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Original article

Preparation of 4-azaindole and 7-azaindole dimers with a bisalkoxyalkyl spacer in order to preferentially target melatonin MT_1 receptors over melatonin MT_2 receptors

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Abstract

Several 4-azaindole and 7-azaindole dimer analogues of melatonin with a bisalkoxyalkyl spacer between the position 5 of each heterocycle were synthetized. Our aim was to investigate the influence of the spacers length on the selectivity of such compounds for the MT_1 receptors over the MT_2 receptors. Our results suggest the distance between indole ring seems to be an important parameter in determining the potency of binding with melatonin receptor site.

Keywords: Melatonin; Azaindole dimers; MT_1 and MT_2 receptors

1. Introduction

Melatonin is a neurohormone secreted by the pineal gland during the night [1]. Many studies have pointed out the major role of this hormone in several physio-pathologic phenomena as well as in the regulation of circadian rhythms. Due to its fast metabolism, the half-life of melatonin is relatively short and thus more stable melatonin analogues with a higher therapeutic effect than melatonin itself would be of great interest for clinicians [2]. Two human melatonin receptors have been cloned and defined as MT_1 and MT_2 [3,4]. These two receptors belong to the family of the seven transmembrane domain G-protein-coupled receptors. Both receptors have similar binding for melatonin and display similar rank order for the binding of reference melatonin ligands despite 60% homology between the two receptors. MT_1 receptors are expressed in several areas of the brain and might be implicated in the sleep promoting effect of melatonin and in the control of reproductive function. MT_2 receptors are essentially localized in suprachiasmatic nuclei and in the retina and might be implicated in the resynchronizing activity of melatonin.

Recently, pharmacological studies [5,6] showed that naphthalene type dimers have a preferential selectivity for the MT_1 receptors over the MT_2 receptors (Fig. 1).

The discovery of MT_1 and MT_2 ligands, particularly selective ones, would be of great help for a better understanding of the physiological function of these receptors. To date, only a few selective ligands have been reported. They principally target the MT_2 subtype [6].

Herein we report the preparation and the structure–selectivity relationship of 4-azaindole and 7-azaindole dimers, with a bisalkoxyalkyl type spacer between the 5 position in each heterocycle (Fig. 2).

2. Chemistry

2.1. Synthesis of 4-azaindole dimers

Using similar methodology as was described by Maskosza et al. [7], the 5-methoxy-4-azaindole **2** was prepared in two

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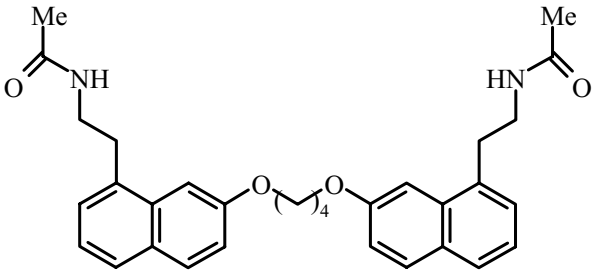


S 26284 [5]
MT_1 Ki = 0.6 nM
MT_2 Ki = 73 nM

Fig. 1. Structure of compound S 26284.

steps from 2-methoxy-5-nitropyridine. The first step involved a vicarious nucleophilic substitution with potassium *tert*-butoxyde and 4-chlorophenoxyacetonitrile in tetrahydrofuran at –10 °C to provide the derivative **1** in 83% yield. Elaboration to the 4-azaindole ring was accomplished by catalytic hydrogenation using palladium on charcoal (71%) (Fig. 3).

Reagents and conditions: (a) 4-Chlorophenoxyacetonirile, *t*-BuOK, THF, –10 °C, 3 h, 83%; (b) H_2, Pd/C, EtOH, 5 h, room temperature, 71%.

The reaction of **2** with benzenesulfonyl chloride in the presence of sodium hydroxide and benzyltriethylammonium chloride in dichloromethane provided the corresponding sulfonamide **3** with good yield (97%). Next, treatment of **3** with aluminum chloride in dichloromethane at reflux lead to the pyridone **4** which was alkylated with alkyl-dibromide in the presence of potassium carbonate in *N,N*-dimethylformamide to give the corresponding *O*-alkylated derivatives **5–7** with moderate yields and *N*-alkylated compounds **8–10**, respectively, in lower yields (Fig. 4).

Reagents and conditions: (a) NaOH, CH_2Cl_2, $C_6H_5CH_2N(C_2H_5)_2$; (b) $C_6H_5SO_2Cl$, 0 °C and 2 h at room temperature, 97%; (c) $AlCl_3$, CH_2Cl_2, reflux 12 h, 83%; (d) K_2CO_3, DMF, (**5**, *n* = 4, 54%), (**6**, *n* = 5, 54%), (**7**, *n* = 6, 51%) and (**8**, *n* = 4, 23%), (**9**, *n* = 5, 24%), (**10**, *n* = 6, 29%).

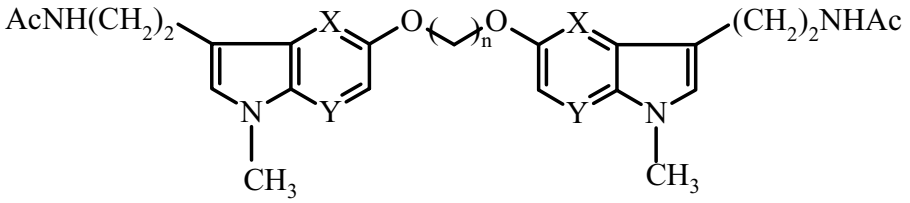
Using the same alkylation described above, dimers **11–13** were prepared from **4** with moderate yields. A small amount of the *N*-alkylated compounds have been formed due to migration of the alkyl group. However, these compounds were not isolated (Fig. 5).

Reagents and conditions: (a) **4**, K_2CO_3, $Br(CH_2)_nBr$, DMF, (**11**, *n* = 4, 57%), (**12**, *n* = 5, 61%), (**13**, *n* = 6, 50%).

Deprotection of **11–13** to **14–16** was carried out in good yield by heating **11–13** with 10% sodium hydroxide in mixture of dichloromethane and methanol. Treatment of **14–16** with methyl iodide in the presence of sodium hydride in *N,N*-dimethylformamide gave products **17–19** in good yield (Fig. 6).

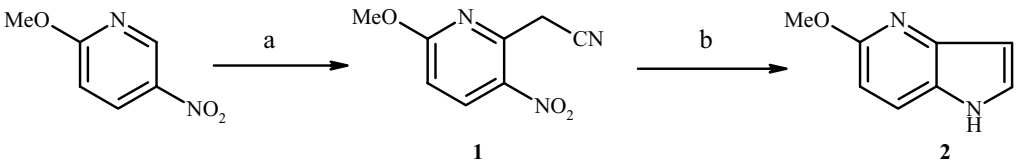
Reagents and conditions: (a) NaOH 2.5 M, MeOH/CH_2Cl_2, reflux, 12 h, (**14**, *n* = 4, 80%), (**15**, *n* = 5, 80%), (**16**, *n* = 6, 83%); (b) NaH, DMF, room temperature, 4 h, (**17**, *n* = 4, 95%), (**18**, *n* = 5, 81%), (**19**, *n* = 6, 83%).

According to the C-3 formylation of the indole ring described in the literature [8], we also introduced a formyl group regioselectively at the C-3 position of compounds **17–19** under Vilsmeier–Haack conditions. Subsequent chemical modifications converted the formyl into *N*-ethylacetamide side chain. Indeed, reaction of aldehydes **20–22** with ammonium acetate in nitromethane led to nitrovinylic derivatives. Treatment of the latter with sodium borohydride



n = 4, 5, 6
X = N and Y = CH 4-azaindolic dimers
X = CH and Y = N 7-azaindolic dimers

Fig. 2. 4- and 7-azaindolic dimers.



1 **2**

Fig. 3. Synthetis of compound **2**.

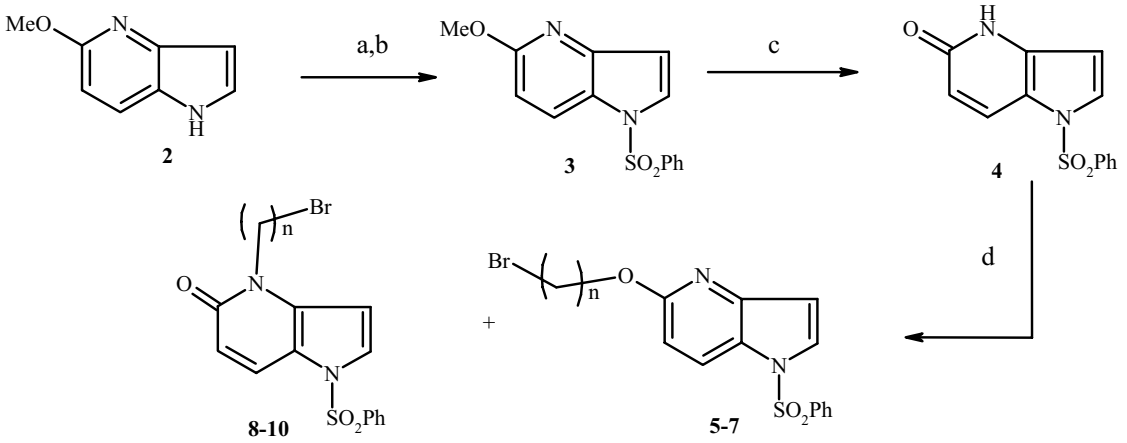


Fig. 4. Synthesis of **5–7** and **8–10**.

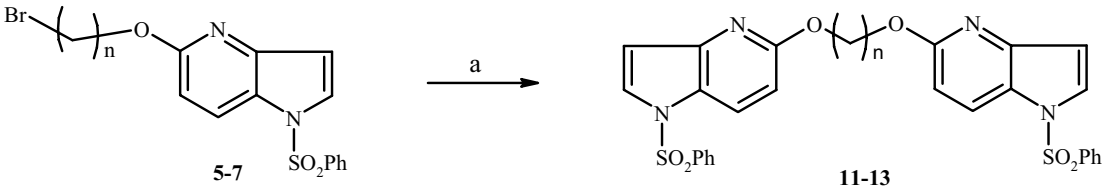


Fig. 5. Synthesis of **11–13**.

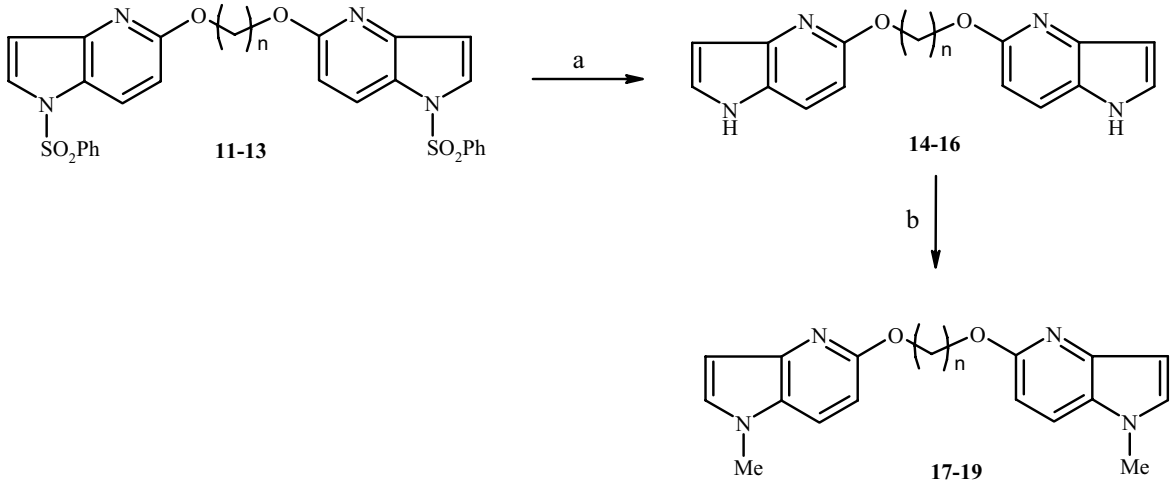


Fig. 6. Synthesis of **17–19**.

and silica gel in a mixture of chloroform and 2-propanol furnished the corresponding nitro derivatives. Next, the amido derivative was obtained by catalytic hydrogenation on Raney nickel in methanol followed by acetylation using acetic anhydride and pyridine in dichloromethane. The expected amides **23–25** were prepared in overall yield between 10% and 16% (Fig. 7).

Reagents and conditions : (a) $POCl_3$, DMF, room temperature, 2 h (**20**, $n = 4$, 95%), (**21**, $n = 5$, 95%), (**22**, $n = 6$, 90%); (b) CH_3NO_2, NH_4Ac, 120 °C, 4 h; (c) *i*-PrOH, $CHCl_3$, SiO_2, $NaBH_4$, room temperature, 20 min; (d) MeOH, Ni Raney, H_2, 60 °C, 12 h; (e) Ac_2OH, CH_2Cl_2 (**23**, $n = 4$, 80%), (**24**, $n = 5$, 80%), (**25**, $n = 6$, 83%).

2.2. Synthesis of 7-azaindole-dimers

The enamine in **26** [9] had to be protected with a methyl group after replacement of the bromine with a methoxy group. Thus, the expected 5-methoxy-1*H*-pyrrolo[2,3-*b*]pyridine **27** was prepared in 64% yield in two steps (Fig. 8).

Reagents and conditions: (a) MeONa, CuBr, DMF, MeOH, reflux; (b) NaH, DMF, CH_3I, room temperature, 64% within two steps.

The dimers **38–40** were prepared according to the synthetic route illustrated in Figs. 5 and 6. The first step involved a reaction of **27** with boron tribromide in dichloromethane to generate compound **28** in 85%. Coupling using alkyl dibro-

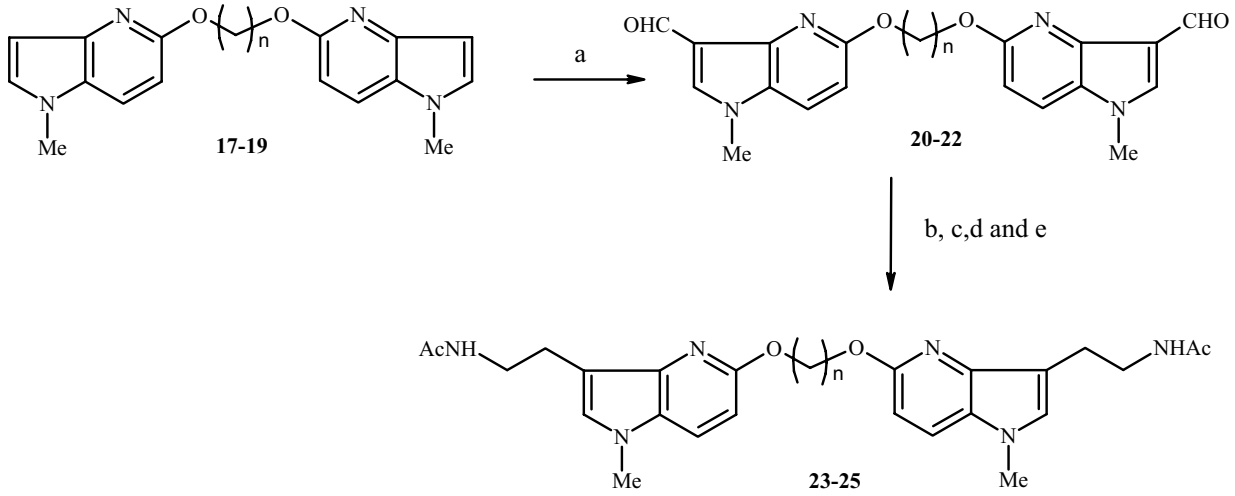


Fig. 7. Synthesis of dimers **23–25**.

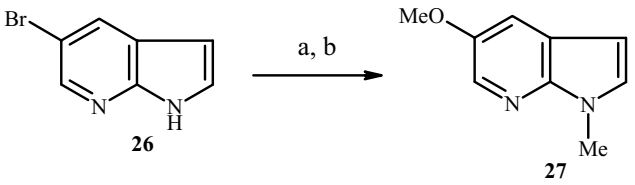


Fig. 8. Synthesis of **27**.

mide and potassium bicarbonate provided the corresponding dimers **32–34**. The formyl group was introduced under Vilsmeier–Haack conditions in good yield and was then converted to the *N*-ethylacetamide side chain using the method mentioned previously for 4-azaindole dimers to give the final compounds **38–40** in satisfactory yields (Fig. 9).

Reagents and conditions: (a) BBr_3, CH_2Cl_2, 0 °C to room temperature, 85%; (b) K_2CO_3, DMF, (**29**, *n* = 4, 88%), (**30**, *n* = 5, 82%), (**31**, *n* = 6, 84%); (c) **28**, K_2CO_3, DMF, (**32**, *n* = 4, 99%), (**33**, *n* = 5, 99%), (**34**, *n* = 6, 71%); (d) $POCl_3$, DMF, room temperature, 2 h (**35**, *n* = 4, 88%), (**36**, *n* = 5, 82%), (**37**, *n* = 6, 84%); (e) CH_3NO_2, NH_4Ac, 120 °C, 4 h; (f) *i*-PrOH, $CHCl_3$, SiO_2, $NaBH_4$, room temperature, 20 min; (g) MeOH, Ni Raney, H_2, 60 °C, 12 h; (h) Ac_2O, CH_2Cl_2 (**38**, *n* = 4, 5% within four steps), (**39**, *n* = 5, 7% within four steps), (**40**, *n* = 6, 15% within four steps).

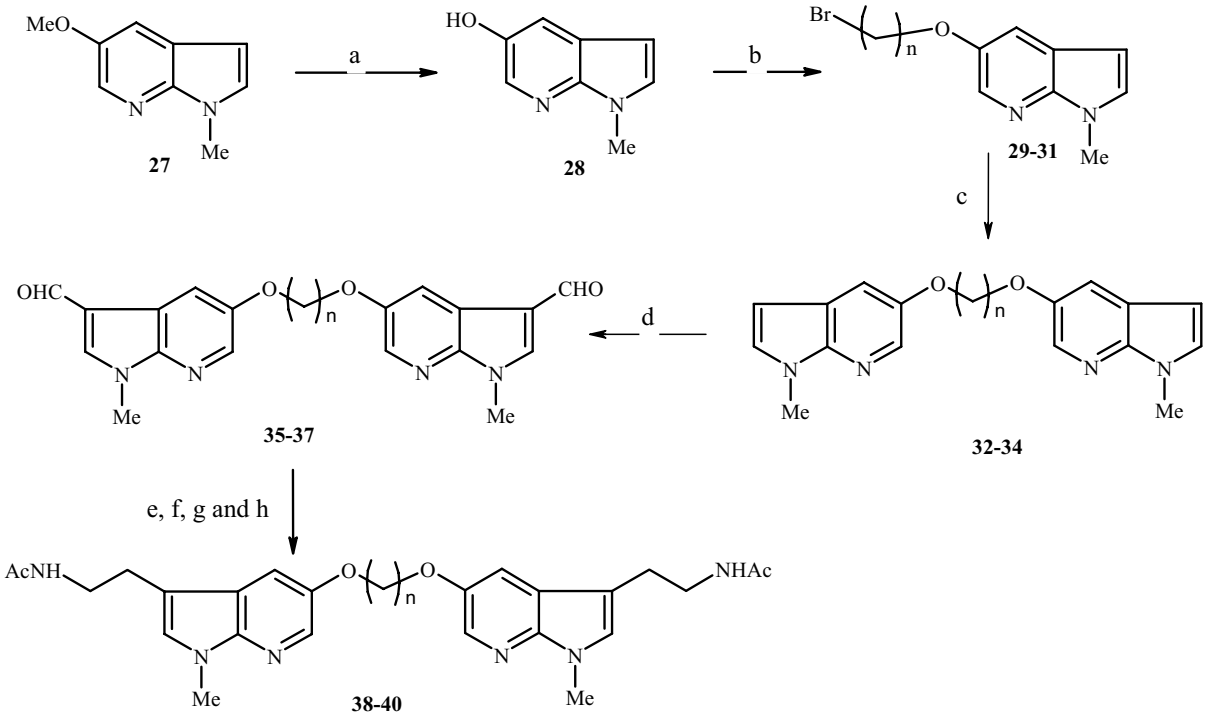


Fig. 9. Synthesis of dimers **38–40**.

Table 1
Binding affinity of derivatives **40** and **23–25**

Compound	*n*	MT_1 K_i ± S.E.M. (nM)	MT_2 K_i ± S.E.M. (nM)	MT_2/MT_1
S 26284	4	0.6 ± 0.12	73 ± 22	122
40	6	253 ± 130	1610 ± 100	6
23	4	56.8 ± 7.1	98.5 ± 19.6	1.7
24	5	33.3 ± 3.6	131 ± 18	4
25	6	8.5 ± 2.2	174 ± 89	20

3. Pharmacology

The affinities of the compounds **40** and **23–25** for melatonin receptors subtypes were evaluated in vitro using binding assays with 2-[^{125}I]-iodomelatonin on membranes from human embryonic kidney (HEK 293) cell line stably expressing human MT_1 or MT_2 receptors. The results of the binding assays are presented in Table 1.

4. Results and discussion

Comparison of the relative MT_1 and MT_2 binding affinities of the 4-azaindole dimers **23** and **24** show that as the number of methylene group in the linking chain from 4 to 5, the MT_1 binding affinities slightly increase from 56.8 to 33.3 nM whereas the MT_2 affinities decrease from 98.5 to 131 nM. The most interesting result is obtained with the compound **25** which shows a loss of MT_2 binding affinity but a 20-fold better affinity for the MT_1 subtype. In contrast, compound **40** with six methylene groups in the linker show strong decrease in MT_1 and MT_2 affinities compared to S 26284.

5. Conclusion

In conclusion, we have described the synthesis of analogues of melatonin which possess a 7- or 4-azaindole skeleton among which the derivative **25** exhibits a weak selectivity ratio. Nevertheless, for these azaindolic compounds both affinity for the two receptor subtypes and the selectivity for MT_1 are weaker than the parent compound.

6. Experimental protocols

6.1. Chemistry

Melting points are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AM-300 WB (300 MHz). The coupling constants are recorded in Hz and the chemical shifts are reported in ppm (δ, ppm) downfield from TMS which was used an internal standard. IR spectra were obtained with a Perkin–Elmer FT Paragon 1000 PC. MS spectra were registered on a Perkin–Elmer SCIEX API 3000 spectrometer. Reaction products were purified by flash chromatography using silica gel (Merck 230–400 mesh). Analytical TLC was carried out on silica gel F_{254} plates. All anhydrous reactions were performed in over-dried glassware under an atmosphere of argon. Anhydrous solvents were transferred via syringe.

*6.1.1. Cyanomethyl-6-methoxy-3-nitropyridine (**1**)*

Under an inert atmosphere, a solution of 2-methoxy-5-nitropyridine (15.00 g, 97.30 mmol) and 4-chlorophenoxyacetonitrile (17.90 g, 107 mmol) in dry THF (290 ml) was added dropwise to a stirred solution of potassium *tert*-butoxide (24.00 g, 214 mmol) in dry THF (220 ml) at –10 °C during 30 min. The addition was finished, the mixture was stirred an additional time (3 h) under continued cooling. After, the mixture was acidified using 5% solution of hydrochloric acid (167 ml) at –10 °C until pH 7 and extracted with ethyl acetate. The combined extracts were dried over anhydrous $MgSO_4$. After removal of the solvent, the crude residue was chromatographed over silica gel (eluent: light petroleum/ethyl acetate: 7:3) to afford **1** (17.7 g, 94%) as a brown solid; m.p. 116–117 °C (pentane); IR (KBr): ν 2923 (CH), 2259 (CN), 1506 (NO_2), 1337 (NO_2) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 4.13 (s, 3H, OC**H**$_3$), 4.43 (s, 2H, C**H**$_2$), 6.87 (d, 1H, J = 9.0 Hz, **H**$_5$), 8.42 (d, 1H, J = 9.0 Hz, **H**$_4$). ^{13}C-NMR ($CDCl_3$): δ 28.5 (**C**H$_2$), 56.4 (O**C**H$_3$), 112.8 (**C**$_5$), 116.4 (**C**N), 137.7 (**C**$_4$), 139.5 (**C**$_q$), 147.2 (**C**$_q$), 166.7 (**C**$_q$); MS (IS) *m/z* = 194 (M + 1).

*6.1.2. 5-Methoxy-1*H*-pyrrolo[3,2-*b*]pyridine (**2**)*

The nitrile **1** (17.7 g, 91.7 mmol) was dissolved in ethanol (300 ml). To this solution was added 10% palladium on charcoal (2.49 g) and the mixture was hydrogenated (45 psi) in a Parr shaker at room temperature during 5 h. The catalyst was filtered off and the solvent was removed under reduced pressure. The crude azaindole was purified by flash chromatography on silica gel (eluent: light petroleum/ethyl acetate: 8:2) to afford compound **2** (9.71 g, 71%) as a white solid; m.p. 111–112 °C (pentane); IR (KBr): ν 3412 (NH), 2960 (CH) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 3.88 (s, 3H, OC**H**$_3$), 6.44 (s, 1H, **H**$_3$), 6.57 (d, 1H, J = 8.8 Hz, **H**$_6$), 7.48 (dd, 1H, J = 3 Hz, **H**$_2$), 7.72 (d, 1H, J = 8.8 Hz, **H**$_7$), 11.17 (s, 1H, N**H**); ^{13}C-NMR (DMSO-d_6): δ 51.9 (O**C**H$_3$), 100.2 (**C**$_3$), 103.7 (**C**$_6$), 121.6 (**C**$_7$), 123.6 (**C**$_q$), 126.8 (**C**$_q$), 141.6 (**C**$_q$), 158.2 (**C**$_q$); MS (IS) *m/z* = 149 (M + 1).

*6.1.3. 1-Benzenesulfonyl-5-methoxypyrrolo[3,2-*b*]pyridine (**3**)*

Under an inert atmosphere, tribenzylammonium chloride (0.21 g, 0.67 mmol) and **2** (5.00 g, 37.70 mmol) were added to a suspension of sodium hydroxide (4.2 g, 104 mmol) in dry dichloromethane (100 ml) at 0 °C. Benzenesulfonyl chloride (5.4 ml, 42.00 mmol) was then added dropwise under continued cooling. The addition was finished, the mixture was stirred 15 min at 0 °C and 2 h at room temperature. After this time, this mixture was filtered on büchner and precipitated was purified by flash chromatography on silica gel (eluent: light petroleum/ethyl acetate: 9:1) to afford compound **3** (9.72 g, 99%) as a white solid; m.p. 127–128 °C (pentane);

IR (KBr): *v* 2942 (CH) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.94 (s, 3H, OC**H**$_3$), 6.70 (d, 1H, *J* = 9.1 Hz, **H**$_6$), 6.72 (d, 1H, *J* = 3.8 Hz, **H**$_3$), 7.44 (t, 2H, *J* = 7.2 Hz, **H**$_{arom}$), 7.55 (t, 1H, *J* = 7.2 Hz, **H**$_{arom}$), 7.66 (d, 1H, *J* = 3.8 Hz, **H**$_2$), 7.84 (d, 2H, *J* = 7.2 Hz, **H**$_{arom}$), 8.15 (d, 1H, *J* = 9.1 Hz, **H**$_7$); ^{13}C-NMR ($CDCl_3$): δ 53.5 (O**C**H$_3$), 108.0 (**C**$_6$), 109.1 (**C**$_3$), 123.6 (**C**$_q$), 124.1 (**C**$_7$), 126.8 (2 × CH), 128.5 (**C**$_2$), 129.4 (2 × CH), 134.1 (**C**H), 138.0 (**C**$_q$), 145.9 (**C**$_q$), 162.0 (C$_q$); MS (IS) *m/z* = 289 (M + 1).

*6.1.4. 1-Benzenesulfonylpyrrolo[3,2-b]pyridin-5-one (**4**)*

Under an inert atmosphere, aluminum chloride (9.91 g, 74.30 mmol) was added to a solution of 1-benzenesulfonyl-5-methoxypyrrolo[3,2-*b*]pyridine (**3**) (2.14 g, 7.43 mmol) in dichloromethane (100 ml) at room temperature. The reaction was heated at reflux for 18 h. The mixture was cooled at 0 °C, neutralized to pH 8 using saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane. The combined extracts were dried over anhydrous $MgSO_4$ and the solvent was removed in vacuo. The crude residue was chromatographed over silica gel (eluent: ethyl acetate) to afford **4** (1.62 g, 81%) as a white solid; m.p. 209–210 °C (pentane); IR (KBr): *v* 3442 (NH), 1651 (CO), 1377 (SO_2) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.46 (d, 1H, *J* = 3.9 Hz, **H**$_3$), 6.47 (d, 1H, *J* = 5.7 Hz, **H**$_{arom}$), 7.44–7.52 (m, 3H, **H**$_{arom}$), 7.60 (t, 1H, *J* = 7.2 Hz, **H**$_{arom}$), 7.83 (d, 1H, *J* = 3.9 Hz, **H**$_2$), 7.82 (d, 1H, *J* = 9.7 Hz, **H**$_6$), 8.10 (d, 1H, *J* = 9.7 Hz, **H**$_7$); ^{13}C-NMR ($CDCl_3$): δ 103.6 (**C**$_3$), 119.0 (**C**$_q$), 126.3 (**C**H), 127.1 (2 × CH), 128.0 (**C**H), 129.2 (**C**H), 130.0 (2 × **C**H), 134.8 (**C**$_6$), 136.0 (**C**$_q$), 138.2 (**C**$_q$), 165.0 (**C**O); MS (IS) *m/z* = 275 (M + 1).

*6.1.5. General procedure for compounds **5–7** and **8–10***

Under an inert atmosphere, potassium carbonate (0.20 g, 1.46 mmol) was added to a stirred solution of 1-benzenesulfonylpyrrolo[3,2-*b*]pyridin-5-one (**4**) (0.10 g, 0.36 mmol) in *N,N*-dimethylformamide (15 ml) at room temperature. Alkyl-dibromide (0.17 ml, 1.46 mmol) was added dropwise and the mixture was stirred an additional time (12 h) at room temperature. The solvent was removed under reduced pressure and the crude was taken up in water and extracted with ethyl acetate. The combined extracts were dried over anhydrous $MgSO_4$. The solvent was evaporated and the products **5–7** and **8–10** were purified by column chromatography (eluent: light petroleum/ethyl acetate: 8:2).

*6.1.5.1. 1-Benzenesulfonyl-5-(4-bromobutoxyloxy)pyrrolo [3,2-*b*]pyridine (**5**).* Colorless oil (54%); IR (KBr): *v* 2939 (CH), 1373 (SO_2) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.89–2.07 (m, 4H, C**H**$_2$C**H**$_2$CH$_2$O), 3.47 (t, 2H, *J* = 6.6 Hz, C**H**$_2$Br), 4.33 (t, 2H, *J* = 6.2 Hz, C**H**$_2$O), 6.68 (d, 1H, *J* = 9.1 Hz, **H**$_6$), 6.68 (d, 1H, *J* = 9.1 Hz, **H**$_6$), 6.69 (dd, 1H, *J* = 3.7 Hz, *J* = 0.6 Hz, **H**$_3$), 7.41–7.58 (m, 3H, **H**$_{arom}$), 7.66 (d, 1H, *J* = 3.7 Hz, **H**$_2$), 7.84 (d, 2H, *J* = 7.2 Hz, **H**$_{arom}$), 8.15 (dd, 1H, *J* = 9.1 Hz, *J* = 0.6 Hz, **H**$_7$); ^{13}C-NMR ($CDCl_3$): δ 28.1 (**C**H$_2$), 29.9 (**C**H$_2$), 33.9 (**C**H$_2$Br), 65.4 (O**C**H$_2$), 108.4 (**C**$_3$), 110.3 (**C**H), 124.5 (**C**$_7$ + **C**$_q$), 127.1 (2 × **C**H), 128.9 (**C**H), 129.8 (2 × **C**H), 134.5 (**C**H), 138.4 (**C**$_q$), 146.3 (**C**$_q$), 162.1 (**C**$_q$); MS (IS) *m/z* = 409 (M + 1 for ^{79}Br), *m/z* = 411 (M + 1 for ^{81}Br).

*6.1.5.2. 1-Benzenesulfonyl-5-(5-bromopentyloxy)pyrrolo [3,2-*b*]pyridine (**6**).* Green oil (54%); IR (film): *v* 2951 (CH), 1374 (SO_2) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.46–1.93 (m, 6H, C**H**$_2$C**H**$_2$C**H**$_2$CH$_2$O), 3.36 (t, 2H, *J* = 6.7 Hz, C**H**$_2$Br), 4.26 (t, 2H, *J* = 6.2 Hz, CH$_2$O), 6.65 (d, 1H, *J* = 3.2 Hz, **H**$_3$), 6.66 (d, 1H, *J* = 8.9 Hz, **H**$_6$), 7.33–7.41 (m, 3H, **H**$_{arom}$), 7.64 (d, 1H, *J* = 3.2 Hz, **H**$_2$), 7.80 (d, 2H, *J* = 7.0 Hz, **H**$_{arom}$), 8.13 (d, 1H, *J* = 8.9 Hz, **H**$_7$). ^{13}C-NMR ($CDCl_3$): δ 25.4 (**C**H$_2$), 28.7 (**C**H$_2$), 33.0 (**C**H$_2$), 34.4 (**C**H$_2$), 66.3 (O**C**H$_2$), 108.7 (**C**$_3$), 110.5 (**C**H), 124.4 (**C**$_q$), 124.7 (**C**$_7$), 127.1 (2 × **C**H), 128.9 (**C**H), 129.8 (2 × **C**H), 134.5 (**C**H), 138.3 (**C**$_q$), 146.3 (**C**$_q$), 162.2 (**C**$_q$). MS (IS) *m/z* = 423 (M + 1 for ^{79}Br), *m/z* = 425 (M + 1 for ^{81}Br).

*6.1.5.3. 1-Benzenesulfonyl-5-(6-bromohexyloxy)pyrrolo[3,2-*b*]pyridine (**7**).* White solid (53%); m.p. 90–91 °C; IR (Kbr): *v* 2941 (CH) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.42 (sb, 4H, C**H**$_2$C**H**$_2$C**H**$_2$CH$_2$O), 1.78–1.80 (m, 4H, CH$_2$CH$_2$CH$_2$C**H**$_2$ CH$_2$O) 3.33 (t, 2H, *J* = 6.7 Hz, C**H**$_2$Br), 4.25 (t, 2H, *J* = 6.4 Hz, C**H**$_2$O), 6.65 (m, 2H, **H**$_6$), 7.26–7.51 (m, 3H, **H**$_{arom}$), 7.62 (d, 1H, *J* = 3.6 Hz, **H**$_2$), 7.84 (d, 2H, *J* = 7.9 Hz, **H**$_{arom}$), 8.14 (d, 1H, *J* = 9.1 Hz, **H**$_7$); ^{13}C-NMR ($CDCl_3$): δ 25.7 (**C**H$_2$), 28.3 (**C**H$_2$), 29.2 (**C**H$_2$), 34.3 (**C**H$_2$Br), 66.3 (O**C**H$_2$), 108.7 (**C**$_3$), 110.3 (**C**H), 124.4 (**C**$_q$), 124.5 (**C**$_7$), 127.1 (2 × **C**H), 128.9 (**C**H), 129.8 (2 × **C**H), 134.5 (**C**H), 138.3 (**C**$_q$), 146.3 (**C**$_q$), 162.3 (**C**$_q$). MS (IS) *m/z* = 437 (M + 1 for ^{79}Br), *m/z* = 439 (M + 1 for ^{81}Br).

*6.1.5.4. 1-Benzenesulfonyl-4-(4′-bromobutyl)pyrrolo[3,2-*b*] pyridone (**8**).* Yellow oil (23%); IR (film): *v* 1645 (CO), 1374 (SO_2) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.77–2.01 (m, 4H, C**H**$_2$C**H**$_2$CH$_2$N), 3.43 (t, 2H, *J* = 6.0 Hz, CH$_2$Br), 4.07 (t, 2H, *J* = 6.2 Hz, C**H**$_2$N), 6.37 (dd, 1H, *J* = 3.7 Hz, *J* = 0.6 Hz, **H**$_3$), 6.46 (d, 1H, *J* = 9.7 Hz, **H**$_6$), 7.46–7.69 (m, 4H, **H**$_{arom}$), 7.82–7.90 (m, 2H, **H**$_{arom}$), 7.98 (dd, 1H, *J* = 9.7 Hz, *J* = 0.6 Hz, **H**$_7$); ^{13}C-NMR ($CDCl_3$): δ 26.9 (**C**H$_2$), 30.0 (**C**H$_2$), 33.5 (**C**H$_2$Br), 44.00 (N**C**H$_2$), 102.2 (**C**$_3$), 117.2 (**C**H), 117.9 (**C**$_q$), 127.1 (2 × **C**H + **C**H), 127.2 (**C**H), 130.0 (2 × **C**H), 134.9 (**C**H), 136.6 (**C**$_q$), 138.2 (**C**$_q$), 161.8 (**C**O); MS (IS) *m/z* = 409 (M + 1 for ^{79}Br), *m/z* = 411 (M + 1 for ^{81}Br).

*6.1.5.5. 1-Benzenesulfonyl-4-(4′-bromopentyl)pyrrolo[3,2-*b*] pyridone (**9**).* Yellow oil (24%); IR (film): *v* 1642 (CO) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.77–2.05 (m, 6H, C**H**$_2$C**H**$_2$C**H**$_2$CH$_2$), 3.43 (t, 2H, *J* = 6.0 Hz, C**H**$_2$Br), 4.07 (t, 2H, *J* = 6.2 Hz, CH$_2$N), 6.37 (dd, 1H, *J* = 3.2 Hz, *J* = 0.6 Hz, **H**$_3$), 6.46 (d, 1H, *J* = 9.5 Hz, **H**$_6$), 7.46–7.69 (m, 4H, **H**$_{arom}$), 7.82–7.90 (m, 2H, **H**$_{arom}$), 7.98 (dd, 1H, *J* = 9.5 Hz, *J* = 0.6 Hz, **H**$_7$). ^{13}C-NMR ($CDCl_3$): δ 25.9 (**C**H$_2$), 26.9 (**C**H$_2$), 30.0 (**C**H$_2$), 33.5 (**C**H$_2$), 44.0 (N**C**H$_2$), 102.2 (**C**$_3$), 117.2 (**C**H), 117.9 (**C**$_q$), 127.1 (2 × **C**H + **C**H), 127.2 (**C**H), 130.0 (2 × **C**H), 134.9 (**C**H), 136.6

($\mathbf{C}_q$), 138.2 ($\mathbf{C}_q$), 161.8 (**C**O). MS (IS) *m/z* = 423 (M + 1 for ^{79}Br), *m/z* = 425 (M + 1 for ^{81}Br).

*6.1.5.6. 1-Benzenesulfonyl-4-(4′-bromohexyl)pyrrolo[3,2-b] pyridone (**10**).* White solid (39%); m.p. 111–112 °C; IR (KBr): *v* 1642 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.26–1.51 (m, 4H, C$\mathbf{H}_2$C$\mathbf{H}_2$CH_2CH_2N), 1.59–1.84 (m, 4H, C$\mathbf{H}_2$CH_2CH_2C$\mathbf{H}_2$CH_2N), 3.32 (t, 2H, *J* = 6.7 Hz, C$\mathbf{H}_2$Br), 3.98 (t, 2H, *J* = 7.6 Hz, C$\mathbf{H}_2$N), 6.31 (d, 1H, *J* = 3.6 Hz, $\mathbf{H}_3$), 6.41 (d, 1H, *J* = 9.6 Hz, $\mathbf{H}_6$), 7.39–7.63 (m, 4H, $\mathbf{H}_{arom}$), 7.76–7.85 (m, 2H, $\mathbf{H}_{arom}$), 7.92 (dd, 1H, *J* = 9.6 Hz, *J* = 0.5 Hz, $\mathbf{H}_7$); ^{13}C-NMR ($CDCl_3$): δ 26.4 ($\mathbf{C}H_2$), 28.2 ($\mathbf{C}H_2$), 28.3 ($\mathbf{C}H_2$), 32.9 ($\mathbf{C}H_2$), 34.2 ($\mathbf{C}H_2$Br), 45.0 (N$\mathbf{C}H_2$), 102.3 (**C**H), 117.2 (**C**H), 117.9 ($\mathbf{C}_q$), 127.0 (**C**H + **C**H), 127.2 (2 × **C**H), 130.0 (2 × **C**H), 134.9 (**C**H), 136.8 ($\mathbf{C}_q$), 138.1 ($\mathbf{C}_q$), 161.8 (**C**O). MS (IS) *m/z* = 437 (M + 1 for ^{79}Br), *m/z* = 439 (M + 1 for ^{81}Br).

*6.1.6. General procedure for compounds **11–13***

Under an inert atmosphere, potassium carbonate (1.87, 13.28 mmol) was added to a stirred solution of 1-benzenesulfonyl-5-(bromoalkyloxy)pyrrolo[3,2-*b*]pyridine 5–7 (3.32 mmol) in *N,N*-dimethylformamide (100 ml) at room temperature. 1-Benzenesulfonylpyrrolo[3,2-*b*]pyridin-5-one (**4**) (1.36 g, 4.99 mmol) was then added dropwise and the mixture was stirred an additional time (24 h) at room temperature. The solvent was removed under reduced pressure and the crude was taken up in water and extracted with ethyl acetate. The combined extracts were dried over anhydrous $MgSO_4$. The solvent was evaporated and the products **11–13** were purified by column chromatography (eluent: light petroleum/ethyl acetate: 6:4).

*6.1.6.1. 1.4-Bis[1-benzenesulfonylpyrrolo[3,2-*b*]pyridin-5-yloxy]butane (**11**).* Colorless oil (57%); IR (KBr): *v* 2963 (CH) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.90–1.98 (m, 4H, C$\mathbf{H}_2$CH_2O), 4.35 (t, 4H, *J* = 5.3 Hz, C$\mathbf{H}_2$O), 6.68 (d, 2H, *J* = 9.1 Hz $\mathbf{H}_6$), 6.69 (dd, 2H, *J* = 3.7 Hz, *J* = 0.6 Hz, $\mathbf{H}_3$), 7.41–7.58 (m, 6H, $\mathbf{H}_{arom}$), 7.63 (d, 2H, *J* = 3.7 Hz, $\mathbf{H}_2$), 7.82 (d, 4H, *J* = 7.2 Hz, $\mathbf{H}_{arom}$), 8.14 (dd, 2H, *J* = 9.1 Hz, *J* = 0.6 Hz, $\mathbf{H}_7$); ^{13}C-NMR ($CDCl_3$): δ 26.1 (2 × C$\mathbf{H}_2$CH_2), 66.1 (2 × O$\mathbf{C}H_2$), 108.5 (2 × $\mathbf{C}_3$), 110.3 (2 × **C**H), 124.5 (2 × **C**H + 2 × $\mathbf{C}_q$), 127.1 (4 × **C**H), 128.9 (2 × **C**H), 129.8 (4 × **C**H), 134.5 (2 × **C**H), 138.4 (2 × $\mathbf{C}_q$), 146.3 (2 × $\mathbf{C}_q$), 162.1 (2 × $\mathbf{C}_q$). MS (IS) *m/z* = 603 (M + 1).

*6.1.6.2. 1.5-Bis[1-benzenesulfonylpyrrolo[3,2-*b*]pyridin-5-yloxy]pentane (**12**).* White solid (60%); m.p. 181–182 °C (pentane); IR (KBr): *v* 2949 (CH) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.64 (t, 2H, *J* = 10.0 Hz, C$\mathbf{H}_2$CH_2CH_2O), 1.76–1.92 (m, 4H, CH_2C$\mathbf{H}_2$CH_2O), 4.30 (t, 4H, *J* = 6.3 Hz, C$\mathbf{H}_2$O), 6.68 (d, 2H, *J* = 9.6 Hz $\mathbf{H}_6$), 6.69 (dd, 2H, *J* = 3.2 Hz, *J* = 0.6 Hz, $\mathbf{H}_3$), 7.40–7.59 (m, 6H, $\mathbf{H}_{arom}$), 7.63 (d, 2H, *J* = 3.2 Hz, $\mathbf{H}_2$), 7.82 (d, 4H, *J* = 8.2 Hz, $\mathbf{H}_{arom}$), 8.14 (dd, 2H, *J* = 9.6 Hz, *J* = 0.6 Hz, $\mathbf{H}_7$). ^{13}C-NMR ($CDCl_3$): δ 22.7 (C$\mathbf{H}_2$CH_2CH_2O), 28.7 (2 × CH_2C$\mathbf{H}_2$CH_2O), 65.9 (2 × O$\mathbf{C}H_2$), 108.1 (2 × $\mathbf{C}_3$), 109.9 (2 × **C**H), 124.1 (2 × $\mathbf{C}_7$), 126.6 (4 × **C**H), 128.4 (2 × **C**H), 128.5 (2 × $\mathbf{C}_q$), 129.4 (4 × **C**H), 134.1 (2 × **C**H), 138.0 (2 × $\mathbf{C}_q$), 145.8 (2 × $\mathbf{C}_q$), 161.9 (2 × $\mathbf{C}_q$); MS (IS) *m/z* = 617 (M + 1).

*6.1.6.3. 1.6-Bis[1-benzenesulfonylpyrrolo[3,2-*b*]pyridin-5-yloxy]hexane (**13**).* White solid; m.p. 203–204 °C; IR (KBr): *v* 2980 (CH) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.50 (sb, 4H, C$\mathbf{H}_2$CH_2CH_2O), 1.75–1.85 (m, 4H, C$\mathbf{H}_2$CH_2O), 4.28 (t, 4H, *J* = 6.6 Hz, C$\mathbf{H}_2$O), 6.68 (d, 2H, *J* = 8.9 Hz $\mathbf{H}_6$), 6.69 (d, 2H, *J* = 3.7 Hz, $\mathbf{H}_3$), 7.41–7.60 (m, 6H, $\mathbf{H}_{arom}$), 7.63 (d, 2H, *J* = 3.7 Hz, $\mathbf{H}_2$), 7.82 (d, 4H, *J* = 7.2 Hz, $\mathbf{H}_{arom}$), 8.16 (d, 2H, *J* = 8.9 Hz, $\mathbf{H}_7$). ^{13}C-NMR ($CDCl_3$): δ 26.3 (2 × C$\mathbf{H}_2$CH_2CH_2O), 29.4 (2 × C$\mathbf{H}_2$CH_2O), 66.5 (2 × O$\mathbf{C}H_2$), 108.6 (2 × $\mathbf{C}_3$), 110.4 (2 × **C**H), 124.5 (2 × $\mathbf{C}_7$ + 2 × $\mathbf{C}_q$), 127.1 (4 × **C**H), 128.8 (2 × **C**H), 129.8 (4 × **C**H), 134.5 (2 × **C**H), 138.5 (2 × $\mathbf{C}_q$), 146.3 (2 × $\mathbf{C}_q$), 162.4 (2 × $\mathbf{C}_q$). MS (IS) *m/z* = 631 (M + 1).

*6.1.7. General procedure for compounds **14–16***

Under an inert atmosphere, sodium hydroxide (0.29 g, 7.31 mmol) was added a solution of compound **11** or **12** or **13** (1.83 mmol) in methanol (47 ml). When the addition was finished, the mixture was heated at reflux for 12 h. The solvent was removed in vacuo, the crude was then taken up in water and extracted with dichloromethane. The combined extracts were dried over anhydrous $MgSO_4$. The solvent was evaporated and the product **14** or **15** or **16** was purified by column chromatography (eluent: light petroleum/ethyl acetate).

*6.1.7.1. 1,4-Bis[1*H*-pyrrolo[3,2-*b*]pyridin-5-yloxy]butane (**14**) (*n = *4).* White solid (80%); m.p. 97–98 °C (pentane); IR (KBr) *v*: 3441 (NH), 2885 (CH) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.83–1.96 (m, 4H, C$\mathbf{H}_2$CH_2O), 4.29 (t, 4H, *J* = 5.3 Hz, C$\mathbf{H}_2$O), 6.36 (s, 2H, $\mathbf{H}_3$), 6.51 (d, 2H, *J* = 8.7 Hz, $\mathbf{H}_6$), 7.63 (d, 2H, *J* = 3.3 Hz, $\mathbf{H}_2$), 7.66 (d, 2H, *J* = 8.7 Hz, $\mathbf{H}_7$) 11.11 (s, 2H, N**H**). ^{13}C-NMR (DMSO-d_6): δ 26.5 (2 × $\mathbf{C}H_2$), 65.5 (2 × O$\mathbf{C}H_2$), 101.7 (2 × $\mathbf{C}_3$), 105.4 (2 × $\mathbf{C}_7$), 123.2 (2 × $\mathbf{C}_7$), 125.1 (2 × $\mathbf{C}_q$), 128.5 (2 × $\mathbf{C}_2$), 143.2 (2 × $\mathbf{C}_q$), 159.6 (2 × $\mathbf{C}_q$). MS (IS) *m/z* = 323 (M + 1).

*6.1.7.2. 1,5-Bis[1*H*-pyrrolo[3,2-*b*]pyridin-5-yloxy]pentane (**15**) (*n = *5).* White solid (80%); m.p. 179–180 °C (pentane); IR (KBr): *v* 3146 (NH), 2878 (CH) cm^{-1}; ^{1}H-NMR (CD_3OD): δ 1.61–1.79 (t, 2H, *J* = 9.5 Hz, C$\mathbf{H}_2$CH_2CH_2O), 1.80–1.96 (m, 4H, C$\mathbf{H}_2$CH_2O), 4.29 (t, 4H, *J* = 6.1 Hz, C$\mathbf{H}_2$O), 6.43 (d, 2H, *J* = 2.8 Hz, $\mathbf{H}_3$), 6.58 (d, 2H, *J* = 8.7 Hz, $\mathbf{H}_6$), 7.37 (d, 2H, *J* = 2.8 Hz, $\mathbf{H}_2$), 7.68 (d, 1H, *J* = 8.7 Hz, $\mathbf{H}_7$). ^{13}C-NMR (CD_3OD): δ 23.1 (C$\mathbf{H}_2$CH_2CH_2O), 29.2 (2 × C$\mathbf{H}_2$CH_2O), 66.2 (2 × O$\mathbf{C}H_2$), 100.8 (2 × $\mathbf{C}_3$), 105.0 (2 × $\mathbf{C}_6$), 122.8 (2 × $\mathbf{C}_7$), 125.2 (2 × $\mathbf{C}_q$), 127.5 (2 × $\mathbf{C}_2$), 142.7 (2 × $\mathbf{C}_q$), 160.1 (2 × $\mathbf{C}_q$). MS (IS) *m/z* = 337 (M + 1).

*6.1.7.3. 1,6-Bis[1*H*-pyrrolo[3,2-*b*]pyridin-5-yloxy]hexane (**16**) (*n = *6).* White solid (83%); m.p. >245 °C (pentane); IR (KBr): *v* 3422 (NH), 2864 (CH) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 1.46 (sb, 4H, C$\mathbf{H}_2$CH_2CH_2O), 1.73 (sb, 4H, CH_2C$\mathbf{H}_2$CH_2O), 4.23 (t, 4H, *J* = 6.4 Hz, C$\mathbf{H}_2$O), 6.35 (sb,

2H, $\mathbf{H}_3$), 6.49 (d, 2H, J = 8.7 Hz, $\mathbf{H}_6$), 7.63 (sl, 2H, $\mathbf{H}_2$), 7.65 (d, 2H, J = 8.7 Hz, $\mathbf{H}_7$), 11.08 (s, 2H, N**H**). ^{13}C-NMR (DMSO-d_6) δ: 26.5 (2 × $\mathbf{C}H_2$), 29.6 (2 × $\mathbf{C}H_2$), 65.7 (2 × O$\mathbf{C}H_2$), 101.7 (2 × $\mathbf{C}_3$), 105.4 (2 × $\mathbf{C}_6$), 123.2 (2 × $\mathbf{C}_7$), 125.1 (2 × $\mathbf{C}_q$), 128.4 (2 × $\mathbf{C}_2$), 143.2 (2 × $\mathbf{C}_q$), 159.6 (2 × $\mathbf{C}_q$). MS (IS) m/z = 351 (M + 1).

6.1.8. General procedure for compounds ***17–19***

Under an inert atmosphere, sodium hydride (60% in oil, 0.14 g, 5.60 mmol) was added to a stirred solution of compound **14** or **15** or **16** (1.40 mmol) in *N,N*-dimethylformamide (35 ml) at 0 °C for 30 min. The mixture was stirred an additional time (30 min) under continued cooling. Then methyl iodide (0.79 ml, 5.6 mmol) was added dropwise and the mixture was stirred for 3 h, allowing the temperature to increase at room temperature. Then, water was added and the product was extracted with dichloromethane. The product **17** or **18** or **19** was purified by flash chromatography on silica gel (eluent: light petroleum/ethyl acetate : 1:1).

*6.1.8.1. 1,4-Bis[1-methylpyrrolo[3,2-*b*]pyridin-5-yloxy]butane (**17**) (*n = *4).* Yellow oil (99%); m.p. 134–135 °C (pentane); IR (film): ν 2945 (CH) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ: 1.95–2.06 (m, 4H, C$\mathbf{H}_2$CH$_2$O), 3.76 (s, 6H, NC$\mathbf{H}_3$), 4.43 (t, 4H, J = 5.2 Hz, C$\mathbf{H}_2$O), 6.49 (dd, 2H, J = 3.1 Hz, J = 0.9 Hz, $\mathbf{H}_3$), 6.61 (d, 2H, J = 8.8 Hz, $\mathbf{H}_6$), 7.13 (d, 2H, J = 3.1 Hz, $\mathbf{H}_2$), 7.52 (dd, 1H, J = 8.8 Hz, J = 0.9 Hz, $\mathbf{H}_6$). ^{13}C-NMR ($CDCl_3$): δ: 26.5 (2 × $\mathbf{C}H_2$), 33.6 (2 × N$\mathbf{C}H_3$), 65.9 (2 × O$\mathbf{C}H_2$), 101.3 (2 × $\mathbf{C}_3$), 105.8 (2 × $\mathbf{C}_6$), 120.4 (2 × $\mathbf{C}_7$), 126.1 (2 × $\mathbf{C}_q$), 130.8 (2 × $\mathbf{C}_2$), 143.4 (2 × $\mathbf{C}_q$), 160.3 (2 × $\mathbf{C}_q$). MS (IS) m/z = 351 (M + 1).

*6.1.8.2. 1,5-Bis[1-methylpyrrolo[3,2-*b*]pyridin-5-yloxy]pentane (**18**) (*n = *5).* White solid (81%); m.p. 119–120 °C (pentane); IR (KBr): ν 2945 (CH) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.61–1.79 (t, 2H, J = 9.5 Hz, C$\mathbf{H}_2$CH$_2$CH$_2$O), 1.80–2.05 (m, 4H, CH$_2$C$\mathbf{H}_2$CH$_2$O), 3.71 (s, 6H, NC$\mathbf{H}_3$), 4.38 (t, 4H, J = 6.2 Hz, C$\mathbf{H}_2$O), 6.49 (s, 2H, $\mathbf{H}_3$), 6.58 (d, 2H, J = 8.7 Hz, $\mathbf{H}_6$), 7.10 (s, 2H, $\mathbf{H}_2$), 7.48 (d, 2H, J = 8.7 Hz, $\mathbf{H}_6$). ^{13}C-NMR ($CDCl_3$): δ 23.3 (**C**H$_2$CH$_2$CH$_2$O), 29.5 (2 × CH$_2$**C**H$_2$CH$_2$O), 33.6 (2 × N$\mathbf{C}H_3$), 66.1 (2 × O$\mathbf{C}H_2$), 101.3 (2 × $\mathbf{C}_3$), 105.8 (2 × $\mathbf{C}_6$), 120.4 (2 × $\mathbf{C}_7$), 126.1 (2 × $\mathbf{C}_q$), 130.8 (2 × $\mathbf{C}_2$), 143.4 (2 × $\mathbf{C}_q$), 160.3 (2 × $\mathbf{C}_q$). MS (IS) m/z = 365 (M + 1).

*6.1.8.3. 1,6-Bis[1-methylpyrrolo[3,2-*b*]pyridin-5-yloxy]hexane (**19**) (*n = *6).* White solid (83%); m.p. 104–105 °C (pentane); IR (KBr): ν 2940 (CH) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.53–1.63 (m, 4H, C$\mathbf{H}_2$CH$_2$CH$_2$O), 1.76–1.88 (m, 4H, CH$_2$C$\mathbf{H}_2$CH$_2$O), 3.72 (s, 6H, NC$\mathbf{H}_3$), 4.36 (t, 4H, J = 6.6 Hz, C$\mathbf{H}_2$O), 6.49 (d, 2H, J = 3.1 Hz $\mathbf{H}_3$), 6.59 (d, 2H, J = 8.8 Hz, $\mathbf{H}_6$), 7.13 (d, 2H, J = 3.1 Hz, $\mathbf{H}_2$), 7.49 (d, 1H, J = 2.6 Hz, $\mathbf{H}_7$). ^{13}C-NMR ($CDCl_3$): δ 26.5 (2 × $\mathbf{C}H_2$), 29.7 (2 × $\mathbf{C}H_2$), 33.6 (2 × N$\mathbf{C}H_3$), 66.2 (2 × O$\mathbf{C}H_2$), 101.3 (2 × $\mathbf{C}_3$), 105.8 (2 × $\mathbf{C}_6$), 120.4 (2 × $\mathbf{C}_7$), 126.1 (2 × $\mathbf{C}_q$), 130.8 (2 × $\mathbf{C}_2$), 143.4 (2 × $\mathbf{C}_q$), 160.3 (2 × $\mathbf{C}_q$). MS (IS) m/z = 379 (M + 1).

6.1.9. General procedure for compounds ***20–22***

Under an inert atmosphere, phosphorus oxychloride (0.13 ml, 1.38 mmol) was added to *N,N*-dimethylformamide (2 ml) at 0 °C. After 10 min of stirring, a solution of dimers **17–19** (0.23 mmol) in *N,N*-dimethylformamide (2 ml) was added. The reaction was stirred for 30 min at 0 °C, then heated at room temperature during 2 h. Then the solvent was removed under reduced pressure and the residue diluted with water. After extraction with ethyl acetate, the organic layers were dried over anhydrous $MgSO_4$ and evaporated in vacuo. The products **20–22** were purified by column chromatography (eluent: ethyl acetate).

*6.1.9.1. 1,4-Bis[3-formyl-1-methylpyrrolo[3,2-*b*]pyridin-5-yloxy]butane (**20**) (*n = *4).* White solid (95%); m.p. 234–235 °C (pentane); IR (KBr): ν 2951 (CH), 1660 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.01–2.05 (m, 4H, C$\mathbf{H}_2$CH$_2$O), 3.85 (s, 6H, NC$\mathbf{H}_3$), 4.53 (t, 4H, J = 5.2 Hz, C$\mathbf{H}_2$O), 6.72 (d, 2H, J = 9.0 Hz, $\mathbf{H}_6$), 7.58 (d, 2H, J = 9.0 Hz, $\mathbf{H}_7$), 7.13 (s, 2H, $\mathbf{H}_2$), 10.27 (s, 2H, C**H**O). ^{13}C-NMR ($CDCl_3$): δ 26.4 (2 × $\mathbf{C}H_2$CH$_2$O), 34.7 (2 × N$\mathbf{C}H_3$), 66.4 (2 × O$\mathbf{C}H_2$), 107.9 (2 × $\mathbf{C}_6$), 121.2 (2 × $\mathbf{C}_q$), 121.4 (2 × $\mathbf{C}_q$), 126.1 (2 × $\mathbf{C}_q$), 134.7 (2 × $\mathbf{C}_2$), 143.4 (2 × $\mathbf{C}_q$), 162.2 (2 × $\mathbf{C}_q$), 185.4 (2 × **C**HO). MS (IS) m/z = 407 (M + 1), 429 (M + 23).

*6.1.9.2. 1,4-Bis[3-formyl-1-methylpyrrolo[3,2-*b*]pyridin-5-yloxy]pentane (**21**) (*n = *5).* Yellow oil (95%); IR (film): ν 2939 (CH), 1660 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.59–1.68 (m, 2H, C$\mathbf{H}_2$CH$_2$CH$_2$O), 1.75–2.01 (m, 4H, CH$_2$C$\mathbf{H}_2$CH$_2$O), 3.81 (s, 6H, NC$\mathbf{H}_3$), 4.44 (t, 4H, J = 6.4 Hz, C$\mathbf{H}_2$O), 6.67 (d, 2H, J = 8.8 Hz, $\mathbf{H}_6$), 7.53 (d, 2H, J = 8.8 Hz, $\mathbf{H}_7$), 7.74 (s, 2H, $\mathbf{H}_2$), 10.22 (s, 2H, C**H**O). ^{13}C-NMR ($CDCl_3$): δ 23.3 (**C**H$_2$CH$_2$CH$_2$O), 29.3 (2 × CH$_2$**C**H$_2$CH$_2$O), 34.6 (2 × N$\mathbf{C}H_3$), 66.4 (2 × O$\mathbf{C}H_2$), 107.7 (2 × $\mathbf{C}_6$), 116.8 (2 × $\mathbf{C}_q$), 121.3 (2 × $\mathbf{C}_7$), 126.5 (2 × $\mathbf{C}_q$), 139.8 (2 × $\mathbf{C}_2$), 142.3 (2 × $\mathbf{C}_q$), 162.0 (2 × $\mathbf{C}_q$), 185.1 (2 × **C**HO). MS (IS) m/z = 421 (M + 1).

*6.1.9.3. 1,4-Bis[3-formyl-1-methylpyrrolo[3,2-*b*]pyridin-5-yloxy]hexane (**22**) (*n = *6).* White solid (90%); m.p. 192–193 °C (pentane); IR (KBr): ν 2961 (CH), 1620 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.45–1.70 (m, 4H, C$\mathbf{H}_2$CH$_2$CH$_2$O), 1.78–1.95 (m, 4H, CH$_2$C$\mathbf{H}_2$CH$_2$O), 3.85 (s, 6H, NC$\mathbf{H}_3$), 4.44 (t, 4H, J = 6.5 Hz, C$\mathbf{H}_2$O), 6.70 (d, 2H, J = 8.8 Hz, $\mathbf{H}_6$), 7.57 (d, 2H, J = 8.8 Hz, $\mathbf{H}_7$), 7.78 (s, 2H, $\mathbf{H}_2$), 10.27 (s, 2H, C**H**O). ^{13}C-NMR ($CDCl_3$): δ 26.5 (2 × $\mathbf{C}H_2$CH$_2$CH$_2$O), 29.5 (2 × $\mathbf{C}H_2$CH$_2$O), 34.6 (2 × N$\mathbf{C}H_3$), 66.5 (2 × O$\mathbf{C}H_2$), 107.8 (2 × $\mathbf{C}_6$), 116.9 (2 × $\mathbf{C}_q$), 121.4 (2 × $\mathbf{C}_7$), 126.5 (2 × $\mathbf{C}_q$), 134.6 (2 × $\mathbf{C}_2$), 142.5 (2 × $\mathbf{C}_q$), 162.1 (2 × $\mathbf{C}_q$), 185.2 (**C**HO). MS (IS) m/z = 435 (M + 1).

6.1.10. General procedure for compounds ***23–25***

To a solution of aldehyde **20–22** (0.76 mmol) in nitromethane (10 ml) was added to ammonium acetate (0.29 g, 3.82 mmol) and then the mixture was stirred at 120 °C during 4 h. After cooling and dilution with dichloromethane, the mixture was hydrolyzed and extracted. The organic layers

were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude nitrovinyl compound obtained which was used without further purification in the next step. Thus, to a stirred solution of nitro compound in a mixture of isopropanol (30 ml) and chloroform (30 ml) was added at room temperature under inert atmosphere silica gel 230–400 mesh (0.70 g). To this suspension was added portionwise sodium borohydride (0.14 g, 3.82 mmol) and then, the mixture was stirred at room temperature during 12 h. After this time, this mixture was filtered on Celite and filtrate was concentrated in vacuo. The crude compound obtained was used without further purification in the next step. Thus the saturated nitro compound (0.25 g) was dissolved in methanol (4 ml). To this solution was added Raney nickel (0.05 g) and the mixture was hydrogenated (40 psi) in a Parr shaker at 60 °C during 6 h. The catalyst was filtered off and the solvent was removed under reduced pressure. The crude amino derivative was obtained as a yellow oil which was used without purification in the next step. Under an inert atmosphere, the crude amino-derivative was dissolved in dichloromethane (20 ml), pyridine (20 ml) and acetic anhydride (0.22 ml, 2.28 mmol) at 0 °C. The mixture was stirred during 12 h at room temperature before hydrolysis. The aqueous phase was neutralized with saturated sodium hydrogencarbonate and extracted with dichloromethane. The organics layers were dried over anhydrous $MgSO_4$, the solvent was removed under reduced pressure. The products **23–25** were then purified by column chromatography (eluent: ethyl acetate/methanol: 95:5).

*6.1.10.1. 1,4-Bis[3-(2-acetylaminoethyl)-1-methylpyrrolo [3,2-*b*]pyridin-5-yloxy]butane (**23**) (*n = *4).* White solid (16% within four step); m.p. 213–214 °C (pentane); IR (KBr): *ν* 1660 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): *δ* 1.87 (s, 6H, $COCH_3$), 1.90. 2.01 (m, 4H, CH_2CH_2O), 2.90 (t, 4H, *J* = 7.0 Hz, H_1), 3.47 (t, 4H, *J* = 7.0 Hz, $H_{2'}$), 3.74 (s, 6H, NCH_3), 4.41 (sb, 4H, CH_2O), 6.58 (d, 2H, *J* = 8.8 Hz, H_6), 7.13 (s, 2H, H_2), 7.64 (d, 2H, *J* = 8.8 Hz, H_7). ^{13}C-NMR ($CDCl_3$): *δ* 21.6 (2 × $COCH_3$), 23.9 (2 × $C_{1'}$), 26.3 (2 × CH_2CH_2O), 32.1 (2 × NCH_3), 40.6 (2 × $C_{2'}$), 65.7 (2 × OCH_2), 104.5 (2 × CH), 111.6 (2 × C_q), 120.6 (2 × CH), 126.5 (2 × C_q), 129.7 (2 × CH), 142.2 (2 × C_q), 159.5 (2 × C_q), 172.1 (2 × CO). MS (IS) *m/z* = 521 (M + 1). *Anal*. Calc. for $C_{28}H_{36}N_6O_4$: C, 64.60; H, 6.97; N, 16.14. Found: C, 64.30; H, 6.86; N, 15.62.

*6.1.10.2. 1,5-Bis[3-(2-acetylaminoethyl)-1-methylpyrrolo [3,2-*b*]pyridin-5-yloxy]pentane (**24**) (*n = *5).* White solid (13% within four steps); m.p. 203–204 °C; IR (KBr): *ν* 1655 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): *δ* 1.62–1.77 (m, 2H, $CH_2CH_2CH_2CH_2O$), 1.82–2.01 (m, 4H, CH_2CH_2O), 1.90 (s, 6H, $COCH_3$), 2.92 (t, 4H, *J* = 7.0 Hz, $H_{1'}$), 3.50 (t, 4H, *J* = 7.0 Hz, $H_{2'}$), 3.76 (s, 6H, NCH_3), 4.38 (sb, 4H, CH_2O), 6.59 (d, 2H, *J* = 8.8 Hz, H_6), 7.15 (s, 2H, H_2), 7.65 (d, 2H, *J* = 8.8 Hz, H_7). ^{13}C-NMR ($CDCl_3$): *δ* 21.8 (2 × $COCH_3$), 23.2 ($CH_2CH_2CH_2O$), 24.2 (2 × $C_{1'}$), 29.5 (2 × $CH_2CH_2CH_2O$), 32.2 (2 × NCH_3), 40.8 (2 × $C_{2'}$), 66.1 (2 × OCH_2), 104.6 (2 × CH), 111.6 (2 × C_q), 120.7 (2 × CH), 126.7 (2 × C_q), 129.9 (2 × CH), 142.1 (2 × C_q), 159.7 (2 × C_q), 172.1 (2 × CHO). MS (IS) *m/z* = 535 (M + 1), 557 (M + 23). *Anal*. Calc. for $C_{29}H_{38}N_6O_4$: C, 65.15; H, 7.16; N, 15.72. Found: C, 65.12; H, 7.16; N, 15.21.

*6.1.10.3. 1,4-Bis[3-(2-acetylaminoethyl)-1-methylpyrrolo [3,2-*b*]pyridin-5-yloxy]hexane (**25**) (*n = *6).* White solid (10% within four steps); m.p. 179–180 °C (pentane); IR (KBr): *ν* 1640 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): *δ* 1.49–1.65 (m, 4H, $CH_2CH_2CH_2$), 1.73–1.90 (m, 4H, CH_2CH_2O), 1.87 (s, 6H, $COCH_3$), 2.89 (t, 4H, *J* = 7.0 Hz, $H_{1'}$), 3.47 (t, 4H, *J* = 7.0 Hz, $H_{2'}$), 3.72 (s, 6H, NCH_3), 4.31 (sb, 4H, CH_2O), 6.55 (d, 2H, *J* = 8.8 Hz, H_8), 7.12 (s, 2H, H_2), 7.62 (d, 2H, *J* = 8.8 Hz, H_7). ^{13}C-NMR ($CDCl_3$): *δ* 21.8 (2 × $COCH_3$), 23.9 (2 × $CH_2CH_2CH_2O$), 26.1 (2 × $C_{1'}$), 29.3 (2 × CH_2CH_2O), 32.1 (2 × NCH_3), 40.6 (2 × $C_{2'}$), 66.0 (2 × OCH_2), 104.4 (2 × CH), 111.6 (2 × C_q), 120.5 (2 × CH), 126.7 (2 × C_q), 129.7 (2 × CH), 142.1 (2 × C_q), 159.7 (2 × C_q), 172.1 (CO). MS (IS) *m/z* = 549 (M + 1), 571 (M + 23). *Anal*. Calc. for $C_{30}H_{40}N_6O_4$: C, 65.67; H, 7.35; N, 15.32. Found: C, 65.23; H, 7.22; N, 15.09.

*6.1.11. 5-Methoxy-1-methylpyrrolo[2,3-*b*]pyridine (**27**)*

Under an inert atmosphere, copper bromide (1.43 g, 10.00 mmol) was added to a stirred solution of 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (**26**) (0.98 g, 5.00 mmol) in the mixture of *N,N*-dimethylformamide (32 ml) and methanol (20 ml) at room temperature. Sodium methoxide was added dropwise and the mixture was heated at reflux during 2.5 h. The solvent was removed under reduced pressure and the crude was taken up in water, basified with saturated sodium hydrogencarbonate solution and extracted with ethyl acetate. The combined extracts were dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo, the product was purified by flash chromatography on silica gel (eluent: light petroleum/ethyl acetate: 7:3) which was used in the next step as yellow solid. ^{1}H-NMR ($CDCl_3$): *δ* 3.83 (s, 3H, OCH_3), 6.38 (d, 1H, *J* = 2.9 Hz, H_3), 7.28 (d, 1H, *J* = 2.9 Hz, H_2), 7.41 (d, 1H, *J* = 2.6 Hz, H_4), 8.06 (s, 1H, *J* = 2.6 Hz, H_6); ^{13}C-NMR ($CDCl_3$): *δ* 56.9 (CH_3O), 101.1 (C_3), 112. 1 (C_4), 120.4 (C_q), 126.0 (C_2), 134.1 (C_6), 144.4 (C_q), 151.9 (C_q).

Under an inert atmosphere, sodium hydride (60% in oil, 0.23 g, 9.72 mmol) was added to a stirred solution of 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (0.72 g, 4.86 mmol) in *N,N*-dimethylformamide (10 ml) at 0 °C for 30 min. Then the mixture was stirred an additional time (30 min) under continued cooling. Then methyl iodide (0.6 ml, 9.72 mmol) was added dropwise and the mixture was stirred for 12 h, allowing the temperature to increase at room temperature. Then, water was added and the product was extracted with dichloromethane, purified by flash chromatography on silica gel (eluent: light petroleum/ethyl acetate: 9:1) to give 5-methoxy-1-methylpyrrolo[2,3-*b*]pyridine (**27**) (0.51 g, 64% within two steps) as yellow oil; IR (film): *ν* 1590 cm^{-1}; ^{1}H-NMR ($CDCl_3$): *δ* 3.86 (s, 3H, CH_3), 3.88 (s, 3H, CH_3),

6.36 (d, 1H, J = 3.3 Hz, $\mathbf{H}_3$), 7.15 (d, 1H, J = 3.3 Hz, $\mathbf{H}_2$), 7.41 (d, 1H, J = 2.7 Hz, $\mathbf{H}_4$), 8.12 (d, 1H, J = 2.7 Hz, $\mathbf{H}_6$); ^{13}C-NMR ($CDCl_3$): δ 31.8 (N$\mathbf{C}$H$_3$), 56.8 (O$\mathbf{C}$H$_3$), 98.9 ($\mathbf{C}_3$), 111.9 ($\mathbf{C}_4$), 120.6 ($\mathbf{C}_q$), 130.1 ($\mathbf{C}_2$), 133.9 ($\mathbf{C}_6$), 144.0 ($\mathbf{C}_q$), 151.6 ($\mathbf{C}_q$); MS (IS) m/z = 163 (M + 1).

*6.1.12. 5-Hydroxy-1-methylpyrrolo[2,3-*b*]pyridine (**28**)*

Under an inert atmosphere, boron tribromide (17.3 ml 1 M solution in dichloromethane, 17.3 mmol) was added to a stirred solution of **27** (0.7 g, 4.32 mmol) in dichloromethane (10 ml) at 0 °C. After all boron tribromide was added, the mixture was stirred an additional time (1 h) at room temperature. Then the mixture was taken up in water, basified with saturated hydrogenocarbonate solution and extracted with dichloromethane. The combined extracts were dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo, the product was purified by flash chromatography on silica gel (eluent: light petroleum/ethyl acetate: 1:1) to provide **28** (0.54 g, 85%) as a white solid; m.p. 139–140 °C (pentane); IR (KBr): ν 3417 (OH), 2945 (CH) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.86 (s, 3H, NC$\mathbf{H}_3$), 6.31 (d, 1H, J = 3.3 Hz $\mathbf{H}_3$), 7.11 (d, 2H, J = 3.3 Hz, $\mathbf{H}_2$), 7.49 (d, 2H, J = 2.5 Hz, $\mathbf{H}_4$), 8.16 (d, 1H, J = 2.5 Hz, $\mathbf{H}_6$); ^{13}C-NMR ($CDCl_3$): δ 32.3 (N$\mathbf{C}$H$_3$), 99.0 ($\mathbf{C}_3$), 116.5 ($\mathbf{C}_4$), 122.3 ($\mathbf{C}_q$), 130.9 ($\mathbf{C}_2$), 132.6 ($\mathbf{C}_6$), 143.3 ($\mathbf{C}_q$), 148.4 ($\mathbf{C}_q$); MS (IS) m/z = 149 (M + 1), 171 (M + 23).

*6.1.13. General procedure for compounds **29–31***

Under an inert atmosphere, potassium carbonate (0.93 g, 6.75 mmol) was added to a stirred solution of 5-hydroxy-1-methylpyrrolo[2,3-*b*]pyridine (**28**) (0.25 g, 1.69 mmol) in *N,N*-dimethylformamide (10 ml) at room temperature. Alkyl dibromide (6.75 mmol) was added dropwise and the mixture was stirred an additional time (4 h) at room temperature. The solvent was removed under reduced pressure and the crude was taken up in water and extracted with ethyl acetate. The combined extracts were dried over anhydrous $MgSO_4$. The solvent was evaporated and the products **29–31** were purified by column chromatography (eluent: light petroleum/ethyl acetate: 6:4).

*6.1.13.1. 5-(4-Bromobutyloxy)-1-methylpyrrolo[2,3-*b*]pyridine (**29**) (*n = *4).* Colorless oil (88%); IR (film): ν 2970–2945 (CH) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.89–2.19 (m, 4H, C$\mathbf{H}_2$C$\mathbf{H}_2$CH$_2$O), 3.50 (t, 2H, J = 6.6 Hz, C$\mathbf{H}_2$Br), 3.86 (s, 3H, NC$\mathbf{H}_3$), 4.05 (t, 2H, J = 6 Hz, C$\mathbf{H}_2$O), 6.35 (d, 1H, J = 3.4 Hz $\mathbf{H}_3$), 7.15 (d, 1H, J = 3.4 Hz, $\mathbf{H}_2$), 7.40 (d, 1H, J = 2.7 Hz, $\mathbf{H}_4$), 8.09 (d, 1H, J = 2.7 Hz, $\mathbf{H}_6$). ^{13}C-NMR ($CDCl_3$): δ 28.4 (CH$_2$), 29.9 ($\mathbf{C}$H$_2$), 31.8 (N$\mathbf{C}$H$_3$), 33.9 ($\mathbf{C}$H$_2$Br), 68.9 (O$\mathbf{C}$H$_2$), 98.9 ($\mathbf{C}_3$), 113.1 ($\mathbf{C}_4$), 120.8 ($\mathbf{C}_q$), 130.2 ($\mathbf{C}_2$), 134.4 ($\mathbf{C}_6$), 144.5 ($\mathbf{C}_q$), 150.7 ($\mathbf{C}_q$). MS (IS) m/z = 283 (M + 1 for ^{79}Br), m/z = 285 (M + 1 for ^{81}Br).

*6.1.13.2. 5-(4-Bromopentyloxy)-1-methylpyrrolo[2,3-*b*]pyridine (**30**) (*n = *5).* Colorless oil (82%); IR (film): ν 2970–2950 (CH) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.51–1.99 (m, 6H, C$\mathbf{H}_2$C$\mathbf{H}_2$C$\mathbf{H}_2$CH$_2$O), 3.38 (t, 2H, J = 6.7 Hz, C$\mathbf{H}_2$Br), 3.79 (s, 3H, NC$\mathbf{H}_3$), 3.95 (t, 2H, J = 6.3 Hz, C$\mathbf{H}_2$O), 6.30 (d, 1H, J = 3.3 Hz $\mathbf{H}_3$), 7.09 (d, 1H, J = 3.3 Hz, $\mathbf{H}_2$), 7.35 (d, 1H, J = 2.5 Hz, $\mathbf{H}_4$), 8.07 (d, 1H, J = 2.5 Hz, $\mathbf{H}_6$). ^{13}C-NMR ($CDCl_3$): δ 25.2 ($\mathbf{C}$H$_2$), 28.9 ($\mathbf{C}$H$_2$), 31.8 (N$\mathbf{C}$H$_3$), 32.9 ($\mathbf{C}$H$_2$Br), 34.1 ($\mathbf{C}$H$_2$), 69.5 (O$\mathbf{C}$H$_2$), 98.9 ($\mathbf{C}_3$), 113.0 ($\mathbf{C}_4$), 120.7 ($\mathbf{C}_q$), 130.2 ($\mathbf{C}_2$), 134.4 ($\mathbf{C}_6$), 143.9 ($\mathbf{C}_q$), 150.8 ($\mathbf{C}_q$). MS (IS) m/z = 297 (M + 1 for ^{79}Br), m/z = 299 (M + 1 for ^{81}Br).

*6.1.13.3. 5-(4-Bromohexyloxy)-1-methylpyrrolo[2,3-*b*]pyridine (**31**) (*n = *6).* Colorless oil (84%); IR (film): ν 2950–2875 (CH) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.35–1.53 (m, 4H, CH$_2$CH$_2$C$\mathbf{H}_2$C$\mathbf{H}_2$CH$_2$O), 1.60–1.90 (m, 4H, C$\mathbf{H}_2$C$\mathbf{H}_2$CH$_2$CH$_2$CH$_2$O), 3.34 (t, 2H, J = 6.7 Hz, C$\mathbf{H}_2$Br), 3.77 (s, 3H, NC$\mathbf{H}_3$), 3.92 (t, 2H, J = 6.3 Hz, C$\mathbf{H}_2$O), 6.26 (d, 1H, J = 3.4 Hz $\mathbf{H}_3$), 7.06 (d, 1H, J = 3.4 Hz, $\mathbf{H}_2$), 7.32 (d, 1H, J = 2.7 Hz, $\mathbf{H}_4$), 8.02 (d, 1H, J = 2.7 Hz, $\mathbf{H}_6$). ^{13}C-NMR ($CDCl_3$): δ 25.7 ($\mathbf{C}$H$_2$), 28.3 ($\mathbf{C}$H$_2$), 29.6 ($\mathbf{C}$H$_2$), 31.8 (N$\mathbf{C}$H$_3$), 33.1 ($\mathbf{C}$H$_2$), 34.2 ($\mathbf{C}$H$_2$Br), 69.7 (O$\mathbf{C}$H$_2$), 98.9 ($\mathbf{C}_3$), 113.0 ($\mathbf{C}_4$), 120.7 ($\mathbf{C}_q$), 130.1 ($\mathbf{C}_2$), 134.3 ($\mathbf{C}_6$), 143.9 ($\mathbf{C}_q$), 150.8 ($\mathbf{C}_q$). MS (IS) m/z = 311 (M + 1 for ^{79}Br), m/z = 313 (M + 1 for ^{81}Br).

*6.1.14. General procedure for compounds **32–34***

Under an inert atmosphere, potassium carbonate (0.98 g, 6.77 mmol) was added to a stirred solution of 5-bromoalkyloxy-1-methylpyrrolo[2,3-*b*]pyridine (**29–31**) (1.41 mmol) in *N,N*-dimethylformamide (20 ml) at room temperature. 5-Hydroxy-1-methylpyrrolo[2,3-*b*]pyridine (**28**) (0.25 g, 1.69 mmol) was then added dropwise and the mixture was stirred an additional time (6 h) at 80 °C. The solvent was removed under reduced pressure and the crude was taken up in water and extracted with ethyl acetate. The combined extracts were dried over anhydrous $MgSO_4$. The solvent was evaporated and the products **32–34** were purified by column chromatography (eluent: light petroleum/ethyl acetate: 6:4).

*6.1.14.1. 1,4-Bis[1-methylpyrrolo[2,3-*b*]pyridin-5-yloxy]butane (**32**) (*n = *4).* White solid (99%); m.p. 134–135 °C (pentane); IR (KBr): ν 2960–2885 (CH) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.02 (sb, 4H, C$\mathbf{H}_2$CH$_2$O), 3.84 (s, 6H, NC$\mathbf{H}_3$), 4.09 (sb, 4H, C$\mathbf{H}_2$O), 6.34 (d, 2H, J = 3.3 Hz $\mathbf{H}_3$), 7.13 (d, 2H, J = 3.3 Hz, $\mathbf{H}_2$), 7.42 (d, 2H, J = 2.6 Hz, $\mathbf{H}_4$), 8.12 (d, 1H, J = 2.6 Hz, $\mathbf{H}_6$). ^{13}C-NMR ($CDCl_3$): δ 26.5 (2 × C$\mathbf{H}_2$), 31.8 (2 × N$\mathbf{C}$H$_3$), 69.5 (2 × O$\mathbf{C}$H$_2$), 99.1 (2 × $\mathbf{C}_3$), 113.2 (2 × $\mathbf{C}_4$), 120.8 (2 × $\mathbf{C}_q$), 130.2 (2 × $\mathbf{C}_2$), 134.3 (2 × $\mathbf{C}_6$), 143.9 (2 × $\mathbf{C}_q$), 150.8 (2 × $\mathbf{C}_q$). MS (IS) m/z = 351 (M + 1).

*6.1.14.2. 1,5-Bis[1-methylpyrrolo[2,3-*b*]pyridin-5-yloxy]pentane (**33**) (*n = *5).* White solid (99%); m.p. 92–93 °C (pentane); IR (KBr): ν 2960–2860 (CH) cm^{-1}; ^{1}H-NMR ($CDCl_3$: δ 1.56–1.78 (m, 2H, C$\mathbf{H}_2$CH$_2$CH$_2$O), 1.79–1.96 (m, 4H, CH$_2$C$\mathbf{H}_2$CH$_2$O), 3.81 (s, 6H, NC$\mathbf{H}_3$), 4.00 (t, 4H, J = 6.2 Hz, C$\mathbf{H}_2$O), 6.32 (d, 2H, J = 3.3 Hz $\mathbf{H}_3$), 7.10 (d, 2H, J = 3.3 Hz, $\mathbf{H}_2$), 7.41 (d, 2H, J = 2.6 Hz, $\mathbf{H}_4$), 8.11 (d, 2H, J = 2.6 Hz, $\mathbf{H}_6$); ^{13}C-NMR ($CDCl_3$): δ 23.2 (C$\mathbf{H}_2$CH$_2$CH$_2$O), 29.5 (2 × CH$_2$C$\mathbf{H}_2$CH$_2$O), 31.8 (2 × N$\mathbf{C}$H$_3$), 69.6 (2 ×

O**C**H_2), 99.0 (2 × **C**$_3$), 112.9 (2 × **C**$_4$), 120.7 (2 × **C**$_q$), 130.1 (2 × **C**$_2$), 134.3 (2 × **C**$_6$), 143.9 (2 × **C**$_q$), 150.8 (2 × **C**$_q$). MS (IS) *m/z* = 365 (M + 1).

*6.1.14.3. 1,6-Bis[1-methylpyrrolo[2,3-*b*]pyridin-5-yloxy] hexane (**34**) (*n *= 6).* White solid (71%); m.p. 106–108 °C (pentane); IR (KBr): *ν* 2970–2875 (CH) cm^{-1}; ^{1}H-NMR ($CDCl_3$): *δ* 1.49–1.62 (m, 4H, C**H**$_2$CH_2CH_2O), 1.69–1.85 (m, 4H, CH_2C**H**$_2$CH_2O), 3.80 (s, 6H, NC**H**$_3$), 3.97 (t, 4H, *J* = 6.3 Hz, C**H**$_2$O), 6.32 (d, 2H, *J* = 3.3 Hz **H**$_3$), 7.07 (d, 2H, *J* = 3.3 Hz, **H**$_2$), 7.38 (d, 2H, *J* = 2.6 Hz, **H**$_4$), 8.13 (d, 1H, *J* = 2.6 Hz, **H**$_6$); ^{13}C-NMR ($CDCl_3$): *δ* 26.3 (2 × **C**H_2), 29.7 (2 × **C**H_2), 31.7 (2 × N**C**H_3), 69.7 (2 × O**C**H_2), 98.9 (2 × **C**$_3$), 113 (2 × **C**$_4$), 120.7 (2 × **C**$_q$), 130.1 (2 × **C**$_2$), 134.4 (2 × **C**$_6$), 143.9 (2 × **C**$_q$), 150.9 (2 × **C**$_q$). MS (IS) *m/z* = 379 (M + 1).

*6.1.15. General procedure of compounds **35–37***

Under an inert atmosphere, phosphorus oxychloride (2.65 ml, 28.40 mmol) was added to *N,N*-dimethylformamide (20 ml) at 0 °C. After 10 min of stirring, a solution of dimers **32–34** (1.42 mmol) in *N,N*-dimethylformamide (10 ml) was added. The reaction was stirred for 30 min at 0 °C, then heated at room temperature during 3 h. Then the solvent was removed under reduced pressure and the residue diluted with water. After extraction with ethyl acetate, the organic layers were dried over anhydrous $MgSO_4$ and evaporated in vacuo. The products **35–37** were purified by column chromatography (eluent: ethyl acetate).

*6.1.15.1. 1,4-Bis[3-formyl-1-methylpyrrolo[2,3-*b*]pyridin-5-yloxy]butane (**35**) (*n *= 4).* Yellow solid (90%); m.p. 225–226 °C (pentane); IR (KBr): *ν* 1660 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): *δ* 2.01–2.09 (m, 4H, C**H**$_2$CH_2O), 3.94 (s, 6H, NC**H**$_3$), 4.16 (sb, 4H, C**H**$_2$O), 7.78 (s, 2H, **H**$_2$), 8.05 (d, 2H, *J* = 2.8 Hz, **H**$_4$), 8.17 (d, 2H, *J* = 2.8 Hz, **H**$_6$), 9.91 (s, 2H, C**H**O). ^{13}C-NMR ($CDCl_3$): *δ* 26.4 (2 × **C**H_2CH_2O), 32.7 (2 × N**C**H_3), 69.1 (2 × O**C**H_2), 113.3 (2 × **C**$_4$), 116.3 (2 × **C**$_q$), 118.1 (2 × **C**$_q$), 137.1 (2 × **C**$_2$), 139.4 (2 × **C**$_6$), 144.2 (2 × **C**$_q$), 153.4 (2 × **C**$_q$), 184.9 (2 × **C**HO). MS (IS) *m/z* = 407 (M + 1), 429 (M + 23).

*6.1.15.2. 1,4-Bis[3-formyl-1-methylpyrrolo[2,3-*b*]pyridin-5-yloxy]pentane (**36**) (*n *= 5).* White solid (95%); m.p. 162–163 °C (pentane); IR (KBr): *ν* 1660 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): *δ* 1.63–1.82 (m, 2H, C**H**$_2$CH_2CH_2O), 1.85–2.02 (m, 4H, CH_2C**H**$_2$CH_2O), 3.94 (s, 6H, NC**H**$_3$), 4.11 (t, 4H, *J* = 6.3 Hz, C**H**$_2$O), 7.78 (s, 2H, **H**$_2$), 8.04 (d, 2H, *J* = 2.7 Hz, **H**$_4$), 8.17 (d, 1H, *J* = 2.7 Hz, **H**$_6$), 9.91 (s, 2H, CHO). ^{13}C-NMR ($CDCl_3$): *δ* 23.2 (**C**H_2CH_2CH_2O), 29.4 (2 × CH_2**C**H_2CH_2O), 32.7 (2 × N**C**H_3), 69.3 (2 × O**C**H_2), 113.3 (2 × **C**$_4$), 116.3 (2 × **C**$_q$), 118.1 (2 × **C**$_q$), 137.1 (2 × **C**$_2$), 139.4 (2 × **C**$_6$), 144.2 (2 × **C**$_q$), 153.4 (2 × **C**$_q$), 184.9 (2 × **C**HO). MS (IS) *m/z* = 421 (M + 1), 443 (M + 23).

*6.1.15.3. 1,4-Bis[3-formyl-1-methylpyrrolo[2,3-*b*]pyridin-5-yloxy]hexane (**37**) (*n *= 6).* White solid (84%); m.p. 166–167 °C (pentane); IR (KBr): *ν* 1620 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): *δ* 1.48-1.61 (m, 4H, C**H**$_2$CH_2CH_2O), 1.70–1.91 (m, 4H, CH_2C**H**$_2$CH_2O), 3.91 (s, 6H, NC**H**$_3$), 4.06 (t, 4H, *J* = 6.1 Hz, C**H**$_2$O), 7.74 (s, 2H, **H**$_2$), 8.01 (d, 2H, *J* = 2.8 Hz, **H**$_4$), 8.15 (d, 2H, *J* = 2.8 Hz, **H**$_6$), 9.89 (s, 2H, C**H**O). ^{13}C-NMR ($CDCl_3$): *δ* 26.3 (2 × **C**H_2CH_2CH_2O), 29.6 (2 × **C**H_2CH_2O), 32.6 (2 × N**C**H_3), 69.4 (2 × O**C**H_2), 113.3 (2 × **C**$_4$), 116.3 (2 × **C**$_q$), 118.1 (2 × **C**$_q$), 137.1 (2 × **C**$_2$), 139.3 (2 × **C**$_6$), 144.2 (2 × **C**$_q$), 153.4 (2 × **C**$_q$), 184.8 (**C**HO). MS (IS) *m/z* = 435 (M + 1), 457 (M + 23).

*6.1.16. General procedure of compounds **38–40***

To a solution of aldehyde **35–37** (1.72 mmol) in nitromethane (30 ml) was added to ammonium acetate (0.66 g, 8.61 mmol) and then the mixture was stirred at 120 °C during 4 h. After cooling and dilution with dichloromethane, the mixture was hydrolyzed and extracted. The organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude nitrovinyl compound obtained which was used without further purification in the next step. Thus, to a stirred solution of nitro compound in a mixture of isopropanol (30 ml) and chloroform (50 ml) was added at room temperature under inert atmosphere silica gel 230–400 mesh (0.65 g). To this suspension was added portionwise sodium borohydride (0.32 g, 8.61 mmol) and then, the mixture was stirred at room temperature during 12 h. After this time, this mixture was filtered on Celite and filtrate was concentrated in vacuo. The crude compound obtained was used without further purification in the next step. Thus the saturated nitro compound (0.75 g) was dissolved in methanol (4 ml). To this solution was added Raney nickel (0.015 g) and the mixture was hydrogenated (40 psi) in a Parr shaker at 60 °C during 6 h. The catalyst was filtered off and the solvent was removed under reduced pressure. The crude amino derivative was obtained as a yellow oil which was used without purification in the next step. Under an inert atmosphere, the crude amino-derivative was dissolved in dichloromethane (20 ml), pyridine (20 ml) and acetic anhydride (0.49 ml, 3.48 mmol) at 0 °C. The mixture was stirred during 12 h at room temperature before hydrolysis. The aqueous phase was neutralized with saturated hydrogenocarbonate and extracted with dichloromethane. The organics layers were dried over anhydrous $MgSO_4$, the solvent was removed under reduced pressure. The products **38–40** were then purified by column chromatography (eluent: ethyl acetate/methanol: 95:5).

*6.1.16.1. 1,4-Bis[3-(2-acetylaminoethyl)-1-methylpyrrolo [2,3-*b*]pyridin-5-yloxy]butane (**38**) (*n *= 4).* Colorless oil (5% within four steps); IR (film): *ν* 1620 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): *δ* 1.46–1.96 (m, 4H, C**H**$_2$CH_2O), 1.94 (s, 6H, COC**H**$_3$), 2.92 (t, 4H, *J* = 7.1 Hz, **H**$_{1'}$), 3.45 (t, 4H, *J* = 7.1 Hz, H$_{2'}$), 3.80 (s, 6H, NC**H**$_3$), 4.12 (t, 4H, *J* = 6.2 Hz, C**H**$_2$O), 7.14 (s, 2H, **H**$_2$), 7.60 (d, 2H, *J* = 2.6 Hz, **H**$_4$), 7.98 (d, 2H, *J* = 2.6 Hz, **H**$_6$). ^{13}C-NMR ($CDCl_3$): *δ* 21.7 (2 × $COCH_3$), 25.3 (2 × **C**H_2CH_2O), 30.2 (2 × N**C**H_3), 41.2 (2 × **C**$_{2'}$), 69.5 (2 × O**C**H_2), 109.6 (2 × **C**$_q$), 112.1 (2 × **C**H), 121.3 (2 × **C**$_q$), 128.7 (2 × **C**H), 133.2 (2 × **C**H), 143.8 (2 × **C**$_q$), 150.9 (2 × **C**$_q$), 172.5 (2 × **C**O). MS (IS) *m/z* = 521 (M + 1).

*6.1.16.2. 1,4-Bis[3-(2-acetylaminoethyl)-1-methylpyrrolo [2,3-*b*]pyridin-5-yloxy]pentane (**39**) (*n = *5).* Colorless oil (5% within four steps); IR (film): *ν* 1630 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): *δ* 1.38–1.98 (m, 2H, C**H**$_2$C**H**$_2$CH$_2$CH$_2$O), 1.92 (s, 6H, COC**H**$_3$), 2.89 (t, 4H, *J* = 7.2 Hz, **H**$_{2'}$), 3.78 (s, 6H, NC**H**$_3$), 4.10 (t, 4H, *J* = 6.2 Hz, C**H**$_2$O), 7.12 (s, 2H, **H**$_2$), 7.55 (d, 2H, *J* = 2.6 Hz, **H**$_4$), 7.92 (d, 1H, *J* = 2.6 Hz, **H**$_6$). ^{13}C-NMR ($CDCl_3$): *δ* 21.8 (2 × COCH$_3$), 23.6 (**C**H$_2$CH$_2$CH$_2$O), 25.3 (2 × CH$_2$**C**H$_2$CH$_2$O), 29.6 (2 × **C**$_{1'}$), 30.5 (2 × N**C**H$_3$), 41.1 (2 × C$_{2'}$), 69.5 (2 × O**C**H$_2$), 109.6 (2 × **C**$_q$), 112.1 (2 × **C**H), 121.3 (2 × **C**$_q$), 128.7 (2 × **C**H), 133.2 (2 × **C**H), 143.6 (2 × **C**$_q$), 150.9 (2 × **C**$_q$), 172.5 (2 × **C**HO). MS (IS) *m/z* = 535 (M + 1), 557 (M + 23).

*6.1.16.3. 1,4-Bis[3-(2-acetylaminoethyl)-1-methylpyrrolo [2,3-*b*]pyridin-5-yloxy]hexane (**40**) (*n = *6).* White solid (14% within four steps); m.p. 176–180 °C (pentane); IR (KBr): *ν* 1640 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): *δ* 1.38–1.70 (m, 4H, C**H**$_2$CH$_2$CH$_2$), 1.40–1.93 (m, 4H, C**H**$_2$CH$_2$O), 1.91 (s, 6H, COC**H**$_3$), 2.86 (t, 4H, *J* = 7.2 Hz, **H**$_{1'}$), 3.43 (t, 4H, *J* = 7.2 Hz, **H**$_{2'}$), 3.78 (s, 6H, NC**H**$_3$), 4.10 (t, 4H, *J* = 6.2 Hz, C**H**$_2$O), 7.15 (s, 2H, **H**$_2$), 7.58 (d, 2H, *J* = 2.6 Hz, **H**$_4$), 7.96 (d, 2H, *J* = 2.6 Hz, **H**$_6$). ^{13}C-NMR ($CDCl_3$): *δ* 21.8 (2 × CO**C**H$_3$), 23.8 (2 × **C**H$_2$CH$_2$CH$_2$O), 25.3 (2 × **C**H$_2$CH$_2$O), 29.6 (2 × C$_{1'}$), 30.5 (2 × N**C**H$_3$), 41.0 (2 × C$_{2'}$), 69.5 (2 × O**C**H$_2$), 109.6 (2 × **C**$_q$), 112.1 (2 × **C**$_4$), 121.3 (2 × **C**$_q$), 128.7 (2 × **C**$_2$), 133.2 (2 × **C**$_6$), 143.8 (2 × **C**$_q$), 150.9 (2 × **C**$_q$), 172.5 (**C**O). MS (IS) *m/z* = 549 (M + 1), 571 (M + 23). *Anal*. Calc. for $C_{30}H_{40}N_6O_4$: C, 65.67; H, 7.35; N, 15.32. Found: C, 65.01; H, 7.72; N, 14.67.

6.1. Pharmacology

6.1.1. Reagents and chemicals

2-[^{125}I]-Iodomelatonin (2200 Ci $mmol^{-1}$) was purchased from NEN (Boston, MA). Other drugs and chemicals were purchased from Sigma-Aldrich (Saint Quentin, France).

6.1.2. Cell culture

HEK (provided by A.D. Strosberg, Paris, France) and CHO cell lines stably expressing the human melatonin MT_1 or MT_2 receptors were grown in DMEM medium supplemented with 10% fetal calf serum, 2 mM glutamine, 100 IU ml^{-1} penicillin and 100 μg ml^{-1} streptomycin. Grown at confluence at 37 °C (95%O_2/5%CO_2), they were harvested in PBS containing EDTA 2 mM and centrifuged at 1000 × *g* for 5 min (4 °C). The resulting pellet was suspended in Tris 5 mM (pH 7.5), containing EDTA 2 mM and homogenized using a Kinematica polytron. The homogenate was then centrifuged (95 000 × *g*, 30 min, 4 °C) and the resulting pellet suspended in 75 mM Tris (pH 7.5), 12.5 mM $MgCl_2$ and 2 mM EDTA. Aliquots of membrane preparations were stored at –80 °C until use.

6.1.3. Binding assays

2-[^{125}I]-Iodomelatonin binding assay conditions were essentially as previously described (Audinot, 2003). Briefly, binding was initiated by addition of membrane preparations from stable transfected HEK or CHO cells diluted in binding buffer (50 mM Tris–HCl buffer, pH 7.4 containing 5 mM $MgCl_2$) to 2-[^{125}I]-iodomelatonin (25 or 200 pM nM for MT_1 and MT_2 receptors, respectively, due to a MT_1/MT_2 ratio of approximately 0.125 for cold 2-iodo-melatonin) and the tested drug. Nonspecific binding was defined in the presence of 1 μM melatonin. After a 120 min incubation at 37 °C, reaction was stopped by rapid filtration through GF/B filters presoaked in 0.5% (v/v) polyethylenimine. Filters were washed three times with 1 ml of ice-cold 50 mM Tris–HCl buffer, pH 7.4.

Data from the dose–response curves (seven concentrations in duplicate) were analyzed using the program PRISM (Graph Pad Software Inc., San Diego, CA) to yield IC_{50} (inhibitory concentration 50). Results are expressed as $K_i = IC_{50}/1 + ([L]/K_D)$, where [*L*] is the concentration of radioligand used in the assay and K_D, the dissociation constant of the radioligand characterizing the membrane preparation.

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