HETEROCYCLES, Vol. 75, No. 1, 2008, pp. 43 - 56. © The Japan Institute of Heterocyclic Chemistry
Received, 27th June, 2007, Accepted, 5th September, 2007, Published online, 10th September, 2007. COM-07-11154

# SYNTHESIS OF CYCLOALKANOINDOLES, THE CARBA ANALOGS OF PHYSOSTIGMINE

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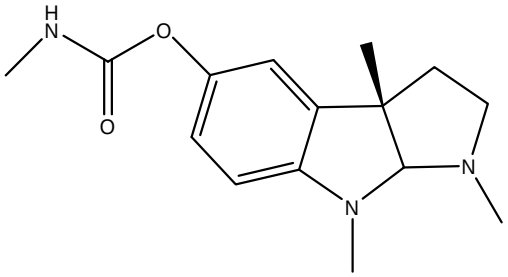
**Abstract** – The title compounds **9** were prepared by combined aza-Claisen rearrangement/intramolecular ring-closure reaction of *N*-allylaniline derivatives **3**, followed by $BBr_3$ mediated cleavage of methoxy group and subsequent formation of the phenylcarbamyl derivatives.

## INTRODUCTION

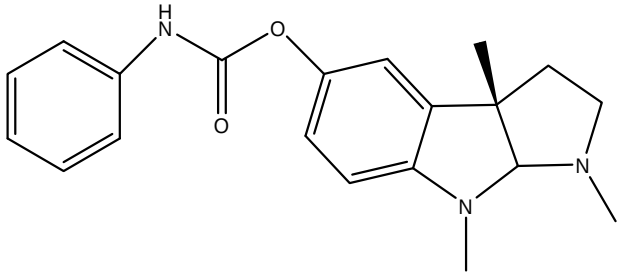
Alzheimer's disease is one of the leading cause of death in the Western societies. The disease is a progressive dementia associated with the cholinergic system. Acetylcholinesterase enzyme rapidly metabolizes the naturally released acetylcholine causing a lack in this neurotransmitter.[1-3] An alkaloid of the African Calabar bean (*Physostigma venesonum),* (-)-physostigmine, inhibits the acetylcholinesterase by transcarbamylation. This inhibition reduces the rate of hydrolysis of acetylcholine in the brain and increases its colinerg activity. Physostigmine has been used medically to improve memory and relief in Alzheimer's disease.[4-6] Phenserine, in which the methylcarbamyl group of physostigmine was substituted by phenylcarbamyl group, is highly potent in inhibiting acetylcholinesterase due to its increased ability to cross the blood-brain barrier.

The growing need for new acetylcholinesterase inhibitors in clinical trials and applications had focused interest on the preparation of physostigmine congeners.[7-9] For instance, the pyrrolo[2,3-*b*]indole skeleton had been replaced by furo[2,3-*b*]indole and furo[2,3-*b*]benzofuran ring.[10] However, the carba analogs, in which one of the nitrogen-containing ring had been substituted by cycloalkano skeleton, have not got attention.

Our general interest in the preparation of new heterocyclic compounds, which might be promising in the treatment of mental diseases, prompted us to elaborate methods for the synthesis of the carba analogs of pyrrolo[2,3-*b*]indole. In this report we present methods for the preparation of the cycloalkano-indole derivatives (Scheme 1, **5** and **6**).[11]



(-)-physostigmine



phenserine

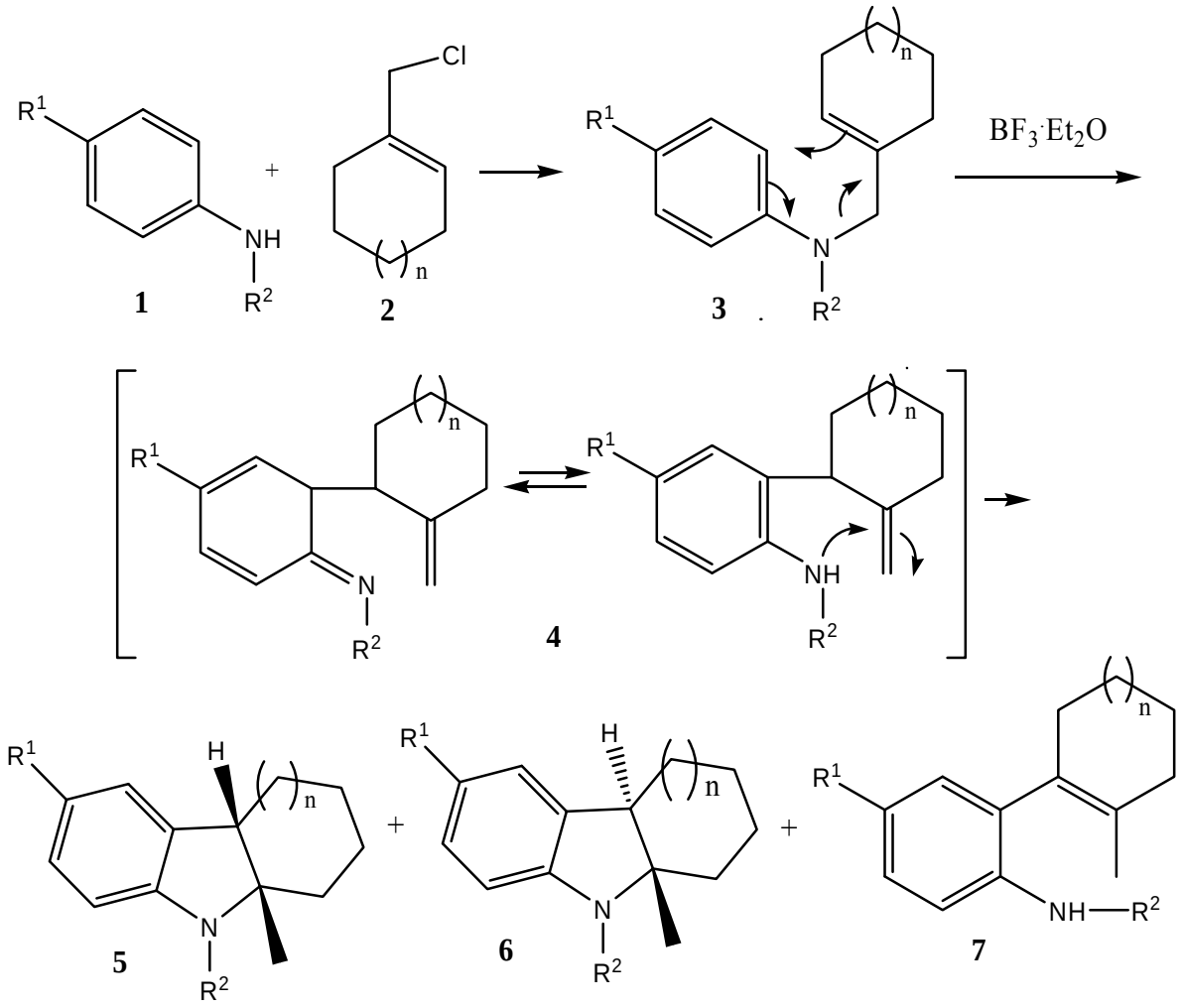
## RESULTS AND DISCUSSION

Our synthesis was based on combined aza-Claisen rearrangement/intramolecular ring-closing reaction of *N*-allylaniline derivatives **3**.[12] Treatment of aniline with 1-(chloromethyl)cyclohex-1-ene (**2a)** afforded *N*-(cyclohexenylmethyl)benzeneamine (**3a**), which was subjected to thermal rearrangement using $BF_3{\cdot}OEt_2$ as a catalyst. A mixture of three products (**5a**, **6a** and **7a**) were formed, which was easily separated by column chromatography, in (20 %, 7 %, and 6 %) yields, respectively (Table 1, Entries 1 and 8).

The structure of these compounds were determined based on their spectroscopic properties. The stereochemistry of **5a** and **6a** were established on the basis of NOE difference experiments. Irradiation of $CH_3$-8a of **5a** (1.24 ppm) showed NOE on H-4b (2.67 ppm, 1.9 %), indicating a *cis* relationship between H-4b/$CH_3$-8a. Furthermore, irradiation of H-4b (2.67 ppm) also showed an increase (5 %) in the intensity of methyl signal. However, in the case of **6a** irradiation of $CH_3$-8a (0.87 ppm) did not give significant change of the H-4b signal (2.49 ppm). Likewise, irradiation of H-4b (2.49 ppm) resulted only a moderate increase of the intensity of $CH_3$-8a signal (2 %), indicating a *trans* relationship between these groups.

Compound **7a** was formed from the product of rearrangement reaction (**4a**) by double bond migration.

Likewise, reaction between aniline and (*E*)-1-(chloromethyl)cyclohept-1-ene (**2b**) afforded compound **3b**. Thermal rearrangement of the latter, followed by ring-closure, furnished **5b** and **6b** in (27 % and 9 %) yields, respectively. Here the side product **7b** was formed in 9 % yield (Entries 2 and 9).

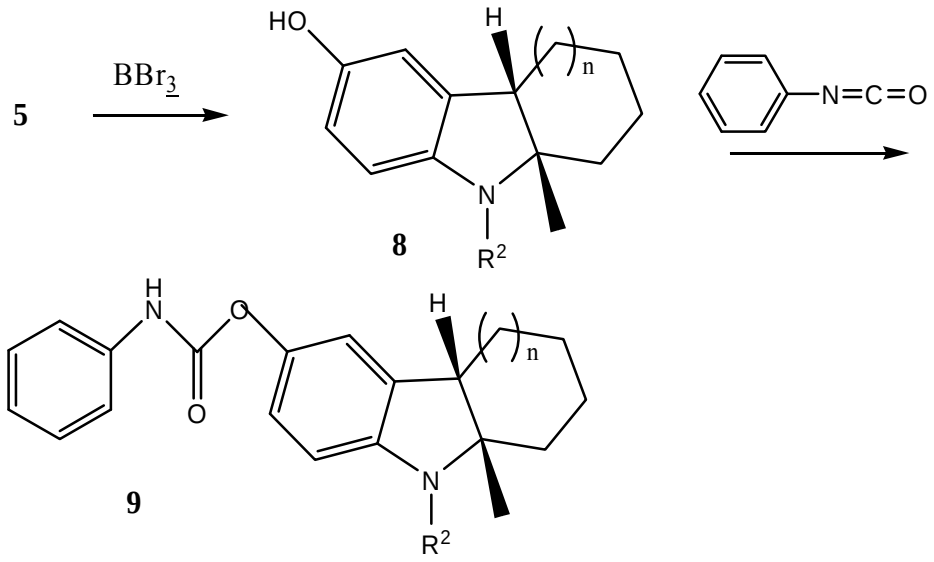



Scheme 1

Attempted reaction of **1a** with 1-(chloromethyl)cyclopent-1-ene (**2c**) afforded compound **3c**. Thermal rearrangement of this compound, followed by ring-closure reaction, furnished only the *cis*-isomer (**5c**) and the side-product (**7c**) in 50% and 8% yields, respectively (Entries 3 and 10).

Having achieved the synthesis of **5a,b** and **6a,b**, we turned our attention to obtain substituted analogs, too. Reaction of **1b** with **2a** afforded **3d** in 65 % yield. However, the attempted rearrangement of the latter failed. From the reaction mixture we could isolate only the unchanged starting compound and some degradation products (Entries 4 and 11).

In the case of alkylation of compound **1b** with **2c** gave the wanted product **3e** in moderate yield (44 %). Then **3e** underwent thermal rearrangement followed by ring closure to afford the single stereoisomer **5e** and the side-product **7e** (Entries 5 and 12).




Scheme 2

Table 1. Compounds Prepared

| Entry | Substrate | Reagent | $R^1$ | $R^2$ | n | Product(s) | Yields (%) |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | **2a** | H | H | 1 | **3a** | 68 |
| 2 | **1a** | **2b** | H | H | 2 | **3b** | 71 |
| 3 | **1a** | **2c** | H | H | 0 | **3c** | 59 |
| 4 | **1b** | **2a** | OMe | H | 1 | **3d** | 65 |
| 5 | **1b** | **2c** | OMe | H | 0 | **3e** | 44 |
| 6 | **1c** | **2c** | OMe | Me | 0 | **3f** | 36 |
| 7 | **1c** | **2a** | OMe | Me | 1 | **3g** | 78 |
| 8 | **3a** | $BF_3{\cdot}Et_2O$ | H | H | 1 | **5a, 6a, 7a** | 20, 7, 6 |
| 9 | **3b** | $BF_3{\cdot}Et_2O$ | H | H | 2 | **5b, 6b, 7b** | 27, 9, 9 |
| 10 | **3c** | $BF_3{\cdot}Et_2O$ | H | H | 0 | **5c, 7c** | 50, 8 |
| 11 | **3d** | $BF_3{\cdot}Et_2O$ | OMe | H | 1 | - | - |
| 12 | **3e** | $BF_3{\cdot}Et_2O$ | OMe | H | 0 | **5e, 7e** | 40, 11 |
| 13 | **3f** | $BF_3{\cdot}Et_2O$ | OMe | Me | 0 | **7f** | 53 |
| 14 | **3g** | $BF_3{\cdot}Et_2O$ | OMe | Me | 1 | **5g, 7g** | 51, 18 |

During the synthesis of compounds **3** we got a dialkylated side-product in all cases. In order to overcome this difficulty, 4-methylaminoanisole (**1c**) was prepared and treated by the 5 and 6-membered cyclic alkylatig agents (**2a**, **2c**) to obtain the products **3g** and **3f**, respectively.

However the ring-closure reaction of **3f** was unsuccessful, we got only the rearranged form (**7f**) of the expected product (Entry 13). Finally we could prepare **5f** from **5e** with the reaction of NaH and methyl iodide (Table 2, Entry 1).

Fortunately **3g** underwent ring-closure reaction in the high boiling sulfolane, in the presence of $BF_3 \cdot OEt_2$ catalyst, providing two main compounds, such as the *cis*-isomer of the product (**5g**) and the rearranged derivative (**7g**) (Entry 14). Presumably the sterical hindrance of the methyl group could be attributed to the absence of *trans*-isomer (**6g**).

Table 2. Compounds Prepared

| Entry | Substrate | Reagent | $R^1$ | $R^2$ | n | Product(s) | Yields (%) |
|---|---|---|---|---|---|---|---|
| 1 | **5e** | NaH, MeI | OMe | Me | 0 | **5f** | 71 |
| 2 | **5g** | $BBr_3$ | OH | Me | 1 | **8a** | 73 |
| 3 | **5f** | $BBr_3$ | OH | Me | 0 | **8b** | 93 |
| 4 | **8a** | PhNCO | - | Me | 1 | **9a** | 48 |
| 5 | **8b** | PhNCO | - | Me | 0 | **9b** | 58 |

To finish the synthesis, **5g** and **5f** had been treated with $BBr_3$ and the hydroxyl derivatives **8a,b** formed were then reacted with phenyl isocyanate to afford the carba analog of physostigmine **9b** and its congeners **9a** (Scheme 2. Table 2, Entries 2-5).

In summary, we have developed a straightforward approach to the analogs of physostigmine based on the combined aza-Claisen rearrangement/intramolecular ring-closure reaction of the *N*-allylaniline derivatives, followed by $BBr_3$ mediated cleavage of methoxy group and subsequent formation of the phenylcarbamyl derivatives.

## EXPERIMENTAL

IR spectra were recorded on Spekord 75 IR spectrometer. $^1H$ and $^{13}C$ NMR spectra were obtained with a Bruker DRX-500 spectrometer; internal standard TMS. All solvents were dried by means of standard methods. Reactions were followed by TLC on Merck pre-coated silica gel 60F254 plates. Merck Kieselgel® 60 was employed for column chromatography.

1-(Chloromethyl)cyclohex-1-ene (**2a**)[13] was prepared by known procedure. 1-(Chloromethyl)cyclohept-1-ene (**2b**) was prepared from cycloheptanone according to the procedure

used for the preparation of **2a**, in 30 % overall yield. 1-(Chloromethyl)cyclopent-1-ene (**2c**) was prepared from methyl-2-oxocyclopentanecarboxylate by $LiAlH_4$-reduction[14] followed by the chlorination step according to that of **2a** and **2b**, in 54 % overall yield.

**1-(Chloromethyl)cyclohept-1-ene (2b).** Yellowish oil. TLC ($CH_2Cl_2$): $R_f$ = 0.77. $^1$H NMR ($CDCl_3$): δ 1.53 (m, 4H, 2 $CH_2$), 1.75 (m, 2H, $CH_2$), 2.15 (m, 2H, $CH_2$), 2.26 (m, 2H, $CH_2$), 4.02 (s, 2H, $CH_2$-Cl), 5.95 (t, *J* = 6.4 Hz, 1H, HC=). $^{13}$C NMR ($CDCl_3$): δ 24.20, 25.12, 28.71, 31.35, 32.61, 53.22 ($CH_2Cl$), 132.54, 140.61.

**1-(Chloromethyl)cyclopent-1-ene (2c).** TLC (hexane/EtOAc 9:1): $R_f$ = 0.66. $^1$H NMR ($CDCl_3$): δ 1.87 (m, 2H, $CH_2$), 2.42 (m, 4H, 2 $CH_2$), 4.29 (s, 2H, $CH_2$-Cl), 5.75 (s, 1H, HC=). $^{13}$C NMR ($CDCl_3$): δ 22.88, 32.05, 32.42, 43.53, 129.82, 140,14.

***N*-(Cyclohexenylmethyl)benzenamine (3a).** A mixture of **2a** (0.5 g, 3.8 mmol) and freshly distilled aniline (1.43 g, 15 mmol) in water (3 mL) was vigorously stirred at rt for 1 h. The reaction mixture was extracted with ether, the ethereal extract was dried ($MgSO_4$) and then concentrated in vacuo. The residue was purified by column chromatography using hexane/EtOAc (9:1) as eluent to yield **3a** as yellow oil (0.49 g, 68 %). TLC (hexane/EtOAc 9:1): $R_f$ = 0.4. $^1$H NMR ($CDCl_3$): δ 1.59 (m, 4H, 2 $CH_2$), 2.00 (br. s, 4H, 2 $CH_2$), 3.60 (s, 2H, N-$CH_2$), 4.35 (br. s, 1H, NH), 5.67 (m, 1H, HC=), 6.64 (d, *J* = 7.95 Hz, 2H, ArH), 6.71 (t, *J* = 7.2 Hz, 1H, ArH), 7.50 (t, *J* = 7.50 Hz, 2H,ArH). $^{13}$C NMR ($CDCl_3$): δ 22.50, 22.71, 26.83, 50.80 (N-$CH_2$), 113.32, 117.74, 119.32, 123.50, 129.16, 134.80, 148.00. Anal. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48. Found: C, 83.20; H, 8.91; N, 7.36.

***N*-(Cycloheptenylmethyl)benzenamine (3b).** Compound **2b** (0.4 g, 2.8 mmol) was added dropwise to a mixture of aniline (1.03 g, 11 mmol) and water (3 mL). The two phase system was vigorously stirred at rt for 2.5 h and then extracted with ether. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography using hexane/EtOAc (9:1) as eluent to afford **3b** as light yellow liquid (0.39 g, 71 %). TLC (hexane/EtOAc 9:1): $R_f$ = 0.61. $^1$H NMR ($CDCl_3$): δ 1.48 (m, 4H, 2 $CH_2$), 1.73 (m, 2H, $CH_2$), 2.11 (m, 2H, $CH_2$), 2.16 (m, 2H, $CH_2$), 3.60 (br.s, 1H, NH), 3.61 (s, 2H, $CH_2$), 5.80 (t, *J* = 6.3 Hz, 1H, HC=), 6.60 (d, *J* = 8.5 Hz, 2H, ArH), 6.68 (t, *J* = 7.2 Hz, 1H, ArH), 7.15 (t, *J* = 8.5 Hz, 2H, ArH). $^{13}$C NMR ($CDCl_3$): δ 26.85, 27.11, 28.19, 31.12, 32.47, 51.90, 112.93, 117.18, 127.79, 129.12, 141.29, 148.41. Anal. Calcd for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.27; H, 9.29; N, 7.02.

***N*-(Cyclopentenylmethyl)benzenamine (3c).** This compound was prepared accordingly to the method applied for **3b**, using **1a** and **2c** as starting materials. **3c** was yielded as a yellowish oil in 59 %. TLC ($CH_2Cl_2$/MeOH 99:1): $R_f$ = 0,71. $^1$H NMR ($CDCl_3$): δ 1.93 (m, 2H, $CH_2$), 2,36 (m, 4H, 2 $CH_2$), 3.78 (br.s, 1H, NH), 3.81 (s, 2H, N-$CH_2$), 5.62 (br.s, 1H, HC=), 6.68 (d, *J* = 8.0 Hz, 2H, ArH), 6.74 (t, *J* = 7.4 Hz, 1H, ArH), 7.20 (t, *J* = 7.7 Hz, 2H, ArH). $^{13}$C NMR ($CDCl_3$): δ 23.58, 32.55, 33.89, 45.19, 113.29, 117.73, 125.98, 129.07, 141.60, 147.78

***N*-(Cyclohexenylmethyl)-4-methoxybenzenamine (3d).** This compound was prepared using the same procedure as for the preparation of **3b** and compounds **1b** and **2a** as starting materials: yield 65 %. Light yellow liquid. TLC (hexane/EtOAc 4:1): $R_f$ = 0.49. $^1$H NMR ($CDCl_3$): δ 1.60 (m, 4H, 2 $CH_2$), 2.01 (m, 4H, 2 $CH_2$), 3.58 (s, 2H, N-$CH_2$), 3.76 (s, 3H, $OCH_3$), 3.90 (s, 1H, NH), 5.68 (s, 1H, HC=), 6.57 (d, *J* = 8.45 Hz, 2H, ArH), 6.79 (d, *J* = 8.8 Hz, 2H, ArH). $^{13}$C NMR ($CDCl_3$): δ 22.60, 22.93, 25.32, 27.10, 52.21 (N-$CH_2$), 56.00 ($OCH_3$), 115.02, 115.20, 123.90, 135.11, 141.91, 152.80. Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.27; H, 9.05; N, 6.22.

***N*-(Cyclopentenylmethyl)-4-methoxybenzenamine (3e).** This compound was prepared accordingly to that method applied for **3b**, using **1b** and **2c** as starting materials and was yielded as a yellowish oil in 44%.TLC (hexane/EtOAc 9:1): $R_f$ = 0.51. $^1$H NMR ($CDCl_3$): δ 1.90 (m, 2H, $CH_2$), 2,33 (m, 4H, 2 $CH_2$), 3,74 (s, 5H, N-$CH_2$ + $CH_3$), 4.10 (s, 1H, NH), 5.59 (s, 1H, HC=), 6.61 (d, *J* = 8.5 Hz, 2H, ArH), 6.77 (d, *J* = 9.0 Hz, 2H, ArH). $^{13}$C NMR ($CDCl_3$): δ 23.57, 32.57, 33.94, 46.07, 56.01, 114.66, 115.03, 125.94, 142.39, 142.65, 152.46

***N*-(Cyclopentenylmethyl)-4-methoxy-*N*-methylbenzenamine (3f).** Compound **2c** (2.87 g, 25 mmol) was added dropwise to a mixture of **1c** (3.43 g, 25 mmol), triethylamin (5.06 g, 50 mmol) and water (25 mL). The two phase system was vigorously stirred at rt for 1.5 h and then extracted with dichloromethane. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography using hexane/EtOAc (7:3) as eluent to afford **3f** as light yellow liquid (1.95 g, 36 %). TLC (hexane/EtOAc 7:3): $R_f$ = 0.73. $^1$H NMR ($CDCl_3$): δ 1.87 (m, 2H, $CH_2$), 2.22 (m, 2H, $CH_2$), ), 2.30 (m, 2H, $CH_2$), 2.86 (s, 3H, $CH_3$), 3.75 (s, 3H, $CH_3$), 3.84 (s, 2H, N-$CH_2$), 5.47 (s, 1H, HC=), 6.71 (d, *J* = 8.4 Hz, 2H, ArH), 6.82 (d, *J* = 8.7 Hz, 2H, ArH). $^{13}$C NMR ($CDCl_3$): δ 23.66, 32.44, 33.85, 39.12, 54.75, 56.00, 114.5, 114.85, 126.71, 141.60, 141.64, 151.77

***N*-(Cyclohexenylmethyl)-4-methoxy-*N*-methylbenzenamine (3g).** To a suspension of **1c** (0.5 g, 3.6 mmol) in water (5 mL) were added successively compound **2a** (0.47 g, 3.6 mmol) and triethylamine (1

mL), and the resulting mixture was stirred at rt for 3 h. The reaction mixture was extracted with ether (2x20 mL), the ethereal extracts were dried ($MgSO_4$), and the solvent was evaporated in vacuo. The residue was purified by flash chromatography using hexane/acetone (7:3) as eluent to afford **3f** as light yellow oil (0.63 g, 78 %). TLC (hexane/EtOAc 7:3): $R_f$ = 0.67. $^1$H NMR ($CDCl_3$): δ 1.60 (m, 4H, 2 $CH_2$), 1.9 (m, 2H, $CH_2$), 2.82 (s, 3H, N-$CH_3$), 3.64 (s, 2H, N-$CH_2$), 3.74 (s, 3H, $OCH_3$), 5.53 (s, 1H, =CH), 6.69 (m, 2H, ArH), 6.80 (m, 2H, ArH). $^{13}$C NMR ($CDCl_3$): δ 2.66, 22.75, 25.07, 26.58, 38.55 (N-$CH_3$), 55.84 (O-$CH_3$), 60.42 (N-$CH_2$), 114.15, 114.69, 122.76 (=CH), 134.53 (=C), 145.14, 151.48. Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.59; H, 8.82; N, 6.21.

**5,6,7,8,8a,9-Hexahydro-8a-methyl-4bH-carbazole (5a and 6a).** To a solution of compound **3a** (0.48 g, 2.6 mmol) in sulfolane (10 mL) was added $BF_3{\cdot}OEt_2$ (0.33 mL, 2.6 mmol) and the resulting mixture was stirred at 170-175 $^o$C for 2 h under Ar. After cooling, water (10 mL) was added and the mixture was extracted with chloroform. The organic extract was dried ($MgSO_4$), concentrated in vacuo, and the sulfolane was removed by column chromatography (using hexane/EtOAc 9:1 as eluent). The crude product was purified by preparative thin layer chromatography to give **5a** (95 mg, 20 %), **6a** (32 mg, 7 %), and **7a** (30 mg, 6 %).

Compound **5a**: yellow oil. TLC (hexane/EtOAc 9:1): $R_f$ = 0.29. $^1$H NMR (DMSO-$d_6$): δ 1.20 (m, 2H, $C_6$-H and $C_7$-H), 1.24 (s, 3H, $CH_3$), 1.39 (m, 2H, $C_6$-H and $C_7$-H), 1.42 (m, 2H, $C_8$-H), 1.67 (m, 1H, $C_5$-H), 1.82 (m, 1H, $C_5$-H), 2.67 (m, 1H, $C_{4b}$-H), 5.31 (s, 1H, NH), 6.47 (d, $J$ = 7.6 Hz, 1H, $C_1$-H), 6.53 (t, $J$ = 7.4 Hz, 1H, $C_3$-H), 6.88 (t, $J$ = 7.6 Hz, 1H, $C_2$-H), 6.95 (d, $J$ = 7.3 Hz, 1H, $C_4$-H). $^{13}$C NMR (DMSO-$d_6$): δ 21.94 (C-7), 21.96 (C-6), 25.05 (C-5), 25.93 ($CH_3$), 35.11 (C-8), 46.98 (C-4b), 63.08 (C-8a), 108.83 (C-1), 116.69 (C-3), 122.38 (C-4), 126.65 (C-2), 132.11 (C-4a), 150.42 (C-9a). Anal. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48. Found: C, 83.44; H, 9.02; N, 7.21.

Compound **6a**: yellow oil. TLC (hexane/EtOAc 9:1): $R_f$ = 0.23. $^1$H NMR (DMSO-$d_6$): δ 0.87 (s, 3H, $CH_3$), 1.35 (m, 1H, $C_7$-H), 1.40 (m, 1H, $C_5$-H), 1.47 (m, 1H, $C_6$-H), 1.64 (m, 2H, $C_6$-H and $C_7$-H), 1.80 (m, 2H, $C_7$-H and $C_8$-H), 2.05 (m, 1H, $C_5$-H), 2.49 (m, 1H, $C_{4b}$), 5.40 (s, 1H, NH), 6.54 (d, $J$ = 7.7 Hz, 1H, $C_1$-H), 6.55 (t, $J$ = 7.4 Hz, 1H, $C_3$-H), 6.89 (t, $J$ = 7.6 Hz, 1H, $C_2$-H), 6.92 (d, $J$ = 7.0 Hz, 1H, $C_4$-H). $^{13}$C NMR (DMSO-$d_6$): δ 17.74 ($CH_3$), 21.77 (C-5), 22.52 (C-6), 25.68 (C-7), 37.70 (C-8), 51.42 (C-4b), 65.84 (C-8a), 109.28 (C-1), 117.01 (C-3), 121.34 (C-4), 126.27 (C-2), 131.32 (C-4a), 150.84 (C-9a). Anal. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48. Found: C, 83.09; H, 8.87; N, 7.57.

Compound **7a**: light yellow oil. TLC (hexane/$CH_2Cl_2$ 1:1): $R_f$ = 0.27. $^1$H NMR (DMSO-$d_6$): δ 1.40 (s, 3H, CH3), 1.68 (m, 4H, 2 $CH_2$), 2.05 (m, 4H, 2 $CH_2$), 4.50 (br.s, 2H, $NH_2$), 6.16 (t, $J$ = 7.5 Hz, 1H, ArH), 6.64 (d, $J$ = 8.0 Hz, 1H, ArH), 6.75 (d, $J$ = 6.5 Hz, 1H, ArH), 6.91 (t, $J$ = 6.5 Hz, 1H, ArH). $^{13}$C NMR

(DMSO-$d_6$): δ 21.29 ($CH_3$), 23.87, 24.16, 31.47, 31.73, 115.00, 117.02, 128.94, 129.31, 129.83, 130.69, 145.31. Anal. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48. Found: C, 83.57; H, 8.93; N, 7.52.

**5a-Methyl-5,5a,6,7,8,9,10,10a-octahydrocyclohepta[*b*]indole (5b and 6b).** To a solution of **3b** (0.35 g, 1.7 mmol) in sulfolane (13 mL) was added $BF_3{\cdot}OEt_2$ (0.22 mL, 1.7 mmol) and the resultant mixture was stirred at 160-170 °C for 40 min under Ar. After cooling, water (15 L) was added and the reaction mixture was extracted with chloroform. The organic layer was dried ($MgSO_4$), concentrated in vacuo, and the sulfolane was removed by column chromatography using hexane/EtOAc (9:1) as eluent. The crude product was purified by preparative thin layer chromatography to yield **5b** (93 mg, 27 %), **6b** (31 mg, 9 %), and **7b** (30 mg, 9 %).

Compound **5b**: colorless semisolid. TLC (hexane/EtOAc 9:1): $R_f$ = 0.51. $^1$H NMR ( $CDCl_3$): δ 1.27 (s, 3H, $CH_3$), 1.38 (m, 1H, $C_7$-H), 1.40 (m, 1H, $C_8$-H), 1.42 (m, 1H, $C_9$-H), 1.63 (m, 1H, $C_8$-H), 1.70 (m, 1H, $C_7$-H), 1.74 (m, 1H, $C_6$-H), 1.76 (m, 2H, $C_9$-H and $C_{10}$-H), 1.80 (m, 2H, $C_6$-H and $C_{10}$-H), 2.95 (dd, $J$ = 8 and 2 Hz, 1H, $C_{10a}$-H), 3.1 (br.s, 1H, NH), 6.53 (d, $J$ = 7.8 Hz, 1H, $C_4$-H), 6.68 (t, $J$ = 7.4 Hz, 1H, $C_2$-H), 7.00 (t, $J$ = 7.4 Hz, 1H, $C_3$-H), 7.01 (d, $J$ =7.4 Hz, 1H, $C_1$-H). $^{13}$C NMR ($CDCl_3$): δ 24.65 (C-7), 28.50 (C-9), 30.81 ($CH_3$), 31.37 (C-8), 32.33 (C-10), 40.39 (C-6), 53.96 (C-10a), 65.94 (C-5a), 108.75 (C-4), 118.07 (C-2), 124.64 (C-1), 127.38 (C-3), 133.28 (C-10b), 149.08 (C-4a). Anal. Calcd for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.36; H, 9.27; N, 7.05.

Compound **6b**: colorless semisolid. TLC (hexane/EtOAc 9:1): $R_f$ = 0.42. $^1$H NMR ( $CDCl_3$): δ 1.12 (s, 3H, $CH_3$), 1.37 (m,1H, $C_7$-H), 1.52 (m, 1H, $C_8$-H), 1.55 (m, 1H, $C_9$-H), 1.63 (m, 1H, $C_{10}$-H), 1.75 (m, 1H, $C_8$-H), 1.80 (m, 1H, $C_6$-H), 1.91 (m, 2H, $C_6$-H and $C_7$-H), 2.00 (m, 2H, $C_9$-H), 2.25 (m, 1H, $C_{10}$-H), 3.19 (dd, $J$ = 12.5 and 5.5 Hz, 1H, $C_{10a}$-H), 3.3 (br.s, 1H, NH), 6.55 (d, $J$ = 7.6 Hz, 1H, $C_4$-H), 6.70(t, $J$ = 7.5Hz, 1H, $C_2$-H), 6.95 (t, $J$ = 7.5 Hz, 1H, $C_3$-H), 6.98 (d, $J$ = 8 Hz, 1H, $C_1$-H). $^{13}$C NMR ($CDCl_3$): δ 20.48 ($CH_3$), 23.55 (C-10), 25.76 (C-8), 26.05 (C-9), 27.49 (C-7), 42.58 (C-6), 48.12 (C-10a), 69.38 (C-5a), 109.02 (C-4), 118.37 (C-2), 122.75 (C-1), 126.90 (C-3), 133.32 (C-10b), 149.76 (C-4a). Anal. Calcd for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.42; H, 9.32; N, 6.68.

Compound **7b**: yellow oil. TLC hexane/EtOAc 9:1): $R_f$ = 0.47. $^1$H NMR ($CDCl_3$): δ 1.55 (m, 1H, $CH_2$), 1.56 (s, 3H, $CH_3$), 1.60 (m, 3H, $CH_3$), 1.77 (m, 1H, $CH_2$), 1.85 (m, 1H, $CH_2$), 2.22 (m, 1H, $CH_2$), 2.32 (m, 1H, $CH_2$), 2.34 (m, 1H, $CH_2$), 2.42 (m, 1H, $CH_2$), 3.60 (br.s, 2H, $NH_2$), 6.68 (d, $J$ = 8.3 Hz, 1H, ArH), 6.71 (t-d, $J$ = 7.5 and 1 Hz, 1H, ArH), 6.90 (dd, $J$ = 7.5 and 1 Hz, 1H, ArH, 7.02 (t-d, $J$ = 7.5 and 1.5 Hz, 1H, ArH). $^{13}$C NMR ($CDCl_3$): δ 22.63($CH_3$), 26.36, 27.39, 32.48, 35.09, 35.39, 114.93, 118.30, 127.03, 128.77, 131.95, 134.60, 138.15, 142.58. Anal. Calcd for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.72; H, 9.39; N, 7.16.

**3a-Methyl-1,2,3,3a,4,8b-hexahydrocyclopent[*b*]indole and 2-(2-methylcyclopent-1-enyl)benzenamine (5c and 7c)** To a solution of **3c** (0.155 g, 0.9 mmol) in sulfolane (6 mL) was added $BF_3 \cdot OEt_2$ (0.14 mL, 1.1 mmol) and the resultant mixture was stirred at 160-170 $^oC$ for 100 min under Ar. After cooling, water (10 L) was added and the reaction mixture was extracted with chloroform. The organic layer was dried ($MgSO_4$), concentrated in vacuo, and the sulfolane was removed by column chromatography on $Al_2O_3$ gel using hexane/EtOAc (9:1) as eluent. The crude product was purified by preparative thin layer chromatography to yield **5c** (77 mg, 50 %), **7c** (12 mg, 8 %).

Compound **5c**: yellow oil. TLC (hexane/EtOAc 9:1): $R_f$= 0.45. $^1$H NMR (DMSO-$d_6$): δ 1.28 (s, 3H, $CH_3$), 1.45 (m, 1H, $CH_2$), 1,55 (m, 3H, $CH_2$), 1,72 (m, 1H, $CH_2$), 2,00 (m, 1H, $CH_2$), 3,13 (d, $J$ = 8.5 Hz, 1H, CH), 5.50 (br.s, 1H, NH), 6.32 (d, $J$ = 7.5 Hz, 1H, ArH), 6.44 (t, $J$ = 7.0 Hz, 1H, ArH), 6.84 (t, $J$ = 7.5 Hz, 1H, ArH), 6.89 (d, $J$ = 7.0 Hz, 1H, ArH). $^{13}$C NMR (DMSO-$d_6$): δ 25.35, 28.04, 35.39, 42.41, 53.42, 70.59, 107.03, 116.21, 124.28, 127.23, 132.28, 151.43.

Compound **7c**: yellow oil. TLC hexane/EtOAc 9:1): $R_f$= 0.36. $^1$H NMR (DMSO-$d_6$): δ 1.53 (s, 3H, $CH_3$), 1.88 (m, 2H, $CH_2$), 2.42 (m, 2H, $CH_2$), 2.53 (m, 2H, $CH_2$), 4.54 (br.s, 2H, $NH_2$), 6.50 (t, $J$ = 7.5 Hz, 1H, ArH), 6.64 (d, $J$ = 8.0 Hz, 1H, ArH), 6.81 (d, $J$ = 7.5 Hz, 1H, ArH), 6.92 (t, $J$ = 8.0 Hz, 1H, ArH). $^{13}$C NMR (DMSO-$d_6$): δ 15.11, 22.0, 37.19, 38.22, 114.51, 115.96, 122.95, 127.38, 128.84, 133.47, 135.31, 145.27.

**7-Methoxy-3a-methyl-1,2,3,3a,4,8b-hexahydrocyclopent[*b*]indole and 4-metoxy-2-(2-methylcyclopent-1-enyl)benzenamine (5e and 7e)** These compounds were prepared accordingly to the method applied for **5c** and **7c** using **3e** as a starting material.

Compound **5e**: yellow oil, yielded in 40%. TLC (hexane/EtOAc 9:1): $R_f$= 0.48. $^1$H NMR ($CDCl_3$): δ 1.40 (s, 3H, $CH_3$), 1.63 (m, 3H, $CH_2$), 1,17 (m, 2H, $CH_2$), 2,00 (m, 1H, $CH_2$), 3,00 (br.s, 1H, NH), 3,25 (d, $J$ = 7.8 Hz, 1H, CH), 3.74 (s, 3H, $CH_3$), 6.55 (d, $J$ = 20.4 Hz, 1H, ArH), 6.62 (d, $J$ = 20.4 Hz, 1H, ArH), 6.65 (br.s, 1H, ArH). $^{13}$C NMR ($CDCl_3$): δ 25.77, 28.26, 35.23, 43.19, 54.72, 56.17, 72.05, 110.03, 111.53, 112.77, 135.40, 144.33, 153.85.

Compound **7e**: yellow oil, yielded in 11%. TLC (hexane/EtOAc 9:1): $R_f$= 0.41. $^1$H NMR ($CDCl_3$): δ 1.61 (s, 3H, $CH_3$), 1.95 (m, 2H, $CH_2$), 2,45 (m, 2H, $CH_2$), 2,62 (m, 2H, $CH_2$), 3,77 (br.s, 5H, $NH_2$+$CH_3$), 6.57 (s, 1H, ArH), 6.68 (m, 2H, ArH). $^{13}$C NMR ($CDCl_3$): δ 15.27, 22.65, 37.98, 38.86, 55.91, 113.59, 114.71, 116.77, 126.65, 133.45, 137.00, 137.32, 152.74.

**4-Metoxy-*N*-methyl-2-(2-methylcyclopent-1-enyl)benzenamine (7f)** The preparation of **7f** was similar to that of **5c** and **7c** using **3f** as a starting material.

Compound **7f**: yellow oil, yielded in 53%. TLC (hexane/EtOAc 9:1): $R_f$= 0.61. $^1$H NMR ($CDCl_3$): δ 1.57

(s, 3H, $CH_3$), 1.94 (m, 2H, $CH_2$), 2,47 (m, 2H, $CH_2$), 2,59 (m, 2H, $CH_2$), 2.81 (s, 3H, N-$CH_3$), 3,18 (br.s, 1H, NH), 3.74 (s, 3H, O-$CH_3$), 6.59 (s, 2H, ArH), 6.76 (m, 1H, ArH). $^{13}$C NMR ($CDCl_3$): δ 15.17, 22.60, 32.03, 38.04, 38.83, 56.00, 111.00, 113.02, 115.31, 123.23, 133.33, 137.46, 141.04, 151.51.

**5,6,7,8,8a,9-Hexahydro-3-methoxy-8a,9-dimethyl-4bH-carbazole (5g).** To a solution of **3g** (0.5 g, 2.2 mmol) in sulfolane (6 mL) was added $BF_3{\cdot}Et_2O$ (0.28 mL, 2.2 mmol) and the resulting mixture was heated at 185-190 $^o$C for 30 min. After cooling, the reaction mixture was diluted with water (20 mL) and extracted with $CH_2Cl_2$ (3x50 mL). The combined extracts were dried ($MgSO_4$), the solvent was evaporated in vacuo, and the sulfolane was removed by column chromatography on $Al_2O_3$ gel using hexane/EtOAc (9:1) as eluent. The resulting mixture of **5g** and side product **7g** ($R^1$= OMe, $R^2$= Me, *n*= 1) was dissolved in ether (15 mL) and treated with phenylisocyanate (0.185 mL). After stirring at rt for 18 h, the solvent was evaporated in vacuo, and the residue was purified by chromatography on $Al_2O_3$ gel (using hexane/EtOAc 9:1 as eluent) to afford **5g** (0.26 g, 51 %) and the phenylcarbamate of **7g** (0.14 g, 18 %).
Compound **5g:** light yellow oil. TLC (hexane/EtOAc 9:1, $Al_2O_3$): $R_f$ = 0.62. $^1$H NMR (DMSO-$d_6$): δ 1.19 (s, 3H, $CH_3$), 1.50 (m, 8H, 4 $CH_2$), 2.7 (s, 3H, N-$CH_3$), 3.66 (s, 3H, O-$CH_3$), 6.28 (d, *J* = 4.05 Hz, 1H, ArH), 6.66 (s, 1H, ArH), 6.72 (m, 1H, ArH). $^{13}$C NMR (DMSO-$d_6$): δ 21.49, 21.58, 21.94, 24.29, 28.38, 29.07 ($CH_3$), 46.83 (O-$CH_3$), 67.06 (N-$CH_3$), 106.91, 109.89, 110.86, 133.56, 145.76, 152.12. Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.60; H, 9.02; N, 5.86.
Compound phenylcarbamate of **7g**: yellow oil. TLC (hexane/EtOAc 7:3): $R_f$ = 0.41. $^1$H NMR ($CDCl_3$): δ 1.42 (s, 3H, $CH_3$), 1.66 (m, 4H, 2 $CH_2$), 2.04 (br.s, 3H, 2 $CH_2$), 2.10 (br.s, 1H,$CH_2$), 3.12 (s, 3H, N-$CH_3$), 3.84 (s, 3H, O-$CH_3$), 6.18 (s, 1H, NH), 6.71 (d, *J* = 3.0 Hz, 1H, ArH), 6.86 (dd, *J* =8.5 and 3.0 Hz, 1H, ArH), 6.96 (t, *J* =6.5 Hz, 1H, ArH), 7.23 (m, 5H, ArH). $^{13}$C NMR ($CDCl_3$): δ 21.14 ($CH_3$), 22.96, 23.29, 30.95, 31.28, 36.23 (N-$CH_3$), 55.55 (O-$CH_3$), 113.55, 116,79, 119.14, 122.65, 128.78, 129.29, 130.32, 130.72, 132.83, 139.11, 144.87, 154.79 (CO), 159.19.

**7-Methoxy-3a,4-dimethyl-1,2,3,3a,4,8b-hexahydrocyclopent[*b*]indole (5f).** To a solution of **5e** (0,54 g , 2,7 mmol) in dry DMF (5 mL) sodium-hydride (0,19 g, 8 mmol) was added and the resulting mixture was cooled down to 0 °C and stirred for 10 minutes. Methyl iodide was added dropwise to the mixture at 0 °C, then it was allowed to reach the ambient temperature and stirred 1 h additionally. The mixture was quenched by water (40 mL) and extracted three times with $Et_2O$ (30 mL). The combined ethereal phases were dried and the solvent was evaporated in vacuo. The crude product **5f** (0,54 g, 93%) was used without further purification.
Compound **5f:** light yellow oil. TLC (hexane/EtOAc 9/1): $R_f$ = 0,63. $^1$H NMR (DMSO-$d_6$): δ 1.22 (s, 3H, $CH_3$), 1.38 (m, 1H, $CH_2$), 1.44 (m, 1H, $CH_2$), 1.59 (m, 1H, $CH_2$), 1.62 (m, 1H, $CH_2$), 1.79 (m, 1H,

$CH_2$), 2.05 (m, 1H, $CH_2$), 2.59 (s, 3H, N-$CH_3$), 3.10 (m, 1H, CH), 3.62 (s, 3H, $OCH_3$), 6.14 (d, *J*= 8.3 Hz, 1H, ArH), 6.54 (dd, *J*= 8.3 and 2.4 Hz, 1H, ArH), 6.60 (d, *J*= 2.4 Hz, 1H, ArH).
$^{13}$C NMR (DMSO-$d_6$): δ 23.34, 25.20, 29.15, 34.19, 36.43, 52.91, 55.67, 75.55, 104.97, 11.49, 111.92, 133.81, 146.15, 151.62. Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.22; H, 8.57; N, 6.30.

**5,6,7,8,8a,9-Hexahydro-8a,9-dimethyl-4bH-carbazol-3-ol (8a).** To a solution of **5g** (0.25 g, 1.13 mmol) in chloroform (6 mL) was added $BBr_3$ (0.3 mL) and the resulting mixture was stirred at rt for 1 h. The reaction mixture was then treated with MeOH (15 mL) and concentrated in vacuo. The residue was dissolved in aqueous $NaHCO_3$ solution (25 mL) and extracted with $Et_2O$ (3x15 mL). The combined ethereal extracts were dried ($MgSO_4$), the solvent was evaporated in vacuo, and the residue was purified by column chromatography using $CH_2Cl_2$/MeOH (20:1) as eluent to afford **8a** (0.18 g, 73 %), light yellow oil. TLC ($CH_2Cl_2$/MeOH 20:1): $R_f$ =0.58. $^1$H NMR (DMSO-$d_6$): δ 1.13 (m, 1H, $CH_2$), 1.15 (m, 1H, $CH_2$), 1.21 (s, 3H, $CH_3$), 1.23 (m, 1H, $CH_2$), 1.35 (m,2H, $CH_2$), 1.40 (m, 1H, $CH_2$), 1.65 (m, 1H, $CH_2$), 1.84 (m, 1H, $CH_2$), 2.45 (s, 3H, N-$CH_3$), 2.66 (m, 1H, CH), 6.18 (d, *J* = 8.1 Hz, 1H, ArH), 6.40 (dd, *J* = 8.1 and 1.9 Hz, 1H, ArH), 6.48 (br.s, 1H, ArH), 8.40 (br.s, 1H, OH). $^{13}$C NMR (DMSO-$d_6$): δ 21.78, 22.15, 24.58, 28.71 ($CH_3$), 29.14, 47.06, 67.08, 107.49, 110.66, 112.57, 133.47, 144.62, 149.71. Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.57; H, 8.62; N, 6.21.

**5,6,7,8,8a,9-Hexahydro-8a,9-dimethyl-4bH-carbazol-3-yl phenylcarbamate (9a).** To a stirred solution of **8a** (0.45 g, 2 mmol) in dry THF (30 mL) was added phenyl isocyanate (0.24 mL, 2.2 mmol) and the resulting mixture was refluxed for 36 h. The solvent was evaporated in vacuo and the residue was purified by column chromatography using hexane/EtOAc (7:3) as eluent to yield **9a** as a gray semisolid (0.32 g, 48 %). TLC (hexane/EtOAc 7:3): $R_f$ = 0.20. $^1$H NMR (DMSO-$d_6$): δ 1.16 (m, 1H, $CH_2$), 1.23 (m, 1H, $CH_2$), 1.27 (s-m, 4H, $CH_3$, $CH_2$), 1.43 (m, 2H, $CH_2$), 1.44 (m, 1H, $CH_2$), 1.68 (m, 1H, $CH_2$), 1.94 (m, 1H, $CH_2$), 2.56 (s, 3H, $CH_3$), 2.76 (m, 1H, CH), 6.35 (d, *J* = 8.2 Hz, 1H, ArH), 6.80 (d, *J* = 8.2 Hz, 1H, ArH), 6.85 (s, 1H, ArH), 7.02 (t, *J* = 7.3 Hz, 1H, ArH), 7.30 (t, *J* = 7.7 Hz, 2H, ArH), 7.49 (d, *J* = 7.9 Hz, 2H, ArH), 10.02 (s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$): δ 21.52, 21.89 ($CH_3$), 22.04, 24.35, 28.33 ($CH_3$), 29.59, 46.80, 67.65, 106.58, 116.57, 118.49, 120.02, 122.85, 128.97, 133.15, 139.08, 142.24, 149.25, 152.76 (CO).

**7-Hydroxy-3a,4-dimethyl-1,2,3,3a,4,8b-hexahydrocyclopenta[b]indole (8b).** This compound was prepared accordingly to the method applied for **8a**, using **5f** as a starting material. The crude **8b** was yielded as a yellowish oil in 93 % and was used without further purification. TLC (hexane/EtOAc 7:3): $R_f$

=0.51. $^1$H NMR (DMSO-$d_6$): δ 1.21 (s, 3H, $CH_3$), 1.36 (m, 1H, $CH_2$), 1.45 (m, 1H, $CH_{32}$), 1.59 (m, 2H, $CH_2$), 1.77 (m, 1H, $CH_2$), 2.04 (m, 1H, $CH_2$), 2.55 (s, 3H, $CH_3$), 3.05 (m, 1H, CH), 6.05 (d, *J* = 8,2 Hz, 1H, ArH), 6.38 (dd, *J* = 8,2 and 1,8 Hz, 1H, ArH), 6.42 (br.s, 1H, ArH), 8.29 (s, 1H, OH). $^{13}$C NMR (DMSO-$d_6$): δ 23.32, 25.18, 29.45, 33.99, 36.23, 52.95, 75.46, 105.52, 112.15, 113.16, 133.65, 144.85, 149.04.

**Phenylcarbamate of 8b (9b).** This compound was prepared accordingly to the method applied for **9a**, using **8b** as a starting material and yielded in 58 %. TLC (hexane/EtOAc 7:3): $R_f$ =0.30. $^1$H NMR (DMSO-$d_6$): δ 1.26 (s, 3H, $CH_3$), 1.44 (m, 2H, $CH_2$), 1.62 (m, 2H, $CH_2$), 1.85 (m, 1H, $CH_2$), 2.07 (m, 1H, $CH_2$), 2.66 (s, 3H, $CH_3$), 3.17 (m, 1H, CH), 6.19 (d, *J* = 8.2 Hz, 1H, ArH), 6.75 (dd, *J* = 8.2 and 2,1 Hz, 1H, ArH), 6.78 (br.s, 1H, ArH), 7.02 (t, *J* = 7.4 Hz, 1H, ArH), 7.30 (t, *J* = 7.7 Hz, 2H, ArH), 7.49 (d, *J* = 7.9 Hz, 2H, ArH), 10.00 (br.s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$): δ 23.67, 25.23, 28.63, 34.69, 36.90, 52.58, 75.67, 104.04, 118.06, 118.44, 120.44, 122.80, 128.96, 133.13, 139.11, 141.20, 149.21, 152.84.

## ACKNOWLEDGEMENTS

Financial support from the Hungarian OTKA Foundation (F 034544 and T 42515) is gratefully acknowledged.

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