–d** and *n*-butyllithium (4 equiv). The step by step rearrangements: reaction of an indole β-carboanion with the carbonyl group of the bromoacetaldehyde, protonation with water, closure of the C ring by intramolecular alkylation of the pyridine nitrogen with methylene group from indole β-chain –CHOHCH$_2$–Br, dehydration–aromatization of the C-ring and hydrolysis of the phenylsulfonyl group (deprotection of the indole nitrogen), resulted in the formation of the final pentacyclic alkaloids **9a–d** and **10a–d**. They were extracted in their free base forms to chloroform phase during partitionating with 20% sodium hydroxide, and next purified by preparative thin-layer chromatography on silica gel plates using polar eluent, dichloromethane/methanol 5:1. Yellowish-green to orange-brown, amorphic substances were obtained in 48–58% yields. We observed that in methanolic solution the inert forms come slowly into cations, which are more polar and were visualized on TLC plates (as possessing lower R_f) together with the inert forms. This is in accordance to the investigations of other zwitterionic alkaloids, e.g., by Fujii et al.[22] Alkaloids **9a–d** and **10a–d** itself and their solutions were stored at temperature below 0 °C for several months, but they are sensitive if are exposed to the room temperature and air, when degradation processes were observed.

Chromatographic analysis (TLC) and isolation (column and thin layer preparative chromatography) were very useful in our total synthesis. Therefore, in Table 2, the R_f values for all intermediates, final alkaloids and model compound are shown. In particular, the compounds with methoxy group in indole moiety are more polar then their analogues without OMe in all steps of the synthesis. The main tendency can be observed in Table 2, relies on augmentation polarity of all compounds coming from **3a–d** and **4a–d** towards products **9a–d** and **10a–d**.

We obtained the final alkaloids **9a–d** and **10a–d** in overall yields of 4.1–10.1% in the total synthesis from the substrate **1** (five steps), the highest for **10a**,**b** and the lowest for **9d**.

2.4. Comparative study of the spectroscopic data

The structure of all intermediates and the final pentacyclic cycloalk[*g*]indolo[2,3-*a*]quinolizines, shown in Schemes 1 and 2, were determined by the spectroscopic method. As we prepared and investigated two four-membered series of the final products and three kinds of the consecutive intermediates and also appropriate model compounds, we had the ability for interpretation of their spectroscopic data by comparative study.

The UV spectra of four sempervirine methoxy analogues **10a–d** are shown in Figure 3, together with the spectrum of our synthetic model alkaloids **17**.

The structure variables of the intermediates and the final products can be well observed in their NMR spectra. Table 3 shows the data from the ^{1}H NMR spectra of the three kinds of the succeeding intermediates with the five-membered C ring only. Since differences in the chemical shifts of the two methylene group bonded with pyridine ring exist in the cases of **3a–d** and **4a–d** (as is shown in Table 3 for **3a** and **4a**), we can conclude that the presence of methylthio group gives upfield effect to the nearer one. The methylthio

Table 2. Polarity comparison of the intermediates, the final alkaloids **9a–d**, **10a–d** as well as appropriate model compounds **12–17** as their retention factors (R_f) observed on silica TLC plates with four different eluents

No. compd	R_f [a]	No. compd	R_f [b]	No. compd	R_f [c]	No. compd	R_f [d]
—	—	**12**	0.46	**14**	0.57	**16**	0.25
3a	0.51	**5a**	0.45	**7a**	0.50	**9a**	0.59
3b	0.53	**5b**	0.46	**7b**	0.57	**9b**	0.62
3c	0.54	**5c**	0.48	**7c**	0.59	**9c**	0.64
3d	0.57	**5d**	0.49	**7d**	0.60	**9d**	0.65
—	—	**13**	0.33	**15**	0.35	**17**	0.07
4a	0.18	**6a**	0.32	**8a**	0.32	**10a**	0.17
4b	0.20	**6b**	0.33	**8b**	0.36	**10b**	0.21
4c	0.21	**6c**	0.36	**8c**	0.38	**10c**	0.26
4d	0.23	**6d**	0.37	**8d**	0.41	**10d**	0.30

[a] Obtained with dichloromethane/hexane 1:1.
[b] Obtained with dichloromethane/acetone 50:1.
[c] Obtained with dichloromethane/acetone 30:1.
[d] For inert forms, obtained with dichloromethane/methanol 5:1.

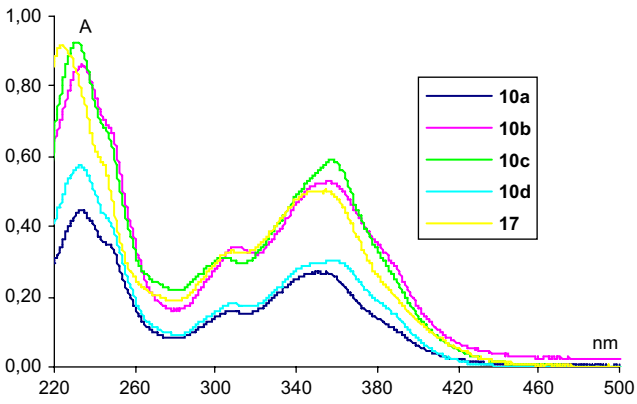
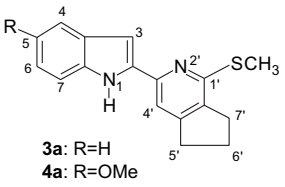
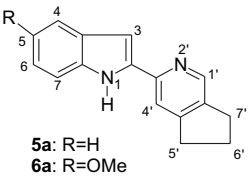
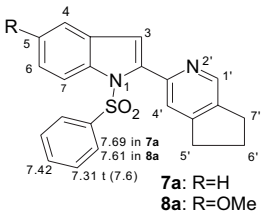


Figure 3. The UV spectra of **10a–d** and **17** in MeOH [c~10^{-4} mol/L].

Table 3. Comparison of the ^{1}H NMR data for the three kinds of consecutive intermediates with five-membered E ring: **3a** and **4a**, **5a** and **6a**, **7a** and **8a** from their simple spectra in $CDCl_3$ (400 MHz)







Position	**3a** δ_H (J in Hz)[a]	**4a** δ_H (J in Hz)[a]	**5a** δ_H (J in Hz)	**6a** δ_H (J in Hz)	**7a** δ_H (J in Hz)	**8a** δ_H (J in Hz)
1 (NH)	9.39 br s	9.24 br s	9.55 br s	9.84 br s	—	—
3	6.96 dd (2.0, 0.9)	6.86 d (2.0)	6.97 dd (2.2, 07)	6.87 d (1.8)	6.85 s	6.82 s
4	7.66 dd (7.0, 1.3)	7.09 d (2.4)	7.65 dd (7.9, 1.3)	7.07 d (2.4)	7.33 d (7.2)	6.88 d (2.4)
5	7.4 ddd (7.6, 7.0, 1.1)	OCH_3: 3.87 s, 3H	7.11 ddd (7.9, 7.6, 1.2)	OCH_3: 3.85 s, 3H	7.24 m	OCH_3: 3.80 s, 3H
6	7.21 ddd (7.9, 7.6, 1.3)	6.89 dd (8.9, 2.4)	7.20 ddd (8.2, 7.6, 1.3)	6.84 dd (8.8, 2.4)	7.44 m	6.94 dd (8.8, 2.4)
7	7.46 dd (7.9, 1.1)	7.28 d (8.9)	7.42 dd (8.2, 1.2)	7.24 d (8.8)	8.18 d (8.4)	8.07 d (8.8)
1′	SCH_3: 2.55 s, 3H	SCH_3: 2.71 s, 3H	8.42 s	8.38 s	8.54 s	8.54 s
4′	7.42 s	7.38 s	7.70 s	7.65 s	7.59 s	7.61 s
5′	2.89 t, 2H (7.5)	2.94 t (7.6)	2.97 t (7.4)	2.93 t (7.5)	3.03 t (7.6)	3.03 t (7.6)
6′	2.19 quintet, 2H (7.5)	2.19 quintet (7.6)	2.15 quintet (7.4)	2.12 quintet (7.5)	2.19 quintet (7.6)	2.19 quintet (7.6)
7′	2.74 t, 2H (7.5)	2.81 t (7.6)	2.97 t (7.4)	2.93 t (7.5)	3.03 t (7.6)	3.03 t (7.6)

[a] Compound described in Ref. 21.

group is visible in the spectra of **3a–d** and **4a–d** as a singlet at δ 2.55–2.72. After its removal, a new singlet emerges in aromatic region (at δ 8.38–8.54) in the spectra of the consecutive compounds **5a–d**, **6a–d**, **7a–d** and **8a–d**, as a signal of the C1′ proton. The spectra of all methoxy analogues in the aromatic region are more simple than the spectra of the intermediates and the final products without methoxy group. It is important, because it allows comparative interpretation of the ^{1}H NMR spectra. Figure 4 shows examples of the ^{1}H NMR data of one pair: **9c** and **10c** of the final products. They are in accordance with the earlier determined ^{1}H NMR for yohimbane anhydronium bases.[23] We can conclude that the chemical shifts of the aromatic protons of the indolo[2,3-*a*]quinolizinium ring system are higher than those observed for the protons of the AB–DE synthons **5a–d** and **6a–d** at the appropriate positions. The two vicinal protons of the new-formed bridge in the C ring of **9a–d** and **10a–d** can be observed as doublets with the J=6.8 Hz. The ^{13}C NMR spectra also show well the changes in the structure of the intermediates and the final products.

We have examined and compared the fragmentation paths of all intermediates and the final products, which are visible in their EI mass spectra. In the mass spectra of the compounds with the methylthio group (**3a–d** and **4a–d**) the removal of the SH radical $[M-33]^+$ can be observed as a tendency to

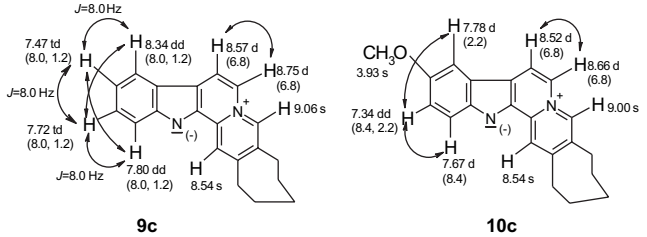


Figure 4. Comparison of the ^{1}H NMR data of the indolo[2,3-*a*]quinolizine ring system in the pair **9c** and **10c** of the final alkaloids from their simple spectra in CD_3OD (400 MHz).

an azatrophylic cation formation. Existence of the methoxy group is indicated by removal of the methyl radical and next carbon oxide from the parent cations, which give peaks $[M-15]^+$ and $[M-43]^+$ in the mass spectra of **4a–d**, **6a–d** and **8a–d** and also **10a–d**, **13**, **15** and **17**. It is interesting that the peaks corresponding to the double charged cations (M^{++}, m/z=M/2) as an ionization possibility in the two points (indole and pyridine moieties of the molecules) can be observed in the mass spectra of all compounds, apart from the *N*-protected indoles **7a–d** and **8a–d**. In the mass spectra of the *N*-protected indoles **7a–d** and **8a–d** the parent cations have been observed, but more intensive peaks: $[M-64]^+$ and $[M-141]^+$ indicate the loss of SO_2 and $PhSO_2$ by molecular cations. Molecules of the final alkaloids can be analyzed with the electron impact mass spectrometer, only in their inert (free bases) forms as they are more volatile than the salts (protonated forms). All intermediates and final products have indicated the parent peaks in their electron impact mass spectra. However, the final alkaloids are unstable during the high-temperature EIMS experiments and the high-resolution measurements of their molecular ions were carried out with an electron-spray technique.

3. Conclusions

A unified synthetic strategy for the zwitterionic indolo[2,3-*a*]quinolizine alkaloid group has been developed, allowing the total synthesis of the pentacyclic sempervirine analogues to be carried out using the same starting material and similar conditions. 5-Acetyl-3-methylthio-1,2,4-triazine has been used as azadiene in Diels–Alder reaction with cyclic enamines and the acetyl derivatives of cycloalka[*c*]pyridines (DE ring systems, differentiation of E ring) have been obtained in the first key step. In the Fischer indolization as the second crucial step, the AB–DE synthons (indole or 5-methoxyindole as AB moiety) have been prepared in satisfying yields thanks to discovery of the new procedure for performing Fischer synthesis. Anhydrous zinc chloride

solution in triethylene glycol has been used as a homogeneous Lewis acid catalytic system and the Fischer reaction has been carried out under controlled microwave irradiation for several minutes. After removal of the methylthio group, the middle C ring has been formed via indole *N*-protection, direct metalation and reaction with the bromoacetaldehyde as a 1,2-dielectrophile. In result, the sempervirine and its seven new analogues have been obtained for the biological evaluation since these structures modification can remain or change the therapeutic profile (anticancer, immunostimulating, antiviral, antipsychotic) of the sempervirine itself.

In the model synthesis, two tetracyclic alkaloids: indolopyridocoline and its new analogue, 9-methoxyindolo[2,3-*a*]quinolizine, have been obtained easily.

Comparative studies on molecular structures and spectroscopic and chemical properties of intermediates and final alkaloids have been performed and their most important results are described in this paper.

4. Experimental

4.1. General

Commercial 2-acetylpyridine **11** was used for model studies. The temperature-controlled microwave-assisted reactions were performed using a microwave reactor Synthewave 402 (Prolabo, 300 W, focused microwaves, open rotating system of reaction vessel) with software (feedback temperature monitoring). Raney nickel W2 was used for desulfurization. Anhydrous bromoacetaldehyde solution in methylene chloride/hexane was obtained by ozonolysis of (*E*)-1,4-dibromo-2-butene.[24] Other reagents were used as commercial. Anhydrous solvents were prepared via standard procedures.[25] The course of reactions was monitored by thin-layer chromatography (TLC), which was carried out on 0.25 mm Merck silica gel plates ($60F_{254}$). Column chromatography was performed on Merck silica gel 60 (230–400 mesh). Melting points were determined on Boëtius microscopic plate and were not corrected. All new compounds were determined to be >95% pure by ^{1}H NMR. The ^{1}H and ^{13}C NMR spectra were recorded with Varian Gemini (200 MHz), Mercury 400BB (400 MHz) or Bruker GRX (500 MHz) spectrometers. IR spectra (KBr pellets) were recorded on FTIR Magna 760 (Nicolet) apparatus. Mass spectrometer AMD 604 (Intectra, GmbH, Germany) was used for EI mass spectra and high-resolution measurements. High-resolution electron spray measurements were carried our with Mariner mass spectrometer (with methanol). The UV measurements were recorded digitally (0.5 nm step) for $c=5\times10^{-4}$ mol/dm^3 solutions in methanol with a BECKMAN DU-68 spectrophotometer using 1-cm quartz cell at a room temperature.

4.2. General procedures for the microwave-assisted Fischer synthesis of indoles 3a–d, 4a–d, 12, 13

4.2.1. Method A: Fischer synthesis in polyphosphoric acid for preparation model indole 12 only. To a solution of 2-acetylpyridine **11** (2.42 g, 20 mmol) in anhydrous ethanol (25 mL) were added phenylhydrazine (2.37 g, 2.33 mL, 22 mmol) and glacial acetic acid (four drops, ~50 mg). The mixture was refluxed under argon for 30 min: the complete disappearance of substrate was observed by TLC monitoring (dichloromethane/acetone 50:1). Solvents were removed under reduced pressure and crude phenylhydrazone was placed into cylindrical quartz vessel. Polyphosphoric acid (~10 g) was added and mixed manually. Irradiation by microwaves was performed at temperature programed at 180 °C for 4 min. Having been cooled, the reaction mixture was quenched with cooled 20% NaOH (150 mL). The aqueous layer was extracted with dichloromethane (3×50 mL), the combined organic phases were dried ($CaCl_2$) and evaporated. Purification of the crude product by flash chromatography on silica gel using hexane/dichloromethane 1:1 as eluent afforded **12** as yellow crystals (2.30 g, 60%), mp 152–153 °C, lit.[26a] mp 154–155 °C. Recrystallization with diethyl ether/hexane gives yellow crystals with mp 156.0–156.5 °C.

4.2.2. Method B: solvent-free Fischer synthesis. The first, solvent-free procedure with modified solid support MK10/$ZnCl_2$ was elaborated in model synthesis of **12** (45%),[20] next it was extended to synthesis of **3a–d** (26–29%)[15] and then was adapted to the preparation of model **13** (43%) and **4a–d** (38–43%).[16]

4.2.3. Method C: controlled microwave irradiation of phenylhydrazones with 0.16 M zinc chloride solution in triethylene glycol. This efficient procedure has been recently described.[21] Indole **12** was obtained in 65% yield and methoxyindole **13** in 63% yield from 2-acetylpyridine **11** (see Table 1). The Fischer indolization of ketones **2a–d** towards indoles **3a–d** was carried out in 50–53% yields and towards methoxyindoles **4a–d** in 60–63% yields.[21]

Model 2-(2-pyridyl)indole **12** was described earlier.[26] Additional characterization data: IR (KBr): ν_{max} 3134, 3078, 1598, 1562, 1546, 1470, 1443, 1416, 1345, 1304, 1155, 997, 758, 755, 733 cm^{-1}; GC–MS: t_R=12.3 min, *m*/*z* 194 (M^+, 100), 167 (10), 139 (6), 97 (M^{2+}, 25), 89 (11), 83 (22), 78 (10), 70 (11); ^{1}H NMR (200 MHz, CD_3OD): δ 8.56 (1H, ddd, *J*=5.0, 1.7, 1.0 Hz), 7.89 (1H, ddd, *J*=8.0, 1.5, 1.0 Hz), 7.81 (1H, ddd, *J*=8.0, 7.1, 1.7 Hz), 7.57 (1H, ddd, *J*=8.1, 1.1, 0.9 Hz), 7.43 (1H, dd, *J*=8.0, 1.1 Hz), 7.24 (1H, ddd, *J*=7.1, 5.0, 1.5 Hz), 7.14 (1H, ddd, *J*=8.1, 7.0, 1.1 Hz), 7.06 (1H, d, *J*=0.9 Hz), 7.01 (1H, ddd, *J*=8.0, 7.8, 1.1 Hz).

Model 5-methoxy-2-(2-pyridyl)indole **13** and compound **4c** were characterized in Ref. 16, compound **3b** in Ref. 14b and all compounds **3a–d** and **4a–d** in Ref. 21.

4.3. Preparation of the synthons 5a–d and 6a–d in the desulfurization process

General procedure: compound **3a** (280 mg, 1 mmol) was dissolved in anhydrous ethanol (50 mL) at room temperature and the rapidly stirred solution was cooled to 0 °C. The first portion of the W2 Raney nickel (~2 g) was added and the temperature was maintained between 3–6 °C. At this temperature next portions of Raney nickel were added. Reaction was monitored by TLC (dichloromethane), where substrate **3a** (R_f=0.87) disappeared and product **5a** (R_f=0.17) was

formed. Optimal reaction time was 45–60 min for complete desulfurization. Reaction mixture was cooled to −10 °C and quickly filtered through Celite. Reaction flask and Celite were washed with a cooled mixture of ethanol/acetone 2:1. Solvents evaporated under reduced pressure and green residue was obtained. After treatment with 5% hydrochloric acid (10 mL) the yellow precipitate was obtained, to which the cooled 10% EDTA solution in 10% ammonium hydroxide (10 mL) and diethyl ether (50 mL) were added. The mixture was shaken and organic layer separated. The aqueous phase was extracted with diethyl ether (2×50 mL), combined organic phases were washed with brine and dried with sodium sulfate. Removing the solvent led to **5a** as a white solid, which was purified by recrystallization with dichloromethane/hexane. Characterization data of **5a** are given in Section 4.3.1.

According to the general procedure mentioned above the following products were obtained: **5b–d** from **3b–d** (1 mmol) and **6a–d** from **4a–d** (1 mmol). The yields and the characterization data are given below.

4.3.1. 2-(6,7-dihydro-5*H*-[2]pyrindin-3-yl)-1*H*-indole (5a). Yield 160 mg (68%); mp 160–161 °C; IR (KBr): 3216, 2952, 2923, 2860, 1654, 1608, 1556, 1425, 1344, 1299, 1117, 1055, 873, 792, 739 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.15 (2H, quintet, J=7.6 Hz), 2.97 (4H, 2×t, J=7.6 Hz), 6.97 (1H, dd, J=2.2, 0.7 Hz), 7.11 (1H, ddd, J=7.9, 7.6, 1.2 Hz), 7.20 (1H, ddd, J=8.2, 7.6, 1,3 Hz), 7.42 (1H, dd, J=8.2, 1.2 Hz), 7.65 (1H, dd, J=7.9, 1.3 Hz), 7.70 (1H, s), 8.42 (1H, s), 9.55 (1H, br s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.1, 30.1, 32.6, 99.4, 111.2, 115.9, 119.9, 120.9, 122.7, 129.1, 136.4, 137.4, 139.0, 144.7, 148.2, 154.6; EIMS m/z (%): 234 (M^+, 100), 204 (8), 117 (M^{++}, 12); HRMS (EI, M^+) found 234.1157, calcd for $C_{16}H_{14}N_2$ 234.1157.

4.3.2. 3-(Indol-2-yl)-5,6,7,8-tetrahydroisiquinolie (5b). Yield 174 mg (70%); mp 160–161 °C lit.[12] 158.0–158.5 °C, lit.[13a] 159.5–160.5 °C, lit.[14b] 158–159 °C; IR (KBr): 3131, 3069, 2925, 2854, 1604, 1608, 1550, 1473, 1426, 1346, 1305, 1141, 1070, 1014 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.83 (4H, m), 2.75 (2H, m), 2.80 (2H, m), 6.93 (1H, d, J=1.6 Hz), 7.08 (1H, dd, J=8.1, 7.2 Hz), 7.17 (1H, ddd, J=7.9, 7.2, 1,3 Hz), 7.36 (1H, d, J=8.1 Hz), 7.49 (1H, s), 7.62 (1H, dd, J=7.9, 1.3 Hz), 8.25 (1H, s), 9.86 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.4, 22.6, 26.2, 28.9, 99.5, 111.3, 119.9, 120.0, 120.9, 122.7, 129.2, 131.9, 136.5, 137.0, 147.1, 147.2, 149.2; EIMS m/z (%): 248 (M^+, 100), 232 (5), 220 (18), 124 (M^{++}, 6), 116 (5).

4.3.3. 3-(Indol-2-yl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*c*]-pyridine (5c). Yield 172 mg (65%); mp 141–142 °C; IR (KBr): 3213, 3013, 2921, 2848, 1654, 1602, 1552, 1479, 1425, 1348, 1311, 1225, 1185, 792, 743 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.60–180 (4H, m), 1.81–1.90 (2H, m), 2.81–2.98 (4H, m), 6.98 (1H, dd, J=2.0, 0.8 Hz), 7.09, (1H, ddd, J=7.8, 7.0, 1.1 Hz), 7.22 (1H, ddd, J=7.2, 7.0, 1.3 Hz), 7.38 (1H, dd, J=2.2, 1.1 Hz), 7.57 (1H, s), 7.65 (1H, dd, J=7.8, 1.3 Hz), 8.28 (1H, s), 9.71 (1H, br s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.5, 28.1, 32.6, 33.1, 36.4, 99.7, 111.2, 115.8, 119.9, 120.9, 122.7, 129.1, 136.3, 137.1, 137.5, 148.4, 148.5, 152.7; EIMS m/z (%): 262 (M^+, 100), 233 (9), 221 (5), 131 (M^{++}, 5) 116 (5); HRMS (EI, M^+) found 262.14732, calcd for $C_{18}H_{18}N_2$ 262.14700.

4.3.4. 3-(Indol-2-yl)-5,6,7,8,9,10-heksahydrocyclo-octa[*c*]pyridine (5d). Yield 168 mg (61%); mp 144–145 °C; IR (KBr): 3174, 3150, 3077, 2923, 2851, 1602, 1550, 1477, 1446, 1424, 1344, 1344, 1321, 1227, 1182, 1070, 1003, 793, 746 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.35–1.45 (4H, m), 1.67–1.79 (4H, m), 2.74–2.82 (4H, m), 6.98 (1H, d, J=1.8 Hz), 7.08, (1H, ddd, J=8.1, 7.0, 1.2 Hz), 7.17 (1H, ddd, J=7.8, 7.0, 1,2 Hz), 7.32 (1H, dd, J=8.1, 1.2 Hz), 7.56 (1H, s), 7.63 (1H, dd, J=7.8, 1.2 Hz), 8.28 (1H, s), 10.09 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$), δ 25.6, 25.8, 29.2, 31.4, 31.7, 32.1, 99.9, 111.4, 119.9, 120.0, 120.9, 122.7, 129.2, 135.9, 136.6, 136.9, 148.3, 148.5, 151.2; EIMS m/z (%): 276 (M^+, 100), 247 (4), 233 (9), 220 (4), 138 (M^{++}, 5), 116 (4); HRMS (EI, M^+) found 276.16234, calcd for $C_{19}H_{20}N_2$ 276.16265.

4.3.5. 2-(6,7-Dihydro-5*H*-[2]pyrindin-3-yl)-5-methoxy-1*H*-indole (6a). Yield 185 mg (70%); mp 144–145 °C; IR (KBr): 3192, 3063, 2927, 2831, 1609, 1549, 1461, 1433, 1336, 1308 1294, 1260, 1225, 1152, 1034, 856, 785 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.19 (2H, quintet, J=7.6 Hz), 3.03 (4H, 2×t, J=7.6 Hz), 3.85 (3H, s), 6.84 (1H, dd, J=8.8, 2.4 Hz), 6.87 (1H, d, J=1.8 Hz), 7.07 (1H, d, J=2.4 Hz), 7.24 (1H, d, J=8.8 Hz), 7.65 (1H, s), 8.28 (1H, s), 9.85 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.0, 30.1, 32.7, 55.8, 99.5, 102.3, 112.0, 113.4, 115.9, 129.5, 131.8, 137.8, 138.9, 144.4, 148.1, 154.3, 154.8; EIMS m/z (%): 264 (M^+, 100), 249 (65), 221 (28), 192 (4), 132 (M^{++}, 6), 116 (4); HRMS (EI, M^+) found 264.12601, calcd for $C_{17}H_{16}N_2O$ 264.12626.

4.3.6. 5-Methoxy-2-(5,6,7,8-tetrahydroisoquinolin-3-yl)-1*H*-indole (6b). Yield 189 mg (68%); mp 129–130 °C; IR (KBr): 3127, 3060, 2927, 2890, 1621, 1604, 1549, 1480, 1447, 1423, 1350, 1302, 1226, 1199, 1156, 1117, 1073, 885, 839, 797 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.83 (4H, m), 2.74 (2H, m), 2.79 (2H, m), 3.84 (3H, s), 6.84 (1H, dd, J=8.8, 2.4 Hz), 6.85 (1H, d, J=2.2 Hz), 7.06 (1H, d, J=2.4 Hz), 7.25 (1H, d, J=8.8 Hz), 7.45 (1H, s), 8.23 (1H, s), 9.71 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.4, 22.6, 26.2, 28.9, 55.8, 99.3, 102.3, 112.0, 113.3, 119.8, 129.5, 131.8, 131.9, 137.5, 147.1, 147.2, 149.2, 154.2; EIMS m/z (%): 278 (M^+, 100), 263 (40), 235 (18), 207 (5), 139 (M^{++}, 9), 116 (4); HRMS (EI, M^+) found 278.14128, calcd for $C_{18}H_{18}N_2O$ 278.14191.

4.3.7. 5-Methoxy-2-(5,6,7,8-tetrahydro-5*H*-cyclohepta[*c*]-pyridine-3yl)-1*H*-indole (6c). Yield 192 mg (66%); mp 126–127 °C; IR (KBr): 3160, 3055, 2923, 2848, 1621, 1604, 1546, 1451, 1421, 1352, 1294, 1223, 1159, 1112, 1028, 830, 788 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.64–1.73 (4H, m), 1.89 (2H, m), 2.80 (2H, m), 2.85 (2H, m), 3.86 (3H, s), 6.86 (1H, dd, J=9.0, 2.0 Hz), 6.89–6.91 (1H, m), 7.09 (1H, d, J=2.0 Hz), 7.25 (1H, d, J=9.0 Hz), 7.53 (1H, s), 8.25 (1H, s), 9.87 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 27.5, 28.1, 32.5, 33.1, 36.5, 55.8, 99.7, 102.3, 112.0, 113.4, 119.9, 129.5, 131.9, 137.4, 137.5, 148.1, 148.5, 153.1, 154.3; EIMS m/z (%): 292 (M^+, 100), 277 (65), 249 (45), 219 (5), 192 (5), 146 (M^{++}, 11), 119 (6);

HRMS (ESI, $[M+H]^+$) found 293.1655, calcd for $C_{19}H_{21}N_2O$ 293.1648.

4.3.8. 2-(5,6,7,8,9,10-Hexahydrocycloocta[*c*]pyridin-3-yl)-5-methoxy-1*H*-indole (6d). Yield 205 mg (68%); mp 110–111 °C; IR (KBr): 3157, 3055, 2991, 2923, 2851, 1622, 1601, 1547, 1451, 1422, 1299, 1220, 1195, 1156, 1031, 844, 799 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.35–1.45 (4H, m), 1.67–1.79 (4H, m), 2.76–2.84 (4H, m), 3.85 (3H, s), 6.84 (1H, dd, J=8.8, 2.4 Hz), 6.90 (1H, d, J=1.6 Hz), 7.07 (1H, d, J=2.4 Hz), 7.23 (1H, d, J=8.8 Hz), 7.53 (1H, s), 8.26 (1H, s), 9.89 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.5, 25.8, 29.2, 31.4, 31.7, 32.1, 55.8, 99.6, 102.3, 112.0, 113.3, 120.0, 129.5, 131.9, 135.8, 137.5, 148.4, 148.8, 151.2, 154.2; EIMS *m*/*z* (%): 306 (M^+, 100), 291 (68), 263 (32), 219 (5), 207 (4), 153 (M^{++}, 6); HRMS (EI, M^+) found 306.17281, calcd for $C_{20}H_{22}N_2O$ 306.17321.

4.4. Preparation of the *N*-phenylsulfonylindoles: 7a–d, 8a–d and models 14 and 15

General procedure: Sodium hydride as a 60% dispersion (120 mg, 3.0 mmol) was washed twice with anhydrous diethyl ether (5 mL), which was decanted. Anhydrous THF (30 mL) was added immediately, and cooled to 0 °C with stirring. A solution of indole **5a** (117 mg, 0.50 mmol) in THF (10 mL) was added dropwise for 5 min and the reaction mixture was stirred at 0 °C for 1 h and next at 5–10 °C for 2 h. After cooling to 0 °C, phenylsulfonyl chloride (0.6 mL, 5 mmol) was added dropwise for 5 min. The reaction mixture was stirred at 0 °C for 1 h, next at 0–10 °C for 1.5 h and was placed in a refrigerator overnight (5 °C). Saturated aqueous $NaHCO_3$ (10 mL) was added dropwise over 10 min with vigorously stirring at 0 °C, which was continued for 30 min and then the reaction mixture was allowed to warm to ambient temperature for 1 h. The organic layer was separated and the aqueous phase was extracted with diethyl ether (2×20 mL). The combined organic layers were washed with brine (2×10 mL), dried with K_2CO_3 and concentrated under reduced pressure to give an oily residue. Isolation by column chromatography was carried out at first with dichloromethane/hexane 1:1 (phenylsulfonyl chloride was isolated), next with dichloromethane when the substrate **5a** (R_f=0.45, dichloromethane/acetone 50:1) was recovered in 18% yield and then with dichloromethane/acetone 30:1 gave **7a** (R_f=18, dichloromethane/acetone 50:1) as a white solid. Characterization data for **7a** are given in Section 4.4.1.

Following this general procedure, the products **7b–d** were also obtained from **5b–d**, **8a–d** from **6a–d** and **14** and **16** from appropriate model indoles **12** and **13**, respectively. These yields and the identification data are given below.

4.4.1. 2-(6,7-Dihydro-5*H*-[2]pyrindin-3-yl)-1-phenylsulfonyl-1*H*-indole (7a). Yield 110 mg (59%); 147–148 °C; IR (KBr): 3062, 3002, 2958, 2923, 2858, 1607, 1548, 1449, 1371, 1305, 1189, 1176, 1115, 1089, 1059, 996, 888, 829, 755, 728 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.19 (2H, quintet, J=7.6 Hz), 3.03 (4H, 2×t, J=7.6 Hz), 6.85 (1H, s), 7.24 (1H, m), 7.31 (2H, t, J=7.6 Hz), 7.33 (1H, d, J=7.6 Hz), 7.42 (1H, t, J=7.6 Hz), 7.44 (1H, m), 7.59 (1H, s), 7.69 (2H, d, J=7.6 Hz), 8.18 (1H, d, J=8.4 Hz), 8.54 (1H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.0, 30.2, 32.6, 114.6, 116.2, 121.2, 122.4, 124.3, 125.1, 127.0, 128.6, 130.5, 133.5, 137.1, 137.9, 140.0, 141.7, 144.6, 148.9, 153.3; EIMS *m*/*z* (%): 374 (M^+, 27), 310 (97), 233 (100), 205 (17); HRMS (EI, M^+) found 374.1088, calcd for $C_{22}H_{18}N_2O_2S$ 374.1089.

4.4.2. 1-Phenylsulfonyl-2-(5,6,7,8-tetrahydroisoquinolin-3-yl)-1*H*-indole (7b). Yield 116 mg (60%); mp 160–161 °C lit.[13a] 158.5–159.5 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 1.84–192 (4H, m), 2.80–2.90 (4H, m), 6.85 (1H, s), 7.23 (1H, dd, J=7.2, 1.2 Hz), 7.28–7.39 (3H, m), 7.41 (1H, s), 7.42–7.48 (2H, m) 7.69 (2H, d, J=7.2 Hz), 8.18 (1H, dd, J=8.3, 0.7 Hz), 8.39 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 22.5, 26.2, 28.8, 115.0, 116.3, 121.3, 122.4, 125.2, 126.5, 127.1, 128.7, 130.5, 133.1, 133.5, 137.0, 138.0, 140.0, 146.2, 147.6, 148.9; EIMS *m*/*z* (%): 388 (M^+, 20), 324 (100), 261 (17), 247 (75), 231 (7), 219 (22), 205 (6), 192 (5); HRMS (EI, M^+) found 388.12414, calcd for $C_{23}H_{20}N_2O_2S$ 388.12455.

4.4.3. 1-Phenylsulfonyl-2-(6,7,8,9-tetrahydro-5*H*-cyclohepta[*c*]pyridine-3yl)-1*H*-indole (7c). Yield 112 mg (56%); mp 149–150 °C; IR (KBr): 3062, 2998, 2923, 2858, 1616, 1604, 1483, 1446, 1370, 1317, 1189, 1168, 1115, 1090, 1069, 995, 823, 751, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.65–1.81 (4H, m), 1.82–1.97 (2H, m), 2.85–2.92 (4H, m), 6.84 (1H, d, J=0.7 Hz), 7.24–7.48 (6H, m) 7.43 (1H, s), 7.69 (2H, dt, J=7.2, 1.4 Hz), 8.20 (1H, dd, J=8.3, 0.7 Hz), 8.39 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.4, 27.9, 32.6, 33.2, 36.3, 114.7, 116.2, 121.2, 124.3, 125.1, 126.3, 127.0, 128.6, 130.5, 133.5, 137.0, 138.0, 138.4, 141.4, 148.3, 149.3, 151.5; EIMS *m*/*z* (%): 402 (M^+, 21), 338 (100), 275 (15), 261 (56), 245 (6), 219 (10), 205 (7), 192 (4); HRMS (EI, M^+) found 402.1382, calcd for $C_{24}H_{22}N_2O_2S$ 402.1402.

4.4.4. 2-(5,6,7,8,9,10-Hexahydrocycloocta[*c*]pyridin-3-yl)-1-phenysulfonyl-1*H*-indole (7d). Yield 114 mg (55%); mp 162–163 °C; IR (KBr): 3062, 3003, 2979, 2923, 2858, 1616, 1601, 1514, 1476, 1374, 1327, 1165, 1143, 1105, 1090, 1055, 985, 845, 759, 723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.35–1.47 (4H, m), 1.69–1.80 (4H, m), 2.76–2.83 (4H, m), 6.86 (1H, d, J=0.7 Hz), 7.22–7.44 (6H, m), 7.47 (1H, s), 7.67 (2H, dt, J=7.2, 1.4 Hz), 8.15 (1H, dd, J=8.3, 0.7 Hz), 8.33 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.3, 25.6, 29.1, 30.6, 31.8, 32.0, 115.1, 116.1, 121.3, 124.2, 125.4, 126.7, 127.0, 128.7, 130.5, 133.1, 133.3, 137.1, 138.4, 139.9, 148.9, 148.5, 148.7; EIMS *m*/*z* (%): 416 (M^+, 15), 352 (100), 288 (15), 275 (52), 259 (5), 219 (10), 205 (7), 192 (4); HRMS (ESI, $[M+H]^+$) found 417.1637, calcd for $C_{25}H_{25}N_2O_2S$ 417.1637.

4.4.5. 2-(6,7-Dihydro-5*H*-[*c*]pyrindin-3-yl)-5-methoxy-1-phenylsulfonyl-1*H*-indole (8a). Yield 115 mg (57%); mp 101.5–102.5 °C; IR (KBr): 3063, 2930, 2859, 1604, 1552, 1466, 1447, 1370, 1292, 1214, 1181, 1157, 1090, 1029, 855, 809, 734, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.19 (2H, quintet, J=7.6 Hz), 3.03 (4H, 2×t, J=7.6 Hz), 3.85 (3H, s), 6.82 (1H, s), 6.88 (1H, d, J=2.4 Hz), 6.94 (1H, dd J=8.8, 2.4 Hz), 7.30 (2H, t, J=7.6 Hz), 7.42 (1H, t, J=7.6), 7.60 (2H, d, J=7.6 Hz), 7.61 (1H, s), 8.07 (1H, d, J=8.8 Hz), 8.54 (1H, s); ^{13}C NMR (100 MHz,

$CDCl_3$): δ 25.0, 30.2, 32.7, 55.5, 103.6, 114.2, 115.8, 117.4, 122.8, 127.0, 128.6, 131.7, 132.6, 133.5, 136.5, 140.2, 141.8, 144.0, 148.4, 154.0, 157.1; EIMS *m/z* (%): 404 (M^+, 28), 340 (65), 263 (100), 248 (14), 219 (22), 192 (5), 168 (9); HRMS (EI, M^+) found 404.11920, calcd for $C_{23}H_{20}N_2O_3S$ 404.11946.

4.4.6. 5-Methoxy-1-phenylsulfonyl-2-(5,6,7,8-tetrahydroisoquinolin-3-yl)-1*H*-indole (8b). Yield 117 mg (56%); mp 125–126 °C; IR (KBr): 3065, 3005, 2956, 2927, 2844, 1606, 1545, 1469, 1369, 1215, 1182, 1144, 1099, 1029, 865, 822, 733, 721 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.83–1.92 (4H, m), 2.81–2.90 (4H, m), 3.79 (3H, s), 6.80 (1H, s), 6.87 (1H, d, *J*=2.4 Hz), 6.93 (1H, dd, *J*=9.2, 2.4 Hz), 7.30 (2H, t, *J*=7.6 Hz), 7.40 (1H, s), 7.42 (1H, t, *J*=7.6 Hz), 7.60 (2H, d, *J*=7.6 Hz), 8.06 (1H, d, *J*=9.2 Hz), 8.38 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$), δ 22.3, 22.4, 28.3, 28.8, 55.5, 103.6, 114.6, 115.6, 117.4, 122.6, 127.0, 128.6, 131.7, 132.6, 133.1, 133.5, 136.6, 141.5, 146.4, 148.8, 154.1, 157.1; EIMS *m/z* (%): 418 (M^+, 27), 354 (85), 339 (6), 291 (6), 277 (100), 262 (20), 249 (10), 234 (19), 218 (8), 182 (7); HRMS (ESI, $[M+H]^+$) found 419.1445, calcd for $C_{24}H_{23}N_2O_3S$ 419.1424.

4.4.7. 5-Methoxy-1-phenylsulfonyl-2-(5,6,7,8-tetrahydro-5*H*-cyclohepta[*c*]pyridin-3-yl)-1*H*-indole (8c). Yield 119 mg (55%); mp 132.5–133.5 °C; IR (KBr): 3063, 2998, 2923, 2850, 1605, 1550, 1471, 1447 1371, 1294, 1217, 1179, 1150, 1091, 1031, 807, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ.1.65–1.81 (4H, m), 1.82–1.97 (2H, m), 2.86–2.96 (4H, m), 3.83 (3H, s), 6.81 (1H, s), 6.87 (1H, d, *J*=2.4 Hz), 6.93 (1H, dd, *J*=9.2, 2.4 Hz), 7.30 (2H, t, *J*=7.6 Hz), 7.42 (1H, t, *J*=7.6 Hz), 7.46 (1H, s), 7.58 (2H, d, *J*=7.6 Hz), 8.07 (1H, d, *J*=9.2 Hz), 8.38 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.4, 27.8, 32.6, 33.2, 36.3, 55.5, 103.6, 114.6, 115.6, 117.4, 122.7, 127.0, 128.6, 131.7, 132.7, 133.1, 133.5, 136.6, 141.8, 146.4, 148.8, 154.0, 157.1; EIMS *m/z* (%): 432 (M^+, 23), 368 (100), 353 (5), 305 (5), 291 (96), 276 (17), 263 (6), 248 (17), 219 (9), 205 (5), 196 (5); HRMS (ESI, $[M+H]^+$) found 433.1602, calcd for $C_{25}H_{25}N_2O_3S$ 433.1580.

4.4.8. 2-(5,6,7,8,9,10-Hexahydrocycloocta[*c*]pyridin-3-yl)-5-methoxy-1-phenylsulfonyl-1*H*-indole (8d). Yield 116 mg (52%); mp 116–117 °C; IR (KBr): 3063, 2997, 2925, 2853, 1606, 1549, 1470, 1447, 1371, 1298, 1214, 1178, 1148, 1090, 1031, 912, 859, 809, 757, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.37–1.50 (4H, m), 1.71–1.81 (4H, m), 2.80–2.90 (4H, m), 3.85 (3H, s), 6.79 (1H, s), 6.88 (1H, d, *J*=2.4 Hz), 6.92 (1H, dd, *J*=9.2, 2.4 Hz), 7.29 (2H, t, *J*=7.6 Hz), 7.41 (1H, t, *J*=7.6 Hz), 7.45 (1H, s), 7.56 (2H, d, *J*=7.6 Hz), 8.05 (1H, d, *J*=9.2 Hz), 8.36 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.2, 25.5, 29.0, 30.3, 31.7, 31.9, 55.5, 103.6, 114.6, 115.5, 117.4, 122.5, 127.0, 128.6, 131.7, 132.6, 133.0, 133.5, 136.3, 141.6, 146.1, 148.8, 154.1, 157.1; EIMS *m/z* (%): 446 (M^+, 15), 382 (100), 367 (5), 319 (4), 305 (63), 290 (5), 290 (5), 262 (7), 247 (4), 233 (5), 219 (6), 206 (6); HRMS (EI, H^+) found 446.1673, calcd for $C_{26}H_{26}N_2O_3S$ 445.1664.

4.4.9. 1-Phenylsulfonyl-2-(pyridin-2-yl)-1*H*-indole (14). Yield 124 mg (74%); mp 113–114 °C (diethyl ether); IR (KBr): 3079, 3059, 3010, 2998, 1585, 1550, 1480, 1450, 1425, 1375, 1310, 1260, 1223, 1159, 1195, 1180, 1055, 1018, 1001, 980, 905, 838, 805, 760 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.88 (1H, s), 7.21–7.50 (7H, m), 7.62–7.84 (4H, m), 8.20 (1H, dd, *J*=8.3, 1.5 Hz), 8.69 (1H, ddd, *J*=5.0, 1.7, 1.0 Hz); EIMS *m/z* (%): 334 (M^+, 35), 270 (100), 241 (5), 209 (4), 193 (98), 166 (80), 140 (34); HRMS (EI, M^+) found 334.0770, calcd for $C_{19}H_{14}N_2O_2S$ 334.0776; Elem. anal. Found C, 68.15; H, 4.25; N, 8.33. Calcd for $C_{19}H_{14}N_2O_2S$: C, 68.25; H, 4.22; N, 8.38.

4.4.10. 5-Methoxy-1-phenylsulfonyl-2-(pyridin-2yl)-1*H*-indole (15). Yield 127 mg (70%); mp 92–93 °C (diethyl ether); IR (KBr): 3063, 2997, 2925, 1600, 1544, 1460, 1443, 1375, 1290, 1210, 1130, 1100, 1090, 1021, 902, 869, 803, 755, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.77 (3H, s), 6.82 (1H, s), 6.88 (1H, d, *J*=2.2 Hz), 6.95 (1H, dd, *J*=8.7, 2.2 Hz), 7.26–7.35 (3H, m), 7.42 (1H, t, *J*=7.6 Hz), 7.56 (2H, d, *J*=7.9 Hz), 7.71–7.78 (2H, m), 8.08 (1H, d, *J*=8.3 Hz), 8.36 (1H, d, *J*=5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.8, 103.9, 114.6, 116.4, 117.7, 123.4, 126.7, 128.8, 131.8, 132.6, 133.0, 133.7, 135.8, 136.7, 142.0, 148.9, 151.5, 157.3; EIMS *m/z* (%): 364 (M^+, 55), 300 (88), 221 (100), 206 (16), 177 (27); HRMS (ESI, $[M+H]^+$) found 365.0967, calcd for $C_{20}H_{17}N_2O_3S$ 365.0954.

4.5. The final alkaloids 9a–d, 10a–d and model compounds 16 and 17 preparation in modified Gribble's procedure one pot annulation of the C ring

A solution of the protected indole **7a** (75 mg, 0.02 mmol) in THF (15 mL) was stirred under argon and cooled to −70 °C. A 1.6 M solution of *n*-butyllithium in hexane (0.63 mL, 1.0 mmol) was added dropwise for 2 min, and stirring was continued for 1 h at −70 °C and then the reaction mixture was warmed to −20 °C for 1 h. A orange solution was obtained and then it was cooled to −70 °C and a 0.62 M dry bromoacetaldehyde solution in dichloromethane/hexane[24] (2.5 mL, 1.55 mmol) was added dropwise for 5 min. The reaction mixture was stirred at −70 °C for 1 h and then it was allowed to warm to −10 °C for another hour. The reaction mixture was cooled to −70 °C and water (0.18 mL, 10 mmol) was added dropwise with stirring for 1 h, then it was allowed to warm to 0 °C over another hour, and saturated ammonium chloride (10 mL) and CH_2Cl_2 (30 mL) were added. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2 (30 mL). The combined organic phases were dried with Na_2SO_4 and concentrated. A yellow oily residue was obtained, which was dissolved in $CHCl_3$ (5 mL) and was refluxed for 30 min. The solvent was removed and the residue was washed with diethyl ether (3×4 mL). The pale yellow crude powder (salt) was quenched with methanol (20 mL) and 10% sodium hydroxide (4 mL) and it was heated at reflux for 1 h. The reaction mixture was cooled and concentrated in vacuo. The residue was partitioned between $CHCl_3$ (40 mL) and 20% sodium hydroxide (5 mL). The organic layer was washed with water (15 mL) and dried with Na_2SO_4 and concentrated. Purification of the residue by preparative thin-layer chromatography on silica gel plates using dichloromethane/methanol 5:1 as an eluent afforded pure **9a** (28 mg, 55%) as a dark yellow amorphic powder, shows decomposition above 250 °C

during the measurement of the melting point. Identification data for **9a** is given in Section 4.5.1.

Following this general procedure, the products **9b–d** were obtained from **7b–d**, **10a–d** from **8a–d** and model **16** and **17** from appropriate model protected indoles **14** and **15**, respectively. These yields and the identification data are given below.

4.5.1. 2,3-Dihydro-1*H*-cyclopent[*g*]indolo[2,3-*a*]quinolizine (9a). Yellow powder, yield 28 mg (55%); mp 260–265 °C (dec); IR (KBr): 3060, 2950, 2924, 2854, 1635, 1603, 1448, 1410, 1366, 1330, 1171, 1084, 747, 570, 463 cm^{-1}; UV (MeOH) λ_{max}: 235, 302, 333, 360, 382 nm; ^1H NMR (400 MHz, CD_3OD): δ 2.20 (2H, m), 2.87 (2H, m), 3.04 (2H, m), 7.45–7.49 (1H, m), 7.69–7.73 (1H, m), 7.79 (1H, d, J=8.4 Hz), 8.33 (1H, d, J=8.0 Hz), 8.55 (1H, d, J=6.8 Hz), 8.61 (1H, s), 8.78 (1H, d, J=6.8 Hz), 9.10 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.0, 30.8, 32.9, 113.3, 117.0, 118.8, 122.1, 122.0, 122.5, 125.0, 128.3, 129.1, 132.9, 133.9, 135.2, 140.5, 144.4, 156.1; EIMS (temp=306 °C: spectrum showed some products of the thermal decomposition of the product), *m/z* (%): 258 (M^+, 9), 129 (M^{++}, 15), 126 (18), 111 (25), 95 (42), 83 (49), 69 (61), 57 (100); HRMS (ESI, $[M+H]^+$) found 259.1238, calcd for $C_{18}H_{15}N_2$ 259.1213.

4.5.2. 2,3,4,13-Tetrahydro-1*H*-benz[*g*]indolo[2,3-*a*]quinolizin-6-ium inner salt (9b). Orange-red powder, yield 32 mg (58%); mp 259–262 °C (dec), lit.[11] 258–260 °C; IR (KBr): 3055, 2935, 2860, 1650, 1635, 1603, 1560, 1464, 1447, 1375, 1164, 1094, 747, 620 cm^{-1}; UV (MeOH) λ_{max}: 238.5, 294.0, 330.5, 366.0, 385.5 nm; ^1H NMR (400 MHz, CD_3OD): δ 1.97–2.04 (4H, m), 3.08 (2H, m), 3.24 (2H, m) 7.46 (1H, td, J=8.0, 1.2 Hz), 7.70 (1H, td, J=8.0, 1.2 Hz), 7.79 (1H, dd, J=8.0, 1.2 Hz), 8.32 (1H, dd, J=8.0, 1.2 Hz), 8.50 (1H, s), 8.53 (1H, d, J=6.8 Hz), 8.72 (1H, d, J=6.8 Hz), 9.05 (1H, s); ^{13}C NMR (100 MHz, CD_3OD): δ 22.4, 22.5, 26.3, 28.5, 115.6, 117.7, 119.5, 120.5, 121.0, 121.7, 123.6, 125.8, 126.9, 131.3, 134.5, 134.9, 140.8, 144.1, 155.1; EIMS (temp=231 °C: spectrum showed some products of the thermal degradation), *m/z* (%): 272 (M^+, 9), 136 (M^{++}, 9), 128 (18), 111 (25), 95 (42), 83 (49), 69 (61), 57 (100); HRMS (ESI, $[M+H]^+$) found 273.1374, calcd for $C_{19}H_{17}N_2$ 273.1386.

4.5.3. 2,3,4,5-Tetrahydro-1*H*-cyclohept[*g*]indolo[2,3-*a*]quinolizine (9c). Pale brown powder, yield 30 mg (53%); mp 269–272 °C (dec); IR (KBr): 3061, 2925, 2853, 1649, 1633, 1600, 1521, 1470, 1410, 1370, 1329, 1261, 1226, 1191, 1096, 800, 775, 766, 746, 659, 599, 568, 468 cm^{-1}; UV (MeOH) λ_{max}: 238.0, 294.5, 330.5, 366.5, 385.0 nm; ^1H NMR (400 MHz, CD_3OD): δ 1.80 (4H, m), 1.95 (2H, m), 3.06 (2H, m), 3.12 (2H, m), 7.47 (1H, td, J=8.0, 1.2 Hz), 7.72 (1H, td, J=8.0, 1.2 Hz), 7.80 (1H, dd, J=8.0, 1.2 Hz), 8.34 (1H, dd, J=8.0, 1.2 Hz), 8.54 (1H, s), 8.57 (1H, d, J=6.8 Hz), 8.75 (1H, d, J=6.8 Hz), 9.06 (1H, s); ^{13}C NMR (100 MHz, CD_3OD): δ 27.4, 27.8, 32.8, 33.6, 36.2, 115.1, 117.3, 121.6, 122.1, 123.0, 124.5, 125.6, 127.5, 128.1, 132.3, 133.1, 136.9, 140.5, 144.2, 155.9; EIMS (temp=298 °C: in the spectrum appeared some products of the thermal degradation), *m/z* (%): 286 (M^+, 12), 257 (13), 143 (M^{++}, 5), 128 (15), 111 (28), 95 (38), 83 (47), 69 (57), 57 (100); HRMS (ESI, $[M+H]^+$) found 287.1542, calcd for $C_{20}H_{19}N_2$ 287.1543.

4.5.4. 9,10,11,12,13,14-Hexahydrocyclooct[*g*]indolo[2,3-*a*]quinolizine (9d). Dark yellow powder, yield 33 mg (55%); mp 254–256 °C (dec); IR (KBr): 3058, 2940, 2865, 1648, 1630, 1601, 1555, 1454, 1417, 1380, 1175, 1099, 747, 620, 455 cm^{-1}; UV (MeOH) λ_{max}: 245.0, 297.0, 330.5, 360.0, 383.5 nm; ^1H NMR (400 MHz, CD_3OD): δ 1.57–1.47 (4H, m), 1.86–2.00 (4H, m), 3.10 (2H, t, J=6.0 Hz), 3.20 (2H, t, J=6.0 Hz), 7.46 (1H, t, J=8.0 Hz), 7.70 (1H, t, J=8.0 Hz), 7.79 (1H, d, J=8.0 Hz), 8.32 (1H, d, J=8.0 Hz), 8.54 (1H, d, J=6.8 Hz), 8.58 (1H, s), 8.75 (1H, d, J=6.8 Hz), 9.10 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.0, 28.1, 31.7, 32.2, 34.5, 34.6, 115.1, 118.6, 122.3, 124.1, 124.6, 125.5, 127.7, 128.8, 132.0, 133.0, 134.6, 137.4, 140.7, 144.4, 156.9; EIMS (temp=294 °C) *m/z* (%): 300 (M^+, 100), 271 (9), 256 (10), 243 (7), 218 (4), 205 (3), 150 (M^{++}, 4), 128 (6), 109 (6), 95 (9), 83 (10), 69 (13), 57 (21); HRMS (ESI, $[M+H]^+$) found 301.1718, calcd for $C_{21}H_{21}N_2$ 301.1705.

4.5.5. 9-Methoxy-2,3-dihydro-1*H*-cyclopent[*g*]indolo[2,3-*a*]quinolizine (10a). Yellow-green powder, yield 31 mg (54%); mp 275–278 °C (dec); IR (KBr): 3065, 2960, 2925, 2870, 1647, 1599, 1470, 1440, 1366, 1270, 1160, 1014, 758, 779, 555, 469 cm^{-1}; UV (MeOH) λ_{max}: 232.5, 248.0, 307.0, 352.5, 385.5 nm; ^1H NMR (400 MHz, $CDCl_3$): δ 2.22 (2H, m), 3.01 (2H, m), 3.12 (2H, m), 3.95 (3H, s), 7.19 (1H, m), 7.47 (1H, m), 7.90 (1H, d, J=8.6 Hz), 8.00 (1H d, J=6.8 Hz), 8.07 (1H, d, J=6.8 Hz), 8.33 (1H, s), 8.94 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.7, 30.1, 32.5, 55.9, 100.7, 115.7, 116.9, 119.6, 122.3, 125.2, 128.2, 129.0, 129.5, 130.5, 132.0, 137.9, 145.1, 159.1, 160.8; EIMS (temp=344 °C), *m/z* (%): 288 (M^+, 9), 273 (100), 245 (43), 216 (4), 144 (M^{++}, 12), 122 (12); HRMS (ESI, $[M+H]^+$) found 289.1344, calcd for $C_{19}H_{17}N_2O$ 289.1335.

4.5.6. 10-Methoxy-2,3,4,13-tetrahydro-1*H*-benz[*g*]indolo[2,3-*a*]quinolizin-6-ium inner salt (10b). Yellow-green powder, yield 34 mg (56%); mp 277–280 °C (dec); IR (KBr): 3065, 2960, 2925, 2855, 1646, 1600, 1449, 1360, 1310, 1220, 1117, 1017, 875, 770, 618, 554, 470 cm^{-1}; UV (MeOH) λ_{max}: 233.5, 248.0, 308.5, 354.0, 392.0 nm; ^1H NMR (400 MHz, $CDCl_3$): δ 1.84–1.98 (4H, m), 2.90 (2H, m), 3.06 (2H, m), 3.95 (3H, s), 7.21 (1H, dd, J=8.8, 2.0 Hz), 7.53 (1H, d, J=2.0 Hz), 7.80 (1H, d, J=6.0 Hz), 7.93 (1H, d, J=8.8 Hz), 8.12 (1H, d, J=6.0 Hz), 8.17 (1H, s), 8.92 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 26.3, 28.9, 29.7, 55.9, 100.6, 115.7, 116.9, 119.6, 121.1, 126.3, 127.7, 129.4, 130.7, 132.1, 138.3, 145.2, 159.6, 160.8; EIMS (temp=353 °C), *m/z* (%): 302 (M^+, 86), 287 (100), 259 (21), 231 (4), 207 (4), 151 (M^{++}, 16), 127 (18), 112 (31); HRMS (ESI, $[M+H]^+$) found 303.1503, calcd for $C_{20}H_{19}N_2O$ 303.1492.

4.5.7. 11-Methoxy-2,3,4,5-tetrahydro-1*H*-cyclohept[*g*]indolo[2,3-*a*]quinolizine (10c). Yellow-green powder, yield 31 mg (49%); mp 270–275 °C (dec); IR (KBr): 3060, 2924, 2853, 1638, 1550, 1480, 1448, 1390, 1280, 1218, 1124, 1037, 875, 770, 696, 551, 470 cm^{-1}; UV (MeOH) λ_{max}: 232.5, 249.0, 303.5, 355.0, 385.0 nm; ^1H NMR (400 MHz, CD_3OD): δ 1.78–196 (6H, m), 3.04–3.08 (4H,

m), 3.87 (3H, s), 7.33 (1H, dd, J=8.4, 2.2 Hz), 7.66 (1H, d, J=8.4 Hz), 7.78 (1H, d, J=2.2 Hz), 8.46 (1H, s), 8.52 (1H, d, J=6.8 Hz), 8.66 (d, J=6.6 Hz), 8.17, 9.00 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$), δ 26.8, 27.5, 28.3, 34.5, 36.2, 55.9, 100.3, 115.3, 118.9, 122.5, 123.9, 126.2, 128.4, 129.1, 129.5, 130.8, 132.5, 137.8, 145.4, 159.9, 160.0; EIMS (temp=342 °C), m/z (%): 316 (M^+, 6), 301 (7), 273 (3), 205 (4), 162 (4), 158 (M^{++}, 3), 127 (28), 110 (20), 84 (100); HRMS (ESI, $[M+H]^+$) found 317.1651, calcd for $C_{21}H_{21}N_2O$ 317.1648.

4.5.8. 3-Methoxy-9,10,11,12,13,14-hexahydrocyclooct[*g*]quinolizine (10d). Yellow-green powder, yield 36 mg (55%); mp 262–266 °C (dec); IR (KBr): 3060, 2923, 2853, 1646, 1590, 1475, 1450, 1410, 1366, 1297, 1223, 1193, 1170, 1016, 878, 813, 553, 470 cm^{-1}; UV (MeOH) λ_{max}: 232.5, 248.0, 305.5, 340.5, 362.5, 385.0 nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50–185 (8H, m), 2.78–2.88 (2H, m), 2.90–2.98 (2H, m), 3.95 (3H, s), 7.35 (1H, d, J=8.4 Hz), 7.46 (1H, s), 7.91 (1H, d, J=8.4 Hz), 8.03 (1H, d, J=6.8 Hz), 8.07 (d, J=6.6 Hz), 8.31 (1H, s), 8.91 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.5, 25.6, 29.5, 29.7, 31.7, 32.3, 55.9, 100.7, 115.9, 121.4, 125.3, 127.9, 128.1, 128.8, 129.0, 129.6, 130.9, 132.2, 137.8, 145.8, 159.9, 161.1; EIMS (temp=259 °C), m/z (%): 330 (M^+, 77), 315 (100), 287 (15), 271 (4), 245 (4), 223 (11), 205 (6), 194 (27), 165 (M^{++}, 15), 121 (10); HRMS (ESI, $[M+H]^+$) found 331.1816, calcd for $C_{22}H_{23}N_2O$ 331.1805.

4.5.9. Indolo[2,3-*a*]quinolizine (16). Yellow powder, yield 28 mg (65%); mp 277–280 °C (dec); IR (KBr): 3065, 1647, 1599, 1470, 1427, 1366, 1195, 1160, 748, 770, 550, 475 cm^{-1}; UV (MeOH) λ_{max}: 236.0, 243.5, 291.5, 342.5, 385.5 nm; lit.[27] UV (perchlorate, MeOH) λ_{max}: 222, 237, 244, 293, 344, 386; lit.[27] UV (MeOH/KOH) λ_{max}: 225, 240, 287, 319, 361, 435; EIMS (temp=322 °C), m/z (%): 218 (M^+, 100), 194 (7), 143 (4), 109 (M^{++}, 18), 95 (20); HRMS (EI, M^+) found 218.08431, calcd for $C_{15}H_{10}N_2$ 218.08440.

4.5.10. 9-Methoxyindolo[2,3-*a*]quinolizine (17). Yellow-green powder, yield 30 mg (60%); mp 267–271 °C (dec); IR (KBr): 3060, 2970, 2865, 1646, 1600, 1449, 1310, 1220, 1117, 875, 770, 618, 554, 470 cm^{-1}; UV (MeOH) λ_{max}: 224.0, 243.5, 307.5, 351.5, 386.5 nm; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.97 (3H, s), 7.23 (1H, dd, J=8.6, 2.0 Hz), 7.56 (1H, d, J=2.0 Hz), 7.68 (1H, d, J=2.0 Hz), 7.80–7.95 (3H, m), 8.12 (1H, d, J=6.4 Hz), 8.33 (1H, d, J=6.4 Hz), 8.48 (1H, s), 9.12 (1H, d, J=5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), δ 55.9, 100.5, 113.7, 122.4, 125.2, 127.7, 127.8, 128.0, 128.8, 129.0, 131.9, 135.5, 141.8, 148.8, 159.1, 161.0; EIMS (temp=305 °C), m/z (%): 248 (M^+, 68), 233 (100), 205 (55), 177 (4), 151 (5), 124 (M^{++}, 10), 102 (8), 89 (8); HRMS (ESI, $[M+H]^+$) found 249.1035, calcd for $C_{16}H_{13}N_2O$ 249.1022.

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References and notes

1. Part 35 in a series '1,2,4-Triazines in Organic Synthesis'. For Part 34, see: Mojzych, M.; Rykowski, A. *Heterocycl. Commun.*, in press.
2. Le Hir, A. *Ann. Pharm. Fr.* **1955**, *13*, 368–372.
3. (a) Beljanski, M.; Beljanski, M. S. *Expl. Cell Biol.* **1982**, *50*, 79–87; (b) Bassler, R.; Clermont, D.; Marnette, J. M.; Caprasse, M.; Tits, M.; Angenot, L. *Ann. Pharm. Fr.* **1984**, *43*, 83–88; (c) Beljanski, M.; Beljanski, M. S. *Oncology* **1986**, *43*, 198–203; (d) Beljanski, M.; Crochet, S. *Int. J. Oncol.* **1996**, *8*, 1143–1148 and lit cit therein.
4. (a) Caprasse, M.; Houssier, C. *Biochimie* **1984**, *66*, 31–41; (b) *Nucleic Acid Targeted Grug Design*; Propst, C. L., Perum, T. J., Eds.; Marcel Dekker: New York, NY, 1992.
5. (a) Bousta, D.; Soulimani, R.; Jarmouni, I.; Belon, P.; Falla, J.; Froment, N.; Younos, C. *J. Ethnopharmacol.* **2001**, *74*, 205–215; (b) Saxena, G.; Tudan, C. R.; Solari, H.; *Patent Cooperation Treaty Application Nov. 2002, WO02094270*; European Patent Office: http://v3.espancenet.com/texdoc?DB=EDODOC&IDX=WO02094270&F=0.
6. (a) Costa-Campos, L.; Lara, D. R.; Nunes, D. S.; Elisabetsky, E. *Pharmacol., Biochem. Behav.* **1998**, *60*, 133–141; (b) Costa-Campos, L.; Dasspler, S. C.; Rigo, A. P.; Iwu, M.; Elisabetsky, E. *Pharmacol., Biochem. Behav.* **2004**, *77*, 481–489.
7. Ingelman-Sundberg, M. *Pharmacogenomics J.* **2005**, *5*, 6–13.
8. For a review on structure and synthesis of the indolo[2,3-*a*]quinolizine alkaloids see: Gribble, G. W. *Studies in Natural Products. Stereoselective Synthesis,* Part A; Atta ur-Rahman, Ed.; Elsevier: Amsterdam, 1988; Vol. 1, pp 123–162.
9. For a review on heterocyclic mesomeric betaines and zwitterions in natural products, see: Schmidt, A. *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Elsevier Science: USA, 2003; Vol. 85, pp 68–171; imprinted by Academic Press, 2004.
10. (a) For the farmacognostic determination of the *Gelsemium*: Sayre's Organic Materia Medica, 1917: Gelsemium Sempervirens, Gelsemium, Yellow Jasmine: http://www.ibiblio.org/herbmed/eclectic/sayre/gelsemium.html; (b) Sempervirine Nitrate exists as a Bioreagent in Fisher Scientific International, Cat. No. ICN218419.
11. Chaterjee, A.; Sahu, A.; Saha, M.; Banerji, J. *Monatsh. Chem.* **1996**, *127*, 1259–1262.
12. Bently, R.; Stevens, T. S.; Thompson, M. *J. Chem. Soc. C* **1970**, 791–795.
13. (a) Gribble, G. W.; Barden, T. C.; Johnson, D. A. *Tetrahedron* **1988**, *44*, 3195–3202; (b) Gribble, G. W.; Johnson, D. A. *Tetrahedron Lett.* **1987**, *28*, 5259–5262.
14. (a) Rykowski, A.; Mąkosza, M. *Tetrahedron Lett.* **1984**, *25*, 4795–4798; (b) Rykowski, A.; Lipińska, A. *Synth. Commun.* **1996**, *26*, 4409–4414; (c) Rykowski, A.; Olender, E.; Branowska, D.; van der Plas, H. C. *Org. Prep. Proced. Int.* **2001**, *33*, 501–503.
15. (a) Rykowski, A.; Lipińska, T. *Pol. J. Chem.* **1997**, *71*, 83–90; (b) Lipińska, T. *Tetrahedron Lett.* **2002**, *43*, 9565–9657.
16. Lipińska, T. *Tetrahedron Lett.* **2004**, *45*, 8331–8334.
17. Paudler, W. W.; Chen, T. K. *J. Heterocycl. Chem.* **1970**, *7*, 767–770.
18. Lipińska, T. *Tetrahedron* **2005**, *61*, 8148–8158.
19. Sugasawa, S.; Terashima, M.; Kanaoka, Y. *Chem. Pharm. Bull. Jpn.* **1956**, *4*, 16–19.
20. Lipińska, T.; Guibe-Jampel, E.; Petit, A.; Loupy, A. *Synth. Commun.* **1999**, *29*, 1349–1354.

21. Lipińska, T. M.; Czarnocki, S. J. *Org. Lett.* **2006**, *8*, 367–370.
22. Fujii, T.; Ohba, M.; Ohashi, T. *Tetrahedron* **1993**, *49*, 1879–1890.
23. Wachsmuth, O.; Matuch, R. *Phytochemistry* **2002**, *61*, 705–709.
24. Kraus, G. A.; Guttschalk, P. *J. Org. Chem.* **1983**, *48*, 2111–2211.
25. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon: Oxford, 1992.
26. For the 2-(2-pyridyl)indole recent data, see: (a) Amat, M.; Hadida, S.; Pshenichnyi, G.; Bosch, J. *J. Org. Chem.* **1997**, *62*, 3158–3175; (b) Liu, S.-F.; Wu, Q.; Schmider, H. L.; Aziz, H.; Hu, N.-X.; Popković, Z.; Wang, S. *J. Am. Chem. Soc.* **2000**, *122*, 3671–3678; (c) Barlo, S. M.; Lukach, A. E.; Rossi, R. A. *J. Org. Chem.* **2003**, *68*, 2807–2811.
27. Fürstner, A.; Ernst, A. *Tetrahedron* **1995**, *51*, 773–786.