SYNTHESIS OF *N*-SUBSTITUTED IMIDOETHYL-3-AMINOMETHYL-2,3-DIHYDRO-1,4-DIOXINO-[2,3-*b*]PYRIDINES

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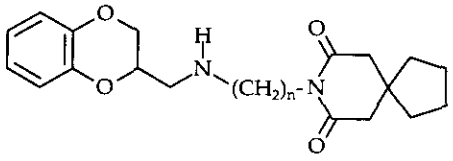
Abstract - The multistep synthesis of *N*-substituted imidoethyl-3-aminomethyl-2,3-dihydro-1,4-dioxino[2,3-*b*]pyridines using as a final step the Mitsunobu reaction between aliphatic alcohols and imides is described.

In 1981, the 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) was discovered to be a potent centrally active 5-HT (serotonin, 5-hydroxytryptamine) receptor agonist,[1] and subsequently, selectively a 5-HT_{1A} receptor agonist.[2] The existence of this selective ligand has led to an understanding of the 5-HT_{1A} receptor agonists which as well as play an important role in the control of anxiety and depression without hallucinogenic activity[3] and in the regulation of sympathetic nerve activity which may regulate blood pressure.[4]

Recent investigations[5,6] have shown that some 2,3-dihydro-1,4-benzodioxines, such as MDL 72832 and MDL 73005, are excellent binding agents with high affinity to 5-HT_{1A} receptors (Figure 1).

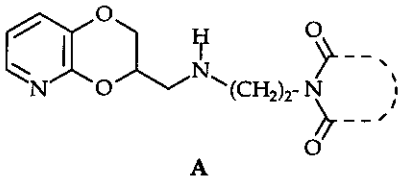
Figure 1



n = 4 , MDL 72832
n = 2 , MDL 73005

As part of our work on the preparation of products liable to affect the central nervous system (CNS), [7-10] we have directed now our research towards the elaboration of dihydropyridinic isosters of MDL 73005 which may show a high affinity and selectivity for 5-HT_{1A} receptors (Figure 2).

Figure 2



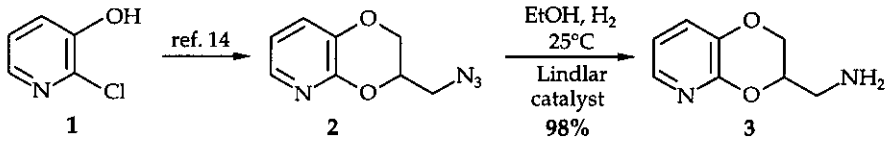
A

The substitution of nitrogen for a carbon in the benzene ring is often compatible with retention of biological activity even in the presence of the unshared basic pair of electrons in pyridine. There are, however, cases where the heterocyclic forms are an indispensable part of pharmacophore.

Although a few papers[11-13] report preparation in low yield of substituted 2,3-dihydro-1,4-dioxino-[2,3-*b*]pyridines on aromatic ring, no description of *N*-substituted 3-aminomethyldioxinopyridines exists, apart from our recent publication.[14]

To prepare MDL 73005 pyridinic analogues **A** (Figure 2), the first step consisted in synthesis of 3-(2,3-dihydro-1,4-dioxino[2,3-*b*]pyridin)ylmethanamine (**3**) (Scheme 1).

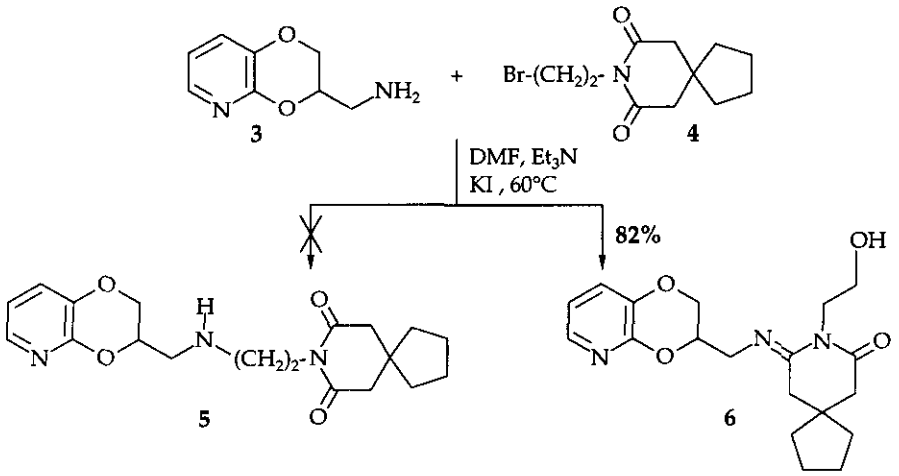
Scheme 1



1 **2** **3**

This primary amine (**3**) was generated in 98% yield by catalytic hydrogenation from 3-(2,3-dihydro-1,4-dioxino[2,3-*b*]pyridin)ylmethylazide (**2**), which was obtained from 2-chloro-3-pyridinol (**1**).[14] Direct alkylation of amine (**3**), from 8-(2-bromoethyl)-8-azaspiro[4.5]decane-7,9-dione (**4**),[15] triethylamine, potassium iodide in *N,N*-dimethylformamide as a solvent, did not afford the expected derivative (**5**) but gave, in 82% yield, iminoamide (**6**) (Scheme 2). An oxazolinium ion is probably involved in this reaction which applies to all primary amines and 2-bromoethylglutarimides.[15]

Scheme 2



After this failure, a second synthetic approach was adopted for the preparation of the desired dioxinopyridines **A**, without using direct *N*-alkylation, it way consisted in three steps. The first one was a ring opening of the epoxide (**7**) with ethanolamine or its derivatives; this was followed by a cyclisation which gave the dioxinopyridine ring. Finally a Mitsunobu reaction between alcohol and imides might led to the expected compounds (Scheme 3).

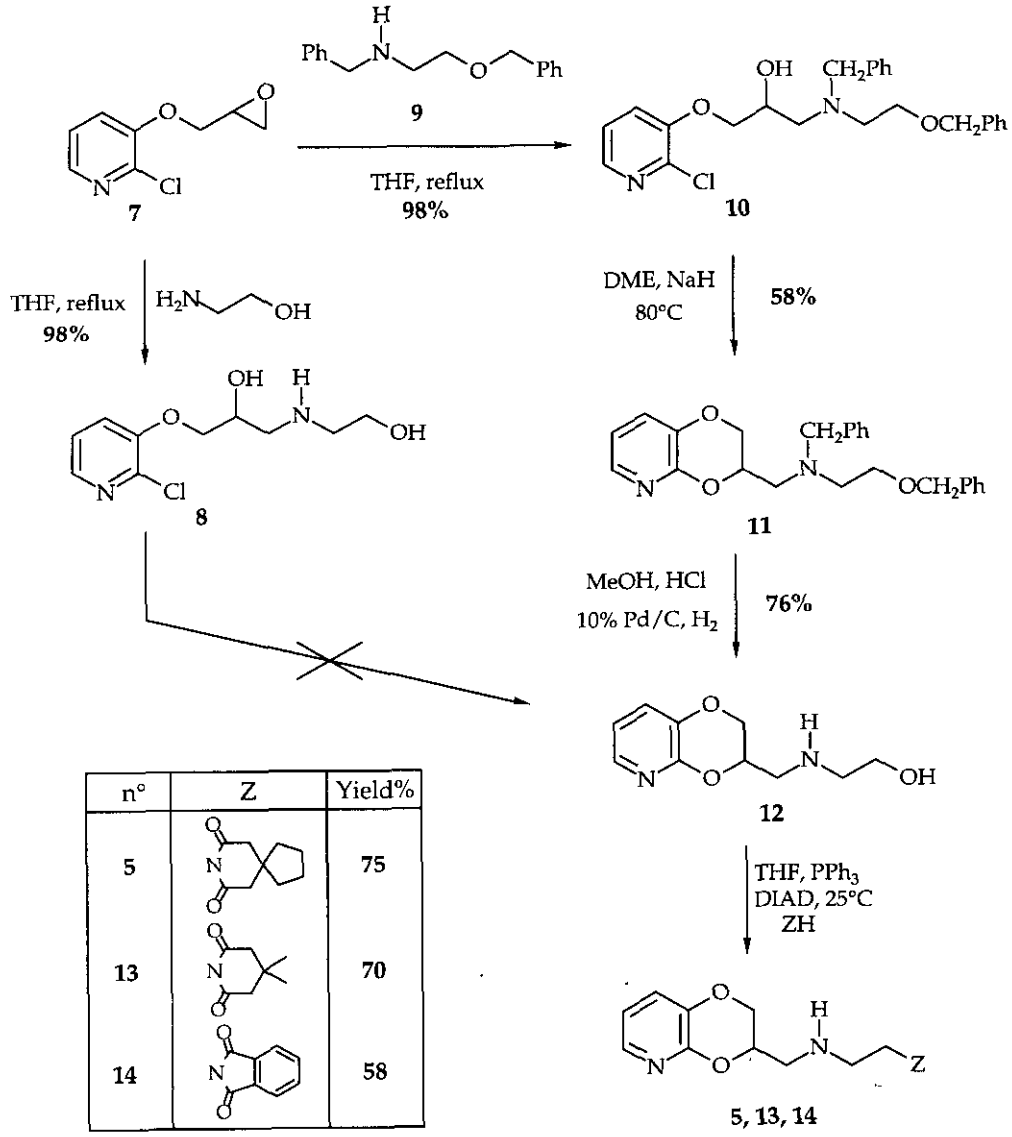
After ring opening of the 2-chloro-3-(oxiranylmethoxy)pyridine (**7**)[14] with ethanolamine in boiling tetrahydrofuran, the obtained alcohol (**8**) in 98% yield could not be cyclized by using sodium hydride in ethylene glycol dimethyl ether (DME). So the method had to be used with an ethanolamine derivative, *N,O*-dibenzylethanolamine.

The expected benzyl derivative (**9**) was obtained by treatment of commercial *N*-benzylethanolamine with sodium hydride and benzyl chloride in tetrahydrofuran, in 86% yield. Epoxide (**7**), obtained from 2-chloro-3-pyridinol (**1**),[14] was opened by compound (**9**) in boiling THF and provided the alcohol (**10**) in 98% yield (Scheme 3). This derivative, which has only one free nucleophile function group, generated the expected dioxinopyridine (**11**) by basic cyclization using sodium hydride in ethylene glycol dimethyl ether in 58% yield. The next step was debenzylation using catalytic hydrogenation in methanol with a few drops of concentrated hydrochloride acid. The desired aminoalcohol (**12**) was obtained in 76% yield.

The relatively low yield and long reaction time (36 hours) are due to difficulties in carrying out *O*-debenzylation in the presence of an amino group, as explained by Bartsch *et al.*[16] The final step, which provided the expected

MDL 73005 analogues, was a Mitsunobu[17,18] reaction between alcohol (**12**) and selected imides in presence of an equimolar quantity of triphenylphosphine and diisopropyl azodicarboxylate. The compounds (**5**,**13** and **14**) were collected in 75, 70 and 58% yield respectively.

Scheme 3



n°	Z	Yield%
5		75
13		70
14		58

Difficulties in carrying out a direct *N*-alkylation of the amine (**3**) were overcome by using the Mitsunobu reaction between alcohol (**12**) and varied imides to obtain the MDL 73005 analogues (**5**,**13** and **14**). These results are highly promising because they afford an access to new compounds which may be active on central nervous system.

EXPERIMENTAL SECTION

Ethers (ether, ethylene glycol dimethyl ether, tetrahydrofuran) were distilled from sodium/benzophenon, chloride solvents and *N,N*-dimethylformamide from phosphorus anhydride, and amines from potassium hydroxide. Analytical thin layer chromatography (tlc) was performed on silica gel (Merck $60F_{254}$). Column chromatography used silica gel Kieselgel (70-230 mesh for gravity columns and 230-400 mesh for flash columns). ^1H Nmr spectra were recorded on a BRUKER AM 300WB spectrometer. The coupling constants were recorded in hertz (Hz) and the chemical shifts were reported in parts per million (δ, ppm) downfield from tetramethylsilane (TMS) which was used as internal standard. Melting points, determined on a Köfler hot-stage apparatus, were uncorrected. Infrared spectra were obtained with a PERKIN ELMER 297 spectrophotometer. Mass spectra were recorded on a R-10-10-C NERMAG apparatus.

3-(2,3-Dihydro-1,4-dioxino[2,3-b]pyridin)ylmethanamine (**3**) **:** Azide (**2**)[14] (0.500 g, 2.6 mmol) in dry ethanol (16 ml) was stirred with Lindlar palladium (0.080 g) in Parr apparatus under hydrogen pressure (30 psi). After 4 h, palladium was filtered and washed with ethanol. The solvent was evaporated and a column chromatography (eluent : $MeOH/CH_2Cl_2$: 1/9) afforded the product as an oil (0.425 g) in 98% yield; ir (film) 3500-3100 (NH), 1185 (C-O-C) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 1.60 (s, 2H, $\mathbf{NH_2}$), 3.05 (d, 2H, $\mathbf{CH_2}$-NH_2, J = 5.7), 4.02 (dd, 1H, O-$\mathbf{CH_2}$-CH, J = 7.6, J = 11.4), 4.26-4.36 (m, 2H, O-$\mathbf{CH_2}$-$\mathbf{CH}$), 6.86 (dd, 1H, $\mathbf{H_\beta}$, J = 4.4, J = 7.6), 7.18 (dd, 1H, $\mathbf{H_\gamma}$, J = 1.3, J = 7.6), 7.82 (dd, 1H, $\mathbf{H_\alpha}$, J = 1.3, J = 4.4); ms (CI/NH_3) *m/z* : 167 (M^++1); *Anal.* Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found : C, 57.65; H, 5.88;N, 16.71.

9-[(2,3-Dihydro-1,4-dioxino[2,3-b]pyridin)-3-ylmethylimino]-8-(2-hydroxyethyl)-8-azaspiro[4.5]decan-7-one (**6**) **:** To a solution of amine (**3**) (1.660 g, 10 mmol) in dry *N,N*-dimethylformamide (DMF) (15 ml) were added bromide derivative (**4**) (3.290 g, 12 mmol) in DMF (4 ml), triethylamine (4.2 ml, 30 mmol) and potassium iodide (0.330 g, 2 mmol). The mixture was heated to 60°C until total consumption of amine (**3**).

After hydrolysis and extraction with methylene chloride (CH_2Cl_2), the organic layers were washed with saturated sodium hydrogen carbonate solution. The product was purified by silica gel column chromatography (eluent : Ether/CH_2Cl_2/ MeOH : 48/48/4) to give an oil (2.944 g) in 82% yield; ir (film) 3400 (OH), 1665 (C=O), 1630 (CN) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 1.39-1.78 (m, 8H, C-(**CH_2**)$_4$), 2.56 (s, 2H, N=C-**CH_2**), 2.57 (s, 2H, CO-**CH_2**), 3.57 (dd, 1H, O-CH-**CH_2**-N, J = 7.1, J = 14.2), 3.70 (dd, 1H, O-CH-**CH_2**-N, J = 4.7, J = 14.2), 3.76 (t, 2H, N-CH_2-**CH_2**-OH, J = 4.7), 4.07-4.22 (m, 3H, N-**CH_2**-CH_2-OH, O-**CH_2**-CH), 4.37 (dd, 1H, O-**CH_2**-CH, J = 2.2, J = 11.6), 4.54-4.62 (m, 1H, O-**CH**-CH_2), 6.87 (dd, 1H, **H_β**, J = 4.7, J = 7.7), 7.19 (dd, 1H, **H_γ**, J = 1.2, J = 7.7), 7.83 (dd, 1H, **H_α**, J = 1.2, J = 4.7); ms (CI/NH_3) *m/z* : 360 (M^++1); *Anal.* Calcd for $C_{19}H_{25}N_3O_4$: C, 63.49; H, 7.01; N, 11.69. Found : C, 63.71; H, 7.24; N, 11.92.

1-(2-Chloro-3-pyridinyloxy)-3-[(2-hydroxyethyl)amino]-2-propanol **(8)** : Epoxide **(7)**[14] (0.300 g, 1.62 mmol) and ethanolamine (0.500 g, 8.09 mmol) were heated in boiling tetrahydrofuran (THF) (8 ml) for 6 h. After total reaction, THF and ethanolamine excess were evaporated, giving a white powder (0.391 g) in 98% yield which was used in the next step without purification. The compound **(8)** was washed with ether to give an analytical sample; mp 127-128°C; ir (KBr) 3600-3200 (NH and OH), 1285 and 1200 (C-O-C) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 2.57-2.72 (m, 5H, NH, **CH_2**-NH-**CH_2**), 3.43 (t, 2H, **CH_2**OH, J = 5.7), 3.20 (m, 1H, **OH**), 3.85-3.94 (m, 1H, **CH**-OH), 3.98-4.06 (m, 2H, O-**CH_2**-CH-OH), 7.34 (dd, 1H, **H_β**, J = 8.1, J = 4.7), 7.54 (d, 1H, **H_γ**,J = 8.1), 7.93 (d, 1H, **H_α**, J = 4.7); ms (CI/NH_3) *m/z* : 247 (M^++1); *Anal.* Calcd for $C_{10}H_{15}N_2O_3Cl$: C, 48.67; H, 6.13; N, 11.36; Cl, 14.37. Found : C, 48.89; H, 6.31; N, 11.57; Cl, 14.58.

N,O-Dibenzylethanolamine **(9)** : Sodium hydride (2.110 g, 60% dispersion in mineral oil, 44 mmol) was added slowly to a solution of *N*-benzylethanolamine (6.050 g, 40 mmol) in dry THF (40 ml). When the mixture was refluxed, benzyl chloride (5.070 g, 40 mmol) was added dropwise. The reactional solution was stirred 3 h, then hydrolyzed and the crude product, which was extracted with CH_2Cl_2, was purified by column chromatography (eluent : Ether) to give an oil (8.305 g) in 86% yield; ir (film) 3500-3200 (NH) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 1.96 (s, 1H, **NH**), 2.83 (m, 2H, CH_2-**CH_2**-NH), 3.59 (m, 2H, CH_2-**CH_2**-O), 3.78 (s, 2H, Ph-**CH_2**-N), 4.50 (s, 2H, Ph-**CH_2**-O), 7.18-7.37 (m, 10H, **H_{arom}**); *Anal.* Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found : C, 79.42; H, 7.69; N, 5.59.

1-(2-Chloro-3-pyridinyloxy)-3-[N-benzyl-N-(2-benzyloxyethyl)amino]-2-propanol (**10**) : Amine (**9**) (4.840 g, 20.1 mmol) in THF (20 ml) was added dropwise to a solution of epoxide (**7**) (1.240 g, 6.7 mmol) in dry THF (20 ml). The mixture was heated to 60°C for 24 h. After the entire reaction, the mixture was cooled at room temperature, then hydrolyzed and the product was extracted with CH_2Cl_2 and the organic layers were washed with saturated sodium hydrogen carbonate solution. Solvents were removed and a flash column purification (eluent : Ether/CH_2Cl_2 : 1/1) gave the required derivative as an oil (2.794 g) in 98% yield; ir (film) 3500-3200 (OH), 1285 and 1200 (C-O-C) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 2.69-2.97 (m, 4H, **CH_2**-N-**CH_2**), 3.61-3.64 (m, 2H, **CH_2**-O-Bn), 3.67 (d, 1H, N-**CH_2**-Ph, J = 13.4), 3.82 (d, 1H, N-**CH_2**-Ph, J = 13.4), 3.94-4.06 (m, 3H, Ar-O-**CH_2**-**CH**), 4.50 (s, 2H, O-**CH_2**-Ph), 7.07-7.36 (m, 12H, **H_β**, **H_γ**, **H_{arom}**), 7.96 (dd, 1H, **H_α**, J = 2.4, J = 3.9); *Anal.* Calcd for $C_{24}H_{27}N_2O_3Cl$: C, 67.52; H, 6.37; N, 6.56; Cl, 8.30. Found : C, 67.35; H, 6.16; N, 6.34; Cl, 8.12.

3-(2,3-Dihydro-1,4-dioxino[2,3-b]pyridin)yl-N-benzyl-N-(2-benzyloxyethyl)methanamine (**11**) : Amino-alcohol (**10**) (0.470 g, 1.1 mmol) in DME (5 ml) was added slowly to a suspension of sodium hydride (0.048 g, 60% dispersion in mineral oil, 2 mmol) in dry ethylene glycol dimethyl ether (DME) (5 ml). The mixture was warmed at 80°C for 24 h. After hydrolysis, extraction with CH_2Cl_2 and washing of the organic layers with saturated sodium hydrogen carbonate solution, the crude product was purified by column chromatography (eluent : Ether/ CH_2Cl_2 : 1/1) and was collected as an oil (0.250 g) in 58% yield; ir (film) 1170 (C-O-C) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 2.74-2.93 (m, 2H, N-**CH_2**-CH_2), 2.80 (dd, 1H, CH-**CH_2**-N, J = 5.5, J = 14.2), 2.97 (dd, 1H, CH-**CH_2**-N, J = 4.7, J = 14.2), 3.58 (t, 2H, **CH_2**-OBn, J = 5.1), 3.68 (d, 1H, N-**CH_2**-Ph, J = 13.4), 3.80 (d, 1H, N-**CH_2**-Ph, J = 13.4), 3.85 (dd, 1H, O-**CH_2**-CH, J = 7.5, J = 1.8), 4.26 (dd, 1H, O-**CH_2**-CH, J = 2.4, J = 11.8), 4.31-4.39 (m, 1H, O-**CH**-CH_2), 4.48 (s, 2H, O-**CH_2**-Ph), 6.81 (dd, 1H, **H_β**, J = 4.7, J = 7.9), 7.12 (dd, 1H, **H_γ**, J = 1.6, J = 7.9), 7.19-7.37 (m, 10H, **H_{arom}**), 7.78 (dd, 1H, **H_α**, J = 1.6, J = 4.7); *Anal.* Calcd for $C_{24}H_{26}N_2O_3$: C, 73.82; H, 6.71; N, 7.17. Found : C, 73.99; H, 6.92; N, 7.36.

3-(2,3-Dihydro-1,4-dioxino[2,3-b]pyridin)yl-N-(1-hydroxyethyl)methanamine (**12**) : A solution containing benzylamine (**11**) (3.910 g, 10 mmol) in methanol (23 ml), a few drops of concentrated hydrochloride acid and Lindlar palladium (0.800 g) was shaken in Parr apparatus under hydrogen pressure (45 psi) for 36 h. The palladium was filtered and washed with methanol, then the mixture was neutralized with potassium carbonate

powder. After removal of the solvents and a column chromatography (eluent : CH_2Cl_2/MeOH : 9/1), the concerning derivative was obtained as an oil (1.600 g) in 76% yield; ir (film) 3500-3100 (OH and NH) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 2.86 (t, 2H, N-**CH_2**-CH_2, J = 4.7), 2.96 (dd, 1H, CH-**CH_2**-NH, J = 4.1, J = 11.8), 3.03 (dd, 1H, CH-**CH_2**-NH, J = 5.9, J = 11.8), 3.70 (t, 2H, **CH_2**-OH, J = 4.7); 4.07 (dd, 1H, O-**CH_2**-CH, J = 7.6, J = 11.2), 4.32 (dd, 1H, O-**CH_2**-CH, J = 3.5, J = 11.2); 4.45-4.55 (m, 1H, O-**CH**-CH_2), 6.89 (dd, 1H, **H_β**, J = 4.7, J = 7.1), 7.21 (d, 1H, **H_γ**, J = 7.1), 7.83 (d, 1H, **H_α**, J = 4.7); *Anal.* Calcd for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.32. Found : C, 56.90; H, 6.52; N, 13.11.

8-[N-(2,3-Dihydro-1,4-dioxino[2,3-b]pyridin)-3-ylmethyl)-2-aminoethyl]-8-azaspiro[4,5]decane-7,9-dione **(5)** : Triphenylphosphine (0.700 g, 2.68 mmol) and tetramethyleneglutarimide (0.514 g, 3.08 mmol) were added to a solution of derivative **(12)** (0.430 g, 2.06 mmol) in dry THF (8 ml). The mixture was stirred at room temperature for 15 min, then it was cooled at 0°C. Diisopropyl azodicarboxylate (DIAD) (0.5 ml, 2.69 mmol) was added dropwise. The mixture was stirred at room temperature for 2 h. After evaporation of solvents, the crude product was chromatographied (eluent : Ether/CH_2Cl_2/MeOH : 47/47/6) and afforded an oil (0.551 g) in 75% yield; ir (film) 3600-3300 (NH), 1720 and 1660 (N-CO), 1170 (C-O-C) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 1.45-1.72 (m, 8H, C-(**CH_2**)$_4$), 1.96 (s, 1H, **NH**), 2.57 (s, 4H, N-CO-**CH_2**-C-**CH_2**-CO), 2.75-3.03 (m, 4H, **CH_2**-NH-**CH_2**), 3.83-3.98 (m, 2H, CH_2-**CH_2**-N-CO), 3.99 (dd, 1H, O-**CH_2**-CH, J = 3.9, J = 11.8), 4.24 (dd, 1H, O-**CH_2**-CH, J = 2.4, J = 11.8), 4.35-4.43 (m, 1H, O-**CH**-CH_2), 6.83 (dd, 1H, **H_β**, J = 4.7, J = 7.7), 7.15 (dd, 11H, **Hγ**, J = 1.2, J = 7.7), 7.79 (dd, 1H, **H_α**, J = 1.2, J = 4.7); ms (CI/NH_3) *m/z* : 360 (M^++1); *Anal.* Calcd for $C_{19}H_{25}N_3O_4$: C, 63.49; H, 7.01; N, 11.69.Found : C, 63.72; H, 7.19; N, 11.90.

1-[N-(2,3-Dihydro-1,4-dioxino[2,3-b]pyridin)-3-ylmethyl)-2-aminoethyl]-4,4-dimethylpiperidine-2,6-dione **(13)** : The compound **(13)** was obtained from aminoalcohol **(12)** (0.500 g, 2.37 mmol) and 3,3-dimethylglutarimide (0.500 g, 3.56 mmol) following the same procedure used for **(5)**. A column chromatography (eluent : Ether/MeOH : 95/5) gave the expected product as an oil (0.555 g) in 70% yield. ; ir (film) 3400-3200 (NH), 1720 and 1660 (N-CO), 1190 (C-O-C) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 1.09 (s, 6H, C-(**CH_3**)$_2$), 1.66 (s, 1H, **NH**), 2.50 (s, 4H, **CH_2**-CO-N-CO-**CH_2**), 2.76-3.03 (m, 4H, **CH_2**-NH-**CH_2**), 3.86-3.98 (m, 2H, CH_2-**CH_2**-N-CO), 3.99 (dd, 1H, O-**CH_2**-CH, J = 7.9, J = 11.4), 4.25 (dd, 1H, O-**CH_2**-CH, J = 2.4, J = 11.4), 4.39-4.48 (m, 1H, O-**CH**-CH_2), 6.83 (dd, 1H, **H_β**, J = 4.7, J= 8.3), 7.16 (dd, 1H, **H_γ**, J = 1.9,

J = 8.3), 7.79 (dd, 1H, $\mathbf{H_\alpha}$, J = 1.9, J = 4.7); ms (CI/NH_3) *m/z* : 334 (M^++1); *Anal.* Calcd for $C_{17}H_{23}N_3O_4$: C, 61.25; H, 6.95; N, 12.60. Found : C, 61.06; H, 6.78; N, 12.39.

1,3-Dihydro-2-[N-(2,3-dihydro-1,4-dioxino[2,3-b]pyridin-3-ylmethyl)-2-aminoethyl]-1,3-dioxo-2H-isoindole **(14)** : The compound **(14)** was obtained from aminoalcohol **(12)** (0.500 g, 2.37 mmol) and phthalimide (0.523 g, 3.56 mmol) following the same procedure used for **5** . A column chromatography (eluent : Ether/CH_2Cl_2/MeOH : 47/47/6) gave the expected product as a white powder (0.468 g) in 58% yield. ; mp 147-148°C; ir (KBr) 3500-3300 (NH), 1750 and 1700 (N-CO), 1185 (C-O-C) cm^{-1}; ^1H nmr ($CDCl_3$) δ : 1.56 (s, 1H, **NH**), 2.90-3.05 (m, 4H, CH-$\mathbf{CH_2}$-NH, NH-$\mathbf{CH_2}$-CH_2), 3.82 (t, 2H, $\mathbf{CH_2}$-N-CO, J = 7.2), 4.00 (dd, 1H, O-$\mathbf{CH_2}$-CH, J = 7.9, J = 11.8), 4.25 (dd, 1H, O-$\mathbf{CH_2}$-CH, J = 1.9, J = 11.8), 4.36-4.46 (m, 1H, O-**CH**-CH_2), 6.85 (dd, 1H, $\mathbf{H_\beta}$, J = 4.8, J = 8.0), 7.18 (dd, 1H, $\mathbf{H_\gamma}$, J = 1.3, J = 8.0), 7.68-7.74 (m, 2H, $\mathbf{H_{arom}}$), 7.80 (dd, 1H, $\mathbf{H_\alpha}$, J = 1.3, J = 4.8), 7.82-7.86 (m, 2H, $\mathbf{H_{arom}}$); ms (CI/NH_3) *m/z* : 340 (M^++1); *Anal.* Calcd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38. Found : C, 63.93; H, 5.26; N, 12.62.

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