A Versatile One-Pot Synthesis of β-Carbolines by Reaction of Pyranoindolones with Phenyl- and Benzoylhydrazine

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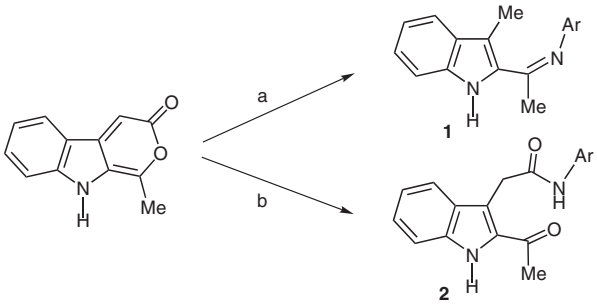
Abstract: The synthesis of a number of 2-anilino- and 2-(benzoylamino)-β-carbolin-3-ones in good yields by a one-step sequence from the reaction of pyranoindolones with phenylhydrazine or benzoylhydrazine is described; the observed good regioselectivity of the reaction is discussed. Full assignment of all ^{1}H and ^{13}C NMR chemical shifts has been unambiguously achieved.

Key words: benzoylhydrazine, *p*-benzylic coupling, bisnucleophiles, one-pot reaction, phenylhydrazine, pyranoindoles

Pyrido[3,4-*b*]indoles, commonly known as β-carbolines, are a widely distributed family of indole alkaloids and are found in several plant families such as Apocynaceae, Elaeagnaceae, Leguminosae, Passifloraceae, and Zygophyllaceae.[1] Moreover, β-carbolines possess a wide diversity of important biological activity, particular concerning the muscular, cardiovascular, and central nervous systems.[2,3] Due to their unique rigid heterocyclic skeleton, many β-carbolines are known to bind with high affinity to benzodiazepine, serotonin, and dopamine receptor sites. They are also DNA intercalating agents[4] and inhibit enzymes,[5] such as monoamine oxidase A.[6] In addition, they show convulsive and anticonvulsive actions, anxiolytic, tremorogenic, and immunomodulatory effects.[7–9] 1-Oxo-β-carbolines are of interest in medicine,[10] as many of them have been patented[11] and described as useful central nervous system depressants. In contrast, few examples of 3-oxo-β-carbolines are known, mainly synthesized by the reaction of 2-acylindole-3-acetic acid esters with primary amines.[12] A four-step synthesis of 1-methylcarbolin-3-one starting from indoleacetic acid has also been reported.[13] More recently, a two-step sequence was used for the synthesis of 1-methyl-2-phenyl or benzyl derivatives starting from the reaction of pyranoindolones with primary amines followed by ring closure of the isolated 2-acetylindole-3-acetic acid amides with triethylamine.[14] Formation of 1-phenyl-3-benzyl-substituted derivatives in low yield through the transformation of 5-benzotriazolyl-3,4-dihydropyridin-2-ones has also been reported.[15]

In the present work we wish to describe a one-pot synthetic methodology for the preparation of a series of 2-anilino- and 2-(benzoylamino)-β-carbolin-3-ones in good yields.

Sometime ago we studied the reaction between 1-methylpyranoindolone using aromatic amines as nucleophiles in boiling bromobenzene, whereupon Schiff bases **1** were isolated as the sole reaction product.[16] More recently, the same reaction was repeated under reflux in isopropyl alcohol and, in this case, 2-acetylindolo-3-acetic acid amides **2** were isolated[14] (Scheme 1). Amides were also isolated from the reaction of 1-methylpyranoindolone with methanolic dimethylamine.[17] In addition, very recently, we studied the reaction of pyranoindolones with the bisnucleophile, methylhydrazine, whereupon diazepinoindole derivatives were isolated.[18] These results are in agreement with the presence of two electrophilic centers at C1 and C3 of the indolones and a strong solvent effect. In the light of the above results and in continuation of our research into the synthesis of compounds containing the indole ring, we studied the reaction of pyranoindolones with the bisnucleophiles phenyl- and benzoylhydrazine.



Scheme 1 *Reagents and conditions*: (a) $ArNH_2$, PhBr, reflux, 2 h; (b) $ArNH_2$, *i*-PrOH, reflux, 0.5–2 h.

When pyranoindolones **3** were allowed to react with two molar equivalents of phenylhydrazine in refluxing bromobenzene for two hours, the β-carbolinones **4** were isolated in good yields (65–69%, Table 1). Analogous was the reaction with benzoylhydrazine, whereupon compounds **5** were formed also in good yields (67–74%, Scheme 2). By lowering the reaction temperature, namely by using boiling xylene, no reaction was observed. In order to examine the solvent effect, the reaction was also carried out in protic solvents, such as boiling propanol and butanol, whereupon several unidentified decomposition products were isolated, as a result of the pyranone ring opening.

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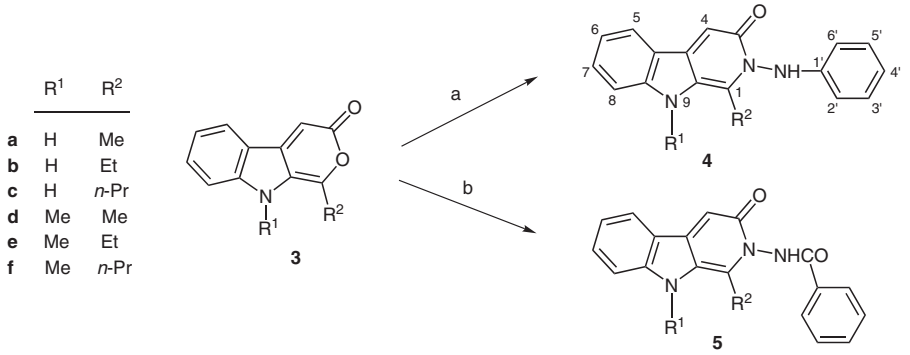


Scheme 2 *Reagents and conditions*: (a) $PhNHNH_2$, PhBr, reflux, 2 h; (b) $BzNHNH_2$, PhBr, reflux, 2 h.

Table 1 Reaction Conditions and Products

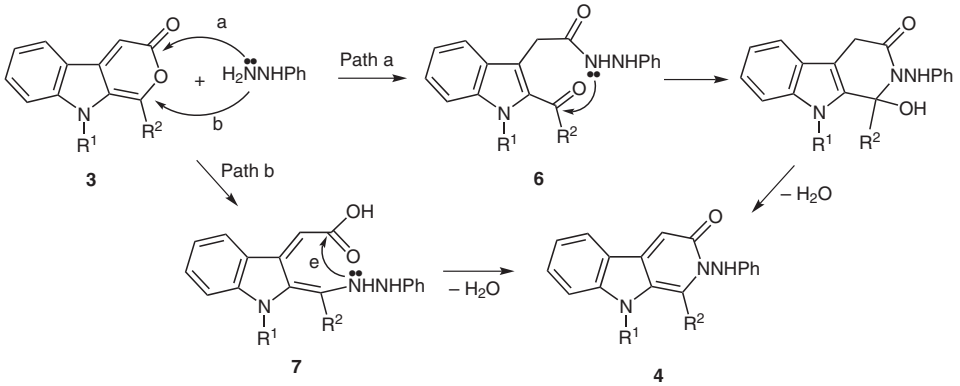
Substrate	Hydrazine	Solvent	Temp (°C)	Time (h)	Product	Yield (%)
3a	$PhNHNH_2$	PhBr	156	2	**4a**	67
3b	$PhNHNH_2$	PhBr	156	2	**4b**	69
3c	$PhNHNH_2$	PhBr	156	2	**4c**	65
3d	$PhNHNH_2$	PhBr	156	2	**4d**	67
3e	$PhNHNH_2$	PhBr	156	2	**4e**	69
3f	$PhNHNH_2$	PhBr	156	2	**4f**	68
3a	$PhNHNH_2$	PrOH	97	4	–	–
3a	$PhNHNH_2$	BuOH	118	6	–	–
3a	$BzNHNH_2$	PhBr	156	2	**5a**	74
3b	$BzNHNH_2$	PhBr	156	2	**5b**	72
3c	$BzNHNH_2$	PhBr	156	2	**5c**	68
3d	$BzNHNH_2$	PhBr	156	2	**5d**	73
3e	$BzNHNH_2$	PhBr	156	2	**5e**	71
3f	$BzNHNH_2$	PhBr	156	2	**5f**	67

Concerning the reaction mechanism, attack of the less hindered NH_2 group of phenylhydrazine[11] to the carbonyl carbon of pyranoindolones, being the more reactive electrophilic center, would be expected (Scheme 3, path a). This attack would lead to the formation of the 2-acyl derivatives **6**, from which, by recyclization and dehydration, carbolines **4** could be formed. However, this path can be excluded since it is known that 2-acetylindoles do not react with nitrogen nucleophiles in bromobenzene even on prolonged heating,[16] and that protic solvents and acidic conditions are required for this reaction.[19] On the other hand, the formation of carbolines **4** is also possible by attack to the less electrophilic center, namely C1, leading to the acid **7** (path b), from which, by dehydration, **4** can be formed. Dehydration is facilitated by the ability of aprotic solvents, in contrast to protic solvents, to carry away the water formed during the reaction.

The isolation of products **4** through path b is also in agreement with the results previously obtained from the reaction of pyranoindolones with aromatic amines,[16] where in aprotic solvents the nucleophilic aromatic amine attacks the less electrophilic center C1 of the pyranoindolone.

The assigned molecular structures of all new compounds **4** and **5** are based on rigorous spectroscopic analysis including IR, NMR (^1H, ^{13}C, COSY, NOESY, HETCOR, and COLOC), MS and elemental analysis data.

Regarding the structure of the isolated β-carbolines **4** and **5** the assignment of **4d** is described. The elemental analysis and mass spectra unequivocally established the reac-



Scheme 3 Plausible mechanism for the formation of **4**

tion of one molecule of pyranoindolone **3d** with one molecule of hydrazine with the loss of a water molecule, a fact that was also confirmed from the ^{13}C NMR spectrum, where 17 different signals were observed. Moreover, in the IR spectra (see Experimental Section) in addition to the carbonyl (1658 cm^{-1}), an NH absorption at 3219 cm^{-1} was identified. From the H–H COSY spectrum two distinguishable proton multiplet groups were defined corresponding to indole and NH-aromatic rings.

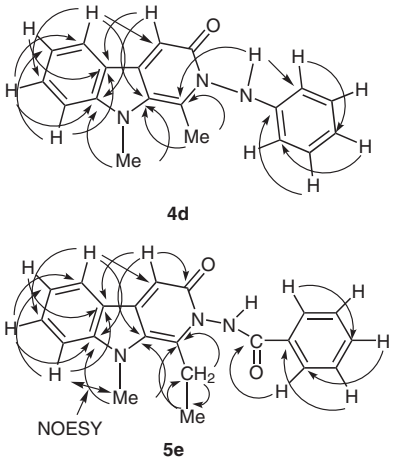


Figure 1 COLOC correlations between protons and carbons (via $^{2}J_{C\text{-}H}$ and $^{3}J_{C\text{-}H}$) in compounds **4d** and **5e**. In **5e**, NOESY correlation has observed between H8 and 9-Me protons.

In the ^{1}H NMR of **4d** the presence of the four indole aromatic protons resonating as a doublet of doublet of doublets at δ = 7.92 (*J* = 0.7, 1.3, 7.8 Hz, H5),[20] a double doublet of doublets at δ = 7.14 (*J* = 0.8, 7.1, 7.8 Hz, H6), a double doublet of doublets at δ = 7.56 (*J* = 1.3, 7.1, 8.4 Hz, H7), and as a doublet of broad signals at δ = 7.22 (*J* = 8.4 Hz, H8), partially overlapped by N-Ph protons, with their carbons resonating at δ = 122.8, 119.4, 130.7, and 109.0, respectively, was identified. Moreover, the 4-position proton appears as a quartet at δ = 7.12 (^{6}J = 0.75 Hz) coupled with 1-methyl protons (analogous to *p*-benzylic coupling) resonating at δ = 2.88 (C at δ = 14.7), verified also from their proton COSY correlation. The presence of the phenyl moiety is identified from the three characteristic proton multiplets at δ = 6.66–6.70 (H2′, H6′), 7.21–7.26 (H3′, H5′), and 6.98 (H4′) with their carbons resonating at δ = 115.0, 129.4, and 122.7, respectively. Finally, the 9-methyl group appears as a singlet at δ = 3.85 with carbon resonating at δ = 33.3. Long range C–H correlation (COLOC) spectra were optimized for *J* = 10 Hz, so aromatic protons show COLOC correlations via ^{3}J, whereas protons on saturated carbons show COLOC via ^{2}J and ^{3}J couplings. Consequently, the 1-methyl group protons gave COLOC correlations with the carbon at δ = 130.4 (C1) and with the quaternary carbon at δ = 126.9 (C9a). The *N*-methyl protons correlated with the same quaternary carbon (C9a) and with the quaternary carbon at δ = 147.7 (C8a). The C4 proton gave COLOC correlations with (C9a) and with the quaternary carbon at δ = 120.7 (C4b). Concerning the indole ring sequence it is characterized by the COLOC correlations of the C5 proton with C7 protonated carbon (δ =130.7) and with the C8a quaternary carbon at δ = 147.7, of the C6 proton (δ = 7.14) with the C8 protonated carbon (δ = 109.0) and of the C8 proton (δ = 7.22) with the C6 protonated carbon (δ = 119.4). Moreover, the NH proton appears in the ^{1}H NMR as a singlet at δ = 8.01 correlating with the quaternary carbon at δ = 130.4 (C1) and also with the protonated carbon at δ = 115.0 (C2′) indicating thus the position of the anilino group. Finally, characteristic COLOC correlations for the phenyl ring are also observed. In Figure 1 all the observed COLOC correlations in compounds **4d** and **5e** are depicted.

It is also noteworthy that ^{1}H NMR of the propyl derivatives **4c**, **4f**, and **5f** show two distinct multiplets for the middle β-methylene protons, whereas the α-methylene protons show two distinct multiplets as clean ddd with couplings, in the case of **4f**, *J* = 5.6, 7.5, and 14.5 Hz. This multiplicity is attributed to the difficulty in spinning of the group. Methylene protons in 1-ethyl-9-methyl derivative **4e** follow the same trend.

In conclusion, we have developed a direct method for the synthesis of a series of 2-anilino - and 2-(benzoylamino)-β-carbolin-3-ones in good yields by a one-step sequence from the reaction of pyranoindolones with phenylhydrazine or benzoylhydrazine. In addition, the observed good regioselectivity of the reaction is discussed. Moreover, this high yielding reaction constitutes one of few examples of a reaction of pyranoindolones with bisnucleophiles. Full assignment of all ^{1}H and ^{13}C NMR chemical shifts has been unambiguously achieved.

Work is continuing in our laboratory in this area and we will report on further studies in the future using other bisnucleophiles.

Melting points were measured on a Kofler hot-stage and are uncorrected. Column chromatography was carried out using Merck silica gel. TLC was performed using precoated silica gel glass plates 0.25 mm containing fluorescent indicator UV_{254} purchased from Macherey–Nagel using a 3:1 mixture of petroleum ether–EtOAc. Petroleum ether (PE) refers to bp 60–80 °C. NMR spectra were recorded at r.t. on a Bruker AM 300 spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C, respectively, using $CDCl_3$ as solvent, unless otherwise indicated. In the case of insoluble substances 5–20% of DMSO-d_6 was added, whereas in one case only DMSO-d_6 was used, as indicated. TMS was used as internal standard for ^{1}H and TMS (δ = 0.00) or to $CDCl_3$ (δ = 77.05) for ^{13}C NMR spectra; in the case of DMSO-d_6 solns the signal of the solvent at δ = 39.7 was used for calibration. Second order ^{1}H NMR spectra were analyzed by simulation.[20] IR spectra were recorded on a Perkin-Elmer 297 spectrophotometer or on a Perkin-Elmer 1600 series FTIR spectrophotometer. LR-MS (EI) were recorded on a 6890N GC/MS system (Agilent Technology); in some cases LC-MS (ESI, 1.65 eV) spectra were recorded on an LCMS-2010 EV system (Shimadzu). Elemental analyses performed with a Perkin-Elmer 2400-II CHN analyzer. Structural assignments of the derived compounds were established by analysis of their IR, MS, and NMR spectra (^{1}H, ^{13}C, DEPT, COSY, NOESY, HETCOR, and COLOC).

2-Anilino-2,9-dihydro-3*H*-β-carbolin-3-ones 4a–f and 2-(Benzoylamino)-2,9-dihydro-3*H*-β-carbolin-3-ones 5a–f; General Procedure

To a refluxing soln of pyranoindolone **3** (1.5 mmol) in PhBr (15 mL), $PhNHNH_2$ (3.0 mmol) or $BzNHNH_2$ (2.0 mmol) was added and refluxing was continued for 2 h. The mixture was cooled down (5–10 °C), whereupon the precipitated product was filtered out, washed with Et_2O, and recrystallized (EtOH). In the cases where crystallization was not possible the solvent was distilled off and the resulting residue was subjected to column chromatography (silica gel, PE–EtOAc, 5:1, slowly increasing the polarity up to 3:1) to give **4a–f** or **5a–f**.

2-Anilino-1-methyl-2,9-dihydro-3*H*-β-carbolin-3-one (4a)

Yellow crystals; yield: 0.290 g (67%); mp 256–258 °C (EtOH).

IR (Nujol): 3228 (NH), 1667 cm^{-1} (NC=O).

^1H NMR ($CDCl_3$, DMSO-d_6): δ = 2.65 (s, 3 H, 1-Me), 6.65 (d, *J* = 8.0 Hz, 2 H, H2′, H6′),[20] 6.93 (t, *J* = 7.1 Hz, 1 H, H4′), 7.01 (s, 1 H, H4), 7.08 (dd, *J* = 7.1, 7.9 Hz, 1 H, H6), 7.20 (dd, *J* = 7.1, 8.0 Hz, 2 H, H3′, H5′), 7.31 (d, *J* = 8.4 Hz, 1 H, H8), 7.46 (dd, *J* = 7.1, 8.4 Hz, 1 H, H7), 7.89 (d, *J* = 7.9 Hz, 1 H, H5), 8.15 (br s, 1 H, 2-NH), 9.93 (br s, 1 H, H9).

^{13}C NMR ($CDCl_3$, DMSO-d_6): δ = 14.1 (1-Me), 101.3 (C4), 111.1 (C8), 113.4 (C2′, C6′), 118.4 (C6), 120.2 (C5), 120.8 (C4b), 122.5 (C4′), 124.7 (C9a), 128.8 (C3′, C5′), 130.0 (C7), 130.5 (C1), 137.8 (C4a), 145.6 (C8a), 147.4 (C1′), 159.4 (C3).

MS (EI, 70 eV): *m*/*z* (%) = 289 (45) [M^+], 281 (46), 260 (85), 198 (100), 169 (85), 154 (20), 128 (30).

Anal. Calcd for $C_{18}H_{15}N_3O$ (289.33): C, 74.72; H, 5.23; N, 14.52. Found: C, 74.76; H, 5.03; N, 14.68.

2-Anilino-1-ethyl-2,9-dihydro-3*H*-β-carbolin-3-one (4b)

Yellow crystals; yield: 0.314 g (69%); mp 243–245 °C (EtOH).

IR (Nujol): 3306 (NH), 1671 cm^{-1} (NC=O).

^1H NMR ($CDCl_3$): δ = 1.31 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 2.96 (q, *J* = 7.5 Hz, 2 H, CH_2CH_3), 6.64 (d, *J* = 8.0 Hz, 2 H, H2′, H6′), 6.96 (t, *J* = 7.2 Hz, 1 H, H4′), 7.10 (s, 1 H, H4), 7.15 (dd, *J* = 7.0, 7.5 Hz, 1 H, H6), 7.21 (dd, *J* = 7.2, 8.0 Hz, 2 H, H3′, H5′), 7.29 (d, *J* = 8.4 Hz, 1 H, H8), 7.50 (dd, *J* = 7.0, 8.4 Hz, 1 H, H7), 7.52 (br s, 1 H, 2-NH), 7.76 (br s, 1 H, H9), 7.92 (d, *J* = 7.5 Hz, 1 H, H5).

^{13}C NMR ($CDCl_3$, DMSO-d_6): δ = 13.2 (CH_2CH_3), 21.8 (CH_2CH_3), 101.7 (C4), 111.3 (C8), 113.6 (C2′, C6′), 118.4 (C6), 120.1 (C4b), 120.9 (C5), 122.5 (C4′), 124.4 (C9a), 128.8 (C3′, C5′), 130.1 (C7), 136.1 (C1), 138.2 (C4a), 145.7 (C1′), 147.8 (C8a), 159.6 (C3).

MS (EI, 70 eV): *m*/*z* (%) = 303 (56) [M^+], 274 (100), 258 (10), 211 (40), 183 (20), 154 (15), 128 (12).

Anal. Calcd for $C_{19}H_{17}N_3O$ (303.36): C, 75.23; H, 5.65; N, 13.85. Found: C, 75.05; H, 5.43, N, 13.67.

2-Anilino-1-propyl-2,9-dihydro-3*H*-β-carbolin-3-one (4c)

Yellow crystals; yield: 0.308 g (65%); mp 252–253 °C (EtOH).

IR (Nujol): 3186 (NH), 1663 cm^{-1} (NC=O).

^1H NMR: δ = 0.97 (t, *J* = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 1.69 and 1.82 (two multiplets of AB system, 2 H, $CH_2CH_2CH_3$), 2.90 and 3.01 (two multiplets of AB system, 2 H, $CH_2CH_2CH_3$), 6.62 (d, *J* = 7.8 Hz, 2 H, H2′, H6′), 6.90 (t, *J* = 7.5 Hz, 1 H, H4′), 7.01 (s, 1 H, H4), 7.06 (ddd, *J* = 0.8, 7.25, 7.75 Hz, 1 H, H6), 7.18 (dd, *J* = 7.5, 7.8 Hz, 2 H, H3′, H5′), 7.30 (dd, *J* = 0.8, 8.4 Hz, 1 H, H8), 7.46 (ddd, *J* = 1.0, 7.25, 8.4 Hz, 1 H, H7), 7.88 (dd, *J* = 1.0, 7.75 Hz, 1 H, H5), 8.65 (br s, 1 H, 2-NH), 10.48 (br s, 1 H, 9-NH).

^{13}C NMR ($CDCl_3$, DMSO-d_6): δ = 13.8 ($CH_2CH_2CH_3$), 22.1 ($CH_2CH_2CH_3$), 30.1 ($CH_2CH_2CH_3$), 101.8 (C4), 111.1 (C8), 113.4 (C2′, C6′), 118.3 (C6), 120.1 (C4b), 120.7 (C5), 122.5 (C4′), 126.9 (C9a), 128.7 (C3′, C5′), 130.0 (C7), 130.1 (C1), 138.1 (C4a), 145.7 (C1′), 148.0 (C8a), 159.6 (C3).

MS (EI, 70 eV): *m*/*z* (%) = 317 (5) [M^+], 296 (42), 198 (100).

Anal. Calcd for $C_{20}H_{19}N_3O$ (317.38): C, 75.69; H, 6.03; N, 13.24. Found: C, 75.81; H, 6.12, N, 13.58.

2-Anilino-1,9-dimethyl-2,9-dihydro-3*H*-β-carbolin-3-one (4d)

Yellow crystals; yield: 0.304 g (67%); mp 218–221 °C (EtOH).

IR (Nujol): 3219 (NH), 1658 cm^{-1} (NC=O).

^1H NMR: δ = 2.88 (d, *J* = 0.75 Hz, 3 H, 1-Me), 3.85 (s, 3 H, 9-Me), 6.68 (AA′, *J* = 1.1, 2.0, 8.2 Hz, 2 H, H2′, H6′), 6.98 (tt, *J* = 1.1, 7.3 Hz, 1 H, H4′), 7.12 (q, *J* = 0.75 Hz, 1 H, H4), 7.14 (ddd, *J* = 0.8, 7.1, 7.8 Hz, 1 H, H6), 7.22 (br d, *J* = 8.4 Hz, 1 H, H8), 7.23 (BB′, *J* = 2.0, 7.3, 8.2 Hz, 2 H, H3′, H5′), 7.56 (ddd, *J* = 1.3, 7.1, 8.4 Hz, 1 H, H7), 7.92 (ddd, *J* = 0.7, 1.3, 7.8 Hz, 1 H, H5), 8.01 (br s, 1 H, 2-NH).

^{13}C NMR: δ = 14.7 (1-Me), 33.3 (9-Me), 102.6 (C4), 109.0 (C8), 115.0 (C2′, C6′), 119.4 (C6), 120.7 (C4b), 122.7 (C4′), 122.8 (C5), 126.9 (C9a), 129.4 (C3′, C5′), 130.4 (C1), 130.7 (C7), 138.8 (C4a), 147.0 (C1′), 147.7 (C8a), 159.7 (C3).

MS (EI, 70 eV): *m*/*z* (%) = 303 (30) [M^+], 212 (100) [M^+ – N-Ph], 197 (38), 183 (40), 169 (25).

Anal. Calcd for $C_{19}H_{17}N_3O$ (303.36): C, 75.23; H, 5.65; N, 13.85. Found: C, 75.54; H, 5.73; N, 13.68.

2-Anilino-1-ethyl-9-methyl-2,9-dihydro-3*H*-β-carbolin-3-one (4e)

Yellow crystals; yield: 0.328 g (69%); mp 199–200 °C (EtOH).

IR (Nujol): 3240 (NH), 1659 cm^{-1} (NC=O).

^1H NMR: δ = 1.35 (t, *J* = 7.5 Hz, 3 H, 1-CH_2CH_3), 3.08 (dq, *J* = 7.5, 14.5 Hz, 1 H, 1-CH_2CH_3), 3.32 (dq, *J* = 7.5, 14.5 Hz, 1 H, 1-CH_2CH_3), 3.84 (s, 3 H, 9-Me), 6.63 (d, *J* = 8.0 Hz, 2 H, H2′, H6′), 6.94 (t, *J* = 7.3 Hz, 1 H, H4′), 7.10 (s, 1 H, H4), 7.12 (dd, *J* = 7.1, 7.6 Hz, 1 H, H6), 7.20 (dd, *J* = 7.3, 8.2 Hz, 2 H, H3′, H5′), 7.22 (d, *J* = 8.4 Hz, 1 H, H8), 7.55 (ddd, *J* = 1.1, 7.1, 8.4 Hz, 1 H, H7), 7.83 (br s, 1 H, NH), 7.89 (dd, *J* = 1.0, 7.6 Hz, 1 H, H5).

^{13}C NMR: δ = 15.1 (1-CH_2CH_3), 21.6 (1-CH_2CH_3), 32.7 (9-Me), 103.2 (C4), 109.0 (C8), 114.5 (C2′, C6′), 119.3 (C6), 120.5 (C4b), 122.3 (C4′), 122.8 (C5), 126.1 (C9a), 129.3 (C3′, C5′), 130.8 (C7), 136.2 (C1), 139.4 (C4a), 147.5 (C1′), 147.5 (C8a), 159.9 (C3).

MS (EI, 70 eV): *m*/*z* (%) = 317 (28) [M^+], 288 (100), 272 (8), 225 (10), 168 (15).

Anal. Calcd for $C_{20}H_{19}N_3O$ (317.38): C, 75.69; H, 6.03; N, 13.24. Found: C, 75.68; H, 6.16; N, 13.38.

2-Anilino-9-methyl-1-propyl-2,9-dihydro-3*H*-β-carbolin-3-one (4f)

Yellow crystals; yield: 0.337 g (68%); mp 242–243 °C (EtOH).

IR (Nujol): 3218 (NH), 1649 cm^{-1} (NC=O).

^1H NMR: δ = 1.01 (t, *J* = 7.5 Hz, 3 H, 1-$CH_2CH_2CH_3$), 1.57–1.75 (m, 1 H, 1-$CH_2CH_2CH_3$), 1.80–1.98 (m, 1 H, 1-$CH_2CH_2CH_3$), 3.05 (ddd, *J* = 5.6, 7.5, 14.5 Hz, 1 H, 1-$CH_2CH_2CH_3$),[20] 3.24 (ddd, *J* = 5.5, 7.5, 14.5 Hz, 1 H, 1-$CH_2CH_2CH_3$), 3.84 (s, 3 H, 9-Me), 6.65 (d, *J* = 7.7 Hz, 2 H, H2′, H6′), 6.96 (t, *J* = 7.3 Hz, 1 H, H4′), 7.11 (s, 1 H, H4), 7.13 (dd, *J* = 7.2, 7.7 Hz, 1 H, H6), 7.22 (dd, *J* = 7.3, 7.7 Hz, 2 H, H3′, H5′), 7.23 (d, *J* = 8.3 Hz, 1 H, H8), 7.56 (dd, *J* = 7.2, 8.3 Hz, 1 H, H7), 7.83 (s, 1 H, 2-NH), 7.90 (d, *J* = 7.7 Hz, 1 H, H5).

^{13}C NMR: δ = 14.0 (1-$CH_2CH_2CH_3$), 24.1 (1-$CH_2CH_2CH_3$), 30.0 (1-$CH_2CH_2CH_3$), 32.7 (9-Me), 103.2 (C4), 109.00 (C8), 114.5 (C2′, C6′), 119.3 (C6), 120.5 (C4b), 122.3 (C4′), 122.8 (C5), 126.3 (C9a), 129.3 (C3′, C5′), 130.8 (C7), 135.1 (C1), 139.3 (C4a), 147.5 and 147.6 (C1′ and C8a), 159.9 (C3).

MS (EI, 70 eV): *m*/*z* (%) = 332 (100) [M$^+$ + 1], 302 (63), 254 (40), 241 (65), 213 (90).

Anal. Calcd for $C_{21}H_{21}N_3O$ (331.41): C, 76.11; H, 6.39; N, 12.68. Found: C, 75.98; H, 6.26; N, 12.78.

2-(Benzoylamino)-1-methyl-2,9-dihydro-3*H*-β-carbolin-3-one (5a)

Yellow crystals; yield: 0.352 g (74%); mp 195–197 °C (EtOH).

IR (Nujol): 3299 (NH), 1681 cm^{-1} (NC=O).

^{1}H NMR (DMSO-d_6): δ = 2.52 (s, 3 H, 1-Me), 6.97 (s, 1 H, H4), 7.05 (dd, *J* = 7.2, 7.7 Hz, 1 H, H6), 7.31 (d, *J* = 8.1 Hz, 1 H, H8), 7.49 (dd, *J* = 7.2, 8.1 Hz, 1 H, H7), 7.58 (dd, *J* = 7.1, 7.5 Hz, 2 H, H3′, H5′), 7.67 (t, *J* = 7.5 Hz, 1 H, H4′), 8.02 (d, *J* = 7.7 Hz, 1 H, H5), 8.04 (d, *J* = 7.6 Hz, 2 H, H2′, H6′), 10.6 (s, 1 H, 2-NH), 11.4 (s, 1 H, H9).

^{13}C NMR (DMSO-d_6): δ = 14.3 (1-Me), 101.6 (C4), 111.2 (C8), 118.6 (C6), 120.4 (C4b), 122.7 (C5), 125.1 (C9a), 128.1 (C2′, C6′), 128.4 (C3′, C5′), 130.3 (C1), 130.4 (C7), 131.9 (C1′), 132.3 (C4′), 139.1 (C4a), 146.0 (C8a), 159.3 (C3), 167.4 (2-C=O).

LC-MS (ESI, 1.65 eV): *m*/*z* (%) = 318 (100), [M$^+$ + 1].

Anal. Calcd for $C_{19}H_{15}N_3O_2$ (317.34): C, 71.91; H, 4.76; N, 13.24. Found: C, 71.74; H, 4.53; N, 13.08.

2-(Benzoylamino)-1-ethyl-2,9-dihydro-3*H*-β-carbolin-3-one (5b)

Yellow crystals; yield: 0.357 g (72%); mp 274–275 °C (EtOH).

IR (Nujol): 3235 (NH), 1671 cm^{-1} (NC=O).

^{1}H NMR ($CDCl_3$, DMSO-d_6): δ = 1.40 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 3.07 (q, *J* = 7.5 Hz, 2 H, CH_2CH_3), 7.00 (s, 1 H, H4), 7.12 (dd, *J* = 7.1, 7.9 Hz, 1 H, H6), 7.39 (d, *J* = 8.3 Hz, 1 H, H8), 7.54 (dd, *J* = 7.1, 8.3 Hz, 1 H, H7), 7.61 (dd, *J* = 7.1, 7.5 Hz, 2 H, H3′, H5′), 7.67 (t, *J* = 7.5 Hz, 1 H, H4), 7.97 (d, *J* = 8.0 Hz, 1 H, H5), 8.17 (d, *J* = 7.1 Hz, 2 H, H2′, H6′), 10.58 (s, 1 H, 2-NH), 11.50 (br s, 1 H, H9).

^{13}C NMR ($CDCl_3$, DMSO-d_6): δ = 12.9 (CH_2CH_3), 21.8 (CH_2CH_3), 101.6 (C4), 111.2 (C8), 118.4 (C6), 120.1 (C4b), 122.7 (C5), 124.1 (C9a), 127.6 (C2′, C6′), 128.3 (C3′, C5′), 130.4 (C1′), 132.0 (C1), 132.2 (C7), 135.4 (C4′), 139.1 (C4a), 145.9 (C8a), 159.0 (C3), 167.3 (2-C=O).

LC-MS (ESI, 1.65 eV): *m*/*z* (%) = 332 (100), [M$^+$ + 1].

Anal. Calcd for $C_{20}H_{17}N_3O_2$ (331.37): C, 72.49; H, 5.17; N, 12.68. Found: C, 72.74; H, 5.03; N, 12.78.

2-(Benzoylamino)-1-propyl-2,9-dihydro-3*H*-β-carbolin-3-one (5c)

Yellow crystals; yield: 0.352 g (68%); mp 252–253 °C (EtOH).

IR (Nujol): 3218 (NH), 1664 cm^{-1} (NC=O).

^{1}H NMR: δ = 0.96 (t, *J* = 7.4 Hz, 3 H, $CH_2CH_2CH_3$), 1.78 (sext, *J* = 7.4 Hz, 2 H, $CH_2CH_2CH_3$), 2.88 (t, *J* = 7.4 Hz, 2 H, $CH_2CH_2CH_3$), 6.74 (s, 1 H, H4), 6.98 (dd, *J* = 7.7, 7.2 Hz, 1 H, H6), 7.20 (d, *J* = 7.7 Hz, 1 H, H8), 7.35–7.45 (m, 3 H, H3′, H4′, H5′), 7.45–7.50 (m, 1 H, H7), 7.69 (d, *J* = 7.7 Hz, 1 H, H5), 8.06 (d, *J* = 7.3 Hz, 2 H, H2′, H6′), 9.78 (s, 1 H, 2-NH), 11.48 (br s, 1 H, H9).

^{13}C NMR ($CDCl_3$, DMSO-d_6): δ = 13.9 ($CH_2CH_2CH_3$), 21.5 ($CH_2CH_2CH_3$), 30.1 ($CH_2CH_2CH_3$), 101.6 (C4), 111.2 (C8), 118.4 (C6), 120.1 (C4b), 122.8 (C5), 127.1 (C9a), 127.9 (C2′, C6′), 128.4 (C3′, C5′), 130.4 (C1), 131.2 (C7), 132.2 (C4′), 134.1 (C1′), 138.9 (C4a), 145.9 (C8a), 159.0 (C3), 167.1 (2-C=O).

LC-MS (ESI, 1.65 eV: *m*/*z* (%) = 346 (100) [M$^+$ + 1].

Anal. Calcd for $C_{21}H_{19}N_3O_2$ (345.39): C, 73.03; H, 5.54; N, 12.17. Found: C, 73.26; H, 5.67; N, 12.00.

2-(Benzoylamino)-1,9-dimethyl-2,9-dihydro-3*H*-β-carbolin-3-one (5d)

Yellow crystals; yield: 0.362 g (73%); mp 96–98 °C (EtOH).

IR (Nujol): 3300 (NH), 1687 and 1659 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$, DMSO-d_6): δ = 2.85 (s, 3 H, 1-Me), 3.77 (s, 3 H, 9-Me), 7.01 (s, 1 H, H4), 7.10 (dd, *J* = 7.2, 7.7 Hz, 1 H, H6), 7.15 (d, *J* = 8.1 Hz, 1 H, H8), 7.40–7.50 (m, 2 H, H3′, H5′), 7.50–7.58 (m, 2 H, H7, H4′), 7.87 (d, *J* = 7.7 Hz, 1 H, H5), 8.05 (d, *J* = 7.7 Hz, 2 H, H2′, H6′), 10.20 (br s, 1 H, 2-NH).

^{13}C NMR ($CDCl_3$, DMSO-d_6): δ = 14.4 (1-Me), 33.1 (9-Me), 102.1 (C4), 108.9 (C8), 119.0 (C6), 120.7 (C4b), 122.7 (C4′), 122.8 (C5), 126.9 (C9a), 128.0 (C2′, C6′), 128.3 (C3′, C5′), 130.4 (C1), 130.7 (C7), 138.8 (C4a), 147.0 (C1′), 147.7 (C8a), 159.7 (C3), 167.2 (2-C=O).

LC-MS (ESI, 1.65 eV): *m*/*z* (%) = 332 (100), [M$^+$ + 1].

Anal. Calcd for $C_{20}H_{17}N_3O_2$ (331.37): C, 72.49; H, 5.17; N, 12.68. Found: C, 72.34; H, 5.28; N, 12.50.

2-(Benzoylamino)-1-ethyl-9-methyl-2,9-dihydro-3*H*-β-carbolin-3-one (5e)

Yellow crystals; yield: 0.367 g (71%); mp 146–148 °C (EtOH).

IR (Nujol): 3250 (NH), 1660 cm^{-1} (C=O).

^{1}H NMR: δ = 1.37 (br t, *J* = 7.4 Hz, 3 H, 1-CH_2CH_3), 3.09 (br q, *J* = 7.4 Hz, 2 H, 1-CH_2CH_3), 3.63 (s, 3 H, 9-Me), 6.75 (s, 1 H, H4), 6.99 (ddd, *J* = 1.0, 7.4, 7.7 Hz, 1 H, H6), 7.02 (dd, *J* = 1.0, 8.2 Hz, 1 H, H8), 7.20 (t, 7.5 Hz, 2 H, H3′, H5′), 7.33 (t, *J* = 7.5 Hz, 1 H, H4′), 7.44 (ddd, *J* = 1.2, 7.4, 8.2 Hz, 1 H, H7), 7.66 (dd, *J* = 1.2, 7.7 Hz, 1 H, H5), 8.05 (d, *J* = 7.5 Hz, 2 H, H2′, H6′), 10.60 (br s, 1 H, 2-NH).

^{13}C NMR: δ = 14.6 (1-CH_2CH_3), 21.7 (1-CH_2CH_3), 32.4 (9-Me), 102.6 (C4), 108.8 (C8), 119.0 (C6), 120.0 (C4b), 122.4 (C5), 126.4 (C9a), 128.1 (C2′, C6′), 128.4 (C3′, C5′), 130.9 (C7), 131.2 (C1′), 132.2 (C4′), 136.4 (C1), 140.0 (C4a), 147.3 (C8a), 159.7 (C3), 167.9 (2-C=O).

MS (EI, 70 eV): *m*/*z* (%) = 327 (100) [M$^+$ – 18], 312 (78), 207 (5), 195 (10), 181 (13), 163 (10), 105 (30).

Anal. Calcd for $C_{21}H_{19}N_3O_2$ (345.39): C, 73.03; H, 5.54; N, 12.17. Found: C, 72.89; H, 5.43; N, 12.25.

2-(Benzoylamino)-9-methyl-1-propyl-2,9-dihydro-3*H*-β-carbolin-3-one (5f)

Yellow crystals; yield: 0.361 g (67%); mp 124–126 °C (EtOH).

IR (Nujol): 3268 (NH), 1685, 1651 cm^{-1} (C=O).

^{1}H NMR: δ = 1.01 (t, *J* = 7.3 Hz, 3 H, 1-$CH_2CH_2CH_3$), 1.82 (m, 2 H, 1-$CH_2CH_2CH_3$), 3.06 (dt, *J* = 7.5, 7.5 Hz, 2 H, 1-$CH_2CH_2CH_3$), 3.70 (s, 3 H, 9-Me), 6.88 (s, 1 H, H4), 7.04 (dd, *J* = 7.2, 7.6 Hz, 1 H, H6), 7.09 (d, *J* = 8.4 Hz, 1 H, H8), 7.27 (t, *J* = 7.6 Hz, 2 H, H3′, H5′), 7.40 (t, *J* = 7.6 Hz, 1 H, H4′), 7.48 (dd, *J* = 7.2, 8.4 Hz, 1 H, H7), 7.75 (d, *J* = 7.6 Hz, 1 H, H5), 8.02 (d, *J* = 7.6 Hz, 2 H, H2′, H6′), 11.2 (br s, 1 H, 2-NH).

^{13}C NMR: δ = 14.1 (1-$CH_2CH_2CH_3$), 23.6 (1-$CH_2CH_2CH_3$), 30.1 (1-$CH_2CH_2CH_3$), 32.4 (9-Me), 102.7 (C4), 108.9 (C8), 119.2 (C6), 120.0 (C4b), 122.5 (C5), 126.8 (C9a), 128.0 (C2′, C6′), 128.5 (C3′, C5′), 130.9 (C7), 131.3 (C1′), 132.3 (C4′), 135.3 (C1), 140.0 (C4a), 147.4 (C8a), 159.7 (C3), 168.1 (2-C=O).

LC-MS (ESI, 1.65 eV): *m*/*z* (%) = 360 (100), [M$^+$ + 1].

Anal. Calcd for $C_{22}H_{21}N_3O_2$ (359.42): C, 73.52; H, 5.89; N, 11.69. Found: C, 73.40; H, 5.63; N, 11.92.

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