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ORIGINAL PAPER

Comparative evaluation of a Pictet–Spengler protocol in microwave-assisted conversions of tryptamine with aryl- and carboxyaryl aldehydes: role of ring strain in cyclocondensation of the primarily formed carboxyaryl-substituted β-carbolines

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Abstract An efficient microwave-assisted Pictet–Spengler protocol employing boric acid/acetic acid as a catalytic system was elaborated for the synthesis of 1-aryl-β-carbolines. Under the novel conditions tryptamine and 2-formylbenzoic acid furnished a pentacyclic skeleton in a single step, whereas using *o*-phthalaldehyde as a coupling partner led to the formation of an isoindolone derivative. Three β-carbolines primarily resulted from the reactions involving carboxy-substituted heteroaryl aldehydes and avoided cyclisation to polycondensed skeletons with enhanced ring strain, as was evidenced by density functional theory (DFT) modelling.

Keywords Catalysis · Microwave irradiation · Pictet–Spengler · Anticancer · Improved methods · DFT calculations

Introduction

One of the largest groups of alkaloids are indole derivatives including 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indoles which are also referred to as β-carbolines. These derivatives have potential applications in the chemistry of pharmaceuticals and fluorescent materials. The Pictet–Spengler reaction is a powerful synthetic tool for the synthesis of building blocks of more complex molecules structurally related to indole alkaloids [1]. For instance, Cesati and Katzenellenbogen [2] reported a vinylogous Pictet–Spengler cyclization as the key step of a synthetic route leading to breast tumor imaging agents. A variant of the Pictet–Spengler reaction has also been utilized in the preparation of β-carboline-3-carboxylic acid esters displaying affinity towards benzodiazepine receptors [3]. Moreover, recent studies have demonstrated that some β-carbolines exhibit antidepressant and monoamine oxidase inhibitory effects [4] and may also be used as a last resort when treatment with all available serotonin reuptake inhibitors and tricyclic antidepressants fails [5]. The discovery that HR22C16, a linearly fused β-carboline-based heterocyclic scaffold, and its analogues are highly efficient Eg5 inhibitors inducing mitotic arrest and cell death in taxol-resistant cancer cell lines is another important development with potential pharmaceutical applications [6, 7].

β-Carbolines have been synthesized on solid supports using strong acidic conditions [8]. However, the conventional acid-catalysed reactions of tryptamine often require harsher conditions and have poor yields [9]. The Pictet–Spengler reactions involving aliphatic aldehydes have a wide coverage in the literature [10], whereas much less attention has been paid to analogous transformations using the less reactive aromatic aldehydes as coupling partners [11–15]. The methods providing 1-aryl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indoles suffer a range of disadvantages including low yields [11], prolonged reaction times [12, 13], the use of toxic solvents and reagents, or the requirement of special conditions and time-consuming purification methods [14, 15]. Yu et al. [16] used trifluoroacetic acid (TFA) in dichloromethane (DCM) at room temperature to promote Pictet–Spengler reactions of aliphatic and aromatic aldehydes with tryptamine to afford β-carboline products; however, satisfactory yields (68–88 %) could only be achieved by employing prolonged reaction times. A similar range of products was obtained by Liu and You employing

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microwave (MW) irradiation of the neat mixture of the reactants to produce yields which were highly dependent on the parameters of the MW irradiation used [17, 18]. It is also well documented that MW-assisted chemistry can be applied in diverse synthetic protocols, including conventional condensation, aza-Wittig, aza-Diels–Alder, and electrocyclisation reactions, that afford further aza-heterocycles with pharmaceutically useful structures, such as pyrazoles, diazepines [19], pyrrolines, tetrahydropyridines [20], isoquinolines [21], oxazocines along with other medium size heterocycles [22] and pyrido[4,3-*d*]pyrimidines [23]. The reader is referred to an extended review highlighting the efficiency and general importance of MW-based strategies in heterocyclic chemistry [24].

Results and discussion

In this work we undertook a comparative evaluation of four methods (methods A–D) employing aromatic aldehydes as substrates and acetic acid as solvent at reflux temperature (120 °C) in search for more expedient and high efficiency protocols with satisfactory yields, reasonable reaction time, and facile work-up to establish easy access to representative 1-aryl-β-carbolines **3a**–**3i** (Scheme 1). Transformation of **1** to **3a**–**3i** was first attempted by simply heating the reactants in acetic acid for 2–3 h (method A, Tables 1, 2, 3). When the reactions were conducted in the presence of TFA employed as catalyst no dramatic increase in the yields could be achieved (method B, Tables 1, 2, 3).

At this stage we resorted to the use of boric acid suspended in acetic acid (method C, Tables 1, 2, 3) which had been recognized as an efficient catalytic system promoting Biginelli reactions [25] that are related to Pictet–Spengler condensations. Since this method proved to be slightly superior to methods A and B (i.e. resulting in higher yields), we attempted to improve this approach by MW irradiation of the reaction mixture (method D). Under these conditions the reactions were completed in 30–60 min (Tables 1, 2, 3), whereas prolonged irradiation and heating decreased the isolated yields. It is noteworthy that the reaction of **2e** performed by method D afforded **3e** in a relatively low yield (45 %), whereas the transformations of other substrates with decreased electrophilic character including the highly sensitive 10-methyl-10*H*-phenothiazine-3-carbaldehydes (**2g**–**2i**, Table 2) led to significantly higher yields of the targeted β-carbolines. On the other hand, successful transformations of chlorophenothiazines **2h**, **2i** could only be effected by method D using MW irradiation, although the formation of undefined decomposition products in reaction with 2-chloro derivative **2h** afforded **3h** in low yield (10 %).

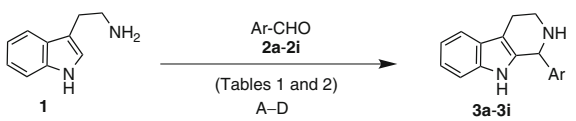
Methods C and D were also evaluated in the attempted condensation of **1** with 2-formylbenzoic acid **2j** which constructed 7,8,13,13*b*-tetrahydro-5*H*-benz[1,2]indolizino[8,7-*b*]-indol-5-one (**4**) [26] (Scheme 2) in high isolated yields (82 % by method C and 96 % by method D). In the hope of finding an expedient synthetic route to novel heterocyclic ring systems, the promising MW-based methodology was extended to the utilization of 2-formyl-5-methyl-1*H*-indole-3-carboxylic acid (**2k**), 3-formyl-1*H*-indole-4-carboxylic acid (**2l**), and 4-formyl-1*H*-pyrazole-5-carboxylic acid (**2m**) as coupling partners (Scheme 2).

The attempted reactions of **2k**–**2m** with tryptamine performed under the conditions of method D afforded carboxyaryl-substituted β-carbolines **5**–**7** with zwitterionic structures and avoided further cyclisation to the targeted fused lactams. These steps are probably prevented by the increase of overall ring strain associated with cyclisation. This was supported by the results of density functional theory (DFT) modelling of cyclocondensations of **5**–**7** constructing the targeted lactams (**8**–**10**, Scheme 3) at the B3LYP/6-31 G(d) level of theory [27–30]. For comparison, the cyclisation of the assumed intermediate **11** yielding the isolable benz[1,2]indolizino[8,7-*b*]indol-5-one (**4**) was also subjected to DFT study (Scheme 3).

The tendency of the energetic data calculated for the optimized structures of highly ring-size- and annulation-dependent internal strain is in good agreement with the outcome of preparative experiments showing that—contrary to cyclisation **11** → **4** with slightly endothermic character—the analogous reactions of **5**–**7** are highly endothermic processes.

The reaction of **1** and phthalaldehyde (**2n**) was also attempted under the conditions of method D and resulted in 2-[2-(1*H*-indol-3-yl)ethyl]isoindolin-1-one (**13**, Scheme 4). Its relatively low yield (50 %) might be ascribed to the partial polymerization of the presumed hydroxyisoindole intermediate **12**. However, in a competitive way, this intermediate is supposed to undergo tautomerization facilitated by the aromatization of the condensed benzene ring, avoiding further cyclization leading to **14** with retained quinoid-type structure of decreased stability, although its benz[1,2]indolizino[8,7-*b*]indole-type skeleton might accumulate a relatively small degree of overall ring strain. It is also noteworthy that conversion **1** + **2n** → **13** could not

Scheme 1



A: AcOH, 120 °C, 2-6 h. B: TFA/AcOH, 120 °C, 1-4 h. C: H_3BO_3/AcOH, 120 °C, 1-5 h. D: H_3BO_3/AcOH, 120 °C, MW, 200 W, mono mode, 1-2 h.

Table 1 Yields obtained for Pictet–Spengler reactions of tryptamine with commercial aryl aldehydes promoted by different catalytic systems (methods A–D, cf. Scheme 1)

Ar-CHO	Method								Product
	A[a]		B[b]		C[c]		D[d]		
	Yield/%	Reaction time/min	Yield/%	Reaction time/min	Yield/%	Reaction time/min	Yield/%	Reaction time/min	
4-Nitrobenzaldehyde (**2a**)	62	120	76	60	96	120	69	30	**3a**
4-Chlorobenzaldehyde (**2b**)	79	120	73	60	75	60	74	30	**3b**
1-Naphthaldehyde (**2c**)	51	120	70	120	83	60	83	30	**3c**
4-Methoxybenzaldehyde (**2d**)	72	180	84	60	65	90	75	30	**3d**
3,4-Dimethoxybenzaldehyde (**2e**)	78	120	37	240	75	60	45	30	**3e**
3-Methylbenzaldehyde (**2f**)	70	180	40	240	74	80	69	30	**3f**

[a] Acetic acid (2 cm^3), 120 °C, normal heating

[b] TFA (3 drops)/acetic acid (2 cm^3), 120 °C, normal heating

[c] Boric acid (35 mg)/acetic acid (2 cm^3), 120 °C, conventional heating

[d] Boric acid (35 mg)/acetic acid (2 cm^3), 120 °C, 200 W, MW (mono mode)

Table 2 Yields obtained for Pictet–Spengler reactions of tryptamine with phenothiazine carbaldehydes (cf. Scheme 1)

Ar-CHO	Method								Product
	A[a]		B[b]		C[c]		D[d]		
	Yield/%	Reaction time/min	Yield/%	Reaction time/min	Yield/%	Reaction time/min	Yield/%	Reaction time/min	
10-Methyl-10*H*-phenothiazine-3-carbaldehyde (**2g**)	52	360	69	240	83	300	95	30	**3g**
2-Chloro-10-methyl-10*H*-phenothiazine-3-carbaldehyde (**2h**)							10	60	**3h**
8-Chloro-10-methyl-10*H*-phenothiazine-3-carbaldehyde (**2i**)							48	60	**3i**

[a] Acetic acid (2 cm^3), 120 °C, normal heating

[b] TFA (3 drops)/acetic acid (2 cm^3), 120 °C, normal heating

[c] Boric acid (35 mg)/acetic acid (2 cm^3), 120 °C, conventional heating

[d] Boric acid (35 mg)/acetic acid (2 cm^3), 120 °C, 200 W, MW (mono mode)

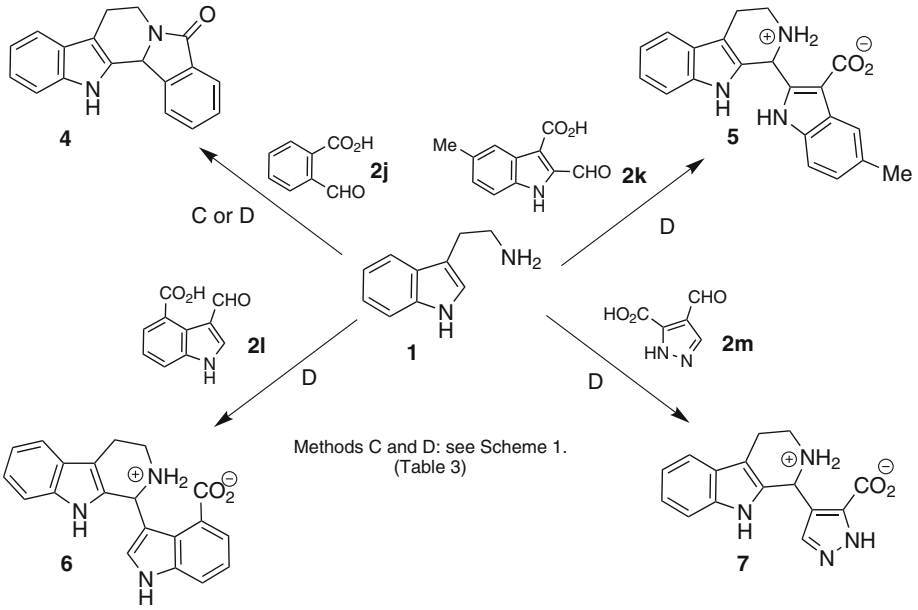
Table 3 Yields obtained for the products of Pictet–Spengler reactions involving tryptamine and carboxyaryl aldehydes conducted under the conditions of methods C and D (cf. Scheme 2)

Ar-CHO	Method				Product
	C[a]		D[b]		
	Yield/%	Reaction time/min	Yield/%	Reaction time/min	
2-Formylbenzoic acid (**2h**)	82	1,440	96	60	**4**
2-Formyl-5-methyl-1*H*-indole-3-carboxylic acid (**2k**)			62	120	**5**
3-Formyl-1*H*-indole-4-carboxylic acid (**2l**)			55	120	**6**
4-Formyl-1*H*-pyrazole-5-carboxylic acid (**2m**)			79	120	**7**
Phthalaldehyde (**2n**)			50	60	**13**

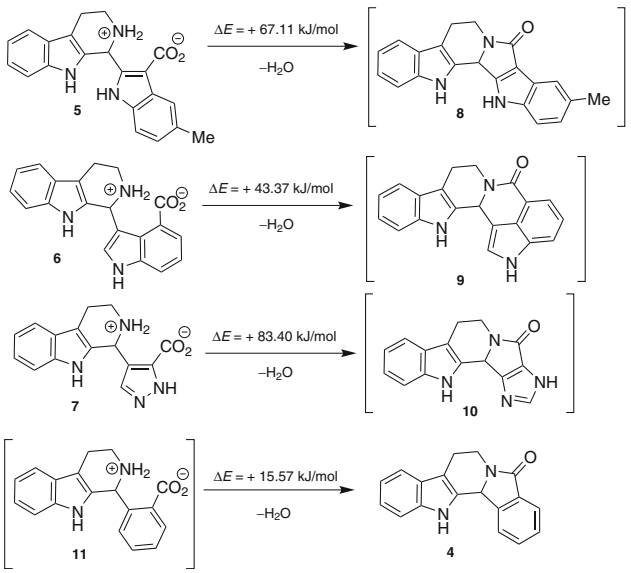
[a] Boric acid (35 mg)/acetic acid (2 cm^3), 120 °C, conventional heating

[b] Boric acid (35 mg)/acetic acid (2 cm^3), 120 °C, 200 W, MW (mono mode)

Scheme 2



Scheme 3

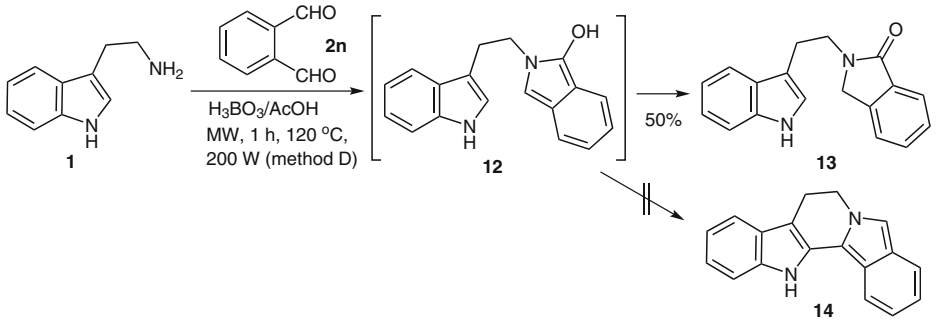


be effected by conventional heating (methods A–C) as the attempted reactions resulted in the formation of mixtures of undefined products.

The presence of the β-carboline unit in each Pictet–Spengler product is evidenced by the singlet signal of the H-1 proton and the separated multiplets of the skeletal diastereotropic H-3_A and H-3_B protons situated in the proximity of the stereogenic C-1 centre. While the signals of the NCH_2 protons of zwitterions **5–7** are discernible below 3 ppm, owing to the anisotropic deshielding effect of the adjacent lactam carbonyl group, a significant downfield shift was measured for the signal originating from the equatorial H-3 proton (4.88 ppm) of the pentacyclic fused isoindolone **4**. The presence of the five-membered lactam ring was also supported by the characteristic amide-I IR frequency at 1,667 cm^{-1} and the cross peak discernible in the ^1H–^{13}C HMBC spectrum between the signals of the NCH_2 protons and the carbonyl group separated by three bonds. On the other hand, besides the aforementioned upfield-shifted NCH_2 signals, the absence of this diagnostic cross peak in their ^1H–^{13}C HMBC spectra, the appearance of characteristic IR bands around 1,600 cm^{-1}, and the highly diffuse IR bands with higher frequencies (between ca. 3,100 and 2,500 cm^{-1}, cf. "Experimental") refer to the ammonium carboxylate structure of compounds **5–7**.

In conclusion, we demonstrated that 1-aryl-substituted 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indoles **3** can be prepared rapidly under the conditions provided by the catalytic system composed of boric acid and acetic acid, the efficiency of which was enhanced by MW irradiation. This method is also suitable for the expedient construction of 7,8,13,13*b*-tetrahydro-5*H*-benz[1,2]indolizino[8,7-*b*]indol-5-one (**4**). On the other hand, the construction of polycondensed heterocyclic skeletons with enhanced ring strain cannot be achieved by this method which promotes the formation of carboxyaryl-substituted β-carbolines. The use of these conditions also failed to produce the benz[1,2]indolizino[8,7-

Scheme 4



b]indole skeleton incorporating an isoindole unit with quinoidal structure; however, this opened up a novel pathway to phthalides. The elaboration of methods that are suitable to efficiently promote the conversions of the isolated carboxyaryl-substituted β-carbolines into the targeted heterocyclic skeletons with inherent ring strain is in progress.

Experimental

All chemicals were purchased from commercially available sources (Aldrich, Fluka) and used without further purification. The MW-assisted reactions by method D were conducted in new quartz tubes (10 cm^3) placed in a CEM Discovery LabMate instrument run in mono mode ensuring highly reproducible conditions. MW irradiation was employed at 120 °C with a power level of 200 W. Melting points were determined with an Electrothermal 1A 9200 digital melting point apparatus. The IR spectra were run by the ATR method on a Bruker IFS-55 FT spectrophotometer controlled by Opus 3.0 software. The ^1H and ^{13}C NMR spectra were recorded in 5-mm tubes at room temperature, on a Bruker DRX-500 spectrometer at 500 (^1H) and 125 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. All calculations were carried out with the Gaussian 03 suite of programs [31]. Optimized structures are available from the authors.

*General procedure for the synthesis of 1-aryl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indoles (**3a–3i**), 7,8,13,13b-tetrahydro-5H-benz[1,2]indolizino[8,7-b]indol-5-one (**4**), zwitterions **5–7**, and phthalide **13***

Tryptamine (0.160 g, 1 mmol), the aldehyde component (1 mmol), and the appropriate catalyst (3 drops of TFA in method B or 35 mg of H_3BO_3 in methods C and D) were dissolved in 2 cm^3 acetic acid. The solution was heated at 120 °C for the time of period given in Tables 1, 2 and 3 and the reaction was monitored by TLC (silica) using DCM/EtOH (99:1) as eluent. After completion the reaction mixture was evaporated to dryness in vacuo and the residue was triturated with 2 cm^3 20 % KOH solution. The resulted solid was filtered, washed thoroughly with cold water (in case of **3a–3i**, **4**, and **13**) or EtOH (in case of **5–7**), and dried over P_2O_5 to obtain the product. The yields of the crude products are listed in Tables 1, 2 and 3. Analytical samples were recrystallized from EtOH. The analytical and NMR data of **3a–3f** and **4** were practically identical to those reported in Refs. [32] and [14, 15], respectively.

10-Methyl-3-(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-10H-phenothiazine (**3g**, $C_{24}H_{21}N_3S$)
White powder; m.p.: 196–199 °C; IR (ATR): $\bar{\nu} = \sim$3,200 br, 1,543, 1,497, 1,462, 1,443, 1,396, 1,332, 1,305, 1,287, 1,249, 1,203, 1,144, 1,110, 1,006, 881, 742, 717 cm^{-1}H NMR (500 MHz, DMSO-d_6): $\delta = 2.65$ (m, 1H, H-4_A), 2.74 (m, 1H, H-4_B), 2.93 (m, 1H, H-3_A), 3.08 (m, 1H, H-3_B), 3.33 (s, 3H, NCH_3), 5.06 (s, 1H, H-1), 6.91–6.98 (overlapping m's, 4H, H-6, H-1′, H-7′, H-9′), 7.03 (t, $J = 7.7$ Hz, 1H, H-7), 7.07 (br s, 1H, H-4′), 7.15 (exactly overlapping d's, 2H, $J = 7.7$ Hz, H-2′ and H-6′), 7.23 and 7.24 (overlapping t and d, $J = 7.7$ Hz, 2H, H-8′ and H-8), 7.43 (d, $J = 7.7$ Hz, 1H, H-5), 10.38 (s, 1H, NH) ppm (protons H-1, H-3–H-8 belong to the β-carboline skeleton, whereas protons H-1′, H-2′, H-4′, H-6′, H-9′ are attached to the phenothiazine ring); ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 23.1$, 36.1, 42.6, 56.9, 109.4, 111.9, 115.1, 115.4, 118.4, 119.0, 121.4, 122.6, 122.9, 123.3, 127.58, 127.64, 127.7, 128.6, 128.7, 136.3, 136.8, 138.4, 145.4, 146.3 ppm.

2-Chloro-10-methyl-3-(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-10H-phenothiazine (**3h**, $C_{24}H_{20}ClN_3S$)
Orange powder; m.p.: 240–242 °C; IR (ATR): $\bar{\nu} = \sim$3,200 br, 1,572, 1,492, 1,460, 1,439, 1,390, 1,319, 1,296, 1,252, 1,142, 1,110, 848, 742 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): $\delta = 2.67$ (m, 1H, H-4_A), 2.78 (m, 1H, H-4_B), 2.94 (m, 1H, H-3_A), 3.04 (m, 1H, H-3_B), 3.36 (s, 3H, NCH_3), 5.40 (s, 1H, H-1), 6.67 (s, 1H, H-4′), 6.97–7.02 (overlapping m's, 3H, H-6,

H-7′, H-9′), 7.03 (t, $J = 7.7$ Hz, 1H, H-7), 7.07 (s, 1H, H-1′), 7.09 (dd, 1H, $J = 7.7$ Hz, 1.9 Hz, H-6′), 7.24 and 7.25 (overlapping t and d, $J = 7.7$ Hz, 2H, H-8′ and H-8), 7.45 (d, $J = 7.7$ Hz, 1H, H-5), 10.46 (s, 1H, NH) ppm (protons H-1, H-3–H-8 belong to the β-carboline skeleton, whereas protons H-1′, H-4′, H-6′, H-9′ are attached to the phenothiazine ring); ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 23.0$, 36.2, 41.9, 53.5, 110.1, 112.1, 115.8, 116.1, 118.5, 119.2, 121.6, 121.7, 122.4, 123.8, 127.6, 127.8, 128.4, 128.9, 133.5, 134.7, 135.0, 136.8, 145.5, 146.4 ppm.

8-Chloro-10-methyl-3-(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-10H-phenothiazine (**3i**, $C_{24}H_{20}ClN_3S$)
Light orange powder; m.p.: 208–211 °C; IR (ATR): $\bar{\nu} = \sim$3,200 br, 1,571, 1,495, 1,460, 1,426, 1,395, 1,318, 1,305, 1,267, 1,246, 1,225, 1,139, 881, 847, 805, 750, 720 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 2.67$ (m, 1H, H-4$_A$), 2.75 (m, 1H, H-4$_B$), 2.93 (m, 1H, H-3$_A$), 3.04 (m, 1H, H-3$_B$), 3.33 (s, 3H, NCH_3), 5.02 (s, 1H, H-1), 6.96–6.98 (overlapping m's, 4H, H-6, H-7, H-1′, H-9′), 7.00 (br s, 1H, H-9′), 7.07 (br s, 1H, H-4′), 7.15 (exactly overlapping d's, 2H, $J = 7.7$ Hz, H-2′ and H-8′), 7.23 (d, $J = 7.7$ Hz, 1H, H-8), 7.42 (d, $J = 7.7$ Hz, 1H, H-5), 10.36 (s, 1H, NH) ppm (protons H-1, H-3–H-8 belong to the β-carboline skeleton, whereas protons H-1′, H-2′, H-4′, H-6′, H-8′, H-9′ are attached to the phenothiazine ring); ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 23.0$, 36.2, 42.3, 56.6, 109.1, 111.9, 115.3, 115.6, 118.4, 119.1, 121.4, 121.9, 122.2, 122.9, 127.6, 127.7, 128.6, 128.9, 133.5, 136.2, 136.9, 138.9, 144.6, 147.7 ppm.

5-Methyl-2-(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-2-ium-1-yl)-1H-indole-3-carboxylate (**5**, $C_{21}H_{19}N_3O_2$)
White powder; m.p.: 196–199 °C; IR (ATR): $\bar{\nu} = 3{,}453$, 3,314, 3,045, 1,637, 1,622, 1,537, 1,446, 1,348, 1,257, 1,230, 1,155, 802, 755, 732, 625, 544, 490 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 2.42$ (s, 3H, 5′-CH_3), 2.97 (dd, $J = 15.7$, 3.8 Hz, 1H, H-4 $_{eq}$), 3.09 (ddd, $J = 15.7$, 12.3, 4.5 Hz, 1H, H-4$_{ax}$), 3.39 (m, 1H, H-3$_{ax}$, partly overlapped by the HDO signal of the solvent), 3.70 (dd, $J = 11.7$, 4.5 Hz, 1H, H-3$_{eq}$), 6.15 (s, 1H, H-1), 7.00 (t, $J = 7.7$ Hz, 1H, H-6), 7.03 (t, $J = 7.7$ Hz, 1H, H-7), 7.07 (d, $J = 7.7$ Hz, 1H, H-6′), 7.25 (d, 1H, $J = 7.7$ Hz, H-8), 7.38 (d, $J = 7.7$ Hz, 1H, H-7′), 7.46 (d, $J = 7.7$ Hz, 1H, H-5), 7.49 (br s, 1H, H-4′), 10.23 (s, 1H, NH, β-carboline), 11.40 (s, 1H, NH, 3-carboxy-5-methylindole) ppm (protons H-1, H-3–H-8 belong to the β-carboline skeleton, whereas protons H-4′, H-5′ and H-6′ are attached to the 3-carboxy-5-methylindole unit); ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 19.7$, 22.7, 42.2, 49.1, 106.4, 110.1, 112.5, 113.0, 118.7, 119.4, 119.6, 122.0, 125.6, 126.9, 128.5, 128.9, 132.3, 133.7, 134.4, 137.3, 165.6 ppm.

3-(2,3,4,9-Tetrahydro-1H-pyrido[3,4-b]indol-2-ium-1-yl)-1H-indole-4-carboxylate (**6**, $C_{20}H_{17}N_3O_2$)
Yellowish powder; m.p.: 296–300 °C; IR (ATR): $\bar{\nu} = 3{,}133$, ~3,100–2,500 br, 1,580, 1,552, 1,492, 1,411, 1,378, 1,340, 1,302, 1,295, 1,231, 1,197, 1,165, 1,042, 480, 404 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 2.98$ (m, 1H, H-4$_A$), 3.08 (m, 1H, H-4$_B$), 3.32-3.40 (m, 2H, H-3$_{A,B}$), 6.01 (s, 1H, H-1), 6.96 (br s, 1H, H-2′), 7.04 (t, $J = 7.7$ Hz, 1H, H-6), 7.10 (exactly overlapping t's, 2H, $J = 7.7$ Hz, H-7 and H-7′), 7.33 (d, $J = 7.7$ Hz 1H, H-8), 7.42 (d, $J = 7.7$ Hz, 1H, H-7′), 7.44 (d, $J = 7.7$ Hz, 1H, H-5′), 7.50 (d, $J = 7.7$ Hz, 1H, H-5), 10.80 (s, 1H, NH, 5-carboxyindole), 11.17 (s, 1H, NH, β-carboline) ppm (protons H-1, H-3–H-8 belong to the β-carboline skeleton, whereas protons H-2′, H-5′–H-7′ are attached to the 5-carboxyindole ring); ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 19.8$, 39.7, 50.0, 108.2, 111.7, 112.0, 113.0, 118.5, 118.9, 119.5, 121.9 (three coalesced lines), 122.8, 127.2, 128.3, 131.8, 134.8, 173.4 ppm.

4-(2,3,4,9-Tetrahydro-1H-pyrido[3,4-b]indol-2-ium-1-yl)-1H-pyrazole-5-carboxylate (**7**, $C_{15}H_{14}N_4O_2$)
White powder; m.p.: 320–323 °C; IR (ATR): $\bar{\nu} = \sim$3,400–2,400 br, 1,580, 1,560, 1,442, 1,416, 1,391, 1,365, 1,302, 1,237, 1,110, 945, 863, 803, 770, 736, 703 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 2.80$–3.00 (m, 2H, H-4$_{A,B}$), 3.37–3.45 (m, 2H, H-3$_{A,B}$), 5.73 (s, 1H, H-1), 7.03 (t, $J = 7.7$ Hz, 1H, H-6), 7.12 (t, $J = 7.7$ Hz, 1H, H-7), 7.35 (d, $J = 7.7$ Hz, 1H, H-8), 7.46 (s, 1H, H-5′, pyrazole), 7.49 (d, $J = 7.7$ Hz, 1H, H-5), 10.89 (s, 1H, NH, β-carboline), 13.31 (s, 1H, NH, pyrazole) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 19.7$, 41.2, 48.7, 106.6, 112.4, 116.4, 119.0, 119.8, 126.8, 131.1, 137.1, 139.2, 140.3, 123.3, 127.58, 127.64, 127.7, 128.6, 128.7, 136.3, 136.8, 162.9 ppm.

2-[2-(1H-Indol-3-yl)ethyl]isoindolin-1-one (**13**, $C_{18}H_{16}N_2O$)
White powder; m.p.: 186–187 °C; IR (ATR): $\bar{\nu} = 3{,}174$ br, 1,659, 1,452, 1,421, 1,328, 1,285, 1,245, 1,228, 1,212, 1,011, 885, 745, 732 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 3.06$ (t, $J = 6.8$ Hz, 2H, CCH_2), 3.85 (t, $J = 6.8$ Hz, 2H, NCH_2), 4.47 (s, 2H, H-3′), 7.00 (t, $J = 7.5$ Hz, 1H, H-5), 7.09 (t, $J = 7.5$ Hz, 1H, H-6), 7.19 (br s, 1H, H-2), 7.36 (d, $J = 7.5$ Hz, 1H, H-7), 7.49 (t, $J = 7.5$ Hz, 1H, H-6′), 7.54–7.61 (overlapping m's, 3H, H-4, H-4′, H-5′), 7.69 (d, $J = 7.5$ Hz, 1H, H-7′), 10.82 (s, 1H, NH) ppm (protons H-2, H-4–H-7 belong to the indole skeleton, whereas protons H-3′–H-7′ are attached to the isoindolone unit); ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 24.8$, 43.2, 50.5, 112.2, 112.3, 119.1, 119.2, 121.9, 123.52, 123.57, 124.2, 128.0, 128.6, 132.0, 133.5, 137.1, 142.7, 168.0 ppm.

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