Pergamon

Tetrahedron 56 (2000) 9991–9997

TETRAHEDRON

2-Amidinylindole-3-carbaldehydes: Versatile Synthons for the Preparation of α-Carboline Derivatives

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Received 6 July 2000; revised 19 September 2000; accepted 5 October 2000

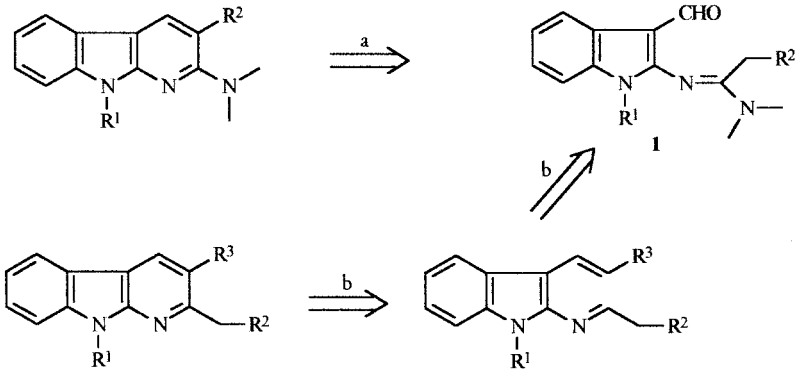
Abstract—The 2-amidinylindole-3-carbaldehydes **1** are the key starting materials for the preparation of three classes of carbolines **2**, **6** and **7** in which the pyridine ring is characterised by a different substitution patterns. The carbolines **2** which are functionalized with an amino group in position 2, were obtained directly by heating **1** in presence of SiO_2. The condensation of amidines **1** with arylmethylketones afforded unsaturated ketones **5** which on heating were transformed into 2,9-dialkyl-3-aroyl-9*H*-pyrido[2,3-*b*]indoles **7**. Instead, prolonged reaction of amidines **1** with arylmethylketones in *t*-BuOH/*t*-BuOK gave 2-aryl-9*H*-pyrido[2,3-*b*]indoles **6**.

Introduction

Previous research work from this laboratory involved an investigation into a new synthesis of heterocyclic compounds starting from 5-amino-*v*-triazolines and their transformation products.[1] New synthetic routes to substituted quinazolines and related heterocycles were discovered and key intermediates for their synthesis were found in special substituted amidines of general structure **1** for which practical preparation procedures were set up.[1] We now report on new synthetic pathways to prepare several substituted α-carbolines in which the above amidine derivatives **1** were successfully used.

The biological importance of α-carboline is well known. This ring is found in several alkaloids [2] and in carcinogenic metabolites.[3] Moreover, some synthetic pyrido[2,3-*b*]indole derivatives are anxiolytic or neuroprotectant agents.[4]

The formation of the α-carboline ring system has already been described in the literature and different routes are known which rely on the formation of the middle ring through intramolecular cyclization of an *N*-containing *ortho*-substituent in a 3-phenylpyridine substrate or on the use of reactions affording the linkage of the *ortho*,*ortho* positions in *N*-(2-pyridyl)anilines.[5] The ready availability of amidines **1** suggested that it would be possible to develop



Scheme 1.

Keywords: 5-amino-*v*-triazolines; amidines; α-carboline; pyrido[2,3-*b*]indole.
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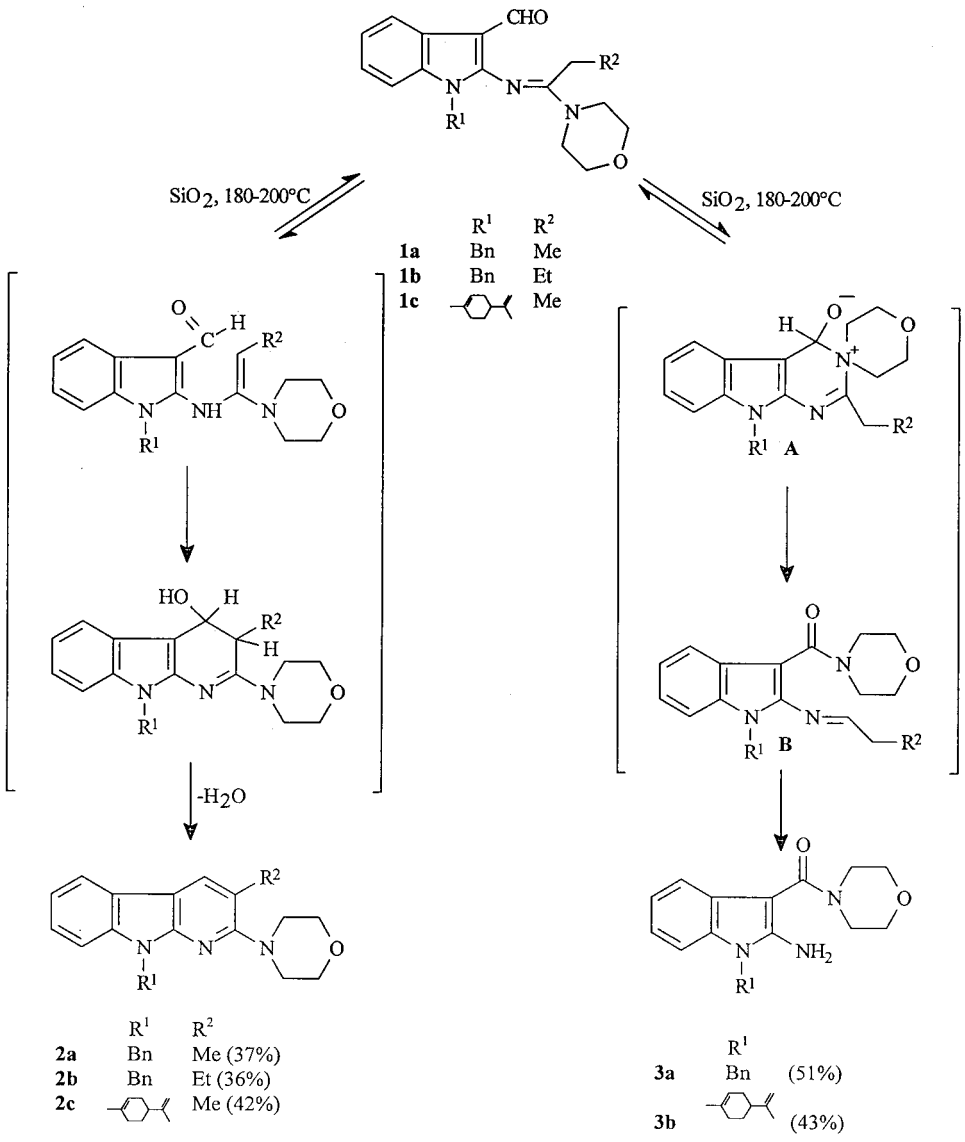
PII: S0040-4020(00)00950-9



Scheme 2.

new synthetic strategies involving the construction of the pyridine ring on the pre-formed indole moiety.

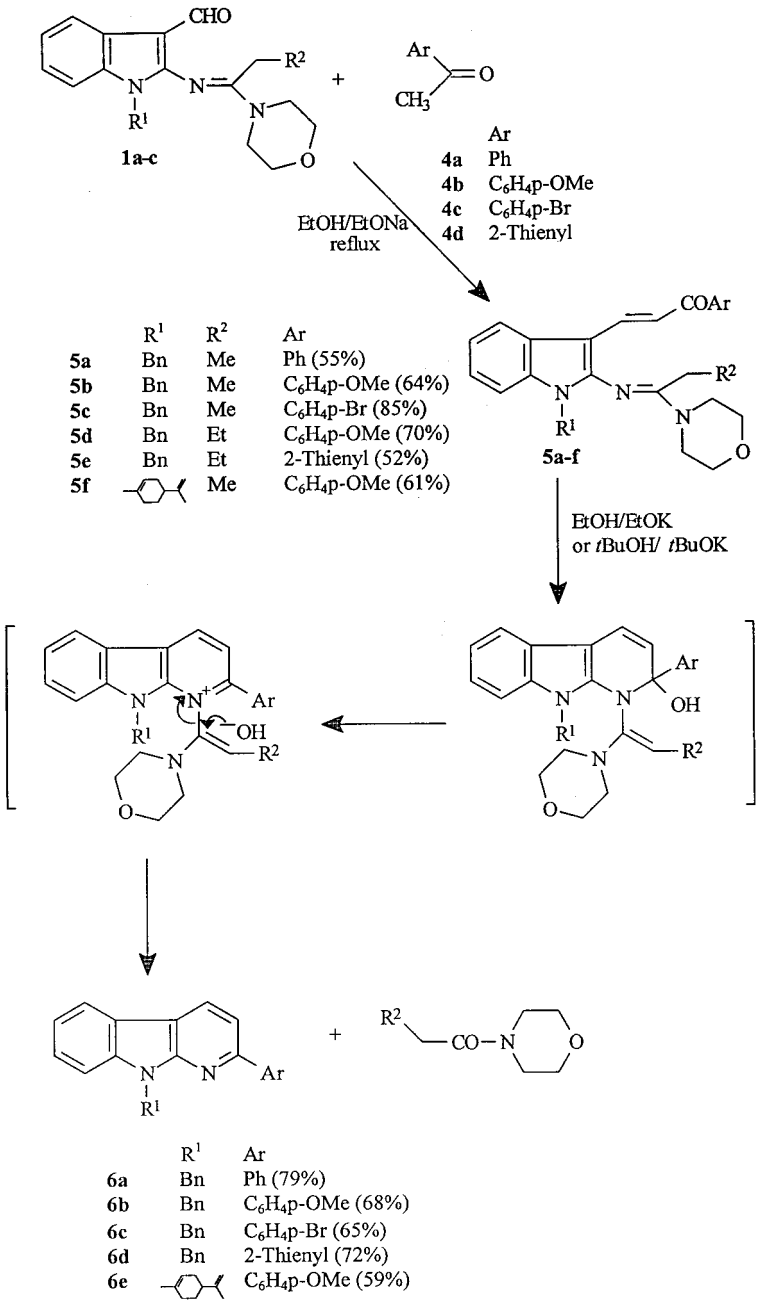
Results and Discussion

Taking into account the structural features of compounds **1** two schemes were firstly planned for the preparation of the carboline ring i.e. (i) the intramolecular condensation of the α-carbon of the amidine group with the formyl group (path a, Scheme 1) and (ii) the synthesis of intermediates containing a 2-azatriene system encompassing the 2,3-bond of the indole moiety followed by an electrocyclization reaction (path b, Scheme 1).

According to path a, the known amidines **1a**,**b**[1] and the newly prepared **1c**, were transformed, both under basic and acid catalysis, into the 3,9-dialkyl-2-morpholino-α-carbolines **2a–c** by an intramolecular condensation reaction. The best results were obtained by heating a mixture of compounds **1a–c** with silica gel at 180–200°C in the absence of solvent. Probably the ring-closure reaction occurs through the isomerization of the amidine into its diaminoalkylidene tautomer followed by intramolecular condensation of the α carbon with the aldehyde group and water elimination (Scheme 2). Products **2** represent a new class of substituted α-carboline derivatives and are characterised in the ^{1}H NMR spectrum by a typical singlet at δ_H 8.0–8.1 associated with H-4.

The desired products **2** were always obtained in mixture with by-products which were identified as 2-amino-3-indolecarboxamides **3a**,**b** on the basis of analytical and spectroscopic evidences. The origin of these compounds was explained by assuming the formation of a cyclic ammonium intermediate (**A**) which produces an imine (**B**) by ring-opening. On hydrolysis, **B** gives the final compound **3** (Scheme 2). The structure of the indole derivatives **3a** was confirmed by the independent synthesis of **3a** from α-(2-nitrophenyl)cyanoacetyl-morpholide (see Experimental).

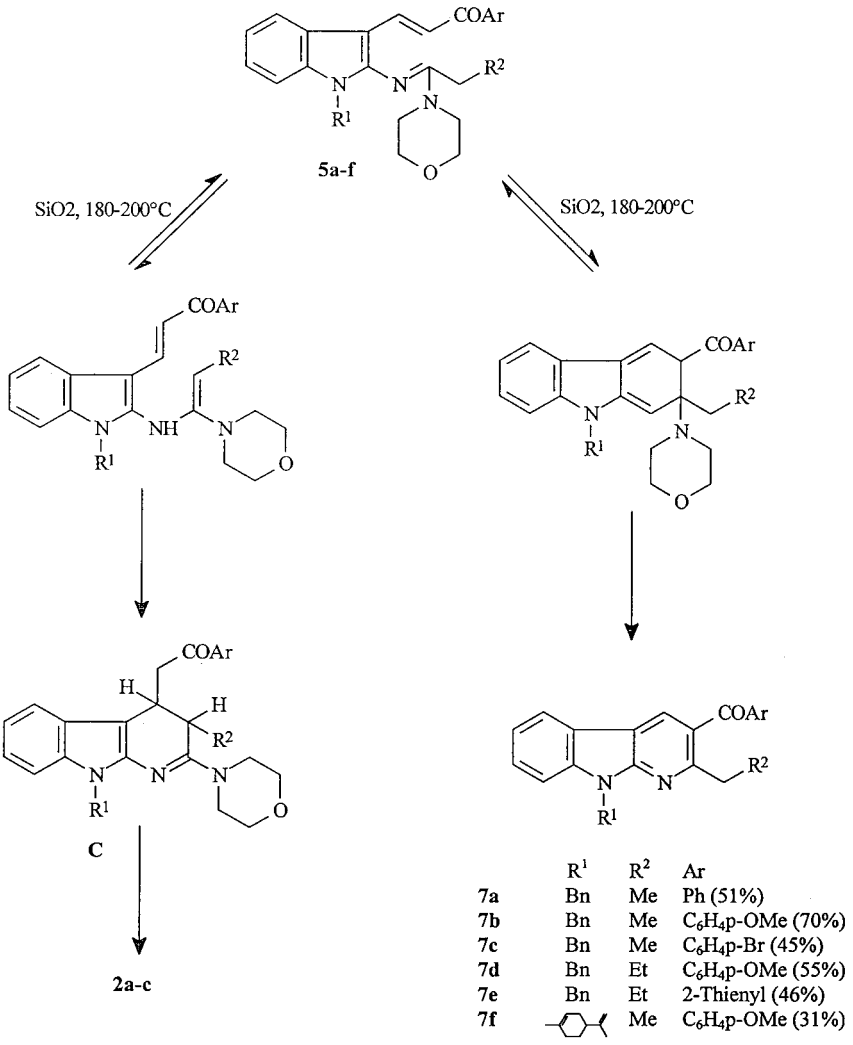
The synthetic procedure indicated as path b in Scheme 1,



Scheme 3.

was achieved by reaction of compounds **1a–c** with arylmethylketones **4a–d** in the presence of sodium ethoxide in ethanol affording the expected unsaturated ketones **5a–f** in satisfactory yield (Scheme 3). Besides the main products **5** an increasingly higher amount of 2-aryl-9-alkyl-α-carbolines **6a–e** was produced, when longer reaction times (35–40 h) were used for the condensation reaction. Compounds **6** were demonstrated to derive from **5**. By prolonged heating of **5a** in presence of sodium ethoxide, **6a** was formed. Better conditions for the formation of **6a–e** were the heating of **5a–f** in presence of potassium *t*-butoxide for 10 h. An explanation of this result is contained in Scheme 3.

Heating of **5a–f** in the presence of silica gel and in the absence of solvent at 180°C for about 10 h afforded the 2,9-dialkyl-3-aroyl-α-carbolines **7a–f** as the main products (about 50% yield) accompanied by a minor amount of compounds **2a–c** (about 10% yield). The expected formation of products **7** occurred though an electrocyclization process which was made irreversible by morpholine elimination and the consequent aromatization the ring (Scheme 4). Products **2** were produced by the process depicted in Scheme 4, according to which an intermediate **C** was produced by a cyclocondensation reaction. Final products **2** are formed by arylmethylketone elimination according to a retro-Michael mechanism.



	R^1	R^2	Ar
7a	Bn	Me	Ph (51%)
7b	Bn	Me	C_6H_4p-OMe (70%)
7c	Bn	Me	C_6H_4p-Br (45%)
7d	Bn	Et	C_6H_4p-OMe (55%)
7e	Bn	Et	2-Thienyl (46%)
7f		Me	C_6H_4p-OMe (31%)

Scheme 4.

In conclusion, readily available starting compounds have been successfully used to develop new synthetic pathways directed toward α-carbolines.

Experimental

Mps were determined by a Büchi 510 (capillary) apparatus. IR spectra were measured with a JASCO IR Report 100 instrument (Nujol; cm^{-1}). NMR spectra were obtained with Bruker AC 200, Bruker Advance 300 and Varian Gemini 200 instruments. *J* values are given in Hz for solutions in $CDCl_3$. 1-Benzyl-2-azido-1*H*-indole-3-carbaldehyde and 1-alkyl-9-benzyl-2-[1-(morpholin-4-yl)propylideneamino]-1*H*-indole-3-carbaldehydes **1a**,**b** are known compounds.[1]

2-(1-Morpholin-4-yl-propylidenamino)-1-(4-isopropenyl-cyclohex-1-enylmethyl)-1*H*-indole-3-carbaldehyde 1c. 2-Bromo-1*H*-indole-3-carbaldheyde[1] (2 g, 8.93 mmol) was suspended in 10 mL of anhydrous THF in N_2 atmosphere. NaH (60% in oil) (0.71 g, 17.8 mmol) was added at room temperature. After 30 min. 1-bromomethyl-4-isopropenyl-cyclohexene (1.75 g, 8.14 mmol) was added and the reaction mixture was kept at room temperature for 5 h. The crude reaction mixture was evaporated at reduced pressure, taken up with water and extracted with CH_2Cl_2. The residue was purified by chromatography [ethyl acetate–cyclohexane (1:9)] giving *2-bromo-1-(4-isopropenyl-cyclohex-1-enylmethyl)-1H-indole-3-carbaldehyde*. Yield 2.88 g, 90%. Pale yellow oil, IR 1660 (CO); ^{1}H NMR 1.32 (7H, m, $3CH_2$+CH), 1.70 (3H, s, CH_3), 4.63–4.82 (4H, m, CH_2N+CH_2=C), 5.42–5.54 (1H, m, CH=C), 7.25–7.40 (3H, m, ArH), 8.28–8.39 (1H, m, H-4), 10.05 (1H, s, CHO). Calcd for $C_{19}H_{20}BrNO$ (358.29) C 63.69, H 5.63, N 3.91 found: C 63.42, H 5.93, N, 3.70. 2-Bromo-1-(4-isopropenyl-cyclohex-1-enylmethyl)-1*H*-indole-3-carbaldehyde (2.23 g, 6.33 mmol) was dissolved in 40 mL of DMSO at room temperature and NaN_3 (0.52 g, 8 mmol) was added. After 48 h the reaction mixture was poured into 100 mL of cold water and extracted with ethyl ether. The organic layer, was dried with Na_2SO_4 and evaporated at reduced pressure affording *2-azido-1-(4-isopropenyl-cyclohex-1-enylmethyl)-1H-indole-3-carbaldehyde*. Yield 2.21 g, 88% of product in sufficiently pure form for direct use; IR 2120 (N_3), 1660 (CHO); ^{1}H NMR 1.40–2.20 (7H, m, $3CH_2$+CH), 1.70

(3H, s, CH_3), 4.55–4.77 (4H, m, CH_2=C and CH_2N), 5.45–5.52 (1H, m, CH=C), 7.22–7.37 (3H, m, ArH), 8.01–8.12 (1H, m, H-4), 10.32 (1H, s, CHO).

2-Azido-1-(4-isopropenyl-cyclohex-1-enylmethyl)-1*H*-indole-3-carbaldehyde (1.7 g, 5.6 mmol) was dissolved in CH_2Cl_2 (20 ml) and propionaldehyde (0.40 g, 7 mmol) and morpholine (0.61 ml, 7 mmol) was added. The reaction mixture was stirred at room temperature for 12 h and the solution was dried with Na_2SO_4 and evaporated. The residue was purified by chromatography [ethyl acetate–cyclohexane (2:3)]. The main fraction was evaporated yielding 3.0 g of a yellow oil. Yield 3.0 g, 70%. IR 1620 (CHO), ^{1}H NMR 1.04 (3H, t, *J*=7.2 Hz, CH_3), 1.32–2.18 (7H, m, 3CH_2+CH), 1.70 (3H, s, CH_3), 2.35–2.70 (2H, m, CH_2), 3.60–3.91 (8H, m, morpholine), 4.43 (2H, s, CH_2N), 4.65–4.77 (2H, m, CH_2=C), 5.44–5.54 (1H, m, CH=C), 7.08–7.29 (3H, m, ArH), 8.05–8.19 (1H, m, H-4), 9.64 (1H, s, CHO). Calcd for $C_{26}H_{33}N_3O_2$ (403.57) C 77.38, N 8.24, N 10.41 found: C 77.10, H 8.46, N 10.05.

Synthesis of 3,9-dialkyl-2-morpholin-4-yl-9*H*-pyrido-[2,3-*b*]indoles 2a–c and (2-amino-1-alkyl-1*H*-indol-3-yl)-morpholin-4-yl-methanones 3a,b. General procedure

Compounds **1a**–**c** (1 mmol) were mixed with silica gel (80 mg) and heated at 180°C for 90 min until disappearance of the starting material by TLC [ethyl acetate–cyclohexane (1:1)]. The crude reaction mixture was purified by chromatography [pentane–ethyl acetate (1:0 to 1:1)] and two main fractions were isolated containing **2a**–**c** (first fraction) and **3a**,**b** (second fraction) respectively.

9-Benzyl-3-methyl-2-morpholin-4-yl-*9H*-pyrido[2,3-*b*]-indole 2a. Yield 37%. Mp 130°C (white crystals from EtOH). ^{1}H NMR 2.45 (3H, s, CH_3), 3.27–3.31, 3.89–3.94 (4H+4H, 2m, morpholine), 5.62 (2H, s, CH_2Ph), 7.18–7.34 (8H, m, ArH), 7.95 (1H, d, *J*=7.7 Hz, H-5), 8.08 (1H, s, H-5). Calcd for $C_{23}H_{23}N_3O$ (357.43) C 77.29 H 6.49 N 11.76 found: C 77.00 H 6.97 N 11.51.

9-Benzyl-3-ethyl-2-morpholin-4-yl-*9H*-pyrido[2,3-*b*]-indole 2b. Yield 36%. Mp 113°C (white crystals from EtOH). ^{1}H NMR 1.38 (3H, t, *J*=7.2 Hz, CH_3), 2.80 (2H, q, *J*=7.2 Hz, CH_2), 3.23–3.27, 3.88–3.93 (4H+4H, 2m, morpholine), 5.62 (2H, s, CH_2Ph), 7.17–7.40 (8H, m, ArH), 7.98 (1H, d, *J*=7.7 Hz, H-5), 8.15 (1H, s, H-4). Calcd for $C_{24}H_{25}N_3O$ (371.46) C 77.60 H 6.78 N 11.31 found: C 77.42 H 6.92 N 11.35.

9-(4-Isopropenyl-cyclohex-1-enylmethyl)-2-methyl-3-morpholin-4-yl-*9H*-pyrido[2,3-*b*]indole 2c. Yield 42%. Mp 116°C (white crystals from EtOH). ^{1}H NMR 1.22–2.21 (7H, m, 3CH_2 and CH), 1.68 (3H, s, CH_3C=), 2.43 (3H, s, CH_3), 3.22–3.34, 3.86–3.99 (4H+4H, 2m, morpholine), 4.63–4.71 (2H, m, CH_2–N), 4.91–5.00 (2H, m, CH_2=C), 5.68–5.77 (1H, m, CH=C), 7.14–7.44 (3H, m, ArH), 7.93 (1H, d, *J*=7.4 Hz, H-5), 8.04 (1H. s, H-4). Calcd for $C_{26}H_{31}N_3O$ (401.56) C 77.77 H 7.78 N 10.46 found: C 77.41 H 8.02 N 10.30.

(2-Amino-1-benzyl-1*H*-indole-3-yl)-morpholin-4-yl-methanone 3a. Yield 51%. Mp 197°C (yellow earth crystal from Et_2O). IR 3250–3350 (NH_2), 1625 (C=O); ^{1}H NMR 3.45–3.92 (8H, m, morpholine), 5.19 (2H, s, CH_2Ph), 5.35 (2H, bs, NH_2), 6.98–7.52 (9H, m, ArH). Calcd for $C_{20}H_{21}N_3O_2$ (335.40) C 71.62 H 6.31 N 12.53 found C 71.43 H 6.65 N 12.24.

[2-Amino-1-(4-isopropenyl-cyclohex-1-enylmethyl)-*1H*-indole-3-yl]morpholin-4-yl-methanone 3b. Yield 43%. Mp 164°C (yellow crystals from Pr^i_2O). IR 3250–3350 (NH_2), 1630 (C=O); ^{1}H NMR 1.60–2.16 (7H, m, 3CH_2 and CH), 1.74 (3H, s, CH_3C=), 3.63–3.82 (8H, m, morpholine), 4.49 (2H, s, CH_2N), 4.71–4.74 (2H, m, CH_2=C), 5.43 (2H, bs, NH_2), 5.58–5.61 (1H, m, CH=C), 7.05–7.33 (4H, m, ArH). Calcd for $C_{23}H_{29}N_3O_2$ (379.50) C 72.79 H 7.70 N 11.01 found: C 72.52 H 7.84 N 10.92.

Synthesis of 3-[1-alkyl-2-(1-morpholin-4-yl-alkyliden-amino)-1*H*-indol-3-yl]-1-phenyl-propenones 5a–f. General procedure

Compounds **1a**–**c** (1 mmol) and Na (2 mmol) were dissolved in anhydrous ethanol (2 mL). 2-Aryl-methanone **4a**–**d** (1 mmol) was added and the mixture was refluxed for 20 h. After solvent evaporation the crude reaction mixture was taken up with water and extracted with CH_2Cl_2 (3×10 mL). The combined extracts were dried with Na_2SO_4 and evaporated at reduced pressure. The crude residue was chromatographed with ethyl acetate–cyclohexane (1:4). The main fraction was crystallised whit the solvent indicated affording pure **5a**–**f**.

3-[1-Benzyl-2-(1-morpholin-4-yl-propylidenamino)-1*H*-indol-3-yl]-1-phenyl-propenone 5a. Yield 55%. Mp 120–121°C (white crystals from EtOH). IR 1660 (C=O); ^{1}H NMR 0.81 (3H, t, *J*=7.2 Hz, CH_3), 2.16–2.19 (2H, m, CH_2), 3.63–3.76 (8H, m, morpholine), 5.15 (2H, s, CH_2Ph), 7.00–8.06 (16H, m, 14 ArH+CH=CH). Calcd for $C_{31}H_{31}N_3O_2$ (477.61) C 77.96 H 6.54 N 8.80 found: C 77.82 H 6.92 N 8.49.

3-[1-Benzyl-2-(1-morpholin-4-yl-propylidenamino)-1*H*-indol-3-yl]-1-(4-methoxyphenyl)-propenone 5b. Yield 64%. Mp 95°C (white crystals from EtOH). IR 1660 (C=O), ^{1}H NMR 0.82 (3H, t, *J*=7.2 Hz, CH_3), 2.13–2.23 (2H, m, CH_2), 3.64–3.78 (8H, m, morpholine), 3.89 (3H, s, OCH_3), 5.18 (2H, s, CH_2Ph), 6.98 and 8,06 (2+2H, 2d, *J*=8.8 Hz, $C_6H_4OCH_3$), 7.12–7.26 (8H, m, ArH), 7.40 (1H, d, J 15.2 Hz, *CH*=CHCO), 7.87 (1H, d, *J*=15.2 Hz, CH=*CH*CO), 7.92 (1H, d, *J*=7.3 Hz, H-4). Calcd for $C_{32}H_{33}N_3O_3$ (507.63) C 75.71 H 6.55 N 8.28 found: C 75.41 H 6.92 N 8.01.

3-[1-Benzyl-2-(1-morpholin-4-yl-propylidenamino)-1*H*-indol-3-yl]-1-(4-bromophenyl)-propenone 5c. Yield 85%. Mp 176°C (white crystals from EtOH). IR 1660 (C=O), ^{1}H NMR 0.81 (3H, t, *J*=7.2 Hz, CH_3), 2.09–2.26 (2H, m, CH_2), 3.53–3.85 (8H, m, morpholine), 5.15 (2H, s, CH_2Ph), 7.15–7.96 (15H, m, 13 ArH+CH=CH). Calcd for $C_{31}H_{30}BrN_3O_2$ (556.50) C 66.91 H 5.43 N 7.55 found: C 66.64 H 5.61 N 7.36.

3-[1-Benzyl-2(1-morpholin-4-yl-butylideneamino)-1*H*-indol-3-yl]-1(4-methoxyphenyl)-propenone 5d. Yield

70%. Mp 97 (white crystals from EtOH). IR 1660 (C═O),^{1}H NMR 0.67 (3H, t, J=7.2 Hz, CH_3), 1.21–1.28 (2H, m, CH_2), 2.10–2.29 (2H, m, CH_2), 3.64–3.79 (8H, m, morpholine), 3.89 (3H, s, OCH_3), 5.15 (2H, s, CH_2Ph), 7.11 and 8,06(2+2H, 2d, J=8.7 Hz, $C_6H_4OCH_3$), 7.14–7.28 (8H, m, ArH), 7.41 (1H, d, J=15.2 Hz, *CH*═CHCO), 7.86 (1H, d, J=15.2 Hz, CH═*CH*CO), 7.92 (1H, d, J=8.0 Hz, H-4). Calcd for $C_{33}H_{35}N_3O_3$ (521.67) C 75.98 H 6.76 N 8.05 found: C 75.72 H 6.95 N 7.89

3-[1-Benzyl-2-(morpholin-4-yl-butylidenamino)-1*H*-indol-3-yl]-1-thien-2-yl-propenone 5e. Yield 52%. Yellow oil. IR 1600 (C═O), ^{1}H NMR 0.68 (3H, t, J=7.2 Hz, CH_3), 1.60–1.63 (2H, m, CH_2), 2.11–2.26 (2H, m, CH_2), 3.65–3.78 (8H, m, morpholine), 5.15 (2H, s, CH_2Ph), 7.10–7.94 (14H, m, ArH). Calcd for $C_{30}H_{31}N_3O_2S$ (497.60) C 72.41 H 6.28 N 8.44 found: C 72.01 H 6.54 N 8.09.

3-[1(4-Isopropenyl-cyclohex-1-enylmethyl)-2-(1-morpholin-4-yl-propylidenamino)-1*H*-indol-3-yl]-1(4-methoxyphenyl)-propenone 5f. Yield 61%.Yellow oil. IR 1605 (C═O), ^{1}H NMR 0.78–2.52 (10H, m, $3CH_2+CH+CH_3$), 3.58–3.95 (8H, m, morpholine), 3.89 (3H. s, OCH_3), 4.45 (2H, s, CH_2N), 4.63–4.78 (2H, m, CH_2═C), 5.48–5.59 (1H, m, CH═C), 6.99–8.06 (10H, m, ArH). Calcd for $C_{35}H_{41}N_3O_3$ (551.73) C 76.19 H 7.49 N 7.62 found: C 75.97 H 7.58 N 7.43.

General procedure for the preparation of 9-alkyl-2-aryl-9*H*-pyrido[2,3-*b*]indoles 6a–e

Compounds **5a–f** (1 mmol) and *t*-BuOK (3 mmol) were dissolved in *t*-BuOH (6 ml) and refluxed for 12 h. The mixture was cooled and the precipitate was filtered. The crude product was dissolved in CH_2Cl_2 and washed with water. The organic layer was dried with Na_2SO_4 ad evaporated. After crystallisation of the residue the pure product **7** was obtained.

9-Benzyl-2-phenyl-9*H*-pyrido[2,3-*b*]indole 6a. Yield 79%. Mp 131°C (white crystals from EtOH). ^{1}H NMR 5.80 (2H, s, CH_2Ph), 7.23–7.57 (11H, m, ArH), 7.72 (1H, d, J=8.2 Hz, H-3), 8.12 (1H, d, J=7.8 Hz, H-5), 8.23 (2H, d, J=8.8 Hz, ArH), 8.40 (1H, d, J=8.2 Hz, H-4). Calcd for $C_{24}H_{18}N_2$ (334.42) C 86.20 H 5.42 N 8.38 found: C 86.05 H 5.51 N 8.14.

9-Benzyl-2-(4-methoxyphenyl)-9*H*-pyrido[2,3-*b*]indole 6b. Yield 68%. Mp 187°C (white crystal from EtOH). ^{1}H NMR 3.89 (3H, s, OCH_3), 5.78 (2H, s, CH_2Ph), 7.02 and 8.17 (2+2H, 2d, J=8.9 Hz, $C_6H_4OCH_3$), 7.10–7.48 (8H, m, ArH), 7.64 (1H, d, J=8.2 Hz, H-3), 8.06 (1H, d, J=8.4 Hz, H-5), 8.35 (1H, d, J=8.2 Hz, H-4). Calcd for $C_{25}H_{20}N_2O$ (364.45) C 82.39 H 5.53 N 7.69 found: C 82.15 H 5.76 N 7.38.

9-Benzyl-2-(4-bromophenyl)-9*H*-pyrido[2,3-*b*]indole 6c. Yield 65%. Mp 137°C (white crystals from EtOH). ^{1}H NMR 5.80 (2H, s, CH_2Ph), 7.28–8.13 (14H, s, ArH), 8.40 (1H, d, J=8.1 Hz, H-4). Calcd for $C_{24}H_{17}BrN_2$ (413.32) C 69.74 H 4.14 N 6.78 found C 69.45 H 4.25 N 6.64.

9-Benzyl-2-thien-2-yl-9*H*-pyrido-[2,3-*b*]indole 6d. Yield 72%. Mp 156°C (white crystal from EtOH). ^{1}H NMR 5.73 (2H, s, CH_2Ph), 7.10–7.74 (11H, m, ArH), 7.61 (1H, d, J=8.0 Hz, H-3), 8.04 (1H, d, J=7.6 Hz, H-5), 8.31 (1H, d, J=8.0 Hz, H-4). Calcd for $C_{22}H_{16}N_2S$ (340.45) C 77.62 H 4.74 N 8.23 found: C 77.58 H 5.02 N 8.10.

9-(4-Isopropenyl-cyclohex-1-enylmethyl)-2-(4-methoxyphenyl)-9*H*-pyrido[2,3-*b*]indole 6e. Yield 59%. Mp 149°C (white crystal from EtOH). ^{1}H NMR 1.23 (7H, m, $3CH_2+CH$), 1.71 (3H, s, CH_3), 3.91 (3H, s, OCH_3), 3.62–3.74 (2H, m, CH_2N), 5.10–5.14 (2H, m, CH_2═C), 5.70–5.74 (1H, m, CH═C), 7.07 and 8.18 (2+2H, 2d, J=8.8 Hz, C_6H_4OMe), 7.20–7.49 (3H, m, ArH), 7.62 (1H, d, J=8.0 Hz, H-3), 8.08 (1H, d, J=7.6 Hz, H-5), 8.34 (1H, d, J=8.0 Hz, H-4). Calcd for $C_{28}H_{28}N_2O$ (408.54) C 82.32 H 6.91 N 6.86 found: C 82.41 H 7.06 N 8.48.

General procedure for the preparation of [2,9-dialkyl-9*H*-pyrido[2,3-*b*]indol-3-yl]aryl-methanones 7a–f

Compounds **5a–f** (1 mmol) were mixed with silica gel (100 mg) and heated at 180–200°C for 10 h until disappearance of the starting material [TLC, ethyl acetate–cyclohexane (3:2)] yielding **7**. The crude reaction product was purified by column chromatography [pentane–ethyl acetate (1:0 to 19:1)].

(9-Benzyl-2-ethyl-9*H*-pyrido[2,3-*b*]indol-3-yl)phenyl-methanone 7a. Yield 51%. Mp 103°C (white crystals from EtOH). IR 1665 (C═O), ^{1}H NMR 1.38 (3H, t, J=7.2 Hz, CH_3), 3.8 (2H, q, J=7.2 Hz, CH_2), 5.76 (2H, s, CH_2Ph), 7.15–7.88 (13H, m, ArH), 7.97 (1H, d, J=7.7 Hz, H-5), 8.30 (1H, s, H-4). Calcd for $C_{27}H_{22}N_2O$ (390.48) C 83.05 H 5.68 N 7.17 found: C 82.87 H 5.92 N 7.95.

(9-Benzyl-2-ethyl-9*H*-pyrido[2,3-*b*]indol-3-yl)-(4-methoxyphenyl)-methanone 7b. Yield 70%. Mp 79°C (white crystals from EtOH). IR 1665 (C═O), ^{1}H NMR 1.36 (3H, t, J=7.2 Hz, CH_3), 3.03 (2H, q, J=7.2 Hz, CH_2), 3.90 (3H, s, OCH_3), 5.75 (2H, s, CH_2Ph), 6.98 and 7.87 (2+2H, 2d, J=8.5 Hz, C_6H_4OMe), 7.26–7.48 (8H, m, ArH), 7.98 (1H, d, J=7.7 Hz, H-5), 8.27 (1H, s, H-4). Calcd for $C_{28}H_{24}N_2O_2$ (420.51) C 79.98 H 5.75 N 6.67 found: C 79.74 H 5.96 N 6.38.

(9-Benzyl-2-ethyl-9*H*-pyrido[2,3-*b*]indol-3-yl)-(4-bromophenyl)-methanone 7c. Yield 45%. Mp 90°C (pale yellow crystals from EtOH). IR 1650 (C═O), ^{1}H NMR 0.38 (3H, t, J=7.5 Hz, CH_3), 3.07 (2H, q, J=7.5 Hz, CH_2), 5.75 (2H, s, CH_2Ph), 7.26–7.80 (12H, m, ArH), 7.98 (1H, d, J=7.7 Hz, H-5), 8.27 (1H, s, H-4). Calcd for $C_{27}H_{21}BrN_2O$ C 69.09 H 4.51 N 5.97 found: C 68.82 H 4.77 N 5.63.

(9-Benzyl-2-propyl-9*H*-pyrido[2,3-*b*]indol-3-yl)-(4-methoxyphenyl)-methanone 7d. Yield 55%. Mp 105°C (white crystals from EtOH). IR 1660 (C═O), ^{1}H NMR 0.90–0.97 (3H, t, J=7.2 Hz, CH_3), 1.80–1.91(2H, m, CH_2), 2.96–3.04 (2H, m, CH_2), 3.91 (3H, s, OCH_3), 5.74 (2H, s, CH_2Ph), 6.95–7.88 (12H, m, ArH), 7.98 (1H, d, J=7.2 Hz, H-5), 8.26 (1H, s, H-4). Calcd for $C_{29}H_{26}N_2O_2$ (434.54) C 80.16 H 6.03 N 6.45 found: C 79.97 H 6.35 N 6.23.

(9-Benzyl-2-propyl-9*H*-pyrido[2,3-*b*]indol-3yl)-thieno-2-yl-methanone 7e. Yield 46%. Mp 99°C (white crystals from EtOH).IR 1650 (C═O). ^{1}H NMR 0.96 (3H, t, *J*=7.2 Hz, CH_3), 1.88 (2H, q, *J*=7.2 Hz, CH_2), 3.07 (2H, t, *J*=7.2 Hz, CH_2), 5.74 (2H, s, CH_2Ph), 7.09–7.80 (11H, m, ArH), 8.01 (1H, d, *J*=7.7 Hz, H-5), 8.44 (1H, s, H-4). Calcd for $C_{26}H_{22}N_2OS$ (410.47) C 76.08 H 5.32 N 6.82 found: C 75.86 H 5.46 N 6.56.

[2-Ethyl-9-(4-isopropenyl-cyclohex-1-enylmethyl)-9*H*-pyrido[2,3-*b*]indol-3-yl]-(4-methoxyphenyl)-methanone 7f. Yield 31%. Mp 115°C (white crystals from Et_2O). IR 1660, ^{1}H NMR 0.80–2.37 (10H, $3CH_2$+CH+CH_3), 1.69 (3H, s, CH_3), 3.02 (2H, q, *J*=7.2 Hz, CH_2), 3.94 (3H, s, OCH_3), 4.62–4.71 (2H, m, CH_2N), 5.02–5.21 (2H, m, CH_2═C), 5.61–5.79 (1H, m, CH═C), 7.13–7.85 (7H, m, ArH), 7.97 (1H, d, *J*=8.4 Hz, H-5), 8.24 (1H, s, H-4). Calcd for $C_{31}H_{32}N_2O_2$ (464.61) C 80.14 H 6.94 N 6.03 found: C 79.87 H 7.13 N 5.75.

Independent synthesis of (2-amino-1-benzyl-1*H*-indol-3-yl)-morpholin-4-yl-methanone 3a

A solution of 3-(morpholin-4-yl)-2-(2-nitrophenyl)-3-oxo-propionitrile (2.9 g, 10.8 mmol), obtained according to the literature method[6] (mp 143°C), in a mixture of acetic acid (5 mL) and toluene (15 mL) was heated until an internal temperature of 80°C was reached. External heating was removed and zinc powder (6.6 g, 101 mmol) was slowly added portionwise to the vigorously stirred mixture maintaining the internal temperature within the range of 80–85°C. After the addition of zinc was complete, the reaction mixture was cooled, filtered and evaporated. The residue was dissolved in ethyl acetate, washed with aqueous $NaHCO_3$. The organic layer was dried and evaporated. The residue was crystallised with ethyl acetate to afford (2-amino-1*H*-indol-3-yl)-morpholin-4-yl-methanone (2.0 g, 75%), mp 209°C. ^{1}H NMR 3.15–3.93 (8H, m, morpholine), 6.46 (2H, bs, NH_2), 6.66–7.38 (4H, m, ArH), 10.59 (1H, bs, NH). Calcd for $C_{13}H_{15}N_3O_2$ (245.28) C 63.66 H 6.16 N 17.13 found C 63.46 H 6.39 N 17.02.

(2-Amino-1*H*-indol-3-yl)-morpholin-4-yl-methanone was alkylated with benzyl chloride according to a literature method[7] and afforded **3a** (Mp 197°C, yield 17%).

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